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REVIEW

Pharmacotherapy of traumatic brain injury

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Abstract
This review describes the pharmacological options in the treatment of severe traumatic brain injury based on the current evidence and guidelines. The ultimate goal of pharmacological treatment is the prevention of brain ischaemia and subsequent secondary brain damage. The focus is on resuscitation fluids and treatment of raised intracranial pressure by means of sedatives and osmotherapy, but also included options for neuroprotection and treatment of epilepsy.

Introduction
Traumatic brain injury (TBI) is a significant cause of mortality and morbidity worldwide. Among patients who are hospitalised with severe TBI, 60% either die or survive with severe disability.[1] With negative results of recent trials testing the effect of hypothermia and decompressive hemicraniectomy, the hallmark of the treatment of patients with TBI is once again reduced to intracranial pressure (ICP) guided management with the use of sedation and osmotherapy.[2,3] It must however be stated that the concept of ICP guided therapy in TBI is not undisputed in itself. One of the central concepts of the pathophysiological mechanisms of brain damage after TBI is that brain damage not only occurs during the trauma (primary injury), but also in the period thereafter (secondary injury).[4] The prevention of this secondary brain injury is the major goal of the treatment of patients with severe TBI during transport to the hospital and treatment in the emergency room and intensive care. One of the most important pathophysiological mechanisms of secondary injury is cerebral ischaemia. Factors that may induce cerebral ischaemia are hypoxia, hypotension and raised intracranial pressure. Both the extent and duration of these variables are associated with the outcome of the patient and it is thus plausible that the prognosis of the patients improves if this disturbed physiology can be prevented or treated in a timely manner. National and international guidelines therefore include strict standards for monitoring and management of several variables related to oxygenation and cerebral perfusion pressure (CPP), e.g. blood pressure and ICP. Intuitively, it seems logical that correcting hypotension and hypoxia improves outcomes; however, clinical studies have failed to provide the supporting data. Moreover, complications that may occur during the attempt to ameliorate the milieu intérieur and maintain the desired CPP affect outcome negatively. There is a precarious balance between avoidance of events associated with secondary injury and overtreatment that may have a negative input on outcome.
This review focuses on the pharmacological options for prevention and treatment of secondary brain damage and extracerebral complications after severe TBI.

Resuscitation
The aim of resuscitation of patients with severe TBI is: 1) to achieve an adequate circulating blood volume by restoration of intravascular volume; 2) to avoid hypotension (systolic blood pressure <90 mmHg) and intracranial hypertension to maintain cerebral blood flow; and 3) limit hypoxia (O2 saturation <90%).[5] Without signs of cerebral herniation there is no place for prophylactic hyperventilation or osmotic therapy as both may have negative consequences for resuscitation: osmotherapy with mannitol may lead to hypovolaemia and subsequent hypotension, and hyperventilation to cerebral ischaemia. It may be valuable to maintain mean arterial pressures above those represented by systolic pressures of 90 mmHg throughout the patient's course of illness, but currently there are no data to support this.
The optimal resuscitation fluid to correct hypotension has yet to be determined. Although the administration of large volumes of intravenous crystalloids inevitably leads to whole-body interstitial oedema and aggressive fluid resuscitation strategies may thus be counterproductive, small-volume resuscitation with colloids and similar agents does not necessarily lead to a better outcome: hypertonic saline confers no survival or neurological

outcome advantage; not any colloid is beneficial in any patient group; and resuscitation with 4% albumin led to a significant increase in mortality for patients with increased intracranial pressure when compared with 0.9% saline (relative risk (RR) 1.63; 95% CI 1.17-2.26), probably related to its hypotonicity and the effect on intracranial pressure.[6]

One randomised, double-blind, multicentre trial compared the efficacy of prehospital administration of 250 ml of 7.5% sodium chloride with or without dextran versus lactated Ringer's solution as the initial resuscitation fluid in 194 hypotensive trauma patients: 144 of these patients (74%) had a severe TBI (defined as an abbreviated injury score for the head of 4, 5, or 6).[7] Hypertonic saline significantly increased blood pressure and decreased overall fluid requirements. Survivors had significantly higher blood pressures than non-survivors. There was no significant increase in the overall survival of patients with severe brain injuries, however, the survival rate in the hypertonic saline group (35%) was higher than that in the lactated Ringer's group (12%) for the cohort with a baseline Glasgow Coma Score (GCS) of 8 or less. However, in a far larger study among patients with severe TBI not in hypovolaemic shock, initial resuscitation with either hypertonic saline or hypertonic saline/dextran, compared with normal saline, did not result in superior six-month neurological outcome or survival.[8] Even in patients with hypotension and severe TBI, hypertonic saline was not better than Ringer's lactate solution.[9] No strong recommendations can be given, but restraint in the use of hypotonic fluids and cautious administration of an isotonic crystalloid, e.g. 0.9% NaCl, seems a justified strategy, although the hypotonic lactated Ringer's solution can also be safely administered in patients with TBI.

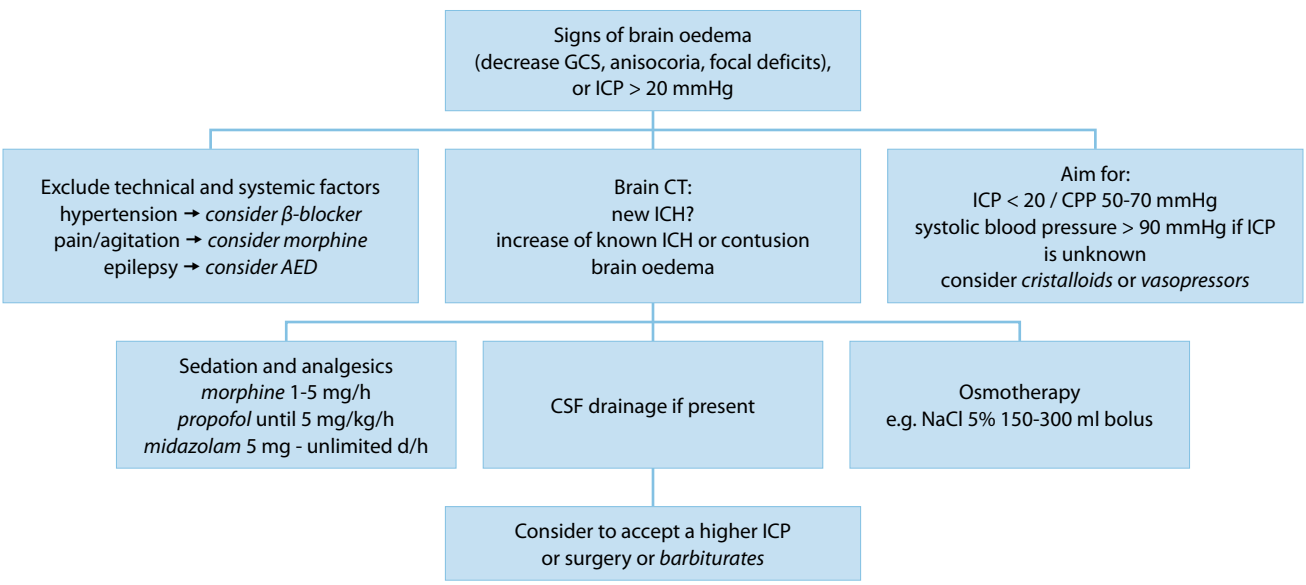
High-quality literature on vasopressor use in TBI is very scarce. Observational studies, clinical experiences, clinical reports and opinions dominate the literature. There is no indication that one vasopressor is superior and phenylephrine, norepinephrine, dopamine, and vasopressin are all commonly used agents that may be considered.[10]

Pharmacological treatment of raised ICP

The CPP value to target lies within the range of 50-70 mmHg which can be achieved by lowering an increased ICP or inducing hypertension. Current data support 20-25 mmHg as an upper threshold above which treatment to lower ICP should generally be initiated. That means that with an ICP below these thresholds, CPP is probably of limited interest as long as hypotension is avoided (*figure 1*).

Sedation

When there is an indication for ICP monitoring, it is usually recommended to sedate the patient for at least 48 hours, even if ICP is not increased. The agent of choice is a short-acting sedative such as propofol to make a prompt neurological examination after tapering sedation possible. Propofol might also slightly lower ICP (*table 1*). It is of note that neither sedatives nor analgesics are neuroprotective in themselves, but used to minimise painful or noxious stimuli as well as agitation that may potentially contribute to elevations in ICP. Furthermore, because of reduced metabolic demand, a sedated brain requires less blood supply, with therefore less intracranial blood volume and lower ICP.



AED = anti-epileptic drugs; CT = computed tomography; CPP = cerebral perfusion pressure; CSF = cerebral spinal fluid; GCS = Glasgow Coma Score; ICH = intracranial haemorrhage; ICP = intracranial pressure;

Figure 1. Flowchart showing pharmacological therapy (in italics) in traumatic brain injury.

Table 1. Effect of common medications on intracranial pressure.

Drug	Effect on brain	ICP response
Drugs to reduce parenchyma volume		
Mannitol	↓ Interstitial fluid	↓
Hypertonic saline	↓ Interstitial fluid	↓
Furosemide	↓ CSF production, cellular oedema	↓
Dexamethasone	No effect in TBI	↔
Anaesthesia or sedative		
Volatile anaesthetics	↑ Arterial/venous volume	↑
Nitrous oxide	↑↔ CMR	↑↔
Intravenous anaesthetics		
Propofol	↓ CBF/CMR	↓
Barbiturate	↓ CBF/CMR	↓
Dexmedetomidine	↓ CBF	↓
Ketamine	↑ CBF,↑CMR	↑↔
Narcotics	↓ CBF/CMR	↔
Benzodiazepines	↓ CBF	↓↔
Muscle relaxants		
Non-depolarising	None	↔
Succinylcholine	↑ CVP	↑ (brief)
Cardiovascular drugs		
Vasodilators	↑ Vascular volume	↑
Vasoconstrictors	↓↔ Vascular volume	↓↔

CBF = cerebral blood flow; CMR = cerebral metabolic rate; CSF = cerebral spinal fluid; CVP = central venous pressure ICP = intracranial pressure; TBI = traumatic brain injury.

Table 2. Dosing regimens for analgesics and sedatives.

Morphine sulphate	1-5 mg/h continuous infusion	Titrate as needed Reverse with naloxone
Midazolam	2–4 mg/h continuous infusion	Titrate as needed (no real maximum dose) Reverse with flumazenil
Propofol	20–75 µg/kg/min continuous infusion (not to exceed 5 mg/kg/h)	
Pentobarbital	Loading dose 10 mg/kg over 30 min; 5 mg/kg every hour x 3 doses; maintenance 1 mg/kg/h	Electroencephalographic pattern of burst suppression (usually serum pentobarbital levels in the range of 3-4 mg%

The most widely used analgesic in the acute setting has been morphine sulphate (*table 2*). The synthetic opioid analgesics fentanyl and sufentanyl have shown a mild but definite elevation in ICP with their utilisation.[11] Most analgesics also have some sedative action and for this reason it is better to avoid an opioid with a long context-sensitive half-time. Morphine has a high level of analgesic efficacy and safety but tachyphylaxis is common leading to a continuous need for dose escalation and a prolonged period of withdrawal when therapy is discontinued.

If ICP continuously stays below 20-25 mmHg without intervention, sedation may be tapered with monitoring of the ICP. In case of increased ICP, sedation should be continued or intensified for at least another 48 hours, but caution must be taken when using propofol doses greater than 4 mg/kg/h to prevent the propofol infusion syndrome. Although there is probably no risk of propofol infusion syndrome when the dose is below this threshold, it may be advisable that irrespective of dosage, long-term propofol sedation should be accompanied by daily 12-lead ECG monitoring and measurements of lactate, pH and creatine kinase.

Despite their neuro-depressant effects and their long duration of action, benzodiazepines such as midazolam are a reasonable alternative or additional agent.

Barbiturates

A number of barbiturates have been studied, with the most information available on pentobarbital. Data from seven trials involving 341 people are included in the most recent Cochrane review.[12] Two trials examined the effect of barbiturate therapy on ICP. In one, a smaller proportion of patients in the barbiturate group had uncontrolled ICP (68% versus 83%); the RR for uncontrolled ICP was 0.81 (95% confidence interval (CI) 0.62 to 1.06). In the other, mean ICP was also lower in the barbiturate group. Barbiturate therapy results in an increased occurrence of hypotension (RR 1.80; 95% CI 1.19 to 2.70). For every four patients treated, one developed clinically significant hypotension. That may be one of the reasons why for barbiturates versus no barbiturates, the pooled RR of death from three trials was 1.09 (95% CI 0.81 to 1.47). Death or disability, measured using the Glasgow Outcome Scale was assessed in two trials, the RR with barbiturates was 1.15 (95% CI 0.81 to 1.64).

Mannitol therapy may have a beneficial effect on mortality when compared with pentobarbital therapy. However, the single trial which tested this yielded an imprecise effect measure, which may also be compatible with no difference, or a beneficial effect of pentobarbital.[13] The trial was testing an initial treatment of mannitol compared with pentobarbital as some patients later received the alternate therapy if the allocated therapy failed to control ICP.

In conclusion, there is no evidence that barbiturate therapy in patients with acute severe head injury improves outcome. Barbiturate therapy results in a fall in blood pressure in one in four patients. This hypotensive effect will offset any ICP lowering effect on cerebral perfusion pressure.

Osmotherapy

Apart from an expending contusion or haematoma, or vascular engorgement, intracranial hypertension after TBI may be caused by brain oedema. The treatment of brain oedema focuses on drawing water out of brain tissue into the intravascular space. This is typically accomplished with osmolar therapy. The hyperosmolar agents currently in clinical use for TBI are mannitol and hypertonic saline. An ideal therapeutic agent for ICP reduction should reduce ICP while maintaining CPP. While mannitol can cause dehydration over time, hypertonic saline helps maintain normovolaemia and cerebral perfusion. To date,

no large clinical trial has been performed to directly compare the two agents. The best current evidence suggests that mannitol is effective in reducing ICP. Current evidence regarding the use of hypertonic saline in severe TBI is limited to smaller studies.

Only one small trial totalling 20 patients compared mannitol with hypertonic saline and included mortality as endpoint.[14] Eligible patients were those with severe head injury (GCS <8) who required intravenous infusions of an osmotic agent to treat episodes of intracranial hypertension resistant to standard therapy (cerebrospinal fluid drainage, volume expansion and/or inotropic support, hyperventilation). The mannitol group received 20% mannitol solution. The hypertonic saline group received 7.5% hypertonic saline. The infused volume was the same for both solutions: 2 ml/kg body weight in 20 minutes. The aim was to decrease ICP to <25 mmHg or to increase CPP to >70 mmHg. If the first infusion failed, the patient received a second infusion within ten minutes after the end of the first infusion. Treatment failure was defined as the inability to decrease ICP to <35 mmHg or to increase CPP to >70 mmHg with two consecutive infusions of the selected osmotic solution. In that case, the protocol was stopped, and patients were followed up for mortality or 90-day neurological status. Because 20% mannitol can crystallise at ambient temperature, injections could not be performed in a blinded manner. Twenty patients were randomised: ten to each group, but allocation concealment was not described. Outcome was assessed at 90 days using the Glasgow Outcome Scale administered by a practitioner who was blind to the acute patient care.

The mean number of intracranial hypertension episodes per day and the daily duration of the episodes of intracranial hypertension were significantly lower in the hypertonic saline solution group. For mannitol compared with hypertonic saline in the treatment of refractory intracranial hypertension episodes in comatose patients with severe head injury, the RR for death was 1.25 (95% CI 0.47 to 3.33).

According to the most recent meta-analysis hypertonic saline may have a more profound and long-lasting effect in reducing intracranial hypertension following TBI when compared with mannitol; at 30 minutes there was no difference in the mean ICP change between the groups, whereas at 60 and 120 minutes after intervention hypertonic saline resulted in a significantly greater decrease in ICP, but the absolute pooled difference in means was low (-1.69 mmHg) and although seven studies were included, the total number of patients analysed was only 169.[15] In a prolonged dosage, both mannitol and hypertonic saline may pass the blood-brain barrier, where they might cause increased intracranial pressure and haematoma enlargement.

In a small trial 60 patients with severe TBI requiring ICP monitoring were randomly allocated to receive a 48-hour continuous infusion at 0.5 ml/kg/h of either sodium lactate or isotonic saline solution within the first 12 hours post-trauma.[16] Sodium lactate decreased the occurrence of episodes of raised ICP in patients with severe TBI, while reducing fluid and chloride balances. These findings suggest that exogenous lactate infusion may be a promising fluid in patients with intracranial hypertension after TBI, but quality data are still limited.

Another approach: the Lund concept

The Lund concept, introduced in Sweden in de mid-1990s, focuses on improving perfusion and oxygenation around contusions (perfusion-targeted goal), and also in reducing intracranial pressure (ICP-targeted goal). For this approach normovolaemia is mandatory, which is accomplished by serum and red blood cell transfusions to achieve a normal haemoglobin, and albumin to preserve plasma oncotic pressure. This fluid therapy was intended to decrease brain oedema and improve the microcirculation. Intracapillary pressure is reduced by the combination of precapillary vasoconstriction (low-dose thiopental, dihydroergotamine) and reduction of mean arterial pressure, the latter attained with a beta1-antagonist (metoprolol) and an alpha2-agonist (clonidine). Clonidine, in combination with normovolaemia, also improves the microcirculation by reducing catecholamines in plasma. Intracranial blood volume is reduced by arterial (low-dose thiopental sodium and dihydroergotamine) and large-vein (dihydroergotamine) vasoconstriction. Diuretics (but not mannitol) are used to avoid hypervolaemia and promote hypernatraemia. They claim good results but the Lund concept has never been tested against the ICP/CPP-guided therapy concept.[17]

NEUROPROTECTION

Erythropoietin

In a large RCT, 606 patients with moderate or severe traumatic brain injury were enrolled and randomly assigned to erythropoietin (n=308) or placebo (n=298). Compared with placebo, erythropoietin did not reduce the proportion of patients with a poor outcome (death, vegetative state, and severe disability): 134 (44%) of 302 patients in the erythropoietin group vs. 132 (45%) of 294 in the placebo group; RR 0·99 [95% CI 0·83-1·18].[18]

Magnesium

In an RCT 499 patients with moderate or severe traumatic brain injury were randomly assigned one of two doses of magnesium or placebo within eight hours of injury and continuing for five days.[19] Magnesium doses were targeted to achieve serum magnesium ranges of 1.0-1.85 mmol/l or 1.25-2.5 mmol/l. The primary outcome was a composite of mortality, seizures, functional measures, and neuropsychological tests assessed up to six months after injury. Magnesium showed no significant positive effect at the higher dose (p=0.70) and those randomly assigned to magnesium at the lower dose did significantly worse on the composite primary outcome measure than those assigned

placebo (48 vs. 54, 95% CI -10.5 to -2; p=0.007). Furthermore, there was higher mortality with the higher magnesium dose than with placebo.

Continuous infusions of magnesium for five days given to patients within eight hours of moderate or severe traumatic brain injury were not neuroprotective and might even have a negative effect in the treatment of significant head injury.

Tranexamic acid

Early administration of tranexamic acid safely reduces the risk of death in bleeding trauma patients and is highly cost-effective.[20] Treatment beyond three hours of injury is unlikely to be effective. The Clinical Randomisation of an Antifibrinolytic in Significant Head injury-3 (CRASH-3) trial will evaluate the effectiveness and safety of tranexamic acid in the treatments of isolated traumatic brain injury (http://crash3.lshtm.ac.uk/).

Steroids

In the CRASH study 10,008 adults with head injury and a GCS of 14 or less within eight hours of injury were randomly allocated to a 48-hour infusion of corticosteroids (methylprednisolone) or placebo.[21] Primary outcomes were death within two weeks of injury and death or disability at six months. Compared with placebo, the risk of death from all causes within two weeks was higher in the group allocated corticosteroids: 1052 (21.1%) vs. 893 (17.9%) deaths; RR 1.18 [95% CI 1.09-1.27]. The increase in mortality with steroids in this trial suggests that steroids should not be used in people with traumatic head injury.

Cannabinoids

In an RCT 861 patients with severe traumatic brain injury were randomised to receive a single intravenous 150 mg dose of dexanabinol or placebo within six hours of injury.[22] The primary outcome extended Glasgow Outcome Scale did not differ between groups: odds ratio for a favourable response 1.04; 95% CI 0.79-1.36. Dexanabinol was not associated with hepatic, renal, or cardiac toxic effects. Dexanabinol is safe, but is not efficacious in the treatment of traumatic brain injury.

Progesterone

Current clinical evidence from six RCTs demonstrated that progesterone was well tolerated but did not reduce the mortality or unfavourable outcomes of adult patients with acute TBI.[23]

Bradykinin beta-2 receptor antagonists

There is no reliable evidence that bradykinin beta-2 receptor antagonists are safe or effective for use in TBI patients, and they should not be used outside the context of well-conducted trials. Further adequately powered and well-conducted randomised controlled trials are required.

Antiepileptic drugs for prevention and treatment of post-traumatic seizures

The updated Cochrane review found low-quality evidence that early treatment with an antiepileptic drug compared with placebo or standard care reduced the risk of early post-traumatic seizures.[24] There was no evidence to support a reduction in the risk of late seizures or mortality. The risk of serious or other adverse events was not greater among treatment versus placebo groups, but this may be due to the limited number of trials included in the comparison and small sample size. Antiepileptic drugs for prevention of post-traumatic seizures should not be routinely prescribed.

If post-traumatic seizures occur, the use of antiepileptic drugs seems justified. If status epilepticus occurs the agent of first choice is a benzodiazepine combined with an antiepileptic drug according to the local protocol. If an epileptic seizure occurs during primary trauma, antiepileptic drugs may be withheld or only used for a short period, e.g. two weeks, and thereafter tapered and stopped.

Antibiotics

There is a lack of RCTs with sufficient numbers of TBI patients to study the effect of prophylactic antibiotics for external ventricular drains and other ICP devices. Recent studies in stroke patients show no beneficial effect of prophylactic antibiotics.[25] Although both selective digestive tract decontamination and selective oropharyngeal decontamination have proven beneficial in reducing 28-day case fatality in the ICU population as a whole,[26] this effect may not be attributed to patients with a neurological injury, based on the results from a study in patients with aneurysmal subarachnoid haemorrhage.[27] A study of experimental TBI in rats shows that even mild experimental TBI induces acute lung injury, although no effects on pulmonary inflammation or damage could be demonstrated after subsequent pneumonitis.[28] Furthermore, the predominance of infection with Gram-positive bacteria after neurological injury may require another approach than selective digestive tract decontamination, which focuses on elimination of Gram-negative bacteria.

Conclusion and personal opinion

In critical care management one should be doing what is necessary, but just that. Overtreatment may be harmful. However, to avoid a systolic blood pressure below 90 mmHg and oxygen saturation below 90%, aiming for a blood pressure around 10 mmHg higher and an oxygen saturation of about 92% might prevent dips below these thresholds. Current evidence does not justify higher figures, at least in patients with a normal ICP, but these seem reasonable margins.

Pathophysiology after TBI is dynamic with data that indicate that low cerebral blood flow and ischaemia probably only occur within the first few hours after injury, thereafter a relationship between raised ICP and hyperaemia has been suspected, but reports have not been consistent and the clinical significance of posttraumatic hyperaemia is unclear. However, it may be sensible to aim for a high CPP, e.g. close to 70 mmHg during the first day and reduce this to a more moderate CPP, e.g. close to 50 mmHg in the days thereafter.

Measurement of ICP is not always necessary when pathology on brain computed tomography is minimal and sometimes the measurements are false, leading to rescue therapy with the possibility of detrimental effects.[29] Computed tomography follow-up may be a reasonable alternative in selected cases.

In case of raised ICP refractory to conventional therapy several rescue therapies may be considered; hypothermia, hemicraniectomy, or barbiturates. Hypothermia is not likely to be beneficial. The effect of hemicraniectomy is being tested in an ongoing trial. The efficacy of barbiturates has not been proven, but its use is widespread practice and may be the most obvious choice. The alternative may be to restrict with conventional therapy and accept a higher ICP, e.g. 40 mmHg, before moving over to experimental methods. For example, after aneurysmal subarachnoid haemorrhage or bacterial meningitis, intracranial pressures far above 20 mmHg are frequently measured by lumbar puncture and many of these patients recover without sequela.

In the face of recently published failures of treatments that focused on controlling raised intracranial pressure, prevention or treatment of secondary organ failure may be a more suitable target to improve outcome. There are reports that suggest that cardiovascular dysfunction contributes to mortality in more than half of the patients.[30] It is plausible that administration of β-blockers can attenuate the cardiac uncoupling associated with severe TBI.[31] Although based on a different philosophy, the Lund group in Sweden has long advocated the use of β1-blockers; they achieve fairly good results so at least an approach including β-blocking seems safe, but robust evidence is absence.

Disclosures

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