ERABI EVIDENCE-BASED REVIEW of moderate to severe ACQUIRED BRAIN INJURY

12. Neuropharmacological Interventions Post ABI

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Abbreviations

5-HT	5-hydroxytryptophan
ABI	Acquired Brain Injury
ADHD	Attention Deficit Hyperactivity Disorder
BTX-A	Botulinum Toxin Type A
CNS	Central Nervous System
CPP	Cerebral Perfusion Pressure
EBIC	European Brain Injury Consortium
EDS	Excessive Daytime Sleepiness
EEG	Electroencephalogram
GABA	Gamma-Aminobutyric Acid
GCS	Glasgow Coma Scale
HAM-D	Hamilton Rating Scale for Depression
HO	Heterotopic Ossification
ICP	Intracranial Pressure
MAP	Mean Arterial Pressure
MABP	Mean Arterial Blood Pressure
NE	Norepinephrine
PCT	Prospective Controlled Trial
PEDro	Physiotherapy Evidence Database rating scale
PTA	Post-traumatic Amnesia
RCT	Randomized Controlled Trial
TBI	Traumatic Brain Injury

Key Points

Different opioids may have different intracranial pressure effects post ABI; where morphine, sufentanil, and alfentanil may increase intracranial pressure, remifentanil may not affect intracranial pressure, and the effect of fentanyl on intracranial pressure post ABI is unclear.

Carbamazepine may decrease agitated behaviour post-traumatic brain injury.

Carbamazepine can maintain or improve seizure control in TBI compared to other anticonvulsants.

Intramuscular midazolam may be effective for acute seizure cessation.

Levetiracetam may be as effective as phenytoin in treating and preventing seizures in individuals in the intensive care unit post ABI.

Anticonvulsants provided immediately post ABI may reduce the occurrence of seizures only within the first week.

Anticonvulsants provided shortly post ABI may not reduce late seizures.

Anticonvulsants may have negative consequences on motor tasks.

Phenobarbital may not be effective in reducing the risk of late seizure development post ABI.

Phenobarbital paired with phenytoin may decrease rate of post-traumatic epilepsy compared to no treatment following a TBI.

Valproic acid and divalproex may be used to decrease the incidence of aggressive behaviour; however, more research is needed.

Lamotrigine may be successful in reducing pathologic laughing post-traumatic brain injury. More research is needed, with a greater number of subjects, to validate these findings.

Cerebrolysin may be beneficial for the improvement of clinical outcome and cognitive functioning following brain injury; however, controlled trials are needed to further evaluate its efficacy.

Donepezil may help to improve attention, short-term, long-term, and visual memory following brain injury.

Physostigmine may improve long-term memory in men with TBI.

The effectiveness of sertraline in treating depression post TBI is unclear.

Citalopram may be helpful in the reduction of depression post ABI.

Citalopram and carbamazepine may be effective in the treatment of mood disorders.

Desipramine may be effective in reducing depression.

Sertraline hydrochloride can be useful in reducing aggressive and irritable behaviours.

Amitriptyline can be used to decrease agitation.

Lithium may reduce behavioural problems but is associated with a high risk of neurotoxicity.

Although there is evidence to suggest that quetiapine can help reduce aggressive behaviour, more research is needed.

Ziprasidone in one small study has been shown to assist in the controlling of agitation; however more research is needed.

Haloperidol appears to have little negative effect on recovery following TBI.

Droperidol may be an effective agent for calming agitated patients.

Methotrimeprazine may be safe for controlling agitation following an acquired brain injury.

Phenol blocks of the musculocutaneous nerve may help decrease spasticity and improve range of motion temporarily up to five months post injection.

Oral baclofen appears to reduce lower extremity spastic hypertonia.

Oral baclofen may not improve tone, spasm frequency of reflexes in the upper extremity.

Botulinum toxin type A injections may reduce localized spasticity and improve range of motion following ABI.

Patients receiving botulinum toxin type A through a single motor point or through multisite distributed injections may both show a reduction in spasticity.

Botulinum toxin type A may effectively improve both upper and lower limb spasticity in children and adolescents following brain injury.

Bolus injections of intrathecal baclofen may produce short-term reductions in upper and lower extremity spasticity post ABI.

Prolonged intrathecal baclofen may reduce upper and lower extremity spasticity post ABI.

Intrathecal baclofen may cause short-term improvements in walking performance in ambulatory patients post ABI.

Intrathecal baclofen pumps may reduce upper and lower limb spasticity in children with hypoxia.

There are conflicting reports regarding the efficacy of pentobarbital and thiopental for controlling elevated intracranial pressure; however, thiopental may be more effective than pentobarbital for controlling elevated intracranial pressure.

Pentobarbital may be less effective than mannitol for controlling elevated intracranial pressure.

Barbiturate therapy should be avoided until all other measures for controlling elevated intra cranial pressure are exhausted; patients undergoing barbiturate therapy should have their immunological response monitored.

Disodium Etidronate may prevent the development of heterotopic ossification.

Dexanabinol in cremophor-ethanol solution may not be effective in controlling intracranial pressure or improving clinical outcomes post TBI; however, dual cannabinol agonists may be effective in increasing cerebral perfusion pressure and reducing mortality post TBI.

Pindolol can decrease aggressive behaviour following brain injury.

Propranolol may reduce the intensity of aggressive and agitated symptoms following brain injury.

Although the administration of chemical deep vein thrombosis prophylaxis within the first 72 hours post ABI has been shown to be effective in reducing the risk of developing deep vein thrombosis or pulmonary embolism without increasing the risk of intracranial bleeding, more research is needed to determine its true effectiveness.

Enoxaparin may be effective for the prevention of VTE after elective neurosurgery and has not been found to cause excessive bleeding.

Mannitol may effectively lower elevated intracranial pressure; furthermore, high doses may yield lower mortality rates and better clinical outcomes.

Mannitol may be equally effective as hypertonic saline and less effective than sodium lactate for reducing elevated intracranial pressure.

Amantadine may improve consciousness, cognitive function, and disability post ABI.

Amantadine and pramipexole may be effective in improving levels of consciousness in children post TBI.

Amantadine has been shown to be ineffective in improving attention and memory deficits. Its impact on executive functioning should be studied further.

Amantadine requires further research before conclusions can be drawn on its effects on aggression.

Dopamine enhancing drugs may accelerate the rate of recovery from a low response state post TBI in children.

Bromocriptine may improve some executive cognitive functions such as dual task performance and motivational deficits but it may not consistently improve memory. More research is needed before the benefits of using bromocriptine to enhance cognitive functioning are known.

Administration of dexamethasone may inhibit endogenous production of glucocorticoids in children.

Dexamethasone administration has no proven impact on recovery post brain injury in children.

Medroxyprogesterone intramuscularly may reduce sexual aggression.

Progesterone may improve Glasgow Outcome Scale scores and reduce mortality rates up to 6 months post injury, without an increased rate of adverse events.

Progesterone may not be effective in lowering intracranial pressure levels.

The effectiveness of methylphenidate treatment to improve cognitive impairment following brain injury is unclear.

Methylphenidate may be effective in improving reaction time for working memory.

Response to methylphenidate may depend on genotype.

Methylphenidate may not have an adverse effect on the sleep-wake cycle of those who have sustained a TBI when given in commonly accepted dosages.

Methylphenidate may be effective in reducing anger following a brain injury.

Evidence regarding the efficacy of methylphenidate to improve cognitive and behavioural function is conflicting in children.

Modafinil has not been shown to be effective in treating fatigue.

Modafinil has been shown to be effective short-term in treating excessive daytime sleepiness, but may also cause insomnia.

Propofol, especially at higher doses may improve intracranial pressure and cerebral perfusion pressure; furthermore, propofol may reduce intracranial pressure and the need for other intracranial pressure interventions when used in conjunction with morphine.

Propofol may be no different than dexmedetomidine or morphine with midazolam in its effect on intracranial pressure.

Midazolam may have no effect on intracranial pressure, but may reduce mean arterial pressure, cerebral perfusion pressured, and systolic blood pressure.

Midazolam may not be different than propofol in its effect on intracranial pressure, cerebral perfusion pressure, or long-term outcomes.

Corticosteriods such as methylprednisolone, dexamethasone, and glucocorticoids may worsen outcomes, with no effect on intracranial pressure levels, and should not be used.

Triamcinolone may improve outcomes in patients with a Glasgow Coma Scale<8 and a focal lesion.

12. Neuropharmacology for Acquired Brain Injury

For a number of years, it has been recognized that brain injury causes alterations in neurotransmitter levels through a number of pathways including direct neuronal trauma, changes in neuronal membranes, and through secondary injury such as alterations in cerebral perfusion. A number of both clinical and basic science researchers have attempted to find pharmacological treatments in an attempt to normalize neurotransmitter levels and enhance brain recovery.

The neurotransmitters of interest include serotonin (5-hydroxytryptophan), acetylcholine, gamma-aminobutyric acid (GABA), and catecholamines such as dopamine and norepinephrine (NE). There are many subtypes of serotonin receptors and medications that have affinity for 5-hydroxytryptophan$_{1a}$, $_{1b}$, and $_{1c}$, which tend to reduce aggression in humans and have effects on sleep, mood, and behaviour. Acetylcholine is most associated with memory in the central nervous system (CNS), but may have other effects. It is synthesized from choline in neurons and is degraded mostly by acetylcholinesterase at the synapse. GABA and glycine are inhibitory neurotransmitters found throughout the CNS. $GABA_A$ receptors affect chlorine channels and hyperpolarize nerve cell membranes. Therefore, the neuron is less likely to activate. $GABA_B$ receptors enhance potassium or decrease calcium conductance across the cell membrane.

The catecholamines dopamine and NE tend to stimulate target receptors. Dopamine has diffuse effects on the CNS and is involved with motor control, arousal, procedural learning, and cognition. There are at least five dopamine receptor variants and abnormalities. The D_2 variant is implicated in Parkinson's disease and the D_4 variant in schizophrenia. The effects of NE are associated with sleep regulation, mood, aggression, and perception of sensation. It results from the conversion of tyrosine into dopamine and then into NE.

This module provides an overview of the medications that have been used in brain injury to enhance recovery of a number of brain functions. Most of these medications' effects are believed to be mediated through alterations in the neurotransmitters mentioned above. The module is organized to provide clinicians with evidence of pharmacological interventions for a number of clinically relevant problems after brain injury.

12.1 Analgesics

12.1.1 Opioids

Opioids are substances that produce morphine-like effects by binding to opioid receptors, found principally in the central nervous system and gastrointestinal tract. Each opioid has a distinct binding affinity to groups of opioid receptors that determines its pharmacodynamic response. Morphine has been the most commonly used opioid following ABI, while fentanyl and its derivatives have gained popularity owing to their more rapid onset and shorter duration of effect (Metz et al., 2000). However, controversy persists regarding the effect of opioids on ICP and CPP. It has been reported that opioids can increase cerebral blood flow, which may lead to an increase in ICP (Bunegin et al., 1989; de Nadal et al., 2000; Marx et al., 1989; Werner et al., 1995) in the presence of intracranial pathology.

Table 12.1 Opioids for the Acute Management of ABI

Author/ Year/ Country/ Study Design/ N	Methods	Outcome
Remifentanil		
Engelhard et al. (2004) Germany Pre-Post N=20	**Population:** TBI; Mean Age=46 yr; Gender: Male=13, Female=7; GCS Range<8. **Intervention:** An intravenous bolus of 0.5 ug/kg remifentanil was administered, followed by a continuous intravenous infusion of 0.25 ug/kg/min remifentanil for 20 min. Outcomes were assessed for 20 min before and after remifentanil administration. **Outcome Measure:** Intracranial Pressure (ICP), Cerebral Perfusion Pressure (CPP), Mean Arterial Pressure (MAP), Cerebral Blood Flow Velocity (CBFV).	1. No changes were observed in ICP, CPP, MAP, or CBFV following administration of bolus or continuous infusion of remifentanil.
Sufentanil		
Werner et al. (1995) Germany/USA Pre-Post N=30	**Population:** TBI; Gender: Male=21, Female=9; GCS Range<6. **Intervention:** Patients received an intravenous bolus of 3 µg/kg sufentanil for 10 sec, and were monitored for 30 min. **Outcome Measure:** Mean Arterial Pressure (MAP), Intracranial Pressure (ICP).	1. MAP decreased by more than 10 mmHg in 12 patients. 2. ICP was constant in patients with stable MAP (n=18), but was significantly increased in those with decreased MAP ($p<0.05$).
Scholz et al. (1994) Germany Pre-Post N=10	**Population:** TBI; Median Age=34 yr; Gender: Male=7, Female=3; GCS Range<6. **Intervention:** Patients received an intravenous bolus of 2 µg/kg sufentanil for 30 min, after which they received an intravenous infusion of sufentanil and midazolam for 48 hr. **Outcome Measure:** Intracranial Pressure (ICP), Cerebral Perfusion Pressure (CPP), Mean Arterial Pressure (MAP).	1. Following treatment, a significant decrease in mean ICP (16.1 mmHg to 10.8 mmHg, $p<0.05$) was noted within 15 min. 2. At 15 min, mean MAP was significantly decreased (85.5 mmHg to 80.2 mmHg, $p<0.05$). 3. CPP remained stable after treatment. 4. The same results were obtained for 2d.
Albanese et al. (1993) France Case Series N=10	**Population:** TBI; Age Range=18-50 yr; Gender: Male=10, Female=0; GCS Range≤8. **Intervention:** Patients received an intravenous bolus of 1 µg/kg sufentanil for 6 min, followed by continuous intravenous infusion of 0.005 µg/kg/min. **Outcome Measure:** Intracranial Pressure (ICP), Mean Arterial Pressure (MAP), Cerebral Perfusion Pressure (CPP), Heart Rate (HR).	1. There was a significant increase in ICP (53%, $p<0.05$) that peaked after 5min and gradually returned to baseline after 15min. 2. There was a significant decrease in MAP (24%, $p<0.05$) and in CPP (38%, $p<0.05$). Though they gradually increased after 5min, they remained significantly reduced from baseline (22% and 23%, respectively). 3. There was a significant decrease in HR (15%, $p<0.05$).
Multiple Opioids		
Karabinis et al. (2004) Greece RCT PEDro=5 N=161	**Population:** TBI. *Remifentanil Group (n=84)*: Mean Age=46.8 yr; Gender: Male=44, Female=40; Time Post Injury<24 hr; Mean GCS=8.4. *Fentanyl Group (n=37)*: Mean Age=49.6 yr; Gender: Male=24, Female=13; Time Post Injury<24 hr; Mean GCS=8.8. *Morphine Group (n=40)*: Mean Age=47.3 yr; Gender: Male=25, Female=15; Time Post Injury<24 hr; Mean GCS=8.6.	1. Sedation with remifentanil required significantly less time to neurological assessments (0.41 hr), compared to fentanyl (0.71 hr, $p=0.001$) or morphine (0.82 hr, $p<0.001$). 2. No differences in ICP or CPP between remifentanil and fentanyl/morphine groups were found.

Author/ Year/ Country/ Study Design/ N	Methods	Outcome
	Intervention: Patients were randomized in a 2:1:1 ratio into one of three treatment arms: 1) analgesia-based sedation with 9 µg/kg/hr remifentanil for 5-1 0min (and propofol at 0.5 mg/kg/hr if necessary); 2) hypnotic-based treatment with fentanyl; or 3) hypnotic-based treatment with morphine. Opioids were titrated to achieve optimal sedation in all three treatment groups. **Outcome Measure:** Time to neurological assessment, Intracranial Pressure (ICP), Cerebral Perfusion Pressure (CPP).	
De Nadal et al. (2000) Spain RCT Crossover PEDro=8 N=30	**Population:** TBI; Mean Age=30 yr; Gender: Male=23, Female=7; Mean Time Post Injury=17.8 hr; GCS Range≤8. **Intervention:** Patients were randomized to receive intravenous 0.2 mg/kg morphine or 2 µg/kg fentanyl over 1 min. Crossover occurred after 24hr. Treatment was initiated at 0 min and measurements were repeated at 5-10 min intervals until 60 min. **Outcome Measure:** Autoregulation, Intracranial Pressure (ICP), Cerebral Perfusion Pressure (CPP), Mean Arterial Pressure (MAP), Central Venous Pressure (CVP), CO_2 and O_2 Partial Pressures (PP), Heart Rate (HR).	1. Autoregulation was abolished in 18 patients and preserved in 12. No significant changes in ICP were observed between those with preserved and abolished autoregulation after treatment. 2. Both morphine and fentanyl induced significant increases in ICP at 5 min (p=0.008 and p=0.044, respectively), which remained significantly higher up to 60 min (p=0.008 and p=0.044, respectively). 3. Both morphine and fentanyl induced significant decreases in MAP at 5 min (p=0.002 and p=0.016, respectively), which remained significantly lower with fentanyl up to 60min (p=0.016). 4. Increase in ICP coupled with decrease in MAP resulted in a transient decrease in CPP, reaching a minimum value of 64 mmHg at 5 min after morphine and 65 mmHg after fentanyl. Both values were significantly lower than baseline (p=0.001 and p<0.0001, respectively). 5. No significant differences were observed after the use of either opioidfor CVP, PPs, or HR.
Albanese et al. (1999) France RCT Crossover PEDro=5 N=6	**Population:** TBI; Age Range=20-45 yr; Gender: Male=6, Female=0; GCS Range≤8. **Intervention:** Patients were randomized to receive an initial 6 min injection of 1 µg/kg sufentanil, 100 µg/kg alfentanil, or 10 µg/kg fentanyl, followed by an infusion of 0.005 µg/kg/min, 0.7 µg/kg/min, and 0.075 µg/kg/min, respectively, for 1 hr. Crossovers occurred at 24 hr intervals. **Outcome Measure:** Intracranial Pressure (ICP), Cerebral Perfusion Pressure (CPP), Mean Arterial Pressure (MAP), Heart Rate (HR), End-Tidal CO_2, O_2 Saturation.	1. Sufentanil, alfentanil, and fentanyl were associated with significant mean increases in ICP peaking before 6 min (9 mmHg, 8 mmHg, and 5.5 mmHg, respectively; p<0.05) and returning to baseline by 15 min. 2. Sufentanil, alfentanil, and fentanyl were associated with significant mean decreases in MAP (21 mmHg, 24 mmHg, and 26 mmHg, respectively; p<0.05) and thus in CPP (30 mmHg, 31 mmHg, and 34 mmHg, respectively; p<0.05). MAP and CPP gradually increased after 5 min, but they remained significantly reduced compared to baseline.

Author/ Year/ Country/ Study Design/ N	Methods	Outcome
		3. No significant difference was observed after the use of any opioid with regard to all other studied variables.
Lauer et al. (1997) USA RCT PEDro=5 N=15	**Population:** TBI. *Morphine Group (n=5)*: Mean Age=21 yr; Mean GCS=6. *Fentanyl Group (n=5)*: Mean Age=22 yr; Mean GCS=5. *Sufentanil Group (n=5)*: Mean Age=35 yr; Mean GCS=6. **Intervention:** Patients were randomized to receive continuous intravenous morphine, fentanyl, or sufentanil over a 5 min interval. Continuous bolus infusion was initiated for 4 hr with the same opioid, if the blood pressure did not change >5%. Assessments were made every 15 min for the first 2 hr, and then in every 30 min for the last 2 hr. **Outcome Measure:** Intracranial Pressure (ICP), Mean Arterial Pressure (MAP), Cerebral Perfusion Pressure (CPP), Heart Rate (HR).	1. Mean doses of morphine, fentanyl, and sufentanil were 2.98 µg/kg, 0.07 mg/kg, and 0.37 µg/kg, respectively. 2. There was no significant difference in MAP from baseline in any group, except the sufentanil group had reduced MAP at 10 and 45 min post bolus administration ($p<0.05$). 3. There was no significant change in ICP from baseline in any group. The fentanyl group had reduced ICP at 150 and 180 min post bolus administration compared to the morphine and sufentanil groups ($p<0.05$). 4. There was no significant change in CPP from baseline in any group. The fentanyl group had reduced CPP at 60 min post bolus administration compared to with the morphine group, and at 70 min compared to the morphine and sufentanil groups ($p<0.05$).
Sperry et al. (1992) USA RCT Crossover PEDro=7 N=9	**Population:** TBI; Mean Age=34 yr; Gender: Male=6, Female=3; Time Post Injury Range=1-3 days; Mean GCS=6. **Intervention:** Patients were randomized to receive an intravenous bolus of 3 µg/kg fentanyl or 0.6 µg/kg sufentanil over 1 min. Crossover occurred after 24 hr. Outcomes were recorded for 1hr after administration. **Outcome Measure:** Intracranial Pressure (ICP), Mean Arterial Blood Pressure (MAP), Cerebral Perfusion Pressure (CPP), Heart Rate (HR).	1. Fentanyl resulted in significant increases in mean ICP (8 mmHg, $p=0.004$), and significant reductions in mean MAP (11 mmHg, $p<0.05$) from baseline. 2. Sufentanil resulted in significant increases in mean ICP (6 mmHg, $p=0.006$), and significant reductions in mean MAP (10 mmHg, $p<0.05$). 3. No significant change in HR was noted after the use of either opioid.

PEDro=Physiotherapy Evidence Database rating scale score (Moseley et al., 2002).

Discussion

Analgesic sedation with opioids is commonly used in conjunction with hypnotic agents (i.e., midazolam, propofol) to reduce nociceptive stimulation, which makes it difficult to evaluate the effects of opioids in isolation. Five studies reported increases in ICP after opioid administration (Albanese et al., 1993; Albanese et al., 1999; de Nadal et al., 2000; Sperry et al., 1992; Werner et al., 1995), while two found no increase in ICP (Engelhard et al., 2004; Karabinis et al., 2004; Lauer et al., 1997) and one reported a decrease (Scholz et al., 1994). However, the mode of administration has been suggested as a determining factor for increases in ICP (Albanese et al., 1993; Albanese et al., 1999). In the studies where patients received only bolus injections of opioids, significant increases in ICP were seen (de Nadal et al., 2000; Sperry et al., 1992; Werner et al., 1995).

Conclusions

There is level 1a evidence that morphine, sufentanil, and alfentanil may result in increased intracranial pressure post ABI.

There is conflicting evidence (level 1b) regarding the effects of fentanyl on intracranial pressure post ABI.

There is level 2 evidence that remifentanil may not affect intracranial pressure post ABI.

Different opioids may have different intracranial pressure effects post ABI; where morphine, sufentanil, and alfentanil may increase intracranial pressure, remifentanil may not affect intracranial pressure, and the effect of fentanyl on intracranial pressure post ABI is unclear.

12.2 Anticonvulsant Medications

Following an ABI, seizures can occur rather quickly due to the increased metabolic demands on the brain, increased ICP and the excessive amounts of neurotransmitters released. Seizures can occur within hours of the initial head trauma (immediate seizures), within the first week of sustaining an injury (early seizures), or within several months post injury (late seizures) (Pagni & Zenga, 2005; Temkin et al., 1995). These seizures can further complicate the injury as they can lead to increased damage (Schierhout & Roberts, 2001). It has also been noted that the risk for developing or having late seizures post ABI is related to the severity of injury; those with a severe ABI are at greater risk (Ferguson et al., 2010; Temkin et al., 1995). For a more detailed discussion on seizures post ABI refer to Module 10.

Medications used to treat seizures post injury include carbamazepine (Tegretol), phenytoin (Dilantin), phenobarbital, primadone (Mysoline) and valporic acid (Depekane)/divalproex (Epival). These treatments have been used with both the adult and paediatric populations and have shown some success. Anticonvulsants have also shown some success in controlling or reducing the incidences of aggressive and agitated behaviours post ABI. For a more detailed discussion on the effects of anticonvulsants on aggression and agitation please refer to Module 8.

12.2.1 Carbamazepine

Carbamazepine has been proposed as an effective substitute for lithium in treating agitation and aggression following severe TBI. It has also been suggested as an alternative to anticonvulsants for controlling seizures without having harmful cognitive and behavioural side effects (Azouvi et al., 1999).

Table 12.2 Effects of Carbamazepine in the Treatment of Aggression

Author/ Year/ Country/ Study Design/ N	Methods	Outcomes
Agitation		
Azouvi et al. (1999) France Pre-Post N=10	**Population:** TBI; Mean Age=33.7 yr; Gender: Male=8, Female=2; Mean GCS Score=5.3; Mean Time Post Injury=58 wk. **Treatment:** Carbamazepine (mean dose=9.47±2.9 mg/kg/day) for 8 wk. **Outcome Measure:** Neurobehavioural Rating Scale-Revised (NRS-R), Agitated Behaviour Scale	1. Dosage and blood work remained within clinical limits for epilepsy. 2. Total NRS-R and ABS scores showed significant improvement (p=0.02); improvements plateaued after 2 wk. 3. At follow-up, significant improvements were shown for only the irritability

Author/ Year/ Country/ Study Design/ N	Methods	Outcomes
Agitation		
	(ABS), Katz Adjustment Scale, and Mini Mental Status Exam (MMSE).	(p<0.01), and disinhibition (p<0.05) portions of NRS-R. 4. Global NRS-R significantly decreased from baseline (p=0.01). 5. No significant changes on MMSE were observed (p>0.01).
Seizures		
Wroblewski et al. (1989) USA Pre-Post N=27	**Population:** TBI; Mean Age=24 yr; Gender: Male=22, Female=5. **Treatment:** Patients taking phenytoin or phenobarbital had these medications stopped and replaced with carbamazepine. **Outcome Measure:** Occurrence of seizures.	1. Patients were on the medication due to previous seizures (n=13) or because they were considered high risk for seizures (n=14). 2. For all participants after the medication switch: 10 had a decrease in seizure frequency, 13 had no change, and 4 reported an increase. 3. For the subgroup of participants with previously documented seizures before the medication switch (n=13): 10 had a decrease in seizure frequency, 1 had no change, and 2 had an increase.

PEDro=Physiotherapy Evidence Database rating scale score (Moseley et al., 2002).

Discussion

Azouvi et al. (1999) in an 8-week open drug trial administered carbamazepine (Tegretol) to 10 individuals with severe brain injury who had significant behavioural challenges that were interfering with care and/or family integration. Results indicated improvement on the behavioural scales at the first assessment (2 weeks), which were maintained only for the scales of irritability and disinhibition by the end of the trial; although, overall neurobehavioural and social functioning had improved. It should be noted that drowsiness was a frequent adverse event which limited the dosage being increased in 40% of the participants.

A systematic review by Thompson et al. (2015) found that the traditional antiepileptic drugs, phenytoin or carbamazepine, decreased the risk of early seizures compared to controls (RR 0.42; 95% CI, 0.23 to 0.73, p=0.003); however, the evidence was low quality. In terms of seizure management, carbamazepine maintained or improved control when it replaced other anticonvulsants (Wroblewski et al., 1989). Particularly, carbamazepine monotherapy improved (50%) or maintained (50%) seizure control when it replaced combination therapy with carbamazepine and phenobarbital or phenytoin.

Conclusions

There is level 4 evidence that carbamazepine may decrease the incidence of aggressive behaviours following a traumatic brain injury.

There is level 4 evidence that carbamazepine may not decrease seizure control compared to other anticonvulsants following a traumatic brain injury.

Carbamazepine may decrease agitated behaviour post-traumatic brain injury.

Carbamazepine can maintain or improve seizure control in TBI compared to other anticonvulsants.

12.2.2 Midazolam

Midazolam has been shown to be effective in controlling seizures post ABI.

Table 12.3 Effects of Midazolam in the Treatment of Seizures

Author/ Year/ Country/ Study Design/ N	Methods	Outcomes
Wroblewski & Joseph (1992) USA Case Series N=10	**Population:** TBI=8, ABI=1, Other=1; Mean Age=32.9 yr; Gender: Male=9, Female=1. **Treatment:** Intramuscular midazolam was administered. **Outcome Measure:** Cessation of seizures.	1. All patients experienced seizure cessation within minutes of midazolam administration. 2. The only reported side effect was slight to moderate sedation.

Discussion

There appears to be very little research evaluating the efficacy of anticonvulsants given to treat seizures following onset. We identified only one such study in this review. Wroblewski et al. (1992) reported on a collection of 10 case studies of patients with TBI treated with intramuscular (IM) midazolam for acute seizure cessation after other benzodiazepine drugs had failed. The authors reported that in all patients, seizures ceased within minutes of midazolam administration, with slight to moderate sedation being the only reported side effects. Midazolam also prevented the onset of prolonged seizures or status epilepticus.

Conclusions

There is level 4 evidence that intramuscular midazolam can be used for acute seizure cessation.

Intramuscular midazolam may be effective for acute seizure cessation.

12.2.3 Phenytoin

Early prevention of seizures has been attempted through administration of various anticonvulsants. It has been suggested that immediate administration of anticonvulsants, among them phenytoin, may be critical in reducing the risk of PTS developing (Pagni & Zenga, 2005).

Table 12.4 Effects of Phenytoin in the Treatment of Seizures

Author/ Year/ Country/ Study Design/ N	Methods	Outcomes
Phenytoin versus Placebo		
Dikmen et al. (1991) USA RCT	**Population:** Head Injury. *Phenytoin Group (n=104)*: Mean Age=30.9 yr; Gender: Male=82, Female=22; Median GCS=11. *Placebo Group*	1. From 1 to 12 mo, more participants in the treatment group stopped receiving

Author/ Year/ Country/ Study Design/ N	Methods	Outcomes
PEDro=6 $N_{initial}$=244, N_{Final}=124	*(n=101):* Mean Age=32.9 yr; Gender: Male=70, Female=31; Median GCS=9. **Treatment:** Patients were randomized to receive phenytoin (prophylactic medications) or a placebo for 1 yr. Patients then observed for another 1 yr while unmedicated. **Outcome Measure:** Halstead –Reitan Neuropsychological Test Battery, Katz Adjustment Scale, Sickness Impact Profile.	their assigned drug (p<0.01) due to idiosyncratic reactions and requests. 2. Those severely injured (GCS≤8) and receiving phenytoin did more poorly on most neuropsychological measures than controls determined by the overall rank-sum type test at 1 mo (p<0.05). No significant differences found at 1yr. 3. No significant differences in neuropsychological performance were found between groups for patients with moderate injuries (GCS≥9) at 1 mo or 1 yr. 4. Changes in neuropsychological measures from 12 to 24 mo showed that phenytoin had a small but negative widespread cognitive effect as evidenced by the overall rank-sum type test (p<0.05).
Temkin et al. (1990) USA RCT PEDro=6 $N_{initial}$=404, N_{final}=123	**Population:** TBI; Mean Age=34 yr; Gender: Male=309, Female=95; GCS≤10=256. **Treatment:** Participants were randomized to either the phenytoin (n=208) or placebo group (n=196). Phenytoin group received an initial dose of 20 mg/kg intravenously, then serum levels were maintained at 3–6 µmol/l. Treatment started within 24 hr of injury and continued for 1 yr. Follow up at 2 yr. **Outcome Measure:** Occurrence of early (<1 wk) and late (>8 days) seizures.	1. Cumulative early seizure rates were 3.6% in the phenytoin group and 14.2% in the control group (p<0.001); Phenytoin was associated with a decrease of 73% in the risk of early seizures. 2. Late seizure occurrence (day 8 to 2 yr) did not differ significantly between the treatment and control group (27.5% vs 21.2%, p>0.2). 3. More participants in the phenytoin group stopped taking the drug between day 8 and 1 yr, mainly due to idiosyncratic reactions or requests (103 vs 67).
Young et al. (1983) USA RCT PEDro=6 N=244	**Population:** TBI; *Phenytoin Group (n=136):* Mean Age=24.4 yr; Gender: Male=110, Female=26. *Placebo Group (n=108):* Mean Age=25.8 yr; Gender: Male=91, Female=71. **Treatment:** Patients were administered phenytoin (concentration between 10 and 20 µg/ml) or placebo, starting within 24 hr of injury. **Outcome Measure:** Occurrence of early seizures (≤1 wk of injury).	1. 5 in the phenytoin group and 4 in the control group had early seizures (p=0.75). 2. Mean time from injury to early seizure in the treatment and control group was 3.2 and 4.5 days, respectively (p=0.41).
Young et al. (1983) USA RCT PEDro=6 $N_{initial}$=214, N_{final}=179	**Population:** TBI; Mean Age=25.2 yr; Gender: Male=178, Female=36. **Treatment:** Participants treated with Phenytoin (n=105; concentration between 10 and 20 µg/ml) or placebo (n=74) starting within 24 hr of injury. Treated for 18 mo, switched to phenobarbital if there was a hypersensitivity to phenytoin (n=20). **Outcome Measure:** Occurrence of late (>7 days post injury) seizures.	1. Late seizures occurred in 11 (12.9%) of the phenytoin group, 2 (10%) of the phenobarbital group, and 8 (10.8%) of controls. 2. There were no significant differences between groups in the percentage of late seizures (p=0.75).
McQueen et al. (1983) UK	**Population:** TBI**;** Age: 5-15 yr=43, 16-65 yr=121; Gender: Male=130, Female=34.	1. Only 48% of the treatment group had plasma levels greater than 40µmol/l.

Author/ Year/ Country/ Study Design/ N	Methods	Outcomes
RCT PEDro=7 N=164	**Treatment:** Patients received either phenytoin (n=84) or placebo (n=80) for 1 yr. Phenytoin administration for adults was 300mg and for children 5 mg/kg. Follow-up continued for 2 yr. **Outcome Measure:** Occurrence of seizures.	2. 9.1% of participants developed post-traumatic epilepsy with first 2 yr. 3. At 1 yr, 6 participants in the treatment group and 5 in the control group developed post-traumatic epilepsy. 4. 8 participants in the treatment group and 7 in the control group developed seizures by 2 yr.
Phenytoin versus Levetiracetam		
Gabriel et al. (2014) USA Cohort N=19	**Population:** TBI; *Phenytoin Group (PHT, n=14):* Mean Age=46.8 yr; Gender: Male=10, Female=4; Mean GCS=3. *Levetiracetam group (LEV, n=5):* Mean Age=48.8 yr; Gender: Male=3, Female=2; Mean GCS=14. **Treatment:** Participants were divided based on prophylactic treatment: PHT or LEV. Follow-up interview conducted. **Outcome Measure:** Glasgow Outcome Scale- Extended **(**GOS-E), occurrence of seizures, medication-related complications.	1. Groups were not similar at baseline in terms of median GCS at presentation (p=0.016) and ICU discharge (p=0.044). The PHT group, compared to LEV group, also had a longer period of time between injury and GOS-E assessment (808.8 versus 484.4d, p=0.001). 2. There was no significant difference in the mean GOS-E scores at follow-up (PHT 5.07 versus LEV 5.60, p=0.58). 3. No significant difference between group for occurrence of early or late seizures (both p=0.53). 4. Compared to the PHT group, LEV group was significantly less likely to experience mediation-related complications (p=0.038); PHT group had a significantly higher rate of days with fever (p=0.014).
Radic et al. (2014) USA Case Control N=288	**Population:** Subdural Hematoma; *Levetiracetam group (LEV; n=164)*: Mean Age=65.96 yr; Gender: Male=98, Female=66; Mean GCS=13.5. *Phenytoin group (PHT; n=124)*: Mean Age=62yr; Gender: Male=85, Female=39; Mean GCS=12.7. **Treatment:** Patients were retrospectively analyzed. Those who received LEV were compared to those who received PHT for seizure prophylaxis. **Outcome Measure:** Seizure rate and adverse drug events.	1. There was no significant difference between LEV and PHT in clinical or electrographic seizure risk for patients without a midline shift. 2. In subjects with midline shift >0 mm, LEV was associated with an increased risk of electrographic seizures during hospitalization (p=0.028) and a decreased risk of adverse drug effects (p=0.001), compared with PHT use.
Inaba et al. (2013) USA PCT N=813	**Population:** TBI; Mean Age=52.6 yr; Gender: Male=580, Female=233; Mean GCS=12.3. **Treatment:** Participants were administered either levetiracetam (LEV; n=406) at 1000mg every 12 hr or phenytoin (PHT; n=407). In the PHT group the loading dose was 20 mg/kg then 5mg/kg/d every 8h. Treatment lasted 7 days. **Outcome Measure:** Occurrence of seizures.	1. There was no significant difference in seizure rates between groups (1.5% versus 1.5%, p=0.997). 2. There was no significant differences between groups (LEV versus PHT) in terms of adverse drug reactions (7.9% versus 10.3%, p=0.227), complications (28.3% versus 27.0%, p=0.679) or mortality rates (5.4% versus 3.7%, p=0.236).
Kruer et al. (2013) USA Cohort	**Population:** TBI; Median GCS=5. *Phenytoin Group (PHT; n=89):* Median Age=43.1 yr; Gender: Male=76, Female=13. *Levetiracetam*	1. 1 patient from each group seized in the first 7d (p=0.335).

Author/ Year/ Country/ Study Design/ N	Methods	Outcomes
N=109	*Group (LEV; n=20):* Median Age=34.1 yr; Gender: Male=19, Female=1. **Treatment:** Retrospective review of patients administered PHT or LEV. **Outcome Measure:** Occurrence of early seizures.	2. Hospital length of stay did not differ significantly between groups (Median days, LEV 26.5 versus PHT 11, p=0.134).
Szaflarski et al. (2010) USA RCT PEDro=8 N=52	**Population:** TBI=46; SAH=6. *Phenytoin group (PHT; n=18)*: Mean Age=35 yr; Gender: Male=13, Female=5; Mean GCS=4. *Levetiracetam group (LEV; n=34)*: Mean Age=44 yr; Gender: Male=26, Female=8; Mean GCS=5. **Treatment:** Patients randomized within 24 hr of injury. Patients received either a loading dose of Intravenous PHT of 20 mg/kg, then 5 mg/kg/day or intravenous LEV at 20mg/kg, and then 1000 mg every 12 hr /7 days. **Outcome Measure:** Occurrence of early seizures, Glasgow Outcome Scale (GOS), GOS-Extended (GOSE), Disability Rating Scale (DRS), Resource Utilization Questionnaire.	1. No significant differences in the occurrence of early seizures were found between the PHT and LEV groups (3 versus 5, p=1.0). 2. There were no significant between-group differences in GOS at discharge (p=0.33) and 6mo post discharge (p=0.89). 3. There were no significant differences in the occurrence of fever, Intracranial pressure, stroke, hypotension, arrhythmia, renal/ liver abnormalities or death between the two groups (p>0.15 for all). 4. Compared to the LEV group, those in the PHT group experienced a significant worsening of their neurological status more often (p=0.024), and experienced anemia less often (p=0.076). 5. Compared to PHT group, the LEV group showed significantly lower DRS at 3 and 6 mo (p=0.006 and p=0.037), and higher GOSE at 6mo (p=0.016) in patients who survived.
Steinbaugh et al. (2012) USA *Addition to Szaflarski et al. 2010 RCT*	**Addition:** Patients received continuous video electroencephalogram (cEEG) for up to 72h which was compared to outcomes collected.	6. The presence of focal slowing, epileptiform discharges, and seizures were not predictive of outcome (GOS-E, DRS). 7. More severe slowing was positively associated with DRS at discharge, 3 and 6mo (p=0.084) and negatively associated with GCS at discharge.
Jones et al. (2008) USA Cohort N=27	**Population:** Severe TBI; Gender: Male=20, Female=7. **Treatment:** Patients received Levetiracetam (n=15; 500 mg IV every 12 hr for 7 days) administered within 24hr of injury and were compared to a retrospective cohort of patients who received phenytoin (n=12). **Outcome Measure:** Occurrence of early seizures.	1. There was a significant difference in the occurrence of abnormal electroencephalogram (EEG) findings (seizure or seizure tendency with epileptiform activity) between groups (p=0.003), with the Levetiracetam group having more abnormal findings. 2. There was no significant difference between groups for actual seizures (p=0.556).
Additional Studies of Phenytoin		
Bhullar et al. (2014) USA Case Control N=93	**Population:** TBI; Gender: Male=70, Female=23; GCS=3-8. **Treatment:** Medical records were reviewed and patients were divided into two groups: no	1. No significant difference in early seizures between the no prophylaxis and phenytoin group (2.3% versus 4.0%, p=1.0).

Author/ Year/ Country/ Study Design/ N	Methods	Outcomes
	prophylaxis (n=43) and Phenytoin prophylaxis (n=50). **Outcome Measure:** Occurrence of early (<7 days post injury) seizures, length of stay (LOS), Glasgow Outcome Scale (GOS), modified Rankin Scale (mRS).	2. The Phenytoin group, compared to no prophylaxis, had longer hospital stays (36± 31 versus 25± 16 days, p=0.03), worse functional outcome at discharge (GOS, 2.9± 1.0 versus. 3.4±1.1, p=0.01; mRS, 3.1± 1.5 versus 2.3±1.7, p=0.02).
Dikmen et al. (2000) USA RCT PEDro=8 $N_{initial}$=279, N_{final}=107	**Population:** TBI; Gender: Male=228, Female=51. *Group 1 (n=94)*: Mean Age=37.14 yr; Mean GCS=11.3. *Group 2 (n=91)*: Mean Age=36.58 yr; Mean GCS=11.23. *Group 3 (n=94)*: Mean Age=35.85 yr; Mean GCS=12.11. **Treatment:** Patients randomized into three groups within 24 hr of injury: 1) valproic acid (VPA) for 1 mo then 5mo of placebo; 2) VPA for 6 mo; and 3) phenytoin (PHT) for 1 wk then placebo until 6 mo post injury. **Outcome Measure:** A battery of neuropsychological measures.	1. There was a trend towards a higher mortality rate in the VPA groups compared to the PHT group (p=0.07). 2. There were no significant differences at 1, 6 or 12 mo on the composite measures based on all the neurospsychological measures, or on only the cognitive measures (0.551<p<0.812). 3. No individual measure showed a significant difference among the treatment groups at 1, 6 or 12 mo post-injury.
Temkin et al. (1999) USA RCT PEDro=7 $N_{initial}$=379, N_{final}=283	**Population:** TBI; Gender: Male=310, Female=69; *Phenytoin Group (n=132)*: Mean Age=36 yr; Mean GCS=11.7. *Valproate (1mo, n=120):* Mean Age=40 yr; Mean GCS=11.6. *Valproate (6mo, n=127)*: Mean Age=36 yr; Mean GCS=11.1. **Treatment:** Patients were divided into three groups within 24 hr of injury: (1) phenytoin for 1 wk (20 mg/kg then 5 mg/kg/day), placebo until 6 mo post injury; (2) Valproate (20 mg/kg, then 15 mg/kg/day) for 1 mo, placebo for 5 mo; or (3) valproate for 6 mo. Follow-up continued for 2 yr. **Outcome Measure:** Incidence of early and late (>7 day post injury) seizures, mortality rates.	1. There was no significant difference in the number of early seizures between the combined valproate (4.5%) and phenytoin (1.5%, p=0.14) groups. 2. There is no significant difference between groups (p=0.19) in the occurrence of late seizures. 3. Late seizures occurred in 11, 17, and 15 participants in the 1 mo and 6 mo valproate groups and the phenytoin group, respectively. 4. There was no significant differences in mortality rates between groups (7.2% phenytoin versus 13.4% in the combined valproate group, p=0.07). 5. In the phenytoin group, a participant had a rash requiring medication at 1 wk and in the valproate (6 mo) group a participant had low neutrophil count at 2-4 wk, both thought to be treatment related.
Servit & Musil (1981) Czechoslovakia PCT N=167	**Population:** TBI; Mean Age=30.6 yr; Gender: Male=128, Female=39. **Treatment:** Participants in the treatment group (n=143) were administered Phenytoin (160-240 mg/day) and phenobarbital (20-60 mg/day). The control group (n=24) was treated with conventional methods for 2 yr. **Outcome Measure:** Occurrence of late seizures.	1. Posttraumatic epilepsy occurred in 25% of the control and 2.1% of the treatment group after discontinuing therapy (p<0.001). 2. One individual (0.7%) had a seizure during prophylactic treatment.

PEDro=Physiotherapy Evidence Database rating scale score (Moseley et al., 2002).

Discussion

When it comes to seizure prophylaxis, phenytoin is the most commonly studied medication. When the administration of phenytoin is compared to a placebo, its effect on the occurrence of early seizures is

inconclusive; Bhullar et al. (2014); Temkin et al. (1990), found it to be effective but Young et al. (1983) did not. A systematic review by Thompson et al. (2015) found that the traditional antiepileptic drugs, phenytoin or carbamazepine, decreased the risk of early seizures compared to controls (RR 0.42; 95% CI, 0.23 to 0.73, p=0.003); however, the evidence was low quality. Moreover, phenytoin was found to be no more effective than placebo in preventing late seizures (McQueen et al., 1983; Temkin et al., 1990; Young et al., 1983). In fact, Formisano et al. (2007) found that the occurrence of late seizures was significantly higher in patients treated with anti-epileptic medications than those who were not. It should be noted that phenytoin has been shown to have a negative impact on recovery. Dikmen et al. (1991) found that severely injured individuals receiving phenytoin performed more poorly on neuropsychological measures than controls at 1 month but no significant differences were found at 1 year. The following year (12 to 24 months), phenytoin was shown to have a small but negative effect on cognition (Dikmen et al., 1991). Further, those taking phenytoin had longer hospital stays and worse functional outcomes at discharge than individuals receiving no treatment (Bhullar et al., 2014). Overall, the evidence for the use of phenytoin for prevention of seizures is not favourable. There was no significant difference in mortality between those treated with antiepileptic drugs (phenytoin and carmazepam) and control subjects (RR 1.08; 95% CI, 0.79 to 1.46, p=0.64) (Thompson et al., 2015).

When phenytoin was compared to levetiracetam, the two drugs were comparable in terms of seizure rates (Inaba et al., 2013; Jones et al., 2008; Kruer et al., 2013; Radic et al., 2014), complications, adverse drug reactions, mortality rates (Inaba et al., 2013) and length of hospital stay (Kruer et al., 2013). A RCT by Szaflarski et al. (2010) found similar results in terms of there being no difference for early seizure rates, death or adverse events between the two drugs; however, the authors found that those on levetiracetam performed significantly better on the Disability Rating Scale at 3 and 6 months (p=0.042), and the Glasgow Outcome Scale at 6 months (p=0.039) post intervention compared to the phenytoin group. Furthermore, upon differentiation Radic et al. Radic et al. (2014) found that individuals with a midline shift greater than 0 millimeters were at a higher risk for electrographic seizures and a lower risk for adverse drug reactions on levetiracetam compared to phenytoin. Overall, a meta-analysis by Zafar et al. (2012) concluded that there was no superiority of either drug at preventing early seizures.

Conclusions

There is level 1b evidence to suggest that levetiracetam may be as safe and effective as phenytoin in the treatment and prevention of early seizures in individuals in the intensive care unit post ABI.

There is level 1b evidence that anticonvulsants given during the first 24 hours post ABI may reduce the occurrence of early seizures (within the first week post injury).

There is level 1a evidence that anticonvulsants given shortly after the onset of injury may not reduce mortality, persistent vegetative state, or the occurrence of late seizures (>1 week post injury).

There is level 1a evidence that seizure prophylactic treatment with either phenytoin or valproate may result in similar incidences of early or late seizures and similar mortality rates.

Levetiracetam may be as effective as phenytoin in treating and preventing seizures in individuals in the intensive care unit post ABI.

Anticonvulsants provided immediately post ABI may reduce the occurrence of seizures only within the first week.

Anticonvulsants provided shortly post ABI may not reduce late seizures.

Anticonvulsants may have negative consequences on motor tasks.

12.2.4 Phenobarbital

Phenobarbital, a barbiturate, has been used to control seizures post ABI. It has also been used as a sedative to relieve anxiety.

Table 12.5 Effects of Phenobarbital in the Treatment of Seizures

Author/ Year/ Country/ Study Design/ N	Methods	Outcomes
Manaka (1992) Japan RCT PEDro=3 $N_{initial}$=244, N_{final}=191	**Population:** Severe Head Injury*; Severe Group*: Mean Age=38.0 yr. *Mild Group*: Mean Age=29.3 yr. **Treatment:** Patients with severe injuries were divided into two groups: phenobarbital (n=50; 10-25 µg/mL) or control (n=76) starting at 4wk post injury for 2 yr, tapering off at 3 yr. Follow-up continued for 5 yr. Participants with mild head injury were in a third group (n=65). **Outcome Measure:** Occurrence of seizures.	**Results of mild head injury group not reported here* 1. At follow-up, 12.7% (n=16) of participants with severe head injury developed epileptic attacks; 8 (16%) in the treatment group and 8 (10.5%) controls.
Servit & Musil (1981) Czechoslovakia PCT N=167	**Population:** TBI; Mean Age=30.6 yr; Gender: Male=128, Female=39. **Treatment:** Participants in the treatment group (n=143) were administered Phenytoin (160-240 mg/day) and phenobarbital (20-60 mg/day). The control group (n=24) was treated with conventional methods for 2 yr. **Outcome Measure:** Occurrence of late seizures.	1. Posttraumatic epilepsy occurred in 25% of the control and 2.1% of the treatment group after discontinuing therapy ($p<0.001$). 2. One individual (0.7%) had a seizure during prophylactic treatment.

PEDro=Physiotherapy Evidence Database rating scale score (Moseley et al., 2002).

Discussion

Individuals who were treated with a combination of phenytoin and phenobarbital as a seizure prophylaxis had a significantly lower incidence of post-traumatic epilepsy upon discontinuation of treatment compared to individuals who did not receive prophylaxis. This decrease was evident up to the two year follow-up. There were also no unfavourable or toxic side effects from either drug, which is important when discussing the risk of side effects versus the risk of post-traumatic epilepsy (Servit & Musil, 1981). Although a combination therapy, the effects of phenobarbital alone are not reported in this study. Manaka (1992) conducted an RCT examining the effects of phenobarbital for seizure control on those who had sustained a severe TBI. Those in the treatment group were administered phenobarbital at the end of the first month of study. Individuals receiving phenobarbital were given 10 to 25 ug/mL for a two year period, at which time individuals were tapered off the medication. All subjects in the study were monitored for the next five years. Study results indicate that phenobarbital did not have a prophylactic effect on post-traumatic epilepsy.

Conclusions

There is level 2 evidence indicating that phenobarbital given post ABI may not reduce the risk of late seizures.

There is level 2 evidence that phenobarbital combined with phenytoin prophylaxis may decrease rate of post-traumatic epilepsy compared to no prophylactic treatment.

Phenobarbital may not be effective in reducing the risk of late seizure development post ABI.

Phenobarbital paired with phenytoin may decrease rate of post-traumatic epilepsy compared to no treatment following a TBI.

12.2.5 Valporic Acid/Divalproex

Valproic acid, an antiepileptic, has been used to successfully treat seizure disorders in both adults and children. Moreover, it has been used to treat bipolar, post-traumatic stress disorder (PTSD) and mania (McElroy et al., 1987). It has also been found to reduce episodic explosiveness with an individual with TBI (Geracioti, 1994). Divalproex, another anticonvulsant, is believed to help reduce aggressive behaviours in individuals post TBI.

Table 12.6 Effects of Valproic Acid and Divalproex on Reducing Aggressive Behaviour

Author/ Year/ Country/ Study Design/ N	Methods	Outcomes
Chatham Showalter & Kimmel (2000) USA Case Series N=29	**Population:** TBI; Mean Age=48.2 yr; Mean Time Post Injury=28.6 days. **Treatment:** A retrospective chart review of patients receiving divalproex treatment in an attempt to reduce symptoms of agitation following injury. Symptoms of agitations included easily aggravated, escalating temper, biting, punching, restless, etc. **Outcome Measure:** Agitated Behaviour Scales.	1. 8 patients had treatment with divalproex (mean 714 mg) leading to rapid resolution of symptoms to near total recovery. 2. For a second subgroup (n=18), progress notes prior to and during treatment demonstrated decreased and significant improvement in symptoms within 7 days of receiving divalproex (mean dose 1,257mg). 3. Most patients were discharged to their homes (n=23) or to other community sites (n=4).
Wroblewski et al. (1997b) USA Case Series N=5	**Population:** TBI; Mean Age=38.2 yr; Gender: Male=4, Female=1. **Treatment:** Valproic acid. **Outcome Measure:** Aberrant Behaviour Checklist.	1. Each patient was reviewed individually, with no cross-case comparisons. All showed a substantial reduction in target behaviours.

Discussion

Wroblewski et al. (1997b) examined the effects of valproic acid (Depakene) on reducing aggressive behaviour in a case series (n=5). Although the study reports that all patients showed a substantial reduction in challenging behaviour (i.e. outbursts, agitation, anger), no statistical analyses were performed. Researchers relied on visual inspection of data, and also presented graphs for only 3 of the 5 participants, rendering the interpretation of the findings difficult and potentially misleading. Further,

patients were also part of a specialized neurobehavioural unit, which may have positively influenced the results.

Divalproex was used to treat symptoms of agitation in 29 patients with brain injuries (Chatham Showalter & Kimmel, 2000). Symptoms decreased in the majority of patients, indicating that divalproex may be an effective treatment to reduce agitation following brain injury.

Conclusions

There is level 4 evidence that valproic acid may decrease the incidence of aggressive behaviours.

There is level 4 evidence that divalproex may decrease the incidence of agitation post TBI.

Valproic acid and divalproex may be used to decrease the incidence of aggressive behaviour; however, more research is needed.

12.2.6 Lamotrigine

The benefits of lamotrigine as an antiepileptic and mood stabilizer have been well established; however, its effectiveness as a mood stabilizer for patients with ABI has yet to be established (Gao & Calabrese, 2005; Tidwell & Swims, 2003).

Table 12.7 Effects of Lamotrigine on Reducing Aggressive Behaviour

Author/ Year/ Country/ Study Design/ N	Methods	Outcomes
Chahine & Chemali (2006) Lebanon Case Series N=4	**Population:** TBI; Mean Age=26 yr; Gender: Male=4, Female=0. **Treatment:** Lamotrigine (range: 125 to 300 mg/day) to reduce inappropriate behaviours (e.g. laughing, impulsivity or verbal aggression). **Outcome Measure:** Frequency of crying, pathological laughing, behaviours of impulsivity, and seizures.	1. All behaviours decreased once the individual was placed on lamotrigine. 2. Crying decreased, and inappropriate laughing ceased. 3. Impulsivity did not cease.

Discussion

Results from a single study indicate that lamotrigine helps to reduce unwanted behaviours such as pathologic laughter but is not effective in reducing impulsivity (Chahine & Chemali, 2006). All four participants were on other medications to control for additional behaviours, however in each case these medications were eventually eliminated once lamotrigine was introduced. No formal outcome assessments were conducted making it challenging to draw conclusions from this study. Further research is needed.

Conclusion

There is Level 4 evidence to suggest that lamotrigine may help to reduce inappropriate behaviours post-traumatic brain injury.

Lamotrigine may be successful in reducing pathologic laughing post-traumatic brain injury. More research is needed, with a greater number of subjects, to validate these findings.

12.3 Anti-Cholinesterase Inhibitors

12.3.1 Cerebrolysin and Cognitive Functioning

As explained by Alvarez et al. (2003), "*Cerebrolysin (*EBEWE Pharma, Unterach, Austria*) is a peptide preparation obtained by standardized enzymatic breakdown of purified brain proteins, and comprises 25% low-molecular weight peptides and free amino acids"* (pg. 272). Cerebrolysin has been demonstrated to have neuroprotective and neurotrophic effects, and has been linked to increased cognitive performance in an elderly population.

Table 12.8 Effects of Cerebrolysin on Cognitive Functioning

Author/ Year/ Country/ Study Design/ N	Methods	Outcomes
Alvarez et al. (2003) Spain Pre-Post N=20	**Population:** TBI; Mean Age=30.1 yr; Gender: Male=15, Female=5; Mean GCS=6.1; Time Post Injury Range=23-1107 day. **Treatment:** Patients with TBI received a total of 20 intravenous infusions of cerebrolysin solution (30 mL/infusion) over 4 wk. Assessments were made at baseline, during treatment, and after the 4 wk treatment period. **Outcome Measure:** Syndrome Kurztest (SKT), electroencephalogram (EEG)/brain mapping recordings, and Glasgow Outcome Scale (GOS).	1. Compared to baseline, patients with TBI showed a significant decrease in slow bioelectrical activity frequencies (delta: $p<0.01$; theta: $p<0.05$), and a significant increase in fast frequencies (beta: $p<0.01$) after receiving cerebrolysin, suggesting improvement in brain bioelectrical activity. 2. Significant improvements in SKT performance was noted from pre to post treatment (15.9±2.4 versus12.0±2.1; $p<0.01$). 3. GOS scores significantly improved from pre to post treatment (3.7±0.3 versus 3.95±0.3; $p<0.05$).

Discussion

In an open-label trial of 20 patients with TBI Alvarez et al. (2003) found that cerebrolysin was associated with improved brain bioelectrical activity, as evidenced by a significant increase in fast beta frequencies. A brief neuropsychological battery (Syndrome Kurztest) consisting of nine subtests was administered to evaluate memory and attentional functions in patients undergoing treatment with cerebrolysin. There was an overall significant improvement in performance post treatment, suggesting patients experienced cognitive benefits from cerebrolysin treatment. Improvements were also seen in terms of recovery, as measured by the GOS (Alvarez et al., 2003). Together these findings suggest that cerebroylsin may represent an effective neuroprotective therapy with tangible cognitive benefits for individuals living with an ABI. Controlled trials are necessary to further explore the efficacy of this drug.

Conclusions

There is level 4 evidence that cerebrolysin may improve attention and memory function post ABI, as well as clinical outcome.

Cerebrolysin may be beneficial for the improvement of clinical outcome and cognitive functioning following brain injury; however, controlled trials are needed to further evaluate its efficacy.

12.3.2 Donepezil and Cognitive Functioning

The effectiveness of donepezil, a cholinesterase inhibitor, in improving cognitive and memory functions following brain injury has been assessed. Cognitive impairments affect one's ability to return to work or school, as well as their ability to live alone (Masanic et al., 2001). When tested with individuals diagnosed with Alzheimer's disease, donepezil has been found to be useful in treating memory problems (Morey et al., 2003; Walker et al., 2004). Its impact on cognitive function and memory in a TBI population is explored in the table below.

Table 12.9 Effects of Donepezil on Cognitive Functioning and Memory

Author/ Year/ Country/ Study Design/ N	Methods	Outcomes
Khateb et al. (2005) Switzerland Pre-Post $N_{initial}$=15, N_{final}=10	**Population:** TBI; Mean age=43 yr; Gender: Male=8, Female=7; Mean Time Post Injury=42 mo. **Treatment:** Patients were administered donepezil 5 mg/day for 1 month, followed by 10 mg/day for 2 months. **Outcome Measure:** Stroop test, trail making test (TMT), Rey Auditory Verbal Memory Test (RAVMT) and Test for Attentional Performance (TAP).	1. 4 of 15 participants stopped due to side effects within the first week (e.g., nausea, sleep disorders, anxiety, dizziness, etc.). 2. Changes on the neuropsychological evaluation show modest improvement, the comparison of the global score of all questionnaires before and after therapy was marginally significant (p=0.058). 3. A significant improvement in executive function was only found for the Stroop Colour naming test (87.3±22.9 to 79.5±19.1, p=0.03); for learning and memory the RAVMT-learning (47.7±6.9 to 53.5±5.0, p=0.05); and for attention, the errors subsection of divided attention (5.8±3.3 to 2.9±2.7, p=0.03).
Zhang et al. (2004) USA RCT PEDro=7 N=18	**Population:** TBI; *Group A (n=9)*: Mean Age=33 yr; Gender: Male=6, Female=3; Mean GCS=9.3; Mean Time Post Injury=4.6 mo; *Group B (n=9)*: Mean Age=31 yr; Gender: Male=7, Female=2; Mean GCS=8.9; Mean Time Post Injury=3.9 mo. **Treatment:** In a randomized crossover trial, Group A received oral donepezil for the first 10 wk, followed by a washout period of 4 wk, then followed by 10 wk of placebo. Group B received the treatments in the opposite order. Donepezil was administered at 5 mg/day for the first 2 wk, and at 10 mg/day for the remaining 8 wk. **Outcome Measure:** Auditory (AII) and Visual (VII) subtests of Wechsler Memory Scale-III, and the Paced Auditory Serial Addition Test (PASAT).	1. At week 10, Group A achieved significantly better scores in AII (95.4±4.5 versus 73.6±4.5; p=0.002), VII (93.5±3.0 versus 64.9±3.0; p<0.001), and in the PASAT (p≤0.001) compared to Group B. 2. This increase in scores in Group A were sustained after washout and placebo treatment (week 24), leading to no significant differences in AII (105.9±4.5 versus 102.4±4.5; p=0.588), VII (91.3±3.0 versus 94.9±3.0; p=0.397), and PASAT (p>0.1) compared to Group B at study end. 3. Within-group comparisons showed that patients in both Group A and Group B improved significantly in AII and VII (p<0.05), as well as in PASAT (p<0.001), after receiving donepezil.

Author/ Year/ Country/ Study Design/ N	Methods	Outcomes
Morey et al. (2003) USA Case Series N=7	**Population:** TBI; Mean Age=30.7 yr; Gender: Male=5, Female=2; Mean Time Post Injury=33.3 mo. **Treatment:** Following baseline cognitive testing (T1), each participant began a 6mo treatment phase with 5 mg/day donepezil for the first 4 wk, then with 10 mg/day for the final 5 mo (T2). Washout period then occurred for 6 wk (T3). Another 6 mo treatment period took place with participants receiving 5 mg/day donepezil for the entire period (T4). **Outcome Measure:** Brief Visual Memory Test-Revised (BVMT-R), Hopkins Verbal Learning Test, digit span and letter-number sequence subtests of Wechsler Adult Intelligence Scale-Revised III, Controlled Oral Word Association Test, and Memory Functioning Questionnaires.	1. Significant improvements ($p<0.05$) from T1 to T2 were observed for the following: Trial 1 of the BVMT-R, Trial 3 of the BVMT-R, total score of the BVMT-R, and delayed recall trial of the BVMT-R. No significant differences were identified for other measures, or across other testing intervals.
Masanic et al. (2001) Canada Pre-Post N=4	**Population:** TBI; Age Range=24-35yr; Gender: Male=4, Female=0; GCS Range=3-8; Time Post Injury Range=35-46mo. **Treatment:** Participants received 5 mg donepezil daily for 8 wk, followed by 10 mg daily for 4 wk. Washout period then occurred for 4 wk. Assessments occurred at baseline, and at weeks 4, 8, 12, and 16. **Outcome Measure:** Rey Auditory Verbal Learning Test (RAVLT), Complex Figure Test (CFT), Rivermead Behavioural Memory Test (RBMT).	1. Mean scores for short-term and long-term recall on the RAVLT improved by 1.03 (1.25±1.89 at baseline to 3.00±2.70 at week 12) and 0.83 (0.50±0.58 at baseline to 2.50±2.38 at week 12) standard deviations above baseline, respectively. 2. Mean scores for short-term and long-term recall on the CFT improved also by 1.56 (13.88±8.45 at baseline to 20.13±12.93 at week 12) and 1.38 (14.00±5.60 at baseline to 19.38±11.46 at week 12) standard deviations above baseline, respectively. 3. Perceived memory deficit (RBMT) showed a trend toward improvement over the first 12 wk, followed by deterioration after the washout period.

PEDro=Physiotherapy Evidence Database rating scale score (Moseley et al., 2002).

Discussion

In a RCT, Zhang et al. (2004) demonstrated that donepezil was associated with improvements in tasks of sustained attention and short-term memory, and that these improvements were sustained even after the washout period. Benefits associated with donepezil were also documented in an open-label study by Masanic et al. (2001) who found that the treatment tended to improve both short- and long-term memory of patients living with TBI. Improvements in memory were also reported by Morey et al. (2003) in their retrospective study who demonstrated that donepezil led to significant benefits in visual memory function.

Khateb et al. (2005) found only modest improvement on the various neuropsychological tests used to measure executive function, attention and learning and memory. Of note results from the learning phase of Rey Auditory Verbal Memory Test (RAVMT) showed significant improvement ($p<0.05$). To assess improvement in executive function, results from the Stroop-colour naming test showed

significant changes (p<0.03). On the test for Attentional Performance (TAP) a significant change was noted on the divided attention (errors) subsection of the test.

Conclusions

There is level 1b evidence that donepezil may improve attention and short-term memory post ABI.

There is level 4 evidence that donepezil may be effective in improving short-, long-term, and visual memory post ABI.

Donepezil may help to improve attention, short-term, long-term, and visual memory following brain injury.

12.3.3 Physostigmine

Physostigmine is a cholinergic agonist that temporarily stops acetylcholinesterase which in turn slows the destruction of, and thereby increases the concentration of, acetylcholine at the synapse. Its use in Alzheimer's disease has been examined at length. It has been proposed to improve memory in patients with head injury (McLean et al., 1987).

Table 12.10 Effects of Physostigmine on Memory

Author/ Year/ Country/ Study Design/ N	Methods	Outcomes
Cardenas et al. (1994) USA RCT PEDro=6 N=36	**Population:** TBI; Mean Age=29.5 yr; Gender: Male=36, Female=0; Mean GCS=5.31; Mean Time Post Injury=4.33 yr. **Treatment:** Patients randomized to one of 4 treatment protocols: 1) scopolamine, oral physostigmine, washout, placebo (for scopolamine), then placebo (for physostigmine); 2) placebo (for scopolamine), oral physostigmine, washout, scopolamine, then placebo (for physostigmine); 3) placebo (for scopolamine), placebo (for physostigmine), washout, scopolamine, then oral physostigmine; and 4) scopolamine, placebo (for physostigmine), washout, placebo (for scopolamine), then oral physostigmine. Scopolamine was administered at 5µg/hr via a transdermal patch placed behind the ear. Oral physostigmine was administered initially at 2mg 3×/day, but titrated up to 4mg 3×/day over 1 wk. Washout period was 1wk, and each treatment phase lasted 8d. **Outcome Measure:** Selective Reminding Test (SRT), Wechsler Memory Scale I & II, Digit Symbol, Trail Making Test A & B, Memory Questionnaire, clinical balance tests, serum cholinesterase levels.	1. A total of 16 (44%) participants had improved memory scores while taking oral physostigmine (improvement was defined as >50% increase on Long-term storage or Sum Consistent Long-term Retrieval of the SRT). 2. Participants were divided into either responder (n=16) or non-responder (n=20) groups based on the SRT. 3. Responders showed significantly improved standing time compared to non-responders (p<0.05), suggesting better balance.

PEDro=Physiotherapy Evidence Database rating scale score (Moseley et al., 2002).

Discussion

In a double-blind, placebo-controlled randomized trial, oral physostigmine was administered to males with TBI as an active treatment (Cardenas et al., 1994). The authors found that physostigmine led to significant improvements in long-term memory scores in 44% (n=16) of study participants. Those who responded favourably to the treatment, as indicated by their performance on the Selective Reminding Test (SRT), also demonstrated improved balance compared to non-responders (Cardenas et al., 1994).

Conclusions

Based on a single RCT, there is level 1b evidence that oral physostigmine may improve long-term memory in men with TBI.

Physostigmine may improve long-term memory in men with TBI.

12.4 Anti-Depressants

Disorders of mood, including agitation, anxiety disorders, and major depression are all common following an ABI and are associated with suffering, worsening of other ABI sequelae, and poorer outcomes. The most common mood disorder after brain injury is a major depressive episode or depression (Jorge et al., 2004). A major depressive episode can result in hopelessness, feelings of grief or guilt, agitation, hopelessness, poor appetite, loss of libido and alterations in sleep. While ABI itself may also cause symptoms of sadness, grief, hopelessness, etc., a major depressive episode may slow the process of rehabilitation and may interfere with an individual's ability to return to work or their relationships with family and friends (Jorge et al., 2004). For a more detailed discussion of anti-depressants and the effect on depression post ABI please refer to Module 8.

Depression is often treated pharmacologically following an ABI. Included among these Interventions are various antidepressants: serotonin selective re-uptake inhibitors such as sertraline, or citalopram; serotonin norepinephrine reuptake inhibitors such as duloxetine; and tricyclic antidepressants such as amitriptyline and desipramine. The following sections discuss the use of antidepressants following a brain injury.

12.4.1 Sertraline

Table 12.11 Effects of Sertraline on Depression

Author/ Year/ Country/ Study Design/ N	Methods	Outcomes
Ashman et al. (2009) USA RCT PEDro=10 N=41	**Population:** TBI; Mean Age=49.1 yr; Gender: Male=24, Female=17; Severity of Injury: Mild=15, Moderate=16, Severe=10; Mean Time Post Injury=17.7 mo. **Treatment:** The treatment group (n=22) was given sertraline (25 mg adjusted every 2 wk, range 25-100 mg) and the control group (n=19) received a placebo for 10wk. **Outcome Measure:** Structured Clinical Interview	1. Treatment responders, based on HAM-D (score <10 or decreased by 50%) were 59% in the treatment group and 32% in the control (p=0.08). 2. Changes in scores on the HAM-D, the BAI and the QOL scales did show improvement (p<0.001) but no group effects were found.

Author/ Year/ Country/ Study Design/ N	Methods	Outcomes
	for DSM-IV Axis I Disorders, Hamilton Rating Scale for Depression (HAM-D), Beck Anxiety Inventory (BAI), and Life-3 scale (QOL).	
Lee et al. (2005) Korea RCT PEDro=8 N=30	**Population:** TBI; Gender: Male=24, Female=6; *Group A*: N=10; Mean Age=35.3 yr; Mean Time Post Injury=34.8 days. *Group B*: N=10; Mean Age=33.6 yr; Mean Time Post Injury=31.9 days. *Group C*: N=10; Mean Age=35.5 yr; Time Post Injury=30 days. **Treatment:** Patients assigned to one of three groups: Group A: methylphenidate (5 mg/day increased to 20 mg/day); Group B: sertraline group (25 mg/day increased to 100 mg/day); or Group C: placebo. **Outcome Measure:** Beck Depression Inventory (BDI) and the Hamilton Rating Scale for Depression (HAM-D).	1. In all 3 groups scores on the HAM-D and BDI improved from the baseline and week 4 (Group A, p<0.001 on both measures; Group B, p<0.01, for both; Group C, p<0.05 BDI and p<0.01 for HAM-D). 2. Groups A (p=0.005) and B (p=0.05) were significantly superior to Group C on the HAM-D. 3. The number of adverse events was higher in Group B than Group A (13 versus 6, p=0.010).

PEDro=Physiotherapy Evidence Database rating scale score (Moseley et al., 2002).

Discussion

Two RCTs looked at the effects of sertraline on depression post ABI (Ashman et al., 2009; Lee et al., 2005). Ashman et al. (2009) compared sertraline to placebo and found improvements over time for both groups on all three outcomes (the Hamilton Rating Scale for Depression, the Beck Depression Inventory, and the Life-3 Quality of Life scales). No statistically significant differences were shown between the two groups; therefore the changes may not have been related to sertraline. The second RCT added a third arm to their trial. The authors randomized individuals with mild or moderate TBI to a sertraline, methylphenidate or placebo group (Lee et al., 2005). Similar to the first study, all participants improved on the depression measures (Beck Depression Inventory and the Hamilton Rating Scale for Depression). However, the study results indicated that those assigned to the sertraline and the methylphenidate groups reported significantly less depressive symptoms on these measures than the placebo group at study's end (Lee et al., 2005). Further, fewer adverse events were reported for individuals receiving methylphenidate than those administered sertraline.

Conclusions

There is conflicting evidence that sertraline may be effective in the treatment of major depression post TBI.

The effectiveness of sertraline in treating depression post TBI is unclear.

12.4.2 Citalopram

Table 12.12 Effects of Citalopram on Depression

Author/ Year/ Country/ Study Design/ N	Methods	Outcomes
Rapoport et al. (2010) Canada RCT PEDro=9 $N_{Initial}$=21, N_{Final}=18	**Population:** TBI; Mean Age=47.67 yr; Gender: Male=11, Female=10; Severity of Injury: Mild=16, Moderate/Severe=5. *Treatment Group*: Mean Time Post Injury=105 days. *Control Group:* Mean Time Post Injury=107 days. **Treatment:** Individuals who had a DSM-IV diagnosis of major depression but met the criteria for remission were assigned to either the treatment group (n=10) who were given citalopram (~40m g/day) or the control group (n=11) which received a placebo for 40 wk. **Outcome Measure:** Cumulative Illness Rating Scale, Hamilton Depression Rating Scale (HDRS), Mini Mental State Examination and the Rivermead Post Concussion Symptoms Questionnaire.	1. Comparing the treatment and control groups, relapse rates (p=0.835) and time to relapse (24.8 versus 22.3 wk, respectively, p=0.700) were not significantly different. 2. All participants experienced adverse events regardless of the group they were placed in (e.g. headache, muscle/ joint pain, and dizziness). 3. On the HDRS, patients with "more than mild agitation" relapsed sooner than those without that level of agitation (8.0 versus 27.18 wk, p=0.013). 4. On the HDRS, those with "more than mild psychic anxiety" relapsed at a mean of 19.7 wk compared to those with "none to mild" who did not relapse (p=0.046).
Rapoport et al. (2008) Canada PCT $N_{Initial}$=65, N_{Final}=54	**Population:** TBI; Mean Age=39.7yr; Gender: Male=38, Female=27; Injury Severity: Mild=33, Moderate to severe=32. **Treatment:** Group A (n=29) received 20 mg/day of citalopram for 6 wk whereas group B (n=36) received 20 mg titrated to 50 mg/day for 10 wk. **Outcome Measure:** The Hamilton Rating Scale for Depression (HAM-D), Clinical Global Impression, and the Rivermead Post Concussion Symptoms Questionnaire (RPQ).	1. Mean HAM-D scores decreased from baseline to 6 wk (23.66 versus 16.30, p<0.0001). Scores also decreased significantly from baseline to 10 wk (12.96, p<0.001). 2. 84.6% reported ≥1 adverse event; most often, dry mouth. 3. Of the 54 subjects who started the study, 24.1% were in remission at 6 wk. Of the 26 assessed, 26.9% were in remission at 10 wk. 4. The somatic score on the RPQ decreased significantly from 15.38 to 11.35 (p<0.001) at 6 wk; but not at 10 wk (10.82, p=0.0632).
Perino et al. (2001) Italy Pre-Post N=20	**Population:** TBI; Gender: Male=11, Female=9; *Group A*: N=11; Mean Age=26.9 yr; Mean GCS Score=5.5; Mean Time Post Injury=4.7 mo. *Group B*: N=9; Mean Age=31.3 yr; Mean GCS Score=6.1; Mean Time Post Injury=34.6 mo. **Treatment:** Patients received citalopram (20 mg/day) and carbamazepine (600 mg/day), and were divided into subgroups based on time post injury (Group A: <6 mo; Group B: 24-36 mo). **Outcome Measure:** Brief Psychiatric Rating Scale (BPRS) and the Clinical Global Impression (CGI).	1. The total sample significantly improved from baseline to 12 weeks on the BPRS (62.3±17.6 versus 51.7±12.8, p≤0.05) and CGI (4.4±1.1 versus 3.4±0.8, p≤0.005). 2. When comparing groups, group B had higher global scores on the BPRS at baseline and 12 wk.

PEDro=Physiotherapy Evidence Database rating scale score (Moseley et al., 2002).

Discussion

Rapoport and colleagues Rapoport et al. (2008) administered 20 mg/day of citalopram for 6 weeks to one group while the second group began with 20 mg/day which was titrated to a maximum of 50 mg/day. The second group was studied for 10 weeks. For participants in both groups, their depression scores significantly decreased compared to baseline. In another study participants were randomly assigned to receive citalopram or placebo (Rapoport et al., 2010). Post-treatment relapse rates were

calculated for each group and there were no significant differences noted between the groups with individuals relapsing (meeting criteria for major depressive disorder) 22 to 24 weeks post treatment; relapse occurred in 52.4% of patients. In both studies, adverse events were common (Rapoport et al., 2008; Rapoport et al., 2010). While citalopram on its own has shown potential to aid with depression, a study by Perino et al. (2001) found that when both citalopram and carbamazepine were given to patients diagnosed with post-TBI depression, scores on the Brief Psychiatric Rating Scale (BPRS) and the Clinical Global Impression significantly improved after 12 weeks.

Conclusions

There is level 2 evidence that citalopram may aid in the reduction of depression post ABI.

There is level 4 evidence that citalopram and carbamazepine may be efficacious in the treatment of depression, anxiety and mood disorders.

Citalopram may be helpful in the reduction of depression post ABI.

Citalopram and carbamazepine may be effective in the treatment of mood disorders.

12.4.3 Desipramine

Table 12.13 Effects of Desipramine on Depression

Author/ Year/ Country/ Study Design/ N	Methods	Outcomes
Wroblewski et al. (1996) USA RCT PEDro=4 N=10	**Population:** TBI; Mean Age=32.2 yr; Gender: Male=7, Female=3; Mean Time Post Injury=1.5 yr; Severity of Injury=Severe. **Treatment:** The treatment group (n=6) received desipramine (150 mg/day for 30 days, 150-300 mg/day after) and the control group (n=4) received a placebo. The control group crossed over and received desipramine after day 30. **Outcome Measure:** Diagnostic and Statistical Manual of Mental Disorders checklist and Affect/Mood Scale.	1. 3 individuals from each group had nearly complete resolution of depression on desipramine. 2. 70% of subjects showed improvement over time on the affect/mood scale (p=0.001). 3. There were different rates of improvement over time in those started on the desipramine rather than placebo; with the treatment group making more rapid and greater improvements.

PEDro=Physiotherapy Evidence Database rating scale score (Moseley et al., 2002).

Discussion

A single, small sample RCT found that desipramine was effective in treating long-standing depression (Wroblewski et al., 1996). Three of those in the treatment group and three in the control group had near complete resolution of depression; however, because the control group was crossed over to the treatment group, further studies are necessary before firm conclusions are drawn on this medication.

Conclusions

There is level 2 evidence to suggest that the administration of desipramine may assist in improving mood and reducing depression.

Desipramine may be effective in reducing depression.

12.4.4 Sertraline and Amitriptyline

Two studies examined the effect of antidepressants on reducing agitation and/or aggression in patients with brain injuries (Kant et al., 1998; Mysiw et al., 1988). Kant et al. (1998) examined the effect of sertraline, a serotonin selective reuptake inhibitors (SSRI), on reducing aggression and irritability in patients with brain injury, whereas Mysiw et al. (1988) examined the effect of amitriptyline (a tricyclic antidepressant (TCA) with both serotonergic and noradrenergic reuptake inhibition).

Table 12.14 Effects of Sertraline and Amitriptyline on Reducing Aggression and Irritability

Author/ Year/ Country/ Study Design/ N	Methods	Outcomes
Kant et al. (1998) USA Pre-Post N=13	**Population:** CHI; Mean Age=37.6 yr; Gender: Male=10, Female=3; Severity of Injury: Mild=5, Moderate=6, Severe=6; Mean Time Post Injury=2 yr. **Treatment:** 8 wk trial of sertraline HCl (Zoloft; 50 mg/day to a max of 200 mg/day). **Outcome Measure:** Overt Aggression Scale-Modified (OAS-M), Beck Depression Inventory (BDI), Anger Irritability Assault Questionnaire.	1. Significant improvement in aggression ($p<0.001$) and irritability ($p<0.01$) measures were shown at week 4 and 8 based on the OAS-M. 2. Results from the BDI indicate there was a significant improvement at 4wk post baseline ($p=0.04$), but not at 8wk ($p=0.14$).
Mysiw et al. (1988) USA Pre-Post N=58	**Population:** TBI; Mean Age=26.9 yr; Gender: Male=43, Female=15. **Treatment:** Traditional behavioural techniques were used but if agitation interfered with rehabilitation, or persisted more than 7 days, then participants were administered amitriptyline (n=20; 25-150 mg/day). The remaining participants received no medication but did not serve as a true control group. **Outcome Measure:** Orientation Group Monitoring Scale (OGMS).	1. 13 of 20 patients treated with amitriptyline experienced significantly reduced levels of agitation after 1 wk ($p<0.001$); decrease in agitation was maintained in the ensuing weeks ($p<0.001$), but did not significantly drop when compared to the 1 wk ($p>0.6$). 2. 30% of patients experienced no significant change in agitation levels, despite increasing the dose at 1 wk ($p>0.7$) and beyond ($p>0.3$).

Discussion

Both studies showed potential to improve aggressive and agitated behaviour in patients with brain injuries. Kant et al. (1998) examined the effect of sertraline HCl (Zoloft) on reducing aggression and irritability in patients with closed head injuries of varying severities, two years post injury. The patients responded positively at both the four and eight week follow-ups, showing significant reduction in aggressive and irritable behaviour (Kant et al., 1998). The patients treated also had improvements in depression at week four. Mysiw et al. (1988) focused on 20 individuals who displayed agitation during their rehabilitation program and received amitriptyline. 70% of patients displayed significant reductions agitation within the first week (Mysiw et al., 1988). Both studies had similar limitations, those being small sample sizes and no true control groups.

Conclusions

There is level 4 evidence that sertraline hydrochloride can decrease the incidence of aggression and irritability.

There is level 4 evidence that amitriptyline can be useful in reducing the incidence of agitated behaviour.

Sertraline hydrochloride can be useful in reducing aggressive and irritable behaviours.

Amitriptyline can be used to decrease agitation.

12.5 Anti-Psychotics

12.5.1 Lithium Carbonate

Lithium carbonate has been used for many years in the treatment of mania and bipolar disorder (Kim, 2002). It has been suggested that mood disorders, such as mania, occurring after TBI, may contribute to the development of aggression (Kim, 2002; Wroblewski et al., 1997a). In the search for a pharmacological agent that reduces aggression following TBI with limited side effects in comparison to antipsychotics and benzodiazepines, lithium has been tried. Lithium carbonate also functions as a mood stabilizer.

Table 12.15 Effects of Lithium Carbonate on Aggressive Behaviour

Author/ Year/ Country/ Study Design/ N	Methods	Outcomes
Glenn et al. (1989) USA. Case Series N=10	**Population:** TBI=8, CVA=2; Mean Age=31.6 yr; Gender: Male=5, Female=5. **Treatment:** Patients showing mood disorders, aggressive, combative, self-destructive behaviour and/or affective instability were administered lithium. **Outcome Measure:** Observed improvement.	1. Five participants showed a significant improvement in rehab programs with no decrease in motor or cognitive performance; 1 showed moderate response, 1 improved dramatically but regressed after 7 wk. 2. Four regressed after medications stopped. 3. Three participants had neurotoxic side effects.

Discussion

Lithium carbonate was used in a series of case reports with ten individuals with either TBI or stroke (Glenn et al., 1989). Glenn et al. (1989) reported favourable outcomes for the majority of patients (i.e., a decrease in observed aggressive, combative, or self-destructive behaviour or severe affective instability). However, this study highlights that there is a high risk of potential neurotoxicity among individuals with brain injuries, specifically in combination with neuroleptic drugs.

Conclusions

There is level 4 evidence to suggest that an antimanic agent (lithium carbonate) may reduce aggressive/agitated behaviour following a brain injury.

Lithium may reduce behavioural problems but is associated with a high risk of neurotoxicity.

12.5.2 Quetiapine (Seroquel)

Quetiapine has been used to reduce aggressive behaviour among those diagnosed with schizophrenia and Alzheimer's disease (Volavka et al., 2004; Webb & Glueckauf, 1994). A closer examination of its impact within a brain injury population is discussed below.

Table 12.16 Effects of Quetiapine on Aggressive Behaviour

Author/ Year/ Country/ Study Design/ N	Methods	Outcomes
Kim & Bijlani (2006) USA Case Series N=7	**Population:** CHI; Mean Age=48.9 yr; Gender: Male=4, Female=3; Mean Time Post Injury=23.1mo. **Treatment:** Patients received Quetiapine (50-100 mg/day, max 800 mg) Quetiapine daily in bedtime for the first week, then titrated every 3-4 days to a maximum of 800 mg for 6 wk in total (dose ranged from 25 to 300 mg). **Outcome Measure:** Overt Aggression Scale-Modified (OAS-M), Clinical Global Impression (CGI), Neurobehavioural Functioning Inventory, Repeatable Battery for the Assessment of Neuropsychological Status (RBANS).	1. Mean dose of Quetiapine was 110.7 mg. As a result of the medication, subjects' OAS scores were significantly reduced (p=0.002). 2. The CGI score significantly improved (p=0.002). 3. Significant improvements were also noted on the aggression subscale (p=0.036). 4. RBANS overall scores indicated a mean improvement of 8.02% (p=0.027).

Discussion

In one case series quetiapine assisted in helping to reduce aggressive behaviour in seven individuals (Kim & Bijlani, 2006). They also noted significant improvements in the Overt Aggression Scale-Modified, the Clinical Global Impression scores, and the overall scores of the Repeatable Battery for the Assessment of Neuropsychological Status. Quetiapine may be considered as an alternative to haloperidol or chlorpromazine if additional research finds it is just as effective in treating aggressive behaviours without the side effects (Kim & Bijlani, 2006).

Conclusions

There is Level 4 evidence (from one small study) to suggest that quetiapine may help reduce aggressive behaviour.

Although there is evidence to suggest that quetiapine can help reduce aggressive behaviour, more research is needed.

12.5.3 Ziprasidone

Ziprasidone has been approved for acute agitation in those diagnosed with schizophrenia. It has also been found to work in the treatment of acute mania, often associated with bipolar disorder. For those

who sustain a TBI, the period of post-traumatic amnesia (PTA) is defined as a period during which the individual is disorientated, have difficulty learning new concepts, and/or suffer from behaviour alterations (Brooke et al., 1992b). Researchers believe that these behaviour alternations may result from the individual's lack of self-awareness which may be related to memory alterations that appear after the injury (Noé et al., 2007).

Table 12.17 Effects of Ziprasidone on Agitation

Author/ Year/ Country/ Study Design/ N	Methods	Outcomes
Noe et al. (2007) USA Case Series N=5	**Population:** TBI; Mean Age=26.8 yr; Gender: Male=3, Female=2; Mean GCS Score=6; Mean Time Post Injury=54.6 days. **Treatment:** Ziprasidone (30-80mg/d for 35-68d) was given to participants. **Outcome Measure:** Agitation Behaviour Scale (ABS).	1. Mean dose of the drug was 52.8 mg/days. 2. Scores on the ABS decreased within the first 14 days (27.3 to 18). 3. Scores on the disinhibition portion of the ABS decreased from 28.6 to 17.1, while scores on the aggressiveness subsection of the scale decreased from 26.1 to 20.4. 4. No side effects were noted.

Discussion

Noé et al. (2007) studied individuals who were still in PTA stage at admission to rehabilitation. Within these participants, a decrease in agitation scores was reported during the first two weeks of ziprasidone administration. It was also noted that all who participated tolerated the medication with no clinical side effects observed. A larger RCT would be beneficial before any firm conclusions are made.

Conclusions

There is level 4 evidence from one study to suggest that ziprasidone can assist in the controlling of agitation post TBI.

Ziprasidone in one small study has been shown to assist in the controlling of agitation; however more research is needed.

12.5.4 Haloperidol

Haloperidol is a psychotropic drug found to reduce agitation. It also blocks or disrupts dopamine receptors. Thus, while it improves agitation, there is a theoretical concern that it may impede recovery by reducing arousal.

Table 12.18 Effects of Haloperidol on Agitation

Author/ Year/ Country/ Study Design/ N	Methods	Outcomes
Rao et al. (1985) USA Case Series N=26	**Population:** Severe TBI; Age Range=16-48 yr. **Treatment:** Retrospective review of individuals whose agitation was treated with haloperidol (n=11; 2-15 mg/day) and those who were not (n=15).	1. Those treated had a longer length of PTA ($p<0.03$). 2. No statistically significant differences were shown between those who were and were not treated in terms of

Author/ Year/ Country/ Study Design/ N	Methods	Outcomes
	Outcome Measure: Patient Evaluation Conference Systems.	independent living at discharge (64% versus 60%, respectively) or independence in managing behaviour (40% versus 60%). 3. 3 of those non treated obtained independence in intellectual skills but none of the treated patients did this.

Discussion

In a retrospective chart review, agitation was managed in eleven patients with haloperidol and in fifteen patients without haloperidol (Rao et al., 1985). No significant differences were found between the two groups with regards to success of rehabilitation outcome; however, none of the patients in the treatment group obtained independence in intellectual skills (Rao et al., 1985).

Conclusions

There is level 4 evidence that haloperidol may not have a negative effect on the success of rehabilitation.

Haloperidol appears to have little negative effect on recovery following TBI.

12.5.5 Droperidol (Inapsine)

Droperidol is a butyrophenone antipsychotic agent that closely resembles haloperidol in structure. It has been used for the treatment of psychosis in Europe (Stanislav & Childs, 2000).

Table 12.19 Effects of Droperidol on Improving Behaviour

Author/ Year/ Country/ Study Design/ N	Methods	Outcomes
Stanislav & Childs (2000) USA Pre-Post N=27	**Population:** TBI; Gender: Male=21, Female=6. **Treatment:** Intramuscular injection of droperidol administered as needed to relieve agitation. **Outcome Measure:** Observation.	1. Mean dose was 3.25 mg; a single dose reduced agitation in 96% of patients. 2. The time to achieve calming following episodes of agitation was significantly shortened with droperidol compared to haloperidol, lorazepam, or diphenhydramine (p=0.02).

Discussion

When an individual is agitated, not only is the effectiveness of the medication administered important but also the time it takes to have a calming effect. One retrospective controlled trial found that a single-dose of droperidol calmed patients displaying agitated behaviour faster than other drugs such as haloperidol, lorazepam, and diphenhydramine (Stanislav & Childs, 2000). The study also found that droperidol calmed individuals without heavily sedating the patients like some of the comparative medications did. It is worth noting however that a large proportion of the sample had psychiatric co-morbidities; this should be kept in mind when generalizing the findings.

Conclusions

There is level 4 evidence that administration of a single-dose droperidol may calm agitated patients with ABI more quickly than other agents.

Droperidol may be an effective agent for calming agitated patients.

12.5.6 Methotrimeprazine

Methotrimeprazine (Nozinan) is a psychotropic medication. It has antipsychotic (mediated by dopamine blocking), tranquilizing, and analgesic properties. It appears to have an effect on opiate (pain) receptors as well (Maryniak et al., 2001).

Table 12.20 Effects of Methotrimeprazine on Agitation Post ABI

Author/ Year/ Country/ Study Design/ N	Methods	Outcomes
Maryniak et al. (2001) Canada Case Series N=120	**Population:** TBI=95, ABI=25; Mean Age=37.8 yr; Gender: Male=89, Female=31. **Intervention:** Retrospective review of patients attending an inpatient ABI rehabilitation unit. Patients administered methotrimeprazine (MTZ) were analyzed. **Outcome Measure:** Agitated Behaviour Scale.	1. 58% had agitation but 56 patients were treated with MTZ (10-25 mg, 4×/day) with a mean length of treatment of 41.9 day. 2. MTZ, for the most part (96% of patients), was both safe and effective for controlling agitation.

Discussion

The oral administration of methotrimeprazine (MTZ) for agitation was evaluated in a retrospective chart review of 56 patients during inpatient rehabilitation (Maryniak et al., 2001). This was the first report on MTZ's use in treating agitation after ABI and the authors found that in most cases MTZ was both safe and effective for controlling agitation. No standardized outcome measures were used within this study, and there was no control group; therefore, a more rigour study examining the safety and efficacy of MTZ within an ABI population is necessary before a level of evidence statement can be provided.

Conclusions

There is level 4 evidence that methotrimeprazine may be safe and effective for controlling agitation after an acquired brain injury.

Methotrimeprazine may be safe for controlling agitation following an acquired brain injury.

12.6 Antispasticity Treatments

Spasticity is a common symptom encountered post ABI and is an element of the upper motor neuron syndrome. Spasticity has been formally defined as "a motor disorder characterized by a velocity-dependent increase in tonic stretch reflexes with exaggerated tendon reflexes, resulting from

excitability of the stretch reflex" (Lance, 1980). Common features of spasticity include increased muscle tone, exaggerated tendon jerks, and clonus.

Management of spasticity is not unique to brain injury survivors, since it is often associated with other conditions affecting the CNS such as spinal cord injury (SCI) and multiple sclerosis (MS). Spasticity may require intervention when it interferes with functional abilities such as mobility, positioning, hygiene, or when it is the cause of deformity or pain. Factors that must be taken into consideration when proposing treatment of spasticity include chronicity of the problem, the severity, the pattern of distribution (focal versus diffuse), and the locus of injury (Gormley et al., 1997), as well as comorbities. Some studies have found that spasticity of cerebral origin versus SCI respond differently to the same medications (Katz & Campagnolo, 1993). Typically, the clinical approach to spasticity is to first employ treatments that tend to be less interventional and costly; however, multiple strategies may need to be administered concurrently.

12.6.1 Nerve Block

Local nerve blocks may be a potential management solution in circumstances where there is muscle spasticity affecting only a few muscle groups in a focal pattern. Essentially, a nerve block involves the application of a chemical agent to impair nerve functioning. The effect of the chemical agent may be temporary or permanent (Katz et al., 2000). Temporary acting agents include local anesthetic agents that block sodium ion channels, typically lasting only a few hours. Local anesthetic agents are used for diagnostic procedures or for assistance with activities such as casting (Gracies et al., 1997). Agents used for permanent nerve blocks to treat spasticity include ethyl alcohol (>10%) and phenol (>3%). The duration of effect for these agents is between 2 and 36 months. Complications of this type of block have included chronic dysesthesia, pain and permanent peripheral nerve palsies (Gracies et al., 1997).

Table 12.21 Effects of Percutaneous Phenol Block on Reducing Spasticity

Author/ Year/ Country/ Study Design/ N	Methods	Outcomes
Keenan et al. (1990) USA Case Series N=17	**Population:** TBI; Mean Age=25 yr; Gender: Male=12, Female=5; Mean Time Post Injury=6 mo. **Intervention:** Subjects received a phenol block (3 ml of 5% phenol solution in sterile saline) followed by a daily program of active/passive range of motion therapy. Assessments conducted pre-post block, 24hr after, then weekly intervals while hospitalized for rehabilitation. Post discharge follow-up occurred for a minimum of 2 yr. **Outcome Measure:** Muscle tone/ control and range of motion.	1. 93% of extremities showed a short term decrease in motor tone and improved resting position of the elbow. 2. Maximum improvements occurred 4wk post block. 3. Resting position improved from 120° to 69°, active arc increased from 46° to 60°, and passive arc from 65° to 118°. 4. At follow-up (mean 27mo post injection), 9 extremities that had relief of spasticity, had recurrence of flexor tone and loss of motion in elbow.
Garland et al. (1984) USA Case Series N=11	**Population:** TBI=11; Mean Age=24 yr; Gender: Male=8, Female=3; Mean Time Post Injury=5.8 mo. **Intervention:** Subjects received percutaneous phenol injections (1-2 ml of 3 or 5% phenol solution) at motor points of spastic wrist and finger flexors identified using a nerve stimulator. Injected muscles included: the flexor carpi radialis, flexor carpi ulnaris, flexor	1. Mean resting position of the wrist prior to injection was 53°. 9 patients increased resting extension by a mean of 34° and 2 patients lost a mean of 15° of extension. 2. Overall, there was a mean increase in resting wrist angle following motor point injections of 25°.

Author/ Year/ Country/ Study Design/ N	Methods	Outcomes
	digitorumsublimus, flexor digitorumprofundus, and flexor pollicislongus. **Outcome Measure:** Resting angle of wrist and passive/active extension of wrist.	3. Active wrist extension improved an average of 30°. Mean increase in passive wrist extension with finger flexed of 5°.

Discussion

We identified two studies which evaluated the efficacy of nerve blocks as a treatment for spasticity. Keenan et al. (1990) evaluated the effect of percutaneous phenol block of the musculocutaneous nerve to decrease elbow flexor spasticity. The results indicated that there was improved range of motion of the elbow lasting a mean of five months. In the second study, 11 closed head injury patients with spastic paralysis of the upper extremity were treated with percutaneous phenol injections into the spastic wrist and finger flexors (Garland et al., 1984). The authors reported that relaxation of muscle tone persisted for up to two months following the injections. Furthermore, there was a mean increase in resting wrist angle, active wrist extension, and passive wrist extension with finger flexed of 25, 30, and 5°, respectively (Garland et al., 1984). Evidently, these studies found that percutaneous phenol blocks are effective in temporarily controlling spasticity in patients post TBI.

Conclusions

There is level 4 evidence that phenol nerve blocks may reduce contractures and spasticity at the elbow, wrist and finger flexors for up to five months post injection.

Phenol blocks of the musculocutaneous nerve may help decrease spasticity and improve range of motion temporarily up to five months post injection.

12.6.2 Oral Antispasticity Drugs

Oral agents are often used to manage spasticity particularly when a systemic agent to treat upper and lower extremity spasticity is required (Gracies et al., 1997). Although anti-spasticity agents may be used with other medical conditions such as spinal cord injury or multiple sclerosis (Gracies et al., 1997), the effectiveness should not be presumed to be similar for brain injury survivors. Multiple medications have been evaluated to treat spasticity of both cerebral and spinal cord origin. The more common medications include GABA agonists that effect ion flux such as baclofen, benzodiazepines, dantrolene sodium, as well as agents that effect alpha-2 adreno receptors such as tizanidine and clonidine. The use of any of these drugs must be weighed against potential side effects, such as sedation, which are complicated by the cognitive and behavioural changes associated with brain injury.

Table 12.22 Effects of Oral Anti-Spasticity Agents on Reducing Spasticity

Author/ Year/ Country/ Study Design/ N	Methods	Outcomes
Meythaler et al. (2004) USA Case Series N=35	**Population:** TBI=22, ABI=6, Stroke=7; Mean Age=31 yr; Gender: Male=22, Female=13. **Intervention:** Oral baclofen regimen beginning at 5 mg 3x/day increased per protocol to 80	1. Mean dose was 57±26 mg/day for all patients and 55 ± 28 mg/day for patients with TBI.

Author/ Year/ Country/ Study Design/ N	Methods	Outcomes
	mg/day. Follow-up occurred between 1 and 3mo after initiation of oral baclofen. **Outcome Measure:** Ashworth Rigidity Scale (ARS), Spasm Frequency Scale (SFS), and deep tendon reflexes (DTR).	2. After treatment lower extremity ARS (3.5±1.1 to 3.2±1.2, p=0.0003) and DTR scores (2.5±0.9 to 2.2±1.2, p=0.0274) decreased significantly. 3. No significant changes in lower extremity spasm scores (p>0.05). 4. Patients with TBI saw a significant decrease in scores on the ARS (p=0.0044) and DTR (p=0.0003) but not on the SFS (p>0.05). 5. Upper extremities showed no significant changes for tone, spasm frequency, or reflexes (p>0.05).

Discussion

Oral Baclofen

Meythaler et al. (2004) completed a retrospective study evaluating the use of oral baclofen to manage spasticity in a mixed brain injury and stroke population. Pre and post testing revealed that oral baclofen improved spasticity in the lower extremity assessed using the Ashworth Rigidity Scale and Spasm Frequency Scale; however, no changes for tone, spasm frequency or reflexes were found for the upper extremity (Meythaler et al., 2004). The authors suggest that the lack of effect may be due in part to receptor specificity issues. Of note, a common adverse effect of the oral baclofen was the onset of considerable sleepiness in 17% of patients (Meythaler et al., 2004).

Oral Tizanidine

Meythaler et al. (2001) completed a randomized, double blinded placebo controlled cross over trial examining tizanidine for the management of spasticity. This study evaluated both stroke (53%) and TBI (47%) survivors. For both lower and upper extremity, there was a significant decrease in the Ashworth scores on the affected side with the active drug compared to placebo. However, significant differences between interventions were not found for upper and lower extremity spasm and reflex scores. Overall the authors felt that tizanidine was effective in decreasing the spastic hypertonia associated with ABI; however, a common side effect was increased somnolence (41%) Meythaler et al. (2001). Despite the study showing effectiveness, no level of evidence will be assigned for this drug due to more than 50% of the population being stroke.

Conclusions

There is level 4 evidence that oral baclofen may improve lower extremity spasticity but not upper extremity spasticity.

Oral baclofen appears to reduce lower extremity spastic hypertonia.

Oral baclofen may not improve tone, spasm frequency of reflexes in the upper extremity.

12.6.3 Botulinum Toxin Injections

Botulinum toxin type A (BTX-A) acts at pre-synaptic terminals to block acetylcholine released into the neuromuscular junction. When selectively injected into a specific muscle, BTX-A is thought to cause local muscle paralysis, thereby alleviating hypertonia caused by excessive neural activity (Jankovic & Brin, 1991). It has been suggested that BTX-A may be useful in the treatment of localized spasticity if oral treatments such as benzodiazepines, baclofen, dantrolene sodium, or tizanidine cause significant adverse effects (Gracies et al., 1997). The following sections review the use of botulinum toxin injections to remediate spasticity post-ABI in both the adult and paediatric population.

12.6.3.1 Botulinum Toxin Injections and the Adult Population

Table 12.23 Effects of Botulinum Toxin on Reducing Spasticity in Adults

Author/ Year/ Country/ Study Design/ N	Methods	Outcomes
Intiso et al. (2014) Italy Pre-Post N=22	**Population:** ABI=16, Cerebral Palsy=6; Mean Age=38.1 yr; Gender: Male=12, Female=10; *Brain Injury*: Mean Time Post Injury=3.8 yr. **Intervention:** Patients with severe spasticity of the upper and lower limbs received injections of incobotulinum toxin A (BoNT-A; up to 840 IU). **Outcome Measure:** Modified Ashworth Scale (MAS), Glasgow Outcome Scale (GOS), Frenchay Arm Test (FAT), Barthel Index (BI), Visual Analog Scale, and Visual Analogue Scale–Pain (VAS).	1. 17 patients had spastic hemiparesis and 5 had paraparesis. 2. A significant reduction in spasticity was seen at 4 and 16 wk post intervention, shown by a decrease in mean MAS scores in the elbow, wrist, finger and hand (all $p<0.05$) and ankle ($p<0.03$). 3. No significant improvements were seen on the GOS, BI, or FAT at 4 or 16 wk. 4. A significant reduction in pain was seen from baseline (7.6±1.1) to 4 (3.5±0.7) and 16wk (3.6±0.5) post intervention ($p<0.001$).
Clemenzi et al. (2012) Italy Pre-Post N=21	**Population:** TBI=11, ABI=10; Mean Age=42.2 yr; Gender: Male=16, Female=5; Median Time Post Injury=5 yr; Severity: Severe. **Intervention:** Repeated injections of Botulinum Toxin Type A (maximum dose 600U diluted in 50ml^{-1}) followed by rehabilitation program that consisted of hand and/or foot adhesive taping maintained for 7 days and checked daily. **Outcome Measure:** Barthel Index (BI), Modified Ashworth Score (MAS), and Visual Analogue Scale- pain (VAS).	1. Spasticity was in the lower limb in 33.3% of patients, upper limb in 9.5%, and both in 57.1%. 2. MAS lowered at the follow up, and improvement in spasticity was seen at the second and last injection (T3) time points compared to baseline ($p<0.0001$). 3. BI significantly improved at follow up (T3) in relation to initial scores ($p=0.0001$). 4. VAS score improved at the end of the second injection, a reduction in score was noted after each injection. 5. Greater improvement on BI was correlated to a shorter period between ABI onset and first injection ($p<0.0001$), the same effect was not discovered for MAS or VAS.the same effect was not discovered for MAS or VAS.
Mayer et al. (2008) USA RCT PEDro=6 N=31	**Population:** TBI=21, Stroke=8, Hypoxic encephalopathy=2; *Motor Point Group:* Mean Age=37.9 yr; Mean Time Post Injury=256.7 days. *Distributed Group:* Mean Age=34.7 yr; Mean Time Post Injury=481.9 yr.	1. The median decrease in Ashworth Scores after intervention was 1 point in both groups ($p=0.53$) and the Tardieu catch angle post intervention did not differ significantly between groups ($p=0.31$).

Author/ Year/ Country/ Study Design/ N	Methods	Outcomes
	Intervention: Patients with severe elbow flexor hypertonia received one of two interventions: the motor point injection technique (1 site biceps and 1 site brachioradialis), or the distributed quadrants technique (4 sites rectangularly configured – 2 biceps and 2 brachioradialis). Following two baseline measures, each elbow was randomized to receive injections of Botox. In total 90 units were given to patients in each group; however the sites and injection techniques varied between the groups. Mean follow up was 23.5±4.4 days. **Outcome Measure:** The Ashworth scale and Modified Tardieu Scale.	2. However, each group showed significant improvement from baseline ($p<0.001$) on all outcome measures. 3. For both groups a clinicophysiologic effect was observed at 3 wk post-intervention.
Fock et al. (2004) Australia Pre-Post N=7	**Population:** TBI; Mean Age=29.9 yr; Gender: Male=5, Female=2; Mean Time Post Injury=14 mo. **Intervention:** Subjects received botulinum toxin A (total of 300 U) into the lower extremities. Muscles targeted for injections included the gastrocnemius and soleus. The tibialis posterior was also injected in some subjects. **Outcome Measure:** Modified Ashworth Scale (MAS) scores, walking speed, cadence, stride length, peak ankle dorsiflexion angle during walking over a 10 m level track, and ankle range of motion.	1. 12 wk post-injection, there were significant improvements in walking speed, stride length, cadence, dorsiflexion on contact with the ground and passive dorsiflexion in supine position (all $p<0.03$). 2. None of these measures showed significant changes at 2 wk post-injection. 3. There were no significant changes in dorsiflexion at mid-stance, active dorsiflexion in supine position, and MAS scores at 2 or 12 wk post-injection. 4. At 12wk, chronic patients had a mean improvement in ankle dorsiflexion range of 19% (3.3°); those who had their injury sooner had a mean range improvement of 41% (7.4°).
Yablon et al. (1996) USA Case Series N=21	**Population:** TBI; Mean Age=28.2 yr; Gender: Male=12, Female=9; Mean Time Post Injury: Acute Group=142.7 days, Chronic Group=89.5 mo. **Intervention:** Subjects received Botulinum Toxin A injections (20-40 units per muscle) into the upper extremity. Targeted muscles included: the flexor carpi radialis, flexor carpi ulnaris, flexor digitorumprofundus, and flexor digitorumsuperficialis. Some patients also received injections into the biceps and brachialis due to coexisting spasticity in the elbow flexors. After injection, patients received therapeutic modalities as needed. Patients were grouped based on time between injury and injection: acute (<12 mo; n=9) or chronic (≥12 mo; n=12). **Outcome Measure:** Modified Ashworth Scale (MAS) and passive ROM at the wrist.	1. The acute group showed significant improvements in ROM (wrist extension improved by a mean of 42.9±24.7°, $p=0.001$) and spasticity severity (mean MAS improvement 1.5±0.5 points, $p=0.01$). 2. All patients in the acute group showed an improvement in spasticity and no patient worsened or remained unchanged. The chronic group showed significant improvements in ROM (wrist extension improved by a mean of 36.2±21.7°, $p<0.001$) and spasticity severity (mean MAS improvement 1.47±0.9 points, $p=0.002$).

PEDro=Physiotherapy Evidence Database rating scale score (Moseley et al., 2002).

Discussion

Five studies examining the effects of BTX-A on spasticity following ABI were identified. Intiso et al. (2014) showed a reduction in spasticity for the upper extremity (elbow, wrist, and hand), as well as ankle joints at one and four months post intervention. Although pain was also significantly reduced, no significant improvements in function were shown, measured by the Glasgow Outcome Scale and the Frenchay Arm Test (Intiso et al., 2014). These findings were similar to those found by Yablon et al. (1996) who reported that BTX-A injections into the upper extremities improved range of motion and spasticity in 21 patients with ABI. These improvements were shown for patients who received the injections within one year of injury and also for those greater than one year post (Yablon et al., 1996). The time between injury and injection was also studied by Clemenzi et al. (2012). The results were similar to the previous study for pain and spasticity; however, the time between onset and injection did have an effect on functional outcomes. Patients with a shorter period of time between their injury and first injection had greater improvements on the Barthel Index (Clemenzi et al., 2012).

For the lower extremity, Fock et al. (2004) reported that BTX-A injections improved measures of walking performance including walking speed, stride length, cadence, dorsiflexion on contact with the ground and passive dorsiflexion. In terms of the administration of BTX-A, Mayer et al. (2008) found that a single motor point injection and multisite distributed injection resulted in similar outcomes, with both groups showing a clinical effect at three weeks post-intervention.

Conclusions

There is level 2 evidence that botulinum toxin type A injections can be effective in the management of localized spasticity following ABI.

There is level 1b evidence to suggest that patients receiving botulinum toxin type A through a single motor point or through multisite distributed injections may both show a reduction in spasticity regardless of the drug administration method.

Botulinum toxin type A injections may reduce localized spasticity and improve range of motion following ABI.

Patients receiving botulinum toxin type A through a single motor point or through multisite distributed injections may both show a reduction in spasticity.

12.6.3.2 Botulinum Toxin Injections and the Paediatric Population

Table 12.24 Effectiveness of Botulinum Toxin Injections for Spasticity in Children post ABI

Author/ Year/ Country/ Study Design/ N	Methods	Outcome
Guettard et al. (2009) France Case Series N=25	**Population:** ABI: TBI=12, Stroke=6, Brain Tumour=5, Anoxia=2; Mean Age=9.3 yr, Gender: Male=14, Female=11; Mean Time Post Injury=3.0 yr. **Treatment:** Patients received botulinum toxin type A (BTX-A) to lower or upper limbs,	1. Following the injections, spasticity was significantly reduced on the AS from baseline to 4 wk ($p<0.0001$). 2. Quality of opening hand improvement significantly according to the ZS ($p<0.001$).

Author/ Year/ Country/ Study Design/ N	Methods	Outcome
	or both. Doses were given in accordance with the patient's age and muscle size and did not exceed 10 U/kg or 300 U. All participants received physical therapy, occupational therapy and auto-exercises. Assessments were taken at baseline, 4 wk post-injection and 3 mo follow-up. **Outcome Measure:** Ashworth scale (AS), Zancolli scale (ZS), Range of Motion (ROM).	3. Mean ROM (p=0.04) improved from pre-injection to 4 wk. 4. Overall, 68.6% of treatment sessions led to positive results, whereas 23.6% did not have as good as expected for functional outcomes.
Van Rhijn et al. (2005) Belgium PCT N=21	**Population:** TBI; Age Range=2.7-19.8yr; Gender: Male=15, Female=6. *Group 1 (n=4)*: Mean Time Post Injury=35.8 mo. *Group 2 (n=10):* Mean Time Post Injury=11.3 mo. *Group 3 (n=7):* Mean Time Post Injury=18.0mo. **Treatment:** Patients in Group 1 (spastic quadriparesis with impaired consciousness) received bilateral injections of botulinum toxin type A (BTX-A) to the hip adductors, knee and plantar flexors. Group 2 (patients with upper limb spasticity) received unilateral injections to the elbow, fingers, wrist flexors, and/or shoulder muscles. Group 3 patients with lower limb spasticity) received bilateral and unilateral injections to the plantar, knees, hip flexors, and/or hip adductors. Following the injections, all patients received a cast or an orthosis with Groups 2 and 3 receiving additional physiotherapy, ergotherapy and functional exercises. Assessments were conducted at baseline, and at 1, 3 and 5 mo follow-ups. **Outcome Measure:** Modified Ashworth Scale (MAS), range of motion (ROM) goniometry assessment.	1. All groups demonstrated improvements in spasticity on MAS from baseline to 1mo follow-up. 2. At 3mo follow-up, Group 1 demonstrated the greatest level of improvement in spasticity on MAS compared to baseline. Groups 2 and 3 also demonstrated improvements from baseline to 3mo follow-up. 3. At 5 mo follow-up, Group 2 continued to demonstrate improvements in spasticity on MAS compared to baseline. Groups 1 and 3 also exhibited improvements compared to baseline, but improvements had declined in comparison to 3mo follow-up. 4. Group 2 exhibited the greatest level of improvement in ROM with mean increases of 23°, 36° and 53° at 1 mo, 3 mo and 5 mo follow-ups compared to baseline. 5. ROM in Group 3 improved by a mean of 4° from baseline to 1 mo follow-up but then experienced a -6° decline at 3 mo follow-up and a -3° decline at 5 mo follow-up compared to baseline ROM. 6. Group 1 exhibited moderate improvements in ROM with mean increases of 5°, 7° and 2° at 1 mo, 3 mo and 5 mo follow-ups compared to baseline.

PEDro=Physiotherapy Evidence Database rating scale score (Moseley et al., 2002).

Discussion

Two studies evaluated the effectiveness of botulinum toxin type A (BTX-A) for the management of spasticity in children with an ABI. Overall, BTX-A improved spasticity and range of motion in children and adolescents that sustained an ABI (Guettard et al., 2009; van Rhijn et al., 2005). When BTX-A for both upper and lower extremities was paired with other therapies (physical, occupational and exercise therapy) there was also an improvement in voluntary motor control, in addition to the improvements seen in spasticity and range of motion. However, due to the lack of comparison group, conclusive statements cannot be made; it is difficult to determine if the effects were due to the combination of therapy, BTX-A alone, or the standard therapy. Future research should differentiate these groups to compare effectiveness (Guettard et al., 2009). Importantly, BTX-A treatment did not cause any adverse side effects for injection doses under 10 U/kg of botulinum toxin (Guettard et al., 2009; van Rhijn et al., 2005). Intra-muscular BTX-A injections may be considered an effective treatment for severely brain-

injured children, especially in combination with orthotic devices and specific functional exercise programs. A review of the literature on botulinum toxin suggests that injections are effective for lower limb functional improvements, however future research is needed to determine the effects for the upper limb (Gordon & di Maggio, 2012).

Conclusions

There is level 2 evidence that botulinum toxin type A may be an effective treatment for children and adolescents with upper and lower limb spasticity.

Botulinum toxin type A may effectively improve both upper and lower limb spasticity in children and adolescents following brain injury.

12.6.4 Intrathecal Baclofen

A limitation of oral baclofen is the inability to achieve sufficient concentrations in the cerebrospinal fluid in order to modify spasticity without first causing significant sedation (Gracies et al., 1997). Intrathecal baclofen refers to direct administration of baclofen into the intrathecal space and cerebrospinal fluid at the lumbar level. For therapeutic treatment, a subcutaneously placed pump is required to provide continuous administration of the medication into the intrathecal space. This treatment procedure is more invasive and is associated with complications including infection, pump failure and tube complications such as kinking or disconnection (Gracies et al., 1997). The following sections review the current evidence for the use of intrathecal baclofen post-ABI in both the adult and paediatric population.

12.6.4.1 Intrathecal Baclofen and the Adult Population

Table 12.25 Effects of Intrathecal Baclofen in Modifying Spasticity

Author/ Year/ Country/ Study Design/ N	Methods	Outcomes
Wang et al. (2016) Singapore Case Series $N_{Initial}$=6, N_{Final}=5	**Population:** TBI=5, Encephalopathy=1; Mean Age=31.6 yr; Gender: Male=3, Female=2; Mean Time Post Injury=39.4 mo. **Intervention:** A retrospective review of patients that were recruited to undergo surgical implantation of an intrathecal baclofen (ITB) pump. After implantation patients received daily physical therapy. Upon discharge patients continued to receive regular outpatient rehabilitation therapies for 3 mo, ITB pump refills and monitoring by the neurosurgical team for 3-4 mo. Outpatient follow-up was 3-6mo. **Outcome Measure:** Modified Ashworth Scale (MAS).	1. The mean reduction in MAS was 1.2 (SD 1.1; p<0.05) a 3 months and 1.0 (SD 1.2; p=0.06) at the last follow-up. All patients but 1 (no change) had significant reductions in spasticity.
Chow et al. (2015) Canada	**Population:** TBI=11, Stroke=8; Mean Age=34.2 yr; Gender: Male=9, Female=10; Mean Time Post Injury=48.7 mo. **Intervention:** All patients underwent a 50 µg	1. There was no significant difference in gait speed, stride length, cadence, or stance duration across evaluation points.

Author/ Year/ Country/ Study Design/ N	Methods	Outcomes
Pre-Post N=19	intrathecal baclofen (ITB) bolus injection via lumbar puncture. Patients were evaluated at baseline, 2 hr, 4 hr, and 6 hr post injection. **Outcome Measure:** Gait speed, stride length, cadence, stance duration, ankle range of motion (ROM)-stance & swing, peak medial gastrocnemius (MG) lengthening velocity, average Ashworth Score, plantar flexors Ashworth Score, electromyography-lengthening velocity (EMG-LV), Coactivation Duration (CoD), and Coactivation Index (CI).	2. Ankle ROM in the more-affected leg during stance phase was significantly increased from baseline to 6hr (p=0.009); however, was not significantly different during swing phase. 3. Peak MG lengthening velocity significantly increased from baseline to 4hr in the less-affected leg (p=0.005) and to 6hr in both legs (p≤0.01). 4. Average Ashworth Score and plantar flexors Ashworth scores were significantly different across all time posts in the more-affected leg only (p<0.001). 5. Compared with baseline, both frequency (p=0.02) and average gain (p=0.007) of EMG-LV were significantly lower at 2hr post but did not reach the significance at 4hr and 6hr post (p≤0.040). 6. Slope parameters of EMG-LV in the less-affected leg did not change over time (p≥0.129). 7. CoD significantly decreased over time in the more affected leg during all phases of gait (p≤0.013); and CoI did not significantly change over time in either leg (p>0.107).
Margetis et al. (2014) Greece Pre-Post N=8	**Population:** TBI=6, Hydrocephalus=1, Cardiac Arrest=1; Mean Age=31.5 yr; Gender: Male=8, Female=0; Mean Time Post Injury=37.25 mo. **Intervention:** Patients who were resistant to oral spasticity treatments received an implanted intrathecal baclofen pump. Mean follow-up period was 38.4 mo. **Outcome Measure:** Modified Ashworth Scale.	1. All patients showed improvement in their spasticity scores; mean Modified Ashworth Scale scores were 3.375 pre- and 1.125 post-intervention.
Posteraro et al. (2013) Italy Pre-Post N=12	**Population:** TBI=8, Hemorrhage=2, Anoxia=2; Mean Age=36 yr; Gender: Male=9, Female=3; Time Post Injury Range=31-150 days. **Intervention:** Patients not experiencing reductions in spasticity following initial interventions with oral baclofen received intrathecal baclofen (ITB). The initial dosage was 50 or 100 mcg depending on the severity of the impairment and was increased by 10% every 3 days until the maximum dosage of 800mcg was achieved. Assessments occurred before the implant, and at 3 mo and 12 mo follow-ups. **Outcome Measure:** Modified Ashworth Scale (MAS), Spasm Frequency Scale (SFS), Disability Rating Scale (DRS), and Level of Cognitive Functioning (LCF).	1. Mean ITB dose for participants was 380mcg. 2. 6 patients received ITB within 3mo of injury (early); 6 patients received ITB between 3 and 6 mo post injury (late). 3. At 3 mo, both spasticity and spasms significantly decreased compared to the baseline, based on MAS and SFS scores (p<0.001 and p<0.002, respectively). 4. At 3 mo, improvements in DRS and LCF were seen (p<0.001 and p=0.002, respectively). 5. At 12 mo (n=5) all patients demonstrated further improvements in spasticity and spasms, but this was non-significant compared to results at 3 mo. 6. There were no differences in global outcomes (DRS and LCF) between

Author/ Year/ Country/ Study Design/ N	Methods	Outcomes
		patients in early ITB initiation group and those in late ITB initiation group.
Hoarau et al. (2012a) France Post-Test N=43	**Population:** TBI; Mean Age=23.3 yr; Gender: Male=33, Female=10; Mean GCS score=4.6. **Treatment:** After initial injury, participants who were started on Intrathecal Baclofen Therapy (IBT) to treat dysautonomia and hypertonia were included for evaluation of long-term outcomes (mean 10±0.6 yr post implantation). **Outcome measure:** Coma Recovery Scale-Revised (CRS-R), Modified Ashworth Scale (MAS), Barthel Index (BI).	1. At follow-up, 9 participants had died, 13 were severely disabled or in an unresponsive wakefulness syndrome and 21 had a good recovery of consciousness. 2. Mean CRS-R score was 18.9 (Range 1-23), mean BI score was 50.1 (Range 0-100), 34.9% were living at home, and mean MAS for upper limb was 1.6 (Range 0-4). 3. Most of the participants who had a positive recovery received IBT later than the other participants. 4. Complications occurred in 62.8% of patients; the most common being operative site infections (20.9%) and overdoses with profound flaccidity, sedation and vomiting (16.3%).
Horn et al. (2010) USA Pre-Post N=28	**Population:** TBI=12, Hypoxic Encephalopathy=3, Stroke=13; Mean Age=35 yr; Gender: Male=12, Female=16; Mean Time Post Injury=45 mo. **Intervention:** The subjects received a 50 µg bolus of baclofen injected into the lumbar intrathecal space. **Outcome Measure:** Ashworth Scale and a video-based motion analysis program.	1. The range of motion (ROM) increased in the ankle on both the more involved side (13±6 versus 15±7, p=0.008) and the less involved side (22±8 versus 24±8, p=0.031) from baseline to post-injection. 2. ROM improvement occurred most often at 4 and 6 hr after injection (p<0.05). 3. There was a significant correlation between the magnitude of change in ROM at the time of peak response and the magnitude of gait speed change (r=0.1, p<0.001). 4. Significant reductions in Ashworth scores compared to baseline (2.0±0.5) at 2 hr (1.6±0.4), 4 hr (1.4±0.4) and 6 hr (1.3±0.3) post-injection (all p<0.001).
Francisco et al. (2005) USA Case Series N=14	**Population:** Anoxic Encephalopathy=6, TBI=5, Stroke=3; Mean Age=35.9 yr; Gender: Male=6, Female=8. **Intervention:** Patients were surgically fitted with an infusion pump for continuous intrathecal baclofen delivery. This took place a mean of 5.62 mo (range 2-12 mo) post injury. Follow up occurred at a mean of 13.9 mo post pump implantation. **Outcome Measure:** Modified Ashworth Scale (MAS) and Disability Rating Scale (DRS).	1. Participants received a mean daily intrathecal baclofen dose of 591.5 µg (93-2000.2 µg). 2. From baseline to follow-up, the mean decrease in MAS scores for upper extremities was 1±1.4 (p<0.02) and lower extremities was 2.1±1.4 (p<0.001). 3. The changes in DRS scores were not significant.
Horn et al. (2005) USA Pre-Post N=28	**Population:** TBI=12, Stroke=13, Hypoxic Encephalopathy=3; Mean Age=35 yr; Gender: Male=12, Female=16; Mean Time Post Injury=45 mo. **Intervention:** Subjects received a single 50 µg	1. Mean change in hip and knee range of motion (ROM) during gait was less than ±2° after injection. 2. ROM in ankles increased from baseline to post-injection on both the more

Author/ Year/ Country/ Study Design/ N	Methods	Outcomes
	intrathecal baclofen bolus injection via lumbar puncture. **Outcome Measure:** Walking Performance and Ashworth scores.	involved (13° versus 15°, p<0.01) and less involved side (22° versus 24°, p<0.05). 3. For all joints (n=168), ROM significantly improved in 42%, significantly worsened in 34%, and did not change in 24%. 4. Significant reductions in Ashworth scores compared to baseline (2.0±0.5) at 2 hr (1.6±0.4), 4hr (1.4±0.4) and 6hr (1.3±0.3) post-injection (all p<0.001).
Stokic et al. (2005) USA Case Series N=30	**Population:** TBI=17, Anoxic=4, Stroke=9; Mean Age=31 yr; Gender: Male=17, Female=13; Mean Time Post Injury=3 yr. **Intervention:** Participants received a single 50 µg intrathecal baclofen bolus injection via a lumbar puncture. **Outcome Measure:** Ashworth Scale, H-Reflex from soleus muscle and F waves from abductor hallucis in supine position.	1. Ashworth score on the more involved side significantly decreased between baseline (2.4±0.7) and 4 (1.5±0.6) and 6hr (1.4±0.6) post-injection (p<0.001). 2. Maximal individual change in Ashworth scores ranged from 0 to 2.6 points (mean 1.0±0.7). 3. H/M ratio significantly decreased bilaterally (p<0.001). 4. F-wave persistence significantly decreased on the more involved side (p<0.05) with no change in F/M ratio.
Dario et al. (2002) Italy Pre-Post N=14	**Population:** TBI=6, Anoxic ABI=8; Mean Age=38.8 yr; Gender: Male=10, Female=4; Mean Time Post Injury=36.7 mo. **Intervention:** Patients received continuous intrathecal baclofen infusions through the implantation of a subcutaneous pump. Mean length of spasticity was 36.7 mo post injury. **Outcome Measure:** Ashworth Scale (AS) and Spasm Frequency Scale (SFS).	1. Between pre-operative to last follow up, there was a significant decrease in AS scores in both lower (4.3±0.5 versus 2.7±0.7) and upper (4.1±0.8 versus 2.3±0.9) extremities (both p<0.05). 2. Significant reduction in SFS scores was found between preoperative and postoperative values (2.5±0.5 versus 0.4±0.6, p<0.001). 3. Mean daily dose of baclofen was 305 µg (range 90-510 µg).
Francois et al. (2001) France Case Series N=4	**Population:** TBI; Mean Age=19.5 yr; Gender: Male=1, Female=2, Unknown=1; Mean GCS=3.5. **Intervention:** Intrathecal baclofen infusion. The intervention was started within 1 mo following injury onset. **Outcome Measure:** Ashworth scores, and frequency and intensity of autonomic disorders.	1. Reductions in spasticity, and lower limb Ashworth scores at 6 mo post intervention were reported in three of the four cases. In the last case, a substantial reduction in autonomic disorders and spasticity enabling passive physiotherapy was reported.
Meythaler et al. (1999) USA Pre-Post N=17	**Population:** ABI; Mean Age=29 yr; Gender: Male=14, Female=3. **Intervention:** Patients with spasticity and/ or dystonia were surgically fitted with an infusion pump into the lower abdominal wall for continuous administration of continuous intrathecal baclofen (100 µg/d). Patients assessed at 1 yr. **Outcome Measure:** Ashworth Rigidity Scale (ARS), Spasm Frequency Scale and Deep Tendon Reflex Score.	1. 1 year of intrathecal baclofen treatment (average dose: 302 ug/day) resulted in a decrease in scores on the ARS (mean 2.2 points), spasm frequency (mean 1.6 points), and reflex scores (mean 2.4 points) for the lower extremity (all p<0.0001) 2. For upper extremity the ARS, spasm frequency, and reflex scores decreased by a mean of 1.4, 1.0, and 1.2 points respectively (all p<0.0001). 3. No cognitive side effects observed after 1 yr.

Author/ Year/ Country/ Study Design/ N	Methods	Outcomes
Meythaler et al. (1999) USA Pre-Post N=6	**Population:** TBI=3, Stroke=3; Mean Age=50 yr; Gender: Male=2, Female=4. **Intervention:** Surgically fitted with a programmable infusion pump into the lower abdominal wall for continuous administration of baclofen using the same methodology as Meythaler et al. (1997). **Outcome Measure:** Ashworth Rigidity Scale, Spasm Frequency Scale and Deep Tendon Reflex scores.	1. Lower extremities showed a significant reduction in Ashworth scores (p<0.0001); affected lower limb reflex score (p=0.0208); normal side (p=0.0051), but not significant changes in affected lower limb spasm score (p=0.5). 2. Upper extremities showed significant reductions in Ashworth scores on affected side (p=0.0002) but were not significant for Biceps Reflex score (affected and normal: p=0.1088 and p=0.0679), or spasm score (affected: p=0.1797). 3. No patient complained of subjective weakness on the normal side.
Meythaler et al. (1997) USA Pre-Post N=12	**Population:** TBI=9, ABI=3; Mean Age=28 yr; Gender: Male=11, Female=1. **Intervention:** Continuous intrathecal baclofen delivery for 3 mo via an implanted infusion pump-catheter system. **Outcome Measure:** Ashworth Rigidity Scale, Spasm Frequency Score and Deep Tendon Reflex Score.	1. For lower extremity, Ashworth Scale Scores decreased by a mean of 1.4 points, spasm frequency by 1.5, and reflex scores by 2.5 (all p<0.0001). 2. For upper extremity, the mean decrease in scores was 1.4 points for the Ashworth Scale (p=0.0033), 1.2 for spasm frequency (p=0.007) and 1.0 for reflex (p=0.0111).
Becker et al. (1997) Germany Case Series N=18	**Population:** TBI=9, Hypoxic Brain Injury=9; Mean Age=41yr; Gender: Male=13, Female=6; Mean Time Post Injury=11.6 mo. **Intervention:** Continuous intrathecal baclofen infusion. **Outcome Measure:** Ashworth Scale and Spasm Frequency Scale.	1. In all patients spasticity was reduced. 2. Mean Ashworth scores reduced from 4.5 to 2.33 and the mean Spasm Frequency scores from 2.16 to 0.94. 3. Reduction in spasticity led to a reduction in pain.
Meythaler et al. (1996) USA RCT PEDro=7 N=11	**Population:** TBI=10, Anoxia=1; Mean Age=25yr; Gender: Male=9, Female=2. **Intervention:** Patients with chronic spastic hypertonia received either a bolus injection of intrathecal baclofen (50 µg) or placebo (normal saline), then crossed-over (minimum 48 hr later). Assessment at 1, 2, 4, and 6 hr post injection. **Outcome Measure:** Ashworth Scale (AS), Spasm Score, and deep tendon reflexes.	1. For lower extremity, after baclofen AS scores decreased by a mean of 2points (p=0.0033), Spasm scores by 2.1 points (p=0.0032), and reflex scores by 2.3 points (p=0.0032) at 4 hr. 2. For upper extremity, after baclofen AS scores decreased by a mean of 1.4points (p=0.0033), Spasm scores by 1.2 (p=0.0070), and reflex scores by 1.0 (p=0.0111) at 4 hr. 3. No significant differences were shown for placebo. Between group differences were significant for all measures for both lower and upper extremity (p≤0.0272).

PEDro=Physiotherapy Evidence Database rating scale score (Moseley et al., 2002).

Discussion

Meythaler et al. (1996) confirmed the effectiveness of intrathecal baclofen in decreasing upper and lower extremity spasticity in a randomized, double blinded, placebo controlled cross-over trial. In subsequent studies, the same investigators went on to demonstrate the effectiveness of intrathecal baclofen for decreasing spasticity for up to three months (Meythaler et al., 1997) and 1 year (J. M.

Meythaler et al., 1999). Investigations carried out by other research groups have reported similar findings regarding the efficacy of intrathecal baclofen for the management of spasticity post-ABI (Becker et al., 1997; Chow et al., 2015; Dario et al., 2002; Francisco et al., 2005; Hoarau et al., 2012b; Margetis et al., 2014; Posteraro et al., 2013; Stokic et al., 2005; Wang et al., 2016). However, a common limitation of these studies is the lack of a control group. Regardless, it appears that intrathecal baclofen is an effective treatment for spasticity; however, some adverse effects such as urinary hesitancy were reported. Hoarau et al. (2012a) conducted a 10-year follow up of individuals with dysautonomia and hypertonia treated with intrathecal baclofen therapy. The study found that 62.8% of participants had some type of complication; infections at the operative site was the most frequent complication (20.9%), followed by overdosed with profound flaccidity, sedation, and vomiting (16.3%) (Hoarau et al., 2012a).

Studies have also evaluated the functional consequences by assessing walking performance, gait speed and range of motion following a bolus injection of intrathecal baclofen (Chow et al., 2015; Horn et al., 2010; Horn et al., 2005). Horn et al. (2005) and Horn et al. (2010) found that although the injections produced changes in joint range of motion during gait, only ankles showed a significant result. Chow et al. (2015) similarly found an increase in ankle range of motion but found no significant differences in terms of gait speed, stride length, cadence or stance. Future studies should be conducted using a prospective controlled trial or RCT study design that includes control groups to further establish the efficacy of intrathecal baclofen for the management of spasticity post ABI.

Conclusions

There is level 1b evidence that bolus intrathecal baclofen injections may produce short-term (up to six hours) reductions in upper and lower extremity spasticity following ABI.

There is level 4 evidence to suggest that prolonged intrathecal baclofen may result in longer-term (three months, and one year) reductions in spasticity in both the upper and lower extremities following an ABI.

There is level 4 evidence, from two studies, to suggest that intrathecal baclofen can result in short-term improvements of walking performance in ambulatory patients, particularly gait velocity, stride length, and step width.

Bolus injections of intrathecal baclofen may produce short-term reductions in upper and lower extremity spasticity post ABI.

Prolonged intrathecal baclofen may reduce upper and lower extremity spasticity post ABI.

Intrathecal baclofen may cause short-term improvements in walking performance in ambulatory patients post ABI.

12.6.4.2 Intrathecal Baclofen and the Paediatric Population

Table 12.26 Effectiveness of Intrathecal Baclofen for Spasticity in Children post ABI

Author/ Year/ Country/ Study Design/ N	Methods	Outcome
Walter et al. (2015) Switzerland Case Series N=3	**Population:** ABI: Hypoxia=3; Mean Age=4.0 yr; Gender: Male=2, Female=1; Mean Time Post Injury=64.3 days. **Treatment:** Patients received intrathecal baclofen pump implants and were monitored for a mean of 2315 day (approximately 6.3 yr). Dosage increased from 117 mcg at baseline to 660mcg at the study end. Assessments were conducted at baseline and annually for at least 5 yr. **Outcome Measure:** Modified Ashworth Scale (MAS), complication rate.	1. Spasticity on MAS decreased from baseline to post-treatment in the upper and lower extremities. 2. Five occurrences of pump-related complications were observed including two cases of skin protrusion, one case of infection, one case of lumbar cerebrospinal fluid leak, and one case of intractable spasticity requiring a pump replacement.

PEDro=Physiotherapy Evidence Database rating scale score (Moseley et al., 2002).

Discussion

An intrathecal baclofen injection pump improved spasticity in three young children (Walter et al., 2015). However, unlike botulinum toxin, baclofen side effects were more common. Two of the three patients had complications and five of the complications were related to the device. Two of these complications were due to skin protrusions. The pumps must be implanted in the skin and one child experienced problems with epifascial implantation. However these effects were minimized with subfascial implantation, which has become the sole technique for intrathecal baclofen pump implantations for children (Walter et al., 2015). Other complications were due to wound infection, cerebrospinal fluid leakage, and intractable spasticity. All complications were reversed with treatment or relocation of the pump.

Conclusions

There is level 4 evidence that intrathecal baclofen pumps may be effective at reducing spasticity in the upper and lower limbs for children with hypoxia.

Intrathecal baclofen pumps may reduce upper and lower limb spasticity in children with hypoxia.

12.7 Barbiturates

Barbiturates have long been proposed as a useful intervention in the control of ICP. They are thought to reduce ICP by suppressing cerebral metabolism and reducing metabolic demands and cerebral blood volume (Roberts, 2000). Early reports indicated that barbiturates reduced ICP in patients reported to be unresponsive to rigorous treatments with conventional ICP management techniques, including mannitol and hyperventilation (Marshall et al., 1979; Rea & Rockswold, 1983; Rockoff et al., 1979). However, most of these early investigations provided only anecdotal or poor evidence, as they were conducted in very small cohorts of patients lacking control comparisons. Later studies explored the negative side effects associated with barbiturate coma, such as adrenal insufficiency (Llompart-Pou et al., 2007) and bone marrow suppression (Stover & Stocker, 1998).

The AANS made Level II B recommendations that high-dose barbiturates can be used to control elevated ICP that is refractory to maximum standard medical and surgical treatment (Carney et al., 2017). They also reported Level II evidence against the use of prophylactic barbiturates for inducing electroencephalogram burst suppression. The EBIC guidelines recommended barbiturate use to increase sedation only after previous sedation, analgesia, hyperventilation, osmotic therapy, and cerebrospinal fluid drainage have failed to control ICP (Maas et al., 1997).

Table 12.27 Barbiturates for the Acute Management of ABI

Author/ Year/ Country/ Study Design/ N	Methods	Outcome
Thiopental		
Stover et al. (1998) Germany Case Control N=52	**Population:** TBI. *Thiopental (n=23)*: Mean Age=27 yr; Severity: Severe. *Control (n=29)*: Mean Age=44 yr; Severity: Severe. **Intervention:** Patients were included in retrospective analysis. Some received intravenous thiopental (at 5-11 mg/kg as a bolus, followed by continuous infusion of 4-6 mg/kg/hr and 4-6 bursts/min). Others received sedation with fentanyl and midazolam. **Outcome Measure:** Hematological Outcomes.	1. Patients requiring barbiturates were significantly younger than those not requiring it (27 yr versus 44yr, p<0.01). 2. Barbiturates were shown to induce reversible leukopenia and granulocytopenia as well as an increased infection rate. 3. Several patients showed suppressed bone marrow production on histological examination.
Schalen et al. (1992) Sweden Case Series N=38	**Population:** TBI; Median Age=20 yr; Gender: Male=30, Female=8. **Intervention:** Patients received high-dose intravenous thiopental at 5-11 mg/kg, followed by a continuous infusion at 4-8 mg/kg/hr for at least 12 hr. **Outcome Measure:** Intracranial Pressure (ICP), Mean Arterial Pressure (MAP), Cerebral Perfusion Pressure (CPP).	1. There was a decrease in MAP in 31 patients, a small increase in 3, and no change in 4. 2. There was a decrease in ICP in 26 patients, a small increase in 2, and no change in 3. 3. There was a decrease in CPP in 18 patients, an increase in 10, and no change in 3. 4. Though the fall in ICP immediately following infusion of thiopentone reduced the number of patients with decreased CPP (≤60mmHg), continued treatment led to a fall in MABP, ultimately contributing to the decrease in CPP.
Nordby & Nesbakken (1984) Norway PCT N=38	**Population:** TBI. *Thiopental (n=16)*: Mean Age=20yr; Mean GCS Score=4.3. *Control (n=15)*: Mean Age=26yr; Mean GCS=5.2. **Intervention:** Patients received continuous intravenous thiopental: a loading infusion of 10-20mg/kg and a maintenance infusion of 3-5mg/kg/hr. Mild hypothermia (32-35ºC) was maintained as soon as barbiturate loading was achieved. Controls consisted of patients not requiring barbiturate infusion. **Outcome Measure:** Glasgow Outcome Scale (GOS).	1. Better GOS outcomes at 9-12 mo were noted for the thiopental group compared with the control group (p=0.03). 2. Thiopental resulted in 6 patients with good/moderate outcomes, 3 with severe outcomes, and 7 with dead/vegetative outcomes. 3. In contrast, conventional therapy resulted in 2 patients with good/moderate outcomes, and 13 with dead/vegetative outcomes.
Pentobarbital		
Fried et al. (1989) USA PCT N=7	**Population:** TBI; Mean Age=31 yr; Gender: Male=4, Female=3; Time Post Injury≤1 wk; Mean GCS=4.7. **Intervention:** Patients unresponsive to	1. Patients treated with pentobarbital had significantly lower energy expenditure (p<0.01), lower urinary total nitrogen

Author/ Year/ Country/ Study Design/ N	Methods	Outcome
	conventional therapy received pentobarbital administered as a bolus followed by a continuous infusion to achieve serum concentrations of 20-40 mg/L (n=4). Patients responsive to conventional therapy formed the control group (n=7). **Outcome Measure:** Energy Expenditure, Urinary Nitrogen Excretion, Nitrogen Balance, Urinary 3-Methylhistidine Excretion.	excretion ($p<0.01$), and improved nitrogen balance ($p<0.05$) than the control group. 2. There was no significant difference in urinary 3-methylhistidine excretion between groups.
Eisenberg et al. (1988) USA RCT PEDro=4 N=73	**Population:** TBI. *Pentobarbital (n=37)*: Mean Age=25.3 yr; Gender: Male=29, Female=8; Mean Time Post Injury=83.3 hr; GCS Range=4-7. *Conventional Therapy (n=36):* Mean Age=24.3 yr; Gender: Male=33, Female=3; Mean Time Post Injury=89.0 hr; GCS Range=4-7. **Intervention:** Patients were randomized to receive pentobarbital in addition to ongoing conventional therapy; or continuing with conventional therapy alone. Pentobarbital was administered at an initial bolus of 10 mg/kg over 30 min, infusion of 5 mg/kg/hr for 3 hr, and a maintenance dose at 1 mg/kg. **Outcome Measure:** Intracranial Pressure (ICP), Glasgow Outcome Scale (GOS), Survival.	1. Patients receiving barbiturates were nearly twice as likely to achieve adequate ICP control as those receiving only conventional therapy (OR=1.94, p=0.12). 2. The advantage of barbiturate therapy in those without prior cardiovascular complications was over 4-fold (OR=4.40). 3. After declaration of treatment failure (ICP>20 mmHg), 26 of the patients randomized to conventional therapy were crossed over to receive barbiturates. 4. The likelihood of survival at 1mo was 92% for those who responded to barbiturates while 83% of the non-responders died. 5. At 6mo follow-up, 36% of the responders and 90% of the non-responders were vegetative or had died.
Ward et al. (1985) USA RCT PEDro=6 N=53	**Population:** TBI. *Pentobarbital (n=27)*: Mean Age=31.1 yr; Gender: Male=25, Female=2; Mean GCS=5.1. *Conventional Therapy (n=26)*: Mean Age=35.1 yr; Gender: Male=21, Female=5; Mean GCS=4.9. **Intervention:** Patients were randomized to receive pentobarbital or conventional therapy. Barbiturates were administered an initial bolus of 5-10 mg/kg, an hr bolus and continuous infusion for at least 72 hr, and a maintenance dose of 1-3 mg/kg. **Outcome Measure:** Intracranial Pressure (ICP), Glasgow Outcome Scale (GOS), Mortality.	1. During the first 4 days, there was no significant difference in hr levels of ICP or mortality. 2. Clinical outcomes on the GOS and mortality did not differ between groups at 1 yr.
Schwartz et al. (1984) Canada RCT PEDro=5 N=59	**Population:** TBI; Gender: Male=47, Female=12. *Evacuated Hematoma (n=29): Pentobarbital (n=15):* Mean Age=32.8 yr; Mean GCS=5.1; *Mannitol (n=14):* Mean Age=35.7 yr; Mean GCS=4.9. *No Hematoma (n=30): Pentobarbital (n=13):* Mean Age=24.9 yr; Mean GCS=4.2; *Mannitol (n=17):* Mean Age=24.4 yr; Mean GCS=4.4. **Intervention:** Patients were randomized to receive either 20% mannitol (1 gm/kg) or pentobarbital (initial bolus of 10 mg/kg, then continuous infusion at 0.5-3 mg/kg/hr). The other drug was initiated on top of initial treatment if ICP	1. For patients with evacuated hematomas, no significant difference was observed in mortality at 3 mo between pentobarbital and mannitol groups (40% versus 43%). 2. Nearly twice as many patients in the pentobarbital group required the other regimen (mannitol) to control raised ICP compared to those in the mannitol group ($p=0.04$). 3. For patients without evacuated hematoma, significantly higher proportion of patients treated with pentobarbital died compared to

Author/ Year/ Country/ Study Design/ N	Methods	Outcome
	proved refractory to maximal doses. **Outcome Measure:** Intracranial Pressure (ICP), Mortality.	those treated with mannitol initially (77% versus 41%, p=0.03). 4. In these patients, there was a higher rate of failure to control ICP in the pentobarbital group than in the mannitol group (p<0.001).
Multiple		
Perez-Barcena et al. (2008) Spain RCT PEDro=4 N=44	**Population:** TBI. *Thiopental (n=22):* Median Age=26 yr; Gender: Male=19, Female=3; Median GCS=6.5. *Pentobarbital (n=22):* Median Age=32 yr; Gender: Male=19, Female=3; Median GCS=7. **Intervention:** Participants were randomized to receive thiopental or pentobarbital. Thiopental was delivered in an initial bolus of 2 mg/kg over 20 sec, a second bolus of 3-5 mg/kg was administered if ICP>20 mmHg, followed by continuous infusion of 3 mg/kg/hr once ICP<20mmHg. Pentobarbital was delivered in an initial dose of 1 0mg/kg for 30min, followed by continuous infusion of 5 mg/kg/hr for 3 hr, and then a dose of 1 mg/kg/hr for the last hr. **Outcome Measure:** Intracranial Pressure (ICP).	1. Uncontrolled ICP was significantly lower with thiopental than pentobarbital (50% versus 82%, p=0.03). 2. Thiopental was more effective than pentobarbital for controlling ICP (OR=5.1, p=0.027). 3. Relative risk for good control of ICP between thiopental and pentobarbital was 2.26 in patients with focal lesions and 3.52 in patients with diffuse lesions.
Llompart-Pou (2007) Spain Case Control N=40	**Population:** TBI; *Barbiturates (n=17)*: Mean Age=35yr; Gender: Male=16, Female=1; Mean GCS Score=7. *Control (n=23)*: Mean Age=27 yr; Gender: Male=20, Female=3; Mean GCS=7. **Intervention:** Patients were included in retrospective analysis. Those with elevated intracranial pressure (ICP) refractory to first tier measures received thiopental (n=10) or pentobarbital (n=7). The remaining patients showed controlled ICP in response to first tier measures. **Outcome Measure:** Adrenal function.	1. Within 24hr, adrenal function was similar in both groups. 2. After treatment with barbiturates, patients demonstrated higher adrenal insufficiency compared to those without (53% versus 22%, p=0.03). 3. 94% of patients treated with barbiturates received norepinephrine (NE), while only 39% of those without received NE (p<0.001). 4. Those treated with barbiturates had higher NE doses than those without (1.07 µg/kg/min versus 0.31 µg/kg/min, p=0.03). 5. There was a trend toward a higher incidence of adrenal insufficiency among patients treated with pentobarbital than those treated with thiopental (71% versus 40%, p=0.20).
Perez-Barcena et al. (2005) Spain RCT PEDro=5 N=20	**Population:** TBI; Mean Age=33 yr; Gender: Male=16, Female=4; GCS≤8. **Intervention:** Participants were randomized to receive thiopental (n=10) or pentobarbital (n=10). Thiopental was delivered in an initial bolus of 2 mg/kg over 20s, a second bolus of 3-5 mg/kg was administered if ICP>20 mmHg, followed by continuous infusion of 3 mg/kg/hr once ICP<20 mmHg. Pentobarbital was delivered in an initial dose of 10 mg/kg for 30 min, followed by continuous infusion of 5 mg/kg/hr for 3 hr, and then a dose of 1 mg/kg/hr for the last hr. Outcomes were assessed at discharge and 6mo.	1. Thiopental was able to control ICP in 50% of patients while pentobarbital was only able to control ICP in 20% (p=0.16). 2. 50% of patients in the thiopental group died at discharge while 80% died in the pentobarbital group (p=0.16).

Author/ Year/ Country/ Study Design/ N	Methods	Outcome
	Outcome Measure: Intracranial Pressure (ICP), Mortality.	
Unspecified Barbiturates		
Majdan et al. (2013) Slovakia Case Control N=1172	**Population:** TBI. *High Barbiturate Group (n=71)*: Median Age=36 yr; Gender: Male=51, Female=20; Median GCS=6. *Low Barbiturate Group (n=140)*: Median Age=41 yr; Gender: Male=113, Female=27. *No Barbiturate Group (n=961)*: Median Age=45; Gender: Male=737, Female=224. **Intervention:** Participants were categorized into high barbiturate (≥2 g/day), low barbiturate (<2 g/day), or no barbiturate groups for retrospective analysis. **Outcome Measures:** Intracranial Pressure (ICP), Mean Arterial Pressure (MAP), Glasgow Outcome Scale (GOS), Mortality, Hospital days.	1. Patients treated with high doses of barbiturate had significantly longer intubation days, days on ICU, and days in hospital compared to patients treated with low doses or no barbiturate (all p<0.001). 2. Barbiturate administration was associated with a significant reduction in the daily hr of ICP>25 mmHg, but was also associated with a significant elevation in daily hr of MAP <70mmHg. 3. The effect of barbiturate use on ICP was not associated with improved outcomes, as rates of ICU death, hospital death, 6mo death, and poor outcome were not significantly different between responders and non-responders.
Thorat et al. (2008) Singapore Case Series N=12	**Population:** TBI; Mean Age=38.58 yr; Gender: Male=10, Female=2; Median GCS=6. **Intervention:** Patients received a 250 mg bolus of barbiturates followed by continuous infusion of 4-8 mg/kg/hr. **Outcome Measure:** Intracranial Pressure (ICP), Mean Arterial Pressure (MAP), Cerebral Perfusion Pressure (CPP), Brain Tissue Oxygen Pressure ($P_{ti}O_2$), Pressure Reactivity Index (PRx).	1. Mean duration of barbiturate coma was 61.25 hr. 2. No significant reductions in mean ICP, MAP, CPP, $P_{ti}O_2$, or PRx were reported. 3. 8 of 12 patients experienced reductions in ICP, but only 4 had levels below 20 mmHg and only 3 of them survived. 4. Improved $P_{ti}O_2$was seen in 6 of the 8 patients with initial $P_{ti}O_2$ >10 mmHg. 5. There were no significant differences in initial ICP or $P_{ti}O_2$ levels between survivors and non-survivors, but the difference became significant after treatment (p=0.012 and p=0.042, respectively). 6. Favourable and significant changes in PRx were observed among survivors (p=0.020), but not among non-survivors.

PEDro=Physiotherapy Evidence Database rating scale score (Moseley et al., 2002).

Discussion

The findings of an RCT by Eisenberg et al. (1988) suggested that pentobarbital was an effective adjunctive therapy for the management of elevated ICP refractory to conventional therapeutic measures. However, this study only supported the use of the high dose barbiturate for a small subgroup of patients with severe ABI (GCS≤7). In contrast, the findings of an RCT by Ward et al. (1985) suggested that pentobarbital was no better than conventional ICP management measures, which was corroborated by Schwartz et al. (1984) in an RCT by Thorat et al. (2008) in a smaller case series.

While barbiturate use may decrease elevated ICP, it should be used with caution due to the many reports of adverse events. Schwartz et al. (1984) found that over half of those treated with pentobarbital developed arterial hypotension, an adverse effect that could worsen the condition of patients with severe ABI. Schalen et al. (1992) also noted that decreased ICP was associated with

decreased CPP and MAP. More recently, Majdan et al. (2013) found that barbiturate administration was associated with a significant increase in the amount of time spent with low MAP, despite a decrease in the amount of time with elevated ICP. Furthermore, the authors reported that high doses of barbiturate were associated increased intubation days, days in the ICU, and did not improve clinical outcomes.

In accordance with recommendations made by the Brain Trauma Foundation, (Perez-Barcena et al., 2005; Perez-Barcena et al., 2008) compared the efficacy of pentobarbital and thiopental on the management of refractory ICP unmanageable by conventional measures. In two linked trials, they reported that thiopental was superior to pentobarbital in controlling refractory ICP. In the first report, thiopental was shown to help reduce refractory ICP in a greater number of patients, although these differences were not statistically different (Perez-Barcena et al., 2005). In a follow-up report, the authors found statistically significant results in favour of thiopental using multivariate logistic regression (Perez-Barcena et al., 2008).

Llompart-Pou et al. (2007) found thiopental less likely to induce adrenal insufficiency when compared to pentobarbital, further supporting its use when barbiturate coma is indicated. It should be noted that in an earlier study, Stover and Stocker (1998) reported that use of thiopental significantly reduced white blood cell production and could induce reversible leukopenia and granulocytopenia. The authors also noticed interactions with bone marrow suppressing antibiotics, which further exacerbated the problem. Thus, in instances where barbiturate coma is indicated, monitoring of immunological response is recommended.

There is little evidence that barbiturate therapy contributes to improvements in long-term clinical outcomes. In a prospective trial by Nordby and Nesbakken (1984), the authors reported that thiopental combined with mild hypothermia resulted in better clinical outcomes one year post injury when compared with conventional ICP management measures (including hyperventilation, steroids and mannitol). However, since this study used a combination of thiopental and hypothermia, it is not possible to attribute the better clinical outcomes to thiopental alone.

A Cochrane review of seven trials involving 341 patients stated that there was no evidence that barbiturates decreased blood pressure or reduced mortality for one in four patients post TBI (Roberts & Sydenham, 2012). Therefore it was recommended that barbiturate coma be avoided until all other measures for controlling elevated ICP are exhausted.

Conclusions

There is conflicting (level 1b, level 2, level 3) evidence regarding the efficacy of pentobarbital in improving intracranial pressure over conventional management measures.

There is level 2 evidence that thiopental may be more effective than pentobarbital for controlling elevated intracranial pressure.

There is level 2 evidence that pentobarbital may not be more effective than mannitol for controlling elevated intracranial pressure.

There is level 3 evidence that high-dose barbiturate may result in increase length of stay and may not improve outcomes when compared to low-dose barbiturate.

There is level 4 evidence that barbiturate therapy may cause reversible leukopenia, granulocytopenia, and systemic hypotension, as well as supressed bone marrow production.

There is level 4 evidence that a combination barbiturate therapy and therapeutic hypothermia may result in improved clinical outcomes up to 1 year post injury.

There are conflicting reports regarding the efficacy of pentobarbital and thiopental for controlling elevated intracranial pressure; however, thiopental may be more effective than pentobarbital for controlling elevated intracranial pressure.

Pentobarbital may be less effective than mannitol for controlling elevated intracranial pressure.

Barbiturate therapy should be avoided until all other measures for controlling elevated intra cranial pressure are exhausted; patients undergoing barbiturate therapy should have their immunological response monitored.

12.8 Bisphosphonates

The evidence for nonsteroidal anti-inflammatory drugs (NSAIDs) as prophylactic treatment for heterotopic ossification (HO) comes mostly from the use of indomethacin or ibuprofen as HO prophylaxis in patients following total hip arthroplasty (THA) (Kjaersgaard-Andersen & Schmidt, 1986; Ritter & Sieber, 1985). Although it has been reported that the prophylactic use of these medications significantly decreases HO formation following THA, it is not known if they have the same effect in the post ABI population.

12.8.1 Etidronate Disodium

Ethylhydroxydiphosphonate (EHDP), or more commonly referred to as etidronate disodium, is a bisphosphonate that has been used in the prophylaxis and treatment of HO and remains controversial (Watanabe TK & MO., 2001). EHDP works by preventing the aggregation, growth and mineralization of calcium hydroxyapatite crystals which are essential for bone formation. EHDP may potentially delay fracture healing, as long-term use has been associated with osteomalacia.

Table 12.28 Prophylactic Intervention of Heterotopic Ossification with EHDP

Author/ Year/ Country/ Study Design/ N	Methods	Outcomes
Spielman et al. (1983) USA Cohort N=20	**Population:** Head Injury; Gender: Male=16; Female=4. *Intervention Group (n=10):* Mean Age=31 yr; Mean GCS=5.2. *Control Group (n=10)*: Mean Age=27 yr; Mean GCS=5.5. **Intervention:** The prospective intervention group received EHDP (20 mg/kg/day for 12 wk, 10 mg/kg/day for next 12 wk) within 2-7 days post injury which continued for 6mo. The control group was retrospective and did not receive EHDP.	1. The EHDP treated group showed a significantly lower incidence of HO compared with controls (2 versus 7 patients, p<0.025). 2. Of the 9 that developed HO, 25 sites were affected; elbows (35%), shoulders (29%), hips (18%) and knees (18%) were most common. 7 individuals had restricted limb motion and 2 had ankylosis.

Author/ Year/ Country/ Study Design/ N	Methods	Outcomes
	Outcome Measure: Presence of fractures, development of HO.	

Discussion

Although EHDP has been shown to be effective in reducing HO in other populations, such as spinal cord injury, its effectiveness among individuals with brain injury is less studied. In an ABI population, Spielman et al. (1983) found that patients treated with EHDP showed a significantly lower incidence of HO than the control group. However, due to the small sample size of the study and the research design, additional research assessing the benefit of EHDP for the intervention of HO following brain injury is needed.

Conclusions

There is level 2 evidence that Disodium Etidronate (EHDP) may reduce the development of heterotopic ossification in patients with severe head injury.

Disodium Etidronate may prevent the development of heterotopic ossification.

12.9 Cannabinoids

Dexanabinol (HU-211) is a synthetic, non-psychotropic cannabinoid (Mechoulam et al., 1988). It is believed to act as a non-competitive N-methyl-D-aspartate receptor antagonist to decrease glutamate excitotoxicity (Feigenbaum et al., 1989). It is also believed to possess antioxidant properties (Eshhar et al., 1995) and has shown encouraging neuroprotective effects in animal models of TBI (Shohami et al., 1995).

The AANS and the EBIC made no recommendations regarding cannabinoids in acute ABI.

Table 12.29 Cannabinoids for the Acute Management of ABI

Author/ Year/ Country/ Study Design/ N	Methods	Outcome
Dual Cannabinoid Agonist		
Firsching et al. (2012) Germany RCT PEDro=8 N=97	**Population:** TBI. *High Dose (HD, n=31)*: Mean Age=35.6 yr; Gender: Male=21, Female=10. *Low Dose (LD, n=33)*: Mean Age=36.4 yr; Gender: Male=24, Female=9. *Placebo (n=33)*: Mean Age=38.5 yr; Gender: Male=27, Female=6. **Intervention:** Patients were randomized to receive to placebo, high dose (1000 ug), or low dose (500 ug) of a dual cannabinoid agonist. Outcomes were assessed at 7 days, 14 days, 1 mo, 3 mo, and 6 mo. **Outcome Measure:** Intracranial Pressure (ICP), Cerebral Perfusion Pressure (CPP), Survival.	1. ICP>20 mmHg duration was shorter in the HD and LD groups compared to the placebo group, but this difference was not significant (p>0.05). 2. CPP<60 mmHg duration was significantly lower in the HD group compared to the placebo group (p<0.05). 3. CPP at 7 days was significantly higher in the HD group (p=0.0471) compared to the placebo group, but not in the LD group (p=0.0765) compared to the placebo group.

Author/ Year/ Country/ Study Design/ N	Methods	Outcome
		4. Survival at 1 mo was significantly higher in the HD (p=0.043) and LD (p=0.011) groups compared to the placebo group, but this was not seen at 3 mo and 6 mo.
Dexanabinol		
Maas et al. (2006) Netherlands RCT PEDro=10 N=861	**Population:** TBI; Time Post Injury≤6 hr; GCS Range≤5. *Dexanabinol (n=428)*: Median Age=32 yr; Gender: Male=344, Female=84. *Placebo (n=418):* Median Age=33 yr; Gender: Male=345, Female=73. **Intervention:** Patients were randomized to receive either a single intravenous injection of 150 mg dexanabinol dissolved in cremophor-ethanol solution or placebo for 15 min. Monitoring occurred for first 72 hr. Outcomes were assessed 3 mo and 6 mo post treatment. **Outcome Measure:** Glasgow Outcome Scale Extended (GOSE), Intracranial Pressure (ICP), Cerebral Perfusion Pressure (CPP).	1. GOSE scores at 6 mo did not differ between groups (p=0.78). 2. Unfavourable outcome was found in 50% of the treatment group and 51% of controls (OR=1.07). 3. There were no differences in mortality or neurological deterioration between groups. 4. There were no differences in post-treatment ICP or CPP between groups.
Knoller et al. (2002) Israel RCT PEDro=7 N=67	**Population:** TBI. *Dexanabinol (n=30)*: Mean Age=29 yr; Gender: Male=25, Female=5; Mean Time Post Injury=5 hr Mean GCS=6.3. *Placebo (n=37)*: Mean Age=31 yr; Gender: Male=32, Female=5; Mean Time Post Injury=4.9 hr; Mean GCS=6.2. **Intervention:** Patients were randomized to receive either intravenous injection of 50mg dexanabinol in cremophor-ethanol solution or placebo for 15 min. Monitoring occurred for 10 days. Outcomes were assessed at 10 days 1 mo, 3 mo, and 6 mo. **Outcome Measure:** Intracranial Pressure (ICP), Cerebral Perfusion Pressure (CPP), Glasgow Outcome Scale (GOS), Disability Rating Scale (DRS), Adverse Events (AEs), Mortality.	1. Mean percentage of time that ICP>25 mmHg was significantly lower in the treatment group compared to controls on day 2 and 3 (p<0.02 and p<0.005, respectively). 2. Mean percentage time that CPP<50 mmHg was significantly lower in the treatment group compared to controls on days 2 and 3 (p<0.05). 3. On the GOS, a significantly higher proportion of the treatment group had favourable outcomes compared to controls at 1 mo (20% versus 2.7%, p=0.04), with a trend remaining at 3mo (p=0.1). 4. On the DRS, a higher proportion of the treatment group achieved no disability compared to controls. 5. No significant differences were found in AEs or mortality between groups.

PEDro=Physiotherapy Evidence Database rating scale score (Moseley et al., 2002).

Discussion

In an early RCT, Knoller et al. Knoller et al. (2002) found that dexanabinol (50 mg or 150 mg) showed significant improvements in ICP and CPP over placebo for patients with TBI. Despite showing significant improvements on the GOS and Disability Rating Scale at one month post treatment, these benefits progressively lost significance over the 6-month follow-up. Maas et al. (2006) conducted a large-scale multicenter RCT to better establish the efficacy of dexanabinol in the treatment of TBI. Patients admitted to 86 different centres from 15 countries were randomized to receive dexanabinol or placebo within six hours of injury. The authors reported that dexanabinol did not significantly improve outcomes on the GOSE, Barthel Index, or quality of life measures (SF-36, CIQ) at six months when compared to

placebo. Moreover, dexanabinol failed to provide any acute control of ICP or CPP. These findings suggest that the initial benefits reported by Knoller et al. (2002) may have been due to their small sample size. In a more recent RCT, Firsching et al. (2012) utilized a dual cannabinoid agonist as means of reducing ICP. When compared to placebo, the authors reported significant increases in CPP and greater survival at one month, but non-significant decreases in ICP. These results suggest that the dual cannabinoid agonist may an overall positive effect on patients post TBI and is worth exploring in future research.

Conclusions

There is conflicting (level 1b) evidence as to whether dexanabinol in cremophor-ethanol solution effectively lowers intracranial pressure, increases cerebral perfusion pressure, and improves long-term clinical outcomes post TBI when compared to placebo.

There is level 1b evidence that a dual cannabinoid agonist may significantly increase cerebral perfusion pressure and improves survival post TBI when compared to placebo.

Dexanabinol in cremophor-ethanol solution may not be effective in controlling intracranial pressure or improving clinical outcomes post TBI; however, dual cannabinol agonists may be effective in increasing cerebral perfusion pressure and reducing mortality post TBI.

12.10 Cardiovascular Medication

12.10.1 Beta-Blockers

It has been suggested that beta-blockers may improve agitation, anxiety and aggressive symptoms following brain injury, and reduce restlessness. Often the dosage is high, leaving patients susceptible to adverse effects such as sedation, depression and lethargy (Levy et al., 2005).

12.10.1.1 Pindolol

Pindolol is a beta-blocker unlike many others in that it exerts a partial agonist effect, providing only a slight stimulation of the blocked receptor and maintaining a better resting sympathetic tone.

Table 12.30 Effects of Pindolol on Behaviour

Author/ Year/ Country/ Study Design/ N	Methods	Outcomes
Greendyke & Kanter (1986) USA RCT PEDro=7 N=9	**Population:** ABI**;** Mean Age=52 yr; Gender: Male=9, Female=0; Mean Time Post Injury=7.8 yr. **Treatment:** In a crossover design, patients received pindolol or a placebo capsules for the first half of study. The treatment group received 60 mg/day of pindolol for 10 days, increased up to 100 mg. Groups were then crossed-over. Supplemental psychotropic medication was given as needed. **Outcome Measure:** Frequency of assaultive behaviour.	1. Significant reduction of assaultive episodes, need for supplemental medication and hostility were demonstrated during pindolol treatment ($p<0.05$). 2. Significant improvements in patients' willingness to communicate, and cooperation during treatment ($p<0.025$) and significant reduction of stereotyped behaviours ($p<0.01$).

PEDro=Physiotherapy Evidence Database rating scale score (Moseley et al., 2002).

Discussion

Greendyke and Kanter (1986) investigated the effectiveness of a beta-blocker, pindolol, for the improvement of behavioural disturbances post ABI. A significant reduction in behaviours that led to assaults was demonstrated during treatment with pindolol, with the authors stating the optimal dose ranged between 40-60 mg per day. No therapeutic advantage was gained with doses beyond that but rather it led to adverse events (Greendyke & Kanter, 1986). Although the frequency of supplemented psychotropic medications was reduced in the pindolol group, these medications were still given and may have attributed to the reduction in assaultive episodes.

Conclusions

Based on a single RCT, there is level 1b evidence that pindolol may decrease aggression following brain injury.

Pindolol can decrease aggressive behaviour following brain injury.

12.10.1.2 Propranolol

Propranolol is a non-selective beta-blocker and has been used for the reduction of aggressive behaviours associated with compromised brain function. It is not known how this drug works to affect behaviour, however it appears to lack serious cognitive and affective side effects of other medications or physical restraints used to treat agitation post injury (Levy et al., 2005).

Table 12.31 Effects of Propranolol on Behaviour

Author/Year/ Country/ Study Design/ N	Methods	Outcomes
Brooke et al. (1992a) USA RCT PEDro=7 N=21	**Population:** TBI; Severity of Injury: GCS Score <8. **Treatment:** Patients randomized to either propanol (n=11; 60 mg/day, max 420 mg) or placebo (n=10). **Outcome Measure:** Overt Aggression Scale.	1. Control group had more intense episodes of agitation than the treatment group ($p<0.05$). 2. No significant differences between the two groups in terms of agitation episodes/wk. 3. More participants in the control group were placed in restraints during the study ($p<0.05$). 4. There were no differences between the two groups in the numbers receiving sedating drugs or drugs for agitation.
Greendyke et al. (1986) USA RCT PEDro=7 N=10	**Population:** Mean Age=52 yr; Gender: Male=9, Female=0; Mean Time Post Injury=7.8 yr. **Treatment:** Patients received long-lasting propranolol (520 mg/day) or a placebo. After 11 wk, the groups were crossed-over. **Outcome Measure:** Assaultive behaviour, Supplemental psychotropic medication, daily behaviour, Nurses Observation Scale for Inpatient Evaluation.	1. Significantly fewer assaults and attempted assaults occurred during the 11 wk propranolol treatment as compared to the 11 wk of placebo ($p<0.05$). 2. No significant changes in social interests, irritability or psychomotor retardation were noted. No abnormalities were noted on laboratory measures.

PEDro=Physiotherapy Evidence Database rating scale score (Moseley et al., 2002).

Discussion

Greendyke et al. (1986) investigated the effectiveness of a beta-blocker, propranolol, for the improvement of behaviour associated with brain disease in a randomized, crossover trial. Significantly fewer assaults and attempted assaults occurred during the 11-week propranolol treatment as compared to the placebo group. Of the nine patients, five showed marked improvement, two demonstrated moderate improvement, and two showed little or no improvement in assaultive behaviour. It should be noted that the participants also had severe dementia; therefore, this study was not used to draw conclusions for an ABI population as a whole. A later study by Brooke et al. (1992a) found that propranolol was effective in reducing the intensity of the agitation but was not significantly more effective in reducing the number of episodes compared to a placebo.

Conclusions

There is level 1b evidence that propranolol may reduce the intensity of agitated symptoms following brain injury.

Propranolol may reduce the intensity of aggressive and agitated symptoms following brain injury.

12.11 Anti-Coagulants

Subcutaneous heparin in low doses has been reported to be both safe and effective as prophylaxis against deep venous thrombosis (DVT) development post ABI (Watanabe & Sant, 2001). The route of delivery may also affect the efficacy of anticoagulant prophylaxis (Watanabe & Sant, 2001). For this reason, intravenously delivered heparin may be more effective in the prevention of thromboembolism

compared with subcutaneous administration, although this method of delivery might increase the risk of bleeding (Green et al., 1988). Low-molecular weight heparins (LMWH), which are injected subcutaneously, have gained popularity due to the ease of administration and dosage adjustment. Of note, low-molecular weight variants of unfractionated heparin are significantly more expansive, and thus the risks, benefits, and costs need to be balanced out on an individual basis (Watanabe & Sant, 2001). Carlile et al. Carlile et al. (2006) found that 15 of the 16 rehabilitation centers surveyed reported routinely initiating treatment with either LMWH or low-dose unfractionated heparin. In a study with a mixed trauma population, low-dose heparin was compared to enoxaparin (LMWH) for the treatment of DVT (Geerts et al., 1996). Of those receiving low-dose heparin 44% suffered a DVT compared to 31% of patients receiving enoxaparin (p=0.014) (Geerts et al., 1996).

Table 12.32 Unfractionated Heparin or LMWH versus Placebo for DVT Prevention

Author/ Year/ Country/ Study Design/ N	Methods	Outcome
Byrne et al. (2016) USA Case Control N=3634	**Population:** ABI; Median Age=43 yr; Gender: Male=2798, Female=836; Median Time Post Injury=84 hr; Median GCS=3. **Treatment:** Participants were included in retrospective analysis after having received either unfractionated heparin (UFH) or low molecular weight heparin (LMWH) as either early prophylaxis (<72 hr) or late prophylaxis (≥72 hr) for VTE. **Outcome Measure:** Risk of DVT, PE, late neurosurgical intervention and mortality; abbreviate head injury scale (AIS) and incidence of ischemic (ICH) stroke.	1. PE occurred in 1.7% of participants, and DVT in 6.5%. 2. Early prophylaxis was associated with lower odds of PE (OR=0.48) and DVT (OR=0.51) than late prophylaxis. 3. There was no significant difference in risk of late neurosurgical intervention or death between early and late prophylaxis. 4. LMWH was associated with lower odds of VTE (OR=0.6) and mortality (OR=0.59) than UFH. 5. Late prophylaxis group had significantly higher AIS score, ICH incidence, and early neurosurgical intervention rate than early prophylaxis group. 6. The late group most commonly received LWMH and early group most commonly received UFH.
Daley et al. (2015) USA Case Control N=271	**Population:** TBI; *Intervention Group (n=45):* Mean Age=42 yr; Gender: Male=38, Female=7; Mean GCS=10. *Control Group (n=226):* Mean Age=47 yr; Gender: Male=173, Female=53; Mean GCS=10. **Treatment:** Participants were categorized based on exposure (intervention) or lack of exposure (control) to enoxaparin during the acute phase after undergoing an emergency craniotomy, post-TBI. **Outcome Measure:** Rate of DVT and PE, days on ventilation (DOV), length of stay (LOS), mortality rate.	1. No significant differences between groups (intervention and control) were found in terms of rate of DVT (2% vs 3%, p=0.87) and PE (0% vs 1%, p=0.99), as well as LOS and DOV. 2. The intervention group had a significantly lower rate of mortality in hospital compared to the control group (4% vs 24%, p=0.01).
Kim et al. (2014) USA Case Control N=75	**Population:** TBI; Mean Age=44 yr; Gender: Male=59, Female=16; Mean GCS=4. **Treatment:** Participants received heparin prophylaxis at early (<3 days, n=22), intermediate (3-5 days, n=34), or late (>5 days, n=19) time intervals post injury. **Outcome Measure:** Rate of DVT, PE, and morality, number of ventilator and Intensive care unit (ICU) days, Glasgow Coma Scale	1. There was no significant difference between groups in mean rates of DVT, PE, or mortality; mean days on ventilator or in ICU; or mean scores on GCS, AIS, or Marshall CT. 2. There was a significant difference in mean ISS score between the early and intermediate groups (28 vs 35, p=0.02) and between the early and late groups (28 vs 36, p=0.007).

Author/ Year/ Country/ Study Design/ N	Methods	Outcome
	(GCS), Abbreviated Injury Scale (AIS), Injury Severity Score , Marshall CT), neurological improvement.	3. There was a significant difference in cumulative neurological improvement between the early and late groups (p<0.05), with greater improvement the early group.
Lin et al. (2013) USA Case Series N=3812	**Population:** TBI, Abbreviated Injury Severity Scale>3. **Treatment:** Patient records were reviewed. Participants were grouped based on intervention without the heparin prophylaxis protocol (n=1970) and treatment after the implementation of a heparin prophylaxis protocol (n=1842). **Outcome Measure:** Rate of DVT and PE.	1. Rate of DVT was 0.97% without the protocol and 1.21% with the heparin prophylaxis protocol. 2. A single patient had PE in each group.
Farooqui et al. (2013) USA Case Control N=236	**Population:** TBI; Gender: Male=146, Female=90. *Group A (n=107):* Mean Age=53.3 yr. *Group B (n=129):* Mean Age=57.4 yr. **Treatment:** Group A had no routine administration of chemoprophylaxis and Group B received either Lovenox (30 mg, 2x/day) or Heparin (5000U, 3x/day) 24 hr after stable CT. **Outcome Measure:** Rate of DVT and PE.	1. DVT rate was higher in group A than group B (5.6% vs 0%, p=0.008). 2. PE rate was 3.74% in group A and 0.78% in group B (p=0.18). 3. Progression of intracranial hemorrhage did not differ significantly between groups (p=0.33).
Phelan et al. (2012) USA Pilot Study-RCT PEDro=8 N=62	**Population:** TBI; *Intervention Group (n=34):* Mean Age=40.7 yr; Gender: Male=22, Female=12. *Control Group (n=28):* Mean Age=42.6 yr; Gender: Male=16, Female=12. **Treatment:** The intervention group received enoxaparin (30 mg, 2x/day) within 24-96 hr after injury, whereas the control group received a placebo. **Outcome Measure:** Radiographic worsening of TBI, VTE, and extracranial hemorrhagic complications.	1. 1 DVT occurred in the control group; however, no mention of DVT occurrence was made for the intervention group. 2. No clinical TBI progressions were found.
Kwiatt et al. (2012) USA Case Control N=1215	**Population:** TBI; Gender: Male=836, Female=379. *Control Group (n=995):* Mean Age=52.9 yr; Mean GCS=11.4. *LMWH Group (n=220):* Mean Age=46.2 yr; Mean GCS=8. **Treatment:** Retrospective comparison of patients who received LMWH for VTE prophylaxis and those who did not. **Outcome Measure:** Progression of intracranial hemorrhage.	1. Patients receiving LMWH were significantly older and had more severe injuries (p<0.001) than those who did not. 2. LMWH compared to the control had greater hemorrhage progression (42% vs 24%, p<0.001). 3. For those receiving LMWH, when it was initiated did not impact the rate of hemorrhage progression. 4. The LMWH compared to the control group had a greater number of VTE episodes (9.1% vs 3.1%, p<0.001).
Praeger et al. (2012) Australia Observational N=36	**Population:** TBI; Mean age=40.3 yr; Gender: Male=28, Female=8; Mean GCS=8. **Treatment:** Thromboprophylaxis included compression stockings and compression devices, and/or LMWH. **Outcome Measure:** Rate of DVT and PE assessed with compression ultrasound.	1. The rate of DVT was 6%, PE was 6%, and total VTE was 11%. 2. Among individuals with severe TBI the rates of DVT, PE, and total VTE were 10%, 10% and 19%, respectively.

Author/ Year/ Country/ Study Design/ N	Methods	Outcome
Minshall et al. (2011) USA Case Series N=386	**Population**: TBI; Gender: Male=293, Female=93. **Treatment:** Chart review of patients receiving LMWH (30 mg, 2x/day; n=158), unfractionated heparin (UFH; 5000 IU 3x/day; n=171) or sequential compression devices alone (n=57). **Outcome Measure:** Rate of DVT, PE, and intracranial hemorrhage complications.	1. Mortality in the sequential compression devices alone group was higher (47%) compared to the LMWH (5%) and UFH (16%) groups. 2. Those in the UFH group had a significantly higher rate of DVT and PE than those in the LMWH group ($p<0.05$). 3. 5% of those in the LMWH group and 12% in the UFH group had progression of their intracranial hemorrhage, compared to 25% in the untreated group.
Koehler et al. (2011) USA Cohort N=669	**Population:** TBI; Gender: Male=487, Female=182. *Early Group (n=268):* Mean Age=39.8 yr. *Late Group (n=401):* Mean Age=40.2 yr. **Treatment:** Enoxaparin (30 mg 2x/day) was administered to all patients. The early group received the VTE prophylaxis within 0-72 hr and the late group at 73 hr or later. **Outcome Measure:** Incidence of DVT and PE.	1. Those in the early group compared to the late group spent significantly fewer days on a ventilator ($p<0.001$), fewer days in ICU ($p<0.002$) and hospital ($p<0.004$). 2. Intracranial hemorrhage progression for the early vs late groups was 9.38% vs 17.41% ($p<0.001$) before prophylaxis and 1.46% vs 1.54% after ($p=0.912$). 3. The proportion of DVTs and PEs were not significantly different ($p=0.117$ and $p=0.49$, respectively).
Scudday et al. (2011) USA Case Series N=812	**Population:** TBI; Gender: Male=560, Female=252. *Intervention Group (n=402):* Mean Age=45.2 yr. *Control Group (n=410):* Mean Age=51.5 yr. **Treatment:** Retrospective review comparing patients that received chemical thromboprophylaxis (91% Heparin, 9% Enoxaparin) to an untreated control group. **Outcome Measure:** Incidence of VTE.	1. A lower incidence of VTE was found in the treated group compared to the untreated group (1% vs 3%, $p=0.019$).
Salottolo et al. (2011) USA Case Series N=480	**Population:** TBI; Mean Age=53 yr; Gender: Male=296, Female=184; Mean GCS=12.2. **Treatment:** Retrospective review of patients considered for thrombus prophylaxis (lovenox 30 mg 2x/day or heparin 5000 U, 2x/day), timing of administration, and whether or not the intervention was interrupted. **Outcome Measure:** Development of VTE or DVT.	1. 53.1% of patients received pharmacological thromboprophylaxis (PTP); median time to start was 3d and it was continuous in 73.7%. 2. Medications began <72 hr post injury in 108 patients and >72 hr post injury in 147. 3. The no PTP group had 4 DVTs and 2 PEs compared to the PTP group which had 8 DVTs and 3 PEs. 4. Neither the administration of these medications ($p=0.29$) or the timing of administration ($p=0.26$) had any effect on the development of VTE.
Norwood et al. (2008) USA Case Series N=525	**Population:** TBI; Mean Age=39.6 yr; Gender: Male=387, Female=138; Abbreviated Injury Scale ≥2; Mean Time Post-Injury=36.2 hr. **Treatment:** Patients were given Enoxaparin sodium (30 mg, 2x/day). **Outcome Measure:** Incidence of DVT and PE, mortality rates.	1. 4.0% of patients died. 2. Of 151 patients that underwent a lower extremity venous Doppler ultrasound, 6 patients were diagnosed with a DVT. 3. No patients within the study group were diagnosed with a PE.
Kleindienst et al. (2003) USA Case Series	**Population:** Head Injury=344, Elective Surgery (tumors)=294, Intracranial Hemorrhage (ICH)=302; Mean Age=57.3 yr.	1. 155 patients were excluded due to coagulation abnormalities or significant bleeding.

Author/ Year/ Country/ Study Design/ N	Methods	Outcome
N=940	**Treatment:** A retrospective review of patients either receiving 18 mg/d of Certoparin-sodium (3000 U anti-factor Xa) for prophylaxis on the evening prior to elective neurosurgery (ES) and within 24 hr after surgery, or admission whenever a CT showed an absence of a progressive haematoma. **Outcome Measure:** Incidence of bleeding complications, VTE events, and morbidity/mortality rates.	2. Intracranial bleeding was found in 1.5% of the total sample. 3. The incidence of VTE and PE was 0.2% and 0.1% of patients respectively, with no associated mortality. 4. No heparin induced thrombocytopenia was observed.
Norwood et al. (2002) USA Pre-Post N=150	**Population:** Traumatic Intracranial Hemorrhagic injuries (IHI); Mean Age=39.5 yr; Mean GCS=10. **Treatment:** Patients received Enaxoparin-sodium (30 mg, 2x/day) beginning 24 hr after initial evaluation. **Outcome Measure:** Incidence of DVT or PE, Progression of IHI, mortality, Glasgow Outcome Scale (GOS).	1. At discharge (n=106), 2% of patients had a DVT and no PE 2. 23% of patients had CT progression of IHI pre-treatment. Rate of progression of IHI significantly decreased after initiation of the intervention (p=0.002). 3. Study group mortality was 7%. 4. On the GOS, the majority (76%) of patients showed good recovery.
Kim et al. (2002) USA Cohort N=64	**Population:** ABI; Gender: Male=49, Female=15. *Early Group (n=47):* Mean Age=37.7 yr; Mean GCS=9.1. *Late Group (n=17):* Mean Age=44 yr; Mean GCS=9.4. **Treatment:** Retrospective review of patients who received unfractionated heparin (UFH) within 72 hr of admission (Early Group) and those who received it after the third day (Late Group). **Outcome Measure:** VTE events, bleeding complications.	1. There was no increase in intracranial bleeding or deterioration on neurological examination due to UFH administration. 2. There was no statistical difference in VTE events between groups.

Discussion

The effect of administering chemical prophylaxis for DVT post ABI has been reviewed. Results indicate that early treatment (within the first 72 hours) may reduce the risk of developing DVT post injury (Byrne et al., 2016; Farooqui et al., 2013; Kim et al., 2002; Kim et al., 2014; Norwood et al., 2008; Salottolo et al., 2011; Scudday et al., 2011) without increasing the risk of intracranial hemorrhagic injury (Byrne et al., 2016; Koehler et al., 2011; Scudday et al., 2011) or deterioration on neurological examination (Kim et al., 2002).

Patients with ABI who were started on unfractionated heparin within three days of injury onset, compared to those who started after this time period, did not differ significantly in terms of the number of thromboembolic events (Kim et al., 2002; Kim et al., 2014). However, individuals who were administered heparin within three days of injury had slower progression of neurological impairments on computed tomography scans compared to late administration (Kim et al., 2014).

Norwood and colleagues conducted two studies examining the benefits of administering enoxaparin (LMWH) prophylaxis to those who sustain a severe ABI within the first 48 hours post injury (Norwood et al., 2008; Norwood et al., 2002). Results from both studies indicate that administering enoxaparin post ABI reduces the risk of developing DVT and PE, without increasing the risk of bleeding post injury.

Scudday et al. (2011) also found that patients who received chemical prophylaxis within 72 hours of injury had a significantly lower incidence of developing VTE post ABI ($p<0.019$) compared to those not receiving chemical prophylaxis (Kim et al., 2014). Overall, a meta-analysis by Jamjoom and colleagues Jamjoom and Jamjoom (2013) conclude that individuals who begin pharmacological thromboprophylaxis within 72 hours of injury have half the risk of VTE without significant risk of intracranial hemorrhage progression, than those who start after 72 hours.

On the contrary, few studies have demonstrated these medications may not be beneficial or superior treatments. In one study with individuals who underwent a craniotomy post-ABI, no significant differences were reported for rate of DVT and PE when comparing those administered enoxaparin prophylaxis compared to those without (Daley et al., 2015). Further, Kwiatt et al. (2012) reported patients' receiving LMWH were at higher risk for hemorrhage progression and the risk of using LMWH may exceed its benefit. Similarly for heparin, Lin et al. Lin et al. (2013) did not find a reduction in DVT or PE once individuals with a severe TBI were administered a heparin prophylaxis protocol.

In conclusion, a systematic review of twelve studies report that evidence is insufficient to determine effectiveness of these medications for VTE prevention; however despite the aforementioned studies without significant findings, overall evidence supports the use of enoxaparin for reduction of DVT and UFH for decreased mortality rates compared to no chemoprophylaxis (Chelladurai et al., 2013).

Conclusions

There is level 2 evidence supporting the administration of low molecular weight herapin within the first 72 hours post ABI to reduce the risk of developing deep vein thrombosis and pulmonary embolisms post injury.

There is level 2 evidence that administering low molecular weight herapin (enoxaparin) or heparin post ABI may not increase the risk of intracranial bleeding, compared to no treatment.

There is level 4 evidence that the use of chemoprophylaxis 24 hours after stable head computed tomography scan may decrease the rate of deep vein thrombosis formation post ABI.

Although the administration of chemical deep vein thrombosis prophylaxis within the first 72 hours post ABI has been shown to be effective in reducing the risk of developing deep vein thrombosis or pulmonary embolism without increasing the risk of intracranial bleeding, more research is needed to determine its true effectiveness.

Enoxaparin may be effective for the prevention of VTE after elective neurosurgery and has not been found to cause excessive bleeding.

12.11 Diuretics

12.11.1 Mannitol

Rapid administration of mannitol is among the first-line treatments recommended for the management of increased ICP. However, this treatment is reported to be associated with significant diuresis and can

cause acute renal failure, hyperkalemia, hypotension, and in some cases rebound increments in ICP (Battison et al., 2005; Doyle et al., 2001). For these reasons, the Brain Trauma Foundation recommends that mannitol only be used if a patient has signs of elevated ICP or deteriorating neurological status. Under such circumstances the benefits of mannitol for the acute management of ICP outweigh any potential complications or adverse effects. There is also some evidence that with prolonged dosage, mannitol may penetrate the blood brain barrier, thereby exacerbating the elevation in ICP (Wakai et al., 2013). Despite the effectiveness of mannitol in ICP management, recent evidence points to HTS as a potentially more effective hyperosmotic agent.

Although mannitol is commonly used in acute ABI, the AANS concluded that there was insufficient evidence available to support a formal recommendation (Carney et al., 2017). The EBIC recommended mannitol as the preferred osmotic therapy, with administration via repeated bolus infusions or as indicated by monitoring to a serum osmolarity of ≤315 (Maas et al., 1997).

Table 12.33 Mannitol for the Acute Management of Post ABI

Author/ Year/ Country/ Study Design/ N	Methods	Outcome
Tang et al. (2015) Taiwan Pre-Post N=21	**Population:** TBI=8, Stroke=10, Tumor=3; Mean Age=52.05 yr; Gender: Male=12, Female=9; Mean GCS=10.6. **Intervention:** Participants received 1 g/kg of 20% mannitol. **Outcome Measure:** Intracranial Pressure (ICP), Pressure Reactivity Index (PRx), Cerebral Perfusion Pressure (CPP), Cerebrovascular Pressure Reactivity (CVPR).	1. At baseline, ICP was significantly correlated with PRx (p=0.0044). 2. There was a significant decrease in ICP after mannitol (p=0.036). 3. Low baseline CPP was the only significant association with the improvement of CVPR after mannitol (p=0.039).
Diringer et al. (2012) USA Pre-Post N=6	**Population:** TBI; Mean Age=30.2 yr; Gender: Male=5, Female=1; Median GCS=6. **Intervention:** Participants received 1 g/kg of 20% mannitol. **Outcome Measure:** Intracranial Pressure (ICP), Cerebral Blood Volume (CBV), Blood Pressure (BP), Cerebral Blood Flow (CBF), Cerebral Metabolic Rate for Oxygen (CMRO2), Oxygen Content.	1. There was a significant reduction in ICP 1 hr after mannitol (21.5 mmHg to 13.7 mmHg, p<0.003). 2. There was no significant change in CBV, BP, CBF, CMRO2 or oxygen content 1 hr after mannitol (all p>0.05).
Scalfani et al. (2012) USA Pre-Post N=8	**Population:** TBI; Mean Age=37.4 yr; Gender: Male=7, Female=1; Median Time Post Injury=3 day; Median GCS=7. **Intervention:** Participants received 20% mannitol (n=6) or 23.4% saline (n=2) infused over 15min. **Outcome Measure:** Intracranial Pressure (ICP), Mean Arterial Pressure (MAP), Cerebral Perfusion Pressure (CPP).	1. Mannitol resulted in a significant reduction in ICP (22.4 mmHg to 15.7 mmHg, p<0.05). 2. Mannitol resulted in a significant elevation in CPP (75.7 mmHg to 81.9 mmHg, p<0.05) 3. Mannitol resulted in a stable MAP (103. 3mmHg versus 102.6 mmHg, p>0.05).
Ichai et al. (2009) France RCT PEDro=6 N=34	**Population:** TBI. *Mannitol (MAN, n=17)*: Mean Age=33.8 yr; Gender: Male=11, Female=6; Time Post Injury<8 hr; Median GCS=6. Sodium *Lactate (SL, n=17)*: Mean Age=37.6 yr; Gender: Male=13, Female=4; Time Post Injury<8 hr; Median GCS=4. **Intervention:** Patients were randomized to receive intravenous infusion of 20% MAN (1.5	1. 9 patients received only mannitol, 12 received only lactate, and 13 received both MAN and SL. 2. Both treatments were effective in reducing ICP from baseline (p<0.0001). 3. SL showed significantly lower ICP levels compared to MAN (p=0.016).

Author/ Year/ Country/ Study Design/ N	Methods	Outcome
	mL/kg) and/or SL over 15 min. **Outcome Measure:** Intracranial Pressure (ICP).	4. The effect of SL alone on ICP was more pronounced (p=0.0061) and more prolonged (p=0.0049) than MAN alone. 5. The percentage of episodes requiring rescue treatment was higher with mannitol than lactate (29.6% versus 9.6%, p=0.053).
Francony et al. (2008) France RCT PEDro=6 N=20	**Population:** TBI=17, ABI=3. *Mannitol (MAN, n=10)*: Mean Age=43 yr; Gender: Male=7, Female=3; Mean GCS=8; Mean Time Post Injury=6 days. *Hypertonic Saline (HTS, n=10)*: Mean Age=37 yr; Gender: Male=9, Female=1; Mean GCS=7; Mean Time Post Injury=5 days. **Intervention:** Patients were randomized to receive a single intravenous infusion of 20% MAN (231 mL) or of 7.45% HTS (100 mL) administered over 20 min. **Outcome Measure:** Intracranial Pressure (ICP), Mean Arterial Pressure (MAP), Cerebral Perfusion Pressure (CPP), Urine Output, Serum Sodium/Chloride.	1. ICP was reduced in both groups of patients following treatment. 2. In MAN, ICP was significantly reduced by 45% of baseline values (-14 mmHg) at 60 min and by 32% of baseline values (-10 mmHg) at 120 min. 3. In HTS, ICP was significantly reduced by 35% of baseline values (-10 mmHg) at 60 min and by 23% of baseline values (-6 mmHg) at 120 min. 4. MAP was unchanged and comparable between groups (F=1.2, p=0.32). 5. CPP was significantly elevated only in the MAN (p<0.05). 6. MAN showed significantly greater increase in urine output (p<0.05). 7. HTS showed significantly greater increase in serum sodium and chloride after 120min (p<0.01).
Sorani et al. (2008) USA Case Control N=28	**Population:** TBI; Mean Age=39.3 yr; Gender: Male=24, Female=4; Median GCS=8. **Intervention:** Patients treated with 100 g, 50 g, or both doses of mannitol were included in retrospective analysis. **Outcome Measure:** Intracranial Pressure (ICP).	1. Initial mean ICP was slightly higher in the 100 g group compared to the 50 g group (23.9 mmHg versus 20.9 mmHg, p=0.14), 2. By 100 min post treatment, mean ICP was significantly lower in the 100 g group than the 50 g group (14.2 mmHg versus 18.6 mmHg, p=0.001). 3. Over time, mean ICP decrease in the 50 g group was 3.6 mmHg, which was nearly two-fold lower than that of the 100 g group (8.8 mmHg). 4. ICP response to mannitol was dose-dependent: every 7 g achieved an additional reduction of ~1.0 mmHg in ICP.
Cruz et al. (2004) Brazil RCT PEDro=5 N=44	**Population:** TBI. *High-Dose Mannitol (HDM, n=23)*: Mean Age=34 yr; Mean GCS=3. *Conventional-Dose Mannitol (CDM, n=21)*: Mean Age=31 yr; Mean GCS=3. **Intervention:** Patients were randomized to receive rapid intravenous infusion of HDM (up to 1.4 g/kg) or CDM (up to 0.7 g/kg). Both groups received normal saline infusions immediately after the mannitol infusions. **Outcome Measure:** Intracranial Pressure (ICP), Glasgow Outcome Scale (GOS).	1. At 6 mo, mortality rates were 39.1% and 66.7% for the HDM and CDM groups, respectively. 2. Clinical outcome on the GOS was significantly better for the HDM group, with a greater number of patients in this group showing a favourable outcome (GOS≥4) compared with the CDM group (43.5% versus 9.5%, p<0.02). 3. No significant difference was found between the HDM and CDM groups in percentage of patients requiring decompressive surgery for

Author/ Year/ Country/ Study Design/ N	Methods	Outcome
		refractory ICP elevations (43.5% versus 47.6%).
Cruz et al. (2002) Brazil RCT PEDro=5 N=141	**Population:** TBI. *High-Dose Mannitol (HDM, n=72)*: Mean Age=29 yr; Mean GCS=5.3. *Conventional-Dose Mannitol (CDM, n=69)*: Mean Age=31yr; Mean GCS=5.5. **Intervention:** Patients were randomized to receive rapid intravenous infusion of HDM (up to 1.4 g/kg) or CDM (up to 0.7 g/kg). **Outcome Measure:** Intracranial Pressure (ICP), Glasgow Outcome Scale (GOS).	1. At 6 mo, mortality rates were 19.4% and 36.2% for the HDM and CDM groups, respectively. 2. Clinical outcome on the GOS was significantly better for the HDM group, with a greater number of patients in this group showing favourable outcome (GOS≥4) compared with the CDM group (61.1% versus 33.3%, p<0.005). 3. A greater proportion of patients in the CDM group required decompressive surgery for refractory ICP elevations than the HDM group (24.6% versus 9.7%, p<0.03).
Cruz et al. (2001) Brazil RCT PEDro=4 N=178	**Population:** TBI. *High-Dose Mannitol (HDM, n=91)*: Mean Age=30 yr; Mean GCS=6. *Conventional-Dose Mannitol (CDM, n=87)*: Mean Age=28 yr; Mean GCS=6.2. **Intervention:** Patients were randomized to receive intravenous infusion of HDM (0.6-0.7 g/kg, HDM) or CDM. **Outcome Measure:** Intracranial Pressure (ICP), Glasgow Outcome Scale (GOS).	1. At 6 mo, mortality rates were 14.3% and 25.3% for the HDM and CDM groups, respectively. 2. Clinical outcome on the GOS was significantly better for the HDM group, with a greater number of patients in this group showing favourable outcome (GOS>4) compared with the CDM group (69.2% versus 46%, p<0.01). 3. No significant difference between HDM and CDM groups in percentage of patients requiring barbiturate therapy for refractory ICP elevations (46.1% versus 54%).
Hartl et al. (1997) Germany Pre-Post N=11	**Population:** TBI; GCS<9. **Intervention:** Patients received 30 intravenous administrations of 20% mannitol (125 mL) infused over 30 min. **Outcome Measure:** Intracranial Pressure (ICP), Cerebral Perfusion Pressure (CPP).	1. When initial ICP was <20 mmHg, neither ICP nor CPP change significantly during or after mannitol infusion. 2. When initial ICP was >20 mmHg, there was a significant decrease in mean ICP (maximal decrease from 23 mmHg to 16 mmHg at 60 min) and a significant increase in mean CPP (maximal increase from 68 mmHg to 80mmHg at 120 min) in response to mannitol.
Sayre et al. (1996) USA RCT PEDro=7 N=41	**Population:** TBI; *Mannitol (MAN, n=20)*: Mean Age=29 yr; Gender: Male=19, Female=1; Mean GCS=7.1. *Hypertonic Saline (HTS, n=21)*: Mean Age=27 yr; Gender: Male=20, Female=1; Mean GCS=6.4. **Intervention:** Patients were randomized to receive either intravenous infusion of 20% MAN (5 mL/kg) or 0.9% HTS (5 mL/kg). **Outcome Measure:** Intracranial Pressure (ICP), Mortality, Urine Output, Serum Sodium.	1. Mortality was 25% in MAN and 14% in HTS (p=0.38) 2. Mean systolic BP was significantly lower in MAN than in HTS (116 mmHg versus 142 mmHg, p<0.003) 2 hr after admission; however, when all time periods were compared there was no overall difference between groups. 3. Urine output (p<0.001) was significantly greater and serum sodium (p<0.00001) was significantly lower in MAN compared with HTS.

Author/ Year/ Country/ Study Design/ N	Methods	Outcome
Smith et al. (1986) USA RCT PEDro=4 N=77	**Population:** TBI; Mean Age=27 yr; Gender: Male=60, Female=17; Time Post Injury ≤6hr; GCS ≤8. **Intervention:** Patients were randomized to receive intravenous infusion of mannitol based on careful monitoring (Group 1; n=37) or irrespective of monitoring (Group 2; n=40). For Group 1, an initial bolus of 20% mannitol (250 mL, 0.75 gm/kg) was administered at ICP>25 mmHg; pentobarbital coma was induced if ICP>25 mmHg while mannitol was administered. For Group 2, initial bolus of 20% mannitol (250 mL, 0.75 gm/kg) was given, followed by 0.25 gm/kg boluses administered every 2 hr. **Outcome Measure:** Mortality, Glasgow Outcome Scale (GOS), Intracranial Pressure (ICP).	1. There was no significant difference in mortality between Groups 1 and 2 (35% versus 42.5%, p=0.26). 2. There were no significant differences in GOS between groups. 3. The proportion of patients achieving favourable outcome (GOS≥4) in Group 1 was 54% and in Group 2 was 47.5%. 4. Mean highest ICPs for survivors in Groups 1 and 2 were 35.2 mmHg and 29.7 mmHg, respectively, and for non-survivors were 46.2 mmHg and 40.7 mmHg, respectively. 5. Mean highest ICP in all non-survivors was significantly higher (by ~11mmHg) than that in all survivors (p=0.0002).

PEDro=Physiotherapy Evidence Database rating scale score (Moseley et al., 2002).

Discussion

Overall, findings of single group interventions suggest that mannitol is effective in significantly reducing ICP following TBI (Diringer et al., 2012; Scalfani et al., 2012; Tang et al., 2015). Cruz and colleagues conducted three separate trials to investigate the effects of high dose mannitol on clinical outcomes in patients with ABI at six months post injury (Cruz et al., 2001, 2002; Cruz et al., 2004). All three trials reported that high dose mannitol (1.4 g/kg) was superior to conventional mannitol (0.7 g/kg) in lowering elevated ICP and improving clinical outcomes. In a retrospective study, Sorani et al. Sorani et al. (2008) found that for every 0.1 g/kg increase in mannitol dosage there was a 1.0 mmHg drop in ICP.

In a later trial, Francony et al. (2008) found that equimolar doses of mannitol and HTS were comparable in reducing ICP in stable patients with intact autoregulation post ABI. Mannitol was shown to improve brain circulation through possible improvements in blood rheology, but also significantly increased urine output. The authors suggested that both treatments may be effective, but patient pre-treatment factors should be considered before selection. In another trial, Ichai et al. (2009) reported that an equimolar dose of sodium lactate had a significantly greater effect on lowering elevated ICP that lasted longer than treatment with mannitol. Sodium lactate was also successful in reducing elevated ICP more frequently. Based on these results, further research into the effectiveness of sodium lactate in reducing ICP is warranted.

Most reports have recommended administering mannitol only when elevated ICP is proven or strongly suspected. Hartl et al. (1997) indicated that mannitol was only effective in diminishing ICP when the initial ICP was hypertensive (>20 mmHg). However, an RCT by Smith et al. (1986) reported that patients who received mannitol only after the onset of intracranial hypertension (>25 mmHg) were not significantly different from those who received mannitol irrespective of ICP measurements in terms of mortality rates or neurological outcomes. Thus it is unclear whether the use of mannitol as a prophylactic measure against potential elevations in ICP is appropriate.

Other reports have discouraged the use of mannitol before volume resuscitation and patient stabilization, due to potential osmotic diuresis and hypotension. These adverse effects could further

compromise CPP, but such an approach may deprive patients of the potential benefits of mannitol on ICP. With this in mind, Sayre et al. (1996) conducted an RCT to investigate the effects of early mannitol administration in an out-of-hospital emergency care setting. The authors reported that mannitol did not significantly affect blood pressure when compared to saline.

In a 2013 Cochrane review, Wakai et al. (2013) suggested that mannitol may have beneficial effects on mortality when compared to pentobarbital but detrimental effects when compared to HTS. However, there was a small benefit when mannitol treatment was monitored by a measurement of ICP when compared to standard care. The authors also reported that there was insufficient data on the effectiveness of pre-hospital administration of mannitol.

Conclusions

There is level 4 evidence that mannitol may be effective in controlling elevated intracranial pressure.

There is level 2 evidence that early administration of mannitol may not effectively lower elevated intracranial pressure, but may not adversely affect blood pressure.

There is level 2 evidence that high-dose mannitol may be more effective than conventional mannitol in reducing mortality rates and improving clinical outcomes.

There is level 1b evidence that mannitol may be no more effective than hypertonic saline in controlling elevated intracranial pressure.

There is level 1b evidence that mannitol may be less effective than sodium lactate in controlling elevated intracranial pressure.

Mannitol may effectively lower elevated intracranial pressure; furthermore, high doses may yield lower mortality rates and better clinical outcomes.

Mannitol may be equally effective as hypertonic saline and less effective than sodium lactate for reducing elevated intracranial pressure.

12.12 Dopaminergic Medications

Although it is a very small and simple molecule, dopamine fulfills many functions in the brain. It acts as a neurotransmitter activating dopamine receptors and when released by the hypothalamus it inhibits the release of prolactin from the anterior lobe of the pituitary gland. Dopaminergic medications are often used by individuals with Parkinson's disease and those who have sustained an ABI.

12.12.1 Amantadine

12.12.1.1 Amantadine in Acute Care

Amantadine is a dopamine agonist that acts both pre- and post-synaptically to enhance dopamine activity (Meythaler et al., 2002). Dopamine is thought to be involved in frontal lobe stimulation and plays a role in behavior, mood, language, motor control, hypothalamic function and arousal (Sawyer et

al., 2008). Amantadine was initially developed for prophylactic use as an antiviral agent in the prevention of influenza A, but is now commonly used in the treatment of Parkinson's disease. Amantadine's properties as a potential neuro-active agent were quickly recognized (Zafonte et al., 2001). Researchers believe that amantadine could significantly improve arousal in comatose patients. Potential side effects include over-stimulation, peripheral edema, livedo reticularis, and lowering of the seizure threshold (Schneider et al., 1999a). The favourable risk-benefit profile of amantadine suggests that it may be an attractive treatment option for inducing arousal from coma (Hughes et al., 2005).

Table 12.34 Effects of Amantadine on Arousal from Coma in Adult and Paediatric Populations

Author/ Year/ Country/ Study Design/ N	Methods	Outcomes
Giacino et al. (2012) USA RCT PEDro=7 N=184	**Population:** TBI. *Amantadine Group (n=87)*: Mean Age=35.5 yr; Gender: Male=64, Female=23; Median Time Post Injury=48d. *Placebo Group (n=97)*: Mean Age=37.2 yr; Gender: Male=69, Female=28; Median Time Post Injury=47 days. **Intervention:** Participants were randomized to receive either amantadine or a placebo for 4 wk. Outcomes were assessed at baseline, 4 wk and 6 wk. **Outcome Measure:** Disability Rating Scale (DRS).	1. DRS scores were significantly more improved in the amantadine group compared to the placebo group at 4 wk (p=0.007). 2. Rate of improvement on DRS was significantly slowed from 4-6 wk (p=0.02). 3. The overall improvement on DRS from baseline to 6 wk was not statistically different between groups (p>0.05).
McMahon et al. (2009) USA RCT PEDro=6 $N_{Initial}$=7, N_{Final}=6	**Population:** ABI: TBI=5, Stroke=1, Anoxia=1; Mean Age=12.7 yr; Gender: Male=6, Female=1; Mean Time Post Injury=6.7 wk; Mean GCS=4. **Treatment:** Patients were randomized to receive either 4 mg/kg body weight of amantadine for 1 wk followed by 6 mg/kg body weight for 2 wk or a placebo. After a 1 wk washout period, the patients were crossed over and treated for another 3 wk. Assessments were conducted up to 3 x/wk. **Outcome Measure:** Coma/Near-Coma Scale (CNCS), Coma Recovery Scale Revised (CRS-R), Sleep Scale, Wee-FIM, physician evaluation, parents' evaluation.	1. There were no significant differences in recovery between amantadine and placebo according to CNCS, CRS-R or Wee-FIM scores (p=0.24, p=0.28, p=0.33 respectively). 2. Physician's evaluations revealed significantly greater improvements in consciousness (p=0.02) but not for changes in arousal (p=0.17). 3. Parent's evaluations did not reveal any significant differences in consciousness or arousal (p=0.50, p=0.12 respectively).
Vargus-Adams et al. (2010) USA *A secondary analysis of McMahon et al. (2009)*	**Treatment:** A secondary analysis to determine the pharmacokinetic properties of amantadine in children. **Outcome Measure**: Coma/Near-Coma Scale (CNCS), Coma Recovery Scale Revised (CRS-R), Sleep Scale.	1. A significant correlation was reported between CRS-R and maximum concentration of Amantadine (p=0.01), however, scatterplots did not reveal any observable relationship. 2. There was only one significant association between CNCS (p=0.38, p=0.39, p=0.79) or CRS-R scores (p=0.06, p=0.11, p=0.01) and average concentration of Amantadine. However, the only significant CRS-R score did not reveal any relationship on the scatterplot. 3. Sleep Scale mean scores for nights on Amantadine and placebo were not found to be significantly different (p=0.20).

Author/ Year/ Country/ Study Design/ N	Methods	Outcomes
Patrick et al. (2006) USA RCT PEDro=5 N_I=25, N_F=10	**Population:** TBI; Amantadine (n=6): Mean Age=16.7 yr; Gender: Male=2, Female=4; Mean Time Post Injury=82.8 days; Mean GCS=3. Pramipexole (n=4): Mean Age=16.8 yr; Gender: Male=2, Female=2; Mean Time Post Injury=39.5 days; Mean GCS=3. **Treatment:** Patients were randomly assigned to receive either amantadine or pramipexole over an 8wk course of treatment. Dosage was increased weekly over 4 wk followed by a 2 wk weaning phase and 1 wk washout. **Outcome Measure**: Coma/Near-Coma Scale (CNCS), Western NeuroSensory Stimulation Profile (WNSSP), Disability Rating Scale (DRS), Rancho Los Amigos Scale (RLAS).	1. No significant differences were found in response rate between the two drugs (p>0.05). 2. The weekly rate of change over the course of treatment was significant on the CNCS (p=0.0131), WNSSP (p=0.0098) and DRS (p=0.0239) for all patients. 3. Significant improvement was reported in all patients from baseline to peak dosage (week 5) on the CNCS (p=0.002), WNSSP and DRS (both p=0.0039). 4. Patients at RLAS Level III demonstrated a significantly greater response to the medications than those at RLAS Level II (p<0.05).
Hughes et al. (2005) Canada Observational N=123	**Population:** TBI; *Amantadine Group (n=28)*: Mean Age=37.36 yr; Gender: Male=17, Female=11; Mean GCS=4.14; *No Amantadine Group (n=95)*: Mean Age=38.76 yr; Gender: Male=58, Female=37; Mean GCS=4.18. **Treatment:** A retrospective chart review. Patients were divided into two groups based on whether or not they received amantadine (~6 wk post injury). Most patients received an initial dose of 100 mg 2×/day that increased to 200 mg 2×/day if there was no improvement. Medication was discontinued 3 wk after emergence from coma. **Outcome Measure:** Emergence from coma.	1. The proportion of patients emerging from coma between amantadine and no amantadine groups were similar (46% versus 38%; p=0.42). 2. Survival analysis identified age (p=0.004), GCS (p=0.008) and somatosensory evoked potential (p=0.0002) to be significant predictors of time to emerge from coma. Controlling for these variables, amantadine did not significantly contribute to the emergence from coma.
Whyte et al. (2005) USA Observational N=122	**Population:** TBI; Mean Age=34.2 yr; Gender: Male=88, Female=34; Mean GCS=4.9. **Treatment:** Patients in a vegetative or minimally conscious state 4-16 wk post injury were assessed for various outcomes. **Outcome Measure:** Disability Rating Score (DRS), and time to follow command.	1. Patients receiving amantadine showed significant improvements in DRS scores in the first week following administration (p<0.01) which remained in the second week post treatment (p=0.06). No improvement was seen during weeks leading up to the amantadine treatment.
Green et al. (2004) USA Case Control N=54	**Population:** TBI; *Amantadine Group (n=54)*: Mean Age=11.8 yr; Gender: Male=33, Female=21; Mean GCS=5.6; *Control Group (n=64)*: Mean Age=10.3 yr; Gender: Male=47, Female=17; Mean GCS=7.4. **Treatment:** Retrospective chart review. Groups based on whether the paediatric patients were treated with amantadine or were not treated with any neurostimulant (control group). **Outcome Measure:** Ranchos Los Amigos Scale (RLAS), side effects.	1. Initial mean GCS score for the treatment group was significantly lower than that of the control group (5.6 versus 7.4; p<0.01). 2. 5 patients in the amantadine group (9%) had reversible side effects (e.g. hallucinations, delusions, increased aggression, and nausea/vomiting). 3. The treatment group started with lower RLAS levels and demonstrated greater improvements compared to the control group (3.2 versus 2.3, p<0.01). 4. Subjective improvement was revealed in 63% of the treatment group (i.e., increased alertness, initiation, and verbalizations and decreased agitation).
Saniova et al. (2004) Slovak Republic	**Population:** TBI; *Group 1 (n=41)*: Mean Age=42.12 yr; Gender: Male=35, Female=6; Mean GCS=4.74;	1. At discharge, patients treated with amantadine showed significantly higher

Author/ Year/ Country/ Study Design/ N	Methods	Outcomes
Case Control N=74	*Group 2 (n=33)*: Mean Age=43.91 yr; Gender: Male=30, Female=3; Mean GCS=4.70. **Treatment:** Group 1 received both standard therapy and 200 mg of IV amantadine sulphate (2×/day). Group 2 received only standard therapy. **Outcome Measure:** GCS and mortality rates.	GCS scores (9.76±3.95 versus 5.73±3.57, p<0.0001) and decreased mortality (6.06% versus 51.51%, p<0.001) than those treated with standard therapy alone.
Meythaler et al. (2002) USA RCT PEDro=6 N=35	**Population:** TBI; Mean Age=31 yr; Gender: Male=26, Female=9; Mean GCS=5.4; Time Post Injury <6 wk. **Treatment:** In a crossover design, patients were initially treated with 200 mg/day amantadine (Group 1, n=15) or placebo (Group 2, n=20) for 6wk, after which they received the opposite treatment for the subsequent 6 wk. **Outcome Measure:** Mini Mental Status Exam (MMSE), Disability Rating Scale (DRS), Functional Independence Measure-Cognitive (FIM-cog), Galveston Orientation and Amnesia Test.	1. In Group 1, there was an improvement in MMSE scores (14.3 points, p=0.0185), DRS (9.8 points, p=0.0022), GOS (0.8 points, p=0.0077), and FIM-cog (15.1 points, p=0.0033) with amantadine; no improvements occurred during placebo phase (p>0.05). 2. In Group 2, there was an improvement in MMSE scores (10.5 points, p=0.0015), DRS (9.4 points, p=0.0006), GOS (0.5 points, p=0.0231), and FIM-cog (11.3 points, p=0.003) on placebo. 3. On amantadine Group 2 continued to make significant gains in MMSE (6.3 points; p=0.0409), DRS (3.8 points; p=0.0099), and FIM-cog (5.2 points; p=0.0173).

PEDro=Physiotherapy Evidence Database rating scale score (Moseley et al., 2002).

Discussion

Three retrospective studies that assessed amantadine were identified. In a case-control study, Hughes et al. (2005) found that patients receiving amantadine were no more likely to emerge from coma compared to those not receiving it. However, the authors mentioned that potential confounders may have affected the results, and that the point at which patients were considered to have emerged from the coma was arbitrarily assessed. In a chart review, Whyte et al. (2005) only selected patients who received amantadine 4-16 weeks post injury, in order to assess its potential in improving consciousness after medical stability was reached. The authors noted that patients who received amantadine showed significant improvements in disability one week after administration when compared to patients treated by other methods. They also reported no significant difference between groups in the time to first response to directions. In another chart review, patients who were treated with amantadine showed significant improvements in consciousness at discharge and decreased mortality rates when compared to those who did not receive it (Saniova et al., 2004). While the retrospective nature of these studies makes it difficult to draw conclusions, all authors recommended amantadine as a safe intervention with promising potential but suggested that further research was warranted.

Two RCTs have evaluated the effectiveness of amantadine in improving consciousness in adults. Using a crossover design, Meythaler et al. (2002) assessed patients for orientation, cognitive function, functional independence, and disability. The authors found that patients who received amantadine made significant gains on all outcome measures over six weeks, but made no further gains when switched to placebo for another six weeks. Patients initially receiving placebo made small gains, but went on to make further improvements after amantadine induction. While patients made some natural recovery on placebo, the authors noted that patients made more pronounced improvements on amantadine. They also suggested that amantadine aids in recovery regardless of the time of administration. Similarly, a

trial by Giacino et al. (2012) found a significant improvement in disability in participants who received amantadine over four weeks when compared to placebo. However, following a two-week follow-up without amantadine treatment, their recovery slowed such that overall improvements were similar between the two groups (Giacino et al., 2012). The authors recommended that amantadine treatment may continue until recovery goals are reached, although it should be approached with caution.

When examining the use of Amantadine for children, two RCTs have been conducted. Amantadine was compared to a placebo in a cross-over study by McMahon et al. (McMahon et al., 2009). Although no significant differences were noted between the drugs in terms of recovery using standardized measures, physicians noted greater improvements in consciousness when amantadine was administered. It is possible the benefits of amantadine were not shown due to the small sample size of this study (n=7) and the fact two patients dropped out. A child was withdrawn due to medical complications and another was removed because the family requested unblinded administration of amantadine in the second three weeks. In the second RCT, Patrick et al. Patrick et al. (2006) compared amantadine to pramipexole (both dopamine agonists) for children and adolescents who remained in a low-responsive state one month post injury. Patients in both groups made significant improvements on the Coma/ Near Coma Scale (CNCS), the Western NeuroSensory Stimulation Profile (WNSSP), and the DRS weekly gains. Patients also improved on Rancho Los Amigos Scale level. There were no significant side effects to treatment which, combined with the positive results, suggest that dopamine agonists may be a viable option for coma arousal in children and adolescents. However, the lack of control group and small sample size warrant further study before conclusions are drawn.

Green et al. (2004) evaluated the safety of amantadine in a paediatric population. In this study, five out of 54 patients experienced side effects which were all readily reversible. The significant change in Rancho Los Amigos Scale level in the treatment group was questionable due to differences in baseline. There were no significant differences in post-traumatic amnesia (PTA) or length of stay. The subjective improvements reported were difficult to distinguish from natural recovery.

Conclusions

There is level 1b evidence that pramipexole, and level 1a evidence that amantadine, may be effective in improving levels of consciousness in children with ABI.

There is level 1a evidence that amantadine may effectively improve consciousness, cognitive function, and disability when compared to placebo.

Amantadine may improve consciousness, cognitive function, and disability post ABI.

Amantadine and pramipexole may be effective in improving levels of consciousness in children post TBI.

12.12.1.2 Amantadine and Cognitive Rehabilitation

Amantadine is a non-competitive N-methyl-D-aspartate receptor antagonist and has been used as an antiviral agent, as a prophylaxis for influenza A, for the treatment of neurological diseases such as Parkinson's disease, and in the treatment of neuroleptic side-effects such as dystonia, akinthesia and

neuroleptic malignant syndrome (Schneider et al., 1999a). It is also thought to work pre- and post-synaptically by increasing the amount of dopamine (Napolitano et al., 2005).

Table 12.35 Effects of Amantadine on Executive Functioning and Learning and Memory Deficits

Author/ Year/ Country/ Study Design/ N	Methods	Outcomes
Kraus et al. (2005) USA Pre-Post N=22	**Population:** TBI; Mean Age=36yr; Gender: Male=17, Female=5; Severity of Injury: Mild=6, Moderate=6, Severe=10; Mean Time Post Injury=63.2mo. **Treatment:** Positron emission tomography (PET) scan was done and participants received amantadine (100mg titrated to up to 400mg/d over 3wk). Amantadine was administered 3×/d (200mg at 8AM, 100mg at 12PM, and 100mg at 4PM) for 12wk. **Outcome Measure:** Trail Making Test part A and B (TMT A, TMT B), Controlled Oral Word Association Test (COWAT), Digit Span, California Verbal Learning Test (CVLT), Rey Osterreith Complex Figure-immediate (Rey Im) and delayed (Rey De) recall.	1. Measures of executive function, as indicated by TMT B and COWAT, were significantly improved in patients following treatment with amantadine (t=-2.47; p<0.02). 2. No significant differences were found on measures of attention (TMT A and Digit Span) or memory (CVLT, Rey Im, and Rey De). 3. Correlational analyses with PET scan results suggest that there may be a strong relationship between executive domain improvement and changes in left pre-frontal metabolism (r=0.92; p=0.01) and left medial temporal metabolism (r=0.91; p=0.01).
Schneider et al. (1999b) USA RCT PEDro=5 N=10	**Population:** TBI; Mean Age=31yr; Gender: Male=7, Female=3; GCS Score Range=3-11. **Treatment:** Patients randomized to either amantadine (50-150mg 2x/d) or placebo for 2wk in a crossover design with a 2wk washout period. **Outcome Measure:** Battery of Neuropsychological tests, Neurobehavioural Rating Scale.	1. There was a general trend towards improvement in the study sample over the 6wk. 2. There were no significant between group differences in terms of orientation (p=0.062), attention (p=0.325), memory (p=0.341), executive flexibility (p=0.732) or behaviour (p=0.737).

Discussion

In a small sample RCT by Schneider et al. (1999a) the effects of Amantadine on cognition and behaviours was assessed. In this six week cross-over study, patients received both placebo and amantadine. Although the study found that patients improved over the six week study period, statistical comparison of results evaluating the five subsets of attention, executive/flexibility, memory, behaviour and orientation did not demonstrate any significant effect for the use of Amantadine. Similarly, Kraus et al. (2005) demonstrated that the administration of amantadine over a 12-week treatment period does not improve memory deficits or attention; however, significant improvements in executive functioning were observed. Given the quality and sample size of the current studies, future studies exploring the efficacy of amantadine for learning and memory are warranted.

Conclusions

There is level 2 evidence that Amantadine may not help to improve learning and memory deficits.

Amantadine has been shown to be ineffective in improving attention and memory deficits. Its impact on executive functioning should be studied further.

12.12.1.3 Amantadine and Aggression

Amantadine is a non-competitive N-methyl-D-aspartate receptor antagonist that decreases glutamate levels, which may improve learning, memory, and behaviour deficits (Hammond et al., 2014). However, the effects of amantadine on reducing irritability and aggression have yet to be established among the TBI population.

Table 12.36 Effects of Amantadine on Reducing Aggression

Author/ Year/ Country/ Study Design/ N	Methods	Outcomes
Hammond et al. (2015) USA RCT PEDro=10 $N_{Initial}$=168, N_{Final}=157	**Population:** TBI=168; *Amantadine (n=82)*: Mean Age=40.2 yr; Gender: Male=66, Female=16; Severity: Mild=20, Moderate=3, Severe=59. *Placebo (n=86)*: Mean Age=38.2 yr; Gender: Male=64, Female=22; Severity: Mild=22, Moderate=1, Severe=63. **Intervention:** Participants were randomized to receive either 100 mg of amantadine or a placebo every morning and at 12pm for 60 days. Assessments to determine state of irritability were conducted at baseline, 28 days, and 60 days. **Outcome Measure:** Neuropsychiatric Inventory Irritability (NPI-I) Most Problematic, NPI-I Most Aberrant, NPI-I Distress.	1. No significant differences in irritability between groups on observer NPI-I ratings at 28 days or 60 days, but both groups showed improvement in irritability. 2. Participant-rated NPI-I Most Problematic (p=.0353) and Distress (p=.0362) scores were significantly different between amantadine and placebo at 60 days, however after adjustment multiple comparisons revealed no significant difference.
Hammond et al. (2014) USA RCT PEDro=9 $N_{Initial}$=76, N_{Final}=72	**Population:** TBI=76; *Amantadine Group (n=38)*: Mean Age=34.7 yr; Gender: Male=25, Female=13; Mean Time Post Injury=5.3 yr; Mean GCS=9.5. *Placebo Group (n=38)*: Mean Age=42.1 yr; Gender: Male=22, Female=16; Mean Time Post Injury=4.7 yr; Mean GCS=7.5. **Intervention:** Participants were randomized to receive placebo or 100 mg of amantadine hydrochloride in the morning and at 12pm every day for 28 days. Participants were assessed for effects of amantadine on irritability and aggression at baseline and post-treatment. **Outcome Measure:** Neuropsychiatric Inventory (NPI) Irritability (NPI-I) and NPI Agitation/Aggression (NPI-A), NPI Distress (NPI-D), Beck Depression Inventory-II (BDI-II), Brief Symptom Inventory (BSI), Global Mental Health Scale (GMHS).	1. 81% of patients with a TBI who took amantadine had improved irritability by at least 3 points on NPI-I, compared to 44% of placebo (p=.0016). 2. Significant difference in frequency and severity of irritability on NPI-I between amantadine and placebo groups (p=.0085). 3. No significant differences between amantadine and placebo on NPI-D, BDI-II, GMHS, or BSI-anxiety. 4. Only individuals with moderate to severe aggression at baseline on NPI-A had significant change in aggression after amantadine treatment compared to placebo (p=.046).

Discussion

One placebo-controlled RCT compared the effects of amantadine on irritability and aggression. The frequency and severity of irritability were reduced when individuals were on Amantadine for 28 days, compared to placebo. However, Amantadine only significantly reduced aggression in individuals who had moderate-severe aggression at baseline (Hammond et al., 2014). A second RCT furthered Hammond et al. Hammond et al. (2014) findings by assessing the effects of Amantadine on irritability and aggression for up to 60 days. Amantadine produced a non-significant reduction in irritability compared to placebo at 28 and 60 days, according to the most problematic and aberrant items on the neuropsychiatric inventory (Hammond et al., 2015).

Conclusions

There is conflicting evidence of the effects of amantadine on reducing irritability and aggression in individuals with moderate-severe traumatic brain injury.

Amantadine requires further research before conclusions can be drawn on its effects on aggression.

12.12.2 Dopamine Medications used in the Paediatric Population

Table 12.37 Effects of Dopamine Enhancing Medication in Children

Author/ Year/ Country/ Study Design/ N	Methods	Outcomes
Patrick et al. (2003) USA Case Series N=10	**Population:** TBI=7, CVA=2, Encephalopathy=1; Mean Age=13.7 yr; Gender: Male=7, Female=3; Mean GCS=3.1; Mean Time Post Injury=52.5 days. **Treatment:** Each child in a low response state (i.e., vegetative or minimally conscious) was placed on a dopaminergic agonist: amantadine (n=3), pramipexole (n=3), bromocriptine (n=1), levodopa (n=1) or methylphenidate (n=4) for a mean of 39 days. Two received multiple agonists. **Outcome Measure:** Western NeuroSensory Stimulation Profile (WNSSP).	1. Final WNSSP assessments (87.5±27.7) significantly improved from baseline (14.4±3.0; p<0.01). 2. Rate of improvement in WNSSP scores was significantly greater during the medication phase (0.89±0.31) than in the pre-medication phase (0.68±0.15; p=0.02)

Discussion

Patrick et al. (2003) examined the effect of a number of dopamine enhancing medications on improvement in arousal and awareness for individuals in a low response state. This study suggests a positive relationship between rate of recovery for children in a low response state and administration of dopamine-enhancing drugs. Limitations of this study include: a retrospective design, a small sample size (n=10), and multiple medications being studied.

Conclusions

There is level 4 evidence that dopamine-enhancing drugs may accelerate the rate of recovery from a low response state for children post TBI.

Dopamine enhancing drugs may accelerate the rate of recovery from a low response state post TBI in children.

12.12.3 Bromocriptine

Bromocriptine is a dopaminergic agonist which primarily affects D_2 receptors (Whyte et al., 2008). It has been suggested that dopamine is an important neurotransmitter for prefrontal function (McDowell et

al., 1998). In a study looking at the effects of bromocriptine on rats, Kline et al. (2002) noted that the animals showed improvement in working memory and spatial learning; however, this improvement was not seen in motor abilities. Three studies have been identified investigating the use of bromocriptine as an adequate treatment for the recovery of cognitive impairments following brain injury.

Table 12.38 Effects of Bromocriptine on Executive Functioning

Author/ Year/ Country/ Study Design/ N	Methods	Outcomes
Whyte et al. (2008) USA RCT PEDro=7 N=12	**Population**: Moderate/ Severe TBI; Mean Age=35.75 yr; Gender: Male=8, Female=4; Median Time Post Injury=3.3 yr. **Treatment:** In a crossover design, participants were randomly assigned to receive bromocriptine (1.25 mg 2×/day titrated to 5 mg 2×/day over a 1wk), followed by placebo or the reverse order. Each lasted 4 wk with a 1 wk washout period. **Outcome Measure:** Attention Tasks.	1. Though some improvements were observed in certain subtests of attentional tasks (e.g. speed decline, decline in responding, test of everyday attention), they were not significant. 2. Overall results suggest bromocriptine had little effect on attention.
McDowell et al. (1998) USA RCT PEDro=4 N=24	**Population:** TBI; Median Age=32.5 yr; Gender: Male=20, Female=4; GCS Range=3-8; Time Post injury Range=27 days-300 mo. **Treatment:** In a crossover design, participants were randomly assigned to receive 2.5 mg bromocriptine (2.5 mg) then placebo, or receive treatment in the reverse order. **Outcome Measure:** Dual-task paradigm (counting and digit span), Stroop Test, spatial delayed-response task, Wisconsin Card Sorting Test (WCST), reading span test, Trail Making Test (TMT), controlled oral word association test (COWAT), and control tasks.	1. Following bromocriptine treatment there were significant improvements on the dual-task counting (p=0.028), dual-task digit span (p=0.016), TMT (p=0.013), Stroop Test (p=0.05), COWAT (p=0.02), and WCST (p=0.041). 2. Bromocriptine had no significant effects on working memory (e.g. spatial delayed-response task and reading span test; p=0.978), or on control tasks (p=0.095).
Powell et al. (1996) UK Case Series N=11	**Population:** TBI=8, SAH=3; Mean Age=36 yr; Gender: Male=6, Female=5; Time Post Injury Range=2 mo-5 yr. **Treatment:** Patients received bromocriptine (a maximum dose of 5-10 mg/day). Patient assessments included two baseline evaluations (BL1 and BL2), evaluation when stabilized at maximum bromocriptine dose (MAXBROMO), and two post withdrawal evaluations (POST1 and POST2). **Outcome Measure:** Percentage participation index (PPI), spontaneity, motivation, card arranging reward responsivity objective test (CARROT), digit span, Buschke selective reminding test (BSRT), verbal fluency, and hospital anxiety and depression scale.	1. Reported PPI (p<0.0001), motivation, and spontaneity (both p<0.005) increased significantly from BL2 to MAXBROMO. Improvements were seen in CARROT as well (p<0.0001). 2. Significant improvements were observed from BL2 to MAXBROMO on the digit span (p<0.001), BSRT (p<0.01), and verbal fluency (p<0.001). Scores on all three tests decreased (non-significant) from MAXBROMO to POST1, scores recovered to near MAXBROMO levels by POST2. 3. Bromocriptine was not associated with improvements in mood state.

PEDro=Physiotherapy Evidence Database rating scale score (Moseley et al., 2002).

Discussion

The question of whether bromocriptine improves cognitive function in patients with ABI was explored in two RCTs (McDowell et al., 1998; Whyte et al., 2008) and a case series (Powell et al., 1996). In an earlier investigation, low-dose bromocriptine (2.5 mg daily) improved functioning on tests of executive control including a dual task, Trail Making Test (TMT), the Stroop test, the Wisconsin Card Sorting Test (WCST)

and the controlled oral word association test (COWAT) (McDowell et al., 1998). However, bromocriptine did not significantly influence working memory tasks. Further, a study by Whyte et al. (2008) found that bromocriptine had little effect on attention. It was noted that several participants did experience moderate to severe drug effects and withdrew or were withdrawn from the study.

Although McDowell et al. (1998) demonstrated some benefits following administration of bromocriptine, there was only a single administration of bromocriptine and the dose was considerably lower than that given by Whyte et al. (2008). Spontaneous recovery may have been a factor leading to the improved abilities in individuals receiving a single dose (2.5mg daily) of the medication; however, study results did not answer this question. Results from Whyte et al. (2008) noted that the placebo group demonstrated better (although not significant) trends in improvement on the various tasks administered. Powell et al. (1996) conducted a multiple baseline design on 11 patients with TBI or subarachnoid hemorrhage who received bromocriptine. Improvements were found on all measures assessed except mood.

Conclusions

Based on two RCTs, there is conflicting evidence supporting the use of bromocriptine to enhance cognitive functioning.

There is level 4 evidence that bromocriptine may improve all motivational deficits except mood.

Bromocriptine may improve some executive cognitive functions such as dual task performance and motivational deficits but it may not consistently improve memory. More research is needed before the benefits of using bromocriptine to enhance cognitive functioning are known.

12.13 Hormone Therapy

12.13.1 Dexamethasone and the Paediatric Population

In the past, literature with adult subjects investigating the use of steroids in severe TBI reported conflicting results. The following studies investigated the effects of dexamethasone on children with an ABI.

Table 12.39 Effects of Dexamethasone in Severe TBI

Author/ Year/ Country/ Study Design/ N	Methods	Outcomes
Fanconi et al. (1988) Switzerland RCT PEDro=5 N=25	**Population:** Head Injury; *Dexamethasone Group (n=13)*: Mean Age=7.5 yr; Mean GCS=5.5; *Control Group (n=12)*: Mean Age=7.4 yr; Mean GCS=4.5. **Treatment:** Children with severe head injury were randomized to either receive dexamethasone (1 mg/kg/day for 3 days) or nothing. **Outcome Measure:** Urinary free cortisol, pneumonia, intracranial pressure (ICP), and Glasgow Outcome Scale (GOS).	1. Patients receiving dexamethasone showed depression of endogenous cortisol, while those not receiving dexamethasone had a 5-fold increases in basal mean free cortisol. 2. A higher frequency of pneumonia was reported in the group receiving exogenous steroids. 3. No measurable difference in ICP, duration of ventilation or GOS at 6mo.

Author/ Year/ Country/ Study Design/ N	Methods	Outcomes
Kloti et al. (1987) Switzerland RCT PEDro=3 N=24	**Population:** Head Injury; *Dexamethasone Group (n=12)*: Mean Age=7.83 yr; Mean GCS=5.5; *Control Group (n=12)*: Mean Age=7.58 yr; Mean GCS=4.5. **Treatment:** Children with severe head injury were randomized to receive either dexamethasone (1 mg/kg/day for 3 d) or nothing. **Outcome Measure:** Urinary free cortisol.	1. Children receiving dexamethasone displayed suppression of endogenous cortisol production; the control group produced 20-fold higher free cortisol. The difference in mean values was significant beginning on day 2 and lasting to day 6 ($p<0.05$).
Dearden et al. (1986) UK RCT PEDro=4 N=130	**Population:** TBI; Severity: Mild/ Moderate=23, Severe=107; *Steroid Group (n=68)*: Age Range=7-79 yr; Gender: Male=44, Female=24; Time Post Injury: ≤8hr=50, >8hr=18; *Placebo Group (n=62)*: Age Range=3-74 yr; Gender: Male=49, Female=13; Time Post Injury: ≤8 hr=43, >8 hr=19. **Treatment:** Patients were randomized to receive either intravenous (IV) bolus of dexamethasone or placebo. Children's doses were proportionate to their weight. Adults received an alternate dose. **Outcome Measure:** Intracranial pressure (ICP) and Glasgow Outcome Scale (GOS).	1. Outcome at 6 mo was worse in the steroid group compared to the placebo group, but the difference was not significant (49% versus 35.5% dead or vegetative; p=n.s.). 2. Patients in the steroid group with ICP >20 mmHg showed significantly poorer outcomes compared to similar patients in the placebo group ($p<0.05$). This was also true with patients with ICP >30mmHg (p=0.0377).

PEDro=Physiotherapy Evidence Database rating scale score (Moseley et al., 2002).

Discussion

The paediatric data highlights the fact that dexamethasone suppresses endogenous production of glucocorticoids (Fanconi et al., 1988; Kloti et al., 1987), therefore bringing into doubt any beneficial effect of exogenous glucocorticoids. This evidence, along with findings from Dearden et al. (1986) that dexamethasone failed to show difference in outcome in a mixed adult and paediatric sample, underscores the lack of firm data to support the use of these drugs in individuals with brain injury.

Conclusions

There is level 2 evidence that administration of dexamethasone may inhibit endogenous production of glucocorticoids and has no proven impact on recovery post brain injury.

Administration of dexamethasone may inhibit endogenous production of glucocorticoids in children.

Dexamethasone administration has no proven impact on recovery post brain injury in children.

12.13.2 Medroxyprogesterone

Sexual dysfunction following TBI has been reported to occur in at least 50% of patients (Emory et al., 1995). Hypersexuality is less common than hyposexuality (decreased libido) but results in a greater negative effect for the individual and results in a great burden of care by limiting independence. Hypersexual behaviour can encompass a range of behaviours, from indiscriminate sexual advances,

promiscuity, and exhibitionism, to assault and/or rape (Mania et al., 2006). A recent study revealed inappropriate sexual talk to be the most common inappropriate sexual behaviour in a sample of TBI patients (Simpson et al., 2013). Treatment for sexual offenders without brain injuries has included pharmacological intervention and or counselling and education. Typically, medication is used to reduce the sexual drive, but it is unclear if it has effect on cognitive processing (i.e., preservative thoughts regarding sex).

Table 12.40 Effects of Depo-Provera on Sexually Aggressive Behaviour

Author/ Year/ Country/ Study Design/ N	Methods	Outcomes
Emory et al. (1995) USA Case Series N=8	**Population:** TBI; Mean Age=17.5 yr; Gender: Male=8, Female=0. **Treatment:** Weekly intramuscular injections of Depo-Provera (400 mg) in conjunction with directive, individual-specific counseling for 6mo. **Outcome Measure:** Incidence of hypersexual behaviour, change in testosterone level.	1. Family members report all subjects stopped aberrant behaviour while taking medication. 2. Blood work revealed a drop in testosterone from 834 to 85 mg/dL; 3 subjects returned to previous patterns after stopping medication (due to inconsistent family support). 3. 3 subjects dramatically improved and did not stop medication.

Discussion

In a retrospective study, Depo-Provera, an anti-androgen drug, was evaluated in terms of its efficacy for controlling sexual aggression in eight males with TBI experiencing onset of sexual aggression three years post injury (Emory et al., 1995). Weekly IM injections of Depo-Provera (400 mg) in conjunction with monthly psychoeducational counseling resulted in a cessation of hypersexual behaviour and reduced testosterone levels. Three subjects re-offended when the drug was stopped, three remained on it and two stopped taking the drug and had maintained cessation of hypersexual behaviour.

Conclusions

There is level 4 evidence that Depo-Provera and counselling may reduce sexually aggressive behaviour.

Medroxyprogesterone intramuscularly may reduce sexual aggression.

12.13.3 Progesterone

Progesterone has drawn interest as a potential neuroprotective agent. Animal studies have suggested that progesterone reduces cerebral edema, regulates inflammation, reconstitutes the blood brain barrier, modulates excito-toxicity, and decreases apoptosis (Stein, 2008). In the human population, Groswasser et al. (1998) observed that female patients with TBI recovered better than male patients and suggested progesterone as a possible cause of this disparity. Trials have since been undertaken to accurately assess the effects of progesterone in the ABI population.

The AANS and the EBIC made no recommendations regarding progesterone in acute ABI.

Table 12.41 Progesterone for the Acute Management of ABI

Author/ Year/ Country/ Study Design/ N	Methods	Outcomes
Skolnick et al. (2014) Belgium RCT PEDro=7 N=1195	**Population:** TBI. *Progesterone (n=591)*: Median Age=35yr; Gender: Male=464, Female=127; Median Time Post Injury=7 hr 4 min; GCS Range≤8. *Placebo (n=588)*: Median Age=34 yr; Gender: Male=463, Female=125; Median Time Post Injury=7 hr 2 min; GCS≤8. **Intervention:** Participants were randomized to receive progesterone or placebo for 120 hr. Outcomes were assessed at baseline and 6mo. **Outcome Measure:** Glasgow Outcome Scale (GOS).	1. There was no significant difference in GOS scores between groups among participants with the worst prognosis (n=393; p=0.36). 2. There was no significant difference in GOS scores between groups among participants with intermediate prognosis (n=394; p=0.82). 3. There was no significant difference in GOS scores between groups among participants with the best prognosis (n=392; p=0.38).
Wright et al. (2014) USA RCT PEDro=10 N=882	**Population:** TBI; Median Age=35 yr; Gender: Male=650, Female=232; Mean Time Post Injury=218.1 min; Severity: Moderate=254, Moderate to Severe=472, Severe=156. **Intervention:** Participants were randomized to receive intravenous infusions of progesterone (n=442) or placebo (n=440). Progesterone was administered continuously at 14.3 mL/hr for 1 hr, then at 10 mL/hr for 71 hr. The dose was tapered by 2. 5mL/hr every 8 hr, for total treatment duration of 96 hr. Outcomes were assessed at 6 mo. **Outcome Measure:** Glasgow Outcome Scale Extended (GOSE), Mortality, Adverse Effects.	1. Favourable outcomes occurred in 51% of patients treated with progesterone and in 55.5% of the placebo group. Relative benefit was 0.95, meaning fewer favourable outcomes are expected in the progesterone group. 2. Mortality at 6 mo did not differ significantly between the two groups. 3. The frequency of adverse effects did not differ significantly between the two groups, with the exception of phlebitis or thrombophlebitis, which was higher in the progesterone group (17.2% versus. 5.7%; relative risk, 3.03).
Shakeri et al. (2013) Iran RCT PEDro=7 N=76	**Population:** TBI; Gender: Male=76, Female=0; Time Post Injury≤6 hr. *Progesterone Group (n=38):* Mean Age=33.97 yr; Mean GCS=5.74. *Control Group (n=38):* Mean Age=34.68 yr; Mean GCS=5.79. **Intervention:** Participants were randomized to receive progesterone (1 mg/kg, every 12 hr for 3 days) or no treatment (control). Outcomes were assessed at 3 mo. **Outcome Measure:** GCS, Glasgow Outcome Scale (GOS).	1. Admission and discharge GCS were not significantly different between groups. 2. GOS scores at 3 mo follow-up showed no significant differences between groups in terms of favourable outcomes. 3. In patients with GCS=5-8, there was a significant difference in favourable outcomes between treatment and controls (16.67% versus 10%, p=0.03); this was not seen in patients with GCS<5.
Xiao et al. (2008) China RCT PEDro=7 N=159	**Population:** TBI. *Progesterone (n=82)*: Mean Age=30 yr; Gender: Male=58, Female=24; Mean Time Post Injury=3.80 hr; Mean GCS=6.0. *Placebo (n=77)*: Mean Age=31 yr; Gender: Male=57, Female=25; Mean Time Post Injury=3.65 hr; Mean GCS=6.1. **Intervention:** Patients were randomized to receive intramuscular progesterone or placebo. Progesterone was administered at 1.0 mg/kg twice a day for 5 days. **Outcome Measure:** Intracranial Pressure (ICP), Glasgow Outcome Scale (GOS), Modified Functional Independence Measure (mFIM), Mortality.	1. Progesterone group showed more favourable outcomes on the GOS than controls at 3 mo (47% versus 31%, p=0.034) and 6 mo (58% versus 42%, p=0.048). 2. Progesterone group had higher mean mFIM scores at 3 mo (8.02 versus 7.35, p<0.05) and 6 mo (9.87 versus 8.95, p<0.01). 3. Mortality at 6 mo was significantly lower in the treatment group than the control group (18% versus 32%, p<0.039). 4. No significant difference in ICP was noted between groups. 5. No AEs were reported after treatment of progesterone.

Wright et al. (2007) USA RCT PEDro=10 N=100	**Population:** TBI; Mean Age=35.8 yr; Gender: Male=71, Female=29; Mean Time Post Injury=379.2 min; Severity: Mild/Moderate=28, Severe=72. **Intervention:** Patients were randomized in a 4:1 ratio to intravenous progesterone (n=77) or placebo (n=23). Progesterone was administered at a leading dose of 0.71 mg/kg at 14 mL/hr for 1 hr, then at 10 mL/hr for 11 hr, followed by five 12 hr maintenance infusions at 10 mL/hr over 3 days. Outcomes were assessed 30 days post injury. **Outcome Measure:** Glasgow Outcome Scale Extended (GOSE), Disability Rating Scale (DRS), Adverse Events (AE), Intracranial Pressure (ICP).	1. AE rates and physiological variables (e.g. ICP) were similar between groups. No serious AEs were associated with progesterone. 2. The placebo group had a higher 30 days mortality rate compared to the progesterone group (RR 0.43). 3. Patients with severe injury (GCS=4-8) were functioning at a relatively poor level, regardless of group. 4. For patients with moderate injury (GCS 9-12), those in the progesterone group compared to the placebo group were more likely to have moderate or good recovery on GOSE (55.6% versus 0%, p=0.0202) and better score on DRS (5.0 versus 12.7).

PEDro=Physiotherapy Evidence Database rating scale score (Moseley et al., 2002).

Discussion

In an RCT, Wright et al. (2007) evaluated patients receiving the medication over three days and found no significant improvement in ICP levels over placebo. However, these patients showed a decreased 30-day mortality rate without an increased rate of complications. As well, less severe patients in this group also showed significantly greater rates of favourable outcomes on the GOSE. Noting limitations in group distribution within their study, the authors recommended a larger clinical trial. Xiao et al. (2008) conducted such a trial with patients receiving progesterone or placebo over five days. They similarly reported a lack of improvement in ICP over placebo, but significantly greater GOS and FIM scores at three months and six months, and lower mortality at six months. They also reported no complications associated with progesterone administration.

In contrast, more recent trials have reported no significant differences in outcomes between those receiving progesterone or placebo after three months and six months (Shakeri et al., 2013; Skolnick et al., 2014; Wright et al., 2014). However, in a subgroup analysis of patients with initial GCS≥5, Shakeri et al. (2013) found a significant improvement in GOS scores associated with progesterone. As well, one study reported that progesterone was not associated with increased rate of serious adverse events (Wright et al., 2014). Given the conflicting findings between studies, the evidence regarding progesterone in acute ABI should be taken with caution.

Conclusions

There is level 1a evidence that progesterone may not lower intracranial pressure levels post TBI when compared to placebo.

There is level 1a evidence that progesterone may not be associated with adverse events when compared to placebo.

There is conflicting level 1a evidence as to whether progesterone improves long-term outcomes and reduces mortality post TBI when compared to placebo.

Progesterone may improve Glasgow Outcome Scale scores and reduce mortality rates up to 6 months post injury, without an increased rate of adverse events.

Progesterone may not be effective in lowering intracranial pressure levels.

12.14 (a) Psychostimulants

12.14.1 Methylphenidate

12.14.1.1 Methylphenidate and Cognitive Functioning

Methylphenidate is a stimulant whose exact mechanism is unknown (Napolitano et al., 2005). One theory is that methylphenidate acts on the presynaptic nerve to prevent the reabsorption of serotonin and NE, thereby increasing their concentrations within the synaptic cleft. This in turn leads to increased neurotransmission of serotonin and NE (Kim et al., 2006). Methylphenidate has been extensively used as a treatment for attention deficit disorder, as well as narcolepsy (Glenn, 1998). A total of six RCTs examined the efficacy of methylphenidate as a treatment for the recovery of cognitive deficits post brain injury.

Table 12.42 Effects of Methylphenidate on Cognitive Functioning

Author/ Year/ Country/ Study Design/ N	Methods	Outcomes
Willmott et al. (2013) Australia RCT PEDro=10 N=32	**Population:** TBI; Gender: Male=21, Female=11; Mean Time Post Injury=68 days; *TBI Val/Val Group (n=11)*: Mean Age=22.64yr; Mean GCS=4.67; *TBI Val/Met Group (n=14)*: Mean Age=28.57 yr; Mean GCS=5.38; *TBI Met/Met Group (n=7)*: Mean Age=30.57 yr; Mean GCS=6.83. **Treatment:** Participants with TBI, in a crossover design, received 0.3 mg/kg methylphenidate (2×/day) for 6 sessions in total (spanning 2 wk), alternating between treatment and placebo for every other session. Results were compared against those from healthy controls (n=40). **Outcome Measures:** Ruff 2 & 7 Selective Attention Test – automatic (2 & 7 ASRS) and controlled (2 & 7 CSRS), Selective Attention Task, Four Choice Reaction Time Task (4CRT) – dissimilar compatible (DC) and similar incompatible (SI), Symbol Digit Modalities Test (SDMT), Letter Number Sequencing Task, and Wechsler Test of Adult Reading.	1. At baseline, there were no significant differences across various genotypes on attentional performance. 2. Participants with TBI and Met/Met alleles performed significantly poorer on the SDMT ($p<0.0005$), 2 & 7 ASRS ($p=0.001$), 2 & 7 CSRS ($p<0.0005$), DC RT ($p=0.005$), and SI RT ($p=0.002$), when compared to controls. Analyses with participants with TBI and Val/Val alleles showed even worse outcomes, demonstrating poorer performance on 7/8 outcome measures. 3. Following methylphenidate treatment one significant drug and genotype interaction was seen between Met/Met carriers and performance on the SDMT ($F=4.257$; $p=0.024$), suggesting Met/Met carriers were more responsive to methylphenidate than either the others.
Kim et al. (2012) USA RCT PEDro=7 N=23	**Population:** Moderate/Severe TBI; Mean Age=34.2 yr; Gender: Male=18, Female=5; Mean Time Post Injury=51.1 mo. **Treatment:** In a crossover design, participants were randomly assigned to receive 0.3 mg/kg methylphenidate followed by placebo, or the reverse and were assessed after each. **Outcome Measure:** Visual sustained attention task (VSAT) and two-back task.	1. Relative to placebo, both accuracy (1.62±1.03 versus 2.23±1.07; $p<0.005$) and mean reaction time (827.47±291.17 sec versus 752.03±356.87 sec; $p<0.05$) in the VSAT were improved significantly on MPH. 2. Relative to placebo, mean reaction time (929.31±192.92 sec versus 835.02±136.12 sec; $p<0.05$), but not

Author/ Year/ Country/ Study Design/ N	Methods	Outcomes
		accuracy, in the two-back task was improved significantly when on MPH.
Willmott & Ponsford (2009) RCT PEDro=10 N=40	**Population:** TBI; Mean Age=26.93 yr; Gender: Male=28, Female=12; Time since injury=68.38 days. **Treatment:** Patients received either methylphenidate (0.3 mg/kg 2x/day, rounded to the nearest 2.5 mg) or a placebo. Patients were seen for 6 sessions across 2 week period. Patients then crossed-over. **Outcome Measure:** Ruff 2 and 7 Selective Attention Test, Selective Attention Task, Four Choice Reaction Time Task, Sustained Attention to Response Task, Symbol Digit Modalities Test, Letter Number Sequencing Task, Wechsler Test of Adult Reading.	1. Methylphendiate significantly increased speed of information processing on the Symbol Digit Modalities Test (p=0.02); Ruff 2 and 7 Test-Automatic Condition (p=0.003); Simple Selective Attention Task (p=0.001); Dissimilar compatible (p=0.003), and Similar Compatible (p=0.002).
Pavlovskaysa et al. (2007) Pre-Post Israel N=6	**Population:** TBI; Age Range=18-47 yr; Gender: Male=4, Female=2; GCS ≥8. **Treatment:** Participants were administered 5 to 10 mg of methylphenidate (MHP) over a 2 week period. Participants were evaluated before, during and after the administration of methylphenidate. **Outcome Measure:** Performance on the visual spatial attention task analyzing rightward and leftward shifts of attention.	1. Prior to treatment, patients were found to have great difficulty in shifting attention between hemifields. 2. There was a significant improvement in the asymmetry with MHP (p<0.001). 3. The right side performance was significantly better on average than the left side (0.77 versus 0.59; p<0.05). 4. Performance was significantly better for ipsilateral valid cueing (p<0.01) than for invalid cross-trials (p<0.001). 5. The difference between ipsi- and cross-cueing for left side target performance is significant for each of the stags (p<0.001).
Kim et al. (2006) Korea RCT PEDro=6 N=18	**Population:** TBI; *Methylphenidate Group (n=9)*: Mean Age=30.1 yr; Gender: Male=9, Female=0; Mean Time Post Injury=1.6 yr; *Placebo Group (n=9)*: Mean Age=38.3 yr; Gender: Male=7, Female=2; Mean Time Post Injury=3.6 yr. **Treatment:** Patients were randomly allocated to receive either 20 mg methylphenidate or the placebo. Assessments were done at baseline (T1), 2 hr post treatment (T2), and 2 days later (T3). **Outcome Measure:** Visual sustained attention task (VSAT) and two-back task.	1. At T1 there were no significant differences in mean reaction time or in accuracy between the two groups. 2. For those in the treatment group, the mean reaction time of the two-back task improved significantly compared to those in the placebo group from T1 to T2 (13.74±13.22% versus 4.02±9.48%; p<0.05). 3. No significant difference in improvement as seen with accuracy of the two-back task (p=0.07), nor with the VSAT.
Whyte et al. (2004) USA RCT PEDro=8 N=34	**Population:** TBI; Mean Age=37 yr; Gender: Male=29, Female=5; GCS<12; Median Time Post Injury=3.2 yr. **Treatment:** Participants received 0.3 mg/kg/dose methylphenidate for 3 wk, 2×/day, and placebo for 3 wk, for a total of 6 wk, with conditions alternating weekly. Washout lasted a day, after which time the groups crossed over. **Outcome Measure:** Attention Tasks.	1. Methylphenidate showed significant improvements in information processing speed (p<0.001), work task attentiveness (p=0.01), and caregiver attention ratings (p=0.01), pre-post. 2. No treatment-related improvements were observed in susceptibility to distraction, and divided or sustained attention.
Plenger et al. (1996) USA	**Population:** TBI; Gender: Male=17, Female=6; *Placebo Group (n=13)*: Mean Age=26.6 yr; Mean	1. At 30 days follow-up (n=15), significant differences were obtained on DRS,

Author/ Year/ Country/ Study Design/ N	Methods	Outcomes
RCT PEDro=5 N=23	GCS=8.1; *Methylphenidate Group (n=10)*: Mean Age=31.4 yr; Mean GCS=9.3. **Treatment:** Patients were randomly allocated to receive either methylphenidate or placebo. Methylphenidate was administered at 30 mg/kg, 2×/day, for 30 days. **Outcome Measure:** Disability Rating Scale (DRS), Continuous Performance Test (CPT), 2 & 7 Test (2 & 7), Paced Auditory Serial Addition Test (PASAT), Digit Span & Attention/ Concentration from Wechsler Memory Scale-Revised (Attn/Conc from WMS-R).	suggesting better outcome for the methylphenidate group. This difference however was not seen at the 90 day follow-up (n=11). 2. Significant differences were found on the attention-concentration domain at the 30 day follow-up, as indicated by CPT, PASAT, 2 & 7, and Attn/Conc from WMS-R ($p<0.03$). The treatment group performed better in these measures compared to the placebo group.
Speech et al. (1993) USA RCT PEDro=7 N=12	**Population:** TBI; Mean Age=27.6 yr; Gender: Male=5, Female=7; Mean Time Post Injury=48.5 mo. **Treatment:** In a crossover design, participants were randomly assigned to receive 0.3 mg/kg methylphenidate, 2×/day, for 1 wk, followed by 1 wk of placebo, or receive the treatment in a reverse order. **Outcome Measure:** Gordon Diagnostic System, Digit Symbol and Digit Span subtests of the Wechsler Adult Intelligence Scale-Revised, Stroop Interference Task, Sternberg High Speed Scanning Task, Selective Reminding Test, Serial Digit Test, and Katz Adjustment Scale.	1. No significant differences were found between methylphenidate and placebo condition in any of the outcome measures studied.

PEDro=Physiotherapy Evidence Database rating scale score (Moseley et al., 2002).

Discussion

In an RCT, Whyte et al. (2004) indicated that speed of processing, attentiveness during individual work tasks and caregiver ratings of attention were all significantly improved with methylphenidate treatment. No treatment related improvement was seen in divided or sustained attention, or in susceptibility to distraction. Similarly, Plenger et al. (1996) found methylphenidate significantly improved attention and concentration.

Speech et al. (1993) conducted a double blind placebo controlled trial evaluating the effects of methylphenidate following closed head injury. In contrast to the results noted by Whyte et al. (2004) and Plenger et al. (1996), methylphenidate did not demonstrate significant differences compared to placebo on measures of attention, information processing speed, or learning. Kim et al. (2006) examined the effects of a single-dose treatment of methylphenidate and, although a trend was found in favour of improved working and visuospatial memory for the treatment group, these results did not reach significance. Recently, Kim et al. (2012) found that reaction time improved significantly while on the methylphenidate. This is in line with Willmott and Ponsford (2009) who found that administering methylphenidate to a group of patients during inpatient rehabilitation, did significantly improve the speed of information processing.

In a recent RCT conducted by Willmott et al. (2013), the authors hypothesized that an individuals' response to methylphenidate depends on their genotype. More specifically, that individuals possessing the methionine (Met) allele at the catechol-O-methyltransferase (COMT) gene would confer greater

response to methylphenidate compared to those with the valine (Val) allele. While both Met/Met and Val/Val carriers performed more poorly in various attentional tasks compared to healthy controls, Met/Met carriers did show greater improvements in strategic control in attention than Val/Val carriers. As well, the authors were able to identify one significant drug and genetic interaction between Met/Met carriers and performance on the Symbol Digit Modalities Test (SDMT). These findings suggest Met/Met carriers may in fact be more responsive to methylphenidate than individuals with the Val genotype. However, further studies are needed to draw firm conclusions.

Conclusions

There is conflicting evidence regarding the effectiveness of the administration of methylphenidate following brain injury for the improvement of cognitive functioning.

There is level 1a evidence that methylphenidate may improve reaction time of working memory.

Based on a single RCT, there is level 1b evidence that an individual's response to methylphenidate therapy may be dependent on his/her genotype of the catechol-O-methyltransferase gene.

The effectiveness of methylphenidate treatment to improve cognitive impairment following brain injury is unclear.

Methylphenidate may be effective in improving reaction time for working memory.

Response to methylphenidate may depend on genotype.

12.14.1.2 Methylphenidate and Fatigue

Of the neurostimulants used in the post-acute care of TBI, methylphenidate is common, assisting with memory, attention, verbal fluency, and improving processing speed. While its use is heavily focused on the improvement of functional and cognitive deficits, methylphenidate has been reported to have unfavourable effects on sleep patterns of individuals with brain injuries. However, little has been written focusing directly on the effects of methylphenidate on the sleep-wake cycles of those with ABI (Al-Adawi et al., 2009).

Table 12.43 Effects of Methylphenidate on Sleep Disorders

Author/ Year/ Country/ Study Design/ N	Methods	Outcomes
Al-Adawi et al. (2009) Oman PCT N=30	**Population:** TBI; Mean Age=51 yr; Gender: Male=23, Female=7. **Treatment:** The treatment group (n=17) received methylphenidate (5-10 mg at 8am and 2pm). The control group (n=13) received no medication. **Outcome Measure:** Sleep State, Functional Independence Measure (FIM), Rancho Los Amigo Levels (RLAS) of Cognitive Functioning.	1. The mean hours of sleep during a 24 hr period did not significantly differ between the treatment and control group (8.3 versus 9.0 hr, p=0.096). 2. Mean hours of sleep at night for the treatment and control groups were 6.4 and 6.9 hr, respectively. 3. Mean total FIM score was lower for those in the methylphenidate group than

Author/ Year/ Country/ Study Design/ N	Methods	Outcomes
		for the control group (30.0 versus 34.9, p=0.4). 4. The scores on the RLAS were comparable between groups (p=0.479).

Discussion

In the study by Al-Adawi et al. (2009) no significant differences were found between those who received methylphenidate and those who did not when looking at the scores of various assessment scales (e.g. activities of daily living, mobility and cognition). More importantly, sleep times between the two groups were not significantly different. Based on this study, methylphenidate does not seem to have adverse effects on the sleep-wake cycle.

Conclusions

There is level 3 evidence, based on a single study, that methylphenidate may not have an adverse effect on the sleep-wake cycle of those who have sustained a TBI.

Methylphenidate may not have an adverse effect on the sleep-wake cycle of those who have sustained a TBI when given in commonly accepted dosages.

12.14.1.3 Methylphenidate and Anger

One RCT examined the effect of methylphenidate on the control of anger following a brain injury (Mooney & Haas, 1993).

Table 12.44 Effects of Methylphenidate on Anger Post ABI

Author/ Year/ Country/ Study Design/ N	Methods	Outcome
Mooney & Haas (1993) USA RCT PEDro=5 N=38	**Population:** TBI; Mean Age=29.45 yr; Gender: Male=38, Female=0; Mean Time Post Injury=27.08 mo. **Intervention:** Patients in the treatment group (n=19) received methylphenidate (30 mg/day). Those in the control group received a placebo (n=19) for 6 wk. **Outcome Measure:** State-Trait Anger Scale, the Belligerence cluster score from the Katz Adjustment Scale and the Anger-Hostility factor score of the Profile of Mood States.	1. Following statistical control over the possible bias (difference in baseline anger scores), there was a significant main effect for the drug treatment (p<0.001). 2. Analyzing the anger outcome measures, a significant drug by time interaction effect was noted (p=0.002).

PEDro=Physiotherapy Evidence Database rating scale score (Moseley et al., 2002)

Discussion

In a RCT, Mooney and Haas (1993) demonstrated that methylphenidate helped to significantly reduce anger following brain-injury as demonstrated using several anger outcome measures. Despite the

differences between the groups on one anger measure, a significant group main effect of the drug treatment was demonstrated.

Conclusions

There is level 2 evidence (from one randomized control trial) to suggest that treatment with methylphenidate following brain injury can significantly reduce anger.

Methylphenidate may be effective in reducing anger following a brain injury.

12.14.1.3 Methylphenidate and the Paediatric Population

Methylphenidate, a psychomotor stimulant, is often used in the treatment of attention deficit hyperactivity disorder (ADHD) in children; however, it is also used with children who have sustained a brain injury. It is believed that those with ADHD and those who have sustained a brain injury have similar characteristics including: attention deficits, hyperactivity and impulsivity (Leonard et al., 2004). Methylphenidate has been shown to improve memory and attention in those with ADHD (Kempton et al., 1999).

Table 12.45 Effects of Methylphenidate Interventions in Children with ABI

Author/ Year/ Country/ Study Design/ N	Methods	Outcomes
Nikles et al. (2014) Australia Pre-Post N=10	**Population:** TBI; Mean Age=12.9 yr; Gender: Male=6, Female=4; Mean Time Post Injury=6.1 yr; Mean GCS=8.3. **Intervention:** Patients were randomized to receive either a stimulant (methylphenidate or dexamphetamine) or a placebo for three cycles of 1 wk each. The intervention was provided for 6 wk in total. Assessments were conducted weekly after each 1 wk trial. **Outcome Measure:** Conners' 3 Parent Rating Scales (C3PR), Conners' 3 Teacher Rating Scales (C3TR), Behaviour Rating Inventory of Executive Function (BRIEF), Eyberg Child Behaviour Inventory (ECBI).	1. A trend towards improved ADHD behaviour was noted on the C3TR in favour of the stimulant compared to placebo, however this was not statistically significant. 2. A less pronounced difference was noted on the C3PR in favour of stimulants compared to placebo, however this was not statistically significant. 3. Teacher-reported intensity and parent-reported frequency of problem behaviours on the ECBI during stimulant cycles compared to placebo cycles, however this was not statistically significant. 1. Teacher-reported and parent-reported BRIEF scores revealed a mean score difference of 20.7 and 10.8 respectively in favour of the stimulant cycles but this did not reach statistical significance.
Mahalick et al. (1998) USA RCT PEDro=7 N=14	**Population:** TBI; Mean Age=10.67 yr; Gender: Male=11, Female=3; Mean GCS=6.9; Mean Time Post Injury=14.14 mo. **Treatment:** In a crossover trial, children received either methylphenidate first, then placebo (n=8), or placebo first, then methylphenidate (n=6). Methylphenidate was administered in a dose of 0.3 mg/kg 2×/day for 14 days.	2. Patients performed significantly better on all 3 outcome measures when taking methylphenidate compared to placebo ($p<0.05$).

Author/ Year/ Country/ Study Design/ N	Methods	Outcomes
	Outcome Measure: Gordon Diagnostic System (Model III), Woodcock-Johnson Psychoeducational Test Battery-Revised, and Ruff 2 and 7 Cancellation Test.	
Williams et al. (1998) USA RCT PEDro=8 N=10	**Population:** TBI; Mean Age=10.48 yr; Gender: Male=9, Female=1; Mean Time Post Injury=2.67 yr. **Treatment:** In a crossover trial, children received either methylphenidate first, then placebo (n=6), or placebo first, then methylphenidate (n=4). Methylphenidate was administered 5-10 mg 2×/day according to weight. Placebo or medication was dispensed for 4 day each, followed by 3 day washout. **Outcome Measure:** Behaviour (hyperactivity), attention, memory, processing speed, and psychomotor skills.	1. No significant difference was found between placebo and methylphenidate on measures assessing memory, behaviour, attention, processing speed, and psychomotor skills.
Hornyak et al. (1997) USA Case Series N=10	**Population:** TBI; Mean Age=10.92 yr; Gender: Male=7, Female=3; Mean GCS=6.2; Mean Time Post Injury=10 mo. **Treatment:** A retrospective chart review of children treated with methylphenidate. **Outcome Measure:** Behaviour.	1. Improvements in level of arousal, cognitive and behavioural function, impulsivity, attention, agitation, and participation were noted. Behavioural outcomes worsened when methylphenidate was withheld.

PEDro=Physiotherapy Evidence Database rating scale score (Moseley et al., 2002).

Discussion

Two separate RCTs utilized a series of neurobehavioural tasks of attention, behaviour and concentration to assess children post brain injury. Mahalick et al. (1998) reported significantly improved performance on attention and concentration tasks with methylphenidate treatment, whereas Williams et al. (1998) did not report any significant benefits. As in many paediatric studies, the sample size was small, undermining the quality of the findings. Hornyak et al. (1997) suggest that the introduction of methylphenidate resulted in improved cognitive/behavioural function post TBI. This interpretation however, was based on qualitative data from a retrospective review of 10 charts. To date, no medication has proven to be effective in modifying outcome in the brain injured child. Investigators have studied the role of the psychostimulant methylphenidate and other dopamine enhancing medication including amantadine, pramipexole, bromocriptine, and levodopa.

Conclusions

Based on two small and conflicting RCTs, there is inconclusive evidence whether methylphenidate improves cognitive behavioural function in children post ABI.

Evidence regarding the efficacy of methylphenidate to improve cognitive and behavioural function is conflicting in children.

12.14 (b) Stimulants

12.14.2 Modafinil

Modafinil, a wakefulness promoting agent, was approved to address excessive daytime sleepiness (EDS) (Jha et al., 2008). Additionally, the drug was approved for use to address narcolepsy and sleeping difficulties associated with shift work ("Randomized trial of modafinil as a treatment for the excessive daytime somnolence of narcolepsy: US Modafinil in Narcolepsy Multicenter Study Group," 2000). Modafinil was found to enhance the quality of life for those with narcolepsy (Beusterien et al., 1999). Similar studies exploring the effectiveness of modafinil within the ABI population are limited.

Table 12.46 Effects of Modafinil Treatment on Fatigue

Author/ Year/ Country/ Study Design/ N	Methods	Outcomes
Kaiser et al. (2010) Switzerland RCT PEDro=9 N=20	**Population:** TBI=20; Gender: Male=17, Female=3. *Treatment Group*: N=10; Mean Age=37 yr; Mean GCS Score=7; *Control Group*: N=10; Mean Age=43 yr; Mean GCS Score=8. **Intervention:** Actigraphy and nocturnal polysomnography at baseline. Patients received either modafinil (100 mg 1×/day then 2×/day) or placebo for 6 wk. **Outcome Measure:** Excessive Daytime Sleepiness (EDS), Fatigue Severity Scale (FSS), and Maintenance of wakefulness test (MWT).	1. At 6 wk, the decrease in FSS scores was greater in the modafinil group (-0.8±1.0 versus 0.0±0.6), but this was not significant (p=0.07). 2. The modafinil group had greater decreases in EDS scores versus placebo (p<0.005). 3. On the MWT, a significant increase was shown for the modafinil group when compared to placebo (8.4±9.6 min versus 0.4±6.2 min; p=0.04). 4. Of those patients with fatigue at baseline (FSS≥4), decreases in FSS scores were not greater in the intervention group.
Jha et al. (2008) USA RCT PEDro=8 $N_{initial}$=51, N_{final}=46	**Population:** TBI=51; Mean Age=38.25 yr; Gender: Male=35, Female=16; Mean Time Post Injury=5.77 yr. **Intervention:** Intervention group (n=27) received modafinil (100 mg 1×/day for 3 days, then 2×/day for 11 days). A maintenance dose of 100 mg was given 2×/day. The control group (n=24) received a placebo. At the end of phase 1 both groups crossed-over. **Outcome Measure:** Fatigue Severity Scale (FSS), Modified Fatigue Impact Scale (MFI), and Epworth Sleepiness Scale (ESS).	1. No significant between group differences were found at week 4 or week 10 on the FSS (p=0.80 and p=0.61, respectively) or the MFI (p=0.67 and p=0.73, respectively). 2. The change in ESS scores was significantly greater in the modafinil group versus placebo at week 4 (p=0.02) but not at week 10 (p=0.56). 3. Adverse events included: headaches (29.5%), insomnia (19.6%), fatigue (9.8%), dizziness (7.8%) and tremors (5.9%).

PEDro=Physiotherapy Evidence Database rating scale score (Moseley et al., 2002).

Discussion

Two RCTs examined the effects of modafinil on fatigue and EDS for individuals with TBI (Jha et al., 2008; Kaiser et al., 2010). The two studies followed similar protocols with the initial administration of modafinil 100 mg daily, which was then titrated up to 100 mg twice per day, and both compared with a placebo control group. Both studies found no significant difference in fatigue, as measured by the FSS, between the intervention and control groups. Further, when Kaiser et al. (2010) compared those with fatigue at baseline (FSS ≥4) in both groups, the decreases shown in FSS scores remained non-significant between groups. The two studies also examined EDS using the Epworth Sleepiness Scale (ESS). The

intervention groups both showed a significantly greater decrease in ESS scores when compared with controls, representing a greater improvement in EDS (Jha et al., 2008; Kaiser et al., 2010). It should be noted, however, that Jha et al. (2008) found the improvement to be significant at week 4 (p=0.02) but not at week 10 (p=0.56) highlighting that there was no clear temporal pattern of benefit. Of concern, those receiving modafinil reported more insomnia than controls (p=0.03). These studies suggest that modafinil may not be effective for improving fatigue.

Conclusions

There is level 1a evidence that modafinil may not be effective in treating fatigue but has been shown to be effective short-term in treating excessive daytime sleepiness post ABI.

Modafinil has not been shown to be effective in treating fatigue.

Modafinil has been shown to be effective short-term in treating excessive daytime sleepiness, but may also cause insomnia.

12.15 Sedative Anaesthetic

12.15.1 Propofol

Propofol is a fast acting sedative that is absorbed and metabolized quickly, leading to pronounced effects of short duration. Its beneficial effects occur via decreases in peripheral vascular tension resulting in potential neuroprotective effects, which may be beneficial in acute ABI care. Experimental results have shown positive effects on cerebral physiology including reductions in cerebral blood flow, cerebral oxygen metabolism, electroencephalogram activity, and ICP (Adembri et al., 2007). However, administration of high doses can result in propofol infusion syndrome, which has been characterized by severe metabolic acidosis, rhabdomyolosis, cardiac dysrhythmias, and potential cardiovascular collapse (Corbett et al., 2006).

The AANS reported Level II evidence for the recommendation of propofol in controlling of ICP, but not for improvement in mortality or long-term outcomes (Carney et al., 2017). They also indicated that high-dose propofol can produce significant morbidity. The EBIC recommended sedation as part of the treatment course for ABI but make no specific mention of propofol (Maas et al., 1997).

Table 12.47 Propofol for the Acute Management of ABI

Author/ Year/ Country/ Study Design/ N	Methods	Outcome
James et al. (2012) USA RCT Crossover PEDro=5 N=8	**Population:** TBI=4, SAH=3, ICH=1; Mean GCS=6.1. **Intervention:** Patients were randomized to receive sedation with either propofol (25.5 µg/kg/min) or dexmedetomidine (0.54 µg/kg/hr) for 4 hr. Crossover occurred after 2 hr. **Outcome Measure:** Intracranial Pressure (ICP), Cerebral Perfusion Pressure (CPP).	1. No significant differences between the groups were found for ICP or CPP.

Author/ Year/ Country/ Study Design/ N	Methods	Outcome
Smith et al. (2009) USA Case Series N=146	**Population:** TBI; GCS Range≤8. **Intervention:** Patients who received propofol or vasopressors were included in retrospective analysis. **Outcome Measure:** Propofol Infusion Syndrome (PRIS), Mortality.	1. Only 3 patients on both propofol and vasopressors developed PRIS. 2. There were no patients on only propofol or vasopressors who developed PRIS. 3. PRIS was not linked to mortality (p>0.05).
Kelly et al. (1999) USA RCT PEDro=8 N=42	**Population:** TBI. *Propofol (PROP, n=23)*: Mean Age=39 yr; Gender: Male=18, Female=5; Mean Time Post Injury=34 hr; Median GCS=7. *Morphine (MOR, n=19)*: Mean Age=38 yr; Gender: Male=17, Female=2; Mean Time Post Injury=38 hr; Median GCS=6. **Intervention:** Patients were randomized to receive sedation with either PROP (20 mg/mL) or MOR. Both groups received additional bolus of MOR (1-3 mg/hr) for at least 48 hr for analgesic purposes. Assessments were made at baseline, and on days 1, 2, 3, and 4, and at 6 mo. **Outcome Measure:** Intracranial pressure (ICP), Glasgow Outcome Scale (GOS), Disability Rating Scale (DRS).	1. On day 3, ICP was significantly lower in PROP compared to MOR (p<0.05). 2. ICP therapy in PROP was also less intensive than MOR. 3. At 6mo, scores were not significantly different between groups for mortality or favourable outcome rates (GOS≥4). 4. In subgroup analysis, PROP was divided into high-dose (100 mg/kg, n=10) and low-dose (<100 mg/kg, n=13) groups. 5. The high-dose group showed higher mean CPP on day 2 (81 mmHg versus 68 mmHg) and lower mean ICP on day 3 (14 mmHg versus 15 mmHg) compared to low-dose (p>0.05). 6. High-dose group demonstrated more favourable outcomes in the GOS (70% versus 38.5%) and the DRS (80% versus 46.2%) compared to the low-dose group (p>0.05).
Stewart et al. (1994) UK PCT N=15	**Population:** ABI. *Propofol (PROP, n=9)*: Mean Age=30.5 yr; Gender: Male=8, Female=1; Severity of Injury: Moderate=2, Severe=7; *Morphine and Midazolam (M+M, n=6)*: Mean Age=30.5 yr; Gender: Male=6, Female=0; Severity of Injury: Moderate=1, Severe=5. **Intervention:** Patients received sedation with either PROP (150-400 mg/hr) or morphine (0-4 mg/hr) with midazolam (0-5 mg/hr). **Outcome Measure:** Intracranial Pressure (ICP), Cerebral Perfusion Pressure (CPP), Mean Arterial Pressure (MAP), Global Brain Metabolism ($AVDO_2$), Glasgow Outcome Scale (GOS).	1. PROP led to a decrease in $AVDO_2$ at 4 hr (6.0±2.6 mL/dL to 3.0±0.6 mL/dL, p<0.02). 2. No difference was reported between groups in ICP, CPP, and MAP. 3. No difference was reported between groups in functional outcomes on GOS at 6mo.
Farling et al. (1989) Ireland Case Series N=10	**Population:** TBI; Mean Age=36.8 yr; Gender: Male=9, Female=1; Mean GCS=4.9. **Intervention:** Patients received intravenous infusion of 1% propofol at a rate of 2-4 mg/kg/hr. Measurements were obtained for 24 hr. **Outcome Measure:** Intracranial Pressure (ICP), Cerebral Perfusion Pressure (CPP), Mean Arterial Pressure (MAP), Heart Rate (HR).	1. ICP was significantly reduced by 2.1 mmHg at 2 hr (p<0.05). 2. CPP was significantly increased by 9.8 mmHg at 24 hr (p<0.05). 3. No significant differences were seen in MAP or HR. 4. Propofol was not associated with any adverse outcomes.

PEDro=Physiotherapy Evidence Database rating scale score (Moseley et al., 2002).

Discussion

In two earlier studies, propofol was reported to provide satisfactory sedation with few side effects. Farling et al. (1989) reported that propofol reduced ICP, increased CPP, and provided safe and effective sedation. Stewart et al. (1994) found that propofol provided sedation similar to a combination of midazolam and morphine with no differences in changes to ICP, CPP, and MAP or in outcomes at six months. However, both of these studies had small sample sizes and were lower quality. In a retrospective review, Smith et al. (2009) identified three patients with propofol infusion syndrome. The authors noted that each of these patients was receiving both propofol and vasopressors, and that no patient on either propofol or vasopressors alone developed propofol infusion syndrome.

An RCT by Kelly et al. (1999) compared propofol to morphine for safety and efficacy. Patients were randomly assigned to either a morphine group or a propofol group where they received three simultaneous injections: injection one had propofol or placebo, injection two had morphine or placebo, and injection three had low-dose morphine. This particular design allowed for the comparison of propofol dosing and its effectiveness while maintaining blinding, although all patients received propofol in conjunction with morphine. Propofol was found to reduce ICP when compared to morphine, and higher doses were shown to be more effective than lower doses. As well, patients in the propofol group showed less need for additional therapies for elevated ICP. At six months, there were no significant differences in mortality rates or GOS scores between the two groups. The authors suggested that propofol is a safe, acceptable, and possibly desirable alternative to opiate-based sedation (Kelly et al., 1999).

In a crossover RCT, patients with ABI received both propofol and dexmedetomidine, each over a six-hour period (James et al., 2012). The authors reported no significant differences between the groups after treatment in terms of ICP and CPP. As a result of these findings, they recommend that the *"choice of sedative regimen be based on the profile of the sedative and the individual goals for a patient".*

Conclusions

There is level 1b evidence that propofol may reduce intracranial pressure and the need for other intracranial pressure interventions when used in conjunction with morphine compared to morphine alone.

There is level 1b evidence that a high dose of propofol may improve intracranial pressure and cerebral perfusion pressure compared to a low dose of propofol.

There is level 2 evidence that propofol may not be significantly different from dexmedetomidine in its effect on intracranial pressure.

There is level 2 evidence that propofol may not be significantly different from morphine and midazolam in its effect on intracranial pressure, cerebral perfusion pressure, mean arterial pressure, and long-term outcomes.

There is level 4 evidence that propofol may improve intracranial pressure and cerebral perfusion pressure.

Propofol, especially at higher doses may improve intracranial pressure and cerebral perfusion pressure; furthermore, propofol may reduce intracranial pressure and the need for other intracranial pressure interventions when used in conjunction with morphine.

Propofol may be no different than dexmedetomidine or morphine with midazolam in its effect on intracranial pressure.

12.15.2 Midazolam

Midazolam, another benzodiazepine, works by slowing activity in the brain to allow for relaxation and sleep. Midazolam has been found to reduce cerebrospinal fluid pressure in patients without intracranial mass lesions as well as decrease cerebral blood flow and cerebral oxygen consumption (McClelland et al., 1995). For a more detailed discussion of midazolam please refer to Modules 10 and Module 16.

Table 12.48 Midazolam for the Acute Management of ABI

Author/ Year/ Country/ Study Design/ N	Methods	Outcome
Ghori et al. (2008) Ireland RCT PEDro=8 N=30	**Population:** TBI. *Midazolam* (MDZ, n=15): Age Range: 18-65 yr; Gender: Male=14, Female=1; Mean Time Since Injury=12.86 hr; Median GCS=4.73. *Propofol* (PROP, n=13): Age Range: 18-65 yr; Gender: Male=13, Female=0; Mean Time Since Injury=9.07 hr; Median GCS=5.07. **Intervention:** Patients were randomly allocated to receive MDZ (n=15) or PROP (n=13) sedation. Outcomes were assessed at baseline and 3mo. **Outcome Measure:** Glasgow Outcome Score (GOS), Mortality.	1. There was no significant difference between MDZ and PROP groups in number of patients with good outcomes (53% versus 54%). 2. Of the patients who had a poor outcome, there was no significant difference in the mortality rate between MDZ and PROP groups (20% versus 38%; p=0.07). 3. Of the patients who had a poor outcome, there was no significant difference in the severe disability rate between MDZ and PROP groups (20% versus 15%; p=0.8).
Davis et al. (2001) USA Case Series N=184	**Population:** TBI; *Northern Cohort (n=66)*: Mean Age=32.9 yr; Gender: Male=53, Female=13. *Southern Cohort (n=118)*: Mean Age=31.2 yr; Gender: Male=89, Female=29. **Intervention:** Patients received 0.1 mg/kg midazolam without restricted maximal dose (Group 1) or with a maximal dose of 5 mg (Group 2). **Outcome Measure:** Systolic Blood Pressure (SBP), Hypotension, Dose.	1. Patients in the Group 1 received significantly higher doses than those in Group 2 (0.106mg/kg versus 0.059 mg/kg, p<0.0001). 2. A significant relationship was found between dose and hypotension following intubation (p=0.032) as well as decrease in SBP (p=0.022).
Sanchez-Izquierdo-Riera et al. (1998) Spain RCT PEDro=5 N=100	**Population:** TBI; Mean Age=35.4 yr; Gender: Male=75, Female=25. **Intervention:** Patients were randomized to receive continuous intravenous infusion of midazolam at 0.1-0.35 mg/kg/hr (n=34), propofol at 1.5-6 mg/kg/hr (n=33), or propofol at 0.1-0.2 mg/kg/hr (n=33). All patients received morphine. **Outcome Measure:** Intracranial Pressure (ICP), Cerebral Perfusion Pressure (CPP), Triglyceride levels, Wake-up time, Sedation.	1. No significant differences were found in ICP or CPP among intervention groups. 2. High levels of triglyceride were found in patients receiving propofol (p<0.05). 3. Wake-up time was significantly shorter in patients receiving propofol than midazolam (110 min/190 min versus 660 min, p<0.01). 4. All regimens achieved similar levels of sedation and had similar incidences of adverse effects.
Papazian et al. (1993) France	**Population:** TBI; Mean Age=28.3 yr; Gender: Male=11, Female=1; Mean GCS=5.2.	1. Significant reductions in MAP (89 mmHg to 75 mmHg, p<0.0001) and in CPP (71 mmHg to

Author/ Year/ Country/ Study Design/ N	Methods	Outcome
Case Series N=12	**Intervention:** Patients received intravenous infusion of 0.15 mg/kg midazolam over a 1 min period. **Outcome Measure:** Intracranial Pressure (ICP), Cerebral Perfusion Pressure (CPP), Mean Arterial Pressure (MAP).	55.8mmHg, p<0.0001) were observed, but there was no significant change in ICP. 2. Patients with low initial ICP (<18 mmHg) experienced greater reductions in MAP and greater increases in ICP compared to those with high initial ICP (≥18 mmHg; p<0.0001).

PEDro=Physiotherapy Evidence Database rating scale score (Moseley et al., 2002).

Discussion

An early retrospective study by Papazian et al. (1993) reported that midazolam yielded non-significant reductions in ICP. In patients with severe TBI, those receiving midazolam had similar levels of ICP and CPP after treatment when compared to those receiving propofol, although was propofol associated with a shorter wake-up time (Sanchez-Izquierdo-Riera et al., 1998). The two medications were also found to provide similar long-term outcomes (Ghori et al., 2008). It should be noted that increased doses of midazolam have been associated with significant hypotension (Davis et al., 2001) and decreased levels of CPP and MAP (Papazian et al., 1993).

Conclusions

There is level 4 evidence that midazolam may reduce mean arterial pressure, cerebral perfusion pressure, and systolic blood pressure, but may have no effect on intracranial pressure.

There is level 2 evidence that midazolam may not be different from propofol in its effect on intracranial pressure or cerebral perfusion pressure.

There is level 1b evidence that midazolam may not be different than propofol in its effect on long-term outcomes.

Midazolam may have no effect on intracranial pressure, but may reduce mean arterial pressure, cerebral perfusion pressured, and systolic blood pressure.

Midazolam may not be different than propofol in its effect on intracranial pressure, cerebral perfusion pressure, or long-term outcomes.

12.16 Steroids

12.17.1 Corticosteroids

Numerous corticosteroids have been used in brain injury care including dexamethasone, methylprednisolone, prednisolone, prednisone, betamethasone, cortisone, hydrocortisone, and triamcinolone (Alderson & Roberts, 2005). Using such a broad spectrum of agents within diverse patient groups has made understanding corticosteroid efficacy difficult. Adding to this difficulty is a lack of understanding regarding the mode of steroid action. Grumme et al. (1995) reported that laboratory studies have associated corticosteroid use with reductions in wet brain weight, facilitation of synaptic

transmission, reduction of lipid peroxidation, preservation of electrolyte distribution, enhanced blood flow, and membrane stabilization (Grumme et al., 1995). While it had been thought that the benefits of corticosteroids could arise from reductions in ICP, as well as neuroprotective activity, several studies have suggested limitations in their usage. Focal lesions seem to respond well to corticosteroid therapy, while diffuse intracerebral lesions and hematomas are less responsive (Cooper et al., 1979; Grumme et al., 1995).

In the wake of several large scale trials, questions regarding the safety of corticosteroid administration have been brought to light. Alderson and Roberts (1997) conducted a systematic review of corticosteroid literature and concluded that there was a 1.8% improvement in mortality associated with corticosteroid use. However, their 95% confidence interval ranged from a 7.5% reduction to a 0.7% increase in deaths. Roberts et al. (2004) studied corticosteroid use in acute brain injury with the goal of recruiting 20,000 patients with TBI; after 10,008 patients were recruited it became clear that corticosteroid use caused significant increases in mortality and the trial was halted.

The AANS stated that steroid use was not recommended for reducing ICP or improving outcomes, and that high-dose methylprednisolone was associated with increased mortality (Carney et al., 2017). The EBIC stated that there was no established indication for the use of steroids in acute head injury management (Maas et al., 1997).

Table 12.49 Effects of Corticosteroids in the Management of Elevated Intracranial Pressure and Neuro-Protection

Author/ Year/ Country/ Study Design/ N	Methods	Outcome
Methylprednisolone		
Roberts et al. (2004) International RCT PEDro=10 N=10,008	**Population:** ABI; Mean Age=37 yr; Gender: Male=6104, Female=1904; Median Time Post Injury=3 hr; Severity: Mild=3002, Moderate=3040, Severe=3966. **Intervention:** Patients were randomized to receive either methylprednisolone (n=5007) or placebo (n=5001). Methylprednisolone was administered intravenously at a loading dose of 2 g/hr in a 100 mL infusion, and maintained at 0.4 g/hr for 48 hr in a 20 mL/hr infusion. Outcomes were assessed at 2 wk. **Outcome Measure:** Mortality.	1. Compared with the placebo group, the risk of death was higher in the corticosteroid group (RR=1.18; p=0.0001). 2. Relative risk of death did not differ by injury severity (p=0.22) or time post injury (p=0.05).
Giannotta et al. (1984) USA RCT PEDro=7 N=88	**Population:** TBI; Time Post Injury≤6 hr; GCS Range≤8. **Intervention:** Patients were randomized to receive high-dose methylprednisolone (n=38; 30 mg/kg/6 hr for 2 doses, 250 mg/6 hr for 8 doses, then tapered), low-dose methylprednisolone (n=34; 1.5 mg/kg/6 hr for 2 doses, 25 mg/6 hr for 8 doses, then tapered), or placebo (n=16) over 8 days. **Outcome Measure:** Glasgow Outcome Scale (GOS), Mortality.	1. At 6 mo, there was no significant difference in mortality or morbidity between groups. 2. For patients younger than 40 yr, there was a combined 43% mortality in the low dose and placebo groups compared to a 6% mortality in the high dose group (p<0.05).

Author/ Year/ Country/ Study Design/ N	Methods	Outcome
Saul et al. (1981) USA RCT PEDro=4 N=100	**Population:** TBI; Mean Age=31 yr; Time Post Injury≤6 hr; GCS Range≤7. **Intervention:** Patients were randomized receive to either methylprednisolone or no drug. Methylprednisolone was administered intravenously at 250 mg, followed by 125 mg/6 hr. **Outcome Measure:** Glasgow Outcome Scale (GOS).	1. At 6 mo, no significant difference was seen in proportion of GOS=3-5 compared to GOSE=1-2 between groups (p=0.22).
Dexamethasone		
Dearden et al. (1986) UK RCT PEDro=4 N=130	**Population:** TBI; Age Range=3-79 yr; Gender: Male=93, Female=37; Time Post Injury: ≤8 hr=93, >8 hr=37; Severity: Mild/Moderate=23, Severe=107. **Intervention:** Patients randomized to receive either IV bolus of dexamethasone (n=68) or placebo (n=62). Dexamethasone was administered intravenously at 100 mg/day on days 1-3, 50 mg/day on day 4, and 25 mg on day 5. **Outcome Measure:** Glasgow Outcome Scale (GOS).	1. GOS score at 6 mo was worse in the steroid group than the placebo group (49% versus 35.5% dead or vegetative), but the difference was not significant (p>0.05). 2. Patients in the steroid group with ICP >20 mmHg and >30 mmHg showed significantly poorer outcomes on GOS compared to similar patients in the placebo group (p<0.05).
Braakman et al. (1983) Netherlands RCT PEDro=4 N=161	**Population:** TBI; Time Post Injury<6 hr; Severity: Severe. **Intervention:** Patients were randomized to receive either high-dose dexamethasone (n=81) or placebo (n=80). Dexamethasone was administered intravenously (IV) at 100 mg/day from days 1-4, at 16 mg/day IV or intramuscularly (IM) from days 5 to 7, and at 12 mg on day 8, 8 mg on day 9, and 4 mg on day 10 via IV or IM. **Outcome Measure:** Glasgow Outcome Scale (GOS), Mortality.	1. No significant differences were seen in 1mo mortality rates or in 6mo GOS scores between groups.
Kaktis & Pitts et al. (1980) USA RCT PEDro=4 N=115	**Population:** ABI. **Intervention:** Patients were randomized to receive "mega dose" dexamethasone (50 mg, then 25 mg/6 hr) conventional dose dexamethasone (10 mg, then 4 mg/6 hr) or saline placebo for a maximum of 7 days or until awakening. **Outcome Measure:** Infections of Cerebrospinal Fluid (CSF), Syndrome of Inappropriate Antidiuretic Hormone Secretion (SIADH), Hyperglycemia.	1. Infections of the cerebrospinal fluid was significantly higher in the mega dose group than conventional dose and placebo groups (8% versus 0% versus 0%, p<0.025). 2. SIADH was significantly more prevalent in the conventional dose group than the mega dose and placebo groups (19% versus 10% versus 0%, p<0.05). 3. Hyperglycemia was more prevalent in the mega and conventional dose groups than the placebo (35% versus 34% versus 11%, p=0.05).
Cooper et al. (1979) USA RCT PEDro=8	**Population:** TBI; Mean Age=25.6 yr; Gender: Male=59, Female=17; Mean GCS=5.23. **Intervention:** Patients were randomized to receive low-dose dexamethasone (n=25; 10 mg	1. No significant difference was seen between groups in terms of ICP or 6 mo GOS score.

Author/ Year/ Country/ Study Design/ N	Methods	Outcome
N=76	initially, then 4 mg every 6 hr), high-dose dexamethasone (n=24; 60 mg initially, then 24 mg every 6 hr), or placebo (n=27). **Outcome Measure:** Intracranial Pressure (ICP), Glasgow Outcome Scale (GOS).	
Glucocorticoids		
Watson et al. (2004) USA Cohort N=404	**Population:** TBI. *Glucocorticoid (n=125)*: Mean Age=33 yr; Gender: Male=100, Female=25. *Control (n=279)*: Mean Age=35 yr; Gender: Male=209, Female=70. **Intervention:** Patients treated with glucocorticoids were compared to those not receiving them (control). **Outcome Measure:** Incidence of Post-Traumatic Seizures (PTS).	1. 105 patients received glucocorticoids within 1 day of their injury, and 20 received them ≥2 day. 2. Patients receiving glucocorticoids within 1 day were more likely to develop first late PTS than were those without (HR=1.74, p=0.04). 3. Those receiving glucocorticoids ≥2 days post injury had no similar associations with PTS (HR=0.77, p=0.66). 4. Glucocorticoid administration was not associated with second late PTS development in any group.
Triamcinolone		
Grumme et al. (1995) Germany RCT PEDro=9 N=396	**Population:** TBI. *Triamcinolone (n=187)*: Mean Age=31 yr; Gender: Male=154, Female=33. *Placebo (n=209):* Mean Age=31 yr; Gender: Male=168, Female=41. **Intervention:** Patients were randomized to receive either triamcinolone or placebo. Triamcinolone was administered intravenously at 200 mg within 4 hr of injury, followed by 3×40 mg/day for 4 days and 3×20 mg/day for 4 days. **Outcome Measure:** Glasgow Outcome Scale (GOS).	1. No significant difference was observed between groups in GOS at discharge or at 1 yr follow-up. 2. A significantly greater proportion of patients with GCS<8 and focal lesions treated with triamcinolone achieved good outcomes on GOS compared to those treated with placebo (16/46 versus 10/47, p=0.0145).

PEDro=Physiotherapy Evidence Database rating scale score (Moseley et al., 2002).

Discussion

In light of a series of inconclusive studies into the effectiveness and safety of corticosteroid use, a very large multinational randomized collaboration for assessment of early methylprednisolone administration was initiated in 1999 (Roberts et al., 2004). To achieve 90% power, recruitment of 20,000 patients in the Corticosteroid Randomization after Severe Head Injury (CRASH) trial was the goal. After the random allocation of 10,008 patients, the experiment was halted. Of 4,985 patients allocated corticosteroids, 1052 died within two weeks compared to 893 of 4979 patients in the placebo group. This indicated a relative risk of death equal to 1.8 in the steroid group (p=0.0001). Further analysis showed no differences in outcomes between eight CT subgroups or between patients with major extracranial injury compared to those without. The authors also conducted a systematic review and meta-analysis of existing trials using corticosteroids for head injury. Before the CRASH trial, a 0.96 relative risk of death was seen in the corticosteroid group. Once the patients from the CRASH trial were added, the relative risk changed to 1.12. The authors suggest that based on this large multinational trial, corticosteroids should not be used in head injury care no matter what the severity of injury.

Two other studies assessed methylprednisolone in acute ABI management. Giannotta et al. (1984) conducted an RCT of patients with GCS≤8 treated with methylprednisolone. Patients were divided into one of three groups: a high dose, low dose or placebo group, then assessed at six months based on the GOS grading system. They reported no differences in mortality rates between groups. The authors then compressed the low dose and placebo groups and performed further analyses. They found that patients less than 40 years old in the high dose group showed significant decreases in mortality when compared to the low dose/ placebo group; further, they found no significant differences between these groups in beneficial outcomes. Saul et al. (1981) conducted another RCT where patients received methylprednisolone or no drug at all. They noted that there were no differences between the two groups in GOS scores at 6 months.

Four RCTs were found that assessed dexamethasone in ABI. Dearden et al. (1986) assessed consecutively admitted patients with ABI treated with dexamethasone. They noted that patients experiencing ICP levels >20 mmHg showed significantly poorer outcomes on the GOS at six months. Braakman et al. (1983) found no differences between patients treated with dexamethasone compared to placebo in one month survival rates or six month GOS scores. Similarly, Cooper et al. (1979) performed a double blind randomized controlled study of the effects of dexamethasone on outcomes in severe head injuries. Patients were divided into three groups and no significant differences were seen in outcomes. The authors performed several post-mortem examinations and indicate that often, patients initially diagnosed with focal lesions were in fact suffering from diffuse injuries which are not amenable to corticosteroid treatment. Finally, Kaktis and Pitts (1980) assessed the effects of low-dose (16mg/day) and high-dose (14mg/day) dexamethasone on ICP levels in patients with ABI. They noted no differences in ICP at any point during the 72 hour follow-up period.

In a cohort study conducted by Watson et al. (2004) patients receiving any form of glucocorticoid therapy (dexamethasone 98%, prednisone 2.4%, methylprednisone 1.6%, or hydrocortisone 1.6%) were compared two patients treated without corticosteroids for risk of development of post-traumatic seizures. Their inclusion criteria allowed for patients with only one of a list of complications to be included resulting in a diverse group of patients with TBI. They noted that patients receiving glucocorticoid treatment on the first day post injury were at increased risk of developing first late seizures compared to patients receiving no intervention. They also saw no improvement in patients receiving glucocorticoids after the first day. The authors suggest that this ads further strength to the argument against routine corticosteroid use in TBI (Watson et al., 2004).

Grumme et al. (1995) conducted an RCT in which GOS scores were assessed one year after injury in patients treated with the synthetic corticosteroid triamcinolone. While no overall effect between groups was found, further analysis was performed on subsets of patients. A significant increase in beneficial outcomes was seen in patients who had both a GCS<8 and a focal lesion. The authors suggest that in light of this evidence, patients with both GCS<8 and a focal lesion would benefit from steroid administration immediately after injury.

Conclusions

There is level 1a evidence that methylprednisolone may increase mortality rates in patients post ABI and should not be used.

There is level 1b evidence that dexamethasone may not lower elevated intracranial pressure levels and may worsen outcomes.

There is level 2 evidence that triamcinolone may improve outcomes in patients with a Glasgow Coma Scale<8 and a focal lesion.

There is level 3 evidence that glucocorticoid administration may increase the risk of developing first late seizures.

Corticosteriods such as methylprednisolone, dexamethasone, and glucocorticoids may worsen outcomes, with no effect on intracranial pressure levels, and should not be used.

Triamcinolone may improve outcomes in patients with a Glasgow Coma Scale<8 and a focal lesion.

12.17 Summary

There is level 1a evidence that morphine, sufentanil, and alfentanil may result in increased intracranial pressure post ABI.

There is conflicting evidence (level 1b) regarding the effects of fentanyl on intracranial pressure post ABI.

There is level 2 evidence that remifentanil may not affect intracranial pressure post ABI.

There is level 4 evidence that carbamazepine may decrease the incidence of aggressive behaviours following a traumatic brain injury.

There is level 4 evidence that carbamazepine may not decrease seizure control compared to other anticonvulsants following a traumatic brain injury.

There is level 4 evidence that intramuscular midazolam can be used for acute seizure cessation.

There is level 1b evidence to suggest that levetiracetam may be as safe and effective as phenytoin in the treatment and prevention of early seizures in individuals in the intensive care unit post ABI.

There is level 1b evidence that anticonvulsants given during the first 24 hours post ABI may reduce the occurrence of early seizures (within the first week post injury).

There is level 1a evidence that anticonvulsants given shortly after the onset of injury may not reduce mortality, persistent vegetative state, or the occurrence of late seizures (>1 week post injury).

There is level 1a evidence that seizure prophylactic treatment with either phenytoin or valproate may result in similar incidences of early or late seizures and similar mortality rates.

There is level 2 evidence indicating that phenobarbital given post ABI may not reduce the risk of late seizures.

There is level 2 evidence that phenobarbital combined with phenytoin prophylaxis may decrease rate of post-traumatic epilepsy compared to no prophylactic treatment.

There is level 4 evidence that valproic acid may decrease the incidence of aggressive behaviours.

There is level 4 evidence that divalproex may decrease the incidence of agitation post TBI.

There is Level 4 evidence to suggest that lamotrigine may help to reduce inappropriate behaviours post-traumatic brain injury.

There is level 4 evidence that cerebrolysin may improve attention and memory function post ABI, as well as clinical outcome.

There is level 1b evidence that donepezil may improve attention and short-term memory post ABI.

There is level 4 evidence that donepezil may be effective in improving short-, long-term, and visual memory post ABI.

Based on a single RCT, there is level 1b evidence that oral physostigmine may improve long-term memory in men with TBI.

There is conflicting evidence that sertraline may be effective in the treatment of major depression post TBI.

There is level 2 evidence that citalopram may aid in the reduction of depression post ABI.

There is level 4 evidence that citalopram and carbamazepine may be efficacious in the treatment of depression, anxiety and mood disorders.

There is level 2 evidence to suggest that the administration of desipramine may assist in improving mood and reducing depression.

There is level 4 evidence that sertraline hydrochloride can decrease the incidence of aggression and irritability.

There is level 4 evidence that amitriptyline can be useful in reducing the incidence of agitated behaviour.

There is level 4 evidence to suggest that an antimanic agent (lithium carbonate) may reduce aggressive/agitated behaviour following a brain injury.

There is Level 4 evidence (from one small study) to suggest that quetiapine may help reduce aggressive behaviour.

There is level 4 evidence from one study to suggest that ziprasidone can assist in the controlling of agitation post TBI.

There is level 4 evidence that haloperidol may not have a negative effect on the success of rehabilitation.

There is level 4 evidence that administration of a single-dose droperidol may calm agitated patients with ABI more quickly than other agents.

There is level 4 evidence that methotrimeprazine may be safe and effective for controlling agitation after an acquired brain injury.

There is level 4 evidence that phenol nerve blocks may reduce contractures and spasticity at the elbow, wrist and finger flexors for up to five months post injection.

There is level 4 evidence that oral baclofen may improve lower extremity spasticity but not upper extremity spasticity.

There is level 2 evidence that botulinum toxin type A injections can be effective in the management of localized spasticity following ABI.

There is level 1b evidence to suggest that patients receiving botulinum toxin type A through a single motor point or through multisite distributed injections may both show a reduction in spasticity regardless of the drug administration method.

There is level 2 evidence that botulinum toxin type A may be an effective treatment for children and adolescents with upper and lower limb spasticity.

There is level 1b evidence that bolus intrathecal baclofen injections may produce short-term (up to six hours) reductions in upper and lower extremity spasticity following ABI.

There is level 4 evidence to suggest that prolonged intrathecal baclofen may result in longer-term (three months, and one year) reductions in spasticity in both the upper and lower extremities following an ABI.

There is level 4 evidence, from two studies, to suggest that intrathecal baclofen can result in short-term improvements of walking performance in ambulatory patients, particularly gait velocity, stride length, and step width.

There is level 4 evidence that intrathecal baclofen pumps may be effective at reducing spasticity in the upper and lower limbs for children with hypoxia.

There is conflicting (level 1b, level 2, level 3) evidence regarding the efficacy of pentobarbital in improving intracranial pressure over conventional management measures.

There is level 2 evidence that thiopental may be more effective than pentobarbital for controlling elevated intracranial pressure.

There is level 2 evidence that pentobarbital may not be more effective than mannitol for controlling elevated intracranial pressure.

There is level 3 evidence that high-dose barbiturate may result in increase length of stay and may not improve outcomes when compared to low-dose barbiturate.

There is level 4 evidence that barbiturate therapy may cause reversible leukopenia, granulocytopenia, and systemic hypotension, as well as supressed bone marrow production.

There is level 4 evidence that a combination barbiturate therapy and therapeutic hypothermia may result in improved clinical outcomes up to 1 year post injury.

There is level 2 evidence that Disodium Etidronate (EHDP) may reduce the development of heterotopic ossification in patients with severe head injury.

There is conflicting (level 1b) evidence as to whether dexanabinol in cremophor-ethanol solution effectively lowers intracranial pressure, increases cerebral perfusion pressure, and improves long-term clinical outcomes post TBI when compared to placebo.

There is level 1b evidence that a dual cannabinoid agonist may significantly increase cerebral perfusion pressure and improves survival post TBI when compared to placebo.

Based on a single RCT, there is level 1b evidence that pindolol may decrease aggression following brain injury.

There is level 1b evidence that propranolol may reduce the intensity of agitated symptoms following brain injury.

There is level 2 evidence supporting the administration of low molecular weight herapin within the first 72 hours post ABI to reduce the risk of developing deep vein thrombosis and pulmonary embolisms post injury.

There is level 2 evidence that administering low molecular weight herapin (enoxaparin) or heparin post ABI may not increase the risk of intracranial bleeding, compared to no treatment.

There is level 4 evidence that the use of chemoprophylaxis 24 hours after stable head computed tomography scan may decrease the rate of deep vein thrombosis formation post ABI.

There is level 4 evidence that mannitol may be effective in controlling elevated intracranial pressure.

There is level 2 evidence that early administration of mannitol may not effectively lower elevated intracranial pressure, but may not adversely affect blood pressure.

There is level 2 evidence that high-dose mannitol may be more effective than conventional mannitol in reducing mortality rates and improving clinical outcomes.

There is level 1b evidence that mannitol may be no more effective than hypertonic saline in controlling elevated intracranial pressure.

There is level 1b evidence that mannitol may be less effective than sodium lactate in controlling elevated intracranial pressure.

There is level 1b evidence that pramipexole, and level 1a evidence that amantadine, may be effective in improving levels of consciousness in children with ABI.

There is level 1a evidence that amantadine may effectively improve consciousness, cognitive function, and disability when compared to placebo.

There is level 2 evidence that Amantadine may not help to improve learning and memory deficits.

There is conflicting evidence of the effects of amantadine on reducing irritability and aggression in individuals with moderate-severe traumatic brain injury.

There is level 4 evidence that dopamine-enhancing drugs may accelerate the rate of recovery from a low response state for children post TBI.

Based on two RCTs, there is conflicting evidence supporting the use of bromocriptine to enhance cognitive functioning.

There is level 4 evidence that bromocriptine may improve all motivational deficits except mood.

There is level 2 evidence that administration of dexamethasone may inhibit endogenous production of glucocorticoids and has no proven impact on recovery post brain injury.

There is level 4 evidence that Depo-Provera and counselling may reduce sexually aggressive behaviour.

There is level 1a evidence that progesterone may not lower intracranial pressure levels post TBI when compared to placebo.

There is level 1a evidence that progesterone may not be associated with adverse events when compared to placebo.

There is conflicting level 1a evidence as to whether progesterone improves long-term outcomes and reduces mortality post TBI when compared to placebo.

There is conflicting evidence regarding the effectiveness of the administration of methylphenidate following brain injury for the improvement of cognitive functioning.

There is level 1a evidence that methylphenidate may improve reaction time of working memory.

Based on a single RCT, there is level 1b evidence that an individual's response to methylphenidate therapy may be dependent on his/her genotype of the catechol-O-methyltransferase gene.

There is level 3 evidence, based on a single study, that methylphenidate may not have an adverse effect on the sleep-wake cycle of those who have sustained a TBI.

There is level 2 evidence (from one randomized control trial) to suggest that treatment with methylphenidate following brain injury can significantly reduce anger.

Based on two small and conflicting RCTs, there is inconclusive evidence whether methylphenidate improves cognitive behavioural function in children post ABI.

There is level 1a evidence that modafinil may not be effective in treating fatigue but has been shown to be effective short-term in treating excessive daytime sleepiness post ABI.

There is level 1b evidence that propofol may reduce intracranial pressure and the need for other intracranial pressure interventions when used in conjunction with morphine compared to morphine alone.

There is level 1b evidence that a high dose of propofol may improve intracranial pressure and cerebral perfusion pressure compared to a low dose of propofol.

There is level 2 evidence that propofol may not be significantly different from dexmedetomidine in its effect on intracranial pressure.

There is level 2 evidence that propofol may not be significantly different from morphine and midazolam in its effect on intracranial pressure, cerebral perfusion pressure, mean arterial pressure, and long-term outcomes.

There is level 4 evidence that propofol may improve intracranial pressure and cerebral perfusion pressure.

There is level 4 evidence that midazolam may reduce mean arterial pressure, cerebral perfusion pressure, and systolic blood pressure, but may have no effect on intracranial pressure.

There is level 2 evidence that midazolam may not be different from propofol in its effect on intracranial pressure or cerebral perfusion pressure.

There is level 1b evidence that midazolam may not be different than propofol in its effect on long-term outcomes.

There is level 1a evidence that methylprednisolone may increase mortality rates in patients post ABI and should not be used.

There is level 1b evidence that dexamethasone may not lower elevated intracranial pressure levels and may worsen outcomes.

There is level 2 evidence that triamcinolone may improve outcomes in patients with a Glasgow Coma Scale<8 and a focal lesion.

There is level 3 evidence that glucocorticoid administration may increase the risk of developing first late seizures.

12.18 References

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