ERABI

EVIDENCE-BASED REVIEW
of moderate to severe
ACQUIRED BRAIN INJURY

12. Neuropharmacological Interventions Post ABI

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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.

Remifentanil might not improve intracranial pressure, cerebral perfusion pressure, cerebral blood flow velocity, or mean arterial pressure post ABI

Sufentanil might decrease mean arterial pressure, cerebral perfusion pressure, heart rate and transiently increase intracranial pressure— especially in patients with low blood pressure.

Sufentanil used in combination with midazolam may decrease intracranial pressure and mean arterial pressure post ABI.

Propofol, especially at higher doses, likely improves favourable outcomes, intracranial pressure and cerebral perfusion pressure more effectively than morphine.

Propofol may be no different than dexmedetomidine or morphine with midazolam in its effect on morbidity outcomes, or intracranial, cerebral perfusion, and mean arterial pressure.

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.

Phenytoin may be an effective prophylactic drug for early post-traumatic seizures, however its effectiveness to treat late post-traumatic seizures has not been established.

Phenytoin is more effective than valproate as a prophylactic anti-seizure medication.

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

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 may be effective in reducing aggression following a TBI, although, additional research is needed.

Lamotrigine may be effective in reducing pathologic laughing and crying following a TBI. However, further research with larger sample sizes is needed to validate these findings.

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

It is unclear as to whether donepezil may improve attention in individuals with a moderate to severe ABI.

Physostigmine may improve long-term memory in men with TBI, however, more studies are required.

Rivastigmine may not be effective in treating attention deficits post ABI.

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.

Quetiapine may be effective in reducing aggression following a TBI, although additional research is needed.

Ziprasidone may be effective in reducing agitation following a TBI, although, additional research is needed.

Haloperidol appears to have no benefits, and possible negative effects on recovery, following a TBI.

Droperidol may be effective in reducing agitation following TBI, although additional research is required.

Methotrimeprazine may be safe and effective for controlling agitation following an ABI, although, additional research is required.

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.

Bolus injections of intrathecal baclofen likely produce short-term reductions in upper and lower extremity spasticity and improvements in walking performance post ABI.

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

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

There are conflicting reports regarding whether pentobarbital is superior to conventional management at improving intracranial pressure. The strongest evidence suggests there is no difference.

Thiopental may decrease intracranial pressure, cerebral perfusion pressure, and mean arterial pressure post ABI.

Thiopental may be more effective than pentobarbital at controlled refractory intracranial pressure, and less likely to develop adrenal insufficiency. However, thiopental may still be associated with leuko- and granulocytopenias. When used, combination with hypothermia may result in greater long-term outcomes.

Barbiturate therapy should be avoided until all other measures for controlling elevated intracranial pressure are exhausted; special attention should be paid to monitoring immunological function, adrenal function, and blood pressure status if used.

Pentobarbital might decrease energy expenditure and nitrogen metabolism in individuals with an ABI refractory to standard therapy.

Etidronate Disodium may prevent the development of heterotopic ossification in individuals with ABI.

It is unclear whether Dexanabinol in cremophor-ethanol solution is effective in controlling intracranial pressure and improving cerebral perfusion pressure, and clinical outcomes post TBI. The strongest evidence suggests no beneficial effects.

KN38-7271, a dual cannabinol agonist, is likely effective at improving intracranial pressure, cerebral perfusion pressure and survival post TBI at high doses.

Pindolol may be effective in reducing aggression following an ABI.

Propranolol may be effective in reducing the intensity of agitation and aggression following brain injury.

Administration of pharmacological thromboembolic prophylaxis within the first 72 hours post ABI may be effective for reducing the risk of developing venous thromboembolism.

Enoxaparin is effective for the prevention of venous thromboembolism development after elective neurosurgery and has not been found to cause excessive bleeding.

Mannitol may effectively improve intracranial pressure and cerebral perfusion pressure post ABI; however, this benefit may only be seen in hypertensive (intracranial pressure>20 mmHg) patients.

It is unclear whether hypertonic saline is more effective than mannitol at lowering intracranial pressure or reducing hospital length of stay.

Hypertonic saline can improve cerebral perfusion pressure, cerebral blood flow, and brain tissue oxygenation more effectively than mannitol. However, hypertonic solution is not different than mannitol in terms of morbidity and mortality associated with treatment.

Hypertonic saline is superior to barbiturates, propofol, and fentanyl at lowering intracranial pressure post TBI.

Amantadine may improve consciousness, cognitive function, and disability post ABI; however, it might not affect emergence from coma post ABI. It is important to note that these benefits are only seen during amantadine administration, and so treatment must be continued to sustain the improvements made.

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

Amantadine is not effective at improving generalized cognition. Its impact on executive functioning should be studied further.

Amantadine requires further research before conclusions can be drawn regarding its effects on aggression and irritability following a TBI.

Bromocriptine does not appear to improve attention in those with an ABI.

(-)-OSU6162 treatment may not be effective for reducing fatigue post TBI.

Medroxyprogesterone intramuscularly may reduce sexual aggression.

Progesterone does not improve functional outcomes post TBI, with the potential exception of patients who are not severely ill upon admission (Glasgow coma scale score$\geq$5)

Progesterone is likely associated with the development of phlebitis and thrombophlebitis.

Progesterone has no effect on intracranial pressure, but does reduce mortality, and improves functional and neurological outcomes post ABI.

Growth hormone deficiency may be effectively treated with hormone replacement therapy and insulin growth like factor-1 therapy.

The administration of human growth hormones appears to have positive (although sometimes limited effects) on general and executive functioning in those with an ABI.

Melatonin treatment may improve sleep quality, sleep efficiency, and reduce fatigue in patients post TBI.

Melatonin treatment may not effect sleep onset latency or daytime sleepiness.

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

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

Response to methylphenidate may depend on the presence of the Met 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.

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.

Dextroamphetamine is moderate evidence to suggest that dextroamphetamine is not effective for the remediation of general functioning.

Pramiracetam might improve memory in males post TBI, however, additional studies are required.

Propofol may improve intracranial pressure and cerebral perfusion pressure post ABI, without producing adverse outcomes.

Propofol and vasopressor treatment in combination, but not as monotherapy, might increase the risk of developing propofol infusion syndrome post ABI.

Propofol, especially at higher doses, likely improves favourable outcomes, intracranial pressure and cerebral perfusion pressure more effectively than morphine.

Propofol may be no different than dexmedetomidine or morphine with midazolam in its effect on morbidity outcomes, or intracranial, cerebral perfusion, and mean arterial pressure.

The combination of morphine and midazolam may confound the comparison between propofol and morphine, however, it is prudent to conclude propofol is at least as safe and effective as morphine.

Midazolam is likely not different than propofol at improving mortality, disability, or neurological outcomes.

High doses of midazolam might be associated with hypotension, specially following intubation.

Midazolam may have no effect on intracranial pressure but may reduce mean arterial pressure and cerebral perfusion pressure in patients, post-ABI.

Propofol may be no different than dexmedetomidine or morphine with midazolam in its effect on morbidity outcomes, or intracranial, cerebral perfusion, and mean arterial pressure.

Corticosteriods such as methylprednisolone, dexamethasone, and other glucocorticoids may worsen outcomes, and should not be used. However, methylprednisolone may be effective at improving mortality when specific complications, such as acute respiratory distress syndrome secondary to sepsis, arise.

Triamcinolone may improve outcomes in individuals post ABI with a Glasgow Coma Scale score less than 8 and a focal lesion.

Anatibant, regardless of dose, likely does not cause serious adverse events, affect morbidity, mortality or disability in patients post ABI.

It is unclear if a higher dose of anatibant is superior to a lower dose at improving intracranial pressure, however it may improve functional outcomes up to 6 months post injury.

Bradycor can prevent acute elevations in intracranial pressure and reduce therapeutic intensity levels post ABI; however, its effect on morbidity and mortality outcomes is not clear.

Dimethyl sulfoxide may cause temporary improvements in intracranial pressure and cerebral perfusion pressure post ABI, however these improvements may not be sustained long-term.

DMSO might be able to transiently lower intracranial pressure; however, it is associated with the development of electrolyte imbalances. Both responses appear to be dose-dependent.

Table of Contents

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

Neuropharmacology for Acquired Brain Injury

12.0 Introduction

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 Acquired Brain Injury (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 Intracranial Pressure (ICP) and Cerebral

Perfusion Pressure (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.

The American Association of Neurological Surgeons (AANS) and the European Brain Injury Consortium (EBIC) made no recommendations regarding opioids in acute ABI.

Table 12.1 Opioids for the Acute Management of ABI

Author Year Country Research Design PEDro Sample Size	Methods	Outcomes
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:** Remifentanil was administered first as as intravenous bolus (0.5 ug/kg), and subsequently as a 20 min continuous infusion (0.25 ug/kg/min) . Outcomes were assessed for 20min before and after remifentanil administration. **Outcome Measures:** 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. Patients were monitored for 30min. **Outcome Measures:** 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 ($p<0.05$).
[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 sufentanil (1 µg/kg, 6 min), followed by continuous intravenous infusion (0.005 µg/kg/min). **Outcome Measures:** 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 5 min 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%, $p<0.05$).
Multimodal Opioid Interventions		
[Karabinis et al.](#) (2004) Greece RCT	**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;	1. Sedation with remifentanil required significantly less time to neurological assessments (0.41 hr), compared to

Author Year Country Research Design PEDro Sample Size	Methods	Outcomes
PEDro=5 N=161	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. **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 5-10 min (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 Measures:** Time to neurological assessment, Intracranial Pressure (ICP), Cerebral Perfusion Pressure (CPP).	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.
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=17.8hr; GCS Range≤8. **Intervention:** Patients were randomized to receive intravenous morphine (0.2 mg/kg) or fentanyl (2 µg/kg) over 1 min. Crossover occurred after 24 hr. Treatment was initiated at 0 min and measurements were repeated at 5-10 min intervals until 60 min. **Outcome Measures:** 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 5min (p=0.002 and p=0.016, respectively), which remained significantly lower with fentanyl up to 60 min (p=0.016). 4. Increase in ICP coupled with decrease in MAP resulted in a transient decrease in CPP, reaching a minimum value of 6 4mmHg 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 either 1 µg/kg sufentanil, 100 µg/kg alfentanil, or 10 µg/kg fentanyl, followed by a 1 hr infusion of the same drug at 0.005 µg/kg/min, 0.7 µg/kg/min, and 0.075 µg/kg/min, respectively. Crossovers occurred at 24 hr intervals.	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) that returned to baseline by 15 min. 2. Sufentanil, alfentanil, and fentanyl were associated with significant mean

Author Year Country Research Design PEDro Sample Size	Methods	Outcomes
	Outcome Measures: Intracranial Pressure (ICP), Cerebral Perfusion Pressure (CPP), Mean Arterial Pressure (MAP), Heart Rate (HR), End-Tidal CO_2, O_2 Saturation.	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. 3. No significant difference were observed after the use of any opioid with regard to HR, or End-Tidal CO_2/ O_2 saturation.
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 (Avg. 10 mg/h). Both groups received additional bolus of MOR (1-3 mg/hr) for at least 48 hr for analgesic purposes. Assessments were made at baseline, days 1, 2, 3, and 4, and at 6 mo. **Outcome Measures:** 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 6 mo, scores were not significantly different between groups for mortality or favourable outcome rates (GOS$\geq$4). 4. In subgroup analysis, PROP was divided into high-dose (100 mg/kg, n=10) and low-dose (<100 mg/kg, n=13) groups. The high-dose group showed higher mean CPP on day 2 (81 mmHg versus 68 mmHg) and lower mean ICP on day 3 (14 mmHg versus 15 mmHg) compared to low-dose ($p>0.05$). 5. High-dose group demonstrated more favourable outcomes in the GOS (70% versus 38.5%) and the DRS (80% versus 46.2%) compared to the low-dose group ($p>0.05$).
Lauer et al. (1997) USA RCT PEDro=5 N=15	**Population:** TBI; *Morphine Group (n=5)*: Mean Age=21 yr; Mean GCS=6. *Fentanyl Group (n=5)*: Mean Age=22 yr; Mean GCS=5. *Sufentanil Group (n=5)*: Mean Age=35 yr; Mean GCS=6. **Intervention:** Patients were randomized to receive continuous intravenous morphine, fentanyl, or sufentanil over a 5 min interval. Continuous bolus infusion was initiated for 4 hr with the same opioid, if the blood pressure did not change >5%. Assessments were made every 15 min for the first 2 hr, and then in every 30min for the last 2hr. **Outcome Measures:** Intracranial Pressure (ICP), Mean Arterial Pressure (MAP), Cerebral Perfusion Pressure (CPP), Heart Rate (HR).	1. Mean doses of morphine, fentanyl, and sufentanil were 2.98 µg/kg, 0.07 mg/kg, and 0.37 µg/kg, respectively. 2. There was no significant difference in MAP from baseline in any group, except the sufentanil group had reduced MAP at 10 and 45 min post bolus administration ($p<0.05$). 3. There was no significant change in ICP from baseline in any group. However, the fentanyl group had reduced ICP at 150 and 180 min post bolus administration compared to the morphine and sufentanil groups ($p<0.05$). 4. There was no significant change in CPP from baseline in any group. However, the fentanyl group had reduced CPP at 60 min post bolus administration compared to

Author Year Country Research Design PEDro Sample Size	Methods	Outcomes
		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 Measures:** 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. Both Fentanyl and Sufentanil treatment resulted in significant decreases in CPP from baseline (-17mmHg and -13 mmHg, respectively, p<0.05). 4. No significant change in HR was noted after the use of either opioid.
[Colton et al](#). (2014b) USA Case Series N=117	**Population:** TBI; Mean Age=40.0 yr; Gender: Male=93, Female=24; Median GCS=6. **Intervention:** Participants were included in retrospective analysis after having received one of the following ICP therapies: hypertonic saline (HTS), mannitol, propofol, fentanyl, and barbiturates. **Outcome Measure:** Intracranial Pressure (ICP).	1. Treatment with HTS resulted in the largest ICP decrease of the treatments examined. 2. Propofol and fentanyl escalations resulted in smaller but significant ICP reductions. 3. Mannitol resulted in statistically insignificant reductions in the first hr but rebounded by the second hr.
[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 (150 (25-200) µg base h^{-1}) and midazolam (9.0 (3.6-13.5) mg h^{-1}) for 48 hr. **Outcome Measures:** 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 15min. 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 observed at 2 days.
[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 Measures:** 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.

Discussion

One study researched the effects of IV remifentanil on patients with ABI. The remifentanil was administered first as a bolus, then as a continuous infusion, yet despite the different modes of application the study reported no differences in ICP, CPP, MAP, or cerebral blood flow velocity compared to baseline (Engelhard et al., 2004).

The effects of sufentanil on patients with ABI were researched by Werner et al. (1995) and Albanese et al. (1993). While both studies reported decreases in MAP, only Albanese at al. observed additional decreases in CPP and HR. Interestingly, both groups noted an increase in ICP following sufentanil treatment, albeit only transiently in one study (Albanese et al., 1993) or in patients with decreased MAP (Werner et al., 1995). Although the trials were small and not blinded, these results suggest that sufentanil is not an agent that should be considered when attempting to lower ICP post-ABI.

Several studies conducted RCTs comparing the efficacy of fentanyl to either morphine (de Nadal et al., 2000), sufentanil (Sperry et al., 1992), sufentanil and alfentanil (Albanese et al., 1999), morphine and sufentanil (Lauer et al., 1997) or remifentanil and morphine (Karabinis et al., 2004). Of the studies reviewed, 3 reported increases in ICP after opioid administration (Albanese et al., 1999; de Nadal et al., 2000; Sperry et al., 1992). The ICP increase was transient in Albanese et al. with the pressure returning to baseline 15 min after opiod administration. Of the aforementioned studies, all revealed a decrease in CPP and MAP after any type of opioid treatment. The remaining two studies found ICP did not change after opioid administration ((Engelhard et al., 2004; Karabinis et al., 2004; Lauer et al., 1997). Furthermore, CPP and MAP did not change, save for the sufentanil group in Lauer and colleagues' study where a decrease in mean arterial pressure was found. 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).

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. However, it has been reported that using an opioid such as sufentanil with midazolam significantly improves ICP for a prolonged period of time (2 days), albeit at the expense of decreasing MAP (Scholz et al., 1994). 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. While, Kelly et al. (1999) noted propofol was significantly more effective than morphine at reducing ICP - especially at higher doses. With respect to morbidity outcomes, one study reported no difference (Stewart et al., 1994) and the other an increase (Kelly et al., 1999) in favourable outcomes compared to the other treatment. Despite the disagreement in relationship directionality between studies, it can be concluded that propofol is at least as safe to use as morphine alone, or morphine with midazolam.

Conclusions

There is conflicting (level 1a and level 2) evidence as to whether fentanyl, morphine, or sufentanil increase intracranial pressure, and decrease cerebral perfusion pressure post ABI. The level 1a evidence suggests that it increases intracranial pressure and decreases cerebral perfusion pressure.

There is level 1b evidence that propofol is more effective than morphine at improving favourable outcomes and reducing intracranial pressure post TBI- specially at higher doses.

There is level 2 evidence that alfentanil may result in a decrease in cerebral perfusion pressure and mean arterial pressure, and a transient increase in intracranial pressure, post ABI compared to controls.

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

There is level 2 evidence that propofol is similar to midazolam and morphine with regards to sedation, morbidity, changes in intracranial pressure, cerebral perfusion, and mean arterial pressure post ABI.

There is level 4 evidence that remifentanil may not improve intracranial pressure, cerebral perfusion pressure, mean arterial pressure, or cerebral blood flow velocity post ABI.

There is level 4 evidence that sufentanil may decrease mean arterial pressure, cerebral perfusion pressure, and heart rate post ABI.

There is level 4 evidence that sufentanil may transiently increases intracranial pressure post ABI.

There is level 4 evidence that sufentanil may increase intracranial pressure in patients with low mean arterial pressure post ABI.

There is level 4 evidence that sufentanil with midazolam decreases intracranial pressure and mean arterial pressure for 2 days 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.

Remifentanil might not improve intracranial pressure, cerebral perfusion pressure, cerebral blood flow velocity, or mean arterial pressure post ABI

Sufentanil might decrease mean arterial pressure, cerebral perfusion pressure, heart rate and transiently increase intracranial pressure— especially in patients with low blood pressure.

Sufentanil used in combination with midazolam may decrease intracranial pressure and mean arterial pressure post ABI.

Propofol, especially at higher doses, likely improves favourable outcomes, intracranial pressure and cerebral perfusion pressure more effectively than morphine.

Propofol may be no different than dexmedetomidine or morphine with midazolam in its effect on morbidity outcomes, or intracranial, cerebral perfusion, and mean arterial pressure.

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 Research Design PEDro Sample Size	Methods	Outcome
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 (ABS), Katz Adjustment Scale, and Mini Mental Status Exam (MMSE).	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 (p<0.01), and disinhibition (p<0.05) portions of NRS-R. 4. Global NRS-R significantly decreased from baseline (p=0.01).

Author Year Country Research Design PEDro Sample Size	Methods	Outcome
Agitation		
		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 Midazolam for the Treatment of Seizures Post ABI

Author Year Country Research Design PEDro Sample Size	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.

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

Discussion

There appears to be very little research evaluating the efficacy of Midazolam given to treat seizures. 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 Research Design PEDro Sample Size	Methods	Outcome
Phenytoin versus Placebo		
Dikmen et al. (1991) USA RCT PEDro=6 N$_{initial}$=244, N$_{Final}$=124	**Population:** Head Injury. *Phenytoin Group (n=104)*: Mean Age=30.9 yr; Gender: Male=82, Female=22; Median GCS=11. *Placebo Group (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.	1. From 1 to 12 mo, more participants in the treatment group stopped receiving 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	**Population:** TBI; Mean Age=25.2 yr; Gender: Male=178, Female=36.	1. Late seizures occurred in 11 (12.9%) of the phenytoin group, 2 (10%) of the

Author Year Country Research Design PEDro Sample Size	Methods	Outcome
RCT PEDro=6 N$_{initial}$=214, N$_{final}$=179	**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.	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 RCT PEDro=7 N=164	**Population:** TBI**;** Age: 5-15 yr=43, 16-65 yr=121; Gender: Male=130, Female=34. **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.	1. Only 48% of the treatment group had plasma levels greater than 40µmol/l. 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.
[Bhullar et al.](#) (2014) USA Case Control N=93	**Population:** TBI, GCS=3-8; *No Prophylaxis Group (n=43)*: Gender: Male=28, Female=15. *Phenytoin Prophylaxis Group (n=50)*: Gender: Male=42, Female=8. **Treatment:** Medical records were reviewed and patients were divided into two groups: no prophylaxis and phenytoin prophylaxis. **Outcome Measure:** Occurrence of early (<7d post injury) seizures, length of stay (LOS), Glasgow Outcome Scale (GOS), modified Rankin Scale (mRS).	1. There was no significant difference in the occurrence of early seizures between the no prophylaxis and phenytoin groups (2.3% versus 4.0%, p=1.0). 2. The phenytoin group, compared to no prophylaxis, had longer hospital stays (36± 31 vs 25± 16d, p=0.03), and 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).
Phenytoin versus Levetiracetam		
[Younus et al.](#) (2018) Pakistan RCT PEDro= 6 N = 140	**Population:** *Phenytoin Group (N=69)*: Mean GCS= 11.23. *Levetiracetam group (N=73):* Mean GCS=11.17. *Overall:* 117 males, 23 females; Mean Age= 29.48±16.24y **Intervention:** TBI patients admitted to the hospital were randomized into the Phenytoin medication group, or the Levetiracetam group. Both groups received medication for 7 days. No statistical differences between groups at baseline **Outcomes:** Abnormal EEG, Seizure activity (7-10 days), Glasgow Coma Scale (GCS).	1. The number of abnormal EEGs was found to be significantly different between the two groups (p=0.002) showing the Levetiracetam group had fewer individuals with abnormal EEG. 2. The amount of seizure activity at follow-up was significantly different between groups (p=0.014), showing the Levetiracetam group had fewer instances of seizures. 3. There was no significant difference between GCS scores at follow-up between the two groups.
[Szaflarski et al.](#) (2010) USA RCT PEDro=8 N=52	**Population:** TBI=46; SAH=6; Phenytoin group (PHT; n=18): Mean Age=35yr; Gender: Male=13, Female=5; Mean GCS=4. Levetiracetam group (LEV; n=34): Mean Age=44yr; Gender: Male=26, Female=8; Mean GCS=5.	1. There were no significant differences in the occurrence of early seizures between the PHT and LEV groups (3 versus 5, p=1.0)

Author Year Country Research Design PEDro Sample Size	Methods	Outcome
[Steinbaugh et al.](#) (2012) USA Addition to Szaflarski et al. 2010 RCT	**Treatment:** Patients were randomized within 24h of injury. Patients received either a loading dose of intravenous PHT 20mg/kg, then 5mg/kg/d or intravenous LEV at 20mg/kg, and then 1000mg every 12hr/7d. **Outcome Measure:** Occurrence of early seizures, Glasgow Outcome Scale (GOS), GOS-Extended (GOSE), Disability Rating Scale (DRS), Resource Utilization Questionnaire. **Addition**: Patients received continuous video EEG (cEEG) for up to 72h which was compared to the outcomes collected.	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, increased 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 6mo (p=0.006 and p=0.037), and higher GOSE at 6mo (p=0.016) in patients who survived. The presence of focal slowing, epileptiform discharges, and seizures were not predictive of outcome (GOS-E, DRS). More severe slowing was positively associated with DRS at discharge, 3 and 6mo (p=0.084) and negatively associated with GCS at discharge.
[Khan et al.](#) (2016) Pakistan Cohort N=154	**Population**: Mean Age=24.15yr; Gender: Males=115, Females=29; Mean GCS: 59.1% (8-13), 40.9% (3-7). **Intervention:** Group A received Phenytoin (5 mg/kg/day), group B received Levetiracetam (10-20 mg/kg/day). **Outcome Measure:** Incidence of post-traumatic seizures, efficacy of drug on moderate vs severe TBIs.	1. There were no significant differences between groups in terms of the drug efficacy of Phenytoin vs Levetiracetam. 2. There was no significant difference in how each drug impacted moderate vs severe TBI and seizure rates.
[Javed et al.](#) (2016) Pakistan Cohort N=100	**Population:** *Group 1 (n=50):* Mean Age=31.16yr. *Group 2 (n=50)*: Mean Age=34.96. **Intervention:** Group 1: received IV phenytoin and Levetiracetam (35 mg/kg three times daily). Group 2: EEG monitoring. **Outcome Measure:** Incidence of post-traumatic seizures.	1. There were no significant differences between the number patients in each group which had post-traumatic seizures.
[Radic et al.](#) (2014) USA Case Control N=288	**Population:** Subdural Hematoma; Levetiracetam group (LEV; n=164): Mean Age=65.96yr; 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.	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

Author Year Country Research Design PEDro Sample Size	Methods	Outcome
	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.	electrographic seizures during hospitalization (p=0.028) and a decreased risk of adverse drug effects (p=0.001), compared with PHT use.
Gabriel & Rowe (2014) USA Cohort N=19	**Population**: TBI; Phenytoin Group (PHT, n=14): Mean Age=46.8yr; Gender: Male=10, Female=4; Mean GCS=3. Levetiracetam Group (LEV, n=5): Mean Age=48.8yr; 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 the 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. There was no significant difference between groups for occurrence of early or late seizures (both p=0.53). Compared to the PHT group, the LEV group was significantly less likely to experience mediation-related complications (p=0.038); the PHT group had a significantly higher rate of days with fever (p=0.014).
Inaba et al. (2013) USA Prospective Controlled Trial N=813	**Population:** TBI; Levetiracetam Group (LEV, n=406): Mean Age=51.7yr; Gender: Male=300, Female=106; Mean GCS=12.1. Phenytoin Group (PHT, n=407): Mean Age=53.6yr; Gender: Male=280, Female=127; Mean GCS=12.6. **Treatment:** Participants were administered either LEV at 1000mg every 12h or PHT. In the PHT group the loading dose was 20mg/kg then 5mg/kg/d every 8h. Treatment lasted 7d. **Outcome Measure:** Seizure occurrence.	1. There was no significant difference in seizure rates between groups (1.5% versus 1.5%, p=0.997). 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 Retrospective Cohort N=109	**Population:** TBI; Median GCS=5. Phenytoin Group (PHT, n=89): Median Age=43.1yr; Gender: Male=76, Female=13. Levetiracetam Group (LEV, n=20): Median Age=34.1yr; Gender: Male=19, Female=1. **Treatment:** Retrospective review of patients administered PHT or LEV. **Outcome Measure**: Occurrence of early seizures.	1. One patient from each group seized in the first 7d (p=0.335). Hospital length of stay did not differ significantly between groups (median days, LEV 26.5 versus PHT 11, p=0.134).
Jones et al. (2008) USA Cohort N=27	**Population:** Severe TBI; Gender: Male=20, Female=7. **Treatment:** Patients received Levetiracetam (n=15; 500mg IV every 12h for 7d) administered within 24hr of injury and were compared to a retrospective cohort of patients who received phenytoin (n=12).	1. There was a significant difference in the occurrence of abnormal EEG findings (seizure or seizure tendency with epileptiform activity) between groups (p= 0.003), with the Levetiracetam group having more abnormal findings.

Author Year Country Research Design PEDro Sample Size	Methods	Outcome
	Outcome Measure: Occurrence of early seizures.	There was no significant difference between groups for actual seizures (p=0.556).
**Additional Studies of Phenytoin**	
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.
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 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).	1. No significant difference in early seizures between the no prophylaxis and phenytoin group (2.3% versus 4.0%, p=1.0). 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).
Servit & Musil (1981) Czechoslovakia	**Population:** TBI; Mean Age=30.6 yr; Gender: Male=128, Female=39.	1. Posttraumatic epilepsy occurred in 25% of the control and 2.1% of the treatment

Author Year Country Research Design PEDro Sample Size	Methods	Outcome
PCT N=167	**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.	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 the administration of phenytoin is compared to a placebo, its effect on the occurrence of early seizures is not encouraging; several studies did not find phenytoin to be effective (Bhullar et al., 2014; Temkin et al., 1990; Young et al., 1983). However, one RCT by Temkin et al., (1990) did find that phenytoin reduced the rate of early seizures only compared to placebo. 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. 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 the prevention of seizures is not favorable. 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, many studies have shown the two drugs to be comparable in terms of seizure rates (Inaba et al., 2013; Javed et al., 2016; 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 randomized controlled trial (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 GOS at 6 months (p=0.039) post intervention compared to the phenytoin group. A large RCT by Younus et al. (2018) found that individuals on levetiracetam has a significant decrease in seizure activity at follow-up, and fewer abnormal EEGs compared to those on phenytoin. Furthermore, upon differentiation Radic et al. (2014) found that individuals with any evidence of a midline shift 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.

When examining the effects of phenytoin compared to valproate Temkin et al. (1999) found no significant differences in rates of early seizures, late seizures, or mortality. Dikmen et al. (1991) found that severely

injured individuals receiving phenytoin performed no more poorly on neuropsychological measures than those taking valproic acid and valproate. The following year (12 to 24 months later), phenytoin was shown to have a small but negative effect on cognition (Dikmen et al., 1991).

Conclusions

There is level 1b evidence that phenytoin is effective in reducing the rate of only early onset post-traumatic seizures in patients with TBI.

There is conflicting evidence regarding whether or not phenytoin is effective in preventing post-traumatic seizure disorder long term compared to placebo treatment in patients with TBI.

There is level 1a evidence that valproate is not more effective as a prophylactic anti-seizure medication compared to phenytoin in ABI populations.

There is level 1b evidence that levetiracetam and phenytoin do not show significant differences between them as prophylactic anti-seizure medication for individuals with ABI.

Phenytoin may be an effective prophylactic drug for early post-traumatic seizures, however its effectiveness to treat late post-traumatic seizures has not been established.

Phenytoin is more effective than valproate as a prophylactic anti-seizure medication.

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

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 Research Design PEDro Sample Size	Methods	Outcome
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-	*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.

Author Year Country Research Design PEDro Sample Size	Methods	Outcome
	up continued for 5 yr. Participants with mild head injury were in a third group (n=65). **Outcome Measure:** Occurrence of seizures.	
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 a 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 treat seizure disorders in both adults and children. It has also been used to treat mania, bipolar disorder, and PTSD (McElroy et al., 1987). A case study of an individual with TBI showed a reduction in episodic explosiveness (Geracioti Jr, 1994), and so it has been explored as an intervention for challenging behaviours post ABI.

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

Author Year Country Research Design PEDro Sample Size	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. (1997a) 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. (1997a) 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.

> **Valproic acid may be effective in reducing aggression following a TBI, although, additional research is needed.**

12.2.6 Lamotrigine

Lamotrigine has demonstrated effectiveness as an antiepileptic (Brandt & May, 2018) and mood stabilizer (Baldessarini et al., 2018). Among individuals with ABI, however, its effectiveness as a mood stabilizer has yet to be established (Gao & Calabrese, 2005; Tidwell & Swims, 2003).

Table 12.7 Effects of Lamotrigine on Reducing Aggressive Behaviour

Author Year Country Research Design PEDro Sample Size	Methods	Outcomes
Chahine & Chemali (2006a) 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 and crying but did not address impulsivity (Chahine & Chemali, 2006b). All four participants were on other medications to control for additional behaviours, but these medications were eventually eliminated once lamotrigine was introduced. No formal outcome assessments were conducted, which makes it difficult to draw conclusions from this study.

Conclusion

There is level 4 evidence that lamotrigine may reduce inappropriate behaviours post TBI.

Lamotrigine may be effective in reducing pathologic laughing and crying following a TBI. However, further research with larger sample sizes is needed 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 Research Design PEDro Sample Size	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 d. **Intervention:** 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 Measures:** Syndrome Kurztest (SKT), Electroencephalogram (EEG)/brain mapping recordings, Glasgow Outcome Scale (GOS).	1. Compared to baseline, patients with TBI showed a significant decrease in slow bioelectrical activity frequencies (delta: $p<0.010$; theta: $p<0.050$), and a significant increase in fast frequencies (beta: $p<0.010$) 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 versus 12.0 ± 2.1; $p<0.010$). 3. GOS scores significantly improved from pre to post treatment (3.7 ± 0.3 versus 3.95 ± 0.3; $p<0.050$).

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 neurological recovery, as measured by the Glasgow Outcome Scale (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. However, controlled trials are necessary to further explore the efficacy of this drug.

Conclusions

There is level 4 evidence that cerebrolysin may improve attention scores post ABI.

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

12.3.2 Donepezil and Cognitive Functioning

Originally developed for improving cognitive function and memory in people with Alzheimer's disease, donepezil is an acetylcholinesterase inhibitor (Cacabelos, 2007). Donepezil has been found to be effective at delaying cognitive impairment in people with Alzheimer's disease (Takeda et al., 2006). Since evidence suggests that cholinergic dysfunction may contribute to persistent cognitive deficits for people after traumatic brain injury, improvements in attention, memory, and other aspects of cognition related to the acetylcholine system are expected when cholinergic function is reduced (Arciniegas, 2003).

Table 12.9 Effects of Donepezil on Cognitive Functioning and Memory

Author Year Country Research Design PEDro Sample Size	Methods	Outcome
Zhang et al. (2004) USA RCT PEDro=7 N=18	**Population:** TBI; *Group A (n=9)*: Mean Age=33yr; Gender: Male=6, Female=3; Mean GCS=9.3; Mean Time Post Injury=4.6mo; *Group B (n=9)*: Mean Age=31yr; Gender: Male=7, Female=2; Mean GCS=8.9; Mean Time Post Injury=3.9. **Intervention:** In a randomized crossover trial, Group A received oral donepezil for the first 10wk, followed by a washout period of 4wk, then followed by 10wk of placebo. Group B received the treatments in the opposite order. Donepezil was administered at 5mg/d for the first 2wk, and at 10mg/d for the remaining 8wk. **Outcome Measures:** 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.
Campbell et al. (2018) United States PCT N=129	**Population:** *Donepezil Group (N=55):* Mean Age=34.4yr; Gender: Male=80%, Female=20%; Mean time post injury=28.6d; Injury Severity=Moderate-severe. *Control Group (N=74):* Mean Age=40.8yr; Gender: Male=71.6%, Female=28.4%; Mean time post injury=25.2d; Injury Severity=Moderate-severe. **Intervention:** Individuals were assigned to receive either donepezil or a placebo treatment for an average of 67.5 days. Those receiving donepezil started with a dosage of 5mg/day, increasing to 10mg/day over the course of 7-10 days. Follow-up assessments took place approximately 61.4 days after treatment. **Outcome Measures:** Trail Making Tests (Part A and B), Digit Span index (DS), California Verbal Learning Test-II (CVLT-II), Logical Memory II (LMII), Functional Independence Measure (FIM), Disability Rating Scale (DRS).	1. For both parts of the Trail Making Test (Part A and B), there was a significant effect of time (p<0.001, p<0.001) respectively. Demonstrating that both groups significantly improved over time. No other significant effects were found for the Trail Making Test. 2. Likewise, in the DS, only a significant effect of time (p<0.001) was observed. 3. For both the learning and memory components of the CVLT-II there was only a significant effect of time observed (p<0.001, p<0.001). 4. The LMII showed similar results with only a significant effect of time observed (p=0.005). 5. For measures of disability, both the DRS and the FIM also only showed a significant effect of time for both groups respectively (p<0.001, p<0.001). 6. Overall, there were no significant effects of treatment found, however both groups did demonstrate significant spontaneous recovery.
Khateb et al. (2005) Switzerland Pre-Post	**Population:** TBI; Mean age=43yr; Gender: Male=8, Female=7; Mean Time Post Injury=42mo. **Intervention:** Patients were administered	1. 4 of 15 participants stopped due to side effects within the first week (e.g., nausea, sleep disorders, anxiety, dizziness, etc.).

Author Year Country Research Design PEDro Sample Size	Methods	Outcome
N$_{initial}$=15, N$_{final}$=10	donepezil 5 mg/day for 1mo, followed by 10 mg/day for 2mos. **Outcome Measures:** Stroop test, Trail Making Test (TMT), Rey Auditory Verbal Memory Test (RAVMT) and Test for Attentional Performance (TAP).	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).

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 significantly more improvement in tasks of sustained attention compared to placebo. These improvements were sustained even after the washout period. Once both groups had completed donepezil treatment there were no significant differences between groups on any measures of attention. Khateb et al. (2005) found that individuals did perform significantly better on measures of divided attention after donepezil treatment, however 4/15 participants stopped treatment due to negative side-effects. In contrast to the positive effects found by these studies, one prospective controlled trial found no significant effects of donepezil on any measures of cognition, including attention (Campbell et al., 2018). In both the Campbell et al. (2018) and Zhang et al. (2004) studies, individuals received donepezil for approximately the same duration.

Conclusions

There is conflicting level 1b (positive) and level 2 (negative) evidence that donepezil may improve attention compared to placebo post ABI.

It is unclear as to whether donepezil may improve attention in individuals with a moderate to severe ABI.

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 Research Design PEDro Sample Size	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

There is level 1b evidence that oral physostigmine may improve long-term memory compared to placebo in men with TBI, however more recent studies are required.

Physostigmine may improve long-term memory in men with TBI, however, more studies are required.

12.3.4 Rivastigmine

Rivastigmine is an acetylcholinesterase inhibitor which prevents the enzyme acetylcholinesterase from breaking down acetylcholine. This increases the concentration of acetylcholine in synapses. Acetylcholine has been most strongly linked with the hippocampus and memory impairments; however, it is also implicated in attentional processing.

Table 12.11 The Effect of Rivastigmine on Attention and Processing Speed Post ABI

Author Year Country Research Design PEDro Sample Size	Methods	Outcome
Tenovuo et al. (2009) Finland RCT PEDro=10 N=102	**Population:** Mean age=45.5yr; Gender: Males=61, Female=39; Mean time post-injury=8yr; Mean GCS=11. **Intervention:** Individuals were randomized to receive one of two dosing rivastigmine schedules (placebo then rivastigmine or rivastigmine then placebo). Treatment lasted 8 weeks once a max dose of 12mg per day was reached. **Outcome Measures:** Computer-based reaction time (CRT), subtraction test, vigilance test (0-5mins, 5-10mins, 10-15mins, correct responses), Symptom Checklist-90 (SC), Diener satisfaction of life scale, Finnish Traumatic Brain Injury Questionnaire (FITBIQ).	1. The percentage of right answers in the subtraction tests were significantly different between groups ($p<0.05$), with the 2. Vigilance scores were significantly higher during periods of rivastigmine treatment compared to placebo treatments ($p<0.05$). 3. There were no other significant differences between groups on any other measures.
Silver et al. (2009) USA RCT PEDro=9 N=127	**Population:** TBI. *Ex-Rivastigmine* (n=65): Mean Age=36.9 yr; Gender: Male=43, Female=22; Time Post Injury=73.5 mo. *Ex-placebo* (n=62): Mean Age=38 yr; Gender: Male=42, Female=20; Time Post Injury=100.1 mo. **Intervention:** Participants were randomized to receive rivastigmine injections (1.5 mg 2x/d to a max of 12 mg/d) or placebo injection. **Outcome Measures:** Trails A and B, Hopkins verbal learning test (HVLT), Cambridge Neuropsychological Test Automated Batter Rapid Visual Information Processing (CANTAB RVIP A).	1. The mean final dose of rivastigmine was 7.9 mg/day. 2. 40% of patients were responders on CANTAB RVIP A' or HVLT score at week 38. 3. At the end of the study period all (n=98) were seen to improve of the CANTAB RVIP A' ($p<0.001$), the HVLT ($P<0.001$), and the Trails A and B ($p<0.001$). 4. Further sub-analysis controlling for order effects demonstrated no significant differences between groups.
Silver et al. (2006) USA RCT PEDro=9 N=123	**Population:** TBI. *Rivastigmine* (n=80): Mean Age=37 yr; Gender: Male=53, Female=27. *Placebo* (n=77): Mean Age=37.1 yr; Gender: Male=53, Female=24. **Intervention:** Participants were randomized to receive either rivastigmine (3-6 mg/d) or placebo. At the end of the first 4 wk, rivastigmine doses were increased to 3.0 mg, 2x/d. If necessary, doses were decreased to 1.5 mg or 4.5 mg 2x/d. **Outcome Measures:** Trails A and B, Hopkins verbal learning test (HVLT), Cambridge Neuropsychological Test Automated Batter Rapid Visual Information Processing (CANTAB RVIP A).	1. Results of the CANTAB RVIP A' and HVLT found no significant differences between the placebo group and the treatment group. 2. Rivastigmine was found to be well tolerated and safe.

Discussion

Three studies have concluded that rivastigmine most likely does not improve attention following an acquired brain injury (Silver et al., 2006; Silver et al., 2009; Tenovuo et al., 2009). In Silver's (2009) follow-up open-label cohort study to their original RCT (Silver et al., 2006), participants (n=98) showed significant improvement on the CANTAB RVIP A', the HVLT and the trail A and B scales at the end of 38 week study period; however after further sub-analysis controlling for order effects no significant differences were found between groups. The third study by Tenovuo et al. (2009), did find that rivastigmine significantly improved vigilance following doses of 12mg/day for eight weeks. Tenovuo et al. (2009) on average had higher doses and longer duration of rivastigmine administration compared to both Silver et al. studies, however it is unclear whether this resulted in their conflicting results. The method of rivastigmine administration does not appear to influence its efficacy (injection versus oral administration).

Conclusions

There is level 1b evidence that Rivastigmine compared to placebo is not effective for improving concentration or processing speed in post ABI individualsbut may increase vigilance.

> **Rivastigmine may not be effective in treating attention deficits post ABI.**

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 12.12 Effects of Sertraline on Depression

Author Year Country Research Design PEDro Sample Size	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 for DSM-IV Axis I Disorders, Hamilton Rating Scale for Depression (HAM-D), Beck Anxiety Inventory (BAI), and Life-3 scale (QOL).	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.
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 12.13 Effects of Citalopram on Depression

Author Year Country Research Design PEDro Sample Size	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).

Author Year Country Research Design PEDro Sample Size	Methods	Outcomes
[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 12.14 Effects of Desipramine on Depression

Author Year Country Research Design PEDro Sample Size	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 12.15 Effects of Sertraline and Amitriptyline on Reducing Aggression and Irritability

Author Year Country Research Design PEDro Sample Size	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.

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., 1997b). 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 12.16 Effects of Lithium Carbonate on Aggressive Behaviour

Author Year Country Research Design PEDro Sample Size	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 12.17 Effects of Quetiapine on Aggressive Behaviour

Author Year Country Research Design PEDro Sample Size	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 that quetiapine may reduce aggressive behaviour.

Quetiapine may be effective in reducing aggression following a TBI, although additional research is needed.

12.5.3 Ziprasidone

Ziprasidone is an atypical antipsychotic has been approved for the treatment of acute agitation in schizophrenia as well as acute mania associated with bipolar disorder. Following a TBI, ziprasidone may be similarly effective in reducing agitation.

Table 12.18 Effects of Ziprasidone on Agitation

Author Year Country Research Design PEDro Sample Size	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

The period of post traumatic amnesia has been defined as a period where the individual is disorientated and may suffer from behaviour alterations (Brooke et al., 1992). Researchers have suggested that these changes in behaviour result from a lack of self-awareness, which may be associated with memory alterations that appear after injury (Noé et al., 2007). One study examined individuals who were still suffering from post-traumatic amnesia upon admission to rehabilitation. These patients showed a decrease in agitation during the first two weeks of ziprasidone administration. As well, it was noted that all patients tolerated the medication, with no clinical side effects observed (Noe et al. 2007).

Conclusions

There is level 4 evidence that ziprasidone may reduce agitation post TBI.

Ziprasidone may be effective in reducing agitation following a TBI, although, additional research is needed.

12.5.4 Haloperidol

Haloperidol is a butyrophenone antipsychotic agent that acts as a dopamine receptor antagonist. It is a typical antipsychotic that is used to treat schizophrenia, bipolar disorder, delirium, and agitation.

Haloperidol does have several known side effects, adverse events, and contraindications. Given the former, there is concern that it may impede recovery post ABI.

Table 12.19 Effects of Haloperidol on Agitation

Author Year Country Research Design PEDro Sample Size	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). **Outcome Measure:** Patient Evaluation Conference Systems.	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 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 during inpatient rehabilitation 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, although none of the treated patients obtained independence in intellectual skills (Rao et al., 1985).

Conclusions

There is level 4 evidence that haloperidol may not be effective in treating behavioral disorders post TBI.

Haloperidol appears to have no benefits, and possible negative effects on recovery, following a TBI.

12.5.5 Droperidol (Inapsine)

Droperidol is a butyrophenone antipsychotic agent that acts as a potent dopamine receptor antagonist. It is a typical antipsychotic that has been used for the treatment of psychosis in Europe (Stanislav & Childs, 2000). There is limited research regarding its use as an intervention for post-ABI agitation.

Table 12.20 Effects of Droperidol on Improving Behaviour

Author Year Country Research Design PEDro Sample Size	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

One study found that a single dose of droperidol effectively calmed patients displaying agitated behaviour (Stanislav & Childs, 2000). The study also found that droperidol calmed individuals more quickly than haloperidol, lorazepam, and diphenhydramine, without heavily sedating the patients like the comparative medications. It is worth noting that a standardized outcome measure was not utilized, and that a large proportion of the sample had psychiatric co-morbidities.

> **Droperidol may be effective in reducing agitation following TBI, although additional research is required.**

12.5.6 Methotrimeprazine

Methotrimeprazine is a psychotropic medication that has antipsychotic properties, as mediated by dopamine blocking. It also has tranquilizing and analgesic properties, and appears to have an effect on opiate (pain) receptors (Maryniak et al., 2001). Its effect on challenging behaviours post ABI has received limited investigation.

Table 12.21 Effects of Methotrimeprazine on Agitation Post ABI

Author Year Country Research Design PEDro Sample Size	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 for agitation was evaluated in a retrospective review of 56 patients during inpatient rehabilitation (Maryniak et al., 2001). The authors found that methotrimeprazine was both safe and effective for controlling agitation in nearly all cases. However, the study did not utilize standardized outcome measures, include a control group, or perform statistical analysis. Therefore, a more rigorous study examining the safety and efficacy of methotrimeprazine within an ABI population is necessary before a firm conclusion can be determined.

Conclusions

There is level 4 evidence that methotrimeprazine may be effective for controlling agitation post ABI.

Methotrimeprazine may be safe and effective for controlling agitation following an ABI, although, additional research is required.

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 12.22 Effects of Percutaneous Phenol Block on Reducing Spasticity

Author Year Country Research Design PEDro Sample Size	Methods	Outcome
Keenan et al. (1990) USA Case Series N=17	**Population:** TBI; Mean Age=25yr; Gender: Male=12, Female=5; Mean Time Post Injury=6mo. **Intervention:** Subjects received a phenol block (3ml 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 at weekly intervals while patients were hospitalized for rehabilitation. Post discharge follow-up occurred for a minimum of 2yr. **Outcome Measure:** Muscle tone/control, Range of Motion.	1. Ninety-three percent 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 the elbow.
Garland et al. (1984) USA Case Series N=11	**Population:** TBI=11; Mean Age=24yr; Gender: Male=8, Female=3; Mean Time Post Injury=5.8mo. **Intervention:** Subjects received percutaneous phenol injections (1-2ml 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 digitorum sublimus, flexor digitorum profundus, and flexor pollicis longus. **Outcome Measure:** Resting Angle of Wrist, Passive/active Extension of Wrist.	1. Mean resting position of the wrist prior to injection was 53°. Nine 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°. 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 12.23 Effects of Oral Anti-Spasticity Agents on Reducing Spasticity

Author Year Country Research Design PEDro Sample Size	Methods	Outcome
Meythaler et al. (2004) USA Case Series N=35	**Population:** TBI=22, ABI=6, Stroke=7; Mean Age=31yr; Gender: Male=22, Female=13. **Intervention:** Oral baclofen regimen beginning at 5 mg 3x/day increased per protocol to 80mg/day. Follow-up occurred between 1 and 3mo after initiation of oral baclofen. **Outcome Measure:** Ashworth Rigidity Scale (ARS), Spasm Frequency Scale (SFS), Deep Tendon Reflexes (DTR).	1. Mean dose was 57±26mg/day for all patients and 55 ± 28mg/day for patients with TBI. 2. After treatment, 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 were observed. 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).

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.

Table 12.24 Effects of Botulinum Toxin on Reducing Spasticity

Author Year Country Research Design PEDro Sample Size	Methods	Outcome
Mayer et al. (2008) USA RCT PEDro=6 N=31	**Population:** TBI=21, Stroke=8, Hypoxic encephalopathy=2; *Motor Point Group:* Mean Age=37.9yr; Mean Time Post Injury=256.7 d. *Distributed Group:* Mean Age=34.7yr; Mean Time Post Injury=481.9yr. **Intervention:** Patients with severe elbow flexor hypertonia received one of two	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). 2. Both groups showed significant improvement from baseline on all outcomes measured (all

Author Year Country Research Design PEDro Sample Size	Methods	Outcome
	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±4.4d. **Outcome Measure:** The Ashworth Scale, Modified Tardieu Scale.	p<0.01); however, there were no between-group differences at 3wk. 3. For both groups, a clinicophysiologic effect was observed at 3wk post-intervention.
Verplancke et al. (2005) UK RCT PEDro=4 N=35	**Population:** TBI=20, Neurosurgery=11, Anoxia=4; Gender: Male=25, Female=10. *Group 1 (n=11)*: Median Age=40yr; Mean Time Post Injury=9.3d, Mean Glasgow Coma Scale (GCS) score 4.3. *Group 2 (n=12):* Median Age=33.5yr; Mean Time Post Injury=13.25 days; Mean GCS score=4.7. *Group 3 (n=12):* Median Age=41.5yr; Mean Time Post Injury=10.6d; Mean GCS score=5.2. **Intervention:** Participants entered one of three groups: group 1 received a physical intervention (controls), group 2 received casting plus injections of saline (4 ml), and group 3 received casting with botulinum toxin (100 units per leg) into the gastrocnemius and soleus muscles. Patients were re-cast if a 10° change in dorsiflexion occurred. **Outcome Measure:** Calf contracture, Modified Ashworth Scale (MAS), Passive Range of Motion.	1. Eighty-eight percent of patients developed spasticity within 14 days of injury. 2. Mean change in angle of passive ankle dorsiflexion was 4.59° in controls, 11.69° in group 2 and 13.59° in group 3. 3. There were significant improvements in MAS scores in treated groups (group 2, p<0.03; group 3, p=0.04) but not controls (p>0.05).
Intiso et al. (2014) Italy Pre-Post N=22	**Population:** ABI=16, Cerebral Palsy=6; Mean Age=38.1yr; Gender: Male=12, Female=10; *Brain Injury*: Mean Time Post Injury=3.8yr. **Intervention:** Patients with severe spasticity of the upper and lower limbs received injections of onabotulinum 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, Visual Analogue Scale– Pain (VAS).	1. Seventeen patients had spastic hemiparesis and 5 had paraparesis. 2. A significant reduction in spasticity was seen at 4 and 16wk 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 16 wk (3.6±0.5) post intervention (p<0.001).

Author Year Country Research Design PEDro Sample Size	Methods	Outcome
Clemenzi et al. (2012) Italy Pre-Post N=21	**Population:** TBI=11, ABI=10; Mean Age=42.2yr; Gender: Male=16, Female=5; Median Time Post Injury=5yr; Severity: Severe. **Intervention:** Patients received repeated injections of Botulinum Toxin Type A (maximum dose 600 U diluted in 50 ml^{-1}) followed by rehabilitation program that consisted of hand and/or foot adhesive taping maintained for 7d and checked daily. **Outcome Measure:** Barthel Index (BI), Modified Ashworth Score (MAS), 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.
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=28.2yr; Gender: Male=12, Female=9; Mean Time Post Injury: Acute Group=142.7d, Chronic Group=89.5mo. **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 digitorum profundus, and flexor digitorum superficialis. 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	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. 3. 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).

Author Year Country Research Design PEDro Sample Size	Methods	Outcome
	injection: acute (<12mo; n=9) or chronic (≥12mo; n=12). **Outcome Measure:** Modified Ashworth Scale (MAS), passive ROM at the wrist.	

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.

12.6.4 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 evidence for the use of intrathecal baclofen post-ABI.

Table 12.25 Effects of Intrathecal Baclofen in Modifying Spasticity

Author Year Country Research Design PEDro Sample Size	Methods	Outcome
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 (50µg) or placebo (normal saline). Crossover occurred a minimum of 48hr later. Assessment at 1, 2, 4, and 6hr post injection. **Outcome Measure:** Ashworth Scale (AS), Spasm Score, Deep Tendon Reflexes.	1. For the lower extremity, after baclofen injection, AS scores decreased by a mean of 2 points (p=0.0033), spasm scores decreased by a mean of 2.1 points (p=0.0032), and reflex scores by 2.3 points (p=0.0032) at 4h. 2. For the upper extremity, after baclofen injection, AS scores decreased by a mean of 1.4points (p=0.0033), spasm scores by a mean of 1.2points (p=0.0070), and reflex scores by 1.0points (p=0.0111) at 4h. 3. No significant within-group differences were shown for placebo. Between group differences were significant for all measures for both lower and upper extremity (p≤0.0272).
Wang et al. (2016) Singapore Case Series N_{Initial}=6, N_{Final}=5	**Population:** TBI=5, Encephalopathy=1; Mean Age=31.6yr; Gender: Male=3, Female=2; Mean Time Post Injury=39.4mo. **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 3mo, and ITB pump refills and monitoring by the neurosurgical team for 3-	1. The mean reduction in MAS was 1.2 (SD 1.1; p<0.05) at 3mo 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.

Author Year Country Research Design PEDro Sample Size	Methods	Outcome
	4 mo. Outpatient follow-up was 3-6mo. **Outcome Measure:** Modified Ashworth Scale (MAS).	
Chow et al. (2015) Canada Pre-Post N=19	**Population:** TBI=11, Stroke=8; Mean Age=34.2yr; Gender: Male=9, Female=10; Mean Time Post Injury=48.7mo. **Intervention:** All patients underwent a 50-µg intrathecal baclofen (ITB) bolus injection via lumbar puncture. Patients were evaluated at baseline, 2hr, 4hr, and 6hr 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), Coactivation Index (CI).	1. There was no significant difference in gait speed, stride length, cadence, or stance duration across evaluation points. 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 2 hr 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=31.5yr; Gender: Male=8, Female=0; Mean Time Post Injury=37.25mo. **Intervention:** Patients who were resistant to oral spasticity treatments received an implanted intrathecal baclofen pump. Mean follow-up period was 38.4mo. **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=36yr; Gender: Male=9, Female=3; Time Post Injury Range=31-150d. **Intervention:** Patients not experiencing reductions in spasticity following initial interventions with oral baclofen received intrathecal baclofen (ITB). The initial	1. Mean ITB dose for participants was 380mcg. 2. Six patients received ITB within 3mo of injury (early); 6 patients received ITB between 3 and 6mo post injury (late). 3. At 3mo, both spasticity and spasms significantly decreased compared to the baseline, based on MAS and SFS scores (p<0.001 and p<0.002, respectively).

Author Year Country Research Design PEDro Sample Size	Methods	Outcome
	dosage was 50 or 100mcg depending on the severity of the impairment and was increased by 10% every 3d until the maximum dosage of 800 mcg was achieved. Assessments occurred before the implant, and at 3mo and 12mo follow-ups. **Outcome Measure:** Modified Ashworth Scale (MAS), Spasm Frequency Scale (SFS), Disability Rating Scale (DRS), Level of Cognitive Functioning (LCF).	4. At 3mo, improvements in DRS and LCF were seen ($p<0.001$ and $p=0.002$, respectively). 5. At 12mo (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 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=23.3yr; Gender: Male=33, Female=10; Mean GCS score=4.6. **Intervention:** After initial injury, participants who were started on Intrathecal Baclofen Therapy (IBT) to treat dysautonomia and hypertonia and were included for evaluation of long-term outcomes (mean 10±0.6yr 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=35yr; Gender: Male=12, Female=16; Mean Time Post Injury=45mo. **Intervention:** The subjects received a 50μg bolus of baclofen injected into the lumbar intrathecal space. **Outcome Measure:** Ashworth Scale, 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 6hr 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 2hr (1.6±0.4), 4 hr (1.4±0.4) and 6 hr (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=31yr; Gender: Male=17, Female=13; Mean Time Post Injury=3yr. **Intervention:** Participants received a single 50μg intrathecal baclofen bolus injection via a lumbar puncture.	1. Ashworth score on the more involved side significantly decreased between baseline (2.4±0.7) and 4 (1.5±0.6) and 6 hr (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).

Author Year Country Research Design PEDro Sample Size	Methods	Outcome
	Outcome Measure: Ashworth Scale, H-Reflex from Soleus Muscle, F waves from Abductor Hallucis in Supine Position.	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.
Francisco et al. (2005) USA Case Series N=14	**Population:** Anoxic Encephalopathy=6, TBI=5, Stroke=3; Mean Age=35.9yr; 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 5.62mo (range 2-12mo) post injury. Follow up occurred at a mean of 13.9mo post pump implantation. **Outcome Measure:** Modified Ashworth Scale (MAS), Disability Rating Scale (DRS).	1. Participants received a mean daily intrathecal baclofen dose of 591.5µg (93-2000.2µg). 2. From baseline to follow-up, the mean decrease in MAS scores for upper extremities was 1±1.4 (p<0.020) 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=35yr; Gender: Male=12, Female=16; Mean Time Post Injury=45mo. **Intervention:** Subjects received a single 50µg intrathecal baclofen bolus injection via lumbar puncture. **Outcome Measure:** Walking Performance, Ashworth scores.	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 involved (13° versus 15°, p<0.010) and less involved side (22° versus 24°, p<0.050). 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 2hr (1.6±0.4), 4hr (1.4±0.4) and 6hr (1.3±0.3) post-injection (all p<0.001).
Dario et al. (2002) Italy Pre-Post N=14	**Population:** TBI=6, Anoxic ABI=8; Mean Age=38.8yr; Gender: Male=10, Female=4; Mean Time Post Injury=36.7mo. **Intervention:** Patients received continuous intrathecal baclofen infusions through the implantation of a subcutaneous pump. Mean length of spasticity was 36.7mo post injury. **Outcome Measure:** Ashworth Scale (AS), Spasm Frequency Scale (SFS).	1. Between pre-operative through the 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 305µg (range 90-510µg).
Francois (2001) France Case Series N=4	**Population:** TBI; Mean Age=19.5yr; Gender: Male=1, Female=2, Unknown=1; Mean GCS=3.5. **Intervention:** Patients received intrathecal baclofen infusions within 1mo following injury onset.	1. Reductions in spasticity, and lower limb Ashworth scores at 6mo 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.

Author Year Country Research Design PEDro Sample Size	Methods	Outcome
	Outcome Measure: Ashworth scores, Frequency and Intensity of Autonomic Disorders.	
[Meythaler et al.](#) (1999b) USA Pre-Post N=17	**Population:** ABI; Mean Age=29yr; 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 intrathecal baclofen (100µg/day). Patients were assessed at 1yr. **Outcome Measure:** Ashworth Rigidity Scale (ARS), Spasm Frequency Scale, Deep Tendon Reflex Score.	1. One year of intrathecal baclofen treatment (average dose: 302ug/d) resulted in a decrease in 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 the 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 were observed after 1yr.
[Meythaler et al.](#) (1999a) USA Pre-Post N=6	**Population:** TBI=3, Stroke=3; Mean Age=50yr; Gender: Male=2, Female=4. **Intervention:** Patients were 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, Deep Tendon Reflex scores.	1. Lower extremities showed a significant reduction in Ashworth scores ($p<0.0001$), affected lower limb reflex score ($p=0.021$), normal side ($p=0.0051$), but not significant changes in affected lower limb spasm score ($p=0.500$). 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: $p=0.109$ and $p=0.068$), or spasm score (affected: $p=0.1797$). 3. No patients complained of subjective weakness on the normal side.
[Meythaler et al.](#) (1997) USA Pre-Post N=12	**Population:** TBI=9, ABI=3; Mean Age=28yr; Gender: Male=11, Female=1. **Intervention:** Patients received continuous intrathecal baclofen delivery for 3mo via an implanted infusion pump-catheter system. **Outcome Measure:** Ashworth Rigidity Scale, Spasm Frequency Score, Deep Tendon Reflex Score.	1. For the 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 the upper extremity, the mean decrease in scores was 1.4 points for the Ashworth Scale ($p=0.003$), 1.2 for spasm frequency ($p=0.007$) and 1.0 for reflex ($p=0.011$).
[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=11.6mo. **Intervention:** Patients received continuous intrathecal baclofen infusion. **Outcome Measure:** Ashworth Scale, 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 decreased from 2.16 to 0.94. 3. Reduction in spasticity led to a reduction in pain.

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 (Meythaler et al., 1999b). 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. It should be noted, however, that 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, with infections at the operative site being the most common (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) 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 compared to placebo 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 conflicting level 4 evidence to suggest that intrathecal baclofen may result in short-term improvement of walking performance in ambulatory patients, particularly gait velocity, stride length, and step width, in individuals post ABI.

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.

Bolus injections of intrathecal baclofen likely produce short-term reductions in upper and lower extremity spasticity and improvements in walking performance post ABI.

> **Prolonged intrathecal baclofen may reduce upper and lower extremity spasticity long-term post ABI.**
>
> **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, reducing metabolic demands and decreasing cerebral blood volume (Roberts, 2000). Early reports indicated that barbiturates reduced ICP in patients 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).

A review found no evidence that barbiturates decreased blood pressure or reduced mortality in 25% of patients (Roberts & Sydenham, 2012). Therefore, it was recommended that barbiturate coma be avoided until all other measures for controlling elevated ICP are exhausted.

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 earlier EBIC guidelines recommended barbiturate use to increase sedation only after previous sedation, analgesia, hyperventilation, osmotic therapy, and CSF drainage have failed to control ICP (Maas et al., 1997).

Table 12.26 Barbiturates for the Acute Management of ABI in Adult and Pediatric Populations

Author Year Country Research Design PEDro Sample Size	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 (5-11 mg/kg bolus, followed by continuous infusion of 4-6 mg/kg/hr and 4-6	1. Patients requiring barbiturates were significantly younger than those not requiring it (27 yr versus 44 yr, p<0.01). 2. Barbiturates were shown to induce reversible leukopenia and

Author Year Country Research Design PEDro Sample Size	Methods	Outcome
	bursts/min). Others received sedation with fentanyl and midazolam. ICP was targeted <20 mmHg and mean ar-terial pressure > 90 mmHg. **Outcome Measures:** Infection rate, Granulocyte Count, Leukocyte Count, Bone Marrow Production.	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 Measures:** 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 (≤60 mmHg), 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=20 yr; Mean GCS Score=4.3. *Control (n=15)*: Mean Age=26 yr; Mean GCS=5.2. **Intervention:** Patients received continuous intravenous thiopental: a loading infusion of 10-20 mg/kg and a maintenance infusion of 3-5 mg/kg/hr to maintain ICP<30 mmHg. Mild hypothermia (32-35º C) 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		
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 conventional therapy alone. Pentobarbital was administered first asan initial	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

Author Year Country Research Design PEDro Sample Size	Methods	Outcome
	bolus of 10 mg/kg over 30 min, then as an infusion (5 mg/kg/1hr for 3 hr), and finally as a maintenance dose (1 mg/kg). **Outcome Measures:** Intracranial Pressure (ICP), Glasgow Outcome Scale (GOS), Survival.	randomized to conventional therapy were crossed over to receive barbiturates. 4. The likelihood of survival at 1 mo was 92% for those who responded to barbiturates. In contrast, 83% of the patients who did not respond to barbiturates died. 5. At 6 mo 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 first as a bolus (5-10 mg/kg), subsequently as a 1 hr bolus and continuous infusion for at least 72 hr, and finally as a maintenance dose of 1-3 mg/kg. **Outcome Measures:** 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 treatment was initiated on top of initial one if ICP proved refractory to maximal doses of the original drug. **Outcome Measures:** Intracranial Pressure (ICP), Mortality.	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 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).

Author Year Country Research Design PEDro Sample Size	Methods	Outcome
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 conventional therapy received pentobarbital administered as a bolus followed by a continuous infusion to achieve serum concentrations of 20-40mg/L (n=4). Patients responsive to conventional therapy formed the control group (n=7). **Outcome Measures:** Energy Expenditure, Urinary Nitrogen Excretion, Nitrogen Balance, Urinary 3-Methylhistidine Excretion.	1. Patients treated with pentobarbital had significantly lower energy expenditure ($p<0.01$), lower urinary total nitrogen 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.
	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 20s. A second bolus of 3-5 mg/kg was administered if ICP>20mmHg. Once ICP<20mmHg was achieved, a continuous infusion was administered (3 mg/kg/hr). 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. **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.
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>20mmHg, 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 3hr. For the last hour a dose of 1 mg/kg/hr was administered. Outcomes were assessed at discharge and 6mo. **Outcome Measures:** Intracranial Pressure (ICP), Mortality.	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 ($p=0.16$).
Llompart-Pou (2007) Spain Case Control	**Population:** TBI; *Barbiturates (n=17)*: Mean Age=35 yr; Gender: Male=16, Female=1; Mean GCS Score=7. *Control (n=23)*: Mean Age=27 yr; Gender: Male=20, Female=3; Mean GCS=7.	1. Within 24 hr, adrenal function was similar in both groups.

Author Year Country Research Design PEDro Sample Size	Methods	Outcome
N=40	**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.	2. After treatment with barbiturates, patients demonstrated higher adrenal insufficiency compared to the control group (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).
	Unspecified Barbiturates	
Colton et al. (2014b) USA Case Series N=117	**Population:** TBI; Mean Age=40.0 yr; Gender: Male=93, Female=24; Median GCS=6. **Intervention:** Participants were included in retrospective analysis after having received one of the following ICP therapies: hypertonic saline (HTS), mannitol, propofol, fentanyl, and barbiturates. **Outcome Measure:** Intracranial Pressure (ICP).	1. Treatment with HTS resulted in the largest ICP decrease of the treatments examined. 2. Propofol and fentanyl escalations resulted in smaller but significant ICP reductions. 3. Mannitol resulted in statistically insignificant reductions in the first hr but rebounded by the second hr.
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; Gender: Male=113, Female=27. *No Barbiturate Group (n=961)*: Median Age=45 yr; 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 <70 mmHg (p<0.05). 3. The effect of barbiturate use to treat ICP was not associated with improved outcomes as rates of ICU death, hospital death, 6 mo death, and poor outcome

Author Year Country Research Design PEDro Sample Size	Methods	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 Measures:** 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. Eight 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

Barbiturate administration is used in patients' refractory to conventional treatment to decrease elevated ICP, and the increased cellular metabolism and protein catabolism caused by an ABI. As a result, an early PCT studied the effects of pentobarbital on surrogate markers of metabolism (Fried et al., 1989). The researchers noted lower energy expenditure, lower total urinary nitrogen excretion, and improved nitrogen balance in patients' refractory to conventional therapy when compared to controls. The results brought forth suggest that pentobarbital effectively reduces cellular metabolism and protein catabolism post ABI, and as a result potentially improves patient survival. In order to fully elucidate the effects of pentobarbital on patients post ABI, follow up studies are required.

The findings of a 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 a RCT by Ward et al. (1985) suggested that pentobarbital was no better than conventional ICP management measures; a finding which was corroborated by Schwartz et al. (1984) in a RCT and 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. 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 with 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). In another study, Schalen et al. infused thiopental intravenously for at least 12 hours, and noted a decrease ICP, CPP, and MAP in 82%, 84%, and 58% of patients, respectively. The conclusions drawn from this study should be interpreted with caution, as the small sample size and lack of controls warrant larger studies to further investigate the effects of thiopental.

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 et al. (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.

Conclusions

There is level 2 evidence that thiopental is more effective than pentobarbital for controlling elevated intracranial pressure refractory to conventional treatment, and less likely to induce adrenal insufficiency post ABI.

There is level 2 evidence that thiopental in combination with mild hypothermia has better one-year clinical outcomes compared to conventional management post ABI.

There is level 3 evidence that thiopental induces leukopenia and granulocytopenia in patients post ABI.

There is level 4 evidence that thiopental decreases intracranial pressure, cerebral perfusion pressure, and mean arterial pressure post ABI.

There is conflicting (level 1b and level 2) evidence regarding whether or not pentobarbital improves intracranial pressure compared to conventional management measures post ABI. Level 1b evidence suggests there is no difference.

There is level 2 evidence that barbiturate use is associated with development of hypotension in patients post ABI.

There is level 2 evidence that pentobarbital decreases energy expenditure, total urinary nitrogen excretion, improves nitrogen balance, but has no effect on 3-methylhistidine excretion compared to controls in individuals with an ABI refractory to standard therapy.

There are conflicting reports regarding whether pentobarbital is superior to conventional management at improving intracranial pressure. The strongest evidence suggests there is no difference.

Thiopental may decrease intracranial pressure, cerebral perfusion pressure, and mean arterial pressure post ABI.

Thiopental may be more effective than pentobarbital at controlled refractory intracranial pressure, and less likely to develop adrenal insufficiency. However, thiopental may still be associated with leuko- and granulocytopenias. When used, combination with hypothermia may result in greater long-term outcomes.

Barbiturate therapy should be avoided until all other measures for controlling elevated intracranial pressure are exhausted; special attention should be paid to monitoring immunological function, adrenal function, and blood pressure status if used.

Pentobarbital might decrease energy expenditure and nitrogen metabolism in individuals with an ABI refractory to standard therapy.

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 12.27 Prophylactic Intervention of Heterotopic Ossification with EHDP

Author Year Country Study Design Sample Size	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. **Outcome Measure:** Presence of fractures, development of HO.	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.

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.

> **Etidronate Disodium may prevent the development of heterotopic ossification in individuals with ABI.**

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). Dexanabinol is also believed to possess antioxidant properties 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 12.28 Cannabinoids for the Acute Management of ABI

Author Year Country Research Design PEDro Sample Size	Methods	Outcomes
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 150mg dexanabinol dissolved in cremophor-ethanol solution or placebo for 15 min. Monitoring occurred for the first 72 hr. Outcomes were assessed 3 mo and 6mo post treatment. **Outcome Measures:** Glasgow Outcome Scale Extended (GOSE), Intracranial Pressure (ICP), Cerebral Perfusion Pressure (CPP), Mortality, Neurological Deterioration.	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 50 mg 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 post treatment. **Outcome Measures:** 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.

Author Year Country Research Design PEDro Sample Size	Methods	Outcomes
**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 either 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 after drug administration. **Outcome Measures:** 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. 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 3mo and 6mo.

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

Discussion

In an early RCT, Knoller et al. (2002) found that dexanabinol (50 mg) showed significant improvements in ICP and CPP over placebo in patients with TBI. Despite showing significant improvements on the GOS and Disability Rating Scale at 1 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. 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.

Firsching et al. (2012) utilized KN38-7271, a dual cannabinoid agonist, as means of reducing ICP. After administration of high-dose KN38-7271 (1000 μ), the authors reported significant increases in CPP and greater survival at one month, but non-significant decreases in ICP when compared to low-dose KN38-7271 (500 μ). These results suggest that the dual cannabinoid agonist may an overall positive effect on patients post TBI, especially at high doses, 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 high-dose KN38-7271 (a dual cannabinoid agonist) may improve intracranial pressure and cerebral perfusion pressure, and improves survival post TBI compared to low-dose KN38-7271.

It is unclear whether Dexanabinol in cremophor-ethanol solution is effective in controlling intracranial pressure and improving cerebral perfusion pressure, and clinical outcomes post TBI. The strongest evidence suggests no beneficial effects.

KN38-7271, a dual cannabinol agonist, is likely effective at improving intracranial pressure, cerebral perfusion pressure and survival post TBI at high doses.

12.10 Cardiovascular Medication

12.10.1 Beta-Blockers

Beta-blockers are a class of medications that act as competitive antagonists of the catecholamine receptors. It has been suggested that these medications may reduce restlessness, anxiety, agitation, and aggression following brain injury. Given that dosage is often high, patients may be vulnerable to adverse effects such as lethargy, sedation, and depression; although, motor recovery post injury does not seem to be negatively affected (Levy et al., 2005).

12.10.1.1 Pindolol

Pindolol is an atypical beta-blocker in that it exerts a partial agonist effect on the serotonin 1A receptor which provides a slight stimulation of the blocked receptor and helps maintain a better resting sympathetic tone. The use of pindolol in individuals with aggressive behaviour following ABI was investigated in a clinical trial.

Table 12.29 Effects of Pindolol on Behaviour

Author Year Country Research Design PEDro Sample Size	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 Kantor (1986) investigated the effectiveness of pindolol in improving behavioural disturbances post ABI. A significant reduction in behaviours that lead to assaults was demonstrated during treatment with pindolol, as well as improved communication and cooperation. The authors noted that the optimal dose, in terms of maximizing therapeutic efficacy and minimizing adverse events, ranged between 40-60 mg per day. The frequency of supplemented psychotropic medications was reduced with pindolol treatment, although these medications were still administered and may have contributed to the reduction in assaultive episodes.

Conclusions

There is level 1b evidence that pindolol may reduce aggression compared to placebo post ABI.

Pindolol may be effective in reducing aggression following an ABI.

12.10.1.2 Propranolol

Propranolol is a non-selective beta-blocker that has been used for the reduction of aggressive behaviours associated with compromised brain function. It appears to lack the serious cognitive and affective side effects associated with other medications used to treat agitation post injury (Levy et al., 2005). The use of propranolol in individuals with post-TBI aggression was investigated in two clinical trials.

Table 12.30 Effects of Propranolol on Behaviour

Author Year Country Research Design PEDro Sample Size	Methods	Outcomes
Brooke et al. (1992) 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 propranolol for the improvement of behavioural issues associated with brain disease. Significantly fewer assaults and attempted assaults occurred during the 11-week propranolol treatment as compared to placebo. Of the nine patients in the trial, five showed marked improvement, two showed moderate improvement, and two showed little or no improvement. It should be noted that the patients also had severe dementia, and so this study cannot be used to draw conclusions for the ABI population as a whole. A later study by Brooke et al. (1992) found that propranolol was effective in reducing the intensity of the agitation and use of restraints when compared to placebo. However, propranolol was not more effective than placebo in reducing the frequency of agitation episodes or the number of adjunctive medications for agitation and sedation.

Conclusions

There is level 1b evidence that propranolol compared to placebo reduces the intensity of agitated symptoms post ABI.

There is conflicting evidence (level 1b) that propranolol compared to placebo reduces the frequency of aggressive behaviour post ABI.

> **Propranolol may be effective in reducing the intensity of agitation and aggression following brain injury.**

12.10.2 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 12.31 Unfractionated Heparin or LMWH versus Placebo for DVT Prevention

Author Year Country Research Design PEDro Sample Size	Methods	Outcome
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.
Hachem et al. (2018) Canada PCT N=64	**Population:** TBI; Gender: Male=45, Female=19. Mean Age=44yr; Mean GCS=5. **Intervention:** Prospective evaluation of patients who received enoxaparin within 3 days of admission (Early group), after 3 days (Late group), and no enoxaparin (No treatment group). All patients were provided Thombo-Embolic Deterrent stockings. Doppler ultrasounds (DUS) 7 days (+/- 3d) post admission were used to evaluate DVTs,	1. Progression of ICH after initiation of enoxaparin was similar between the early (0%) and late (7%) groups. 2. VTE incidence was not significantly different between the early (10%) and late (16%) groups (p=0.99).

Author Year Country Research Design PEDro Sample Size	Methods	Outcome
	in addition to care and investigations ordered by the treating clinicians. **Outcome Measure**: VTE events, intracranial hemorrhage (ICH) progression, DUS	
[Seifi et al.](#) (2018) USA Case Control N=155	**Population:** TBI; Gender: Male=119, Female=36. Mean Age=41.6yr. **Intervention:** Retrospective review of patients who received chemical thromboprophylaxis or inferior vena cava (IVC) filter for prevention of VTE. Only patients with clinical suspicion of PE had diagnostic investigations, there was no surveillance for PE. **Outcome Measure:** Incidence of PE	1. 33 patients did not receive chemical thromboprophylaxis. 2. 60 patients received an IVC filter. 3. 4 patients developed a clinically significant PE. They were all in the group of patients that received chemical thromboprophylaxis. None had an IVC filter prior to developing a PE. 4. There was no significant difference between incidence of PE between patients that received chemical thromboprophylaxis and those who did not (p=0.58).
[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 ($\geq$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	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.

Author Year Country Research Design PEDro Sample Size	Methods	Outcome
	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 (GCS), Abbreviated Injury Scale (AIS), Injury Severity Score , Marshall CT), neurological improvement.	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). 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).
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.
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),	1. Mortality in the sequential compression devices alone group was higher (47%) compared to the LMWH (5%) and UFH (16%) groups.

Author Year Country Research Design PEDro Sample Size	Methods	Outcome
	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.	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.
Kurtoglu et al. (2004) Turkey PCT	**Population:** TBI=103, Other=17; Median Age=37.1yr; Gender: Male=47, Female=73.	1. In the IPC group, there were 4 (6.6%) and 2 (3.3%) cases of DVT and PE, respectively.

Author Year Country Research Design PEDro Sample Size	Methods	Outcome
N=120	**Intervention:** Patients admitted to the Intensive Care Unit (ICU) were allocated to receive either Intermittent Pneumatic Compression devices (IPC; n=60) placed below the knee or Low-Molecular-Weight Heparin (LMWH) (n=60) (40 mg/day, enoxaparin sodium) for VTE prophylaxis. **Outcome Measure:** Rate of DVT, PE and mortality.	2. In the LMWH group, there were 3 (5%) and 4 (6.6%) cases of DVT and PE, respectively. 3. Overall, 7 (11.6%) and 8 (13.3%) patients died in the IPC and the LMWH group, respectively. 4. There were no significant differences between groups in rates of DVT (p=0.04), PE (p=0.07), or mortality (p=0.08).
[Kleindienst et al.](#) (2003) USA Case Series N=940	**Population:** Head Injury=344, Elective Surgery (tumors)=294, Intracranial Hemorrhage (ICH)=302; Mean Age=57.3 yr. **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.	1. 155 patients were excluded due to coagulation abnormalities or significant bleeding. 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). However, these results are in conflict with Hachem et al. (2018), which found no increased risk of ICH worsening, but found no benefit regarding VTE incidence.

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 3 evidence that prophylactic anticoagulation is more effective than placebo in reducing the risk of developing deep vein thrombosis in patients post ABI.

There is level 2 evidence that the administration of enoxaparin within the first 72 hours post ABI reduces the risk of developing deep vein thrombosis and pulmonary embolism post injury compared to unfractionated heparin.

There is level 4 evidence that administering enoxaparin or heparin post ABI does not increase the risk of intracranial bleeding compared to no treatment.

> **Administration of pharmacological thromboembolic prophylaxis within the first 72 hours post ABI may be effective for reducing the risk of developing venous thromboembolism.**
>
> **Enoxaparin is effective for the prevention of venous thromboembolism development 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, the 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 12.32 Mannitol for the Acute Management of Post ABI

Author Year Country Research Design PEDro Sample Size	Methods	Outcome
Jagannatha et al. (2016) India RCT PEDro=5 N=38	**Population:** TBI; *Hypertonic Saline (HTS, n=18)*: Mean Age=27 yr; Gender: Male=16, Female=2; Mean Time Post Injury=6.1 hr; Median GCS=4. *Mannitol (MAN, n=20)*: Mean Age=31 yr; Gender: Male=18, Female=2; Mean Time Post Injury=6.7 hr; Median GCS=5. **Intervention:** Participants were randomized to receive HTS (3%) or MAN (20%). Outcomes were assessed daily for 6 days. **Outcome Measures:** Intracranial Pressure (ICP), Mean Arterial Pressure (MAP), Heart Rate (HR), Blood Glucose, Fluid Balance, Serum Osmolality, Serum Sodium.	1. There was no significant difference between groups in reduction in ICP (p=0.135). 2. Blood Glucose significantly decreased over 6 d in the HTS group (p=0.003). 3. There was no significant difference in Blood Glucose over 6 d in the MAN group (p=0.36). 4. There was no significant difference in HR, MAP, Fluid Balance, Serum

Author Year Country Research Design PEDro Sample Size	Methods	Outcome
[Jagannatha et al.](#) 2018 India Post-Hoc Analysis N= 38	**Intervention:** A post-hoc analysis of the study conducted by Jagannatha et al. (2016), focusing on comparing urinary sodium and urine osmolarity in the HTS and Mannitol groups. **Outcome Measures:** Urinary Sodium, Urinary Osmolarity.	Osmolality, or Serum Na+ (all p>0.05) for both MAN and HTS groups over 6 days. 1. Urinary sodium excretion was significantly higher in the HTS group compared to the Mannitol group (p=0.02) 2. Urinary Osmolarity was not different between groups (=0.63)
[Cottenceau et al.](#) (2011) Israel RCT PEDro=6 N=47	**Population:** TBI; *Hypertonic Saline (HTS, n=22)*: Mean Age=42.7 yr; Median GCS=5. *Mannitol (MAN, n=25)*: Mean Age=36.1 yr; Median GCS=7. **Intervention:** Participants were randomized to receive HTS (7.5%, 2 mL/kg) or MAN (20%, 4 mL/kg). Outcomes were assessed at baseline, 30 min, 120 min, and 6 mo. **Outcome Measures:** Intracranial Pressure (ICP), Mean Arterial Pressure (MAP), Cerebral Perfusion Pressure (CPP), Global Cerebral Blood Flow Oxygen (CBF), Arterial Jugular Difference for Oxygen Content (AVDO$_2$), Global Cerebral Metabolic Rate of Oxygen (CMRO$_2$).	1. The HTS group had significantly greater CBF when compared to the MAN group (p=0.0087) over time. 2. There was no significant difference between groups over time in ICP, MAP, CPP, AVDO$_2$, or CMRO$_2$ (all p>0.05).
[Battison et al.](#) (2005) UK RCT Crossover PEDro=5 N=9	**Population:** TBI=6, SAH=3. **Intervention:** Participants received intravenous infusions of 20% mannitol (200 mL), a solution of 7.5% hypertonic saline (100mL) and 6% dextran-70 (HSD) over 5 min in a randomized order. Outcomes were assessed before and after treatment. **Outcome Measure:** Intracranial Pressure (ICP).	1. Both mannitol and HSD were effective in reducing ICP. 2. HSD caused a significantly greater decrease in median ICP than mannitol (13 mmHg versus 7.5 mmHg, p=0.044). 3. HSD had a longer duration of effect than mannitol (p=0.044).
[Harutjunyan et al.](#) (2005) Germany RCT PEDro=5 N=40	**Population:** TBI; *Hypertonic Saline group (HTS; n=17)*: Mean Age=47 yr; Gender: Male=9, Female=8; Mean GCS=6. *Mannitol group (MAN; n=15)*: Mean Age=47 yr; Gender: Male=8, Female=7; Mean GCS=5.8. **Intervention:** Patients at risk of increased ICP were randomized to receive either 7.2% hypertonic saline or 15% mannitol. Treatment was stopped when ICP was <15 mmHg. **Outcome Measures:** Intracranial Pressure (ICP), Cerebral Perfusion Pressure (CPP), Heart Rate (HR), Mean Arterial Pressure (MAP).	1. There was no significant difference over time or between groups for HR (all p>0.05). 2. There was no significant difference in MAP between groups (p>0.05). 3. There was a significant reduction in ICP over time for both the HTS and MAN groups (all p<0.0001), however, there was no significant difference between groups (p>0.05). 4. There was a significant increase in CCP over time for both the HTS and MAN

Author Year Country Research Design PEDro Sample Size	Methods	Outcome
		groups (all p<0.0001); with the HTS group significantly higher than the MAN group (p<0.05).
Vialet et al. (2003) France RCT PEDro=7 N=20	**Population:** TBI;. *Hypertonic Saline (HTS, n=10):* Mean Age=35 yr; Gender: Male=5, Female=5; Mean GCS=4.7. *Mannitol (MAN, n=10):* Mean Age=31 yr; Gender: Male=4, Female=6; Mean GCS=6.0. **Intervention:** Participants were randomized to receive intravenous infusions of 7.5% HTS or 20% MAN. Infused volume was the same for both medications: 2 ml/kg of body weight in 20min. Outcomes were assessed over a mean of 7 days. **Outcome Measures:** Intracranial Pressure (ICP), Cerebral Perfusion Pressure (CPP), Glasgow Outcome Scale (GOS), Mortality.	1. HTS had significantly fewer mean episodes of ICP>25 mmHg per day (6.9 versus 14.6, p<0.01) and shorter mean daily duration of these episodes (67 min versus 131 min, p<0.01) than MAN. 2. There was no significant difference between HTS and MAN in mean episodes of CPP<70 mmHg (4.0 versus 3.1, p>0.05) or mean daily duration of these episodes (58 min versus 62 min, p>0.05). 3. Failure of treatment was significantly greater in MAN than HTS (70% versus 10%, p=0.01). 4. There was no significant difference between HTS and MAN in poor GOS (60% versus 50%, p>0.05) or mortality (40% versus 50%, p>0.05).
Mangat et al. (2015) USA Case Control N=1238	**Population:** TBI; *Hypertonic Saline (HTS, n=45)*: Mean Age=38.37 yr; Mean GCS=5.46. *Mannitol (MAN, n=477)*: Mean Age=36.13 yr; Mean GCS=4.75. *Hypertonic Saline & Mannitol (HTS+MAN; n=137)*: Mean Age=31.42 yr; Mean GCS=4.82. *Control (n=589)*: Mean Age=42.63 yr; Mean GCS=4.96. **Intervention:** Patients who received HTS, MAN, or neither (control) were retrospectively analyzed. **Outcome Measures:** Intracranial Pressure (ICP) Length of Stay (LOS), Mortality.	1. There was no significant difference in total number of ICP recording days between the HTS and MAN groups (p=0.09). 2. The cumulative and daily ICP burdens were significantly lower in patients who received HTS compared to patients who received MAN (p=0.003 and p=0.001, respectively). 3. LOS was significantly lower in the HTS compared to MAN with a 1:1 match (p=0.004); however, this became insignificant with a 1:2 match (p=0.06). 4. There was no significant difference between HTS and MAN in mortality rate (p=0.53).
Tang et al. (2015) Taiwan Pre-Post	**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%	1. At baseline, ICP was significantly correlated with PRx (p=0.0044).

Author Year Country Research Design PEDro Sample Size	Methods	Outcome
N=21	mannitol. **Outcome Measures:** Intracranial Pressure (ICP), Pressure Reactivity Index (PRx), Cerebral Perfusion Pressure (CPP), Cerebrovascular Pressure Reactivity (CVPR).	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).
Colton et al. (2014b) USA Case Series N=117	**Population:** TBI; Mean Age=40.0 yr; Gender: Male=93, Female=24; Median GCS=6. **Intervention:** Participants were included in retrospective analysis after having received one of the following ICP therapies: hypertonic saline (HTS), mannitol, propofol, fentanyl, and barbiturates. **Outcome Measure:** Intracranial Pressure (ICP).	1. Treatment with HTS resulted in the largest ICP decrease of the treatments examined. 2. Propofol and fentanyl escalations resulted in smaller but significant ICP reductions. 3. Mannitol resulted in statistically insignificant reductions in the first hr but rebounded by the second hr.
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 Measures:** 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 1hr 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 1hr after mannitol (all p>0.05).
Sakellaridis et al. (2011) Greece Case Control N=29	**Population:** TBI; Mean Age=36 yr; Mean GCS=5.4. **Intervention:** Participants who received hypertonic saline (HTS) or mannitol were retrospectively analyzed. **Outcome Measures:** Intracranial Pressure (ICP), Duration of effectiveness.	1. There was no significant difference between HTS and mannitol in reducing ICP. 2. There was no significant difference between HTS and mannitol in duration of effectiveness.
Kerwin et al. (2009) USA Cohort N=22	**Population:** TBI; Mean Age=35.7 yr; Gender: Male=16, Female=6; Mean GCS=6.9. **Intervention:** Patients received intravenous infusions of 23.4% hypertonic saline (HTS) or mannitol (15-75 g, at the discretion of the neurosurgeon). **Outcome Measure:** Intracranial Pressure (ICP).	1. Mean ICP reduction was significantly greater by HTS than mannitol (9.3mmHg versus 6.4 mmHg, p=0.0028). 2. Patients with initial ICP>30 mmHg had a significantly greater mean ICP reduction by HTS than mannitol (12.6 mmHg versus 8 mmHg, p=0.0105). 3. More patients responded to HTS than mannitol (93% versus 74%, p=0.002). 4. HTS was more likely to yield an ICP reduction of >10 mmHg, while mannitol

Author Year Country Research Design PEDro Sample Size	Methods	Outcome
		was more likely to yield a reduction of <5 mmHg. 5. There was no significant difference between HTS and mannitol in amount of time ICP>20 mmHg (9.7 hr versus 7.4 hr, p=0.236) or duration of response (4.1 hr versus 3.8hr, p=0.854).
Oddo et al. (2009) USA Cohort N=12	**Population:** TBI; Mean Age=36 yr; Gender: Male=9, Female=3; Mean GCS=3; Mean Time Post Injury=8 hr. **Intervention:** Participants received intravenous infusions of 7.5% hypertonic saline (HTS) or 25% mannitol. **Outcome Measures:** Intracranial Pressure (ICP), Mean Arterial Pressure (MAP), Cerebral Perfusion Pressure (CPP), Brain Tissue Oxygen Tension ($P_{bt}O_2$), Central Venous Pressure (CVP), Cardiac Output (CO).	1. Mean ICP was more significantly reduced (p<0.001) by HTS than mannitol after 60min (15 mmHg versus 23 mmHg) and 120min (15 mmHg versus 24 mmHg). 2. Mean CPP was more significantly increased by HTS than mannitol after 120min (76 mmHg versus 65 mmHg, p=0.02). 3. Mean CO was more significantly increased by HTS than mannitol after 30 min (7.5 L/min versus 5.3 L/min, p=0.003), 60 min (7.8 L/min versus 6.6 L/min, p=0.007), and 120min (7.5 L/min versus 6.1 L/min, p=0.002). 4. Mean $P_{bt}O_2$ was significantly increased by HTS (p<0.01) and decreased by mannitol (p>0.05) over time, with significant differences at 60min (37 mmHg versus 28 mmHg, p<0.05) and 120 min (41 mmHg versus 27.5 mmHg, p<0.01). 5. There were no significant differences in MAP or CVP between groups.
Ware et al. (2005) USA Case Control N=13	**Population:** TBI; Mean Age=42.0 yr; Gender: Male=10, Female=3; Time Post Injury<12 hr; Mean GCS=7.7. **Intervention:** Participants received intravenous infusions of 23.4% hypertonic saline (HTS) and mannitol. **Outcome Measure:** Intracranial Pressure (ICP).	1. Both HTS and mannitol significantly reduced ICP (p<0.001) and there was no significant difference between them (p=0.174). 2. Mean duration of ICP reduction by HTS was significantly longer than mannitol (96 min versus 59 min, p=0.016).

Author Year Country Research Design PEDro Sample Size	Methods	Outcome
[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 Measures:** 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 60min, $p<0.05$) and a significant increase in mean CPP (maximal increase from 68 mmHg to 80 mmHg at 120 min, $p<0.05$) in response to mannitol.

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 (Diringer et al., 2012; Scalfani et al., 2012; Tang et al., 2015), and improving CPP (Hartl et al., 1997; Tang et al., 2015) following TBI. In addition, Tang et al. reported an increase in cerebrovascular pressure reactivity, a measure of cerebrovascular autoregulation, in patients with a low baseline CPP.

The Brain Trauma Foundation recommends that mannitol only be used if a patient has signs of elevated ICP or deteriorating neurological status; this is primarily due to the significant side effects associated with mannitol treatment. While side effects were not reported, one study indicated that mannitol was only effective in diminishing ICP and improving CPP when the initial ICP was hypertensive (>20mmHg(Hartl et al., 1997)).

Several studies have compared HTS to mannitol in terms of efficacy in lowering elevated ICP and improving long-term outcomes. While one case-control study found no significant difference between the treatments in the level or duration of ICP reduction (Sakellaridis et al., 2011), another found that HTS had a longer lasting effect (Ware et al., 2005). Two cohort studies reported significantly greater reductions in ICP from HTS than mannitol (Kerwin et al., 2009; Oddo et al., 2009), with one noting that these ICP reductions were associated with greater increases in CPP (Oddo et al., 2009). The benefits of HTS were also reported in 2 retrospective studies where HTS was compared to mannitol (Mangat et al., 2015), and mannitol, propofol, fentanyl and barbiturates (Colton et al., 2014a). Both studies described improvements in either acute (Colton et al., 2014a) or sustained (Mangat et al., 2015) ICP management, with the latter also reporting a decrease in length of hospitalization compared to mannitol. In a RCT, Vialet et al. (2003) found that patients receiving HTS had fewer episodes of ICP hypertension and fewer clinical failures than those receiving mannitol, although clinical outcomes at three months did not differ between groups. Another small RCT demonstrated that HTS yielded a significantly greater decrease in ICP over a longer period of time when compared to mannitol (Battison et al., 2005). However, three other RCTs were

identified that found no benefit of HTS over mannitol in controlling elevated ICP, despite improvements in CPP (Harutjunyan et al., 2005), Cerebral Blood Flow (Cottenceau et al., 2011), and blood glucose control (Jagannatha et al., 2016). A secondary analysis of the Jagannatha et al. (2006) study attempted to explain the lack of efficacy of HTS over mannitol, and found that urinary sodium concentrations were greater in patients receiving HTS (Jagannatha et al., 2018). The authors suggested that unless sodium excretion could be reduced, the efficacy of HTS would continue to be equivalent to that of mannitol in reducing ICP.

The comparison of HTS and mannitol was not just limited to the treatment's ICP-lowering potential, but also the morbidity and mortality associated with each. Hypertonic Saline was associated with a decrease in hospital length of stay (Mangat et al., 2015); however, no differences were observed in mortality or GOS/GOSE scores when compared to mannitol(Baker et al., 2009; Cooper et al., 2004; Mangat et al., 2015; Vialet et al., 2003).

Conclusions

There is level 1a evidence that hypertonic saline is similar to mannitol in terms of mortality or Glasgow outcome scale (extended) scores in patients post TBI.

There is conflicting (level 1b) evidence as to whether hypertonic solution lowers elevated intracranial pressure more effectively than mannitol post ABI.

There is conflicting (level 2 and level 3) evidence that hypertonic saline lowers intracranial pressure for longer compared to mannitol post ABI. The level 2 evidence suggest that it does.

There is level 2 evidence that hypertonic saline is superior to mannitol at improving cerebral perfusion pressure, cerebral blood flow, and blood-glucose control in patients post ABI.

There is level 2 evidence that urinary sodium excretion is higher in hypertonic saline patients compared to those receiving mannitol post ABI.

There is level 4 evidence that hypertonic saline is superior to barbiturates, propofol, and fentanyl at lowering intracranial pressure post ABI.

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

There is level 4 evidence that mannitol may be effective in increasing cerebral perfusion pressure post ABI.

There is level 4 evidence that mannitol may only improve intracranial pressure and cerebral perfusion pressure post ABI in hypertensive patients (Intracranial pressure>20mmHg).

Mannitol may effectively improve intracranial pressure and cerebral perfusion pressure post ABI; however, this benefit may only be seen in hypertensive (intracranial pressure>20 mmHg) patients.

> **It is unclear whether hypertonic saline is more effective than mannitol at lowering intracranial pressure or reducing hospital length of stay.**
>
> **Hypertonic saline can improve cerebral perfusion pressure, cerebral blood flow, and brain tissue oxygenation more effectively than mannitol. However, hypertonic solution is not different than mannitol in terms of morbidity and mortality associated with treatment.**
>
> **Hypertonic saline is superior to barbiturates, propofol, and fentanyl at lowering intracranial pressure post TBI.**

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 upregulate 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 has been used in the treatment of Parkinson's disease. Its properties as a potential neuroactive agent were quickly recognized (Zafonte et al., 2001), and there is interest in its use as a potential treatment in the management of ABI (Schneider et al., 1999b). Researchers believe that amantadine could significantly improve arousal in patients who are comatose. Potential side effects include over-stimulation, peripheral edema, livedo reticularis, and lowering of the seizure threshold, however, these are easily reversible (Schneider et al., 1999b). The favorable risk-benefit profile of amantadine suggests that it may be an attractive treatment option for inducing arousal from coma (Hughes et al., 2005).

The RCP reported that the preliminary research on amantadine was positive, but suggested that its longer-term effects required further exploration (*Prolonged disorders of consciousness: National clinical guidelines*, 2013). The authors concluded that there was insufficient evidence to make formal recommendations regarding its use in enhancing recovery of consciousness. However, if medication is prescribed for patients with DOC, it was recommended that it be done in the setting of a clinical trial with formal monitoring and blinded assessors

Table 12.33 Effects of Amantadine on Arousal from Coma

Author Year Country Research Design PEDro Sample Size	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=48 days. *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 (100 mg, 2x/ days, 14 days. Dose increased to 150 mg 2x/ day at week 3, and to 200 mg 2x/ day at week 4 if DRS score had not improved by at least 2 points from baseline) 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 improved significantly more 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).
Meythaler et al. (2002) USA RCT Crossover PEDro=6 N=35	**Population:** TBI; Mean Age=31 yr; Gender: Male=26, Female=9; Time Post Injury<6 wk; Mean GCS=5.4. **Intervention:** Patients received amantadine at 200 mg/ day (Group 1, n=15) or placebo (Group 2, n=20) for 6 wk, after which they received the alternate treatment for 6 wk. **Outcome Measures:** Mini Mental Status Exam (MMSE), Disability Rating Scale (DRS), Functional Independence Measure-Cognitive (FIM-cog), Galveston Orientation and Amnesia Test (GOAT).	1. In Group 1, there was a mean improvement in scores on MMSE (+14.3, p=0.0185), DRS (-9.8, p=0.0022), GOS (+0.8, p=0.0077), and FIM-cog (+15.1, p=0.0033) with amantadine. 2. No improvements were observed in Group 1 with placebo administration (p>0.05). 3. In Group 2, there was a mean improvement in scores on MMSE (+10.5, p=0.0015), DRS (-9.4, p=0.0006), GOS (+0.5, p=0.0231), and FIM-cog (+11.3, p=0.003) with placebo. 4. Group 2 continued to make significant gains in mean scores for MMSE (+6.3, p=0.0409), DRS (-3.8, p=0.0099), and FIM-cog (+5.2, p=0.0173) with amantadine.
Hughes et al. (2005) Canada Case Control N=123	**Population:** TBI; *Amantadine Group (n=28)*: Mean Age=37.36 yr; Gender: Male=17, Female=11; Mean Time Post Injury=6 wk; Mean GCS=4.14. *Control Group (n=95)*: Mean Age=38.76; Gender: Male=58, Female=37; Mean Time Post Injury=6 wk; Mean GCS=4.18. **Intervention:** Patients were compared based on whether they received amantadine or not (control). Most patients received an initial dose of 100 mg 2×/ day that increased to 200 mg 2×/ day if there was no improvement. Treatment was discontinued 3wk after emergence from coma. **Outcome Measure:** Emergence from coma.	1. The proportion of patients emerging from coma between amantadine and control groups was 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. 3. After controlling for these variables, amantadine did not significantly contribute to patient's emergence from coma.

Author Year Country Research Design PEDro Sample Size	Methods	Outcomes
[Saniova et al.](#) (2004) Slovakia Case Control N=74	**Population:** TBI; *Amantadine Group (n=41)*: Mean Age=42.12 yr; Gender: Male=35, Female=6; Mean GCS=4.74. *Control Group (n=33)*: Mean Age=43.91 yr; Gender: Male=30, Female=3; Mean GCS=4.70. **Intervention:** Patients were compared based on whether they had received standard therapy and amantadine (200 mg, 2×/ day) or standard therapy alone (control). **Outcome Measures:** Glasgow Coma Scale (GCS), Mortality.	1. At discharge, patients treated with amantadine showed significantly higher GCS scores (9.76 versus 5.73, p<0.0001). 2. At discharge, patients treated with amantadine had a significantly lower mortality rate (6.06% versus 51.51%, p<0.001) than controls.

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

Discussion

One retrospective study that assessed amantadine was identified. The results of the study found that there was no difference in emergence from coma after amantadine administration (Hughes et al., 2005). Upon further analysis, it was found that the only predictors for emergence from coma were age, GCS score, and somatosensory evoked potential.

Two RCTs identified 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 significantly improved 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 administration. While patients made some natural recovery on placebo, the authors noted that patients made more pronounced improvements on amantadine. In addition, the authors went on to suggest that amantadine aids in recovery regardless of the time of administration. Similarly, a trial by Giacino et al. (2012) found a significant reduction in the disability of 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 should be continued until recovery goals are reached, although it should be approached with caution.

In a chart review, patients who were treated with amantadine showed significant improvements in consciousness at discharge and decreased mortality rates when compared to those who received standard therapy (Saniova et al., 2004). While the retrospective nature of this study makes it difficult to draw conclusions, the author recommends amantadine as a safe intervention with promising potential but suggested that further research was warranted.

Conclusions

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

There is level 3 evidence that amantadine treatment does not improve emergence from coma compared to control in patients post ABI.

There is level 3 evidence that amantadine is superior to standard care at improving consciousness in patients in a coma post ABI.

> **Amantadine may improve consciousness, cognitive function, and disability post ABI; however, it might not affect emergence from coma post ABI. It is important to note that these benefits are only seen during amantadine administration, and so treatment must be continued to sustain the improvements made.**

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

Table 12.34 Effects of Amantadine on Executive Functioning and Learning and Memory Deficits

Author Year Country Research Design PEDro Sample Size	Methods	Outcomes
Ghalaenovi et al. (2018) Iran RCT PEDro=10 N=40	**Population:** *Amantadine Group (N=19)*: Mean age=32.16yr; Gender: Males=19, Female=0; Mean GCS=7.1; Mean time post-injury=3.21days. *Control Group (N=21)*: Mean age=40.95yr; Gender: Male=18, Female=3; Mean GCS=6.95; Mean time post-injury=3.42days. **Intervention:** Participants either received a placebo or 100mg of amantadine twice a day for 6 weeks. Assessments were conducted at baseline, day 3 of treatment, day 7 of treatment, at 6-weeks completion of the intervention, and 6 months post initial start time. **Outcomes:** Mini-Mental State exam (MMSE), Glasgow Outcome Scale (GOS), FOUR score, Disability Rating Scale (DRS), Karnofsky	1. There were no significant differences observed on the MMSE, GOS, DRS, or KPS. It should be noted that these measures were only taken at baseline and 6-month follow-up. 2. On day 7 the amantadine group had significantly better rising GCS scores than the control group (p=0.044). No other significant differences were observed between groups.

Author Year Country Research Design PEDro Sample Size	Methods	Outcomes
	Performance Scale (KPS), mean hospitalization time.	
Hammond et al. (2018) United States RCT PEDro= 9 N=119	**Population:** Mean age=38.6yr; Mean time post-injury=6.2yr; Injury severity: GCS<13. **Intervention:** Individuals were allocated to receive either the placebo or 100mg amantadine twice a day for 60 days. Assessments were completed at baseline, day 28, and day 60. **Outcomes:** Digit-span from Wechsler Memory Scale-III (DS), Trail Making Test (TMT), Controlled Oral Word Association Test (COWAT), Learning/Memory Index (LMI), Attention/Processing Speed Index (APSI), overall composite (GCI).	1. No significant differences were seen on the DS, TMT, COWAT, or the APSI between groups at any time point. 2. The treatment group had significantly lower LMI scores at day 28 compared to the control group (p=0.001), this effect was not present at 60-day follow-up. 3. The treatment group had significantly lower scores on the GCI compared to the control group at day 28 (p=0.002), this effect was not present at day 60 follow-up.
Schneider et al. (1999a) 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).
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).

Discussion

Presently, only one study has examined the effects of amantadine on attention and processing speed and found no significant effects on attention or processing speed following treatment, any results which were found to be significant on other cognitive measures were not maintained at 60 day follow-up (Hammond et al., 2018). Further studies are needed to examine whether or not amantadine may be a viable treatment for attention and processing speed deficits following an ABI.

In a small sample RCT by Schneider et al. (1999b) 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. A RCT reinforces these findings after finding no significant differences on measures of cognition following 6-weeks of amantadine treatment (Ghalaenovi et al, 2018). 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 studies, future studies exploring the efficacy of amantadine for learning and memory are warranted.

Conclusions

There is level 1b evidence that amantadine is not effective for improving attention compared to placebo following an ABI.

There is level 1b evidence that Amantadine may not help to improve general functioning deficits in patients with TBI compared to placebo.

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.**
>
> **Amantadine is not effective at improving generalized cognition. 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 12.35 Effects of Amantadine on Reducing Aggression

Author Year Country Research Design PEDro Sample Size	Methods	Outcomes
Hammond et al. (2015) USA RCT PEDro=10	**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:	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.

Author Year Country Research Design PEDro Sample Size	Methods	Outcomes
N_{Initial}=168, N_{Final}=157	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.	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

Two RCTs compared the effects of amantadine and placebo on irritability and aggression post TBI. Hammond and colleagues (2014) found that the frequency and severity of irritability were reduced when individuals received amantadine for 28 days compared to placebo. However, amantadine only significantly reduced aggression in individuals who had moderate to severe aggression at baseline (Hammond et al., 2014). A subsequent trial by Hammond and colleagues (2015) found that 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 level 1b evidence that amantadine compared to placebo may reduce aggression post TBI in individuals with moderate to severe aggression.

There is conflicting (level 1b) evidence as to whether amantadine reduces irritability compared to placebo post TBI.

Amantadine requires further research before conclusions can be drawn regarding its effects on aggression and irritability following a TBI.

12.12.2 Bromocriptine

Bromocriptine is a dopaminergic agonist which exerts its effects primarily through the binding of 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. Two studies have been identified investigating the use of bromocriptine as an adequate treatment for the recovery of cognitive impairments following brain injury.

Table 12.36 Effects of Bromocriptine on Executive Functioning

Author Year Country Research Design PEDro Sample Size	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. **Intervention:** In a crossover design, participants were randomly assigned to receive bromocriptine (1.25 mg 2×/d titrated to 5mg 2×/d over a 1 wk), followed by placebo or the reverse order. Each lasted 4 wk with a 1 wk washout period. **Outcome Measures:** 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=27d-300 mo. **Intervention:** In a crossover design, participants were randomly assigned to receive 2.5 mg bromocriptine followed by placebo, or the reverse order. **Outcome Measures:** 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), 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).

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). 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, the Stroop test, the Wisconsin Card Sorting Test and the controlled oral word association test (McDowell et al., 1998). However, bromocriptine did not significantly influence working memory tasks. However, a later study by Whyte et al. (2008) found that bromocriptine had little effect on attention and 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 (2.5 mg 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.

Conclusions

There is conflicting evidence as to whether bromocriptine improves performance on attention tasks compared to placebo in patients post TBI.

> **Bromocriptine does not appear to improve attention in those with an ABI.**

12.12.3 (-)-OSU6162

(-)-OSU6162 is a monoaminergic stabilizer that has been investigated for the treatment of Huntington's disease, alcohol dependence, and fatigue (Berginstrom et al., 2017; Khemiri et al., 2015; Kloberg et al., 2014; Nilsson et al., 2017). (-)-OSU6162 works on both the dopamine and serotonin systems, but is classified as a dopaminergic stabilizer due to its affinity for D2 and D3 receptors, meaning it can both inhibit and stimulate dopamine behavior (Berginstrom et al., 2017). In this section, we specifically examine the effect of (-)-OSU6162 on fatigue.

Table 12.37 (-)-OSU6162 for the Treatment of Fatigue Post ABI

Author Year Country Study Design Sample Size	Methods	Outcomes
Berginstrom et al. (2017) Sweden RCT	**Population:** TBI; *Treatment Group (n=33)*: Mean Age=41.42yr; Gender: Male=17, Female=16; Mean Time Post Injury=8.58yr. *Control Group (n=31):* Mean Age=42.58yr; Gender: Male=20, Female=11; Mean Time	1. For the FSS, MFS, RPCSQ, and both groups showed significant improvement (all p<0.01) after the trial but not during follow-up. No between group differences were observed.

Author Year Country Study Design Sample Size	Methods	Outcomes
PEDro=10 N=64	Post Injury=8.10yr. **Intervention:** (-)-OSU6162 was compared with placebo during a 4wk treatment period. 5mg of (-)-OSU6162 was given 2x/d in week 1, 10mg 2x/d in week 2, and 15mg 2x/d in weeks 3 and 4. Patients were evaluated at baseline, at days 7, 14, 22, and 28 during treatment, and for follow-up at 2 and 6mo. **Outcome Measure:** Fatigue Severity Scale (FSS), Mental Fatigue Scale (MFS), Rivermead Post-Concussion Symptoms Questionnaire (RPCSQ).	2. During follow-up, the treatment group had significantly larger changes in folic acid (p=0.02), prolactin (p=0.03), and heart rate (p=0.009).

Discussion

In a RCT by Berginstrom et al. (2017) (-)-OSU6162 was compared to placebo in patients with TBI (GCS>5). On both the Fatigue Severity Scale and the Mental Fatigue Scale, both groups showed significant reductions in fatigue; however, no between-group differences were observed. It is worth noting that participants received a dose of 15mg twice per day, and at the end of the trial the mean plasma concentration was lower than expected (0.14μM). However, signficantly larger changes in folic acid, prolactin, and heart rate were recorded for the experimental group, suggesting that these plasma levels may still have been high enough to elicit a physiological effect. Based on this study, (-)-OSU6162 may not be effective in reducing fatigue in patients with TBI.

Conclusions

There is level 1b evidence that (-)-OSU6162 may not be effective for treating fatigue compared to placebo in patients with TBI.

(-)-OSU6162 treatment may not be effective for reducing fatigue post TBI.

12.13 Hormone Therapy

12.13.1 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). One study revealed inappropriate sexual talk to be the most common inappropriate sexual behaviour in a sample of patients

with TBI (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 12.38 Effects of Depo-Provera on Sexually Aggressive Behaviour

Author Year Country Research Design PEDro Sample Size	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.

12.13.2 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 12.39 Effects of Progesterone in ABI

Author Year Country Research Design PEDro Sample Size	Methods	Outcomes
Soltani et al. (2017) Iran RCT PEDro=7 N=48	**Population:** *Experimental Group (n=20)*: Mean age=27.85yr; Mean GCS=7.7. *Control Group (n=24)*: Mean Age=30.37yr; Mean GCS=7.7. **Intervention:** 1 mg/kg of Progesterone was given intramuscularly every 12 hours for 5 days to the experimental group, while the control group received no treatment. Participants received treatment within 12 hours of initial trauma. **Outcome Measure:** Glasgow Outcome Scale-Extended (GOS-E), Functional Independence Measure (FIM), serum progesterone levels, mortality.	1. There were no significant differences between groups at 3 mo post-trauma based on treatment. However, at 6 mo post-trauma the progesterone group had significantly higher GOS-E scores (p=0.03), with only 1 death in the progesterone group compared to 7 in the control group. 2. FIM scores showed a similar trend with no significant difference between groups at 3 mo but 6 mo post-trauma the progesterone group had significantly higher FIM scores (p<0.05). 3. At baseline there was no significant difference between groups in terms of serum progesterone levels, however after the initiation of treatment the progesterone group maintained significantly higher progesterone levels until the end of the trial (p<0.05). 4. The control group experienced significantly higher mortality compared to the progesterone group (p<0.05).
Skolnick et al. (2014a) Belgium RCT PEDro=7 N=1195	**Population:** TBI; *Progesterone (n=591)*: Median Age=35 yr; 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 either progesterone (0.71 mg/kg/hr loading dose, followed by a continuous maintenance infusion of 0.5 mg/kg/hr) or placebo for 120 hr. Outcomes were assessed at baseline and 6mo. **Outcome Measures:** Glasgow Outcome Scale (GOS).	1. There was no significant difference in the GOS scores of patients with the worst prognosis between groups (n=393; p=0.36). 2. There was no significant difference in the GOS scores of patients with intermediate prognosis between groups (n=394; p=0.82). There was no significant difference in the GOS scores of patients with the best prognosis between groups (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 one of 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 2.5 mL/hr every 8hr, for total treatment duration of 96hr. Outcomes were assessed at 6mo. **Outcome Measures:** 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 (RR: 0.95). 2. Mortality at 6mo did not differ significantly between the two groups. 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 either progesterone (1 mg/kg every 12 hr for 3 days) or no treatment (control). Outcomes were assessed at 3mo. **Outcome Measures:** Glasgow Coma Scale (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. 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 Measures:** 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. No AEs were reported after treatment of progesterone.
Wright et al. (2007)	**Population:** TBI; Mean Age=35.8yr; Gender: Male=71, Female=29; Mean	1. AE rates and physiological variables (e.g. ICP) were similar

USA RCT PEDro=10 N=100	Time Post Injury=379.2min; 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 Measures:** Glasgow Outcome Scale Extended (GOSE), Disability Rating Scale (DRS), Adverse Events (AE), Intracranial Pressure (ICP).	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. 5. For patients with moderate injury (GCS 9-12), those in the progesterone 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) when compared to the placebo group.

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

Discussion

In a RCT, progesterone treatment did not appear to improve functionality short-term (<3 mo), however at 6mo follow-up patients had significantly higher Glasgow Outcome Scale Extended and Functional Independence Measure scores (Soltani et al., 2017) . Furthermore, the control group experienced significantly higher mortality than the progesterone group. In contrast to these results, a systematic review of 5 studies concluded that there are no sure benefits to progesterone administration compared to placebo (Ma et al., 2016). Authors consistently found no difference between disability or mortality between groups.

In a RCT, Wright et al. (2007) evaluated patients receiving progesterone 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 additionally 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. The researchers reported a lack of improvement in ICP over placebo, but significantly greater morbidity (GOS) and independence (FIM) scores at three months and six months. In addition, there was significantly lower incidence of mortality at six months associated with the progesterone group. Notably, there were no reported complications associated with progesterone administration. In contrast, other studies have reported no significant differences in favourable outcomes between those receiving progesterone or placebo after three months (Shakeri et al., 2013) or six months (Shakeri et al., 2013; Skolnick et al., 2014b; Wright et al., 2014). However, in a subgroup analysis of patients with initial GCS$\geq$5, Shakeri et al. (2013) found a significant improvement in GOS scores associated with progesterone. As well, one study reported that progesterone was associated with increased rate of serious adverse event such as phlebitis and thrombophlebitis (Wright et al., 2014). Given the conflicting findings between studies, further studies investigating the use of progesterone in ABI are suggested.

Conclusions

There is level 1a evidence that progesterone treatment is no better than placebo at improving Glasgow outcome scale scores at 3 and 6 mo post TBI.

There is level 1b evidence that progesterone is superior to placebo at improving Glasgow outcome scale scores in patients with an initial Glasgow coma scale score >5 post TBI.

There is level 1b evidence that progesterone treatment may be associated with adverse events such as phlebitis and thrombophlebitis.

There is level 1a evidence that progesterone does not improve intracranial pressure compared to placebo post ABI.

There is level 1a evidence that progesterone improves mortality and Glasgow outcome scale scores compared to placebo in patients post ABI.

Progesterone does not improve functional outcomes post TBI, with the potential exception of patients who are not severely ill upon admission (Glasgow coma scale score>5)

Progesterone is likely associated with the development of phlebitis and thrombophlebitis.

Progesterone has no effect on intracranial pressure, but does reduce mortality, and improves functional and neurological outcomes post ABI.

12.13.3 Growth Hormone Replacement Therapy

Following an ABI, it is not uncommon for individuals to be diagnosed with hypopituitarism. It is estimated that as many as 25 to 40% of individuals with a moderate to severe ABI demonstrate chronic hypopituitarism (Bondanelli et al., 2007; Kelly et al., 2006; Schneiderman et al., 2008). Despite this, few patients are screened for Growth Hormone (GH) deficiencies; thus, the link between cognitive impairment and growth hormone deficiencies has not yet been definitively established (High et al., 2010). The benefits of GH replacement therapy on patient's executive and general cognitive function post TBI is investigated below.

Table 12.40 The Effect of rh (GH) on Executive and Cognitive Functioning Post ABI

Author Year Country Research Design PEDro Sample Size	Methods	Outcome
Dubiel et al. (2018) United States RCT PEDro=7 N=40	**Population:** Mean age=31.1yr; Gender: Male=34, Female=6; Mean Time Post-injury=64.1d. GCS: mild=4, Moderate=3, Severe=32, unknown=1. **Intervention:** Individuals were randomized to receive either recombinant human growth hormone or placebo. Follow-up was at 1-mo, 3-mo, 6-mo and 12-mo. 1-mo and 3-mo follow-up was only taken for IGF-1 concentrations. **Outcome Measure:** Disability rating scale scores (DRS), Functional Independence Measure (FIM) motor, FIM Cognitive, FIM total, IGF-1, Peak L-Arginine, California Verbal Learning Test (CVLT), Trail making test-A, Trail Making test-B.	1. At 3-mo and 6-mo follow-up the rhGH group had significantly higher IGF-1 concentrations (p=0.035, p=0.005), these were not observed at 1-mo or 12-mo follow-up. 2. At 6-mo follow-up the rhGH group had a significantly higher positive change in FIM motor scores (p=0.02), FIM cognitive scores (p=0.02), and total change in FIM scores (p=0.02). There were no other significant differences at 6-mo. 3. At 12-mo follow-up the rhGH group had maintained significantly higher positive scores in FIM motor scores (p=0.02), and total FIM change (p=0.01). There were no other significant differences at 12-mo follow-up.
High Jr et al. (2010) USA RCT PEDro=8 N=23	**Population:** TBI. *Placebo* (n=11): Mean Age=39.1 yr; Time Post Injury=5.1 yr. *Active rhGH* (n=12): Mean Age=36.1 yr; Time Post Injury=11 yr. **Intervention:** Participants were randomized to either a growth hormone replacement injection (rhGH) group or a placebo injection. Initially the drug was administered at 200 *ug*, followed by a 200 *ug* increase every month until the dosage reached 600 *ug*. Both groups received these injections for one year. **Outcome Measure:** Wechsler Adult Intelligence Scale-III, Delis-Kaplan Executive Function System.	1. Overall study results did not show great improvements on the majority of assessments between groups. 2. There was a significant improvement on the Finger tapping demonstrated in the treatment group. 3. Processing Speed Index: the treatment group improved significantly over the one-year period (p<0.050). The control group showed improvement at the end of the first 6 mo (p<0.010) but this was not seen at the end of the 1 yr. 4. Significant improvement was also noted on the Wisconsin Card Sorting Test (executive functioning) for the treatment group (p<0.010). 5. On the California Verbal learning Test-II improvement was noted for the treatment group on learning and memory.
Hatton et al. (1997) USA RCT PEDro=5 N=33	**Population:** TBI; *Intervention Group (n=17)*: Mean Age=27.6yr; Gender: Male=14, Female=3; Mean GCS=7; Mean Time Post Injury=56.5hr; *Control Group (n=16)*: Mean Age=27.8yr; Gender: Males=14, Females=2; Mean GCS=6.1; Mean Time Post Injury=57.1 hr. **Intervention:** Patients were randomly allocated to receive either continuous IV IGF-1 (0.01mg/kg/hr, treatment) or no IV treatment (control). IGF-I treatment began within 72hr of injury and continued for up to 14d. Both groups received nutritional support and neurosurgical	1. IGF-1 treatment resulted in lower daily glucose concentration and nitrogen output (p=0.03) when compared to placebo. 2. Patients receiving IGF-1 treatment showed weight gain while those receiving placebo showed significant weight loss (p=0.02). 3. In patients with GCS=5-7, those receiving IGF-1 showed better outcome on GOS than those receiving placebo (p=0.06).

	intensive care. Patient assessments were made on 15d, 30d, discharge, and 3 and 6mo follow-up. **Outcome Measure:** Glasgow Outcome Scale (Klionsky et al.), Weight Loss, Glucose Concentrations, Nitrogen Balance.	
Mossberg et al. (2017) United States Pre-Post N=15	**Population:** TBI=15: Mean Age=45.5yr; Gender: Males=10, Females=5; Mean Time Post-Injury=11.2yr. **Intervention:** Daily injections of recombinant human growth hormone (rhGH) for 12 mo. **Outcome Measure:** Cardiorespiratory symptoms, Muscle force testing, Body composition, Cognitive function (BDI, Fatigue Severity Scale (FSS)).	1. There were no significant differences between pre and post measures of cardiorespiration (oxygen uptake, heart rate, minute ventilation, respiratory exchange ratio, oxygen pulse). 2. Although skeletal muscle fatigue did not decrease over the course of treatment, there was a strong trend for a decrease in perceived fatigue ($p=0.06$). 3. There was a strong trend for an increase in lean mass ($p=0.06$) post-treatment. 4. There was a significant improvement in both BDI ($p=0.019$) and FSS ($p=0.039$) scores post-treatment.
Gardner et al. (2015) Sweden Case Control N=1429	**Population:** *TBI (n=161):* Mean Age=42.6yr; Gender: Male=93, Female=68. *Tumour (n=1268):* Mean Age=53.2yr; Gender: Male=786, Female=482. **Intervention:** Participants diagnosed with GHD and treated with GH therapy were included in retrospective analysis. **Outcome Measures:** Quality of Life Assessment of GHD in Adults (QOL-AGHDA).	1. At baseline, mean QOL-AGHDA scores were significantly worse in the TBI group than in the Tumour group ($p<0.0001$) 2. After 1yr of treatment, mean improvement in QOL-AGHDA was greater in the TBI group than in the Tumour group ($p=0.04$), but the score remained worse in the TBI group. 3. Over 8 yr of treatment, mean improvement in QOL-AGHDA was maintained in both groups, but the score remained worse in the TBI group.
Devesa et al. (2013) Spain Pre-Post N=12	**Population:** TBI; Mean Age=28.4yr; Gender: Male=8, Female=4; Mean Time Post Injury=5.3yr. **Intervention:** Participants received GH therapy (1mg/d, 5d/wk, 8mo) and clinical rehabilitation (3-4hr/d, 5d/wk, 6-12mo). Diagnosis of GHD was made by the following criteria: plasma GH <7ng/mL. **Outcome Measures:** Plasma IGF-1.	1. GHD was diagnosed in 42% of participants. 2. Before treatment, mean plasma IGF-1 levels were significantly lower in the GHD group than in the non-GHD group ($p<0.05$). 3. After treatment, mean plasma IGF-1 levels significantly increased in both the GHD group ($p<0.01$) and non-GHD group ($p<0.05$), such that the two groups were no longer significantly different ($p>0.05$). 4. Percentage increase in IFG-1 levels was significantly higher in the GHD group than in the non-GHD group ($p<0.01$).
Moreau et al. (2013b) France PCT N=50	**Population**: TBI. Treatment Group (TG, n=23): Mean Age=37.9 yr; Gender: Male=19, Female=4; Mean Time Post Injury=7.8 yr; Mean GCS=8.1. Control Group (CG, n=27): Mean Age=37.1 yr; Gender: Male=24, Female=3; Mean Time Post Injury=5.5 yr; Mean GCS=9.4. **Intervention**: Participants were allocated to receive GH therapy (TG, 0.2-0.6mg/d) or no treatment (CG) for 1yr. Outcomes were	1. Both groups showed significant improvement in instrumental ADL (iADL, $p=0.001$) at T2, but not personal ADL (pADL). 2. Both groups showed significant improvement in QOLBI total scores ($p=0.019$) and intellectual ($p=0.001$), functional ($p=0.023$), and personal ($p=0.044$) subscores at T2, but not

	assessed before (T1) and after (T2) treatment. **Outcome Measures**: Activities of Daily Living (ADL); Quality of Life Brain Injury (QOLBI); Verbal Memory (VM); Rey Complex Figure (RCF); Reaction Time (RT).	physical, psychological, and social subscores.
		3. Both groups showed significant improvement (p<0.050) in aspects of attention (RT), memory (VM), and visuospatial (RCF) abilities at T2.
		4. The TG showed significantly greater improvement in QOLBI functional (p=0.023) and personal (p=0.019) subscores, as well as RCF (p=0.037), but no significant difference was found for other outcome measures.
		5. There was a significant correlation (p<0.050) between QOLBI total and pADL (r=0.49).
		6. There was a significant negative correlation (p<0.01) between attention (RT) and pADL (r=-0.59) and iADL (r=-0.56).
Reimunde et al. (2011) Spain Cohort N=19	**Population:** TBI; Gender: Male=19, Female=0. With Growth Hormone Deficiency (GHD) Group (n=11): Mean Age=53.36 yr; Mean Time Post Injury=44.55 mo. Without GHD group (n=8): Mean Age=47.12 yr; Mean Time Post Injury=46.6 mo. **Intervention:** Those with GHD received recombinant human GH (rhGH), subcutaneously (0.5 mg/d for 20d then 1 mg/d for 5 d). Those without GHD were given a placebo. Cognitive rehabilitation was given to everyone (1 hr/d, 5d for 3 mo). **Outcome Measure:** Weschler Adult Intelligence Scale (WAIS).	1. Results of the WAIS indicated that the control group improved significantly on the digits and manipulative intelligence quotient (p<0.050).
		2. For those in the treatment groups improvement was noted in cognitive parameters: understanding digits, numbers and incomplete figures (p<0.050) and similarities vocabulary, verbal IQ, Manipulative IQ, and total IQ (p<0.010).

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

Discussion

Research has found that growth hormone replacement therapy effectively elevates serum IGF-I levels in individuals with GHD post ABI (Devesa et al., 2013; Dubiel et al., 2018), as well as improves their quality of life (Gardner et al., 2015; Moreau et al., 2013a). In a randomized controlled trial (RCT) of individuals with TBI, patients received IGF-I (5mg) via continuous intravenous infusion within 72 hours after injury and continued for 14 days, or placebo (Hatton et al., 1997). The authors found that patients receiving IGF-I treatment showed better outcomes in terms of glucose concentration, nitrogen balance, body weight, and recovery (Hatton et al., 1997). Mossberg et al. (2017) found that although recombinant human growth hormone did not improve respiratory capacity or symptoms, fatigue and depression scores significantly improved with treatment. Similarly, another RCT (Dubiel et al., 2018) found that more than just IGF-1 concentrations improved with recombinant growth hormone (rhGH) treatment. Cogntive and Motor Functional Independence Measure scores were seen to significantly increase in those receiving rhGH treatment at 6-month follow-up (Dubiel et al., 2018).

A 2010 RCT compared the long term (6 mo and 1 yr) effects of rhGH administration to placebo in a TBI population (High Jr et al. 2010). Significant improvements were noted in processing speed, executive functioning (Wisconsin Card Sorting Test), and learning (California Verbal learning test II) for both he rhGH and placebo groups. It is important to note while processing speed also improved in both groups at 6 mo, the improvement was only sustained in the treatment group at 1 year. Further positive results were reported in a PCT by Moreau et al. (2013). Patient quality of life, instrumental activities of daily living, attention, memory and visuospatial ability improved over the treatment period in both the treatment and control group. However, the treatment group improved significantly more in the functional and personal subscales of quality of life assessments. Reimunde et al. (2011) also examined the use of recombinant human growth hormone in a cohort study. Results of the study indicate that those receiving the rhGH improved significantly on the various cognitive subtests such as: understanding, digits, numbers and incomplete figures ($p<0.05$), verbal IQ, Manipulative IQ, and Total IQ ($p<0.01$). The control group also showed significant improvement but only in digits and manipulative intelligence quotient ($p<0.05$). Of note IGF-I levels were similar between both groups at the end of the study. These findings support the consensus that neuroendocrine dysfunction is a heterogeneous topic and treatment intervention may need to be tailored over time to an individual's specific needs.

Conclusions

There is level 1b evidence that growth hormone replacement therapy may improve clinical outcomes compared to placebo in patients with GHD post ABI.

There is level 1b evidence that recombinant human Growth Hormone (rhGH) is superior to placebo at improving processing speed (6 mo), executive function and learning in patients post TBI.

There is level 2 evidence that growth hormone (GH) therapy is effective for improving quality of life, instrumental activities of daily living (iADL), attention, memory, and visuospatial ability in patients post TBI.

There is level 2 evidence that recombinant human Growth Hormone (rhGH) administration improves intelligence and other cognitive subtests in TBI patients with growth hormone deficiency compared to TBI patients without; however, insulin-like growth factor-1 (IGF-1) levels may be the same between groups.

There is level 4 evidence that growth hormone replacement therapy may be effective in treating GHD, fatigue, and depression post ABI.

Growth hormone deficiency may be effectively treated with hormone replacement therapy and insulin growth like factor-1 therapy.

The administration of human growth hormones appears to have positive (although sometimes limited effects) on general and executive functioning in those with an ABI.

12.13.4 Melatonin

Melatonin is an endogenous hormone that plays a role in the regulation of sleep-wake cycles (Driver & Stork, 2018). Individuals with TBI show lower levels of melatonin production in the evening, which may cause disruptions to the sleep-wake cycle (Shekleton et al., 2010). In an observational overnight study, Grima et al. (2016) compared melatonin production of individuals with TBI to healthy controls. Patients with TBI showed 42% less melatonin production, and was delayed by 1.5 hours on average (Grima et al., 2016). Melatonin offers very minimal side effects, enhancing the drugs usefulness in aiding treatment of sleep disorders (Grima et al., 2018). One article met the inclusion criteria investigating a melatonin intervention in individuals with severe TBI.

Table 12.41 Melatonin for the Treatment of Fatigue and Sleep Disorders Post ABI

Author Year Country Study Design Sample Size	Methods	Outcome
Grima et al. (2018) Australia RCT Crossover PEDro=9 N=33	**Population:** *Melatonin-placebo group (N=18)*: Mean Age=35yr; Gender: Male=61%, Female=39%; Median Time Post Injury=61mo; Median GCS= 5. *Placebo-melatonin group (N=15)*: Mean Age=38yr; Gender: Male=73%, Female=27%; Median Time Post Injury= 25mo; Median GCS=8. **Intervention:** Participants with chronic insomnia were randomly allocated to a 4wk melatonin or placebo treatment before crossover. Melatonin formula was a prolonged release formula (2mg). Participants were measured at baseline and at the end of each treatment phase. **Outcomes:** Pittsburgh Sleep Quality Index (PSQI); Sleep onset latency (measured by wrist actigraphy); Epworth Sleepiness Scale (ESS); Hospital Anxiety Depression Scale (HADS); Fatigue Severity Scale (FSS); Short-form health survey (SF-36 v1) subscales: Physical functioning (PF); vRole Physical (RP); Role-emotional (RE); Vitality (VT); Mental Health (MH); Social functioning (SF); bodily pain (BP); general health (GH).	1. PSQI scores were significantly different between melatonin and placebo treatments (p<0.0001) showing the melatonin treatment group had lower scores. 2. Sleep latency scores were not significantly different between treatments (p=0.23). 3. Sleep efficiency scores were significantly different between treatments (p=0.04) showing the melatonin treatment had higher scores. 4. ESS scores were not significantly different between treatments (p=0.15). 5. HADS anxiety scores were significantly different between treatments (p=0.0006) showing the melatonin treatment had lower scores. 6. HADS depression scores were not significantly different between treatments (p=0.68). 7. FSS scores were significantly different between treatments (p=0.03) showing the melatonin treatment had lower scores. 8. VT and MH scores of the SF-36 were significantly different between treatments (p=0.03 and p=0.01, respectively) showing the melatonin treatment had higher scores. 9. The other subscales of the SF-36 were not significantly different between treatments (p>0.05).

Discussion

Using a crossover RCT design, Grima et al. (2018) evaluated the effect of a 4-week melatonin treatment (2 mg prolonged release) on sleep quality, sleep latency and efficiency, fatigue, and areas of general health in a TBI population. Participants showed significant improvements in sleep quality, sleep efficiency, and fatigue scores after the four weeks of the melatonin treatment phase compared to the placebo phase. Participants did not show a significant difference in sleep onset latency or daytime sleepiness scores when comparing the treatment phase to placebo. Based on this study, melatonin treatment may improve sleep quality, latency, and reduce fatigue in individuals post TBI, but not significantly affect sleep onset or daytime sleepiness (Grima et al., 2018).

Conclusions

There is level 1b evidence that melatonin treatment may be effective in improving sleep quality, sleep efficiency, and fatigue compared to a placebo group in patients post TBI.

There is level 1b evidence that melatonin treatment may not effect sleep onset latency or daytime sleepiness in patients post TBI.

Melatonin treatment may improve sleep quality, sleep efficiency, and reduce fatigue in patients post TBI.

Melatonin treatment may not effect sleep onset latency or daytime sleepiness.

12.14 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 Research Design PEDro Sample Size	Methods	Outcomes
Dymowski et al. (2017) Australia RCT PEDro=9 N_Initial=11, N_Final=10	**Population:** TBI. *Methylphenidate Group (n=6)*: Mean Age=35 yr; Gender: Male=4, Female=2; Mean Time Post Injury=366 d; Mean Worst GCS=4.83. *Placebo Group (n=4)*: Mean Age=32.5 yr; Gender: Male=2, Female=2; Mean Time Post Injury=183.5 d; Mean Worst GCS=4.50. **Intervention:** Participants were randomly assigned to receive either methylphenidate (0.6 mg/kg/d rounded to the nearest 5mg with maximum daily dose of 60 mg) or placebo (lactose). Outcomes relating to processing speed, complex attentional functioning, and everyday attentional behaviour were assessed at baseline, 7 wk (on-drug), 8 wk (off-drug), and 9mo follow-up. **Outcome Measures:** Symbol Digit Modalities Test (SDMT), Trail Making Test (TMT) A and B; Hayling (A, B, error), Digit Span (DS-Forward, Backward, Sequencing, Total), Ruff 2&7 Selective Attention Test Automatic Speed Raw Score (2&7 ASRS), Ruff 2&7 Selective Attention Test Controlled Speed Raw Score (2&7 CSRS), Simple Selective Attention Task Reaction Time (SSAT RT), Complex Selective Attention Task Reaction Time (CSAT RT), N-back 0-back RT, N-back 1-back RT, N-back 2-back RT, Rating Scale of Attentional Behaviour Significant Other (RSAB SO).	1. After applying Bonferroni corrections, no significant differences between groups from baseline to 7 wk, baseline to 8 wk, or baseline to 9 mo were observed for SDMT, TMT A, TMT B, Hayling A, Hayling B, Hayling error, DS Forward, DS Backward, DS Sequencing, DS Total, 2&7 ASRS, 2&7 CSRS, SSAT RT, CSAT RT, N-back 0-back RT, N-back 1-back RT, N-back 2-back RT, or RSAB SO.
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.

Author Year Country Research Design PEDro Sample Size	Methods	Outcomes
[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 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	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).

Author Year Country Research Design PEDro Sample Size	Methods	Outcomes
	(T3). **Outcome Measure:** Visual sustained attention task (VSAT) and two-back task.	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 RCT PEDro=5 N=23	**Population:** TBI; Gender: Male=17, Female=6; *Placebo Group (n=13)*: Mean Age=26.6 yr; Mean 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).	1. At 30 days follow-up (n=15), significant differences were obtained on DRS, 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.
Gualtieri & Evans (1988) United States RCT Crossover PEDro=7 N=15	**Population:** Mean age=24.1yr; Gender: Male=10, Female=5; Mean time post-injury=46.8mo. **Intervention:** Participants were assigned to receive three conditions in randomized order. 1) Placebo; 2) Methylphenidate (0.15mg/kg) twice daily; 3) Methylphenidate (0.30mg/kg) twice daily. Each condition was 12 days long, with 2 days washout between conditions.	1. There was a significant improvement in AAS-S and AAS-O scores between the placebo and high-dose conditions (p<0.05). 2. There was a significant difference in SRS scores between the placebo group and the high-dose condition (p<0.05). 3. On the EXRS there was a significant difference between baseline and low-

Author Year Country Research Design PEDro Sample Size	Methods	Outcomes
	Outcomes: Adult Activity Scale self-administered (AAS-S), Adult Activity Scale (administrator)(AAS-O), Examiner's Rating Scale (EXRS), Self-Rating Scale (SRS), Verbal Fluency Test (VFT), Non-verbal Fluency test (NVFT).	dose (p=0.012), placebo and low-dose (p=0.025), baseline and high-dose (p=0.012), with higher doses of methylphenidate having improved effects. 4. There was a significant improvement in VFT scores between baseline and the high-dose groups (p=0.017). 5. There was a significant difference on NVFT scores between baseline and placebo (p=0.008), baseline and low-dose (p=0.008), baseline and high-dose (p=0.008), and the placebo and high-dose group (p=0.018), with methylphenidate improving scores.

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

Discussion

The majority of studies evaluating the efficacy of methylphenidate have been RCTs. In a 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) and Pavlovskaysa (2007) found that methylphenidate significantly improved attention and concentration, and visuo-spatial attention, respectively. 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. A variety of studies with different dosing regimens and durations have found positive effects of methylphenidate (Gualtieri & Evans, 1988; Whyte et al., 1997; Zhang et al., 2004).

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. Conflicting results continue to be reported, as two high-quality RCTs reached different conclusions regarding methylphenidate use. While Dymowski et al. (2017) noted no improvements in any measures of attention and mental processing, Zhang et al. (2017) noted improvements in reaction time, arithmetic tests, and even mental health outcomes after intervention by methylphenidate.

A potential explanation for these conflicting results is proposed 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 level 1a evidence regarding the effectiveness of methylphenidate following brain injury for the improvement of attention and concentration in individuals post ABI.

There is level 1a evidence that methylphenidate improves reaction time of working memory compared to placebo in individuals post ABI.

There is level 1b evidence that individuals carrying the Met allele may be more responsive to methylphenidate than those without the Met allele when it comes to the ABI population.

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

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

Response to methylphenidate may depend on the presence of the Met 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 Sample Size	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 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 Sample Size	Methods	Outcome
[Mooney & Haas](#) (1993) USA RCT	**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	1. Following statistical control over the possible bias (difference in baseline anger scores), there was a significant

Author Year Country Study Design Sample Size	Methods	Outcome
PEDro=5 N=38	(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.	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.

12.15 Stimulants

12.15.1 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 12.45 Effects of Modafinil Treatment on Fatigue

Author Year Country Study Design Sample Size	Methods	Outcome
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.	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).

Author Year Country Study Design Sample Size	Methods	Outcome
	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).	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.

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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.

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12.15.2 Dextroamphetamine

Dextroamphetamine is another central nervous stimulant, and similar to methylphenidate it is used to treat narcolepsy and ADHD. Dextroamphetamine is a non-catecholamine and sympathomimetic amine that acts as a stimulant, unfortunately more direct mechanisms of action are not known.

Table 12.46 The Effects of Dextroamphetamine on General and Executive Functioning

Author Year Country Research Design PEDro Sample Size	Methods	Outcome
Hart et al. (2018) United States RCT PEDro=10 N=32	**Population:** *DEX Group (N=17)*: Mean age=39.6yr; Gender: Male=11, Female=6; Mean GCS=8.2; Mean time post-injury=53.6dy. *Control Group (N=15):* Mean age=38.7yr; Gender: Male=15, Female=0; Mean GCS=7.5; Mean time post-injury=60.2dy. **Intervention:** Participants either received the placebo or 10 mg of dextroamphetamine (DEX). Each treatment was administered once a day, in the morning, for 3 weeks. **Outcome Measures:** Moss Attention Rating Scale (MARS), Hopkins Rehabilitation Engagement Rating Scale (HRER), Cognitive Failures Questionnaire (CFQ), Rating Scale of Attentional Behavior (RSAB), Finger Taping Test (FT), the Symbol Digit Modalities Test (SDMT), Disability Rating Scale (DRS), Agitated Behavior Scale (ABS), Profile of Mood States (POMS),	1. There was a significant difference between groups on the ABS (p=0.04), with the DEX group demonstrating more agitation over time. 2. No other significant differences were found.

Discussion

One RCT evaluated the effects of dextroamphetamine on general and executive functioning using a variety of outcomes (Hart et al., 2018). Although dextroamphetamine was seen to significantly reduce agitation compared to the placebo group, no significant effects were seen on measures of cognition. Given the use of dextroamphetamine in other attentional disorders such as ADHD, the lack of results on any cognitive measures between these two studies is unexpected.

Conclusions

There is level 1b evidence that dextroamphetamine is not effective for the remediation of general cognitive functioning following an ABI.

Dextroamphetamine is moderate evidence to suggest that dextroamphetamine is not effective for the remediation of general functioning.

12.15.3 Pramiracetam

Pramiracetam is a nootropic (cognitive) activator that is used to facilitate learning, memory deficiencies, and other cognitive problems. Pramiracetam produces an increased turnover of acetylcholine in hippocampal cholinergic nerve terminals and it is at least 100 times more potent than its original compound piracetam (McLean et al., 1991).

Table 12.47 The Effect of Pramiracetam on Memory Post ABI

Author Year Country Research Design PEDro Sample Size	Methods	Outcomes
McLean Jr. et al. (1991) USA RCT PEDro=5 N=4	**Population:** TBI; Age Range=23-37 yr; Gender: Male=4, Female=0. **Intervention:** Patients were treated in two, 3 wk blocks of oral pramiracetam (400 mg, 2x/d) and placebo over 12wk. **Outcome Measure:** Wechsler Memory Scale (WMS), Selective Reminding Test, Trail Making Test A&B, Finger Tapping Test, Digit Symbol Test, Word Fluency Test.	1. Improvements in immediate and delayed recall in the WMS (logical memory and selecting reminding test) were found for the treatment group. *statistical values not provided in the study

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

Discussion

McLean Jr. et al. (1991) conducted a study evaluating Pramiracetam in four males post brain injury. Improvements were found for memory and these improvements remained at one month following discontinuation of the drug. Given the small sample size and the lack of data reported to support the findings, future studies should be conducted.

Conclusions

There is level 2 evidence that pramiracetam may improve males' memory compared to placebo post TBI.

> **Pramiracetam might improve memory in males post TBI, however, additional studies are required.**

12.16 Sedative Anaesthetic

12.16.1 Propofol

Propofol is a fast-acting sedative that is absorbed and metabolized quickly, leading to pronounced effects of short duration (Adembri et al., 2007). Propofol decreases 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 is characterized by severe metabolic acidosis, rhabdomyolosis, cardiac dysrhythmias, and potential cardiovascular collapse (Corbett et al., 2006).

The AANS reported 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 earlier EBIC recommended sedation as part of the treatment course for ABI but made no specific mention of propofol (Maas et al., 1997).

Table 12.48 Propofol for the Acute Management of ABI

Author Year Country Research Design PEDro Sample Size	Methods	Outcomes
Colton et al. (2014b) USA Case Series N=117	**Population:** TBI; Mean Age=40.0 yr; Gender: Male=93, Female=24; Median GCS=6. **Intervention:** Participants were included in retrospective analysis after having received one of the following ICP therapies: hypertonic saline (HTS), mannitol, propofol, fentanyl, and barbiturates. **Outcome Measure:** Intracranial Pressure (ICP).	1. Treatment with HTS resulted in the largest ICP decrease of the treatments examined. 2. Propofol and fentanyl escalations resulted in smaller but significant ICP reductions. 3. Mannitol resulted in statistically insignificant reductions in the first hr but rebounded by the second hr.
Smith et al. (2009) USA Case Series N=146	**Population:** TBI; GCS Range≤8. **Intervention:** Patients who received propofol and/or vasopressors were included in retrospective analysis. **Outcome Measures:** 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 ($p>0.05$).
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 an intravenous infusion of 1% propofol (2-4 mg/kg/hr). Measurements were obtained for 24 hr. **Outcome Measures:** Intracranial Pressure (ICP), Cerebral Perfusion Pressure (CPP), Mean Arterial Pressure (MAP), Heart Rate (HR), Adverse Outcomes.	1. ICP was significantly reduced at 2 hr (- 2.1 mmHg, $p<0.05$). 2. CPP was significantly increasedat 24 hr (+9.8 mmHg, $p<0.05$). 3. No significant differences were seen in MAP or HR.

Author Year Country Research Design PEDro Sample Size	Methods	Outcomes
		4. Propofol was not associated with any adverse outcomes.
Multimodal Propofol Interventions		
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 4hr. Crossover occurred after 2 hr. **Outcome Measures:** Intracranial Pressure (ICP), Cerebral Perfusion Pressure (CPP).	1. No significant differences in ICP or CPP were found between the propofol and dexmedetomidine groups.
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 (Avg. 10 mg/h). Both groups received additional bolus of MOR (1-3 mg/hr) for at least 48 hr for analgesic purposes. Assessments were made at baseline, days 1, 2, 3, and 4, and at 6 mo. **Outcome Measures:** 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 6 mo, scores were not significantly different between groups for mortality or favourable outcome rates (GOS$\geq$4). 4. In subgroup analysis, PROP was divided into high-dose (100 mg/kg, n=10) and low-dose (<100 mg/kg, n=13) groups. The high-dose group showed higher mean CPP on day 2 (81 mmHg versus 68 mmHg) and lower mean ICP on day 3 (14 mmHg versus 15 mmHg) compared to low-dose ($p>0.05$). 5. High-dose group demonstrated more favourable outcomes in the GOS (70% versus 38.5%) and the DRS (80% versus 46.2%) compared to the low-dose group ($p>0.05$).
Stewart et al. (1994) UK PCT N=15	**Population:** ABI; *Propofol (PROP, n=9)*: Mean Age=30.5 yr; Gender: Male=8, Female=1; Severity of Injury: Moderate=2, Severe=7; *Morphine and Midazolam (M+M, n=6)*: Mean Age=30.5 yr; Gender: Male=6, Female=0; Severity of Injury: Moderate=1, Severe=5. **Intervention:** Patients received sedation with either PROP (150-400 mg/hr) or morphine (0-4 mg/hr) with midazolam (0-5 mg/hr). **Outcome Measures:** Intracranial Pressure (ICP), Cerebral Perfusion Pressure (CPP), Mean Arterial Pressure (MAP), Global Brain Metabolism (AVDO$_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.

Discussion

Propofol was investigated for its beneficial role as an intervention post-ABI. Farling et al. (1989) in a case series of 10 subjects, reported that propofol administration reduced ICP, increased CPP, and was not associated with any adverse outcomes. Overall, this study suggests that propofol is an effective agent at providing safe and effective sedation. Given the retrospective nature and small sample size, results and conclusions drawn from this study should be taken with caution. The effects of propofol in patients with ABI will be further discussed later in the "comparative section" as its efficacy is directly contrasted to other sedatives.

In a retrospective review, Smith et al. (2009) identified three patients with propofol infusion syndrome. The authors noted that each of these patients were receiving both propofol and vasopressors, and that no patient on either propofol or vasopressors alone developed propofol infusion syndrome. Due to lack of a control group and the retrospective nature of the study, care should be taken when interpreting the conclusions reached. However, the evidence suggests that patients receiving both propofol and vasopressors are at the highest risk of developing propofol infusion syndrome, and thus careful monitoring is needed in this patient population.

Three studies comparing the effects of propofol to other sedatives were reviewed. In a crossover RCT, treated patients with ABI with either propofol or dexmedetomidine initially, followed by a crossover halfway through the treatment 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".*

The remaining 2 studies compared propofol to morphine, or a combination of morphine and midazolam. While 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, Kelly et al. (1999) noted propofol was significantly more effective than morphine at reducing ICP - especially at higher doses. With respect to morbidity outcomes, one study reported no difference (Stewart et al., 1994) and the other an increase (Kelly et al., 1999) in favourable outcomes compared to the other treatment. Despite the disagreement in relationship directionality between studies, it can be concluded that propofol is at least as safe to use as morphine alone, or morphine with midazolam.

Conclusions

There is level 4 evidence that propofol may improve intracranial pressure and cerebral perfusion pressure, with no associated adverse outcomes post ABI.

There is level 4 evidence that propofol and vasopressor treatment may increase the risk of developing propofol infusion syndrome post ABI.

There is level 1b evidence that propofol is more effective than morphine at improving favourable outcomes and reducing intracranial pressure post TBI- specially at higher doses.

There is level 2 evidence that propofol is similar to midazolam and morphine with regards to sedation, morbidity, changes in intracranial pressure, cerebral perfusion, and mean arterial pressure post ABI.

There is level 2 evidence that propofol may not differ from dexmedetomidine in its effect on intracranial pressure and cerebral perfusion pressure post ABI.

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Propofol may improve intracranial pressure and cerebral perfusion pressure post ABI, without producing adverse outcomes.

Propofol and vasopressor treatment in combination, but not as monotherapy, might increase the risk of developing propofol infusion syndrome post ABI.

Propofol, especially at higher doses, likely improves favourable outcomes, intracranial pressure and cerebral perfusion pressure more effectively than morphine.

Propofol may be no different than dexmedetomidine or morphine with midazolam in its effect on morbidity outcomes, or intracranial, cerebral perfusion, and mean arterial pressure.

The combination of morphine and midazolam may confound the comparison between propofol and morphine, however, it is prudent to conclude propofol is at least as safe and effective as morphine.

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12.16.2 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).

Table 12.49 Midazolam for the Acute Management of ABI

Author Year Country Research Design PEDro Sample Size	Methods	Outcomes
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 3 mo. **Outcome Measures:** Glasgow Outcome Score (GOS), Mortality, Disability.	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

Author Year Country Research Design PEDro Sample Size	Methods	Outcomes
		severe disability rate between MDZ and PROP groups (20% versus 15%; p=0.8).
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 (0.1-0.35 mg/kg/hr,n=34), propofol at 1.5- 6mg/kg/hr (n=33), or propofol at 0.1-0.2 mg/kg/hr (n=33). All patients received morphine. **Outcome Measures:** Intracranial Pressure (ICP), Cerebral Perfusion Pressure (CPP), Triglyceride levels, Wake-up time, Sedation.	1. No significant differences were found in ICP or CPP among treatment 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 compared to those receiving 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.
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 a restricted maximal dose (Group 1) or with a maximal dose of 5 mg (Group 2). **Outcome Measures:** Systolic Blood Pressure (SBP), Hypotension, Dose.	1. Patients in the Group 1 received significantly higher doses than those in Group 2 (0.106 mg/kg versus 0.059mg/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).
Papazian et al. (1993) France Case Series N=12	**Population:** TBI; Mean Age=28.3 yr; Gender: Male=11, Female=1; Mean GCS=5.2. **Intervention:** Patients received intravenous infusion of 0.15 mg/kg midazolam over a 1min period. **Outcome Measures:** Intracranial Pressure (ICP), Cerebral Perfusion Pressure (CPP), Mean Arterial Pressure (MAP).	1. Significant reductions in MAP (89 mmHg to 75 mmHg, p<0.0001) and CPP (71 mmHg to 55.8 mmHg, p<0.0001) were observed, but not 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).
Multimodal Midazolam Interventions		
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 Measures:** Intracranial Pressure (ICP),	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.

Author Year Country Research Design PEDro Sample Size	Methods	Outcomes
	Cerebral Perfusion Pressure (CPP), Mean Arterial Pressure (MAP), Global Brain Metabolism (AVDO$_2$), Glasgow Outcome Scale (GOS).	

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 1b evidence that midazolam is no different than propofol at improving Glasgow Outcome Scale scores, mortality, or disability in patients post ABI.

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

There is level 4 evidence that high doses of midazolam are associated with decreases in systolic blood pressure and hypotension following intubation in patients post ABI.

There is level 2 evidence that propofol is similar to midazolam and morphine with regards to sedation, morbidity, changes in intracranial pressure, cerebral perfusion, and mean arterial pressure post ABI.

There is level 4 evidence that midazolam has no effect on intracranial pressure but decreases mean arterial pressure and cerebral perfusion pressure post TBI.

Midazolam is likely not different than propofol at improving mortality, disability, or neurological outcomes.

High doses of midazolam might be associated with hypotension, specially following intubation.

Midazolam may have no effect on intracranial pressure but may reduce mean arterial pressure and cerebral perfusion pressure in patients, post-ABI.

> **Propofol may be no different than dexmedetomidine or morphine with midazolam in its effect on morbidity outcomes, or intracranial, cerebral perfusion, and mean arterial pressure.**

12.17 Anti-Inflammatory Medications

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 12.50 Corticosteroids for Acute Management Post ABI

Author Year Country Research Design PEDro Sample Size	Methods	Outcomes
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 post treatment. **Outcome Measure:** Mortality.	1. Compared with the placebo group, the risk of death was higher in the methylprednisolone 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; 1.5mg/kg/6hr for 2 doses, 25 mg/6 hr for 8 doses, then tapered), or placebo (n=16) over 8 days. **Outcome Measures:** 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).
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 intravenous methylprednisolone (250 mg bolus followed by a continuous 125 mg/6 hr infusion) or no drug. **Outcome Measure:** Glasgow Outcome Scale (GOS).	1. At 6mo, no significant difference was seen in proportion of GOS=3-5 compared to GOSE=1-2 between groups (p=0.22).
Oliynyk et al. (2016) Ukraine & Poland Case Series N=267	**Population:** Severe TBI. **Intervention:** Retrospective analysis of patients with sepsis and acute respiratory distress syndrome (ARDS) secondary to severe TBI who were administered Solu-Medrol (methylprednisolone) for 3 days (500 mg/ day), followed by reductions in dosage by one-half every 3 days after. Patients were further analysed based on the type of respiratory support they received to treat their ARDS: controlled volume forced expiration, or Biphasic Positive Airway Pressure [BiPAP]). **Outcome Measure:** Mortality.	1. Patient mortality decreased by 1.24x when BiPAP mechanical ventilation was used compared to volume-controlled forced ventilation (5-7mL/kg) (p=0.01). For the patients who survived, the duration of BiPAP ventilation was 1.32x shorter than forced ventilation with volume control duration. 2. Corticosteroids improved mortality rate with both ventilation systems. For dead patients, corticosteroids prolonged ventilation time (all p<0.01) and for surviving patients, the ventilation period was shortened (both p<0.01).

Author Year Country Research Design PEDro Sample Size	Methods	Outcomes
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/ days on days 1-3, 50 mg/ days 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). After a 100 mg intravenous (IV) dose, Dexamethasone was administered 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, 8 mg, 4 mg IV or IM on day 8 9, and 10, respectively. **Outcome Measures:** Glasgow Outcome Scale (GOS), Mortality.	1. No significant differences were seen in 1mo mortality rates or in 6 mo GOS scores between groups.
[Kaktis & Pitts et al.](#) (1980) USA RCT PEDro=4 N=115	**Population:** ABI. **Intervention:** Patients were randomized to receive one of "mega dose" dexamethasone (50 mg, then 25 mg/ 6hr), conventional dose dexamethasone (10 mg, then 4 mg/6 hr) or saline placebo for a maximum of 7 days or until awakening. **Outcome Measures:** 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 N=76	**Population**: TBI; Mean Age=25.6 yr; Gender: Male=59, Female=17; Mean GCS=5.23. **Intervention:** Patients were randomized to receive one of low-dose dexamethasone (n=25; 10 mg 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 Measures:** Intracranial Pressure (ICP),	1. No significant difference was seen between groups in terms of ICP or 6 mos GOS score.

Author Year Country Research Design PEDro Sample Size	Methods	Outcomes
	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 Measures:** Incidence of Post-Traumatic Seizures (PTS).	1. One hundred and five patients received glucocorticoids within 1 day of their injury, and 20 received them ≥2 days. 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

Two studies assessed methylprednisolone in ABI management. The studies reported either no difference in morbidity (Giannotta et al., 1984; Saul et al., 1981), or a decrease in mortality (Giannotta et al., 1984) when compared to controls. It is important to note that the decrease in mortality in the study by Giannotta et al. was only observed in patients under 40 years of age receiving high dose methylprednisolone, and not any other group. In light of a series of inconclusive studies concerning 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). The study never reached its conclusion and was stopped early due to increased mortality in the methylprednisolone group. A relative mortality risk of 1.8 (P=0.0001) was reported in the treatment group and as a result the authors suggest that corticosteroids should not be used for the treatment of ABI regardless of injury severity, or refractoriness to first line treatments. Despite the recommendations put forth by this study, a group

analyzed the effects of Solu-Medrol (methylprednisolone) in patients with ARDS secondary to sepsis post ABI (Oliynyk et al., 2016). It was found that both the type of mechanical ventilation received (BiPAP) and methylprednisolone reduced mortality rates in the patient population. The findings of this study suggest that while methylprednisolone is contraindicated as a first line ABI treatment, it might be effective in improving specific complications that develop post-ABI. In light of the overwhelming evidence warning against methylprednisolone use however, extreme caution should be applied when trying to interpret this finding outside of the specific setting in which it was studied.

Four RCTs were found that assessed dexamethasone in ABI. While one study reported no difference in morbidity or mortality (Braakman et al., 1983), other studies reported non-significant decreases in morbidity (Dearden et al., 1986) and an increase in dose-specific complications such a CSF infections, SIADH, and hyperglycemia (Kaktis & Pitts, 1980) when compared to placebo. Lastly, Cooper et al. (1979) compared doses of dexamethasone and their effects on lowering ICP and neurological outcomes (GOS). They found that regardless of the dose of dexamethasone received (low or high), there were no significant differences in ICP or neurological outcomes at 6 months between groups. Given the results of this study, and the guideline reccomendations against the use of corticosteroids for ICP management, corticosteroids may not be effective agents in lowering ICP post ABI.

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 to patients treated without corticosteroids for the risk of development of post-traumatic seizures (PTS). The researchers 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 treatment. There was no increased risk of PTS in patients receiving treatment after the first day. The authors suggest that this adds further strength to the argument against routine corticosteroid use in TBI (Watson et al., 2004).

Grumme et al. (1995) conducted a RCT in which GOS scores were assessed one year after injury in patients treated with the synthetic corticosteroid triamcinolone. While no overall effect was found between groups, 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 conflicting (level 1b) evidence that methylprednisolone increases mortality rates compared to placebo in individuals post ABI. The largest trial strongly recommends against its use due to increased mortality.

There is level 1b evidence that high (60 mg loading dose, 24 mg every 6 hr) and low (10 mg loading dose, 4 mg every 6 hr) dose dexamethasone are the same as placebo at improving intracranial pressure, and neurological outcomes (6 mo) post TBI.

There is conflicting (level 2) evidence that dexamethasone increases mortality and the rate of complications (hyperglycemia, cerebral spinal fluid infections) when compared to placebo post ABI.

There is level 1b evidence that triamcinolone may improve outcomes compared to placebo in individuals post ABI with a Glasgow Coma Scale score less than 8 and a focal lesion.

There is level 2 evidence that glucocorticoid administration on the first day post-injury may increase the risk of developing first late seizures compared to placebo.

There is level 4 evidence that methylprednisolone improves mortality rates in patients with acute respiratory distress syndrome secondary to sepsis post ABI.

> **Corticosteriods such as methylprednisolone, dexamethasone, and other glucocorticoids may worsen outcomes, and should not be used. However, methylprednisolone may be effective at improving mortality when specific complications, such as acute respiratory distress syndrome secondary to sepsis, arise.**
>
> **Triamcinolone may improve outcomes in individuals post ABI with a Glasgow Coma Scale score less than 8 and a focal lesion.**

12.17.2 Bradykinin Antagonists

Any type of tissue injury or cell death following brain injury acts as a strong stimulus for initiation of an inflammatory response. An important player in the acute inflammatory cascade is the kinin-kallikrein pathway; a pathway which generates the compound bradykinin. (Marmarou et al., 1999; Narotam et al., 1998). The binding of bradykinin to its BK_2 receptor leads to a cascade of events, ultimately yielding altered vascular permeability and tissue edema (Francel, 1992). Upregulation of kinins following blunt trauma has been reported, emphasizing their importance in the pathophysiology of brain injury (Hellal et al., 2003). Animal research using BK_2 receptor knockout mice has demonstrated direct involvement of this receptor in the development of the inflammatory-induced secondary damage and subsequent neurological deficits resulting from diffuse TBI (Hellal et al., 2003). These findings strongly suggest that specific inhibition of the BK_2 receptor could prove to be an effective therapeutic strategy following brain injury.

Bradycor is a bradykinin antagonist that acts primarily at the BK_2 receptor (Marmarou et al., 1999; Narotam et al., 1998), making it attractive for the management of post-ABI inflammation. Anatibant is another BK_2 receptor antagonist that is believed to more strongly bind the BK_2 receptor compared to Bradycor (Marmarou et al., 2005).   Animal research has suggested that Anatibant dampens acute inflammation, reduces brain edema, and improves long-term neurological function (Hellal et al., 2003; Kaplanski et al., 2002; Pruneau et al., 1999; Stover et al., 2000).

The AANS and EBIC made no recommendations regarding bradykinin antagonists in acute ABI.

Table 12.51 Bradycor for the Acute Management of Intracranial Pressure Post ABI

Author Year Country Research Design PEDro Sample Size	Methods	Outcomes
Anatibant		
Shakur et al. (2009) UK RCT PEDro=9 N=228	**Population:** TBI; Mean Age=36 yr; Gender: Male=203, Female=25; Mean Time Post Injury=6 hr; Mean GCS=8. **Intervention:** Patients were randomized to receive placebo (n=57), high-dose Anatibant (n=57; 15mg/dY), medium-dose Anantibant (n=56; 10 mg/day) or low-dose Anantibant (n=58; 5 mg/day). Maintenance doses were administered for 4 days. Outcomes were assessed at 2 wk post injury. **Outcome Measures:** Glasgow Coma Scale (GCS), Disability Rating Scale (DRS), Modified Oxford Handicap Scale (HIREOS), Serious Adverse Event (SAE), Mortality.	1. The trial was ended early due to concerns with patient safety. 2. Mortality was slightly higher in patients treated with Anatibant than those with placebo (19.0% versus 15.8%), but the risk was not significant (RR=1.20, p=0.38). 3. There was a greater proportion of SAEs in patients treated with Anatibant than those with placebo (26.4% versus 19.3%), but the risk was not significant (RR=1.37, p=0.19). 4. Mean GCS was higher in the Anatibant group than the placebo group, but the difference was not significant (12.48 versus 9.73, δ=-0.55, p>0.05).

Author Year Country Research Design PEDro Sample Size	Methods	Outcomes
		5. Mean DRS was higher in the Anatibant group than the placebo group, but the difference was not significant (11.18 versus 9.73, δ=1.61, p>0.05).
		6. Mean HIREOS was slightly higher in the Anatibant group than the placebo group, but the difference was not significant (3.94 versus 3.54, δ=0.42, p>0.05).
Marmarou et al. (2005) USA RCT PEDro=4 N=25	**Population:** TBI; GCS Range≤8. *Low Dose (n=10):* Mean Age=31.2 yr; Gender: Male=9, Female=1; Mean Time Post Injury=10.6 hr. *High Dose (n=10):* Mean Age=39.1 yr; Gender: Male=9, Female=1; Mean Time Post Injury=11.3 hr. *Placebo (n=4):* Mean Age=33.5 yr; Gender: Male=2, Female=2; Mean Time Post Injury=8.2 hr. **Intervention:** Participants were randomized to receive placebo, low-dose Anatibant (3.75 mg), or high dose Anatibant (22.5 mg). Monitoring occurred for 5 days and outcomes were assessed at 1 mo, 3 mo, and 6 mo. **Outcome Measures:** Intracranial Pressure (ICP), Cerebral Perfusion Pressure (CPP), Glasgow Outcome Scale (GOS).	1. A greater proportion of patients treated with high dose Anatibant showed favourable outcomes on GOS at 3 mo and 6 mo than those with low dose or placebo. 2. Given small sample size and heterogeneity between groups, conclusions could not be drawn regarding ICP or CPP.
Marmarou et al. (1999) USA RCT PEDro=8 N=136	**Population:** TBI; *Bradycor (n=66):* Mean Age=30 yr; Gender: Male=47, Female=19; Mean Time Post Injury=10 hr; Mean GCS=6.0. *Placebo (n=67):* Mean Age=34 yr; Gender: Male=55, Female=12; Mean Time Post Injury=10 hr; Mean GCS=6.1. **Intervention:** Participants were randomized to receive continuous intravenous infusion of either Bradycor (3.0 µg/kg/min) or placebo for 5 days. Monitoring occurred for 5 days and outcomes were assessed at 3 mo and 6 mo. **Outcome Measures:** Intracranial Pressure (ICP), Glasgow Outcome Scale (GOS), Therapeutic Intensity Levels (TIC), Mortality.	1. Percentage of time ICP>15 mmHg on 4-5 days was significantly lower in the Bradycor group compared with placebo (p=0.035). 2. There were fewer deaths in the Bradycor group than placebo (20% versus 27%). 3. The Bradycor group showed a 10.3% and 12% improvement in GOS at 3mo and 6mo respectively (p=0.26). 4. The Bradycor group had significantly lower TIC than placebo (p<0.05).
Narotam et al. (1998) South Africa RCT PEDro=6 N=20	**Population:** TBI; Time Post-Injury=24-96 hr; GCS Range=9-14. **Intervention:** Participants were randomized to receive continuous intravenous infusion of Bradycor (3.0 µg/kg/min) or placebo for 7 days. **Outcome Measures:** Intracranial Pressure (ICP), Glasgow Coma Scale (GCS), Therapeutic Intensity Levels (TIL).	1. Bradycor group had a longer interval from time of injury to initiation of drug infusion (p=0.027). 2. The mean increase in peak ICP from baseline was greater in the placebo group than Bradycor group (21.9 mmHg versus 9.5 mmHg, p=0.018).

Author Year Country Research Design PEDro Sample Size	Methods	Outcomes
		3. The mean reduction in GCS score in the placebo group was significantly greater than in the Bradycor group (4 versus 0.6, p=0.002). 4. Bradycor had a significant effect in preventing elevation of ICP>20 mmHg compared to placebo (91% versus 78%, p=0.005). 5. Braydcor group had significantly lower TIL than placebo (p<0.05).

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

Discussion

Shakur et al. (2009) conducted a large-scale multicenter trial of Anatibant. The authors reported a non-significant elevated risk of serious adverse events among patients receiving the medication, without improvements in morbidity (DRS, GCS) or mortality. As such, the trial was terminated early on by the investigators, leading to a legal dispute with its sponsors.

Anatibant is believed to be a more potent bradykinin antagonist than Bradycor, and was evaluated by Marmarou et al. (2005) to study its effects on ICP and morbidity outcomes. Due to a small sample size and lack of baseline comparability between groups, the authors were unable to draw any significant conclusions regarding the efficacy of Anatibant in preventing brain edema or deteriorations in ICP and CPP. However, patients who received a higher dose of the medication had more favourable outcomes on the GOS at three months and six months when compared to a lower dose and placebo.

Two trials evaluated the efficacy of Bradycor in the acute treatment of ABI. Both trials reported that treatment with Bradycor resulted in a significant reduction in ICP elevations when compared to placebo - as indicated by the time spent under intracranial hypertension (Narotam et al., 1998). In the smaller of the two trials, Narotam et al. (1998) found that patients in the placebo group experienced a greater deterioration in GCS scores over the course of the study. These findings were not replicated in Marmarou et al., as the researchers reported no significant differences between groups in mortality rates, improvements in GOS scores at three months and six months, or the intensity of additional therapeutic interventions needed to control ICP.

Conclusions

There is level 1b evidence that Anatibant, regardless of dose, has no effect on serious adverse events, mortality, Glasgow Coma Scale, Modified Oxford Handicap Scale, or Disability Rating Scale scores in individuals post ABI.

There is level 2 evidence that high-dose anatibant is superior to low-dose anatibant and placebo at improving Glasgow outcome scale scores at 3 and 6 mos post TBI.

There is level 1a evidence that Bradycor is effective at preventing acute elevations intracranial pressure and reducing therapeutic intensity levels post ABI when compared to placebo.

There is conflicting (level 1b) evidence that Bradycor improves mortality and Glasgow outcome scale scores in patients post ABI.

Anatibant, regardless of dose, likely does not cause serious adverse events, affect morbidity, mortality or disability in patients post ABI.

It is unclear if a higher dose of anatibant is superior to a lower dose at improving intracranial pressure, however it may improve functional outcomes up to 6 months post injury.

Bradycor can prevent acute elevations in intracranial pressure and reduce therapeutic intensity levels post ABI; however, its effect on morbidity and mortality outcomes is not clear.

12.18 Dimethyl Sulfoxide

Dimethyl Sulfoxide (DMSO) is an organic sulfur-containing compound that has been shown to stabilize cell membranes, protect cells from mechanical damage and reduce edema in tissue (Kulah et al., 1990). Furthermore, DMSO is believed to act as an antioxidant and has been credited with the ability to increase tissue perfusion, neutralize metabolic acidosis, and to decrease intracellular fluid retention (Kulah et al., 1990). As a result, DMSO has been suggested for the treatment of elevated ICP following ABI.

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

Table 12.52 Dimethyl Sulfoxide for the Acute Management of Intracranial Pressure Post ABI

Author Year Country Research Design PEDro Sample Size	Methods	Outcomes
Karaca et al. (1991) Turkey & Canada Case Series N=10	**Population:** TBI; Mean GCS=6. **Intervention:** Patients received intravenous infusion of 28% DMSO (1.2 g/kg), every 6 hr for 1-10 days. Monitoring occurred for 10 days and outcomes were assessed at 6 days and 3 mo. **Outcome Measures:** Intracranial Pressure (ICP), Neurological assessment.	1. All patients showed a reduction in ICP after 24 hr and 7 had normal ICP after 6 days. 2. Reductions in ICP were seen within the first 30 min, however the effect was not sustained and most patients required

Author Year Country Research Design PEDro Sample Size	Methods	Outcomes
		maintenance doses for 2-10 days to minimize fluctuations in ICP. 3. Neurological assessment at 6d days showed 2 patients with severe neurological deficits, 2 with moderate impairments, and 6 patients with mild to no deficit. 4. At 3 mo, 1 patient remained severely impaired and 7 patients showed mild to no deficit.
Kulah et al. (1990) Turkey Case Series N=10	**Population:** TBI; Mean Time Post Injury=6hr; GCS Range≤6. **Intervention:** Patients received intravenous infusion of DMSO up to 7 days. **Outcome Measures:** Intracranial Pressure (ICP), Cerebral Perfusion Pressure (CPP), Mean Arterial Pressure (MAP).	1. Three patients died due to uncontrolled ICP. 2. In most cases DMSO reduced ICP within 10min with a parallel increase CPP, but had no effect on MAP. 3. DMSO caused only a temporary decrease in ICP, as continuous infusions did not prevent the ICP from returning to elevated baseline levels.
Marshall et al. (1984) USA Case Series N=5	**Population:** ABI; GCS<7. **Intervention:** Patients received rapid intravenous infusion of 10% or 20% DMSO at a dose of 1 g/kg, with an upper dose limit of 8 g/kg/day. **Outcome Measures:** Intracranial Pressure (ICP), Complications.	1. All patients showed satisfactory control of elevated ICP (ICP<25 mmHg, >15 min) within min (2-24 min). 2. Despite initial improvements in ICP, an ultimate loss of ICP control occurred. 3. Most patients experienced significant hypernatremia as a side effect.

Discussion

Three studies have examined the effects of DMSO in the management of ICP post ABI. In a study by Kulah et al. (1990), the authors reported that in the majority of cases DMSO was effective in controlling ICP elevations within minutes of injection, which was followed by a concomitant increase in CPP. However, continuous infusions of DMSO for up to seven days failed to control elevations in ICP and values returned to baseline. In a similar study conducted by Karaca et al. (1991), patients were treated with repeated injections of DMSO for up to 10 days. Although reductions in ICP were observed within the first 30 minutes after administration, the effect was not sustained and most patients required maintenance doses to minimize fluctuations in ICP. The results from both of these retrospective studies suggest that DMSO may acutely reduce ICP, however it is not an appropriate agent when attempting to maintain long-term ICP control.

Marshall et al. (1984) observed the effects of using DMSO on patients with ABI. Originally, patients received 10% DMSO and temporary ICP decreases were observed; however, ICP quickly returned to baseline (2-24 min) and electrolyte disbalances such as hypernatremia were observed. Subsequently, the remaining patients received 20% DMSO and while ICP reduction was maintained longer, electrolyte imbalances continued to develop despite close patient monitoring.

Conclusions

There is level 4 evidence that dimethyl sulfoxide temporarily reduces intracranial pressure elevations, and increases cerebral perfusion pressure post ABI.

There is level 4 evidence that increasing concentrations of DMSO provide longer intracranial pressure reduction, but are accompanied by an increase in electrolyte imbalances post ABI.

Dimethyl sulfoxide may cause temporary improvements in intracranial pressure and cerebral perfusion pressure post ABI, however these improvements may not be sustained long-term.

DMSO might be able to transiently lower intracranial pressure; however, it is associated with the development of electrolyte imbalances. Both responses appear to be dose-dependent.

12.19 Summary

There is conflicting (level 1a and level 2) evidence as to whether fentanyl, morphine, or sufentanil increase intracranial pressure, and decrease cerebral perfusion pressure post ABI. The level 1a evidence suggests that it increases intracranial pressure and decreases cerebral perfusion pressure.

There is level 1b evidence that propofol is more effective than morphine at improving favourable outcomes and reducing intracranial pressure post TBI- specially at higher doses.

There is level 2 evidence that alfentanil may result in a decrease in cerebral perfusion pressure and mean arterial pressure, and a transient increase in intracranial pressure, post ABI compared to controls.

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

There is level 2 evidence that propofol is similar to midazolam and morphine with regards to sedation, morbidity, changes in intracranial pressure, cerebral perfusion, and mean arterial pressure post ABI.

There is level 4 evidence that remifentanil may not improve intracranial pressure, cerebral perfusion pressure, mean arterial pressure, or cerebral blood flow velocity post ABI.

There is level 4 evidence that sufentanil may decrease mean arterial pressure, cerebral perfusion pressure, and heart rate post ABI.

There is level 4 evidence that sufentanil may transiently increases intracranial pressure post ABI.

There is level 4 evidence that sufentanil may increase intracranial pressure in patients with low mean arterial pressure post ABI.

There is level 4 evidence that sufentanil with midazolam decreases intracranial pressure and mean arterial pressure for 2 days 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 that phenytoin is effective in reducing the rate of only early onset post-traumatic seizures in patients with TBI.

There is conflicting evidence regarding whether or not phenytoin is effective in preventing post-traumatic seizure disorder long term compared to placebo treatment in patients with TBI.

There is level 1a evidence that valproate is not more effective as a prophylactic anti-seizure medication compared to phenytoin in ABI populations.

There is level 1b evidence that levetiracetam and phenytoin do not show significant differences between them as prophylactic anti-seizure medication for individuals with ABI.

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 lamotrigine may reduce inappropriate behaviours post TBI.

There is level 4 evidence that cerebrolysin may improve attention scores post ABI.

There is conflicting level 1b (positive) and level 2 (negative) evidence that donepezil may improve attention compared to placebo post ABI.

There is level 1b evidence that oral physostigmine may improve long-term memory compared to placebo in men with TBI, however more recent studies are required.

There is level 1b evidence that Rivastigmine compared to placebo is not effective for improving concentration or processing speed in post ABI individualsbut may increase vigilance.

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 that quetiapine may reduce aggressive behaviour.

There is level 4 evidence that ziprasidone may reduce agitation post TBI.

There is level 4 evidence that haloperidol may not be effective in treating behavioral disorders post TBI.

There is level 4 evidence that methotrimeprazine may be effective for controlling agitation post ABI.

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 1b evidence that bolus intrathecal baclofen injections may produce short-term (up to six hours) reductions in upper and lower extremity spasticity compared to placebo 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 conflicting level 4 evidence to suggest that intrathecal baclofen may result in short-term improvement of walking performance in ambulatory patients, particularly gait velocity, stride length, and step width, in individuals post ABI.

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 level 2 evidence that thiopental is more effective than pentobarbital for controlling elevated intracranial pressure refractory to conventional treatment, and less likely to induce adrenal insufficiency post ABI.

There is level 2 evidence that thiopental in combination with mild hypothermia has better one-year clinical outcomes compared to conventional management post ABI.

There is level 3 evidence that thiopental induces leukopenia and granulocytopenia in patients post ABI.

There is level 4 evidence that thiopental decreases intracranial pressure, cerebral perfusion pressure, and mean arterial pressure post ABI.

There is conflicting (level 1b and level 2) evidence regarding whether or not pentobarbital improves intracranial pressure compared to conventional management measures post ABI. Level 1b evidence suggests there is no difference.

There is level 2 evidence that barbiturate use is associated with development of hypotension in patients post ABI.

There is level 2 evidence that pentobarbital decreases energy expenditure, total urinary nitrogen excretion, improves nitrogen balance, but has no effect on 3-methylhistidine excretion compared to controls in individuals with an ABI refractory to standard therapy.

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 high-dose KN38-7271 (a dual cannabinoid agonist) may improve intracranial pressure and cerebral perfusion pressure, and improves survival post TBI compared to low-dose KN38-7271.

There is level 1b evidence that pindolol may reduce aggression compared to placebo post ABI.

There is level 1b evidence that propranolol compared to placebo reduces the intensity of agitated symptoms post ABI.

There is conflicting evidence (level 1b) that propranolol compared to placebo reduces the frequency of aggressive behaviour post ABI.

There is level 3 evidence that prophylactic anticoagulation is more effective than placebo in reducing the risk of developing deep vein thrombosis in patients post ABI.

There is level 2 evidence that the administration of enoxaparin within the first 72 hours post ABI reduces the risk of developing deep vein thrombosis and pulmonary embolism post injury compared to unfractionated heparin.

There is level 4 evidence that administering enoxaparin or heparin post ABI does not increase the risk of intracranial bleeding compared to no treatment.

There is level 1a evidence that hypertonic saline is similar to mannitol in terms of mortality or Glasgow outcome scale (extended) scores in patients post TBI.

There is conflicting (level 1b) evidence as to whether hypertonic solution lowers elevated intracranial pressure more effectively than mannitol post ABI.

There is conflicting (level 2 and level 3) evidence that hypertonic saline lowers intracranial pressure for longer compared to mannitol post ABI. The level 2 evidence suggest that it does.

There is level 2 evidence that hypertonic saline is superior to mannitol at improving cerebral perfusion pressure, cerebral blood flow, and blood-glucose control in patients post ABI.

There is level 2 evidence that urinary sodium excretion is higher in hypertonic saline patients compared to those receiving mannitol post ABI.

There is level 4 evidence that hypertonic saline is superior to barbiturates, propofol, and fentanyl at lowering intracranial pressure post ABI.

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

There is level 4 evidence that mannitol may be effective in increasing cerebral perfusion pressure post ABI.

There is level 4 evidence that mannitol may only improve intracranial pressure and cerebral perfusion pressure post ABI in hypertensive patients (Intracranial pressure>20mmHg).

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

There is level 3 evidence that amantadine treatment does not improve emergence from coma compared to control in patients post ABI.

There is level 3 evidence that amantadine is superior to standard care at improving consciousness in patients in a coma post ABI.

There is level 1b evidence that amantadine is not effective for improving attention compared to placebo following an ABI.

There is level 1b evidence that Amantadine may not help to improve general functioning deficits in patients with TBI compared to placebo.

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

There is level 1b evidence that amantadine compared to placebo may reduce aggression post TBI in individuals with moderate to severe aggression.

There is conflicting (level 1b) evidence as to whether amantadine reduces irritability compared to placebo post TBI.

There is conflicting evidence as to whether bromocriptine improves performance on attention tasks compared to placebo in patients post TBI.

There is level 1b evidence that (-)-OSU6162 may not be effective for treating fatigue compared to placebo in patients with TBI.

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

There is level 1a evidence that progesterone treatment is no better than placebo at improving Glasgow outcome scale scores at 3 and 6 mo post TBI.

There is level 1b evidence that progesterone is superior to placebo at improving Glasgow outcome scale scores in patients with an initial Glasgow coma scale score $\geq$5 post TBI.

There is level 1b evidence that progesterone treatment may be associated with adverse events such as phlebitis and thrombophlebitis.

There is level 1a evidence that progesterone does not improve intracranial pressure compared to placebo post ABI.

There is level 1a evidence that progesterone improves mortality and Glasgow outcome scale scores compared to placebo in patients post ABI.

There is level 1b evidence that growth hormone replacement therapy may improve clinical outcomes compared to placebo in patients with GHD post ABI.

There is level 1b evidence that recombinant human Growth Hormone (rhGH) is superior to placebo at improving processing speed (6 mo), executive function and learning in patients post TBI.

There is level 2 evidence that growth hormone (GH) therapy is effective for improving quality of life, instrumental activities of daily living (iADL), attention, memory, and visuospatial ability in patients post TBI.

There is level 2 evidence that recombinant human Growth Hormone (rhGH) administration improves intelligence and other cognitive subtests in TBI patients with growth hormone deficiency compared to TBI patients without; however, insulin-like growth factor-1 (IGF-1) levels may be the same between groups.

There is level 4 evidence that growth hormone replacement therapy may be effective in treating GHD, fatigue, and depression post ABI.

There is level 1b evidence that melatonin treatment may be effective in improving sleep quality, sleep efficiency, and fatigue compared to a placebo group in patients post TBI.

There is level 1b evidence that melatonin treatment may not effect sleep onset latency or daytime sleepiness in patients post TBI.

There is conflicting level 1a evidence regarding the effectiveness of methylphenidate following brain injury for the improvement of attention and concentration in individuals post ABI.

There is level 1a evidence that methylphenidate improves reaction time of working memory compared to placebo in individuals post ABI.

There is level 1b evidence that individuals carrying the Met allele may be more responsive to methylphenidate than those without the Met allele when it comes to the ABI population.

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.

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 dextroamphetamine is not effective for the remediation of general cognitive functioning following an ABI.

There is level 2 evidence that pramiracetam may improve males' memory compared to placebo post TBI.

There is level 4 evidence that propofol may improve intracranial pressure and cerebral perfusion pressure, with no associated adverse outcomes post ABI.

There is level 4 evidence that propofol and vasopressor treatment may increase the risk of developing propofol infusion syndrome post ABI.

There is level 1b evidence that propofol is more effective than morphine at improving favourable outcomes and reducing intracranial pressure post TBI- specially at higher doses.

There is level 2 evidence that propofol is similar to midazolam and morphine with regards to sedation, morbidity, changes in intracranial pressure, cerebral perfusion, and mean arterial pressure post ABI.

There is level 2 evidence that propofol may not differ from dexmedetomidine in its effect on intracranial pressure and cerebral perfusion pressure post ABI.

There is level 1b evidence that midazolam is no different than propofol at improving Glasgow Outcome Scale scores, mortality, or disability in patients post ABI.

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

There is level 4 evidence that high doses of midazolam are associated with decreases in systolic blood pressure and hypotension following intubation in patients post ABI.

There is level 2 evidence that propofol is similar to midazolam and morphine with regards to sedation, morbidity, changes in intracranial pressure, cerebral perfusion, and mean arterial pressure post ABI.

There is level 4 evidence that midazolam has no effect on intracranial pressure but decreases mean arterial pressure and cerebral perfusion pressure post TBI.

There is conflicting (level 1b) evidence that methylprednisolone increases mortality rates compared to placebo in individuals post ABI. The largest trial strongly recommends against its use due to increased mortality.

There is level 1b evidence that high (60 mg loading dose, 24 mg every 6 hr) and low (10 mg loading dose, 4 mg every 6 hr) dose dexamethasone are the same as placebo at improving intracranial pressure, and neurological outcomes (6 mo) post TBI.

There is conflicting (level 2) evidence that dexamethasone increases mortality and the rate of complications (hyperglycemia, cerebral spinal fluid infections) when compared to placebo post ABI.

There is level 1b evidence that triamcinolone may improve outcomes compared to placebo in individuals post ABI with a Glasgow Coma Scale score less than 8 and a focal lesion.

There is level 2 evidence that glucocorticoid administration on the first day post-injury may increase the risk of developing first late seizures compared to placebo.

There is level 4 evidence that methylprednisolone improves mortality rates in patients with acute respiratory distress syndrome secondary to sepsis post ABI.

There is level 1b evidence that Anatibant, regardless of dose, has no effect on serious adverse events, mortality, Glasgow Coma Scale, Modified Oxford Handicap Scale, or Disability Rating Scale scores in individuals post ABI.

There is level 2 evidence that high-dose anatibant is superior to low-dose anatibant and placebo at improving Glasgow outcome scale scores at 3 and 6 mos post TBI.

There is level 1a evidence that Bradycor is effective at preventing acute elevations intracranial pressure and reducing therapeutic intensity levels post ABI when compared to placebo.

There is conflicting (level 1b) evidence that Bradycor improves mortality and Glasgow outcome scale scores in patients post ABI.

There is level 4 evidence that dimethyl sulfoxide temporarily reduces intracranial pressure elevations, and increases cerebral perfusion pressure post ABI.

There is level 4 evidence that increasing concentrations of DMSO provide longer intracranial pressure reduction, but are accompanied by an increase in electrolyte imbalances post ABI.

12.20 References

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