12. Neuropharmacological Interventions Post ABI

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**Key Points**

*Bolus opioid administration results in increased intracranial pressure (ICP).*

*There is conflicting evidence regarding the effects of opioid infusion on ICP.*

*Remifentanil results in faster arousal compared to hypnotic based sedation.*

*Neither carbamazepine nor phenytoin has a positive effect on cognitive performance.*

*Carbamazepine improves seizure control and helps in the reduction of aggression following brain injury.*

*Intramuscular midazolam may be effective for acute seizure cessation.*

*Phenytoin provided immediately post-ABI reduced the occurrence of seizures only within the first week.*

*Phenobarbital has not been shown to be effective in reducing the risk of late seizure development post ABI.*

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

*Lamotrigine may be successful in reducing inappropriate behaviours post TBI.*

*Cerebrolysin may be beneficial for the improvement of cognitive functioning following brain injury.*

*Donepezil helps to improve attention, short-term and long term memory following brain injury.*

*Physostigmine improves memory in men with brain injury, but not attention, concentration, motor speed, or cognitive flexibility.*

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

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

*Desipramine may be effective in improving mood and reducing depression.*

*Sertraline HCL and amitriptyline may be used to decrease aggressive behaviour.*
Lithium may reduce behavioural problems but is associated with neurotoxicity.

Although there is evidence to suggest that quetiapine does help reduce aggressive behavior more research is needed.

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

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

Droperidol may be an effective agent for calming agitated patients.

Phenol blocks of the musculoskeletal nerve may help decrease spasticity and improve range of motion temporarily up to 5 months post injection.

Oral baclofen appears to improve lower extremity spasticity.

Oral tizanidine is effective for improving upper and lower extremity spasticity.

Botulinum toxin type A injections reduces localized spasticity following ABI.

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

Prolonged intrathecal baclofen reduces upper and lower extremity spasticity post ABI.

Intrathecal baclofen may cause short-term improvements in walking performance.

There are conflicting reports regarding the efficacy of pentobarbital for the control of elevated ICP.

There is no difference between thiopental and pentobarbital in the control of elevated ICP.

Pentobarbital is not better than mannitol for the control of elevated ICP.

Barbiturate therapy plus hypothermia may improve clinical outcomes.

Patients undergoing barbiturate therapy should have their immunological response and systemic blood pressure monitored.

Etridonate prevents the development of heterotopic ossification in brain injuries.

Dexanabinol is not effective in controlling ICP or in improving clinical outcomes post ABI.
<table>
<thead>
<tr>
<th>Medicine</th>
<th>Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pindolol</td>
<td>Decreases aggressive behaviour following brain injury.</td>
</tr>
<tr>
<td>Propranolol</td>
<td>May reduce aggressive and agitated symptoms following brain injury.</td>
</tr>
<tr>
<td>Sodium lactate</td>
<td>Is more effective than mannitol for reducing acute elevations in ICP.</td>
</tr>
<tr>
<td>High dose mannitol</td>
<td>Results in lower mortality rates and better clinical outcomes compared with conventional mannitol.</td>
</tr>
<tr>
<td>Early out of hospital administration of mannitol</td>
<td>Does not negatively affect blood pressure.</td>
</tr>
<tr>
<td>Mannitol</td>
<td>May only lower ICP when initial ICP values are abnormally elevated.</td>
</tr>
<tr>
<td>Amantadine</td>
<td>May improve consciousness and cognitive function in comatose ABI patients.</td>
</tr>
<tr>
<td>Amantadine</td>
<td>May be an effective treatment to improve executive function following brain injury but it has not been shown to improve learning and memory.</td>
</tr>
<tr>
<td>Amantadine</td>
<td>May not be an effective treatment for behaviour following brain injury.</td>
</tr>
<tr>
<td>Dopamine</td>
<td>Enhancing drugs may facilitate rate of recovery post traumatic brain injury in children.</td>
</tr>
<tr>
<td>Bromocriptine</td>
<td>Improves some executive cognitive functions such as dual-task performance and motivational deficits, but it does not consistently improve memory. More research is needed before the benefits of using bromocriptine to enhance cognitive functioning are known.</td>
</tr>
<tr>
<td>Administration of dexamethasone</td>
<td>Inhibits endogenous production of glucocorticoids in children.</td>
</tr>
<tr>
<td>Dexamethasone administration</td>
<td>Has no proven impact on recovery post brain injury in children.</td>
</tr>
<tr>
<td>Medroxyprogesterone</td>
<td>Intramuscularly can reduce sexual aggression.</td>
</tr>
<tr>
<td>Progesterone</td>
<td>Decreases 30-day mortality rates.</td>
</tr>
<tr>
<td>Progesterone</td>
<td>Improves GOS and modified FIM scores at 3 and 6 months post-injury.</td>
</tr>
</tbody>
</table>
The effectiveness of methylphenidate treatment to improve cognitive impairment following brain injury is unclear.

Methylphenidate does not improve the sleep-wake cycle of those who have sustained a TBI.

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

Modafinil has not been shown to be effective in treating fatigue or excessive daytime sleepiness post ABI.

Propofol may help to reduce ICP and the need for other ICP and sedative interventions when used in conjunction with morphine.

Both lorazepam and zopiclone are effective in assisting with insomnia symptoms post ABI.

Midazolam has no effect on ICP but may result in systemic hypotension.

Intramuscular midazolam may be effective for acute seizure cessation.

Methylprednisolone increases mortality rates in ABI patients and should not be used.

Triamcinolone may improve outcomes in patients with a GCS<8 and a focal lesion.

Dexamethasone does not improve ICP levels and may worsen outcomes in patients with ICP > 20mmHg.

Glucocorticoid administration may increase the risk of developing first late seizures.
12. Neuropharmacology

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 cell 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-hydroxytryptamine or 5HT), 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 5HT 1a, b, and c, 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, not reuptake 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 norepinephrine tend to stimulate target receptors. Dopamine has diffuse effects on the Central Nervous System and is involved with motor control, arousal, procedural learning, and cognition. There are at least five dopamine receptor variants and abnormalities. The D2 variant is implicated in Parkinson’s disease and the D4 variant in Schizophrenia. Norepinephrine’s effects 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. Included are the psychopharmacological therapies described in the various modules of ERABI.
12.1 Analgesics

12.1.1 Opioids

Opioids are substances that have morphine-like actions. They work by binding to opioid receptors, found principally in the central nervous system and the gastrointestinal tract. Each opioid has a distinct binding affinity to group(s) of opioid receptors that then determines its pharmacodynamic response. Morphine has been the most commonly used opioid following ABI, while fentanyl and its derivatives have gained popularity owing to their more rapid onset and shorter duration of effect (Metz et al., 2000). Controversy persists regarding the effect of opioids on ICP and CPP. It has been reported that opioids can increase cerebral blood flow (CBF), which may lead to an increase in ICP, (Marx et al., 1989; de nadal et al., 2000; Werner et al., 1995; Bunegin et al., 1989) in the presence of intracranial pathology. Our review found 4 RCTs and 5 non-RCTs evaluating opioid use in acute ABI management.

Individual Studies

Table 12.1 Effects of Opioids in Managing Acute ABI

<table>
<thead>
<tr>
<th>Author/Year/Country/Study design/Pedro Score</th>
<th>Methods</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>de Nadal et al., (2000) Spain RCT PEDro = 8</td>
<td>N=30 Severe head injury patients were randomly assigned to receive morphine (0.2 mg/kg) and fentanyl (2 μg/kg) through IV for 1 minute every 24 hours in a crossover fashion. ICP, MAP, and CPP were monitored for 1 hour after administration. Cerebral blood flow was estimated using Transcranial Doppler sonography.</td>
<td>CO₂ reactivity was maintained in all patients but 18 patients showed impaired or abolished autoregulation. Both morphine and fentanyl caused significant increases in ICP and decreases in MAP and CPP. Estimated cerebral blood flow remained the same. No difference was seen in ICP increases between patients with intact autoregulation and those without.</td>
</tr>
<tr>
<td>Sperry et al., (1992) USA RCT PEDro = 7</td>
<td>N=9 Patients with severe head trauma (mean GCS 6 ± 1) received an IV bolus of fentanyl (3μg/kg) or sufentanil (0.6 μg/kg) in a randomized masked fashion. Patients then received the other opioid 24 hrs later. MAP, HR, and ICP were recorded continuously for the first hour after administration.</td>
<td>Both fentanyl and sufentanil resulted in significant increases in ICP (8±2 mmHg and 6±1 mmHg respectively) and statistically significant decreases in MAP (11±6 mmHg and 10±5 mmHg). No changes in heart rate were noted.</td>
</tr>
<tr>
<td>Karabinis et al., (2004) Greece RCT PEDro = 5</td>
<td>N=161 Patients were randomized to receive analgesia-based sedation (remifentanil 9 μg/kg/h and propofol 0.5mg/kg/h (days 1-3) or midazolam 0.03mg/kg/h (days 4-5)), hypnotic-based Sedation with remifentanil permitted significantly faster (p=0.001) and more predictable awakening for neurological assessment (p=0.024).</td>
<td></td>
</tr>
<tr>
<td>Author/Year/ Country/ Study design/ Pedro Score</td>
<td>Methods</td>
<td>Outcome</td>
</tr>
<tr>
<td>-----------------------------------------------</td>
<td>---------</td>
<td>---------</td>
</tr>
<tr>
<td>Lauer et al., (1997) USA RCT PEDro = 5</td>
<td>Sedation (propofol (days 1-3); midazolam days 4-5) and fentanyl, or morphine. Agents were titrated to receive optimal sedation in all three cases.</td>
<td>There was no increase in ICP in any group. There was a significant decrease in MAP in the sufentanil group at 10 min (p&lt;0.05) and 45 min after initial bolus.</td>
</tr>
<tr>
<td>Albanese et al., (1999) France Pre-Post</td>
<td>N=6 Patients randomly received a 6-min injection of either sufentanil (1μg/kg), alfentanil (100μg/kg), or fentanyl (10μg/kg) followed by an infusion of 0.005, 0.7, and 0.075 μg/kg/min respectively for 1 hr. MAP, ICP, CPP, and SjvO2 were continuously measured every minute throughout the hour.</td>
<td>All three medications were associated with significant increases in ICP peaking before 6 minutes and returning to baseline by 15 min. Increases in ICP were accompanied by decreases in MAP and thus CPP. No evidence of cerebral ischemia was noted.</td>
</tr>
<tr>
<td>Scholz et al., (1994) Germany Pre-Post</td>
<td>N=10 Head injured patients (GCS&lt;6) received an IV bolus of sufentanil (2μg/kg) followed at 30 min by infusion of sufentanil (150 μg/hr) and midazolam (median 9 mg/hr) over 48 hrs. Pharmacokinetic and physiological measures were recorded.</td>
<td>Decreases in ICP (16.1±1.7 mmHg to 10.8±1.3 mmHg, p&lt;0.05) and MAP (85.53.9 mmHg to 80.2±4.9 mmHg, p&lt;0.05) were noted. CPP remained stable.</td>
</tr>
<tr>
<td>Albanese et al., (1993) France Case Series</td>
<td>N=10 Head trauma patients sedated with propofol received further sedation using an IV injection of 1 μg/kg over 6 min and infusion of 0.005 μg/kg/min. MAP, ICP and end tidal CO2 were measured every minute for 30 minutes.</td>
<td>Sufentanil injection resulted in a significant increase in ICP (9±7 mmHg) that peaked after 5 min and gradually returned to baseline after 15 minutes. This was accompanied by a significant decrease in MAP and CPP that gradually increased but remained significant throughout the study.</td>
</tr>
<tr>
<td>Engelhard et al., (2004) Germany Pre-Post</td>
<td>N=20 Head trauma patients (GCS&lt;8) sedated with propofol and sufentanil received an IV bolus of remifentanil (0.5 μg/kg) followed by an infusion of 0.25 μg/kg/min for 20 min. Patients were monitored for MAP, ICP, CBFV using transcranial Doppler flowmetry.</td>
<td>No differences were noted in MAP, ICP, or CBFV after remifentanil administration.</td>
</tr>
<tr>
<td>Werner et al., (1995) Germany/USA</td>
<td>N=30 Patients with severe TBI (GCS&lt;6) received an IV bolus of sufentanil (3 μg/kg) and were monitored for 30 min.</td>
<td>Heart rate, arterial blood gases and esophageal temperature did not change. MAP decreased greater than</td>
</tr>
</tbody>
</table>
**Author/Year/Country/Study design/Pedro Score**  
<table>
<thead>
<tr>
<th>Methods</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cohort</td>
<td>10mmHg in 12 patients. ICP was constant in patients with maintained MAP, but was significantly increased in those with decreased MAP.</td>
</tr>
</tbody>
</table>

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

**Discussion**

Analgesic sedation with opioids is commonly used in conjunction with hypnotic agents (i.e. midazolam, propofol) to reduce nociceptive stimulation. This makes it difficult to evaluate the effects of opioids in isolation. Five studies reported increases in ICP after opioid administration (Werner et al., 1995; deNadal et al., 2000; Sperry et al., 1992, Albanese et al., 1993; Albanese et al., 1999), while 2 found no increase (Lauer et al., 1997; Engelhard et al., 2004) and one reported a decrease (Scholz et al., 1994). However, mode of administration has been suggested as a determining factor for increases in ICP (Albanese et al. 1999 & 1993). In those studies where patients received only bolus injections of opioids, significant increases in ICP were seen (Werner et al., 1995; de Nadal et al., 2000; Sperry et al., 1992). Fentanyl and its derivatives have been suggested as more ideally suited for sedation in patients with brain injury due to their rapid onset and short duration (Metz et al., 2000). In our review, one study found remifentanil resulted in significantly faster arousal compared to propofol or midazolam (Karabinis et al., 2004). The authors suggested that this allowed for prompt neurological assessment. However, patients in the treatment group received remifentanil as the primary sedative agent and then a hypnotic agent, while patients in the control groups received fentanyl or morphine in conjunction with a hypnotic agent. Therefore, remifentanil’s efficacy can be compared to hypnotic based sedation but not fentanyl or morphine.

**Conclusions**

*There was Level 1 evidence that bolus opioid administration resulted in increased ICP; however, the evidence regarding the effects of opioid infusion on ICP levels is conflicting.*

*There was Level 2 evidence that remifentanil results in faster arousal compared to hypnotic based sedation.*

**Bolus opioid administration results in increased intracranial pressure (ICP).**
There is conflicting evidence regarding the effects of opioid infusion on ICP.
Remifentanil results in faster arousal compared to hypnotic based sedation.

12.2 Anticonvulsant Medications

Following an ABI, seizures can occur quite quickly due to the increased metabolic
demands on the brain, increased intracranial pressure and the excessive amounts of
neurotransmitters released. Seizure can occur within hours of the initial head trauma
(Immediate seizures), within the first week of sustaining the injury (Early seizures) or
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., 2009; Temkin et al., 1995). For a more detailed
discussion on seizures post ABI please see Module 10.

Medications that have been used to treat seizures post injury include: carbamazepine
(tegretol), phenytoin (dilantin), phenobarbital, primadone (mysoline) and valporic acid
(depekane)/divalproex (epival). These medications 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 see 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; Wroblewski et al., 1989).

Individual Studies

Table 12.2 Effects of Carbamazepine in the Treatment of Seizures and Aggression Post ABI

<table>
<thead>
<tr>
<th>Author/Year/Country/Study design/PEDro Score</th>
<th>Methods</th>
<th>Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Smith JR. et al., (1994) USA RCT N=82</td>
<td>Patients with an ABI who had been treated with either phenytoin or carbamazepine were randomized to continue with their current</td>
<td>No significant differences were found between either medication groups or the placebo group. Following cessation of the anticonvulsant individuals showed</td>
</tr>
</tbody>
</table>
Evidence-Based Review of Moderate to Severe Acquired Brain Injury

<table>
<thead>
<tr>
<th>Author/Year/Country/Study design/PEDro Score</th>
<th>Methods</th>
<th>Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>PEDro = 6</td>
<td>medication or were placed in a placebo group for 4 weeks.</td>
<td>significant improvements on several measures of motor speeded performance.</td>
</tr>
<tr>
<td>Wroblewski et al., (1989) USA Pre-Post N=27</td>
<td>Multiple baseline design of patients treated with carbamazepine. Patients served as their own controls.</td>
<td>No difference in seizure occurrence between pre and post carbamazepine periods.</td>
</tr>
<tr>
<td>Azouvi et al., (1999) France Pre-Post N=10</td>
<td>A single group intervention of involving patients who were treated with 400-800 mg/day of carbamazepine for 8 weeks was conducted.</td>
<td>There was a reduction in aggression for 8 of 10 individuals in the carbamazepine group.</td>
</tr>
<tr>
<td>Lewin and Sumners (1992) UK Case Study Not Scored N=1</td>
<td>A 21 year old male was administered 300 mg of carbamazepine BID, to help treat episodic dyscontrol. Administration of medication began 14 months post injury.</td>
<td>There was a decrease in episodic dyscontrol following administration of the medication.</td>
</tr>
</tbody>
</table>

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

Discussion

Five studies were found evaluated the effectiveness of carbamazepine in the treatment of seizures and behaviour disorders post ABI.

One RCT looked at the effects of both carbamazepine, phenytoin and a placebo in the treatment of seizures post injury. Authors concluded that there were no differences in how individuals performed on various outcome measures regardless of the treatment group they were in. Once patients were withdrawn from both medications improvement in measures of motor and speeded performance was noted (Smith, Jr. et al., 1994). In another study conducted by, Wroblewski et al. (1989) carbamazepine was assessed to determine whether it was a good alternative to other anticonvulsants such as phenytoin, phenobarbital, and primidone for seizure control. They concluded that since carbamazepine, did improve seizure control and it was less harmful to cognitive function and behaviour than the latter medications, it was the preferred drug of choice. Glotzner et al. (1983) found the administration of carbamazepine reduced early post traumatic seizures but it had no effect on late seizures.

In the prospective open trial, Azouvi et al. (1999) examined the effects of carbamazepine on agitation. Out of the ten patients who participated in the study, five had significant results, three had moderate results, and two had insignificant results leaving the authors to conclude only that carbamazepine may reduce agitation. A similar
results was noted by Lewin and Sumners (1992) following the administration of carbamazepine to treat episodic dyscontrol.

**Conclusion**

*There is Level 1 evidence that both phenytoin and carbamazepine have negative effects on cognitive performance, particularly with tasks with motor and speed components.*

*There is Level 4 evidence that carbamazepine improves seizure control while being less harmful to cognitive function and behaviour than other anticonvulsants.*

*There is Level 4 evidence that carbamazepine decreases the incidence of aggressive behaviour following a TBI.*

---

Neither carbamazepine nor phenytoin has a positive effect on cognitive performance.

**Carbamazepine improves seizure control and helps in the reduction of aggression following brain injury.**

### 12.2.2 Midazolam

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

**Individual Studies**

<table>
<thead>
<tr>
<th>Author/Year/Country/Study design</th>
<th>Methods</th>
<th>Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wroblewski &amp; Joseph (1992) USA Case Study No Score</td>
<td>N=10 Patients who had suffered a TBI resulting from a motor vehicle accident, fall or anoxic encephalopathy received intramuscular midazolam after other benzodiazepine drugs proved not useful for acute seizure cessation. Seizure occurrence and behavioural changes were assessed.</td>
<td>All patients experienced seizure cessation within minutes of midazolam administration. Slight to moderate sedation were the only reported side effects. In those individual treated for behavioural problems, midazolam alleviated agitation and violence with no obvious effects on cognition.</td>
</tr>
</tbody>
</table>

**Discussion**

In one case study looking at the effectiveness of midazolam on post traumatic seizures, Wroblewski and Joseph (1992) reported on TBI patients treated with intramuscular midazolam for acute seizure cessation after other benzodiazepine drugs had failed. The
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authors found in all patients, seizures ceased within minutes of midazolam administration. Midazolam also prevented the onset of prolonged seizures or status epilepticus. Slight to moderate sedation were the only reported side effects.

**Conclusion**

*There is Level 5 evidence that acute intramuscular midazolam can be used for acute seizure cessation.*

**12.2.3 Phenytoin**

Early prevention of seizures has been accomplished through the administration of various anticonvulsants. Phenytoin given intravenously has been shown to reduce the risk of early post traumatic seizures (Temkin et al., 1999; Pechadre et al., 1991). It has been suggested that immediate administration of anticonvulsants, among them phenytoin, may be critical in reducing the risk of posttraumatic seizures developing (Pagni & Zenga, 2005).

**Individual Studies**

Table 12.4 Effects of Phenytoin in the Treatment of Seizures Post ABI

<table>
<thead>
<tr>
<th>Author/Year/Country/Study design/ PEDro Score</th>
<th>Methods</th>
<th>Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dikmen et al., (1991) USA RCT PEDro = 6</td>
<td>N=244 High risk patients were given either phenytoin vs placebo for 1 year. Medication was administered 24 hours post injury.</td>
<td>For those with a severe ABI (GCS &lt;=9) performance on neuropsychological measures showed significant impairment at one month post injury while on the phenytoin. There was no difference for neuropsychological performance in moderately injured (GCS 9-12) at 1 month or either severity group at one year.</td>
</tr>
<tr>
<td>McQueen et al., (1983) USA RCT PEDro = 7</td>
<td>N=164 Phenytoin or placebo was administered for one year post injury. Those who experienced early seizures were excluded from the study.</td>
<td>There was no difference between the groups of incidence of post traumatic seizures.</td>
</tr>
<tr>
<td>Pechadre et al., (1991) France</td>
<td>N=91 Patients receiving phenytoin or placebo for 3 months were compared to</td>
<td>Those in the treatment group had significantly fewer seizures following</td>
</tr>
<tr>
<td>RCT</td>
<td>PEDro</td>
<td>Intervention Details</td>
</tr>
<tr>
<td>----------</td>
<td>-------</td>
<td>--------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Temkin et al., (1990) USA RCT PEDro = 6</td>
<td>3</td>
<td>Phenytoin or placebo was given at 1 year post injury, followed by a 2 year follow up.</td>
</tr>
<tr>
<td>Young et al., (1983a) USA RCT PEDro = 6</td>
<td>6</td>
<td>Severe brain injury patients were given phenytoin or a placebo within 24 hours post-injury.</td>
</tr>
<tr>
<td>Young et al., (1983b) USA RCT PEDro = 6</td>
<td>6</td>
<td>Individual were given either phenytoin or placebo within first 24 hours post-injury.</td>
</tr>
</tbody>
</table>

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

**Discussion**
Phenytoin has been shown to be effective in preventing early seizures post ABI (McQueen et al., 1983; Temkin et al., 1990; Young et al., 1983b; Young et al., 1983a). In an RCT conducted by Temkin et al. (1990) results indicate that phenytoin was effective in reducing seizures within the first week of injury. The development of late seizures was however unaffected by the phenytoin. Only one study, Pechadre et al., (1991) found that phenytoin was successful in reducing late onset seizures.

**Conclusion**

*There is Level 1 evidence that phenytoin given during the first week of injury reduces the occurrence of early seizures.*

*There is Level 2 evidence that phenytoin may be effective in reducing the risk of late seizures.*

*Phenytoin provided immediately post ABI reduced the occurrence of seizures but only with the first week.*
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.

Individual Studies

Table 12.5 Effects of Phenobarbital in the Treatment of Seizures Post ABI

<table>
<thead>
<tr>
<th>Author/Year/Country/Study design/PEDro Score</th>
<th>Methods</th>
<th>Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Manaka (1992) Japan RCT PEDro = 3</td>
<td>N=126 Individuals ranging in age from 7 to 88 were randomized to receive either Phenobarbital or placebo for a period ranging from 4 weeks to 2 years. Medication was withdrawn during the third year with follow up continuing for another 5 years.</td>
<td>At the end of the 5 year period there were no differences in the development of late seizures between those treated with Phenobarbital and those treated with the placebo.</td>
</tr>
</tbody>
</table>

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

Discussion
Manaka (1992) in a RCT examined the effects of Phenobarbital for seizure control with 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 25ug/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 posttraumatic epilepsy.

Conclusion

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

Phenobarbital has not been shown to be effective in reducing the risk of late seizure development post ABI.

12.2.5 Valporic Acid/Divalproex
Valporic acid (depakene) and divalproex (epival) have been used successful to treat seizure disorders in both adults and children and more recently they have been used to treat bipolar disorder, post-traumatic stress disorder, aggressive behaviour, episodic explosiveness and mania post ABI (McElroy et al., 1987; Geraciotti, Jr., 1994).
Individual Study

Table 12.6 Effects of Valporic Acid and Divalproex on Reducing Aggressive Behaviour Post TBI

<table>
<thead>
<tr>
<th>Author/Year Country/Study Design</th>
<th>Methods</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wroblewski et al., (1997) USA Case studies No Score</td>
<td>N=5 Four TBI and one non-TBI subject were assessed, observed and treated individually with valporic acid to measure changes in behaviour.</td>
<td>Each patient was reviewed individually, with no cross-case comparisons. All showed a substantial reduction in target behaviours.</td>
</tr>
<tr>
<td>Chatham Showalter and Kimmel (2000) USA Case Series</td>
<td>N=29 Chart reviews of individuals that had been patients at an inpatient brain injury rehabilitation unit (ages ranged from 13-89 years) were treated with divalproex in an attempt to reduce symptoms of agitation following injury. Symptoms of agitation included easily aggravated, escalating temper, insistent, biting, profane, punching, restless, removing braces etc.</td>
<td>Eight patients had been rated on the Agitated Behavior Scale prior to treatment with divalproex. For these individuals, a rapid resolution of symptoms to near total recovery was demonstrated. For a second subgroup (n=18), progress notes prior to and during treatment demonstrated decreased and significantly improved symptoms within 7 days of receiving a mean daily dose of divalproex.</td>
</tr>
</tbody>
</table>

Discussion

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

Wroblewski and colleagues (1997) 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 carried out (instead researchers relied on visual inspection of data graphs and graphs were only presented for 3 of the 5 patients). Patients were also part of a specialized neurobehavioural unit, which may have contributed to the positive results.

Conclusion

*There is Level 4 evidence that divalproex decreases the incidence of aggressive behaviour post TBI.*

*There is Level 5 evidence that valproic acid decreases the incidence of aggressive behaviours.*
Valproic acid and divalproex may be used to decrease the incidence of aggressive behaviour; however, more research is needed.

12.2.6 Lamotrigine

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

Individual Studies

<table>
<thead>
<tr>
<th>Author/Year Country/Study Design</th>
<th>Methods</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chahine &amp; Chemali (2006) Lebanon Case Study</td>
<td>N=4 Males aged 18 to 48 were asked to participate in the study.</td>
<td>All 4 individuals were placed on lamotrigine to help reduce or extinguish inappropriate behaviours such as: laughing, impulsivity or verbal aggression. All behaviours decreased once the individual was placed on lamotrigine.</td>
</tr>
<tr>
<td>Pachet et al., (2003) Canada Case Study</td>
<td>N=1 A 40 yr old male participated in the current study. He was given 25 mg daily of lamotrigine. Agitated behaviour was assessed using the Agitated Behaviour Scale (ABS) the Functional Independence Measure (FIM) and the Functional Assessment Measure (FAM)</td>
<td>Results of the FIM and FAM indicated that scores improved (up to 42 points) following the introduction of lamotrigine. When looking at the scores on the ABS a reduction in aggressive behaviour could be seen. The study participant was discharged home sooner than expected.</td>
</tr>
</tbody>
</table>

Discussion

Results from the two case studies, indicate that lamotrigine helps to reduce unwanted behaviours such as verbal aggression. In both studies, participants were initially placed on other medications to help control these behaviours; however, in each case these medications were eventually eliminated once lamotrigine was introduced. Unwanted behaviours decreased and in some cases were extinguished (Pachet et al. 2003; Chahine and Chemali 2006).

Conclusion
There is limited Level 5 evidence, from two case studies, to suggest that lamotrigine helps to reduce inappropriate behaviours post TBI. More research is needed, with a greater number of subjects, to validate these findings.

Lamotrigine may be successful in reducing inappropriate behaviours post TBI.

12.3 Anti-Cholinesterase Inhibitors

12.3.1 Cerebrolysin

12.3.1.1 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.” Cerebrolysin has been demonstrated to have neuroprotective and neurotrophic effects, and has been linked to increased cognitive performance in an elderly population.

Individual Studies

<table>
<thead>
<tr>
<th>Author/Year/Country/Study design</th>
<th>Methods</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alvarez et al., (2003) Spain Pre-Post N=20 Post-acute TBI subjects (etiology not specified, severity determined by initial GCS score) received 20 – 30 ml I.V. Injections of Cerebrolysin solution over 4 weeks. Research staff measured brain bioelectrical activity, cognitive performance and clinical outcome.</td>
<td>Significant decrease in slow brain bioelectrical activity (delta: p &lt; 0.01; theta: p &lt; 0.05); significantly enhanced relative beta activity power (p &lt; 0.01). EEG power ratio scores significantly reduced (p &lt; 0.01) after treatment. Patients with a multi-point evaluation of EEG/brain mapping activity, power ratio scores decreased significantly after treatment (p &lt; 0.05) compared with baseline. Significant improvement in Syndrom-Kurztest (SKT) cognitive performance test scores after treatment (p &lt; 0.01). Patients with a multi-point cognitive evaluation, SKT scores decreased significantly compared to baseline after treatment (p &lt; 0.05), but not 3 months later. Significant improvement in GOS scores after treatment (p &lt; 0.05). Significant decrease in serum urea levels and body temperature after treatment (p &lt; 0.05).</td>
<td></td>
</tr>
</tbody>
</table>
Discussion
In an open label trial of 20 brain-injured patients, Alvarez et al. (2003) investigated the potential benefits of using Cerebrolysin which was administered intravenously 20 times over a 4-week period. Although the study included patients with mild, moderate or severe traumatic brain injury based on the Glasgow Coma Scale score, all patients had significant disability ranging from moderate disability to persistent vegetative state on the Glasgow Outcome Scale. The time since injury varied from 23 to 1107 days with 9 cases less than 1 year post injury and 11 cases greater than 1 year post injury. A brief neuropsychological battery (SKT) using 9 tests to specifically evaluate memory and attention demonstrated overall significant improvement for the 9 of 20 patients for whom it could be administered. Glasgow Outcome Scores also significantly improved comparing pre to post intervention scores.

Conclusions

*There is Level 4 evidence that cerebrolysin, a neurotrophic and neuroprotective medication appears to have potential benefit to improve outcome and cognitive functioning post-brain injury; however, controlled trials will be necessary to evaluate this further.*

***Cerebrolysin may be beneficial for the improvement of cognitive functioning following brain injury.***

12.3.2 Donepezil

12.3.2.1 Donepezil and Cognitive Functioning

The effectiveness of the cholinesterase inhibitor, Donepezil, for improving cognitive functioning and memory dysfunction following brain injury has been assessed. This long term impairment affects one’s ability to return to work, school and an individual’s ability to live alone (Masanic et al., 2001). When tested with individuals who have been diagnosed with Alzheimers, donepezil has been found to be useful in treating memory problems (Walker et al., 2004; Morey et al., 2003). According to Zhang et al. (2004), pharmacologic intervention using a cholinergic agonist to help facilitate cognitive deficits following TBI had not been studied previously.

Individual Studies

*Table 12.9 Effects of Donepezil on Cognitive Functioning and Memory*
<table>
<thead>
<tr>
<th>Author/Year/Country/Study design/PEDro Score</th>
<th>Methodology</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Zhang et al., (2004)</strong> USA RCT PEDro = 7</td>
<td><strong>N=18</strong> Individuals with a history of TBI of any severity with attention or short-term memory impairments as shown by WMS III, and PASAT were randomly assigned to treatment group A (received donepezil orally for 10 weeks, followed by a 4 week washout period, followed by 10 weeks of a placebo) and group B (opposite order as group A). Outcomes measured at baseline, wk 10 and wk 24. There were no statistical differences between groups at baseline.</td>
<td>Group A (donepezil phase) showed significant improvement over group B (placebo phase) on immediate auditory (p=0.002) and visual memory (p&lt;0.001) measures of WMS-III and PASAT (p&lt;0.001) at wk 10. Increased scores in Group A were continued following washout. Group B improved following donepezil phase (wk 24)– but inter-group comparisons were not significant (audio: p=0.588; visual: p=0.397, PASAT presentation rates p=0.545, 0.12, 0.783, 0.410) due to Group A’s sustained high scores.</td>
</tr>
<tr>
<td><strong>Morey et al., (2003)</strong> USA Case Series</td>
<td><strong>N=7</strong> Single subject ABAC design with patients (5 males and 2 females) who received 5-10 mg/day of donepezil (Aricept). Each participant served as his/her own control. Repeated measures analysis of variance was used.</td>
<td>Significant improvements in immediate and delayed memory were found when taking 10 mg/day of Aricept, as measured by the Brief Visual Memory Test-Revised.</td>
</tr>
<tr>
<td><strong>Masanic et al., (2001)</strong> Pre-Post</td>
<td><strong>N=4</strong> Sixteen-week open-label study of patients with chronic, severe TBI who were given donepezil 5 mg daily for 8 weeks followed by donepezil 10 mg daily for 4 weeks.</td>
<td>Mean scores for short-term and long-term recall on the Rey Auditory Verbal Learning Test improved by 1.04 and .83 standard deviations above baseline. Additionally, Complex Figure Test short-term and long-term recall mean scores improved by 1.56 and 1.38 standard deviations above baseline as well.</td>
</tr>
<tr>
<td><strong>Taverni et al., (1998)</strong> USA Case study No score</td>
<td><strong>N=2</strong> Case study of patients who were treated with donepezil was completed.</td>
<td>Improvements in memory were seen in both patients within 3 weeks of beginning donepezil.</td>
</tr>
</tbody>
</table>

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

**Discussion**

Zhang et al. (2004) conducted a randomized placebo controlled double-blind cross-over trial of 18 post-acute TBI patients which demonstrated that donezepil significantly increased scores on tasks of sustained attention and short-term memory when compared to placebo and that these improved results were sustained after the washout period.

In a sixteen-week open-label study, mean scores for short-term and long-term recall on the Rey Auditory Verbal Learning Test improved by 1.04 and .83 standard deviations above baseline. Complex Figure Test short-term and long-term recall mean scores
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Improved by 1.56 and 1.38 standard deviations above baseline as well (Masanic et al., 2001). In a case study conducted by Taverni et al (1998) patients (n=2) who participated reported improvements in memory within three weeks of beginning donepezil. Similar findings were also reported by Morey et al (2003).

Conclusion

Based on a single RCT, there is Level 1 evidence that Donepezil improves attention and short-term memory.

There is Level 4 evidence from 2 studies indicating that Donepezil is effective in improving memory post ABI.

Donepezil helps to improve attention, short-term and long term memory following brain injury.

12.3.3 Physostigmine

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

Individual Studies

Table 12.10 Effects of Physostigmine on Memory Following an ABI

<table>
<thead>
<tr>
<th>Author/Year Country/Study design/PEDro Score</th>
<th>Methods</th>
<th>Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardenas et al., (1994) USA RCT PEDro=6</td>
<td>N=36 Double blind RCT of men with brain injury who were randomized to receive physostigmine, scopolamine, and placebo.</td>
<td>44% of the participants experienced improved memory scores with the use of physostigmine.</td>
</tr>
<tr>
<td>McLean et al., (1987) USA Case Study No score</td>
<td>N=1 Double blind, placebo-controlled, single-subject ABA design involving 2 single-case studies who received physostigmine combined with a memory training programme.</td>
<td>Both cases experienced a clinically significant improvement in memory function, but no significant improvements in attention, concentration, cognitive flexibility, or motor speed.</td>
</tr>
</tbody>
</table>

PEDro = Physiotherapy Evidence Database rating scale score (Moseley et al. 2002).
Discussion
Cardenas et al. (1994) conducted a double-blind, placebo-controlled study on 36 men with brain injury who were randomized to receive either oral physostigmine, scopolamine, or placebo. Improved memory scores were found for 44% of the subjects who received oral physostigmine with the Long-term Storage section of the Selective Reminding Test being the most sensitive measure of this. A double-blind, placebo-controlled, single-subject ABA design involving two single-case studies examined the effects of physostigmine combined with a memory training programme (McLean, Jr. et al., 1987). In both cases, a clinically significant improvement was experienced in memory function, while no significant changes were experienced in attention, concentration, cognitive flexibility, or motor speed.

Conclusions

Based on a single RCT, there is Level 1 evidence that physostigmine improves memory in men with brain injury.

There is Level 5 evidence, from one case study, that physostigmine combined with a memory training programme produces a clinically significant improvement in memory function, but does not produce significant changes in attention, concentration, cognitive flexibility, or motor speed.

Physostigmine improves memory in men with brain injury, but not attention, concentration, motor speed, or cognitive flexibility.

12.4 Anti-Depressants
Disorders of mood, including agitation, anxiety disorders, major depression, and bipolar illness, are all common following an acquired brain injury 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., 1994). For a more detailed discussion of anti-depressants and the effect on depression post ABI please see Module 8.
12.4.1 Sertraline

Individual Studies

Table 12.11 Effects of Sertraline on Depression Post ABI

<table>
<thead>
<tr>
<th>Author/Year/Country/Study design/PEDro Score</th>
<th>Methods</th>
<th>Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ashman et al., (2009) USA RCT PEDro = 10</td>
<td>N=52 participants were randomly assigned to the treatment or control group. Treatment group received sertraline 25 mg to 100 mg. Those in the control group were given a placebo for 10 weeks. Various scales were used to assess depression.</td>
<td>Overall sertraline was found to have little impact on the depressive symptoms of those who had sustained a TBI. Scores on the various depression scales showed little change post treatment and not significant differences were noted between the two groups.</td>
</tr>
<tr>
<td>Fann et al., (2000) USA Non-RCT</td>
<td>N=15 Individuals with a mild TBI were administered Sertraline or placebo for an 8-week period.</td>
<td>Statistically significant improvements in depression were found with the use of sertraline.</td>
</tr>
</tbody>
</table>

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

Discussion

Ashman et al. (2009), in a blind RCT found no statistical significant differences between baseline measures on various depression scales between both TBI groups. Fann et al. (2000) assessed the effects of sertraline on fifteen patients diagnosed with major depression post-mTBI. The patients experienced statistically significant improvements in depressed mood while using sertraline. The differences in the study groups (mild vs moderate to severe TBI) may help to explain the study results when looking at the effectiveness of sertraline on depression.

Conclusions

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

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

12.4.2 Citalopram

Individual Studies
### Table 12.12 Effects of Citalopram on Depression Post ABI

<table>
<thead>
<tr>
<th>Author/Year/Country/Study design</th>
<th>Methods</th>
<th>Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rapoport et al., (2008) Canada Prospective controlled trial</td>
<td>N=54 Those in the 6 week study (n=29) were given 20 mg/day of citalopram, while those in the 10 week study (n=36) began on 20 mg/day and were titrated to a maximum of 50 mg/day.</td>
<td>Depression scores decreased during the first 6 weeks of treatment and for those who were enrolled in the 10 week program, depression scores decreased significantly</td>
</tr>
<tr>
<td>Perino et al., (2001) Italy Pre-Post</td>
<td>N=20 Individuals were administered either citalopram (20mg/day) and carbamazepine (up to 600mg/day).</td>
<td>Depression scores decreased over the course of the study</td>
</tr>
</tbody>
</table>

**Discussion**

Rapoport et al., 2008 examined the benefits of citalopram on depression post ABI. Fifty-four subjects participated in the study. Participants were divided into two groups. One group (n=29) was given 20 mg/day of citalopram for 6 weeks while the second group (n=36) began with 20 mg/day which was titrated to a maximum of 50 mg/day. The second group was studied for 10 weeks. Scores on the Hamilton Rating Scale for Depression (HAMD) was decreased from baseline (mean 23.66) to the end of the first 6 weeks (mean 16.30), \( p<0.0001 \). Scores decreased significantly (\( p<0.001 \)) from for those in the 10 week program. The somatic score on the Rivermead Post Concussion Symptoms Questionnaire (RPQ) decreased significantly from 15.38 to 11.35 (\( p<0.001 \)) at 6 weeks, but no further changes were noted at the 10 week assessment period.

In the study conducted by Perino et al. (2001), the 20 individuals who participated were divided in two groups based on the length of time since injury. Each was given 20 mg of citalopram per day and 600 mg of carbamazepine per day. When looking at the scores from the Brief Psychiatric Rating Scale and the Clinical Global Impression before and after administration of the medication, scores significantly had decreased at 12 weeks.

**Conclusions:**

*There is Level 2 evidence that citalopram aids in the reduction of depression post ABI. There is Level 4 evidence that citalopram and carbamazepine may be efficacious in the treatment of anxiety and mood disorders.*

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

Individual Studies

Table 12.13 Effects of Desipramine on Depression Post ABI

<table>
<thead>
<tr>
<th>Author/Year Country/Study design</th>
<th>Methods</th>
<th>Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wroblewski et al., (1996) USA RCT PEDro=4</td>
<td>N=10 Individuals were randomly assigned to receive either 150 mg/day for 30 days then 150 to 300 mg/day at the 2 month period or a placebo. The controls were given placebo for the first 30 days before the desipramine was administered.</td>
<td>Three from each group had nearly complete resolution of depression on desipramine. 7 of 10 subjects showed improvement over time on the affect/mood scale (p=0.001).</td>
</tr>
</tbody>
</table>

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

Discussion

Wroblewski et al. (1996) randomized 10 subjects to receive either desipramine or placebo. On those who were started on desipramine (n=6), only 3 were found to have depression symptoms resolved following treatment; however, for those in the placebo group (n=6), 4 were had their symptoms of depression resolved. Significant improvements (p=0.001) were also noted over time on the affect/mood scale.

Conclusions:

There is Level 2 evidence to suggest that the administration of desipramine assists in improving mood and reducing depression.

Desipramine may be effective in improving mood and reducing depression.

12.4.4 Sertraline and Amitriptyline

Studies have examined the effect of an antidepressant on reducing agitation/aggression in brain injured patients (Kant et al., 1998; Mysiw et al., 1988). One study reported the effects of sertraline, a serotonin specific reuptake inhibitor on reducing aggression and irritability in brain injured patients (Kant et al., 1998), whereas another examined the effect of amitriptyline (a tricyclic antidepressant with both serotonergic and noradrenergic reuptake inhibition) on decreasing agitation while the individual was still experiencing post-traumatic amnesia (Mysiw et al., 1988). For a more detailed discussion on the treatment of agitation or aggression post ABI please see Module 8.

Individual Studies
Table 12.14 Effects of Sertraline and Amitriptyline on Reducing Aggression and Irritability Post TBI

<table>
<thead>
<tr>
<th>Author/Year Country/Study Design</th>
<th>Methods</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mysiw et al., (1988) USA Non-RCT</td>
<td>N=43 TBI subjects experiencing non-directed agitation following PTA were treated with a traditional structured program. Of these 20 patients whose agitation interfered with rehabilitation, or persisted more than 7 days were administered amitriptyline daily.</td>
<td>13 of 20 patients treated with amitriptyline experienced significantly reduced levels of agitation after the first week (p&lt;0.001). These levels were maintained in the ensuing weeks (p&lt;0.001), but did not significantly drop when compared to the first week (p&gt;0.6).</td>
</tr>
<tr>
<td>Kant et al., (1998) USA Pre-Post</td>
<td>N=10 CHI subjects (mean age: 37.6, chronicity: 2 years) with complaints of irritability and/or aggression completed an 8-week trial of Sertraline.</td>
<td>Aggression was significantly reduced following treatment.</td>
</tr>
</tbody>
</table>

Discussion

Kant et al. (1998) examined the effect of sertraline HCL (Zoloft) on reducing aggression and irritability in 13 brain injured patients two years post-injury. Positive effects were reported to occur at each follow-up visit compared to baseline. Mysiw et al. (1988) administered amitriptyline to 20 brain injured patients who had not responded to standard behavioural interventions. Results indicated that within 7 days of amitriptyline therapy (mean dosage was 75 mg), 90% of the patients had a dramatic decrease in agitation.

Conclusion

There is Level 4 evidence that sertraline HCL and amitriptyline decrease the incidence of aggressive behaviours.

Sertraline HCL and amitriptyline may be used to decrease aggressive behavior.

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 the TBI, may contribute to the development of aggression (Wroblewski et al. 1997; Kim 2002). 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.
Individual Studies

Table 12.15 Effects of Lithium Carbonate on Aggressive Behaviour post TBI

<table>
<thead>
<tr>
<th>Author/Year</th>
<th>Country/Study Design</th>
<th>Methods</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bellus et al., (1996) USA</td>
<td>Case study</td>
<td>N=2 Male subjects (aged 40 and 24) having a brain-injury were treated with lithium. One patient displayed highly aggressive behaviours (self-injurious), while the 2nd subject’s behaviour was described as “bizarre and inappropriate” such as unwanted touching of females, biting and hoarding material beneath his mattress.</td>
<td>Following lithium treatment, the reduction of aggressive behaviours by 60% was demonstrated for one patient. For the other patient, problematic behaviour decreased dramatically (84%) during the second three-month analysis period and was free of the problematic behaviours during the remaining 6-months of evaluation.</td>
</tr>
<tr>
<td>Glenn et al., (1989) USA.</td>
<td>Case Study</td>
<td>N=10 brain-injured subjects showing mood disorders, aggressive, combative, self destructive behaviour or affective instability were administered lithium. Intervention measured by observed improvement.</td>
<td>Five showed a significant improvement in rehab programs with no decrease in motor or cognitive performance. One showed moderate response, one improved dramatically but</td>
</tr>
</tbody>
</table>

Discussion

Lithium carbonate was used in a series of case reports with 11 brain injured (8 TBI and 3 stroke) (Glenn et al., 1989). Glenn et al. (1989) reported favourable outcomes for all but one patient who received lithium (i.e., a decrease in “severe unremitting, aggressive, combative, or self destructive behaviour or severe affective instability”). No objective measures of behaviour were reported (only descriptive, no frequency, duration/intensity or rating scales). Lithium must also be monitored carefully because of concerns regarding neurotoxicity. Similarly, Bellus et al. (1996) reported lithium treatment reduced aggressive and inappropriate behaviours in two, male patients.

Conclusion

*There is Level 5 evidence to suggest that an antimanic agent (lithium carbonate) reduces aggressive/agitated behavior following a TBI.*

Lithium may reduce behavioral problems but is associated with neurotoxicity.

12.5.2 Quetiapine (Seroquel)

Quetiapine has been used to reduce aggressive behaviour among those diagnosed with schizophrenia and alzheimer disease (Volavka et al., 2004; Webb & Glueckauf, 1994).
Queptiapine may be a better choice since it is just as effective in treating aggressive behaviours without the side effects (Kim & Bijlani, 2006).

**Individual Study**

**Table 12.16 Effects of Quetiapine on Aggressive Behaviour Post TBI**

<table>
<thead>
<tr>
<th>Author/Year Country/Study Design/</th>
<th>Methods</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kim and Bijlani, (2006) USA Case series</td>
<td>N=7 Subjects were given quetiapine (dose ranged from 25 to 300mg). Both male and female subjects participated in the study.</td>
<td>Average does of quetiapine was 110.7 mg. As a result of the medication, subjects OAS scores were significantly reduced (p=0.002). The CGI score improved from a mean of 4.14 to 2.29 (p=0.002). Significant improvements were also noted on the aggression subscale (p=0.036). RBANS overall scores indicated a mean improvement of 8.02% (p=0.027)</td>
</tr>
</tbody>
</table>

**Discussion**

In one case series conducted by Kim and Bijlani (2006) they found that quetiapine assisted in helping to reduce aggressive behaviour in 7 subjects. They also noted that they were significant improvements in the Overt Aggression Scale - Modified (OAS-M), the Clinical Global Impression (CGI) scores, and the overall scores of the Repeatable Battery for the Assessment of Neuropsychological Status (RBANS).

**Conclusion**

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

*Although there is evidence to suggest that quetiapine does help reduce aggressive behavior.*

**12.5.3 Ziprasidone**

Ziprasidone has been approved for acute agitation in those who have been diagnosed with schizophrenia. It has also been found to work in the treatment of acute mania, often associated with bipolar disorder. For those who sustain a TBI, the period of post traumatic amnesia (PTA), has been defined as a period where the individual is disorientated, and may lack the ability to learn new things and suffer from behaviour alterations (Brooke et al., 1992). Researchers believe that these behaviour alternations...
may result from the individual’s lack of self-awareness which may be related to memory alterations that appear after the injury (Noe et al., 2007).

**Individual Study**

**Table 12.17 Effects of Ziprasidone on Agitation Post TBI**

<table>
<thead>
<tr>
<th>Author/Year Country/Study Design</th>
<th>Methods</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Noe et al., (2007) USA Case Series</td>
<td>N=5 Those included in the study, were still in PTA at the start of the study, but were out of it at the end. All subjects were given ziprasidone upon entering the study. Medication given to subjects ranged from 20 mg/day to 80mg/day, lasting from 35 to 68 days. Agitation was assessed with the Agitation Behavior Scale (ABS).</td>
<td>Results of the ABS showed a decrease in the score within the first 14 days from 27.3 to 18. Scores on the disinhibition portion of the scale decreased from 28.6 to 17.1, while scores on the aggressiveness subsection of the scale decreased from 26.1 to 20.4.</td>
</tr>
</tbody>
</table>

**Discussion**

In the current study conducted by Noe et al. (2007), individuals who were still in the PTA stage at admission to rehabilitation, were given 20 to 80 mg/day ziprasidone. The medication was given for 35 to 68 days. Aggressions scores decreased during the first 2 weeks while on the medication. The total ABS score decreased from 27.2 to 18, while the disinhibition score on the scale decreased by 9 points (from 28.6 to 17.1), and the scores on aggressiveness decreased 7.7 points (from 24.5 to 16.8). It was also noted that all who participated tolerated the ziprasidone with no clinical side effects observed.

**Conclusion**

*There is Level 4 evidence from one study to suggest that ziprasidone assists in the controlling of aggressive behaviours post TBI.*

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

**12.5.4 Haloperidol**

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

**Individual Studies**
Table 12.18 Effects of Haloperidol on Agitation Post TBI

<table>
<thead>
<tr>
<th>Author/Year/Country/Study design</th>
<th>Methods</th>
<th>Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rao et al., (1985) USA Case Series</td>
<td><strong>N=26</strong> Retrospective study of patients with severe traumatic closed head injury, of which 11 were treated with haloperidol and 15 were not.</td>
<td>No differences in success of rehabilitation outcome were found between the two groups.</td>
</tr>
</tbody>
</table>

Discussion

In a retrospective chart review, agitation was managed in eleven patients with haloperidol and in fifteen patients without haloperidol (Rao et al., 1985). No differences were found between the two groups with regards to success of rehabilitation outcome.

Conclusion:

*There is Level 4 evidence that haloperidol does not have a negative effect on the success of rehabilitation.*

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

12.5.5 Droperidol (Inapsine)

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

Individual Studies

Table 12.19 Effects of Droperidol on Improving Behaviour Post TBI

<table>
<thead>
<tr>
<th>Author/Year/Country/Study design</th>
<th>Methods</th>
<th>Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stanislav &amp; Childs (2000) USA Pre-Post</td>
<td><strong>N=27</strong> brain-injured subjects were treated with intramuscular droperidol as needed to relieve agitated symptoms. Patients were followed for 2-months and data collected included: dose, number of doses, time to achieve calming, emergent side effects and patient demographics. Data demonstrating the relief of symptoms for three</td>
<td>The time to achieve calming following episodes of agitation was significantly shorted with intramuscular droperidol (mean = 27.0 minutes) compared to intramuscular haloperidol, lorazepam, or diphenhydramine (p = 0.02).</td>
</tr>
</tbody>
</table>
Discussion
One retrospective controlled trial, Stanislav and Childs (2000) found that a single-dose of droperidol calmed an agitated, brain-injured significantly more quickly than other drugs. It is worth noting that a large proportion of the sample had psychiatric comorbidities: organic personality syndromes (48%) and mental retardation (41%).

Conclusion

*There is Level 4 evidence that administration of single-dose droperidol calms brain-injured, agitated patients more quickly than other agents.*

Droperidol may be an effective agent for calming agitated patients.

12.6 Antispasticity Treatments

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 with a typical duration of only a few hours. Typically, 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 from 2 to 36 months. Complications of this type of block have included chronic dysesthesia and pain and permanent peripheral nerve palsies (Gracies et al., 1997).
Individual Studies

Table 12.20 Effects of Percutaneous Phenol Block to Reduce Spasticity Post ABI

<table>
<thead>
<tr>
<th>Author/Year/ Country/ Study design/ PEDro Score</th>
<th>Methods</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Garland et al. (1984)</strong> USA Case series</td>
<td>N=11 closed head injury subjects received percutaneous phenol injections (1-2 ml of 3 or 5% phenol solution) at motor points of spastic wrist and finger flexors identified using a nerve stimulator. Injected muscles were the flexor carpi radialis, flexor carpi ulnaris, flexor digitorum sublimus, flexor digitorum profundus, and flexor pollicis longus. Flexor spasticity was assessed objectively by measuring wrist position in four situations: 1) resting angle of the wrist with elbow flexed to 90 degrees, 2) passive extension of the wrist with the fingers flexed, 3) passive extension of the wrist with the fingers extended, and 4) active extension of the wrist with the elbow flexed 90 degrees. Measures were repeated one week, and then monthly for 3 months following phenol block injections.</td>
<td>Relaxation of muscle tone persisted for up to two months following the injections. Overall, there was a mean increase in resting wrist angle following motor point injections of 25º. Active wrist extension improved an average of 30º. Mean increase in passive wrist extension with finger flexed of 5º.</td>
</tr>
<tr>
<td><strong>Keenan et al. (1990)</strong> USA Case Series</td>
<td>N=17 TBI Subjects (mean age 25 years) received a phenol block (3ml of 5% phenol solution in sterile saline; mean interval 6 months) followed by daily program of active/passive range of motion therapy if experiencing moderate to severe flexor spasticity causing fixed or dynamic flexion elbow deformity, decreased upper extremity function (secondary) and an inability to maintain elbow range of motion using standard PT in any patient still experiencing a spontaneous neurologic recovery. Muscle tone, control and ROM measured pre/post block, 24 hr, then weekly intervals while hospitalized for rehabilitation. Post discharge monthly evaluations until PB effects ended, then followed up for continuing rehabilitation for a minimum of 2 years.</td>
<td>93% showed a short term decrease in motor tone and improved resting position. Maximum improvements occurred 4 weeks post block. Resting position improved to 69 degrees; Active arc increased to 60 degrees; Passive arc to 118 degrees. Mean block duration was 5 months. Long term interval mean: 27 months. 9 extremities that showed signs of spontaneous recovery received additional blocking achieving relief of spasticity (n=2) while 7 required a surgical nerve block. 4 of 5 patients with heterotopic elbow ossification required surgical resection of the ectopic bone to regain motion. Nerve blocks improved joint positioning preventing breakdown of ante-cubital skin, facilitating surgical resection of the heterotopic bone.</td>
</tr>
</tbody>
</table>
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 5 months on average. 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, Lilling, & Keenan, 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 5º respectively (Garland et al., 1984).

Conclusion

There is Level 4 evidence that phenol nerve blocks reduce contractures and spasticity at the elbow, wrist and finger flexors for up to 5 months post injection.

Phenol blocks of the musculoskeletal nerve may help decrease spasticity and improve range of motion temporarily up to 5 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 such as baclofen, benzodiazepines, dantrolene sodium which affects ion flux, and agents that affect alpha-2 adreno receptors such as tizanidine and clonidine. One particular limitation is the associated cognitive and behavioral changes associated with brain injury.
### 12.6.2.1 Oral Baclofen

#### Individual Studies

**Table 12.21 Effects of Oral Baclofen Agents on Spasticity Post ABI**

<table>
<thead>
<tr>
<th>Author/Year/Country/Study design/ PEDro Score</th>
<th>Methods</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Meythaler et al., (2004) USA Case series</td>
<td><strong>N=35</strong> consecutive ABI subjects (including 22 TBI patients) referred to a spasticity clinic for spastic hypertonia (min. chronicity = 6 months) were placed on an oral baclofen regimen starting at 5 mg tid. Dosage determined by caregiver up to 80 mg after which clinic approval was required. Ashworth Rigidity Scale (ARS), Spasm Frequency Scale (SFS), and deep tendon reflexes (DTR) were taken before treatment, and between 1 and 4 months after treatment was initiated.</td>
<td>Average dose at follow up was 57 ± 26 mg/day. TBI patients mean dose was 55 ± 28 mg/day. Lower extremity ARS and DTR decreased significantly (p=.0003 &amp; p=.0274). No significant change in spasm score (p&gt;.05). TBI patients saw ARS and DTR significantly decreased (p=.0044 &amp; p=.0003) and no significant change in spasm score (p&gt;.05). Upper extremities showed no significant changes ARS, SFS, DTR (p&gt;.05).</td>
</tr>
</tbody>
</table>

**Discussion**

Meythaler et al. (2004) completed a retrospective study evaluating the use of oral baclofen to manage spasticity in brain injury survivors. Pre and post testing of spasticity using the Ashworth scale revealed a significant decrease in lower extremity spasticity scores, however, results were not significant for upper extremity spasticity scores or frequency of spasms. A noted common adverse effect of the oral baclofen was the onset of considerable sleepiness in 6 (17%) patients.

**Conclusion**

*There is Level 4 evidence that oral baclofen improves lower extremity spasticity but not upper extremity spasticity.*

*Oral baclofen appears to improve lower extremity spasticity.*
12.6.2.2 Oral Tizanidine

Individual Studies

Table 12.22 Effects of Oral Tizanidine on Spasticity Post ABI

<table>
<thead>
<tr>
<th>Author/Year/Country/Study design/PEDro Score</th>
<th>Methods</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Meythaler et al., (2001) USA RCT PEDro = 7</td>
<td>N=17 TBI and stroke subjects between 16 and 75 diagnosed with severe chronic spastic hypertonia in at least 1 lower extremity for at least 6 months that has not responded to therapy were given either 4 mg of tizanidine or a placebo, gradually increased to 36 mg after 6 weeks. Patients tapered off over one week, then crossed over to the other study. Ashworth Rigidity Scores (ARS), Penn Spasm Frequency Scale (PSFS), ROM, Spasm Scores, motor component of the FIM, Deep Tendon Reflex, CHART and Motor Strength scores taken pre and post treatment.</td>
<td>Maximum tolerated dose achieved at 4 weeks. L.E./U.E. ARS (affected side) and Spasm Scores decreased (p = .0883 /p&lt;.001). No significant changes were found in the, UE spasm and the DTR scores. Medication significantly decreased LE tone (p=.0006) and UE tone (p=.007) compared to placebo. This increased motor strength (p=.0089).</td>
</tr>
</tbody>
</table>

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

Discussion

In a another study Meythaler et al. (2001) completed a randomized, double blinded placebo controlled cross over trial of Tizanidine in the management of spasticity in acquired brain injury. This study evaluated both stroke (53%) and traumatic brain injury (47%) survivors. For both lower and upper extremity, there was a significant decrease in spasticity scores compared to treatment with placebo. However, upper and lower extremity spasm and reflex scores did not improve compared to placebo. A common adverse effect was increased somnolence (41%) compared to placebo (0%).

Conclusions

Based on a single RCT, there is Level 1 evidence that oral tizanidine improves lower and upper extremity spasticity compared to a placebo.

Oral tizanidine is effective for improving upper and lower extremity spasticity.
12.6.3 Botulinum Toxin Injections

Botulinum toxin type A (BTX-A) acts at pre-synaptic terminals to block acetylcholine release into the neuromuscular junction. When selectively injected into a specific muscle, BTX-A is thought to cause local muscle paralysis thereby alleviating hypertonia due to excessive neural activity (Jankovic & Brin, 1991). BTX-A is a relatively new treatment strategy for the management of spasticity in ABI. It's 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).

Individual Studies

Table 12.23 Effects of Botulinum Toxin on Spasticity Post ABI

<table>
<thead>
<tr>
<th>Author/Year/Country/Study design/PEDro Score</th>
<th>Methods</th>
<th>Outcome</th>
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<tbody>
<tr>
<td>Ashford and Turner-Stokes (2009) Cohort</td>
<td><strong>N=16</strong> Study participants were given botulinum toxin type A (BoNT-A/BTX-A) injection along with various therapies to treat spasticity of the shoulder girdle or proximal upper limb. Concurrent therapy included splinting, serial casting, exercise programs, functional electric stimulation, arm supports and patient/career education.</td>
<td>16 weeks post injection, significant improvements were identified in spasticity (Z=-3.535, p&lt;0.0001), pain (Z=-1.942, 0=0.052) and passive function (Z=-3.172, p=0.002). GAS scores improved in all but one subject, with goals either achieved or over-achieved.</td>
</tr>
<tr>
<td>Mayer et al., (2008) RCT PEDro=6</td>
<td><strong>N=36</strong> Patients were randomly assigned to one of two treatments (the motor point injection technique, or the distributed quadrants technique). Following baseline measures, each elbow was randomized to receive injections of Botox. In total 90 units were given to each group; however the sites and injection techniques varied between the groups. Measures used to assess improvement were: the Ashworth scale, and the Tardieu Catch Angle.</td>
<td>Overall no significant differences were noted between the 2 groups on any of the outcome measures used to assess improvement; however each group showed significant improvement from baseline (p&lt;0.001) on all outcome measures.</td>
</tr>
<tr>
<td>van Rhijn et al., (2005) Belgium Pre/Post</td>
<td><strong>N=21</strong> Pediatric patients (2 yrs 7 months – 19 yrs 8 months) were divided into 3 groups according to impairment severity and treatment objectives. Group 1 received bilateral BTX-A injections with specific targeted muscles of the hip abductors, knee and plantar flexors. Group 2 received unilateral BTX-A injections into the elbow, finger and wrist flexors and/or shoulder muscles. Group 3 received BTX-A</td>
<td>Baseline, 1, 3 and 5-month post-treatment assessments were done using joint goniometry, Modified Ashworth Scale (MAS) and video observations. All 3 groups showed improvements in MAS at 1 and 3 months post-treatment, with patients in group 2 showing the greatest overall benefit and a continued improvement seen at 5 months post-treatment.</td>
</tr>
<tr>
<td>Author/Year/Country/Study design/PEDro Score</td>
<td>Methods</td>
<td>Outcome</td>
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<td>---------------------------------------------</td>
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<td>---------</td>
</tr>
<tr>
<td><strong>Fock et al., (2004)</strong> Australia Pre/Post</td>
<td>injections uni or bilaterally to plantar, knee and hip flexors and/or hip adductors. Immediately after injections, all patients received a cast or an orthosis, intensive physiotherapy, ergotherapy, and functional exercises (Groups 2 and 3 only).</td>
<td>group 3, patients received most benefit at 3 months post-injection. All groups showed improvements in range of motion, with greatest improvement seen in group 2 who showed a consistent improvement at 1, 3 and 5 months.</td>
</tr>
<tr>
<td><strong>Francisco et al., (2002)</strong> USA RCT Pedro=5</td>
<td><strong>N=7</strong> TBI subjects received botulinum toxin A (BTX-A) into the lower extremities. Muscles targeted for injections included the gastrocnemius and soleus. The tibialis posterior was also injected in some subjects. Various assessments, using a multiple of scales, were done before and at 2 and 12 weeks post-injection.</td>
<td>12 weeks 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 values &lt; 0.03). None of these measures showed significant changes at 2 weeks post-injection. There were no significant changes in dorsiflexion at mid-stance, active dorsiflexion in supine position, and MAS scores at 2 or 12 weeks post-injection.</td>
</tr>
<tr>
<td><strong>Yablon et al., (1996)</strong> USA Case Series</td>
<td><strong>N=21</strong> severe (GCS score ≤ 8) TBI Subjects received botulinum toxin A (BTX-A) injections (20-40 units per muscle) into the upper extremity. Muscles targeted for injections were the flexor carpi radialis, flexor carpi ulnaris, flexor digitorum profundus, and flexor digitorum superficialis. Flexor pollicis longus was treated if thumb flexor tone was prominent. Some patients also received injections into the biceps and brachialis due to spasticity.</td>
<td>Subjects who were injected within 12 months from injury onset (acute group) showed significant improvements in ROM and spasticity severity, specifically, significant improvements in wrist extension (p = 0.001), and MAS scores (p = 0.001). All patients in the acute group showed an improvement in spasticity and no patient worsened or remained unchanged. Patients who were not injected within 12 months showed no improvements.</td>
</tr>
</tbody>
</table>
to coexisting spasticity in the elbow flexors. Total dose was determined by spasticity severity and the number of muscles treated. After injection, patients received ROM therapy, therapeutic modalities, and splinting and casting as clinically indicated. Various assessments were conducted before injections were given and 2-4 weeks after the injection was given.

injected > 12 months from injury onset (chronic group) showed significant improvements in wrist extension (p < 0.001), and MAS scores (p = 0.002). All patients in the chronic group showed an improvement in spasticity, but one patient with pre-existing contracture did not improve or worsen.

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

Discussion
Ashford and Turner-Stokes (2009) found for patients given BTX-A over a 16 week period, spasticity, passive function and pain improved significantly. For some, improvements were noted within the first 2 to 4 weeks of BTX-A being administered. Yablon et al. (1996) reported that BTX-A injections into the upper extremities improved range of motion, and spasticity as measured by the modified Ashworth scale (MAS) in 21 ABI patients. Fock et al. (2004) reported that BTX-A injections into the lower extremities improved measures of walking performance including walking speed, stride length, cadence, dorsiflexion on contact with the ground and passive dorsiflexion; however, there were no significant improvements in overall spasticity as measured by MAS scores. In the last study conducted in a pediatric cohort, van Rhijn et al. (2005) reported that BTX-A was effective in improving MAS scores up to 5 months post-treatment with concomitant improvements in range of motion. In the remaining two RCTs, Francisco et al. (2002) and Mayer et al. (2008) found that although botulinum toxin was effective in reducing the level of spasticity, there were no differences based on the amount of botox given.

Conclusion

There is Level 2 evidence based on one cohort study and Level 4 evidence from 3 studies that botulinum toxin type A injections may be effective in the management of localized spasticity following ABI.

One RCT found that both groups of patients receiving botulinum toxin type A injections did show reduced spasticity, regardless of the method of drug administration.

Botulinum toxin type A injections reduces localized spasticity following ABI.
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).

We identified ten studies which investigated the efficacy of intrathecal baclofen for the management of upper and lower extremity spasticity following ABI (Meythaler et al., 1999; Meythaler et al., 1997; Meythaler et al., 1996; Stokic et al., 2005; Becker et al., 1997; Horn et al., 2005; Dario et al., 2002; Francois et al., 2001; Francisco et al., 2005).

Individual Studies

<table>
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<tr>
<th>Author/Year/Country/Study design/PEDro Score</th>
<th>Methods</th>
<th>Outcome</th>
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<tr>
<td>Meythaler et al., (1996) USA RCT PEDro = 7</td>
<td>N=11 ABI (9 MVA, 1 gunshot wound, 1 anoxia) patients suffering from spastic hypertonia unresponsive to oral antispastic medications were randomly assigned to receive a bolus injection of intrathecal baclofen (50 ug) or placebo (normal saline). In a cross over fashion, patients received the other treatment (drug or placebo) at least 48 hours after the administration of the first agent. Ashworth Scale, Spasm Score, and deep tendon reflexes were collected at 1, 2, 4, and 6 hours post-injection by a blind investigator.</td>
<td>No significant differences between groups in any of the measures at baseline. Significant reduction following baclofen treatment in both lower and upper extremity Ashworth scores (p=0.0032, p =0.0033), Spasm scores (p=0.0033, p=0.0070), and Deep Tendon Reflex scores (p=0.0033, p=0.011). Maximum reduction for all measures occurred 4 hours post-treatment.</td>
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<tr>
<td>Becker et al., (1997) Germany Case Series</td>
<td>N=18 Severe ABI patients (9 TBI and 9 hypoxic brain injury) received continuous intrathecal baclofen infusion. Ashworth Scale and Spasm Frequency Scale scores were measured at admission and at discharge.</td>
<td>In all patients, spasticity was reduced significantly. Mean Ashworth score was reduced from 4.5 to 2.33 and the mean Spasm Frequency score from 2.16 to 0.94. Reduction in spasticity lead to a reduction in pain.</td>
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<tr>
<td>Dario et al., (2002) Italy Pre/Post</td>
<td>N=14 ABI patients (6 TBI and 8 anoxic ABI) with severe progressive spasticity refractory to medical therapy involving the whole body and interfering with daily care or function received continuous intrathecal baclofen</td>
<td>At last follow up, there was a significant decrease in AS score in both lower and upper extremities (both p&lt;0.05). Significant reduction in SFS scores</td>
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<td>Author/Year/Country/Study design/PEDro Score</td>
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<td>Outcome</td>
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<td>Horn et al., (2005) USA Pre/Post N=28 ABI subjects received a single 50-µg intrathecal baclofen bolus injection. Walking Performance, and Ashworth scores to measure lower-extremity spasticity were assessed before and 2, 4 and 6 hours after intrathecal baclofen bolus injection.</td>
<td>Infusions. Outcomes assessed before pump implantation and at last follow-up (mean follow up of 23.5 months, range 6-65 months). Ashworth Scale (AS) for lower and upper extremities, Spasm Frequency Scale (SFS) for lower and upper extremities. (p&lt;0.001). Mean daily dose of baclofen was 305 µg (range 90-510 µg).</td>
<td>Significant improvements in gait velocity (p&lt;0.001), stride length (p&lt;0.05), and step width (p&lt;0.001). Significant reductions in Ashworth scores at 2, 4 and 6 hours post-injection (p&lt;0.001).</td>
</tr>
<tr>
<td>Francois et al., (2001) France Case study N=4 The use of intrathecal baclofen infusion for the reduction of spasticity was investigated in a collection of case studies of patients with severe ABI (GCS ≤ 4). Treatment was started within 1 month following injury onset. Outcomes included Ashworth scores, frequency and intensity of autonomic disorders.</td>
<td>For both the lower and upper extremities Ashworth scores, spasm frequency and reflex scores significantly decreased after 3 months of treatment (all p&lt;0.05).</td>
<td>Reductions in spasticity, and lower limb Ashworth scores at 6 months post-treatment 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.</td>
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<tr>
<td>Meythaler et al., (1997) USA Pre/Post N=12 ABI subjects (9 TBI and 3 anoxic) who showed a reduction in muscle tone of at least 2 points on the Ashworth scale or a reduction in the number of spasms following a screening trial using a bolus injection on intrathecal baclofen were surgically fitted with an infusion pump for continuous intrathecal baclofen delivery for 3 months. Outcomes included Ashworth Rigidity Scale scores, Spasm Frequency scores, and Deep Tendon Reflex Scores.</td>
<td>For both the lower and upper extremities Ashworth scores, spasm frequency and reflex scores significantly decreased after 3 months of treatment (all p&lt;0.05).</td>
<td>For both the lower and upper extremities Ashworth scores, spasm frequency and reflex scores significantly decreased after 3 months of treatment (all p&lt;0.05).</td>
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<tr>
<td>Meythaler et al., (1999) USA Pre/Post N=17 Consecutive ABI patients diagnosed with severe, chronic, lower extremity spasticity and dystonic hypertonia that proved unresponsive to treatment with oral antispasticity medications 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) with the exception that patients received continuous intrathecal baclofen for 1 year. Ashworth Rigidity Scale scores, Spasm Frequency Scale scores, Deep Tendon Reflex Scores.</td>
<td>1 year of intrathecal baclofen treatment (average dose: 302 µg/day) resulted in a decrease of Ashworth, spasm, and reflex scores in both upper and lower extremities (p&lt;.0001). No cognitive side effects observed after 1 year.</td>
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</table>
### Author/Year/Country/Study design/PEDro Score

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<th>Methods</th>
<th>Outcome</th>
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<td>scores were assessed at 1, 3, 6, 9 and 12 months.</td>
<td>Average baclofen dose at 3 months was $205.3 \pm 148$ µg/day. Lower extremities showed a significant reduction in Ashworth scores ($p&lt;0.0001$); affected lower limb reflex score ($p=0.0208$); normal side ($p=0.0051$), but not significant changes in affected lower limb spasm score ($p=0.5$). Upper extremities showed significant reductions in Ashworth scores on affected side ($p=0.0002$) but were not significant for Biceps Reflex score (affected and normal: $p=0.1088$ and $p=0.0679$), or spasm score (affected: $p=0.1797$). No patient complained of subjective weakness on the normal side.</td>
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<tr>
<td><strong>Meythaler et al., (1999)</strong> USA Pre/Post</td>
<td><strong>Stokic et al., (2005)</strong> USA Case series</td>
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<tr>
<td><strong>Francisco et al., (2005)</strong> USA Case Series</td>
<td><strong>N=30</strong> Head injury patients (17 ABI, 4 anoxia, and 9 stroke) received a single 50-µg intrathecal baclofen bolus injection. Ashworth Scale scored were assessed before, 2, 4, and 6 hours post-injection. H-Reflex from soleus muscle and F waves from abductor hallucis in supine position assessed before and 4 hours post-injection.</td>
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<tr>
<td><strong>N=14</strong> head injury subjects (6 anoxic encephalopathy, 5 TBI and 3 stroke) who had suffered their injuries no more than 1 years before and who experienced spastic hypertonia unresponsive to other treatment modalities including oral spasmyotics, botulinum toxin, phenol neurolysis and physical therapy were involved in this study. Patients who showed a reduction of at least 1 point on the Modified Ashworth Scale (MAS) or any functional improvement 4 hours following a screening trial using a bolus injection of intrathecal baclofen were surgically fitted with an infusion pump for continuous intrathecal baclofen delivery.</td>
<td>Lower and upper extremities MAS scores and Disability Rating Scale (DRS) scores were assessed at baseline and follow up. Period of pump implantation was on average 5.62 months (range 2-12 months) from disease onset. Follow up of participants occurred at a mean of 13.9 months post pump implantation. Significant reductions from baseline to follow up in upper ($p&lt;0.001$) and lower ($p&lt;0.02$) extremity MAS scores. Non-significant improvement in DRS scores ($p=0.75$)</td>
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</table>

PEDro = Physiotherapy Evidence Database rating scale score (Moseley et al. 2002).
Discussion
In the first study, Meythaler and colleagues confirmed the effectiveness of intrathecal baclofen to decrease upper and lower extremity spasticity in a randomized, double blinded, placebo controlled cross-over trial Meythaler et al. (1996). In subsequent studies, the same investigators went on to demonstrate the effectiveness of intrathecal baclofen for decreasing upper extremity spasticity for up to 3 months (Meythaler et al., 1996; Meythaler et al., 1997) and 1 year (Meythaler et al., 1999) duration. However, all of these studies used a single group intervention design lacking a placebo control group during the phase when the subcutaneously placed pump was used to provide continuous administration of the medication into the intrathecal space.

Investigations carried out by other research groups have reported similar findings regarding the efficacy of intrathecal baclofen for the management of spasticity post-ABI (Stokic et al., 2005; Becker et al., 1997; Dario et al., 2002; Francois et al., 2001; Francisco et al., 2005). However, these studies still lacked a control group thereby limiting the conclusions of their findings.

For a total of 154 participants in the nine studies identified by this review, it appears that intrathecal baclofen is an effective treatment for spasticity, however some adverse effects such as urinary hesitancy were reported. Only two of the nine studies examined the long-term effectiveness of the treatment. One study also evaluated the functional consequences by assessing walking performance following a bolus injection of intrathecal baclofen (Horn et al., 2005).

Future studies should be conducted using prospective controlled trials or RCTs that include control or placebo groups to further establish the efficacy of intrathecal baclofen for the management of spasticity.

Conclusions

Based on a single RCT, there is Level 1 evidence that bolus intrathecal baclofen injections produce short-term (up to 6 hours) reductions in upper and lower extremity spasticity.

There is Level 4 evidence to suggest that prolonged intrathecal baclofen results in longer-term (3 months, and 1 year) reductions in spasticity in both the upper and lower extremities following an ABI.

Based on a single study, there is Level 4 evidence to suggest that intrathecal baclofen results in short-term improvements in walking performance, particularly gait velocity, stride length, and step width.
12.7 Barbiturates

It has long been proposed that barbiturates may be useful in the control of ICP. Barbiturates are thought to reduce ICP by suppressing cerebral metabolism to reduce metabolic demands and cerebral blood volume (Roberts, 2000). Early reports indicated that barbiturates reduced ICP even in patients reported to be unresponsive to rigorous treatments with conventional ICP management techniques including mannitol and hyperventilation (Marshall et al., 1979). Further studies supported the therapeutic potential of barbiturates and suggested that failure to control ICP can lead to death (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. More recent studies have explored the negative side effects associated with barbiturate coma such as adrenal insufficiency (Llompart-Pou et al., 2007) and bone marrow suppression (Stover & Stocker, 1998).

The American Association of Neurological Surgeons make Level II recommendations that prophylactic administration of barbiturates to induce EEG burst suppression should not be performed. They also make Level II recommendations that high-dose barbiturate administration can be used to control elevated ICP that is refractory to maximum standard medical and surgical treatment (Bratton et al., 2007a). The EBIC guidelines recommend barbiturate use to increase sedation only after sedation, analgesia, hyperventilation, osmotic therapy, and CSF drainage have failed to control ICP (Maas et al., 1997).

Individual Studies

Table 12.25 Effects of Barbiturates in the Management of Elevated Intracranial Pressure Post ABI

<table>
<thead>
<tr>
<th>Author/Year/Country/Study design/PEDro Score</th>
<th>Methods</th>
<th>Outcome</th>
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<tr>
<td>Eisenberg et al., (1988) USA</td>
<td>N=73 Severe head injury patient (GCS ≤ 7) were randomized to receive either high-dose pentobarbital (loading dose 10</td>
<td>The chance of ICP control in patients with ICP refractory to conventional management was nearly double (ratio 1.94, p=0.12) for</td>
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<td>Author/Year/ Country/ Study design/PEDro Score</td>
<td>Methods</td>
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<td>RCT PEDro = 4</td>
<td>mg/kg over 30 min, 5 mg/kg q 1 hr x 3. Maintenance dose of 1mg/kg/hr or adjusted to achieve serum levels of 3-4mg%) or conventional therapy (elevation of the head, hyperventilation, morphine, pancuronium, mannitol, ventricular drainage) for the reduction of ICP. Changes in ICP and survival at 30 days and 6 months were assessed.</td>
<td>patients in the barbiturate group compared with controls. After declaration of treatment failure, 26 of the patients randomly assigned to conventional therapy were crossed over to receive barbiturates. The likelihood of survival at 1 month was 92% for those who responded to barbiturates while 83% of the non-responders died. 80% of all deaths in each of the groups were due to uncontrolled ICP. Last follow up examination (a median of 6 months post-injury) showed that 36% of the responders and 90% of the non-responders were vegetative or had died.</td>
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<tr>
<td>Schwartz et al., (1984) Canada RCT PEDro = 5</td>
<td>N=59 Severe brain injury patients (GCS ≤ 7) who had elevated intracranial pressure (ICP &gt; 25 torr for more than 15 minutes) were randomized to receive mannitol (20% with an initial dose of 1 gm/kg) or pentobarbital (initial intravenous bolus of up to 10 mg/kg, followed by continuous infusion at 0.5-3 mg/kg/hr provided that cerebral perfusion pressure remained &gt; 50 torr) initially followed by the second drug as required by further elevation of ICP (defined as failure to control ICP by the current treatment). Subjects were stratified at the outset into two groups, those with intracranial hematomas and those without. ICP and survival at 3 months were compared between groups.</td>
<td>No significant difference in mortality of patients with evacuated hematomas in the pentobarbital or mannitol groups (40% and 43% respectively), however in those with evacuated hematomas, twice as many patients in the pentobarbital group required the other regimen (mannitol) to control raised ICP than did patients starting with mannitol indicating that pentobarbital is not better than mannitol for the control of ICP (p=0.04). Patients with no hematoma treated with pentobarbital as initial therapy had 77% mortality compared to 41% mortality in those treated initially with mannitol. In these patients, there was a higher rate of failure to control ICP in the pentobarbital group than in the mannitol group indicating that pentobarbital is not better than mannitol to control ICP (p&lt;0.001).</td>
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<td>Ward et al., (1985) USA RCT PEDro = 6</td>
<td>N=53 Head injury patients (GCS &lt; 8) were randomly assigned for placement into a control group (conventional ICP management measures) or a barbiturate-treated group who received intravenous pentobarbital (loading dose at 5-10 mg/kg or enough to achieve burst suppression on the electroencephalogram. After loading dose, pentobarbital was given hourly, initially as a bolus and then as a</td>
<td>Groups were similar in terms of age, sex distribution, cause of injury, neurological status, intracranial lesions, and initial ICP. Clinical outcome on the GOS at 1 year did not differ between groups (both groups had equal number of deaths, patients with good outcome, moderate or severe disability). During the first 4 days there was no significant difference in hourly levels of ICP levels, the number of patients dying</td>
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<tr>
<td>Author/Year/ Country/ Study design/PEDro Score</td>
<td>Methods</td>
<td>Outcome</td>
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<td>continuous infusion to achieve a maintenance dose of 1-3 mg/kg adjusted to maintain a serum level of 25-45 mg%). Pentobarbital was started as soon as possible after the injury regardless of the ICP and continued for at least 72 hours and was then slowly discontinued. Changes in ICP and outcome on the Glasgow Outcome scale at 1 year were compared.</td>
<td>from uncontrolled ICP hypertension, the duration of ICP elevation.</td>
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<td>Fried et al., (1989) USA Non-RCT</td>
<td>N=7 ABI patients (GCS 4-8) were involved in this study in which one group received a bolus injection of intravenous pentobarbital followed by continuous infusions to achieve a serum pentobarbital concentration of 20-40 mg/L (n=4) or received conventional therapy (n=3). Measured energy expenditure (% of predicted), 24-hour nitrogen excretion and urinary 3-methylhistadine excretions were assessed.</td>
<td>Measured energy expenditure, and 24 hours nitrogen excretion were significantly lower in the pentobarbital group compared with control (p &lt;0.01 in both cases). There was no significant difference in urinary 3-methylhistadine excretions between groups.</td>
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<tr>
<td>Llompart-Pou, (2007) Spain Case control</td>
<td>N=40 Patients were prospectively studied with moderate to severe TBI. Seventeen patients were treated with barbiturate coma and 23 had their ICP controlled through tier I measures and were used as a control. Adrenal function was assessed using the high-dose corticotrophin stimulation test within 24h after brain injury and after barbiturate coma induction.</td>
<td>Within 24h, adrenal function was similar in both groups. After barbiturate coma, patients in group A (barbiturates) presented higher insufficiency vs. control (53% vs 22%, p=0.03). Patients treated with barbiturates who developed insufficiency required higher levels of Norepinephrine to maintain CPP than the barbiturate treated individuals without insufficiency.</td>
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<tr>
<td>Stover et al., (1998) Germany Case control</td>
<td>N=52 Patients with sever head injury were investigated. Twenty three patients did not respond to ICP treatment and were administered Thiopental at 5-11 mg/Kg b.w. as a bolus followed by continuous infusion of 4-6 mg/Kg/h to maintain a burst suppression pattern of 4-6 bursts/min. Patients were monitored for white blood cells while their tracheobronchial secretions and urine were sampled for bacterial growth.</td>
<td>Barbiturate coma was shown to induce reversible leukopenia and granulocytopenia as well as an increased infection rate. Several patients showed suppressed bone marrow production on histological examination.</td>
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<tr>
<td>Author/Year/Country/Study design/PEDro Score</td>
<td>Methods</td>
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<td>Nordby and Nesbakken, (1984) Norway Non-RCT</td>
<td><strong>N=38</strong> Severe brain injury patients (GCS ≤ 6, all younger than 40 years of age) experiencing a progressive rise in ICP to 40 mmHg for 25 min despite intensive therapy with hyperventilation, steroids and mannitol were assigned to receive a continuous infusion of thiopental (loading dose of 10-20 mg/kg and a maintenance dose of 3-5 mg/kg/hour) and hypothermia (32-35 ºC) or to continue conventional intensive care. GOS outcome was assessed at 9-12 months post-injury.</td>
<td>Better GOS outcome in the thiopental group compared with the conventional therapy group (p=0.03). Therapy with thiopental resulted in 6 patients with good/moderate outcome, 3 severe and 7 dead/vegetative. In contrast conventional therapy resulted in 2 patients with good/moderate outcomes and 13 dead/vegetative.</td>
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<tr>
<td>Thorat et al., (2008) Singapore Case Series</td>
<td><strong>N=12</strong> Patients with severe TBI were managed with barbiturate coma if medical therapy failed to control elevated ICP. Patients were continuously monitored for ICP, pressure reactivity and PTiO2. No significant reductions in mean ICP, MAP, CPP, PTiO2, or PRx were reported. Eight of the patients experienced reductions in ICP but only 4 below 20 mmHg. Improved oxygenation was seen in 6 of the 8 patients with PTiO2 levels greater than 10 mmHg prior to coma.</td>
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<tr>
<td>Schalen et al., (1992) Sweden Case Series</td>
<td><strong>N=38</strong> Patients with severe TBI who despite conventional management developed a dangerous increase in ICP were treated with high dose intravenous thiopentone (5-11 mg/kg, followed by a continuous infusion at 4-8 mg/kg/hr to achieve and maintain a burst suppression pattern on the electroencephalogram (EEG). Treatment continued until ICP decreased and remained stable below 20 mmHg for at least 12 h, or until treatment was considered to be ineffective. Changes in ICP and CPP were assessed.</td>
<td>After induction of treatment, a fall in mean arterial blood pressure (MABP) was seen in 31 patients, in 4 patients no change occurred and a small increase was seen 3 patients. There was a simultaneous decrease in ICP in 26 patients, no change in 3 patients, and a small increase in 2 patients. CPP decreased in 18 patients, increased in 10 patients and remained unchanged in 3 patients.</td>
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PEDro = Physiotherapy Evidence Database rating scale score (Moseley et al., 2002).

**Discussion**

The findings of the RCT conducted by Eisenberg et al. (1988) suggest that the use of high dose pentobarbital is an effective adjunctive therapy for the management of elevated ICP refractory to conventional therapeutic measures. However, this study only supported the use of this high dose barbiturate for a small subgroup of severe ABI patients (GCS ≤ 7). In contrast, the findings of another RCT conducted by Ward et al. (1985) suggest that pentobarbital is no better than conventional ICP management...
measures, which was corroborated by Thorat and colleagues in a smaller case series (Thorat et al., 2008). The study performed by Ward et al. (1985) was also conducted in severe ABI patients (GCS ≤ 7) and contradicts the findings of Eisenberg et al. (1988). Schwartz et al. (1984) compared pentobarbital and mannitol for the control of ICP in another RCT. Their findings support Ward and his colleagues, suggesting that pentobarbital is not better than mannitol in the treatment of ICP. Furthermore, the latter study also reported that more than half of those treated with pentobarbital developed arterial hypotension, an adverse effect that could worsen the condition of patients with severe ABI. Similarly, Schalen et al. (1992) noted that although pentobarbital may decrease elevated ICP, it may also decrease cerebral perfusion pressure due to a decrease in arterial pressure.

A meta-analysis conducted by Roberts (2000), reported that although barbiturates may reduce elevated ICP, there is little evidence to link this with reductions in mortality or disability. Furthermore, it was also noted that barbiturate therapy was associated with substantial hypotension and thus would offset any ICP-lowering effect (Roberts, 2000).

Llampart-Pou (2007) found thiopental less likely to induce adrenal insufficiency when compared to pentobarbital further supporting its use when barbiturate coma is indicated. However, in another study the use of thiopental significantly reduced white blood cell production and could induce reversible leukopenia and granulocytopenia relative to TBI patients who did not require barbiturate sedation (Stover & Stocker, 1988). The authors also noticed interactions with bone marrow suppressing antibiotics (specifically, tazobactum/piperacillin) which further exacerbated problem. The monitoring of immunological response during barbiturate coma has been recommended.

Fried et al. (1989) conducted a study to compare the energy expenditure and nitrogen excretion in patients treated with pentobarbital and those who received conventional ICP therapy without pentobarbital. They reported that pentobarbital essentially lowered the energy expenditure and nitrogen excretion, which in turn would better enable the brain to achieve energy and nitrogen equilibrium during metabolic support of acute head-injured patients.

There is some evidence that in addition to potentially controlling elevated ICP acutely, barbiturates may also affect long-term clinical outcomes. In a prospective controlled trial conducted by Nordby and Nesbakken (1984), the authors reported that thiopental combined with mild hypothermia resulted in better clinical outcomes as per the Glasgow Outcome scale 1 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. Further study is needed.
The meta-analysis by Roberts (2000) noted that further randomized trials are needed to determine the effects of barbiturates on clinical outcomes such as mortality and disability following severe ABI. Similarly, a 1999 Cochrane review stated that there was no evidence that barbiturate use in TBI patients improved outcomes and were reported to decrease blood pressure in one of four patients, which will offset the effect of ICP reduction on CPP (Roberts 2000). Therefore, based on current evidence, barbiturate coma should be avoided until all other measures for controlling elevated ICP are exhausted.

**Conclusions**

*There is conflicting evidence regarding the efficacy of pentobarbital over conventional ICP management measures.*

*There is Level 2 evidence that there is no difference between thiopental and pentobarbital in the control of elevated ICP.*

*There is Level 2 evidence that pentobarbital is no better than mannitol for the control of elevated ICP.*

*There is Level 4 evidence that barbiturate therapy may cause reversible leukopenia, granulocytopenia, and systemic hypotension.*

*Based on a single study, there is Level 4 evidence that a combination barbiturate therapy and hypothermia may result in improved clinical outcomes up to 1 year post-injury.*

*There are conflicting reports regarding the efficacy of pentobarbital for the control of elevated ICP.*

*There is no difference between thiopental and pentobarbital in the control of elevated ICP.*

*Pentobarbital is not better than mannitol for the control of elevated ICP.*

*Barbiturate therapy plus hypothermia may improve clinical outcomes.*

*Patients undergoing barbiturate therapy should have their immunological response and systemic blood pressure monitored.*
12.8 Bisphosphonates

The evidence for NSAIDs being used in prophylactic treatment of HO comes mostly from the use of indomethacin or ibuprofen prophylaxis against HO in patients following total hip arthroplasty (THA) (Kjaersgaard-Anderson & Schmid, 1986; Ritter & Sieber, 1985). Although it has been noted that these medications offer a significant benefit in prophylaxis of THA, the correlation of these findings in traumatic brain injuries is not known (Watanabe & Sant, 2001).

12.8.1 Ethylhydroxybiphosphonate (EHDP)

Watanabe and Sant (2001) have noted that bisphosphonates, in particular etridonate (EHDP) in the prophylaxis and treatment of HO is controversial. EHDP works by preventing the aggregation, growth and mineralization of calcium hydroxyapatite crystals which are essential for bone formation. In a small study Spielman et al. (1983) showed EHDP reduced the development of HO in patients with TBI. Most of the research has been on spinal cord injured patients. Finerman and Stover (1981) and Stover et al. (1976) reported that EHDP resulted in a significant reduction in HO in SCI patients while Garland et al. (1983) noted that EHDP failed to prevent HO in the hips of SCI patients being treated for HO already present in other joints (Watanabe and Sant 2001). Pape et al. (2004) have noted that there has been a lack of conclusive evidence to show that etridonate arrests the development of HO (Garland, 1991; Citta-Pietrolungo et al., 1992; Shehab et al., 2002; Pelissier et al., 2002).

Etridonate may potentially delay fracture healing, as long-term use has been associated with osteomalacia. EHDP can lead to nausea, diarrhea and joint pain, which can be improved by dividing the daily dose (Spielman et al. 1983).

Individual Studies

Table 12.26 Effects of Ethylhydroxybiphosphonate in the Treatment of HO Post ABI

<table>
<thead>
<tr>
<th>Author/Year/ Country/ Study design</th>
<th>Methods</th>
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<tr>
<td>Spielman et al., (1983) USA Non-RCT</td>
<td>N=20 2 group non-RCT comparative study to assess the prophylactic effect of EHDP in decreasing the incidence of HO in severe head injury patients (GCS ≤ 8). 10 patients were treated with EHDP while 10 patients received no treatment. Treatment began within 2 – 7 days after injury. EHDP treatment lasted 6 months, at a rate of 20 mg/kg/day for the first 3 months and 10 mg/kg/day for the last 3 months.</td>
<td>There were no statistically significant group differences in terms of injury severity (GCS), age distribution, sex ratios, the presence of fractures, length of coma, type of head injury and limb spasticity. The EHDP treated group showed a significantly lower incidence of HO compared with controls (2 patients in the EHDP treated group developed HO compared with 7 of the control patients, p &lt; 0.025).</td>
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</table>
Discussion
One prospective controlled trial examined the effectiveness of EHDP treatment for the
management of HO following brain injury (Spielman et al. 1983). Treatment began two
to seven days post injury and lasted for a period of six months. The group of patients
treated with EHDP showed a significantly lower incidence of HO when compared with
the control group. Further research assessing the benefit of EHDP for the treatment of
HO following brain injury is needed.

Conclusions

There is Level 2 evidence that etridonate (EHDP) reduces the development of
heterotopic ossification in severe head injury patients.

Etridonate prevents the development of heterotopic ossification in brain injuries.

12.9 Cannaboids

Dexanabinol (HU-211) is a synthetic, non-psychotropic cannabinoid (Mechoulam et al.,
1988), thought to act as a non-competitive N-methyl-D-aspartate receptor antagonist
(Feigenbaum et al., 1989) to decrease glutamate excitotoxicity. This drug is also
believed to possess antioxidant properties (Eshhar, Striem, Kohen, Tirosh, & Biegon,
1995). Dexanabinol has shown very encouraging neuroprotective effects in animal
models of TBI (Shohami, Novikov, & Bass, 1995).

The American Association of Neurological Surgeons and the European Brain Injury
Consortium make no recommendations regarding cannabinoids.

Individual Studies

Table 12.27 Effects of Cannabinoids as an Acute Therapeutic Strategy Post ABI

<table>
<thead>
<tr>
<th>Author/Year/Country/Study design/PEDro Score</th>
<th>Methods</th>
<th>Outcome</th>
</tr>
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<tbody>
<tr>
<td>Knoller et al. (2002) Israel RCT PEDro = 22</td>
<td>N=67 Severe head injury patients (GCS 4-8) were randomized to receive intravenous dexanabinol (50 mg or 150 mg dexanabinol/1 mL of Cremophor-ethanol was diluted in 100 mL of saline) or placebo (vehicle) by fast infusion (over 15 min). ICP, cardiovascular function (HR, mean arterial BP, CPP and electrocardiogram) were</td>
<td>ICP in drug treated group decreased significantly on day 2 and 3 (p&lt; 0.02 and p&lt;0.005 respectively). ICP control achieved without lowering systemic BP. Significant reduction percentage of time CPP was &lt; 50 mmHg in the drug treated group on days 2 &amp; 3 (p &lt; 0.05). No significant differences in mortality</td>
</tr>
</tbody>
</table>

N=861 Severe brain injury patients (GCS motor score 2-5) were randomly assigned to a single intravenous injection of 150 mg dexamabolin or placebo given within 6 hours of injury. Trial drug was given by infusion over 15 min. ICP and CPP were measured hourly for the first 72 hours. The primary outcomes were the: extended GOS, the Barthel Index (BI) measures of quality of life (SF36) and the community reintegration questionnaire (CIQ). All were assessed at 6 months.

The extended GOS scores at 6 months did not differ between groups (p=0.78): 50% of patients in the dexamabolin group and 51% of those in the placebo group had an unfavourable outcome (odds ratio for a favourable outcome was 1.07; 95% CI 0.83 – 1.39). There were no differences in mortality, occurrence of neuroworsening, or in events related to recovery between groups. No beneficial effects of dexamabolin for improving control of ICP and CPP, BI or on quality of life measures (SF36, CIQ).

**Discussion**

Knoller et al. (2002) randomly assigned 67 severe brain injury patients to receive dexamabolin (50 or 150 mg) or placebo. Their findings were encouraging in that the active drug group showed significant improvements in ICP and CPP. However, despite showing initially significant improvements on the GOS and DRS at 1 month post-treatment, these benefits progressively lost significance over the 6-month follow-up (Knoller et al., 2002).

Recently, Maas et al. (2006) conducted a large-scale multi-centre RCT to conclusively establish the efficacy of dexamabolin in the treatment of ABI. In this study, 861 severe...
brain injury patients admitted to 86 different centres from 15 countries were randomized to receive dexanabinol or placebo within 6 hours of injury. The authors reported that compared with placebo treatment, dexanabinol did not significantly improve outcomes on the extended GOS, mortality rates, Barthel index, or quality of life measures (SF36, CIQ) at 6-months. Moreover, dexanabinol failed to provide any acute control of derangements in ICP or CPP (Maas et al., 2006). These strongly negative findings suggest that the initial benefits reported by Knoller et al. (2002) could have simply been due to the small sample size in this earlier study. Overall, this suggests that overt generalizations made from the findings of smaller RCTs should be undertaken with caution.

**Conclusions**

There is Level 1 evidence that treatment with dexanabinol does not provide acute improvements in ICP or long-term clinical benefits post-ABI.

*Dexanabinol is not effective in controlling ICP or in improving clinical outcomes post ABI.*

**12.10 Cardiovascular Medication**

**12.10.1 Beta-Blockers**

It has been suggested that Beta-blockers may improve agitation, anxiety and aggressive symptoms following brain injury, as well as to reduce restlessness. Oftentimes, dosage is high, leaving patients vulnerable to such adverse effects as sedation, depression and lethargy, although it does not seem to negatively affect motor recovery post-injury (Levy et al., 2005).

**12.10.1.1 Pindolol**

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

Table 12.28 Effects of Pindolol on Behaviour Post TBI

<table>
<thead>
<tr>
<th>Author/ Year Country/Study Design/PEDro Score</th>
<th>Methods</th>
<th>Outcome</th>
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<tbody>
<tr>
<td>Greendyke and Kantor (1986) USA RCT PEDro = 7</td>
<td>N=11 ABI subjects were randomly assigned to receive pindolol or an equal number of identical-appearing placebo capsules for the first half of study. Following titration period, treatment group received a daily dose of 60 mg/day for 10 days, when the dose was increased (up to 100 mg) following a tapering-down period, placebo was given in place of the drug. Those in the placebo group were then given pindolol.</td>
<td>Significant reduction of assaultive episodes, need for supplemental medication and hostility were demonstrated during pindolol treatment (p&lt; 0.05). Significant improvements in patients’ willingness to communicate, and cooperation during treatment (p&lt; 0.025) and significant reduction of stereotyped behaviors (p&lt; 0.01).</td>
</tr>
</tbody>
</table>

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

Discussion

Greendyke and Kantor (1986) investigated the effectiveness of the beta-blocker, pindolol, for the improvement of behaviour associated with brain disease or injury in a randomized, crossover trial. Of 11 patients, brain disease was caused by brain injury, anoxia, or encephalitis in seven of them. A significant reduction in behaviours that lead to assaults was demonstrated during treatment with pindolol.

Conclusion

There is Level 1 evidence that pindolol decreases aggression following brain injury.

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 is not known how this drug works to affect behaviour, however it appears to lack the serious cognitive and affective side effects of other medications or physical restraints used to treat agitation post-injury (Levy et al. 2005).
Individual Studies

Table 12.29 Effects of Propranolol on Behaviour Post TBI

<table>
<thead>
<tr>
<th>Author/Year Country/Study Design/PEDro Score</th>
<th>Methods</th>
<th>Outcome</th>
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<tbody>
<tr>
<td>Greendyke et al., (1986) USA RCT PEDro = 7</td>
<td>N=10 Patients were randomly assigned to receive either long-lasting propranolol (520 mg/day) or an equal number of identical-appearing placebo capsules for the first half of study. Following titration period, treatment group received a daily dose of 520 mg/day for 11 weeks. Following a tapering-down period, placebo was given in place of the drug, and patients that had received placebo first were given a daily dose of propranolol to the same effect as the first group.</td>
<td>Significantly fewer assaults and attempted assaults occurred during the 11-week propranolol treatment as compared to the 11 weeks of placebo, F(1, 7) = 6.50, p&lt; 0.05. No significant changes in social interests, irritability or psychomotor retardation were noted. No abnormalities were noted on laboratory measures.</td>
</tr>
<tr>
<td>Brooke et al., (1992) USA RCT PEDro=7</td>
<td>N=21 The experimental group (n=11) was given propranolol while the control group (n=10) was given placebo for 3 weeks at which time the medication or placebo was tapered off. Medication given was begun at 60 mg/day and increased every third day by 60 mg to a max of 420 mg/day.</td>
<td>Both groups were similar at start of study. As a result the control group had a greater number of episodes related to agitation than the treatment group (z=0.889, p&lt;0.05). The patterns of increase or decrease in both groups were not significantly similar (r=0.491). When looking at the number of agitation episodes by week, there were no significantly greater differences between the two groups (z= -1.5213). Patterns of behavior increasing and decreasing were similar between the two groups (r=0.892, p&lt;0.05). It was also found that more participants in the control group were placed in restraints during the study (z= -2.2022, p&lt;0.05) although there were no significant differences in the pattern of restraint used of the two groups (r=0.080). There were no differences between the two groups in the numbers receiving sedating drugs or drugs for agitation.</td>
</tr>
</tbody>
</table>

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

Discussion
Greendyke et al. (1986b) investigated the effectiveness of the beta-blocker, propranolol, for the improvement of behaviour associated with brain disease in a randomized, crossover trial. Significantly fewer assaults and attempted assaults occurred during the 11-week propranolol treatment as compared to the 11 weeks of placebo, F (1, 7) = 6.50, p< 0.05. Of the nine patients, five showed marked improvement, two demonstrated
moderate improvement, and two showed little or no improvement of assaultive behavior.

Following the acute stage of recovery, 11 closed-head-injured (CHI) patients were treated with a maximum dose of 420 mg/day of propranolol while 10 were given a placebo (Brooke et al. 1992). The intensity of agitated symptoms decreased but not the frequency, suggesting that the drug helps to reduce the emotional intensity of agitated responses.

**Conclusion**

*There is Level 1 evidence, from 2 RCTs, that propranolol reduces agitated symptoms following brain injury.*

**Propranolol may reduce aggressive and agitated symptoms following brain injury.**

### 12.11 Diuretics

#### 12.11.1 Mannitol

Mannitol is an osmotic diuretic. It works by increasing the amount of fluid excreted by the kidneys and helps the body to decrease pressure in the brain and eyes. 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., 2001). For these reasons, the Brain Trauma Foundation recommends that mannitol should 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 (Task Force 1995). There is also some evidence that with prolonged dosage, mannitol may penetrate the blood brain barrier thereby exacerbating the elevation in ICP (Wakai, Roberts, & Schierhout, 2005). Despite mannitol’s effectiveness in ICP management, recent evidence points to hypertonic saline as a potentially more effective hyperosmotic agent. See Module 16 for a more detailed discussion.
Individual Studies

Table 12.30 Effects of Mannitol for the Management of ICP and Hypertension Post ABI

<table>
<thead>
<tr>
<th>Author/Year/Country/Study design/PEDro Score</th>
<th>Methods</th>
<th>Outcome</th>
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<tr>
<td>Ichai et al., (2009)  France RCT PEDro = 6</td>
<td>N=34 Patients with severe TBI (GCS ≤ 8) and intracranial hypertension were randomly allocated to receive equally hyperosmolar and isovolumetric therapy with mannitol or sodium lactate followed by cross-over rescue therapy when necessary.</td>
<td>Compared to mannitol, the effect of sodium lactate on ICP was more pronounced more prolonged and more frequently successful.</td>
</tr>
<tr>
<td>Cruz et al., (2001)  Brazil RCT PEDro = 4</td>
<td>N=178 Adult patients with non-missile traumatic acute subdural hematomas were randomly assigned to receive intravenous conventional mannitol treatment or high dose mannitol treatment. Both groups received normal saline infusions to compensate for mannitol-induced urine losses and to prevent arterial hypotension.</td>
<td>Improvement in abnormal pupillary widening was significantly more frequent in the high dose mannitol group than in the conventional mannitol group (p&lt;0.0001). At 6 months after injury, mortality rates were 14.3% and 25.3% for the high dose mannitol and conventional mannitol groups respectively. Overall clinical outcome on the GOS were significantly better for the high dose mannitol group with a greater number of patients in this group showing a favorable outcome (good recovery of moderate disability) compared with the conventional mannitol group (p&lt;0.01).</td>
</tr>
<tr>
<td>Cruz et al., (2002)  Brazil RCT PEDro = 5</td>
<td>N=141 Adult patients with traumatic non-missile acute intraparenchymal temporal lobe hemorrhages (GCS 1-5) and abnormal pupillary widening (partially or fully dilated pupil with a diameter ≥ 4 mm associated with very sluggish or absent light response) were randomized to receive intravenous conventional mannitol treatment (0.7 g/kg) or high dose mannitol treatment (1.4 g/kg). Immediately after the mannitol infusions both groups received normal saline infusions to compensate for mannitol-induced urine losses and to prevent arterial hypotension. Pupillary improvements (partial or full pupillary constriction ≥ 1 mm toward the normal diameter), and GOS at 6 months were assessed.</td>
<td>Improvements in abnormal bilateral pupillary widening were significantly more frequent in the high dose mannitol group than in the control group (p&lt;0.03). At 6 months after injury, mortality rates were 19.4% and 36.2% for the high dose mannitol and conventional mannitol groups respectively. Overall clinical outcome on the GOS were significantly better for the high dose mannitol group with a greater number of patients in this group showing a favorable outcome (good recovery/moderate disability) compared with the conventional mannitol group (p&lt;0.005).</td>
</tr>
<tr>
<td>Author/Year/Country/Study design/PEDro Score</td>
<td>Methods</td>
<td>Outcome</td>
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<tr>
<td>Cruz et al., (2004) Brazil RCT PEDro = 5</td>
<td>N=44</td>
<td>Improvement in bilateral abnormal papillary widening was significantly more frequent in the high-dose group than in the conventional dose group (p&lt;0.02). At 6 months post-injury, mortality rates were 39.1% and 66.7% in the high-dose and conventional dose mannitol groups respectively. Clinical outcomes on the GOS scale were significantly better for the high-dose than for the conventional dose group (p&lt;0.02).</td>
</tr>
<tr>
<td>Sayre et al., (1996) USA RCT PEDro = 7</td>
<td>N=41</td>
<td>Systolic BP or pulse rates did not change significantly throughout the 2 hours observation period and there were no significant differences between groups indicating that mannitol did not cause secondary hypotension. There was no difference in study volume administered to the groups. However, urine output (p&lt;0.001) was significantly greater and serum sodium (p&lt;0.00001) was significantly lower in the mannitol group compared with the placebo group.</td>
</tr>
<tr>
<td>Smith et al., (1986) USA RCT PEDro = 4</td>
<td>N=80</td>
<td>No significant difference in mortality between groups I and II (35% vs. 42.5%, p=0.26). There were also no significant differences in neurological outcome between groups. Mean highest ICP in non-survivors form both groups was significantly higher than that in survivors from both groups (p=0.0002).</td>
</tr>
<tr>
<td>Author/Year/Country/Study design/PEDro Score</td>
<td>Methods</td>
<td>Outcome</td>
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<tr>
<td>Hartl et al., (1997) Germany Pre-Post</td>
<td>N=11 Severe head injury patients (GCS &lt; 9) who were sedated, intubated and mechanically ventilated to maintain an arterial PO$_2$ &gt; 100 mmHg and a PaCO$_2$ of approximately 35 mmHg received mannitol (125 ml of 20% infused over 30 min through a central vein). Changes in ICP were evaluated.</td>
<td>When the initial ICP before mannitol infusion was below 20 mmHg, neither ICP nor any other parameter changed significantly during or after mannitol infusion. When the pre-infusion ICP was above 20 mmHg there was a significant decrease in ICP and a significant increase in CPP; however there was no change in cerebral white matter oxygenation, or jugular bulb oximetry.</td>
</tr>
<tr>
<td>Francony et al., (2008) France RCT PEDro= 6</td>
<td>N=20 Stable patients with a sustained ICP of &gt;20 mmHg secondary to TBI (n=17) or stroke (n=3) were given a single equimolar infusion of either 20% mannitol or 100mL of 7.45% hypertonic saline during 20 mins of administration.</td>
<td>A single equimolar infusion of 20% mannitol is as effective as 7.45% hypertonic saline in decreasing ICP in patients with ABI. Mannitol exerts additional effects on brain circulation through a possible improvement in blood rheology.</td>
</tr>
<tr>
<td>Sorani et al., (2008) US Case Series</td>
<td>N=28 Patients with ABI were continuously monitored for ICP while in the NICU. Patients were administered 50g or 100g doses (or both) of mannitol for management of elevated ICP. Patient data was then retrospectively analyzed to determine the dose-response relationship of mannitol to ICP.</td>
<td>ICP response to mannitol proved to be dose related. Every 0.1 g/Kg of mannitol administered (to a maximum of 100g) resulted in approximately 1.0 mmHG drop in ICP.</td>
</tr>
</tbody>
</table>

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

**Discussion**

In a recent RCT patients were randomized to receive either mannitol or a sodium lactate solution for management of acute episodes of elevated ICP (Ichai et al., 2009). The authors report that an equimolar dose of sodium lactate had a significantly more pronounced effect on acute elevations of ICP. These effects lasted longer than treatment and with mannitol. Sodium lactate was also successful in reducing elevated ICP more frequently. Based on these results, further research into sodium lactate is warranted.

In another trial, equimolar doses (255 mOsm) of mannitol and hypertonic saline were compared (Francony et al., 2008). In this study both interventions were comparable in reducing ICP in stable patients with intact autoregulation. Mannitol was shown to improve brain circulation through possible improvements in blood rheology, but also significantly increased urine output. The authors suggest that both treatments may be effective, but patient pretreatment factors should be considered before selection.
Cruz and colleagues conducted 3 separate RCTs in ABI patients to investigate the effects of high dose mannitol on clinical outcomes 6 months post-injury (Cruz et al., 2004; Cruz et al., 2001; Cruz et al., 2002). All 3 trials reported positive results indicating that high dose mannitol (1.4 g/kg) was superior to conventional mannitol (0.7 g/kg) in improving mortality rates, and clinical outcomes. In a retrospective case study in the US, Sorani found that for every 0.1 g/Kg increase in mannitol dosage there was a 1.0 mmHG drop in ICP which supports Cruz’s findings (Sorani et al., 2008). Further study is still recommended.

Most reports recommend administering mannitol only when elevated ICP is proven or strongly suspected. Some discourage the use of mannitol before volume resuscitation and stabilization of the patient due to the potential osmotic diuresis and hypotension that could result following mannitol administration. These adverse effects could further compromise cerebral perfusion. However, this approach may deprive head injured patients of the potentially beneficial effects of mannitol upon ICP. With this in mind, Sayre et al. (1996) conducted another RCT to investigate the effects or early mannitol administration in head injured patients in an out-of-hospital emergency care setting. The authors reported that compared with patients randomized to receive saline, early out-of-hospital administration of mannitol does not significantly affect blood pressure.

In another RCT by Smith et al. (1986), the authors reported that compared with patients who were randomized to receive empirical mannitol irrespective of ICP measurements, those who received mannitol only after the onset of intracranial hypertension (> 25 mmHg) were not significantly different in terms of mortality rates or neurological outcomes.

The findings of a single group intervention study by Hartl et al. (1997) indicate that mannitol is only effective in diminishing ICP when the initial ICP is hypertensive (>20 mmHg) and not when it is below such values. Thus, the use of mannitol as a prophylactic measure against potential elevations in ICP may not be appropriate. This was corroborated by Sorani in a more recent study (Sorani, Morabito, Rosenthal, Giacomini, & Manley, 2008).

Conclusions

*There is Level 1 evidence that sodium lactate is more effective than mannitol for the management of acute elevations in ICP.*

*There is Level 2 evidence that higher dose mannitol is superior to conventional mannitol in improving mortality rates, and clinical outcomes.*
There is Level 2 evidence that early out-of-hospital administration of mannitol does not adversely affect blood pressure.

There is Level 4 evidence that mannitol is effective in diminishing intracranial hypertension only when initial ICP values are elevated.

Sodium lactate is more effective than mannitol for reducing acute elevations in ICP. High dose mannitol results in lower mortality rates and better clinical outcomes compared with conventional mannitol.

Early out of hospital administration of mannitol does not negatively affect blood pressure.

Mannitol may only lower ICP when initial ICP values are abnormally elevated.

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 up-regulate dopamine activity (Meythaler et al., 2002). Dopamine is thought to be involved in frontal lobe stimulation and plays a role in behavior, mood, language, motor control, hypothalamic function and arousal (Sawyer et al., 2008). Amantadine was initially developed for prophylactic use as an antiviral agent in the prevention of influenza A, but is now in common use in the treatment of Parkinson’s disease. Amantadine’s properties as a potential neuro-active agent were quickly recognized (Zafonte et al., 2001) and there is now interest in its use as a potentially useful treatment in the management of ABI (Schneider et al., 1999). Researchers believe that amantadine could significantly improve arousal in comatose patients. Potential side effects, which are easily reversible, include over-stimulation, peripheral edema, livido reticularis, and lowering of the seizure threshold (Schneider et al., 1999) The favourable risk-benefit profile of amantadine suggests that it may be an attractive treatment option for inducing arousal from coma (Hughes et al., 2005).
Neither the American Association of Neurological Surgeons nor the European Brain Injury Consortium have made recommendations regarding amantadines use in ABI management.

**Individual Studies**

**Table 12.31 Effects of Amantadine on Arousal from Post ABI Coma in both the Adult and Pediatric Populations**

<table>
<thead>
<tr>
<th>Author/Year/Country/Study design/PEDro Score</th>
<th>Methods</th>
<th>Outcome</th>
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<tr>
<td>McMahon et al., (2009) USA RCT PEDro = 7</td>
<td>N=7 Children with ABI were randomized to receive either amantadine or placebo for 3 weeks followed by a wash-out week and three weeks of the other agent. Patients were evaluated on the coma/near-coma scale (CNCS) and the coma recovery scale-revised (CRS-R) three times per week as well as weekly subjective evaluations by arousal and consciousness weekly.</td>
<td>No significant differences were noted in the slopes of recovery between the two agents on either of the outcome scales. Improvements in consciousness were noted by the physician during weeks when amantadine was given.</td>
</tr>
<tr>
<td>Patrick et al., (2006) USA Pre-Post RCT PEDro=7</td>
<td>N=25 Children and adolescents with severe TBI (Rancho Los Amigos Scale level &lt;4) who remained in a low response state at least 1 month post-injury were randomized to receive either amantadine or pramipexole. Subjects were evaluated with the Coma Near Coma Scale, Western NeuroSensory Stimulation Profile, and Disability Rating Scale at baseline and weekly.</td>
<td>The weekly rate of change was significantly better on all three measures on medication than off medication (p&lt;0.05). Rancho Los Amigos Scale levels also improved significantly on medication (p&lt;0.05).</td>
</tr>
<tr>
<td>Meythaler et al., (2002) USA RCT- cross-over PEDro=6</td>
<td>N=35 Patients with severe TBI related diffuse axonal injury (GCS &lt;11) were randomly assigned to a placebo controlled crossover design trial. Patients were administered 200mg amantadine or placebo daily for 6 weeks and then the opposite for the next 6 consecutive weeks. Outcome measures included the Disability Rating Scale, Mini Mental Status Exam, Glasgow Outcome Scale, Galveston Orientation and Amnesia Test, and the Functional Independence Measure (cognitive).</td>
<td>In group one (amantadine first), there was an improvement in MMSE scores of 14.3 points (p=.0185), DRS of 9.8 points (p=0.0022), GOS of 0.8 points (p=0.0077), and FIM-cog of 15.1 points (p=0.0033) but no improvement in the second six weeks on placebo (p&gt;0.05). In group two (placebo first), there was an improvement of MMSE of 10.5 points, in the DRS of 9.4 points (p=0.0006), GOS of 0.5 points (p=0.0231), and FIM-cog of 11.3 points (p=0.003, Wilcoxon signed rank) spontaneously on placebo. In the second six weeks, group two also continues to make significant gains in MMSE (6.3 points, p=0.409), DRS (3.8...</td>
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<td>Author/Year/Country/Study design/PEDro Score</td>
<td>Methods</td>
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<td>Hughes et al., (2005) Canada Chart Review</td>
<td>N=123 Some patients admitted over a 10-year period who remained in coma after becoming medically stable were administered 100-200 mg of amantadine twice daily. Charts for these patients were compared with charts from those who did not receive amantadine and emergence from coma was reviewed.</td>
<td>No significant difference in the number of patients emerging from coma was seen between groups (p=0.42). Somatosensory evoked potential (SSEP) was identified as a significant predictor of emergence (p=0.02).</td>
</tr>
<tr>
<td>Saniova et al., (2004) Slovak Rep. Chart review</td>
<td>N=74 Patients with severe head injury (GCS&lt;8) were retrospectively identified as having been treated with amantadine or not. Groups were assessed for differences in discharge GCS and mortality rates.</td>
<td>Patients treated with amantadine showed significant improvement on discharge GCS scores (p&lt;0.0001) and decreased mortality (p&lt;0.001).</td>
</tr>
<tr>
<td>Green et al., (2004) USA Case-Control</td>
<td>N=54 Patients (age range: 3-18 years) were treated with amantadine treatment or no neurostimulant. Length of stay (LOS), length of post-traumatic amnesia (PTA), initial Ranchos Los Amigos (RLA) level and change in RLA level during rehab stay, complications and any documented improvements were measured.</td>
<td>5 patients in the amantadine group (9%) had reversible side effects. The treatment group started with lower RLA Levels, and demonstrated greater improvements in RLA Levels, p&lt;.01. Subjective improvement was revealed in 63% of patients in the amantadine group.</td>
</tr>
<tr>
<td>Whyte et al., (2005) USA Cohort</td>
<td>N=47 In this longitudinal observational study, comatose brain injured patients (GCS 3-8) were a retrospectively reviewed for exposure to amantadine and assessed for improvements in Disability Rating Score (DRS) and time until commands were followed.</td>
<td>Patients receiving amantadine showed significant improvements in DRS scores in the first week following administration (p&lt;0.01) which remained in the second week post treatment (p=0.06).</td>
</tr>
</tbody>
</table>

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

**Discussion**

In the only RCT regarding amantadine’s effectiveness for improving consciousness in adults, Meythaler and colleagues randomly assigned patients to receive amantadine or placebo for 6 weeks with a crossover to the other for a second 6 week period (Meythaler et al., 2002). All patients had suffered severe TBI related diffuse axonal injuries. Patients were assessed for several indicators of alertness and cognitive function. They found that patients who received amantadine initially made significant gains on all outcome measures but made no further gains when they were switched to
placebo. Patients assigned to the placebo group initially made smaller but still significant gains when on the placebo but then went on to make further improvements on the Disability Rating Scale, Mini Mental Status Exam, Galveston Orientation and Amnesia Test, and the Functional Independence Measure (cognitive) in the second 6 week period after amantadine induction. The authors note that while patients receiving placebo initially made some natural recovery, patients receiving amantadine made more pronounced improvements. Furthermore, the improvements made by patients receiving amantadine in the second 6 week period suggest that amantadine aids in recovery no matter when it is administered.

Two randomized trials of amantadines use in children were located. In the first, children were administered amantadine or placebo for three weeks followed by the opposite for three weeks (McMahon et al., 2009). The authors report that no significant differences were noted in coma recovery during amantadine administration. However, two patients dropped out of the study, one due to medical complications and the other because the family requested unblinded administration of amantadine in the second three weeks. These drop-outs coupled with the small number of subjects may have masked any potential improvements. The authors suggest that amantadine did indeed show signs of improving consciousness and should be studied further.

In the second study, Patrick et al. (2006) conducted a randomized trial in which children and adolescents who remained in a low-responsive state 1 month post-injury were assigned to receive amantadine or pramipexole (both dopamine agonists). Patients in both groups made significant improvements on the Coma Near Coma Scale, the Western NeuroSensory Stimulation Profile, and the Disability Rating Scale weekly gains. Patients also improved on Racho Los Amigos Scale level. There were no significant side effects to treatment which, combined with the positive results, suggest that dopamine agonists may be a viable option for coma arousal in children and adolescents. However, the lack of control group and small sample size warrant further study before conclusions are drawn.

Green et al. (2004) evaluated the safety of amantadine in a paediatric population. In this study, 5 out of 54 patients experienced side effects which were all readily reversible. The significant change in Ranchos Los Amigos level in the treatment group was questionable due to differences in baseline. There were no significant differences in post-traumatic amnesia or length of stay. The subjective improvements reported were difficult to distinguish from natural recovery.

Three other studies were located which assessed amantadine. Hughes et al. (2005) conducted a chart review of all comatose brain injured patients admitted over a 10-year period in which patients who received amantadine were compared with a control group of patients who did not receive amantadine (Hughes et al., 2005). They noted that patients receiving amantadine were no more likely to emerge from coma (p=0.42). The
authors caution of potential confounders, such as potential selection bias, which may have affected the results. Also, the point at which a patient was considered to have emerged from the coma was arbitrarily assessed. Whyte et al. (2005) also conducted a retrospective review of comatose patients who received amantadine (Whyte et al., 2005). They isolated patients who received amantadine in weeks 4-16 post injury to assess its potential in improving consciousness after medical stability was reached. They noted that patients who received amantadine showed significant improvements in DRS scores one week after administration when compared to patients treated by other methods. They also measured the time to first response to directions in which they saw no significant difference in amantadine patients. Saniova et al. (2004) conducted a chart review of patients who were treated with amantadine as a component of standard therapy compared to similar patients who were not. They found that patients treated with amantadine showed significant improvements in GCS at discharge and decreased mortality rates. While the retrospective nature of these three studies makes it difficult to draw conclusions, all three authors suggest that amantadine is a safe option with promising potential and that further study is warranted.

Conclusion

There is Level 1 evidence that amantadine may improve levels of consciousness and cognitive function in patients in various stages of coma.

There is Level 3 evidence that amantadine facilitates rate recovery post-traumatic brain injury.

**Amantadine may improve consciousness and cognitive function in comatose ABI patients.**

**Amantadine may facilitate rate recovery post-traumatic brain injury in children.**

### 12.12.1.2 Amantadine and Cognitive Rehabilitation

One study was identified that investigated the effectiveness of amantadine as a treatment for the remediation of learning and memory deficits and executive function post ABI.
Individual Studies

Table 12.32 Effects of Amantadine on Executive Functioning and Learning and Memory Deficits Following an ABI

<table>
<thead>
<tr>
<th>Author/Year/Country/Study design</th>
<th>Methods</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kraus et al., (2005) USA Pre-Post</td>
<td>N=22 subjects with chronic brain injury and complaints of cognitive impairment participated in this pre- and post- 12-week treatment. Patients were given 400mg of amantadine.</td>
<td>Measures of executive function were significantly improved in patients following treatment of amantadine (p&lt; 0.02); however, no significant differences were noted on measures of attention or memory deficits.</td>
</tr>
</tbody>
</table>

Discussion

Kraus et al. (2005) demonstrated that the administration of amantadine over a 12-week treatment period does not improve measures of memory deficits or attention; however, significant improvements in executive functioning were found.

Conclusions

_There is Level 4 evidence that amantadine does help to improve executive functioning based on the conclusions of a single group intervention; but it does not help improve memory or attention deficits._

_Amantadine may be an effective treatment to improve executive function following brain injury but it has not been shown to improve learning and memory._

12.12.1.3 Amantadine and Behavioural Therapy

Individual Studies

Table 12.33 Effects of Amantadine on Behaviour Post TBI

<table>
<thead>
<tr>
<th>Author/Year/Country/Study Design/PEDro Score</th>
<th>Methods</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Schneider et al., (1999) USA RCT PEDro= 5</td>
<td>N=20 TBI rehabilitation subjects randomly assigned to treatment and placebo groups to test the effectiveness of amantadine on cognitive and behavioural rehabilitation.</td>
<td>Although there was a general trend towards improvement, results did not reach significance when treatment and placebo groups were compared using ANOVA and regression analysis (p=0.732).</td>
</tr>
</tbody>
</table>
### Discussion

Schneider et al. (1999) completed a double-blind RCT evaluating the effects of amantadine on cognition and behavior. Twenty patients were included in the study and each took amantadine for 2 weeks. Statistical comparison of results evaluating the five subsets of attention, executive/flexibility, memory, behavior and orientation did not demonstrate any significant effect for the use of amantadine.

### Conclusion

*There is Level 2 evidence that amantadine did not help to improve behaviour following brain injury.*

*Amantadine may not be an effective treatment for behaviour following brain injury.*

### 12.12.2 Dopamine Medications used in the Pediatric Population

#### Individual Study

<table>
<thead>
<tr>
<th>Author/Year Country/Study Design/PEDro Score</th>
<th>Methods</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nickels et al., (1994) USA Case Series</td>
<td>N=12 Retrospective chart review of subjects with brain injury treated with Amantadine.</td>
<td>10 of the 12 subjects experienced some improvement in cognitive and/or physical function while using Amantadine. 5 of the 12 subjects experienced side effects that included pedal oedema, hypomania, generalized seizure, and visual hallucinations.</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Author/Year</th>
<th>Country/Study design</th>
<th>Methods</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patrick et al., (2003) USA Case Series</td>
<td>N=10 A retrospective, descriptive study of the records for ABI individuals with low response rate (7-TBI, 1-stroke, 1-anoxia, 1-encephalitis) that had been treated with a dopaminergic agonist (amantadine, pramipexole, bromocriptine, levodopa, methylphenidate). Treatment introduced on average 52.5 days post-injury, and lasted an average of 39 days.</td>
<td>Western NeuroSensory Stimulation Profile (WNSSP) taken within 24 hours of admission, and 3 days before medication (baseline), then 15, 26, and 43 days following onset (on average). Final WNSSP assessments significantly improved over baseline (p&lt;0.01). Rate of change significantly greater in medication phase (p=0.02)</td>
<td></td>
</tr>
</tbody>
</table>
Discussion
Patrick et al. (2003) examined the effect of a number dopamine enhancing medication on improvement in low response states. This study suggested a positive relationship between rate of recovery for children in a low response state and administration of dopamine-enhancing drugs. Limitations of this study include the fact that it is retrospective, involving only ten children, studying the use of a number of different medications when children are in the early stage of recovery (average 24 days).

Conclusion

There is Level 4 evidence that dopamine-enhancing drugs facilitate rate recovery post-traumatic brain injury.

Dopamine enhancing drugs may facilitate rate of recovery post TBI in children.

12.12.3 Bromocriptine

Bromocriptine is a dopaminergic agonist, which primarily affects D² 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. Four studies have been identified investigating the use of bromocriptine as an adequate treatment for the recovery of cognitive impairments following brain injury.

Individual Study

Table 12.35 The Effects of Bromocriptine on Executive Functioning Following an ABI

<table>
<thead>
<tr>
<th>Author/Year/Country/Study design PEDro Score</th>
<th>Methods</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Whyte et al., (2008) USA RCT PEDro=7</td>
<td>N=12 Bromocriptine or placebo was administered for 4 weeks, (starting dose was 1.25 mg/BID, final dose was 5 mg/BID). Medication was increased every 2 days until the dose reached 5 mg BID. During week 4 the medication was tapered until it was eliminated. Once this phase was complete the group was put on the placebo. The placebo group then became the bromocriptine group. Study continued</td>
<td>It was noted that several participants did experience moderate to severe drug effects and withdrew or were withdrawn from the study. Test results for all subjects indicate bromocriptine had little significant effect on their abilities to perform on a range of measures of attentional function.</td>
</tr>
<tr>
<td>Author/Year/Country/Study design/PEDro Score</td>
<td>Methods</td>
<td>Outcome</td>
</tr>
<tr>
<td>--------------------------------------------</td>
<td>---------</td>
<td>---------</td>
</tr>
<tr>
<td>McDowell et al., (1998) USA RCT PEDro = 4</td>
<td>N=24 Subjects suffering a TBI (closed or open) with loss of consciousness (GCS &lt; 8). Patients randomized into treatment (Bromocriptine 2.5 mg) and placebo groups. Measures required prefrontal cortex function (working memory, executive control) and were administered using a laptop computer (except trail making and control task) Testing took place 90 minutes after pill administration.</td>
<td>Central executive testing: following drug treatment there were significant improvements on dual task counting (p=0.028), dual task digit span (p=0.016), trail making test (p=0.013), Stroop Interference Test (p=0.05), FAS Test (p=0.02), Wisconsin Card Sorting (p=0.041). The treatment drug had no significant effects on working memory tasks (p=0.978),</td>
</tr>
<tr>
<td>Powell et al., (1996) UK Case series</td>
<td>N=11 An open, multiple baseline design of a group of patients (6 men and 5 women) who were administered bromocriptine.</td>
<td>The use of bromocriptine was associated with improvements in all measures of motivational deficits except mood, as measured by innovative structured tools that could quantify these deficits.</td>
</tr>
<tr>
<td>Dobkin and Hanlon (1993) USA Observational case study No Score</td>
<td>N=1 A blinded, controlled, alternating repeated-measures design of a 33-year-old woman who was treated with bromocriptine.</td>
<td>Significant improvements in verbal learning, functional memory, and daily recall were observed.</td>
</tr>
</tbody>
</table>

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

**Discussion**

Bromocriptine is believed to have an effect on frontal lobe functioning. In a randomized placebo controlled cross over study conducted by Whyte et al. (2008) bromocriptine was administered to a group of individuals. Administration of bromocriptine was begun at 1.25mg/BID and increased to 5mg/BID. Individuals received the medication for 3 weeks before being titrated off the medication and placed on a placebo. Test results for all subjects indicate bromocriptine had little significant effect on their abilities to perform on a range of measures of attentional function. It was noted that several participants did experience moderate to severe drug effects and withdrew or were withdrawn from the study. In an earlier study, McDowell et al. (1998) examined the effects of low dose bromocriptine in a double-blinded, placebo-controlled cross-over...
design trial. Testing revealed that a low dose of bromocriptine (2.5 mg/daily) improved functioning on tests of executive control including a dual task, trailmaking test, the Stroop test, the Wisconsin Card-Sorting Test and the controlled oral word association test (FAS test). However, bromocriptine did not significantly influence working memory tasks.

A blinded, controlled, alternating repeated-measures design by Dobkin and Hanlon (1993) looked at the effects of bromocriptine on memory impairment. The 33-year-old woman included in their study experienced significant improvements in verbal learning, functional memory, and daily recall.

Powell et al. (1996) carried out a multiple baseline design on eleven patients with TBI or subarachnoid haemorrhage who were administered bromocriptine. Motivational deficits were the main outcomes measured and they were quantified using innovative structured tools that could measure anxiety and depression for instance. Improvements were found on all measures assessed except mood.

Although the McDowell et al. (1998) study demonstrated benefits following administration of bromocriptine, there was only a single administration of bromocriptine or placebo and the dose was considerably lower than that given by Whyte et al. (2008). Spontaneous recovery may have been a factor leading to the improved abilities in individuals receiving a single dose (2.5mg daily) of the medication; however, study results did not answer this question. Results from Whyte et al. (2008) noted that the placebo group demonstrated better (although not significant) trends in improvement on the various tasks administered.

**Conclusions**

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

*There is Level 4 evidence that bromocriptine improves all motivational deficits except mood.*

*There is Level 5 evidence, from one observational study, that bromocriptine significantly improves memory impairments.*
12.13 Hormone Therapy

12.13.1 Dexamethasone and the Paediatric Population

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

Individual Studies

Table 12.36 Effects of Dexamethasone in Severe TBI

<table>
<thead>
<tr>
<th>Author/Year/Country/Study design/PEDro Score</th>
<th>Methods</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dearden et al., (1986a) UK RCT PEDro = 7</td>
<td>N=130 Randomized controlled trial comparing treatment with Dexamethasone and placebo in patients with brain injury. It is not clear how many were children. Age range was 3 to 79 years. Dosing for children not clearly reported.</td>
<td>Glasgow Outcome Score at 6 months, peak unstimulated mean ICP and complication rates (gastrointestinal, pulmonary, or other extra-cranial complications) failed to reach significant difference.</td>
</tr>
<tr>
<td>Fanconi et al., (1988) Switzerland RCT PEDro = 3</td>
<td>N=25 Prospective randomized controlled trial with a group of children aged 1.8-15.8 years (average. 7.5) received either dexamethasone (1mg/kg/day for 3days) or placebo.</td>
<td>Patients receiving dexamethasone showed depression of endogenous cortisol, while those not receiving dexamethasone had 5 fold increases in basal mean free cortisol. A higher frequency of pneumonia was reported in the group receiving exogenous steroids. No measurable difference in ICP, other laboratory data, duration of ventilation or Glasgow Outcome Scale (GOS) at 6 months</td>
</tr>
<tr>
<td>Kloti et al., (1987) Switzerland RCT PEDro = 3</td>
<td>N=24 Randomized controlled trial in which children were randomly assigned to one of two conditions: dexamethasone or placebo (control).</td>
<td>Patients receiving dexamethasone suppressed endogenous cortisol, the control produced 20-fold higher free cortisol. It is thought that glucocorticoids did not result in any more beneficial effects than endogenous cortisol.</td>
</tr>
</tbody>
</table>

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

Discussion

The paediatric data highlights the fact that dexamethasone suppresses endogenous production of glucocorticoids therefore bringing into doubt any beneficial effect of exogenous glucocorticoids. This evidence, when added to the mixed adult / paediatric randomized placebo controlled study (Dearden et al., 1986a) which fails to show difference in outcome, highlights the lack of firm data to support the use of these drugs in brain injured individuals.
**Conclusion**

*There is Level 1 evidence based on three RCTs that administration of dexamethasone inhibits endogenous production of glucocorticoids and has no proven impact on recovery post brain injury.*

---

**Administration of dexamethasone inhibits endogenous production of glucocorticoids in children.**

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

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**12.13.2 Medroxyprogesterone**

Sexual dysfunction following TBI has been reported to occur in at least 50% of patients (Emory et al., 1995). Hypersexuality is less common than hyposexuality (decreased libido) but results in a greater negative effect for the individual and results in a great burden of care and limited independence (i.e. is less tolerated in the community). Hypersexual behaviour can range from “indiscriminate sexual overtures, promiscuity, exhibitionism, to assault and/or rape.” Treatment for non-brain injured sexual offenders has included pharmacological intervention and/or counseling/education. Typically, medication is used to reduce the sexual drive, but it is unclear if it has effect on cognitive processing (i.e. perseverative thoughts regarding sex).

**Individual Studies**

<table>
<thead>
<tr>
<th>Author/Year/Country/Study design</th>
<th>Methods</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Emory et al., (1995) USA Case Series</td>
<td>N=8 Blunt trauma, TBI subjects, who were 16 to 27 yrs of age when they began exhibiting inappropriate, contact, hyper-sexual behaviour received weekly injections of Depo-Provera in conjunction with directive, individual-specific counseling for 6 months – with follow-up every 3-6 months for 2 years.</td>
<td>Family members report all subjects stopped aberrant behaviour while taking medication. Blood work revealed a drop in testosterone from 834 to 85 mg/dL. Three subjects returned to previous patterns after stopping medication – due to inconsistent family support. 3 subjects dramatically improved and did not stop medication.</td>
</tr>
</tbody>
</table>

**Discussion**

In a retrospective study, medroxyprogesterone acetate (Depo-Provera; an anti-androgen drug) was evaluated in terms of its efficacy for controlling sexual aggression in
Evidence-based Review of Moderate to Severe Acquired Brain Injury

8 TBI males experiencing onset of sexual aggression 3 years post-injury (Emory et al. 1995). Weekly intramuscular injections of Depo-Provera (400 mg) in conjunction with monthly psychoeducational counseling occurred for 6 months and then follow-up examinations occurred every 3 months for 2 years (mean duration of treatment was 42 months). Results indicate a cessation of hypersexual behaviour and reduced testosterone levels. Three subjects re-offended when the drug was stopped, 3 remained on it and 2 stopped taking the drug and have maintained cessation of hypersexual behaviour.

**Conclusion**

*There is Level 4 evidence that an antiandrogen and counselling reduces sexually aggressive behaviour.*

12.13.3 Progesterone

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

Individual Studies

Table 12.38 Effects of Progesterone in the Treatment of Acute ABI

<table>
<thead>
<tr>
<th>Author/Year/Country/Study design/PEDro Score</th>
<th>Methods</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wright et al., (2007) USA RCT PEDro=10</td>
<td>N=100 Adult TBI patients (GCS 4-12) who arrived within 11 h after injury were randomized 4:1 to IV progesterone or placebo. Treatment patients received 0.71 mg/kg progesterone at 14mL/h for 1 h, then 0.5mg/kg at 10 mL/h for 11 h, and then 10mL/h maintenance infusions every 12h to a total of 3 days treatment. Patients were assessed for adverse event rates, 30-day mortality, and 30 day GOS-E scores.</td>
<td>Adverse event rates were similar between groups and no serious adverse events were associated with progesterone. Patients in the progesterone group had lower 30-day mortality rates (RR 0.43; 95%CI 0.18 – 0.99). Moderately severe patients (GCS 9-12) in the progesterone group were more likely to have a moderate to good recovery on GOS-E (p=0.0202).</td>
</tr>
<tr>
<td>Xiao et al., (2008) China RCT PEDro=7</td>
<td>N=159 Patients with severe TBI (GCS3-8) were prospectively randomized to receive progesterone (1.0 mg/kg via intramuscular injection b.i.d.) or placebo. Neurological outcome was measured using the GOS. Modified FIM and mortality rates were also evaluated.</td>
<td>Patients receiving progesterone showed more favourable outcomes on the GOS at 3 months (p=0.034) and 6 months (p=0.048). Progesterone patients also had higher mFIM scores (p&lt;0.05 and p&lt;0.01) and lower mortality rates (p&lt;0.05) at 3 and 6 month follow-ups. No instances of complications were found after progesterone administration.</td>
</tr>
</tbody>
</table>

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

Discussion

Two RCTs were identified that assessed progesterone use for the treatment of acute ABI. Wright et al. (2007) conducted a phase II clinical trial of progesterone for care of moderate and severe ABI patients (GCS 4-12) in response to positive clinical observations and animal trials (Wright et al., 2007). As a phase II trial, the initial goal was to assess the safety of progesterone administration. For this purpose, patients were allocated 4:1 to the progesterone group compared to the placebo group. Patients were monitored for any complications so that inter-group comparisons could be made. Patients in the progesterone group showed no increase in complication rates and a decreased 30-day mortality rate. Moderately severe patients in this group also showed significantly greater rates of moderate to good GOS-E scores. The authors point to limitations in sample size and group distribution as cautioning factors but feel the results are encouraging and warrant a larger, more thorough clinical trial.

More recently, Xiao et al. (2008) conducted a placebo controlled RCT of progesterone use in TBI patients in China. Patients received a 5-day course of progesterone during acute management. They reported significant improvements in GOS scores, mFIM
scores at 3 and 6-month follow-up and decreases in mortality rates at 6 months. They also reported no complications associated with progesterone administration.

These two studies suggest that progesterone is safe and effective improving patient outcomes after ABI. Further study should be performed to verify these results and identify specific indications for its use.

**Conclusions**

*There is Level 1 evidence that progesterone improves GOS and modified FIM scores, and decreases mortality rates in ABI patients.*

**Progesterone decreases 30-day mortality rates.**

**Progesterone improves GOS and modified FIM scores at 3 and 6 months post-injury.**

### 12.14 (a) Psychostimulants

#### 12.14.1 Methylphenidate

**12.14.1.1 Methylphenidate and Cognitive Functioning**

Methylphenidate is a stimulant whose exact mechanism is unknown (Napolitano, et al., 2005). Although it is thought to act on the presynaptic nerve and acts to restrain the reabsorption of serotonin and norephinephrine (Kim et al., 2006). Methylphenidate has been extensively used as a treatment for attention deficit disorder, as well as narcolepsy (Glenn, 1998). Four randomized controlled trials examined the efficacy of methylphenidate as a treatment for the recovery of cognitive deficits post-brain injury.

### Individual Studies

**Table 12.39 Effects of Methylphenidate on Cognitive Functioning Post ABI**

<table>
<thead>
<tr>
<th>Author/Year/Country/Study design/PEDro Score</th>
<th>Methodology</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kim et al., (2012) USA RCT PEDro = 7</td>
<td>N=33 Participants were randomized to either the treatment (Methylphenidate-MPH) group or a control (placebo) group, although only 18 completed the study. Those in the treatment group were given a single dose of 0.3mg/kg rounded to the nearest 2.5 mg of methylphenidate on each of the testing days. Each group performed a</td>
<td>Those in the MPH group showed an improvement in accuracy and reaction time in the sustained attention task, but only reaction time in the working memory task. Response time on the two-back task was faster on MPH than on placebo Accuracy was also greater for those in the MPH group but this difference was not significant.</td>
</tr>
<tr>
<td>Author/Year/Country/Study design/PEDro Score</td>
<td>Methodology</td>
<td>Outcome</td>
</tr>
<tr>
<td>---------------------------------------------</td>
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<td>---------</td>
</tr>
<tr>
<td><strong>Kim et al., (2006) Korea RCT PEDro = 6</strong></td>
<td>Double-blind placebo-controlled trial of subjects with TBI. The participants were randomly divided into one of two treatment groups: (1) single-dose (20mg) of methylphenidate; or (2) placebo. Outcome measured using visuospatial attention tasks.</td>
<td>Improvements in response accuracy were demonstrated in favour of the treatment group although not to a level of statistical significance.</td>
</tr>
<tr>
<td><strong>Plenger et al., (1996) USA RCT PEDro = 5</strong></td>
<td>N=23 Double-blind RCT of subjects ranging in age from 16 to 64 years administered 0.30 mg/kg of methylphenidate twice a day. 9 subjects completed the study</td>
<td>Methylphenidate significantly improved attention.</td>
</tr>
<tr>
<td><strong>Speech et al., (1993) USA RCT PEDro = 7</strong></td>
<td>N=12 Moderate-to-severe closed-head-injury patients randomly assigned to a treatment group receiving 0.3mg/kg bid of methylphenidate for 1 week followed by placebo, and control group receiving a placebo for 1 week followed by methylphenidate treatment. Attention, cognitive processing speed, learning and social personality functioning measures applied at the end of each week, 1 hr after last dose.</td>
<td>No significant differences found between drug and placebo condition in any outcome measure.</td>
</tr>
<tr>
<td><strong>Whyte et al., (2004) USA RCT PEDro = 8</strong></td>
<td>N=34 Double-blind crossover study of methylphenidate (0.3 mg/kg/dose) versus placebo measured by sustained/divided arousal, attention, distraction tasks with varying target rates on subjects, between 16 and 60 with a non-penetrating TBI resulting in LOC (GCS&lt;12), PTA &gt; 1 hour or a focal abnormality (neuro-imaging); outcome measures included subject response as well as reports from treating clinicians and caregivers.</td>
<td>54 dependent variables reduced to 13 composite factors revealing significance in three treatment effects: information processing speed (p&lt;0.001), work task attentiveness (p=0.01), and caregiver attention ratings (p=0.01). Of 13 independent variables, one showed significant treatment effects: reaction time before errors in sustained attention to response task (p=0.03). No treatment-related improvements observed in susceptibility to distraction, and divided or sustained attention.</td>
</tr>
</tbody>
</table>

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

**Discussion**

In a RCT examining the effects of methylphenidate, a psychostimulant on attention, 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. Another RCT by Plenger et al. (1996) also found that methylphenidate significantly improved attention.

Speech et al. (1993) conducted a double blind placebo controlled trial evaluating the effects of the stimulant medication methylphenidate following closed head injury. In contrast to the results noted by Whyte et al. (2004) and Plenger et al. (1996) methylphenidate did not demonstrate significant differences compared to placebo on measures of attention, information processing speed, or learning. Kim et al. (2006) examined the effects of a single-dose treatment of methylphenidate and, although a trend was found in favour of improved working and visuospatial memory for the treatment group, these results did not reach significance. Recently Kim et al. (2012) found reaction time and accuracy in the sustained attention task improvement significantly while on the methylphenidate.

**Conclusions**

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

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

**12.14.1.2 Methylphenidate and Fatigue**

Of the neurostimulatints used in the post-acute care of those with a TBI, methylphenidate is one of the most common, assisting with memory, attention, verbal fluency, and improving processing speed; however, little has been written on the effects of methylphenidate on the sleep-wake cycles of those with a BI (Al-Adawi, Burke, & Dorvlo, 2006). In one double-blind, placebo-controlled study looking at the effects of methylphenidate, sertraline or placebo on individuals with a mild or moderate TBI, Lee et al. (2005), noted that those on methylphenidate, along with those in the placebo group reported significantly less day-time sleepiness than those in the sertraline group. In this study all medications were given during the day for a total of four weeks which may have impacted on the effectiveness of sertraline (Lee et al. 2005).
Individual Studies

Table 12.40 Effects of Methylphenidate on Sleep Disorders Post ABI

<table>
<thead>
<tr>
<th>Author/Year Country/Study Design</th>
<th>Methods</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Al-Adawi et al., (2006) Oman/USA Non-RCT</td>
<td>N=30 Those in the methylphenidate group (n=17) were given the medication at 8 am and 2 pm. The remaining individuals (n=13) received no medication.</td>
<td>No significant differences were noted when looking at the scores from the activities of daily living, mobility and cognition scales. FIM scores were lower for those in the methylphenidate group 30.0 than for those not in the methylphenidate group their FIM scores were 34.9. No significant differences were noted when looking at the total sleep time between the two groups.</td>
</tr>
</tbody>
</table>

Discussion
In the current study by Al-Adawi et al. (2006) no significant differences were found between the two groups (those receiving methylphenidate and those not receiving the medication) when looking at the scores on various assessment scales (activities of daily living, mobility and cognition, FIM). Sleep times for the two groups also showed no significant differences between the two groups.

Conclusion

*There is Level 2 evidence, based on one cohort study, that methylphenidate does not improve the sleep-wake cycle of those who have sustained a TBI.*

Methylphenidate does not improve the sleep-wake cycle of those who have sustained a TBI.

12.14.1.3 Methylphenidate and the Paediatric Population

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

Methylphenidate has been shown to improve memory and attention in those with ADHD (Kempton et al., 1999).
Individual Studies

Table 12.41 Effects of Methylphenidate Interventions in Children with ABI

<table>
<thead>
<tr>
<th>Author/Year/ Country/Study design/Pedro Score</th>
<th>Methods</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mahalick et al., (1998) USA RCT PEDro = 7</td>
<td>N=14 Double blind placebo controlled crossover study of patients (aged 5 to 14 yrs) treated with 0.3 mg/kg b.i.d methylphenidate or placebo for 2 weeks</td>
<td>Significant difference between performance on attention / concentration tasks on drug in comparison to placebo (alpha = 0.05).</td>
</tr>
<tr>
<td>Williams et al., (1998) USA RCT PEDro = 8</td>
<td>N=10 Double-blind placebo, retrospective controlled trial of patients aged 8 to 16 yrs and between 50 to &gt;75lbs receiving 5-10 mgs of methylphenidate or placebo twice daily for 2 weeks. Medication doses were adjusted in relation to the child’s weight; thus those weighing 50lbs (20kgs) were given 5 mgs and so on. Subjects participated in the study for 2 weeks.</td>
<td>No significant difference between baseline &amp; end of medication / placebo trial in measures of memory, behaviour, attention, behaviour &amp; processing speed.</td>
</tr>
<tr>
<td>Hornyak et al., (1997) USA Case Series</td>
<td>N=10 A retrospective study of moderate to severe TBI children treated with methylphenidate to address cognitive and behavioural problems. In two cases it was used to stimulate minimally responsive patients.</td>
<td>Significant improvement in subject’s level of arousal, cognitive and behavioural functions.</td>
</tr>
</tbody>
</table>

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

Discussion

Mahalick et al. (1998) utilized a series of neurobehavioural tasks of attention and concentration to assess 14 children post brain injury. Significantly improved performance on attention and concentration tasks was reported. A retrospective controlled design was utilized but the period of time post injury varied from 1-60 months. Rapid, active recovery may be ongoing during this period of study.

Williams et al. (1998) using a double-blind retrospective controlled design found no significant difference in behaviour, attention, memory or speed of processing. Subjects in this study were between the ages of 5 and 16 and medication given varied with those weighing <20 kg receiving only 5 mg b.i.d. Those weighing more received a higher medication dose, with the maximum dose administered being 10 mg b.i.d. As in many pediatric studies, numbers were small (n=10). There was also significant variability in time since injury. Six subjects were within the first two years post injury when rapid change is more likely; four were more than two years post injury. Given the difficulties
in determining the extent of injury (mild vs severe), the differences in the length of time since injury and the small “n” size, the results of this study appear to be inconclusive.

The findings of Hornyak et al. (1997) suggested that the introduction of MPH resulted in improved cognitive/behavioural function post traumatic brain injury. This interpretation however, was based on qualitative data from a retrospective review of ten charts.

To date, no medication has proven to be effective in modifying outcome in the brain injured child. Investigators have studied the role of the psychostimulant methylphenidate (MPH) and other dopamine enhancing medication including amantidine, pramipexole, bromocriptine, and levodopa.

**Conclusion**

*Based on two small and conflicting RCTs there is inconclusive evidence that methylphenidate interventions improved cognitive behavioural function in children post acquired brain injury.*

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

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### 12.14 (b) Stimulants

#### 12.14.2 Modafinil

Modafinil, a wakefulness promoting agent, was initially approved for use with those who were having difficulty with excessive daytime sleepiness (EDS) (Jha et al. 2008). The drug was subsequently approved for use with those who suffer from narcolepsy and those who may experience sleeping difficulties associated with shift work (US Modafinil in Narcolepsy Multicenter Study Group, 2000; US Modafinil in Narcolepsy Multicenter Study Group, 1998). One studied investigate the effectiveness of modafinil with the ABI population. For further information on treatments for fatigue post ABI see Module15.

**Individual Studies**

<table>
<thead>
<tr>
<th>Author/Year</th>
<th>Country/Study Design/PEDro Score</th>
<th>Methods</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Jha et al., (2008) USA RCT</td>
<td>N=51 In this double blind cross over study, participants were divided into 2 groups: one group</td>
<td>Overall the medication was well tolerated but not very effective in treating fatigue in this ABI population.</td>
<td></td>
</tr>
</tbody>
</table>
Discussion

One randomized controlled trial (cross over design) was found looking at the effects of modafinil on fatigue and excessive daytime sleepiness (EDS) (Jha et al., 2008). Overall, study results did not find modafinil was very effective in treating fatigue and daytime sleepiness in individuals’ post ABI, although some changes could be seen. These results appear to be similar to those found when using modafinil to treat fatigue in other populations such as Parkinson disease or multiple sclerosis (Jha et al. 2008).

Conclusion

There is Level 1 evidence, based on one RCT, that Modafinil is not effective in treating fatigue or excessive daytime sleepiness post ABI.

12.15 Sedative Anaesthetic

12.15.1 Propofol

Propofol is a drug that reduces anxiety and tension, and promotes relaxation and sleep or loss of consciousness. Propofol provides loss of awareness for short diagnostic tests, surgical procedures, and supplements other types of general anesthetics. It is fast acting and is metabolized quickly. Its beneficial effects occur via decreases in peripheral vascular tension resulting in potential neuroprotective effects, which may be beneficial in acute ABI care. Experimental results have shown positive effects on cerebral physiology including reductions in cerebral blood flow, cerebral oxygen metabolism, EEG activity, and ICP (Adembri et al., 2007).

The American Association of Neurological Surgeons recommends propofol use for the control of ICP but not for improvement in mortality or 6 month outcome. They also indicate that high-dose propofol can produce significant morbidity (Bratton et al., 2007a). The EBIC recommend sedation as part of the treatment course for ABI but make no specific mention of propofol. Caution is recommended in the administration of propofol.
Individual Studies

Table 12.43 Effects of Propofol in the Management of Acute ABI

<table>
<thead>
<tr>
<th>Author/Year/Country/Study design/PEDro Score</th>
<th>Methods</th>
<th>Outcome</th>
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<tbody>
<tr>
<td>Kelly et al., (1999) USA RCT PEDro = 8</td>
<td>N=42 Patients with a GCS 3-12 who required mechanical ventilation were randomly assigned to receive propofol (20mg/ml with 0.005% EDTA) or morphine. Patients were assessed for adverse effects, physiological response (including ICP) and 6 month GOS.</td>
<td>Intracranial pressure therapy in the propofol group was less intensive than the morphine group (less use of neuromuscular blocking agents, benzodiazepines, pentobarbital, and CSF drainage) and ICP on day 3 was significantly lower (p&lt;0.05). Six month GOS scores were not significantly different between groups for mortality or favorable outcome rates.</td>
</tr>
<tr>
<td>Stewart et al., (1994) UK non-RCT</td>
<td>N=15 Patients were sedated with either a continuous infusion of propofol (mean 232 mg/hr, range 150-400 mg/hr) or infusions of morphine (mean rate 2.3 mg/hr, range 0-4mg/hr) and midazolam (mean rate 2.8mg/hr, range 0-5 mg/hr). Continuous collection of AVDO₂, MABP, ICP, and CPP was performed.</td>
<td>Propofol led to a fall in AVDO₂ after 4 hours from 6.0 ±2.6 ml/dl to 3.0 ± 0.6 ml/dl. No significant difference was seen in any of the other measures in either group. No difference was reported between groups on 6 month outcomes as measured by the GOS.</td>
</tr>
<tr>
<td>Farling et al. (1989) Ireland Case Series</td>
<td>N=10 Patients with severe head injuries that required sedation were given intravenous propofol infusions as a 1% solution at a rate of 2-4 mg/kg/hr. Dose was adjusted to maintain ICP below 10 mmHg and CPP above 60 mmHg. Patients were monitored for HR, MABP, ICP, CPP, pupil size and PaCO₂.</td>
<td>A mean infusion rate of 2.88 mg/kg/hr was sufficient for sedation and recovery was rapid. CPP was significantly increased at 24 hrs. No significant differences were seen in any of the other variables.</td>
</tr>
</tbody>
</table>

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

Discussion

In one RCT, propofol sedation was compared to morphine for safety and efficacy (Kelly et al., 1999). All patients received morphine in conjunction with propofol infusion. Propofol tended to reduce ICP generally with significance reached on day 3 (p<0.05). Patients in the propofol group also showed less need for neuromuscular blocking agents, benzodiazepines, pentobarbital, and CSF drainage. Results of the study suggest that propofol is a safe, acceptable, and possibly desirable alternative to opiate-based sedation (Kelly et al., 1999).

In a study conducted by Stewart et al. (1994), propofol was reported to provide satisfactory sedation with few side effects. Propofol provided sedation similar to a
combination of midazolam and morphine with no differences in 6 month outcomes between groups. Farling et al. (1989) also reported that propofol provided safe and effective sedation. Due to the size of the studies and their poor methodological scores further study is warranted.

Conclusions

There is Level 2 evidence that propofol may help to reduce ICP and the need for other ICP and sedative interventions when used in conjunction with morphine.

12.16 Sedative Benzodiazepines Medications

12.16.1 Lorazepam and Zopiclone

Individuals who survive a TBI, for 27 to 56% of the population, insomnia is a common complaint (Thaxton and Patel 2007). Lorazepam, a benzodiazepine (also known has Ativan or Temesta), is primarily an anti-anxiety medication; however, due to its side effects it also has been used for the treatment of sleep disorders (Thaxton and Patel 2007). Zopiclone, a nonbenzodiazepine working at the same receptor sites as benzodiazepines, has been used in the treatment of insomnia in individuals who have identified one of the following problems: sleep onset is delayed, they are having difficulties maintaining sleep or they wake early (Thaxton & Patel, 2007; Hair et al., 2008).

Individual Studies

<table>
<thead>
<tr>
<th>Author/Year Country/Study Design PEDro Score</th>
<th>Methods</th>
<th>Outcome</th>
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<tbody>
<tr>
<td>Li Pi Shan and Ashworth (2004) RCT Canada PEDro = 10</td>
<td>N=18 Individuals who had either a stroke or had sustained a brain injury were recruited to participate in the following study. Individuals were divided into one of two groups: lorazepam group (n=9) received 0 to 1 mg/day PRN; zopiclone group (n=9) received 3.75 to 7.5 mg/day PRN. Participants decided how much medication they would receive. Each medication was given for one</td>
<td>No significant differences were noted between the two groups or between the medications when looking at length of time asleep, alertness, feelings of being refreshed, quality of sleep, depth of sleep or feelings of tiredness or the results of the MMSE.</td>
</tr>
</tbody>
</table>
week with the order being reversed for week two.

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

Discussion
In a randomized, crossover, double-blind trial conducted by Li Pi Shan and Ashworth (2004) a group of stroke and TBI patients were divided into one of two groups. To assist with sleep, one group received lorazepam orally (0 to 1mg/daily PRN) in the evenings while the second group received zopiclone orally (3.75 to 7.5 mg/daily PRN) in the evening. At the end of the two week period, Li Pi Shan and Ashworth (2004) found little differences between the two groups. Differences in the length of sleep each group received were not found. Subjects found no differences on quality of sleep, depth of sleep, feelings of being refreshed or alertness between the two treatments. Cognition scores on the Mini Mental Status Exam (MMSE) were not significantly different between the two time periods.

Conclusion
There is Level 1 evidence, from one RCT, that lorazepam and zopiclone work equally well in assisting with insomnia symptoms post ABI.

Both lorazepam and zopiclone are effective in assisting with insomnia symptoms post ABI.

12.16.2 Midazolam
Midazolam another benzodiazepines 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). It has also been found to be effective in controlling seizures post injury. For a more detailed discussion of Midazolam see Modules 10 and 16.
Individual Studies

Table 12.45 Effects of Midazolam in the Management Acute ABI

<table>
<thead>
<tr>
<th>Author/Year/Country/Study design/PEDro Score</th>
<th>Methods</th>
<th>Outcome</th>
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</thead>
<tbody>
<tr>
<td>Sanchez-Izquierdo-Riera, (1998) Spain RCT PEDro = 5</td>
<td><strong>N=100</strong> Patients were randomly assigned to receive either one a continuous infusion of midazolam (0.1 mg/kg/hr to a max of 0.35 mg/kg/hr) or continuous IV infusion of propofol (1.5 mg/kg/hr to a max of 6 mg/kg/hr) or continuous infusion of midazolam (0.1 mg/kg/hr to a max of 0.2 mg/kg/hr) and propofol (1.5-3 mg/kg/hr) if further sedation was necessary. All patients received morphine as well. Patients were monitored for sedation, hemodynamic and oximetric variables.</td>
<td>All three regimens achieved similar sedation and incidences of adverse effects. No differences were found in ICP, CPP, or jugular venous oxygen saturation in head trauma patients. Serum triglyceride levels were significantly higher in propofol patients but wakeup time was shorter.</td>
</tr>
<tr>
<td>Papazian et al., (1993) France Case Series</td>
<td><strong>N=12</strong> Patients with severe head injury (GCS ≤ 6) were given bolus doses of midazolam (0.15 mg/kg IV). Patients were monitored for MAP, ICP, and CPP.</td>
<td>Significant reductions in MAP (89 mmHg to 75 mmHg, p&lt;0.0001) and in CPP (71 mmHg to 55.8 mmHg, p&lt;0.0001) were observed, but there was no significant change in ICP.</td>
</tr>
<tr>
<td>Davis et al., (2001) USA Case Series</td>
<td><strong>N=219</strong> Patients data was retrospectively reviewed in two facilities: north crews used 0.1 mg/kg for every patient being intubated while south crews used 0.1 mg/kg up to 5mg.</td>
<td>A significant relationship was seen between midazolam dose and both hypotension and decreased systolic blood pressure.</td>
</tr>
</tbody>
</table>

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

Discussion

Infusions of midazolam or propofol were reported to provide similar quality sedation in patients with severe head trauma, although propofol was associated with a high incidence of hypertriglyceridemia (Sanchez-Izquierdo-Riera et al., 1998). In both studies evaluating midazolam and ICP, no significant difference was seen after midazolam administration (Sanchez-Izquierdo-Riera et al., 1998; Papazian et al., 1993). However, significant hypotension related to increased doses of midazolam (Davis et al., 2001) and decreases in MAP resulting in decreased CPP (especially in patients with initial ICP ≤ 18 mmHg) (Papazian et al., 1993) were also reported. The study by Sanchez-Izquierdo-Riera et al. (1998) measured ICP, CPP and MAP in all patients and reported no between group differences. However, they did not report comparisons with baseline values making it unclear whether or not midazolam resulted in any negative effects. Based on current evidence, hypotension should be monitored as a potential side effect during midazolam administration.
Conclusions

There is Level 2 evidence that midazolam has no effect on ICP but conflicting evidence regarding its effect on MAP and CPP.

There is Level 5 evidence that acute intramuscular Midazolam can be used for acute seizure cessation.

Midazolam has no effect on ICP but may result in systemic hypotension.

Intramuscular midazolam may be effective for acute seizure cessation.

12.17 Steroids

12.17.1 Corticosteroids
Numerous corticosteroids have been used in brain injury care including dexamethasone, methylprednisolone, prednisolone, betamethasone, cortisone, hydrocortisone, prednisone 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) report that laboratory studies have associated reductions in wet brain weight, facilitation of synaptic transmission, reduction of lipid peroxidation, enhanced blood flow, preservation of electrolyte distribution, and membrane stabilization with corticosteroid use (Grumme et al., 1995). It is thought that benefits may arise from reductions in ICP as well as neuro-protective activity. However, several studies also suggest some limitations of corticosteroid use. Focal lesions seem to respond well to corticosteroid therapy while diffuse intracerebral lesions and hematomas are less responsive (Grumme et al., 1995; Cooper et al., 1979).

Questions regarding the safety of corticosteroid administration have been brought to light in the wake of several large scale trials. 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 (Alderson & Roberts, 1997). However, their 95% confidence interval ranged from a 7.5% reduction to a 0.7% increase in deaths. This only added to the uncertainty around corticosteroid safety and prompted a large multi-center trial. Roberts et al. (2004) studied corticosteroid use in acute brain injury with the goal of recruiting 20,000 TBI patients; after 10,008 patients were recruited it became clear that corticosteroid use caused significant increases in
Evidence-Based Review of Moderate to Severe Acquired Brain Injury

mortality and the trial was halted (Roberts et al., 2004). The American Association of Neurological Surgeons stated that steroid use was not recommended for improving outcomes or reducing ICP and that high-dose methylprednisolone was associated with increased mortality and was contraindicated (Bratton et al., 2007b). The EBIC state that there was no established indication for the use of steroids in acute head injury management (Maas et al., 1997).

**Individual Studies**

**Table 12.46 Effects of Corticosteroids for the Management of Elevated Intracranial Pressure and Neuro-Protection Post ABI**

<table>
<thead>
<tr>
<th>Author/Year/Country/Study design/PEDro Score</th>
<th>Methods</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Roberts et al., (2004) International RCT PEDro = 10</td>
<td>N=10 008 Patients with head injury (GCS≤14) whose physician was uncertain about administering methylprednisolone were randomized into a treatment group (48h administration) and a control group. Patients were then monitored for death within 2 weeks and death or disability at 6 months.</td>
<td>Compared with the placebo, the risk of death was higher in the corticosteroid group (relative risk 1.18, p=0.0001). The relative increase in deaths due to corticosteroids did not differ by injury severity (p=0.22) or time since injury (p=0.05).</td>
</tr>
<tr>
<td>Grumme et al., (1995) Germany/Austria RCT PEDro = 9</td>
<td>N=396 Patients diagnosed with head injury were randomized to a treatment group (200mg triamcinolone acetonide within 4h of trauma, then 3x40mg/day IV for 4 days, and 3x20 mg/day for 4 days) or placebo. Outcomes were measured using the GOS at discharge and 1 year after trauma.</td>
<td>No significant difference was seen between groups although a trend towards improved outcomes in the treatment groups was noted. A significant difference was seen in the subset of patients with GCS&lt;8 and focal lesions compared to placebo (p=0.0145) when good outcomes were compared.</td>
</tr>
<tr>
<td>Dearden et al., (1986) UK RCT PEDro = 4</td>
<td>N=130 Severely head injured patients were randomly allocated dexamethasone (50mg on admission, 100mg on days 1,2,3, 50mg on day 4 and 25mg on day 5), or placebo. ICP and 6 month GOS scored were measured.</td>
<td>Patients in the placebo group with ICP &gt; 20mmHg showed significantly poorer outcomes compared to similar patients in the placebo group (p=0.0377). No other differences were noted.</td>
</tr>
<tr>
<td>Gianotta et al., (1984) USA RCT PEDro = 7</td>
<td>N=88 Patients with a GCS ≤ 8 6 hours after nonpenetrating head trauma were given either high dose methylprednisolone sodium succinate (30mg/kg q6h x 2, then 250 mg q6h x 6, then tapering over 8 days), low dose methylprednisolone (1.5mg/kg q6h x 2, then 25 mg q6h x 6, then tapering over 8 days) or placebo. Follow-up was performed on all surviving patients at 6 months and were</td>
<td>At six months, no significant differences in mortality was seen between groups. There were also no significant differences in morbidity between groups.</td>
</tr>
<tr>
<td>Author/Year/Country/Study design/PEDro Score</td>
<td>Methods</td>
<td>Outcome</td>
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<tr>
<td>Braakman et al., (1983) Netherlands RCT PEDro = 4</td>
<td><strong>N=161</strong> Comatose patients admitted after a non-missile related head injury were randomized to receive high-dose dexamethasone or placebo. Survival at one month and 6 month GOS scores were used as assessments of effectiveness.</td>
<td>No significant differences were seen in 1 month survival rates or 6 month GOS scores between groups.</td>
</tr>
<tr>
<td>Saul et al., (1981) USA RCT PEDro = 4</td>
<td><strong>N=100</strong> Severely brain injured patients (GCS&lt;8) were given methylprednisolone (5mg/kg/day) or no drug. GCS was measured daily while in hospital and GOS at 6-months was used as the ultimate outcome.</td>
<td>No significant difference was seen in proportion of “good” and “disabled” outcomes compared to “vegetative” and “dead” outcomes between groups (p=0.22).</td>
</tr>
<tr>
<td>Kaktis et al., (1980) USA RCT PEDro = 4</td>
<td><strong>N=76</strong> Head injured adults who were comatose on admission were randomly allocated to a high-dose group (dexamethasone 24mg/day), low-dose group (dexamethasone 16mg/day), or placebo. Patients were monitored for ICP levels in 6 hour increments up until 72 hours after injury.</td>
<td>No significant differences in ICP levels were seen between groups at any point within the first 72 hours after injury.</td>
</tr>
<tr>
<td>Cooper et al., (1979) USA RCT PEDro = 8</td>
<td><strong>N=76</strong> Patients with Grady Coma Grade 3-5 were stratified for severity of injury and then divided into high dose dexamethasone (96mg/day), low dose dexamethasone (16mg/day) or placebo for 6 days. Outcome was assessed at 6 months post treatment with a GOS scoring system.</td>
<td>No significant improvement in outcome was seen between groups for good outcomes at 6 months, ICP patterns, or serial neurological examinations in hospital.</td>
</tr>
<tr>
<td>Watson et al., (2004) USA Cohort</td>
<td><strong>N=404</strong> Patients were included if one of the following criteria was met: a cortical contusion visible on CT; subdural, epidural, or intracerebral hematoma; depressed skull fracture; penetrating head wound; seizure within 24h of injury; or a GCS ≤ 10 (n=125). After controlling for seizure risk, patients treated with glucocorticoids were compared for odds of developing first and second late postraumatic seizures with those receiving no glucocorticoids.</td>
<td>Patients dosed with glucocorticoids within 1 day of their TBI were more likely to develop first late seizures than were those without (p=0.04, hazard ratio = 1.74) Those receiving glucocorticoids ≥ 2 days post injury had no similar associations (p=0.66, HR = 0.77). Glucocorticoid administration was not associated with second late seizure development in any group.</td>
</tr>
</tbody>
</table>

PEDro = Physiotherapy Evidence Database rating scale score (Moseley et al., 2002).
Discussion
In light of a series of inconclusive studies into the effectiveness and safety of corticosteroid use, a very large multinational randomized collaboration for assessment of early methylprednisolone administration was initiated in 1999 (Roberts et al., 2004). In order to achieve 90% power, recruitment of 20,000 patients in the Corticosteroid Randomization After Severe Head Injury (CRASH) trial was the goal. After 10,008 patients had been randomly allocated the experiment was halted. Of 4985 patients allocated corticosteroids, 1052 died within 2 weeks compared to 893 of 4979 patients in the placebo group. This indicated a relative risk of death equal to 1.8 in the steroid group (p=0.0001). Further analysis showed no differences in outcomes between 8 CT subgroups or between patients with major extracranial injury compared to those without. The authors also conducted a systematic review and meta-analysis of existing trials using corticosteroids for head injury. Before the CRASH trial, a 0.96 relative risk of death was seen in the corticosteroid group. Once the patients from the CRASH trial were added the relative risk changed to 1.12. Based on the results of this large multinational trial, the study authors concluded corticosteroids should not be used in head injury care no matter what the severity of injury (Roberts et al., 2004).

Two other studies assessed methylprednisolone in ABI management. Giannotta et al. (1984) conducted an RCT of patients with GCS ≤ 8 treated with methylprednisolone. Patients were divided into a high dose, low dose or placebo group. Patients were then assessed at 6 months based on the GOS grading system. They reported no differences in mortality rates between groups. The authors then compressed the low dose and placebo groups and performed further analyses. They found that patients less than 40 years old in the high dose group showed significant decreases in mortality when compared to the low dose/ placebo group. However, they also found no significant differences between these groups in beneficial outcomes. Even if the decreases in death are taken into account, the authors point out that decreasing mortality without decreasing morbidity may not be valuable (Giannotta et al., 1984). In another RCT, one group of patients received methylprednisolone, while the other group received no medications. Results indicate there were no differences between the two groups for 6 months GOS scores (Saul et al., 1981).

Grumme et al. (1995) conducted an RCT in Germany and Austria in which GOS scores were assessed 1 year after injury in patients treated with the synthetic corticosteroid triamcinolone. While no overall effect was seen between groups, further analysis was performed on subsets of patients. A significant increase in beneficial outcomes was seen in patients who had both a GCS<8 and a focal lesion. The authors suggest that in light of this evidence, patients with both GCS<8 and a focal lesion would benefit from steroid administration immediately after injury (Grumme et al., 1995).

Four randomized trials were found that assessed dexamethasone in ABI. Dearden et al. (1986b) assessed consecutively admitted head injured patients treated with
dexamethasone. They noted that patients experiencing ICP levels > 20mmHg showed significantly poorer outcomes on the 6 month GOS scores. Braakman et al. (1983) found no differences between patients treated with dexamethasone compared to placebo in 1 month survival rates or 6 month GOS scores. Similarly, Cooper et al. (1979) performed a double blind randomized controlled study of the effects of dexamethasone on outcomes in severe head injuries. Patients were divided into three groups and no significant differences were seen in outcomes. The authors performed several post-mortem examinations and indicate that often, patients initially diagnosed with focal lesions were in fact suffering from diffuse injuries which are not amenable to corticosteroid treatment. Finally, in one study assessing the effects of low-dose (16mg/day) and high-dose (14mg/day) dexamethasone on ICP levels in brain injured patients no differences were noted in ICP at any point during the 72 hour follow-up period (Kaktis & Pitts, 1980).

Watson et al. (2004) performed a cohort control study to compare patients receiving any form of glucocorticoid therapy (dexamethasone 98%, prednisone 2.4%, methylprednisone 1.6%, or hydrocortisone 1.6%) to patients treated without corticosteroids for risk of development of post-traumatic seizures. Patient information was drawn from a database acquired in a separate study of posttraumatic seizure prevention with phenytoin and PHT. Their inclusion criteria allowed for patients with only one of a list of complications to be included resulting in a diverse group of TBI patients. They noted that patients receiving glucocorticoid treatment on the first day post injury were at increased risk of developing first late seizures compared to patients receiving no treatment. They also saw no improvement in patients receiving glucocorticoids after the first day. The authors suggest that this adds further strength to the argument against routine corticosteroid use in TBI.

**Conclusions**

*There is Level 1 evidence that methylprednisolone increases mortality rates in ABI patients and should not be used.*

*There is Level 2 evidence that triamcinolone may improve outcomes in patients with a GCS<8 and a focal lesion.*

*There is Level 1 evidence that dexamethasone does not improve ICP levels and may worsen outcomes in patients with ICP > 20mmHg.*

*There is Level 3 evidence that glucocorticoid administration may increase the risk of developing first late seizures.*
Methylprednisolone increases mortality rates in ABI patients and should not be used.

Triamcinolone may improve outcomes in patients with a GCS<8 and a focal lesion.

Dexamethasone does not improve ICP levels and may worsen outcomes in patients with ICP > 20mmHg.

Glucocorticoid administration may increase the risk of developing first late seizures.
12.18 Conclusions

1. There was Level 1 evidence that bolus opioid administration resulted in increased ICP; however, the evidence regarding the effects of opioid infusion on ICP levels is conflicting.

2. There was Level 2 evidence that remifentanil results in faster arousal compared to hypnotic based sedation.

3. There is Level 1 evidence that both phenytoin and carbamazepine have negative effects on cognitive performance, particularly with tasks with motor and speed components.

4. There is Level 4 evidence that carbamazepine improves seizure control while being less harmful to cognitive function and behaviour than other anticonvulsants.

5. There is Level 4 evidence that carbamazepine decreases the incidence of aggressive behaviour following a TBI.

6. There is Level 5 evidence that acute intramuscular midazolam can be used for acute seizure cessation.

7. There is Level 1 evidence that phenytoin given during the first week of injury reduces the occurrence of early seizures.

8. There is Level 2 evidence that phenytoin may be effective in reducing the risk of late seizures.

9. There is Level 2 evidence indicating that phenobarbital given post ABI does not reduce the risk of late seizures.

10. There is Level 4 evidence that divalproex decreases the incidence of aggressive behaviour post TBI.

11. There is Level 5 evidence that valproic acid decreases the incidence of aggressive behaviours.

12. There is limited Level 5 evidence, from two case studies, to suggest that lamotrigine helps to reduce inappropriate behaviours post TBI. More research is needed, with a greater number of subjects, to validate these findings.

13. There is Level 4 evidence that cerebrolysin, a neurotrophic and neuroprotective medication appears to have potential benefit to improve outcome and cognitive
functioning post-brain injury; however, controlled trials will be necessary to evaluate this further.

14. Based on a single RCT, there is Level 1 evidence that donepezil improves attention and short-term memory.

15. There is Level 4 evidence from 2 studies indicating that donepezil is effective in improving memory post ABI.

16. Based on a single RCT, there is Level 1 evidence that physostigmine improves memory in men with brain injury.

17. There is Level 5 evidence, from one case study, that physostigmine combined with a memory training programme produces a clinically significant improvement in memory function, but does not produce significant changes in attention, concentration, cognitive flexibility, or motor speed.

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

19. There is Level 2 evidence that citalopram aids in the reduction of depression post ABI.

20. There is Level 4 evidence that citalopram and carbamazepine may be efficacious in the treatment of anxiety and mood disorders.

21. There is Level 2 evidence to suggest that the administration of desipramine assists in improving mood and reducing depression.

22. There is Level 4 evidence that sertraline HCL and amitriptyline decrease the incidence of aggressive behaviours.

23. There is Level 5 evidence to suggest that an antimanic agent (lithium carbonate) reduces aggressive/agitated behaviour following a TBI.

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

25. There is Level 4 evidence from one study to suggest that ziprasidone assists in the controlling of aggressive behaviours post TBI.

26. There is Level 4 evidence that haloperidol does not have a negative effect on the success of rehabilitation.
27. There is Level 4 evidence that administration of single-dose droperidol calms brain-injured, agitated patients more quickly than other agents.

28. There is Level 4 evidence that phenol nerve blocks reduce contractures and spasticity at the elbow, wrist and finger flexors for up to 5 months post injection.

29. There is Level 4 evidence that oral baclofen improves lower extremity spasticity but not upper extremity spasticity.

30. Based on a single RCT, there is Level 1 evidence that oral tizanidine improves lower and upper extremity spasticity compared to a placebo.

31. There is Level 2 evidence based on one cohort study and Level 4 evidence from 3 studies that botulinum toxin type A injections may be effective in the management of localized spasticity following ABI.

32. One RCT found that both groups of patients receiving botulinum toxin type A injections did show reduced spasticity, regardless of the method of drug administration.

33. Based on a single RCT, there is Level 1 evidence that bolus intrathecal baclofen injections produce short-term (up to 6 hours) reductions in upper and lower extremity spasticity.

34. There is Level 4 evidence to suggest that prolonged intrathecal baclofen results in longer-term (3 months, and 1 year) reductions in spasticity in both the upper and lower extremities following an ABI.

35. Based on a single study, there is Level 4 evidence to suggest that intrathecal baclofen results in short-term improvements in walking performance, particularly gait velocity, stride length, and step width.

36. There is conflicting evidence regarding the efficacy of pentobarbital over conventional ICP management measures.

37. There is Level 2 evidence that there is no difference between thiopental and pentobarbital in the control of elevated ICP.

38. There is Level 2 evidence that pentobarbital is no better than mannitol for the control of elevated ICP.
39. There is Level 4 evidence that barbiturate therapy may cause reversible leukopenia, granulocytopenia, and systemic hypotension.

40. Based on a single study, there is Level 4 evidence that a combination barbiturate therapy and hypothermia may result in improved clinical outcomes up to 1 year post-injury.

41. There is Level 2 evidence that etridonate (EHDP) reduces the development of heterotopic ossification in severe head injury patients.

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

43. There is Level 2 evidence that etridonate (EHDP) reduces the development of heterotopic ossification in severe head injury patients.

44. There is Level 2 evidence that etridonate (EHDP) reduces the development of heterotopic ossification in severe head injury patients.

45. There is Level 1 evidence that treatment with dexanabinol does not provide acute improvements in ICP or long-term clinical benefits post-ABI.

46. There is Level 1 evidence, from 2 RCTs, that propranolol reduces agitated symptoms following brain injury.

47. There is Level 1 evidence that pindolol decreases aggression following brain injury.

48. There is Level 1 evidence, from 2 RCTs, that propranolol reduces agitated symptoms following brain injury.

49. There is Level 1 evidence that sodium lactate is more effective than mannitol for the management of acute elevations in ICP.

50. There is Level 2 evidence that higher dose mannitol is superior to conventional mannitol in improving mortality rates, and clinical outcomes.

51. There is Level 1 evidence that pindolol decreases aggression following brain injury.

52. There is Level 2 evidence that amantadine did not help to improve behaviour following brain injury.
53. There is Level 4 evidence that dopamine-enhancing drugs facilitate rate recovery post-traumatic brain injury.

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

55. There is Level 4 evidence that bromocriptine improves all motivational deficits except mood.

56. There is Level 5 evidence, from one observational study, that bromocriptine significantly improves memory impairments.

57. There is Level 1 evidence based on three RCTs that administration of dexamethasone inhibits endogenous production of glucocorticoids and has no proven impact on recovery post brain injury.

58. There is Level 4 evidence that an antiandrogen and counseling reduces sexually aggressive behaviour.

59. There is Level 1 evidence that progesterone improves GOS and modified FIM scores, and decreases mortality rates in ABI patients.

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

61. There is Level 2 evidence, based on one cohort study, that methylphenidate does not improve the sleep-wake cycle of those who have sustained a TBI.

62. Based on two small and conflicting RCTs there is inconclusive evidence that methylphenidate interventions improved cognitive behavioural function in children post acquired brain injury.

63. There is Level 1 evidence, based on one RCT, that Modafinil is not effective in treating fatigue or excessive daytime sleepiness post ABI.

64. There is Level 2 evidence that propofol may help to reduce ICP and the need for other ICP and sedative interventions when used in conjunction with morphine.

65. There is Level 1 evidence, from one RCT, that lopezapam and zopiclone work equally well in assisting with insomnia symptoms post ABI.
66. There is Level 2 evidence that midazolam has no effect on ICP but conflicting evidence regarding its effect on MAP and CPP.

67. There is Level 5 evidence that acute intramuscular Midazolam can be used for acute seizure cessation.

68. There is Level 1 evidence that methylprednisolone increases mortality rates in ABI patients and should not be used.

69. There is Level 2 evidence that triamcinolone may improve outcomes in patients with a GCS<8 and a focal lesion.

70. There is Level 1 evidence that dexamethasone does not improve ICP levels and may worsen outcomes in patients with ICP > 20mmHg.

71. There is Level 3 evidence that glucocorticoid administration may increase the risk of developing first late seizures.
12.19 Reference List


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