
Article:
Wiles, M.D. orcid.org/0000-0003-2299-0060, Braganza, M., Edwards, H. et al. (3 more authors) (2023) Management of traumatic brain injury in the non-neurosurgical intensive care unit: a narrative review of current evidence. Anaesthesia. ISSN 0003-2409

https://doi.org/10.1111/anae.15898

Review Article

Management of traumatic brain injury in the non-neurosurgical intensive care unit: a narrative review of current evidence

M. D. Wiles,[1,2] **M. Braganza,**[3] **H. Edwards,**[4] **E. Krause,**[5] **J. Jackson**[6] and **F. Tait**[7]

1 Consultant, Department of Critical Care, 4 Clinical Specialist Occupational Therapist, Department of Neurosciences, 6 Clinical Specialist Occupational Therapist, Major Trauma and Head Injuries, Sheffield Teaching Hospital NHS Foundation Trust, Sheffield, UK
2 Honorary Clinical Lecturer, University of Sheffield Medical School, Sheffield, UK
3 Consultant, Department of Intensive Care, Chesterfield Royal Hospital NHS Foundation Trust, Chesterfield, UK
5 Specialist Occupational Therapist, Neurology and Stroke, Doncaster and Bassetlaw Teaching Hospitals NHS Foundation Trust, Doncaster, UK
7 Specialist Registrar, Department of Anaesthesia, Northampton General Hospital NHS Trust, Northampton, UK

Summary

Each year, approximately 70 million people suffer traumatic brain injury, which has a significant physical, psychosocial and economic impact for patients and their families. It is recommended in the UK that all patients with traumatic brain injury and a Glasgow coma scale ≤ 8 should be transferred to a neurosurgical centre. However, many patients, especially those in whom neurosurgery is not required, are not treated in, nor transferred to, a neurosurgical centre. This review aims to provide clinicians who work in non-neurosurgical centres with a summary of contemporary studies relevant to the critical care management of patients with traumatic brain injury. A targeted literature review was undertaken that included guidelines, systematic reviews, meta-analyses, clinical trials and randomised controlled trials (published in English between 1 January 2017 and 1 July 2022). Studies involving key clinical management strategies published before this time, but which have not been updated or repeated, were also eligible for inclusion. Analysis of the topics identified during the review was then summarised. These included: fundamental critical care management approaches (including ventilation strategies, fluid management, seizure control and osmotherapy); use of processed electroencephalogram monitoring; non-invasive assessment of intracranial pressure; prognostication; and rehabilitation techniques. Through this process, we have formulated practical recommendations to guide clinical practice in non-specialist centres.

Correspondence to: M. D. Wiles
Email: matthew.wiles1@nhs.net
Accepted: 7 October 2022
Keywords: intensive care; intracranial pressure monitoring; prognostication; rehabilitation; traumatic brain injury
Twitter: @STHJournalClub

Introduction

Traumatic brain injury (TBI) is defined as ``*an alteration in brain function, or other evidence of brain pathology, caused by an external force*´´ [1]. Each year, approximately 70 million people suffer TBI, which has a significant physical, psychosocial and economic impact for patients and their

families [2]. Traumatic brain injury is a leading cause of disability, especially among younger adults, resulting in over 8 million years lived with disability [3]. This often results in the need for prolonged periods of healthcare and rehabilitation, which is associated with high financial societal costs both in terms of direct clinical care requirements and loss of employment productivity [4].

In conjunction with the global ageing population, patients who suffer TBI are now significantly older, with the median age having doubled since the 1980s [5]. This has added additional complexity to the clinical management, as patients now increasingly have comorbid health conditions. The incidence of TBI is also increasing, with a resulting demand on healthcare services. Within the European Union, it is estimated that 1.5 million patients with TBI require admission to hospital [5]. It is recommended in the UK that all patients with TBI and a Glasgow coma scale (GCS) ≤ 8 should be transferred to a neurosurgical centre [6]. However, many patients, especially those in whom neurosurgery is not required, are not treated in, nor transferred to, a neurosurgical centre. A study of 15,820 patients managed in England and Wales found that 16% of patients with severe TBI and 39% of patients with moderate TBI were managed in non-neurosurgical centres [7]. Advanced cerebral monitoring techniques (including measurement of intracranial pressure (ICP)) are not usually available in non-neurosurgical centres, leaving clinicians in these centres with a degree of uncertainty as to how to optimally manage patients with severe TBI.

The aim of this review is to provide clinicians who work in non-neurosurgical centres with a summary of contemporary studies relevant to the management of patients with TBI.

Search strategy

Searches were performed in MEDLINE, PubMed, Web of Science, EMBASE and Google Scholar for studies relating to the management of adult patients (age ≥ 16 y) with TBI who are cared for in non-neurosurgical centres. The search included guidelines; systematic reviews; meta-analyses; clinical trials; and randomised controlled trials, and was limited to studies published in English between 1 January 2017 and 1 July 2022. Studies involving key clinical management strategies published before this time, but which have not been updated or repeated, were also eligible for inclusion. The studies selected for inclusion in this narrative review are those that, in the opinion of the authors, are of the greatest relevance to current clinical care. Where possible, the studies are discussed in themes relevant to clinical practice.

General management principles

Recent review articles have summarised the key management principles [8] and recent research developments [9] in TBI management. Several guidelines have also recommended a number of physiological targets and interventions to help control intracranial hypertension (Table 1) [6, 10, 11].

The principles underpinning most management strategies are two-fold: maintenance of cerebral homeostasis; and prevention of secondary brain injury. Most interventions to ensure cerebral homeostasis would be considered as standard for any patient who is critically unwell on the ICU and include: mechanical ventilation using lung-protective strategies; fluid and/or vasopressors to maintain adequate end-organ perfusion; nutritional support; physiotherapy; stress ulcer prophylaxis; prevention of venous thromboembolism; and infection control/management. Prevention of secondary brain injury focuses on interventions designed to reduce intracranial hypertension and examples of these which are possible in non-neurosurgical centres include: cerebral metabolic suppression by sedation; control of pyrexia; management of seizures; avoidance of hypoxia and hypercarbia; and hyperosmolar therapy. Pertinent aspects of these are discussed in detail below.

Airway and ventilation

Mechanical ventilation is a key aspect in management of the patient with TBI, both in terms of prevention of secondary brain injury (due to the effect of hypercarbia and hypoxia on ICP) and reducing the incidence of ventilator-associated pneumonia (VAP). Patients with TBI often develop VAP, with studies suggesting an incidence of up to 36% [12]; although the development of VAP results in increased duration of mechanical ventilation and critical care stay, it is not associated with an increase in mortality [12].

Although targets for acceptable arterial oxygen and carbon dioxide are well-established (Table 1), the optimal mechanical ventilation strategy to achieve these goals remains uncertain. Traditional ventilation strategies have been based on a high tidal volume (to ensure $PaCO_2$ control) and low PEEP (to avoid high intrathoracic pressures reducing cerebral venous drainage) [13]. However, with the increasing recognition that high tidal volumes increase the risk of ventilation-induced lung injury, typical lung-protective ventilation strategies used for patients without brain injury are now recommended [14]. This includes the use of individualised PEEP settings to optimise lung compliance and gas exchange.

Early percutaneous tracheostomy, defined as < 7 days from admission, is associated with a reduction in VAP and

Table 1 Guidelines for the management of traumatic brain injury. Adapted from [9].

	Brain Trauma Foundation: Guidelines for the Management of Severe Traumatic Brain Injury [10]	Association of Anaesthetists: Guidelines for safe transfer of the brain-injured patient: trauma and stroke [11]	National Institute for Health and Care Excellence: Head injury: assessment and early management [6]
Blood pressure	SBP > 100 mmHg (age 50–69 y) SBP ≥ 110 mmHg (ages 15–49 and > 70 y)	SBP 110–150 mmHg MAP > 90 mmHg	MAP ≥ 80 mmHg
Ventilation	Avoid $PaCO_2$ < 3.33 kPa	$PaCO_2$ 4.5–5.0 kPa PaO_2 ≥ 13 kPa	$PaCO_2$ 4.5–5.0 kPa PaO_2 > 13 kPa
Steroids	Not recommended	No recommendation made	No recommendation made
Osmotherapy	No recommendation made	Mannitol or hypertonic saline if impending uncal herniation	No recommendation made
Temperature	Prophylactic hypothermia not recommended	Maintain normothermia (36–37°C)	No recommendation made

SBP, systolic blood pressure; MAP, mean arterial pressure.

duration of mechanical ventilation [15]. More recent work has suggested that patients with severe TBI who are likely to require tracheal intubation for ≥ 7 days may benefit from tracheostomy in the first 72 h of their hospital admission [16]. As such, early tracheostomy should be considered in patients with severe TBI even if the long-term prognosis in terms of neurological outcome is uncertain.

Cardiovascular

Hypotension remains the most important cause of secondary brain injury in patients with TBI. A systolic blood pressure < 120 mmHg increases the risk of death by 50% [17]. This risk increases further with lower blood pressures, with the risk of death tripling with a systolic blood pressure < 90 mmHg [17]. In the light of this, permissive hypotension as part of a resuscitation strategy is not appropriate in patients with suspected or confirmed TBI [18]. Suggested targets for blood pressure are shown in Table 1, with most centres aiming to maintain a mean arterial pressure ≥ 80 mmHg.

There is continued debate as to the optimal intravenous fluid to use in patients with TBI. At present, there is no evidence of benefit in terms of neurological outcome for any particular fluid, although albumin should be avoided as this is associated with an increased risk of mortality (OR 0.55 (95%CI 0.35–0.87)) [19]. In the UK, noradrenaline is the most common vasopressor used in ICU to maintain cerebral perfusion and prevent secondary brain injury. However, there is a lack of evidence supporting this practice in terms of improvements in neurological outcomes [20]. Phenylephrine is used in many centres in the USA, and a study suggested that this was associated with a reduction in mortality compared with noradrenaline [21]; but the retrospective nature of this study and the impact of unmeasured confounders means these data should be viewed as hypothesis-generating, with a need for future randomised controlled trials.

Transfusion triggers have traditionally been higher for patients with TBI compared with other patients who are critically ill, with many centres using a haemoglobin concentration of > 90 $g.l^{-1}$. However, although anaemia is a risk-factor for worse outcomes in patients with TBI, this may not be modifiable through transfusion of red blood cells. A retrospective review found that red blood cell transfusion was only of benefit in patients with a haemoglobin concentration of ≤ 80 $g.l^{-1}$ [22]. A more recent systematic review found a reduced risk of poor neurological outcome with a transfusion trigger of 70 $g.l^{-1}$ compared with 90 $g.l^{-1}$ (OR 0.64 (95%CI 0.42–0.97)) [23], although the studies included were rated as being moderate to low in terms of quality. As such, it appears reasonable to use a trigger of 70–80 $g.l^{-1}$ at the present time. It should be noted that this transfusion trigger only applies to patients with TBI who are not bleeding actively. Patients who are bleeding acutely after trauma, especially in the context of polytrauma with extracranial injuries, should be managed in accordance with existing transfusion guidelines, with the use of high-ratio plasma to packed red blood cell transfusion strategies and early (within 3 h of injury) administration of tranexamic acid [24].

Osmotherapy

The most common drugs used in this regard are mannitol and hypertonic saline. Both have been studied extensively in patients with TBI with no clear evidence of outcome benefit for either therapy. A recent meta-analysis involving 464 patients showed similar neurological outcomes and

mortality rates for mannitol and hypertonic saline (relative risk (RR) 1.28 (95%CI 0.86–1.90) and 0.69 (95%CI 0.45–1.04), respectively) [25]. The optimal dose of both remains the subject of research and is complicated by the range of different concentrations available. Typical bolus doses are 0.25–1 $g.kg^{-1}$ mannitol 10% (2.5–10 $ml.kg^{-1}$) or 2 $ml.kg^{-1}$ 3% hypertonic saline 3%. In the absence of ICP monitoring, osmotherapy can contribute to empirical medical management of intracranial hypertension, either based on a fixed administration schedule or with serial computed tomography (CT) scanning to assess response [26]. Typical targets are serum sodium 145–155 $mmol.l^{-1}$ and/or serum osmolality 310–320 $mosm.kg^{-1}$, though the correlation between these values and ICP is questionable [27]. Both approaches lead to a risk of under- or overtreatment of intracranial hypertension, and both drugs have a number of significant adverse effects [28].Whilst both are effective in reducing ICP in the short term, the lack of outcome benefits mean that, within non-neurosurgical centres, these should be best viewed as a temporising measure before definitive care (e.g. transfer for neurosurgical intervention).

Temperature

Maintenance of normothermia (36.5–37.5°C) is recommended, with active aggressive treatment of both hypo- and hyperthermia [29]. Hyperthermia occurs commonly in patients with TBI and is often seen soon after injury, even in the absence of infection [30]. Temperature should be monitored continuously with the early application of surface and/or intravascular cooling devices once hyperthermia is detected; antipyretic drugs such as paracetamol are often ineffective [31]. There is no evidence supporting the use of prophylactic cooling in the absence of fever [32]. Bacterial infection remains the most common cause of fever in patients with TBI who are critically ill. Up to 46% of patients with severe TBI cared for in specialist centres develop a central or neurogenic fever [33] with patients with diffuse axonal or frontal lobe injury at greatest risk [34]. The mechanism underlying this is unknown, but it is thought to be mediated by direct hypothalamic dysfunction or production of endogenous pyrogens. Neurogenic fever is a diagnosis of exclusion and other causes should actively be sought as per recommendations [35]. As procalcitonin and C-reactive protein levels can also be elevated by TBI, these are not useful in the diagnosis of neurogenic fever [36, 37].

Seizure control

In patients with TBI who have had a seizure, anti-epileptic medication is often given for 7 days following injury. Yet, the evidence basis for this is weak, with a review by the Cochrane group judging many of the relevant studies low quality [38]. The occurrence of post-traumatic seizures is not associated with an increase in mortality, although seizures occurring > 7 days post-injury are associated with worse neurological and functional outcome at 6 months; however, this is not attenuated by the prophylactic use of anti-epileptic drugs [39].

When prophylaxis is given, levetiracetam is now the preferred drug, as this has a similar efficacy but fewer adverse effects compared with phenytoin [40]. The optimal dose of levetiracetam for seizure prophylaxis after TBI is unknown. The most common dose used in trials is 500 mg twice daily, but this does not produce therapeutic plasma concentrations [40]. At present, a dose of 20 $mg.kg^{-1}.day^{-1}$ is recommended as this will generate levels in the therapeutic range. There is uncertainty about how to manage ongoing seizures after TBI, as most clinical trials that investigate status epilepticus do not differentiate between aetiologies. As such, the management will be identical to that used in patients without evidence of TBI; this is beyond the scope of this article but has been discussed in a recent review [41].

Processed electroencephalogram monitoring

Although several processed electroencephalogram (EEG) devices are available, most of the published literature has focused on the use of the bispectral index system (BIS; Medtronic Ltd., Watford, UK). The utility of BIS in helping guide depth of sedation is routine in many centres, with moderate to strong correlation between BIS values and traditional clinical sedation scales [42]. Given the difficultly in using clinical sedation measurement tools in patients with TBI, BIS may help clinicians optimise sedation delivered on critical care. However, there is no evidence that this practice improves neurological outcome.

Due to the difficulty in accessing formal EEG recordings in some non-neurosurgical centres, the use of processed EEG measurement as an alternative has been investigated. The most common indications for formal EEG measurement in patients with TBI are the diagnosis of seizures (especially non-convulsive status epilepticus) and monitoring of burst suppression. At present, BIS is insufficiently sensitive to reliably detect seizure activity, although the incorporation of colour density spectral array, which provides a power spectrum representation of the summated EEG activity, shows promise in this regard [43]. The BIS-derived suppression ratio correlates well with the degree of burst-suppression on formal EEG [43]; targeting a suppression ratio of 60–80 is typical when burst suppression is required

[44], with the caveat that the efficacy of this on neurological outcome remains uncertain [41]. BIS also has some limitations when used for burst suppression including the inability to identify spikes and periodic patterns within bursts and an inability to guide therapy as sedation is weaned. At present, the primary use for processed EEG monitoring in non-neurosurgical centres is in helping to ensure adequate depth of sedation in ICU.

Intracranial pressure monitoring

Intracranial pressure monitoring has an important place in the management of patients with severe TBI. The Brain Trauma Foundation recommends monitoring ICP and instituting treatment when > 22 mmHg in order to reduce mortality [10]. Data from an observational study suggests that ICP monitoring is associated with a reduction in mortality and improved neurological outcomes [45]. In patients who do not require intracranial surgery, the perceived need for ICP monitoring is the most common indication for admission to a neurosurgical centre. The decision to admit to a neurosurgical centre for ICP monitoring is complicated by the fact that there is also no agreed consensus as to the precise indication and use of ICP monitoring, with conflicting published guidelines (Table 2) [46, 47]. This has led to widespread variations in practice, with most centres using local protocols. As a result, within non-neurosurgical centres there may be a perception of heterogeneity in decision making regarding referral acceptance by tertiary centres. In the UK, the National Institute of Health and Care Excellence (NICE) recognises that all patients with serious head injuries (GCS ≤ 8) would benefit from admission to a neurosurgical centre irrespective of the need for neurosurgery, whilst acknowledging that this is often not possible due to capacity [6]. As a result, it is recommended that shared guidelines are produced between neurosurgical units and local hospitals to determine local practice regarding admission criteria, and to create a framework for ongoing neurosurgical input into clinical care in those patients who are not admitted.

Where transfer to a neurosurgical centre does not occur and/or direct ICP measurement is not possible, monitoring for neurological deterioration is most often assessed via serial physical examination including: GCS; pupillary size and reactivity; development of seizures; and new neurological deficits. Computed tomography is indicated where there is a suspected progression of intracranial pathology, and should trigger re-discussion of the case with the neurosurgical centre.

A protocol for management of intracranial hypertension in the absence of ICP monitoring has been developed [26], primarily based on the study by Chesnut et al. [48]. This was a randomised controlled trial conducted in South America that compared a management strategy based on ICP monitoring with one based on clinical examination and serial imaging. The study found no difference in the primary outcome measure (which was a complex composite measure of 21 domains) between the strategies. However, the study was

Table 2 Recommendations for insertion of intracranial pressure (ICP) monitoring in patients with traumatic brain injury (TBI).

Brain Trauma Foundation: Guidelines for the management of severe traumatic brain injury [10]	**American College of Surgeons: Best practice in the management of traumatic brain injury [46]**	**Clinical applications of intracranial pressure monitoring in traumatic brain injury: report of the Milan consensus conference [47]**
• All salvageable patients with GCS ≤ 8 post-resuscitation and an abnormal CT (presence of haematoma, contusion, swelling, herniation or compressed basal cistern) • Patients with severe TBI and a normal CT scan and ≥ 2 of the following: age > 40 y; unilateral or bilateral motor posturing; or systolic blood pressure < 90 mm Hg	• Patients with GCS ≤ 8 with evidence of structural brain damage on initial CT • Consider in patients with a GCS > 8 who have structural brain damage with high risk for progression (e.g. large/ multiple contusions, coagulopathy) • Consider in patients who require urgent surgery and/or mechanical ventilation for extracranial injuries because of extracranial injuries, or who evidence progression of pathology on CT imaging or clinical deterioration	• Patients with GCS ≤ 8 post-resuscitation and an initial CT demonstrating diffuse injury with signs of brain swelling (e.g. compressed/absent basal cisterns) • Patients with GCS ≤ 8 post-resuscitation and an initial CT scan showing contusional injury and in whom the interruption of sedation to check the neurological status is considered dangerous (e.g. radiological signs of raised ICP, ongoing emergency extracranial surgery) or when the clinical examination is not completely reliable (severe maxillofacial trauma, spinal cord injury) • Consider in patients with GCS ≤ 8 post-resuscitation and large bifrontal contusional injury and/or haemorrhagic mass lesions close to the brainstem irrespective on initial GCS

GCS, Glasgow coma scale; CT, computed tomography.

conducted in an environment of limited healthcare resources, especially with respect to pre-hospital management; this significantly limits generalisation of the findings to practice in high-income countries. A Delphi process involving 43 intensivists and neurosurgeons from Latin America was undertaken subsequently to create an algorithm for the management of severe TBI based on imaging and clinical examination when ICP monitoring is not employed [49]. This suggests that a CT brain is required at baseline and then repeated at 12 h (if initial scan was done within ≤ 4 h of injury), 24 h and 48 h. However, this protocol has not been validated in terms of clinical outcomes, and again may not be generalisable outside of Latin America.

There are also several non-invasive techniques available to non-specialist centres that may be used as adjuncts to the above.

Pupillometry

Automated pupillometers use a combination of infrared and visible light to capture variability in pupillary light reflexes. They measure the pupil at rest using infrared light and then the pupillary light reflex to a flash of visible light [50], allowing assessment of: minimal and maximal pupil size; constriction latency; constriction velocity; constriction percentage; minimum size; and dilation velocity. One of the most used devices is the NPI-pupillometer (NeuroOptics; Irvine, CA, USA). This uses a proprietary algorithm which combines information about pupil size and reactivity into a 0–5 grade (normal > 3) that can be tracked over time, objectively detecting subtle changes in pupillary responsiveness which may represent an increase in ICP [51]. However, there is no agreed threshold for changes in the indices measured by automated pupillometers that correlates with clinically important changes in ICP, and most studies in this area are of low or very low quality [52]. Further prospective trials are needed to determine the precise utility of these devices in monitoring ICP and to determine the threshold for changes in clinical management (e.g. as a trigger for repeat CT scanning). At present, there is insufficient evidence to support their routine use in clinical practice.

Point-of-care ultrasound

The use of point-of-care ultrasound has increased considerably over recent years with two techniques, optic nerve sheath diameter (ONSD) measurement and transcranial Doppler (TCD), of direct relevance to assessment of ICP. These have both been discussed in detail in a recent review article [53] and therefore are only discussed here in brief. As the optic nerve sheath is a direct extension of the brain meninges, any elevation of ICP is directly transmitted to the sheath. Measuring the ONSD is a bedside, non-invasive means to detect elevated ICP, although there are several approaches described [54]. A meta-analysis showed that ONSD measurement had a reasonable accuracy in diagnosing raised ICP compared with parenchymal measurement (sensitivity 0.90 (95% CI 0.85–0.94), specificity 0.85 (95%CI 0.80–0.89)), although included studies used a range of threshold values (4.8–6.4 mm) [55]. Abnormalities of the meninges may also lead to erroneous measurements.

Transcranial Doppler utilises the thin temporal bone as an acoustic window to assess arterial or venous flow velocity in cerebral vessels. Alterations in flow velocity waveform patterns may reflect changes in ICP. The middle cerebral artery is a target for arterial assessment with systolic, diastolic and mean flow velocities being useful, as well as a derived pulsatility index. A meta-analysis using patient level data found TCD-derived measurements were insufficient to accurately detect raised ICP [56]. In addition, TCD needs advanced training, intra- and interobserver variations can be large, and it sometimes is not possible due to the absence of an adequate bone window. As such, the role for TCD outside of neurosurgical centres is likely to be limited.

Prognostication

Prognostication following TBI is challenging and complex. Traumatic brain injury is not a single clinical entity, but rather a collection of heterogeneous types of cerebral insult, each of which may have differing degrees of severity and prognostic significance [9]. This heterogeneity makes it difficult to prognosticate for an individual patient. Despite this, accurate prognostication in critical care is still needed for families and medical decision-making.

Many individual risk factors that affect prognosis are present on hospital admission. These include: initial GCS (especially the motor component); age; pupillary reaction to light; presence of extracranial injuries; hypoxia; and hypotension [57]. Abnormalities on initial neuroimaging can also be graded using validated scoring systems such as the Rotterdam CT score or Marshall CT classification, which correlate with neurological outcome measures [58]. Although the evidence base to use imaging to guide prognosis is strong, care must be exercised. Normal admission CT scans may not exclude raised ICP and new intracranial pathology develops in up to 40% of patients with TBI [10].

Magnetic resonance imaging (MRI) has also been evaluated as a prognostic tool in TBI. Diffuse axonal injury and the presence of brainstem pathology on MRI may predict unfavourable long-term functional outcomes but

should still be interpreted with caution due to heterogeneity in injury patterns and scanning protocols in published studies [59].

Several prognostic models are also available for patients with TBI, but these are not currently endorsed by national guideline groups. The models that have been studied and externally validated most often are the International Mission for Prognosis and Analysis of Clinical Trials in TBI (IMPACT) and Corticosteroid Randomisation After Significant Head Injury (CRASH) (8509 and 10,008 patients, respectively). These have an area under the curve for detection of functional outcome at 6 months of 0.65–0.90 and 0.66–1.00, respectively [60]. Interestingly, despite widespread availability of both models, clinical uptake remains limited. Clinicians are rightly weary of the generalisability of population-based models and the limits to which data from these can be extrapolated to an individual patient. Given the heterogeneity of TBI, clinical reluctance is understandable, especially as treatment options have advanced since the original study cohorts were managed. Concerns also exist regarding confirmation bias (the `self-fulfilling prophecy´) – a model may predict poor outcome thereby altering treatment approaches, subsequently leading to a worse patient outcome. This is particularly pertinent for TBI, as withdrawal of life-sustaining treatment is the most common factor leading to death within ICU [61]. Neither model allows for the impact of pre-existing comorbidity to be considered nor the nuanced interpretation for functional outcome; patients may recover to limited functional status but still have acceptable quality of life. The prognostic value of a number of biomarkers has also been investigated including: glial fibrillary acidic protein; S100 calcium-binding protein B; total τ; neurofilament protein-light; neuron-specific enolase; and ubiquitin C-terminal hydrolase L1. It is possible that the addition of these to existing models will help improve their prognostic value [62].

Assessment of neurological and functional outcome following TBI is most commonly done using the extended Glasgow outcome scale (GOS-E). This assesses changes in a patient's level of functionality in discrete domains including: level of consciousness; independence with activities of daily living; ability to work and participate in social and leisure activities; psychological impacts on relationships; and return to normal life (Table 3). However, there are limitations to the GOS-E, most importantly that it may not fully represent the patient's assessment of their own quality of life [63]. In addition, most trials limit the assessment of GOS-E to 6 months after injury, even though neurological recovery can improve or deteriorate over subsequent years. A recent study assessed GOS-E at four time-points in 484 patients who suffered moderate to severe TBI (Table 3) [64]. Within this cohort, at 2 weeks 12% of patients with severe TBI had a favourable outcome (classed as GOS-E $\geq$ 4), which improved to 52% at 12 months. There is also evidence that neurological recovery may continue to improve up to 2 y post-injury [65].

Prognostication after TBI, therefore, remains a dynamic process that requires the careful evaluation of multiple clinical parameters. Open family discussions and transparent decision-making are needed from the outset. Undoubtedly, what is most important is re-evaluation over time and this is emphasised in recent national guidance on perceived devastating brain injury [66]. Full functional recovery may take years [67] and it is beyond the ability of the intensivist to predict this accurately during the ICU admission period.

Rehabilitation

As more individuals survive their traumatic event, there is a growing need for assessment and rehabilitation of neurological injury. Patients with TBI can be left with complex long-term difficulties with physical, cognitive and mental health disorders. Only around 50% of patients return to work after severe TBI [68]. Those patients who do not return to work often report difficulties with personal identity, loss of roles within family units and feeling like a burden, which causes tension in relationships.

Gaps in transitioning from hospital to the community exist and community services vary greatly depending on geographical area. It is, therefore, essential that rehabilitation is initiated in the acute setting so patients and families can receive quality assessment, education and physical therapy.

A multidisciplinary approach to assessment is recommended to identify deficits and to ensure signposting to the most effective follow-up services, with nurses, occupational therapists, physiotherapists and speech and language therapists being key members of the team. This section of the review will focus on assessment of cognition, as deficits in this area are not always easily visible in the acute hospital environment but can have significant long-term consequences on an individual patient's ability to return fully to previous roles.

Patients with the most severe TBI can develop disorders of consciousness, which in turn can present a complex array of clinical and ethical challenges to healthcare professionals and family members. Often, these patients begin their rehabilitation journey on ICUs. Emergence from a disorder of consciousness is slow and gradual, and therefore assessment is best made via careful observation over time. Occupational therapists can use assessments tools such as

Table 3 Summary of the extended Glasgow outcome scale. Proportions shown are the number of patients with traumatic brain injury in each group at 2 weeks, 3 months, 6 months and 12 months post-injury (adapted from [64]).

Glasgow outcome scale		Neurological and functional status	Proportion of patients			
			2 weeks	3 months	6 months	12 months
1	Dead	Dead	22%	26%	29%	31%
1	Vegetative state	Vegetative or minimally conscious state Unable to communicate	23%	4%	1%	-
1	Severe disability (lower)	Requires frequent assistance of another person at home for some ADL; cannot be left alone for > 8 h per day Unable to shop and/or travel without assistance	43%	25%	20%	17%
1	Severe disability (upper)	Requires assistance of another person at home for some ADL; can self-care at home alone for up to 8 h per day Able to shop and/or travel without assistance	3%	8%	2%	4%
1	Moderate disability (lower)	Able to work but only in sheltered capacity or non-competitive job Psychological problems affecting relationships (constant) Unable to participate in leisure/social activities	8%	21%	18%	15%
1	Moderate disability (upper)	Able to work but at a reduced capacity Psychological problems affecting relationships (frequent) Participate in leisure/social activities less than half as often as pre-injury	1%	8%	12%	11%
1	Good recovery (lower)	Some physical or neurological deficits that impact on daily life Psychological problems affecting relationships (occur less than weekly) Participate in leisure/social activities at least as half as often as pre-injury	-	3%	9%	10%
1	Good recovery (upper)	Full return to pre-injury activity	-	5%	9%	10%

ADL, activities of daily living.

the Wessex head injury matrix (WHIM), coma recovery scale-revised (CRS-R) or sensory modality assessment and rehabilitation technique (SMART) to provide structure to assessments and quantify changes in states of consciousness over time. Using careful monitoring, the multidisciplinary team can collect evidence to guide treatment escalation and discharge planning to an appropriate unit (which may include neuro-rehabilitation units or specialist long-term care). Long-term tracheostomy or enteral feeding may also influence discharge location. Psychopharmacological therapies can be helpful in enhancing the cognitive domains of attention, memory and executive function [69] and may improve functional performance and decrease duration of stay [70]. A specialist or trauma rehabilitation consultant should be consulted before administering any medication.

For patients who do not have a disorder of consciousness, assessment of neurological deficits (including post-traumatic amnesia) should commence as soon as is reasonably possible. Following a brain injury, patients can have difficulty with attention and memory encoding resulting in islands of memory, disorientation and behavioural disturbances [71]; this period is referred to as post-traumatic amnesia and patients should be screened for this using a standardised tool. The Westhead post-traumatic amnesia scale (full and abbreviated), Galveston orientation and amnesia test and orientation log are used commonly.

Assessment of patients should always be individualised. A comprehensive social history and assessment before cognitive assessment should be undertaken, considering factors such as age, pre-existing cognitive deficits, educational and vocational histories, drug and alcohol abuse and if English is a first language. Visual and communication deficits should also be screened for, although more subtle deficits are often picked up during more detailed cognitive assessments. The choice of standardised cognitive assessment used will be influenced by the factors stated above and patient presentation on initial neurological examination on the acute ward. Medical conditions that may influence cognition should be noted and the assessment tailored where necessary. Although the evidence base around the use of functional assessment in

the acute setting is limited, we would advocate the use of functional assessments to complement standardised assessments. They enable the occupational therapist to review skills that a pen and paper test may not, including insight, risk management and cognitive strategies that a patient may employ.

Challenging behaviour can arise after TBI, often presenting during the earlier stages of recovery. These behaviours are often influenced by cognitive and communication challenges. People working with the patient should seek to evaluate any antecedent to enable staff to employ strategies to reduce negative stimuli in conjunction with de-escalation techniques. Charts to record antecedents, behaviours and consequences (ABC charts) are available. Pharmacological interventions should be used with caution due to limited evidence of efficacy and potential to worsen some symptoms [72]. Traditional antipsychotic and neuroleptic drugs have been shown in human and animal studies to have a negative effect on recovery following TBI [73]. Olanzapine, an atypical antipsychotic drug used commonly to manage delirium in patients who are critically ill, appears to be effective in reducing agitation, anger or irritability in patients who have suffered TBI [72]. Quetiapine may also be effective in managing aggressive behaviour [74], whilst propranolol, methylphenidate and valproic acid may also be helpful in managing agitation [72]. Benzodiazepines are not recommended due their negative effect on neurological recovery and high incidence of adverse effects [73].Trazodone is often used to manage insomnia, although there is little research in its use in patients with TBI [75]. Tools such as the agitated behavioural scale can be used as a serial measure of changes in behaviours over time. Patients presenting with challenging behaviours may require specialist inpatient rehabilitation above and beyond locally commissioned neurological rehabilitation services and funding for enhanced rehabilitation units may need to be sought.

The structure of neurological rehabilitation services varies geographically including inpatient and community teams. Many factors work alongside cognitive challenges to influence rehabilitation needs including: social support; previous roles; risk management; prognosis; and patient goals. The multidisciplinary team must work alongside the patient and their family to access the most appropriate pathway for their individual rehabilitation needs. Assessments of prolonged disorders of consciousness, post-traumatic amnesia and challenging behaviour are specialist roles within the profession of occupational therapy. However, with appropriate resources and training, this patient population can receive high-quality and timely neurological occupational therapy assessment whilst in non-neurosurgical centres.

Areas of uncertainty

The key aspect of any future research is to select outcome measures which are of importance to patients and their families. These should ideally be standardised to facilitate comparison between studies. Patient-reported outcomes are increasingly used and this is vital due to the heterogeneity in perceived acceptable outcomes for individual patients. Uncertainty persists as to which patients benefit most from ICP/multimodal monitoring and what physiological goals should be targeted in ICU. Much of the management of older patients with TBI is based on data extrapolated from younger patients without comorbid medical conditions, and future trials should focus on (or attempt to actively recruit) older patients; this includes the need for more accurate prognostic models and/or biomarkers. There is also a need for outcomes to be measured at longer time-points (e.g. ≥ 12 months) as neurological recovery often occurs over a protracted period.

Conclusion

Given the significant sequelae of TBI to patients, their families and society as a whole, it is vital that patients receive timely and appropriate interventions both in the acute and longer-term setting. Whilst some specialist interventions for the management of TBI (e.g. ICP and multimodal monitoring) are not available outside neurosurgical centres, this does not mean that high-quality care cannot be provided in non-neurosurgical centres. When a decision is made not to transfer a patient to a neurosurgical centre, local clinicians should not view this as a poor prognostic marker and brain-protective management strategies and appropriate ongoing supportive care should be implemented. Many patients with TBI managed outside of neurosurgical centres will make a good neurological recovery from their injury and the delivery of evidence-based targeted neurocritical care should not be limited to specialist centres.

Acknowledgements

MW is an Editor of *Anaesthesia*. No other competing interests declared.

References

1. Menon DK, Schwab K, Wright DW, Maas AI. Position statement: definition of traumatic brain injury. *Archives of Physical Medicine and Rehabilitation* 2010; **91**: 1637–40.
2. Dewan MC, Rattani A, Gupta S, et al. Estimating the global incidence of traumatic brain injury. *Journal of Neurosurgery* 2019; **130**: 1080–97.

3. James SL, Theadom A, Ellenbogen RG, et al. Global, regional, and national burden of traumatic brain injury and spinal cord injury, 1990–2016: a systematic analysis for the global burden of disease study 2016. *Lancet Neurology* 2019; **18**: 56–87.
4. Ma VY, Chan L, Carruthers KJ. Incidence, prevalence, costs, and impact on disability of common conditions requiring rehabilitation in the United States: stroke, spinal cord injury, traumatic brain injury, multiple sclerosis, osteoarthritis, rheumatoid arthritis, limb loss, and back pain. *Archives of Physical Medicine and Rehabilitation* 2014; **95**: 986–95.e1.
5. Maas AIR, Menon DK, Adelson PD, et al. Traumatic brain injury: integrated approaches to improve prevention, clinical care, and research. *Lancet Neurology* 2017; **16**: 987–1048.
6. National Institute for Health and Care Excellence. Head injury: assessment and early management. [CG176]. 2019. https://www.nice.org.uk/guidance/cg176 (accessed 06/10/2022).
7. Lawrence T, Helmy A, Bouamra O, Woodford M, Lecky F, Hutchinson PJ. Traumatic brain injury in England and Wales: prospective audit of epidemiology, complications and standardised mortality. *British Medical Journal Open* 2016; **6**: e012197.
8. Stocchetti N, Carbonara M, Citerio G, et al. Severe traumatic brain injury: targeted management in the intensive care unit. *Lancet Neurology* 2017; **16**: 452–64.
9. Wiles MD. Management of traumatic brain injury: a narrative review of current evidence. *Anaesthesia* 2022; **77**: 102–12.
10. Brain Trauma Foundation. Guidelines for the management of severe traumatic brain injury. 4th edition. 2016. https://braintrauma.org/uploads/03/12/Guidelines_for_Management_of_Severe_TBI_4th_Edition.pdf (accessed 01/09/2022).
11. Nathanson MH, Andrzejowski J, Dinsmore J, et al. Guidelines for safe transfer of the brain-injured patient: trauma and stroke, 2019. *Anaesthesia* 2020; **75**: 234–46.
12. Li Y, Liu C, Xiao W, Song T, Wang S. Incidence, risk factors, and outcomes of ventilator-associated pneumonia in traumatic brain injury: a meta-analysis. *Neurocritical Care* 2020; **32**: 272–85.
13. Asehnoune K, Roquilly A, Cinotti R. Respiratory management in patients with severe brain injury. *Critical Care* 2018; **22**: 76.
14. Robba C, Poole D, McNett M, et al. Mechanical ventilation in patients with acute brain injury: recommendations of the European Society of Intensive Care Medicine consensus. *Intensive Care Medicine* 2020; **46**: 2397–410.
15. de Franca SA, Tavares WM, Salinet ASM, Paiva WS, Teixeira MJ. Early tracheostomy in severe traumatic brain injury patients: a meta-analysis and comparison with late tracheostomy. *Critical Care Medicine* 2020; **48**: e325–e331.
16. Selvakumar S, Chan K, Ngatuvai M, Newsome K, Ang D, Bilski T, Elkbuli A. Timing of tracheostomy in patients with severe traumatic brain injuries: the need for tailored practice management guidelines. *Injury* 2022; **53**: 2717–24.
17. Fuller G, Hasler RM, Mealing N, Lawrence T, Woodford M, Juni P, Lecky F. The association between admission systolic blood pressure and mortality in significant traumatic brain injury: a multi-centre cohort study. *Injury* 2014; **45**: 612–7.
18. Wiles MD. Blood pressure in trauma resuscitation: `pop the clot´ vs. `drain the brain´? *Anaesthesia* 2017; **72**: 1448–55.
19. Tseng CH, Chen TT, Wu MY, Chan MC, Shih MC, Tu YK. Resuscitation fluid types in sepsis, surgical, and trauma patients: a systematic review and sequential network meta-analyses. *Critical Care* 2020; **24**: 693.
20. Lloyd-Donald P, Spencer W, Cheng J, Romero L, Jithoo R, Udy A, Fitzgerald MC. In adult patients with severe traumatic brain injury, does the use of norepinephrine for augmenting cerebral perfusion pressure improve neurological outcome? A systematic review. *Injury* 2020; **51**: 2129–34.
21. Toro C, Ohnuma T, Komisarow J, et al. Early vasopressor utilization strategies and outcomes in critically ill patients with severe traumatic brain injury. *Anesthesia and Analgesia* 2022; **135**: 1245–52. https://doi.org/10.1213/ANE.0000000000005949.
22. Litofsky NS, Martin S, Diaz J, Ge B, Petroski G, Miller DC, Barnes SL. The negative impact of anemia in outcome from traumatic brain injury. *World Neurosurgery* 2016; **90**: 82–90.
23. Florez-Perdomo WA, García-Ballestas E, Martinez-Perez R, et al. Hemoglobin levels as a transfusion criterion in moderate to severe traumatic brain injury: a systematic review and meta-analysis. *British Journal of Neurosurgery* 2021. 1–7. https://doi.org/10.1080/02688697.2021.1940850.
24. Vlaar APJ, Dionne JC, de Bruin S, et al. Transfusion strategies in bleeding critically ill adults: a clinical practice guideline from the European Society of Intensive Care Medicine. *Intensive Care Medicine* 2021; **47**: 1368–92.
25. Schwimmbeck F, Voellger B, Chappell D, Eberhart L. Hypertonic saline versus mannitol for traumatic brain injury: a systematic review and meta-analysis with trial sequential analysis. *Journal of Neurosurgical Anesthesiology* 2021; **33**: 10–20.
26. Godoy DA, Rabinstein AA. How to manage traumatic brain injury without invasive monitoring? *Current Opinion in Critical Care* 2022; **28**: 111–22.
27. Farley P, Salisbury D, Murfee JR, et al. The relationship between serum sodium, serum osmolality, and intracranial pressure in patients with traumatic brain injury treated with hyperosmolar therapy. *American Surgeon* 2021; **88**: 380–3.
28. Freeman N, Welbourne J. Osmotherapy: science and evidence-based practice. *British Journal of Anaesthesia Education* 2018; **18**: 284–90.
29. Pegoli M, Zurlo Z, Bilotta F. Temperature management in acute brain injury: a systematic review of clinical evidence. *Clinical Neurology and Neurosurgery* 2020; **197**: 106165.
30. Birg T, Ortolano F, Wiegers EJA, et al. Brain temperature influences intracranial pressure and cerebral perfusion pressure after traumatic brain injury: a CENTER-TBI study. *Neurocritical Care* 2021; **35**: 651–61.
31. Albrecht RF, Wass CT, Lanier WL. Occurrence of potentially detrimental temperature alterations in hospitalized patients at risk for brain injury. *Mayo Clinic Proceedings* 1998; **73**: 629–35.
32. Wu X, Tao Y, Marsons L, Dee P, Yu D, Guan Y, Zhou X. The effectiveness of early prophylactic hypothermia in adult patients with traumatic brain injury: a systematic review and meta-analysis. *Australian Critical Care* 2021; **34**: 83–91.
33. Hocker SE, Tian L, Li G, Steckelberg JM, Mandrekar JN, Rabinstein AA. Indicators of central fever in the neurologic intensive care unit. *Journal of the American Medical Association Neurology* 2013; **70**: 1499–504.
34. Thompson HJ, Pinto-Martin J, Bullock MR. Neurogenic fever after traumatic brain injury: an epidemiological study. *Journal of Neurology, Neurosurgery and Psychiatry* 2003; **74**: 614–9.
35. Meier K, Lee K. Neurogenic fever: review of pathophysiology, evaluation, and management. *Journal of Intensive Care Medicine* 2016; **32**: 124–9.
36. Halvorson K, Shah S, Fehnel C, Thompson B, Stevenson Potter N, Levy M, Wendell L. Procalcitonin is a poor predictor of non-infectious fever in the neurocritical care unit. *Neurocritical Care* 2017; **27**: 237–41.
37. Toros A, Grodzinsky E, Karlsson N, Nilsson M, Levander MS. Use of temperature changes and pro-inflammatory biomarkers to diagnose bacterial infections in patients with severe cerebral trauma. *Journal of Neurocritical Care* 2022; **15**: 21–31.
38. Thompson K, Pohlmann-Eden B, Campbell LA, Abel H. Pharmacological treatments for preventing epilepsy following traumatic head injury. *Cochrane Database of Systematic Reviews* 2015; **8**: CD009900.
39. Pingue V, Mele C, Nardone A. Post-traumatic seizures and antiepileptic therapy as predictors of the functional outcome in

patients with traumatic brain injury. *Scientific Reports* 2021; **11**: 4708.
40. Fang T, Valdes E, Frontera JA. Levetiracetam for seizure prophylaxis in neurocritical care: a systematic review and meta-analysis. *Neurocritical Care* 2021; **36**: 248–58.
41. Migdady I, Rosenthal ES, Cock HR. Management of status epilepticus: a narrative review. *Anaesthesia* 2022; **77**: 78–91.
42. Heavner MS, Gorman EF, Linn DD, Yeung SYA, Miano TA. Systematic review and meta-analysis of the correlation between bispectral index (BIS) and clinical sedation scales: toward defining the role of BIS in critically ill patients. *Pharmacotherapy* 2022; **42**: 667–76.
43. Gimson A, Smith M. Processed EEG from depth of anaesthesia monitors and seizures: a scoping review. *Seizure* 2021; **91**: 198–206.
44. Riker RR, Fraser GL, Wilkins ML. Comparing the bispectral index and suppression ratio with burst suppression of the electroencephalogram during pentobarbital infusions in adult intensive care patients. *Pharmacotherapy* 2003; **23**: 1087–93.
45. Robba C, Graziano F, Rebora P, et al. Intracranial pressure monitoring in patients with acute brain injury in the intensive care unit (SYNAPSE-ICU): an international, prospective observational cohort study. *Lancet Neurology* 2021; **20**: 548–58.
46. American College of Surgeons. Best practices in the management of traumatic brain injury. 2015. https://www.facs.org/media/mkej5u3b/tbi_guidelines.pdf (accessed 04/10/2022).
47. Stocchetti N, Picetti E, Berardino M, et al. Clinical applications of intracranial pressure monitoring in traumatic brain injury. *Acta Neurochirurgica* 2014; **156**: 1615–22.
48. Chesnut RM, Temkin N, Carney N, et al. A trial of intracranial-pressure monitoring in traumatic brain injury. *New England Journal of Medicine* 2012; **367**: 2471–81.
49. Chesnut RM, Temkin N, Videtta W, et al. Consensus-based management protocol (CREVICE protocol) for the treatment of severe traumatic brain injury based on imaging and clinical examination for use when intracranial pressure monitoring is not employed. *Journal of Neurotrauma* 2020; **37**: 1291–9.
50. Boulter JH, Shields MM, Meister MR, Murtha G, Curry BP, Dengler BA. The expanding role of quantitative pupillometry in the evaluation and management of traumatic brain injury. *Frontiers in Neurology* 2021; **12**: 685313. https://doi.org/10.3389/fneur.2021.685313.
51. Sandroni C, Citerio G, Taccone FS. Automated pupillometry in intensive care. *Intensive Care Medicine* 2022; **48**: 1467–70.
52. Phillips SS, Mueller CM, Nogueira RG, Khalifa YM. A systematic review assessing the current state of automated pupillometry in the neuroICU. *Neurocritical Care* 2019; **31**: 142–61.
53. Dinsmore M, Venkatraghavan L. Clinical applications of point-of-care ultrasound in brain injury: a narrative review. *Anaesthesia* 2022; **77**: 69–77.
54. Stevens RRF, Gommer ED, Aries MJH, Ertl M, Mess WH, Huberts W, Delhaas T. Optic nerve sheath diameter assessment by neurosonology: a review of methodologic discrepancies. *Journal of Neuroimaging* 2021; **31**: 814–25.
55. Aletreby W, Alharthy A, Brindley PG, et al. Optic nerve sheath diameter ultrasound for raised intracranial pressure. *Journal of Ultrasound in Medicine* 2022; **41**: 585–95.
56. Fernando SM, Tran A, Cheng W, et al. Diagnosis of elevated intracranial pressure in critically ill adults: systematic review and meta-analysis. *British Medical Journal* 2019; **366**: l4225.
57. Ho KM. Predicting outcomes after severe traumatic brain injury: science, humanity or both? *Journal of Neurosurgical Sciences* 2018; **62**: 593–8.
58. Wu H, Wright DW, Allen JW, et al. Accuracy of head computed tomography scoring systems in predicting outcomes for patients with moderate to severe traumatic brain injury: a protect iii ancillary study. *The Neuroradiology Journal* 2022. Epub 9 May. https://doi.org/10.1177/19714009221101313.
59. Haghbayan H, Boutin A, Laflamme M, et al. The prognostic value of MRI in moderate and severe traumatic brain injury: a systematic review and meta-analysis. *Critical Care Medicine* 2017; **45**: e1280–e1288.
60. Dijkland SA, Foks KA, Polinder S, Dippel DWJ, Maas AIR, Lingsma HF, Steyerberg EW. Prognosis in moderate and severe traumatic brain injury: a systematic review of contemporary models and validation studies. *Journal of Neurotrauma* 2019; **37**: 1–13.
61. van Veen E, van der Jagt M, Citerio G, et al. Occurrence and timing of withdrawal of life-sustaining measures in traumatic brain injury patients: a CENTER-TBI study. *Intensive Care Medicine* 2021; **47**: 1115–29.
62. Helmrich IRAR, Czeiter E, Amrein K, et al. Incremental prognostic value of acute serum biomarkers for functional outcome after traumatic brain injury (CENTER-TBI): an observational cohort study. *Lancet Neurology* 2022; **21**: 792–802.
63. Flexman AM, Tung A. In search of the perfect outcome in neuroanaesthesia and neurocritical care. *Anaesthesia* 2022; **77**: 3–7.
64. McCrea MA, Giacino JT, Barber J, et al. Functional outcomes over the first year after moderate to severe traumatic brain injury in the prospective, longitudinal TRACK-TBI study. *Journal of the American Medical Association Neurology* 2021; **78**: 982–92.
65. Wilkins TE, Beers SR, Borrasso AJ, et al. Favorable functional recovery in severe traumatic brain injury survivors beyond six months. *Journal of Neurotrauma* 2019; **36**: 3158–63.
66. Harvey D, Butler J, Groves J, Manara A, Menon D, Thomas E, Wilson M. Management of perceived devastating brain injury after hospital admission: a consensus statement from stakeholder professional organizations. *British Journal of Anaesthesia* 2018; **120**: 138–45.
67. Lefkovits AM, Hicks AJ, Downing M, Ponsford J. Surviving the ``silent epidemic´´: a qualitative exploration of the long-term journey after traumatic brain injury. *Neuropsychological Rehabilitation* 2021; **31**: 1582–606.
68. Sigurdardottir S, Andelic N, Wehling E, et al. Return to work after severe traumatic brain injury: a national study with a one-year follow-up of neurocognitive and behavioural outcomes. *Neuropsychological Rehabilitation* 2020; **30**: 281–97.
69. Polich G, Iaccarino MA, Zafonte R. Psychopharmacology of traumatic brain injury. *Handbook of Clinical Neurology* 2019; **165**: 253–67. https://doi.org/10.1016/B978-0-444-64012-3.00015-0.
70. Writer BW, Schillerstrom JE. Psychopharmacological treatment for cognitive impairment in survivors of traumatic brain injury: a critical review. *Journal of Neuropsychiatry and Clinical Neurosciences* 2009; **21**: 362–70.
71. Phyland RK, Ponsford JL, Carrier SL, Hicks AJ, McKay A. Agitated behaviors following traumatic brain injury: a systematic review and meta-analysis of prevalence by post-traumatic amnesia status, hospital setting, and agitated behavior type. *Journal of Neurotrauma* 2021; **38**: 3047–67.
72. Williamson D, Frenette AJ, Burry LD, et al. Pharmacological interventions for agitated behaviours in patients with traumatic brain injury: a systematic review. *British Medical Journal Open* 2019; **9**: e029604.
73. Hoover GL, Whitehair VC. Agitation after traumatic brain injury: a review of current and future concepts in diagnosis and management. *Neurological Research* 2020; 1–9. https://doi.org/10.1080/01616412.2020.1797374
74. Kim E, Bijlani M. A pilot study of quetiapine treatment of aggression due to traumatic brain injury. *Journal of Neuropsychiatry and Clinical Neurosciences* 2006; **18**: 547–9.
75. Driver S, Stork R. Pharmacological management of sleep after traumatic brain injury. *NeuroRehabilitation* 2018; **43**: 347–53.

