

10. Post-Traumatic Seizure Disorder

Robert Teasell MD FRCPC, Shannon Janzen MSc, Rachel Anderson BSc, Heather MacKenzie MD, Shawn Marshall MSc MD FRCPC, Nora Cullen MSc MD FRCPC

ERABI
Parkwood Institute
550 Wellington Road, London ON

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Abbreviations

ABI	Acquired Brain Injury
GCS	Glasgow Coma Scale
LPTS	Late Post-Traumatic Seizure
PTE	Post-Traumatic Epilepsy
PTS	Post-Traumatic Seizure
RCT	Randomized Controlled Trial
TBI	Traumatic Brain Injury

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Key Points

There are several patient and injury characteristics that increase the likelihood for the development of late post-traumatic seizures. Some important patient characteristics include: increasing age, premorbid alcohol abuse, and family history.

In terms of injury characteristics, markers of increasing injury severity such as penetrating injuries and depressed skull fracture increase the risk.

Seizures occurring within the first week post injury (early seizures) increase the risk of late post-traumatic seizures.

The risk of epilepsy is highest within the first two years following brain trauma

As brain injury severity increases, the period of time for which a survivor is at risk of developing post-traumatic seizures also increases.

Individuals who develop seizures after the first week following TBI have an increased chance of experiencing seizure recurrence; seizures occurring immediately following TBI do not increase the risk of recurrence.

The risk associated with a single late post-traumatic seizure is minimal and no different than that seen after any seizure.

Following TBI, seizure recurrence can be a significant source of morbidity. Severe and widespread seizure recurrence during the first six days post TBI can be associated with permanent impairments in functional recovery. Those patients with a higher seizure frequency and severity are at increased risk of complications.

Status epilepticus is a rare complication of post-traumatic seizure.

Mortality rates are higher in those patients with TBI diagnosed with post-traumatic seizures, compared to those without seizures.

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

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

Anticonvulsants provided shortly post ABI do not reduce late seizures.

Anticonvulsants have negative consequences on motor tasks.

Intramuscular midazolam may be effective for acute seizure cessation.

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

Glucocorticoid administration increases the risk of developing first late seizures when administered within one day post injury; however, it does not impact late seizures when administered outside that time frame.

Surgical resection can reduce seizures if the focus of the seizures can be localized.

10. Post-Traumatic Seizure Disorder

Introduction

Post-traumatic seizures (PTS), although identified as a serious consequence of traumatic brain injury (TBI), remain an understudied problem (Ferguson et al. 2010). Post-traumatic seizure disorders have been defined in the *Practice Parameter of the Antiepileptic Drug Treatment of Post-traumatic Seizures* by the Brain Injury Special Interest Group of the American Academy of Physical Medicine and Rehabilitation (1998) and can be found in Table 10.1.

Table 10.1 Definitions of Post-Traumatic Seizures (Brain Injury Special Interest Group 1998) (p. 595)

Seizure: Discrete clinical event that reflects a temporary physiologic dysfunction of the brain characterized by excessive and hypersynchronous discharge of cortical neurons.

Post-Traumatic Seizure: An initial or recurrent seizure episode not attributable to another obvious cause after penetrating or non-penetrating TBI. The term encompasses both single and recurrent events.

Immediate Post-Traumatic Seizure: A seizure due to TBI occurring within the first 24 hours of injury.

Early Post-Traumatic Seizure: A seizure due to TBI occurring within the first week of injury.

Late Post-Traumatic Seizure: A seizure due to TBI occurring after the first week of injury.

Post-Traumatic Epilepsy: A disorder characterized by recurrent late seizure episodes not attributable to another obvious cause in patients following TBI. The term should be reserved for *recurrent*, late post-traumatic seizures.

Nonepileptic Seizures: Episodic behavioural events that superficially resemble epileptic attacks but are not associated with paroxysmal activity within the brain.

Antiepileptic Drug Prophylaxis: In the context of post-traumatic seizures, antiepileptic drug treatment administered to prevent seizures in patients who have not manifested seizures.

Epilepsy: A condition characterized by recurrent unprovoked seizures.

Practice Parameters: Results, in the form of one or more specific recommendations, from a scientifically based analysis of a specific clinical problem.

10.1 Incidence of Post-Traumatic Seizures

It is believed that up to 20% of structural epilepsy in the general population is a result of TBI (Bushnik et al. 2012). Of all patients with TBI who are hospitalized, 5% to 7% will experience PTS. However, the incidence of PTS is much higher on rehabilitation units (as high as 18%), which reflects increased injury severity and the presence of a higher number of risk factors in this population (Armstrong et al. 1990; Bontke et al. 1993; Cohen & Groswasser 1991; Kalisky et al. 1985; Sazbon & Groswasser 1990; Sundararajan et al. 2015; Wang et al. 2013a). The incidence of late post-traumatic seizures (LPTS) ranges

from 5% to 19% for the general population (Bushnik et al. 2012). Zhao and colleagues (2012) found that when seizures occurred post-TBI, 0.4% were immediate, 0.5% were early, and 88.7% were late. A study examining 236,164 individuals with TBI found that 2.4% had pre-existing epilepsy or a seizure disorder (Wilson & Selassie 2014); unfortunately, the consequences of a TBI may be more severe in this population.

For those who sustain a severe non-penetrating TBI, approximately 11% will experience LPTS and for those who have a TBI as the result of a penetrating injury, the incidence increases to 13% to 50% (Ascroft 1941; Caveness & Liss 1961; Malav et al. 2015; Yablon 1993). In young adults TBI is the leading cause of epilepsy (Annegers 1996). Following acquired brain injury (ABI), seizures have been associated with secondary accidental injury, depression, a loss of independence (i.e., driving privileges) and a reduction in employability (Andelic et al. 2009; Brain Injury Special Interest Group 1998).

10.2 Risk Factors for Post-Traumatic Seizures and Post-Traumatic Epilepsy

There are several patient and injury characteristics that increase the likelihood of developing PTS. These include increased injury severity (Glasgow Coma Scale score of less than 10, prolonged length of coma, prolonged length of post-traumatic amnesia), depressed skull fractures, cortical contusions, subdural hematomas, epidural hematomas, intracerebral hematomas, penetrating injuries and wounds with dural penetration, a seizure within the first week of injury, male gender, age, and having had multiple neurosurgical procedures (Brain Injury Special Interest Group 1998; Dikmen et al. 1991; Englander et al. 2003; Krause-Titz et al. 2016; Walker et al. 2015; Wang et al. 2013a; Yablon 1993; Yeh et al. 2013; Zhao et al. 2012). Ferguson et al. (2010) also found those who had other concomitant injuries or comorbid conditions, previous head injuries, stroke, or depression were more likely to develop LPTS, which is congruent with the findings of previous studies (Andelic et al. 2009; Annegers et al. 1998; Weiss et al. 1983). The risk of unprovoked epileptic seizures is greatest during the first six months post injury and higher for individuals with severe injuries (Mahler et al. 2015).

The first year post injury is often when post-traumatic epilepsy (PTE) develops (Di Luca & de Lacerda 2013; Lamar et al. 2014; Lucke-Wold et al. 2015), however, the risk remains high within two years of injury (Lamar et al. 2014). In a cohort study conducted by Ferguson et al. (2010), the incidence of PTE was highest in individuals 30 to 54 years of age. However, higher rates of PTE have also been reported for those 50 to 59 and 60 to 69 years of age (Zhao et al. 2012). According to a meta-analysis conducted by Xu and colleagues (2017), risk factors for PTE include: male gender, previous alcohol abuse, loss of consciousness at time of TBI, post-traumatic amnesia, and focal neurological signs. Moreover, Diamond et al. (2014) recently explored genetic variance and PTE development in 256 individuals with moderate to severe TBI. The study found that higher cerebrospinal fluid and serum IL-1 β (a potential biomarker for epilepsy) ratios were associated with an increased risk of PTE (Diamond et al. 2014). Due to this study being one of the first studies exploring this gene variability, more studies are needed before firm conclusions can be made.

It is important to identify patients who are at high-risk of developing PTS since these patients may benefit from pharmacological seizure prophylaxis. According to Yablon and Dostrow (2001) the clinical characteristics of the patient, the injury, and information obtained from neuroimaging and electrophysiologic assessment techniques can be used to identify those at high risk for developing seizure disorders post injury.

Table 10.2 Studies of Risk Factors for Late Post-traumatic Seizures (Yablon & Dostrow 2001) (p.310)

Risk Factor	Reference
Patient Characteristics	
Age	(Annegers et al. 1980; Asikainen et al. 1999; Hahn et al. 1988; Kollevold 1979)
Alcohol use	(Evans 1962; Heikkinen et al. 1990; Japan Follow-up Group for Posttraumatic Epilepsy 1991; Kollevold 1978)
Family history	(Caveness 1963; Evans 1962; Heikkinen et al. 1990; Hendrick 1968)
Injury Characteristics	
Bone/metal fragments	(Ascroft 1941; Salazar et al. 1985; Walker & Yablon 1959)
Depressed skull fracture	(Hahn et al. 1988; Jennett 1975; Phillips 1954; Wiederholt et al. 1989)
Focal contusions/injury	(Da Silva et al. 1992; De Santis et al. 1992; Eide & Tysnes 1992; Glötzner et al. 1983; Heikkinen et al. 1990)
Focal neurologic deficits	(Da Silva et al. 1992; Jennett 1975; Salazar et al. 1985)
Lesion location	(da Silva et al. 1992; Evans 1962; Grafman 1992)
Dural penetration	(Caveness & Liss 1961; Evans 1962; Salazar et al. 1985)
Intracranial hemorrhage	(Glötzner et al. 1983; Hahn et al. 1988; Japan Follow-up Group for Posttraumatic Epilepsy 1991)
Injury severity	(Evans 1962; Jennett 1975; Salazar 1985; Walker & Yablon 1961)
Other	
Early post-traumatic seizures	(Heikkinen 1990; Jennett 1975; Salazar et al. 1985)

There are several patient and injury characteristics that increase the likelihood for the development of late post-traumatic seizures. Some important patient characteristics include: increasing age, premorbid alcohol abuse, and family history.

In terms of injury characteristics, markers of increasing injury severity such as penetrating injuries and depressed skull fracture increase the risk.

Seizures occurring within the first week post injury (early seizures) increase the risk of late post-traumatic seizures.

10.2.1 Onset

The risk of epilepsy is highest within the first two years following brain trauma (Dikmen et al. 1991; Englander et al. 2003; Yablon 1993). Yablon and Dostrow (2001) have noted that one-half to two-thirds of individuals who suffer PTS will experience seizure onset within the first 12 months, and 75-80% will have seizures within two years of their TBI (Caveness et al. 1979; Da Silva et al. 1992; Da Silva et al. 1990; Pohlmann-Eden & Bruckmeir 1997; Walker & Yablon 1959; Walker & Yablon 1961). Similarly, of those patients with PTE, Zhao et al. (2012) reported that 66% developed seizures within the first 6 months, 9.9% between 7 and 12 months, 11.7% between 13 and 24 months, and 8.5% between 25 and 36 months. Further, Wang et al. (2013b) examined 3039 individuals with TBI and of the 9.8% that experienced PTS within the first 2 years, occurrence rates at 6 months and 1 year were 59.9% and 78.1%, respectively.

Although the risk of developing PTS is highest within months after the injury (Temkin 2001), the risk remains high for a period of years. As brain injury severity increases, the period of time for which a

survivor is at risk of developing PTS also increases. After 5 years, adults with mild TBI no longer have a significantly increased risk relative to the general population (Annegers et al. 1998), whereas those with moderate, severe TBI, or penetrating TBI remain at increased risk for more than five years post injury (Annegers et al. 1998; Da Silva et al. 1992; Pagni 1990; Salazar et al. 1985). Moreover, military personnel suffering severe penetrating missile brain injuries show an elevated risk for more than 15 years after the injury (Annegers et al. 1998; Caveness et al. 1979; Feeney & Walker 1979; Salazar et al. 1985; Weiss et al. 1983). The incidence of seizures beginning later than three years post injury is 5% (Zhao et al. 2012).

Those with penetrating trauma typically have their first unprovoked seizure sooner than those patients with non-penetrating trauma (Kazemi et al. 2012). Unprovoked seizures occurred at a median time of one year post injury in a study of 50 participants (Di Luca & de Lacerda 2013); the former was influenced by injury severity, as well as age at the time of injury (Di Luca & de Lacerda 2013). In contrast, a study by Kazemi et al. (2012) found that for those with penetrating trauma, 78% had their first seizure within 1 year and 22% after 1 year. The mean latency to epilepsy onset was found to be shorter for mesial temporal sclerosis compared to lesional neocortical trauma (Gupta et al. 2014).

10.2.2 Recurrence

Seizure recurrence is an important factor in the determination of disability, likelihood of employment, and quality of life, and has been associated with increased health care costs (Baker et al. 1997; Yablon & Dostrow 2001). After a brain insult, there is a latency period where epileptogenesis can begin, which may progress into unprovoked recurrent seizures. Early seizures are likely due to brain insult and the recurrent rate of seizures in this time period is low (Lamar et al. 2014). Some studies have reported that in patients who experienced early PTS, only one-half had a recurrence while another quarter experienced a total of only two to three seizures (De Santis et al. 1979; Kollevold 1979). After a latent period, epileptogenesis may occur, where a non-epileptic brain increases in excitability due to molecular and cellular alterations from a brain injury. Such alterations in the brain may eventually lead to spontaneous recurrent seizures (Lamar et al. 2014; Lucke-Wold et al. 2015). The risk of seizure recurrence in the late stage post-injury is higher compared to the early stage and may be more representative of epilepsy (Lamar et al. 2014). In a study conducted by Zhao et al. (2012), 5.7% of patients with TBI experienced seizures more than once a week, 69.5% more than once a month, and 24.8% had a seizure frequency greater than once a year. After Vagus Nerve Stimulation, patients with PTE demonstrated a greater reduction in seizure frequency, with 50% fewer seizures occurring at three months and 7% fewer at two years than individuals with non-PTE who received Vagus Nerve Stimulation (Englot et al. 2012).

Table 10.3 Studies of Post-Traumatic Seizure Recurrence

Study	Recurrence Incidence
Haltiner et al. (1997)	63 adults with moderate or severe TBI and LPTS. The cumulative incidence of recurrent late seizures was 86% over 2yrs, 52% had >4 late seizures, and 37% had >9 late seizures.
Pohlmann-Eden & Bruckmeir (1997)	57 patients with PTE were compared to 50 age and sex-matched severe TBI controls. Of those with PTE, 35% became seizure-free over 3 years and 21% had >1 seizure per week.

The following table provides a summary of the natural history for the onset and recurrence of PTS (S. Yablon & Dostrow 2001).

Table 10.4 Summary of Onset and Recurrence of Post-Traumatic Seizures

Feature	Reference
20 – 30 % of patients with early PTS experience a late seizure.	(Yablon & Dostrow 2001)
Seizure onset after the first week is associated with a much higher likelihood of seizure recurrence.	(Haltiner et al. 1997; Walker & Yablon 1961)
Seizure frequency within the first year post injury may predict future seizure recurrence.	(Salazar et al. 1985)
Persistent PTS may be seen more commonly with partial seizures and less commonly with generalized seizures.	(Salazar et al. 1985)
A seizure occurring within a few minutes of a head injury has not been found to increase the risk of recurrence in individuals who sustain a mild TBI.	(Jennett 1975; McCrory et al. 1997)
A small number of patients experience frequent seizure recurrences, apparently refractory to conventional anti-seizure therapy.	(Haltiner et al. 1997; Pohlmann-Eden & Bruckmeir 1997)
Some patients may benefit from surgical intervention.	(Diaz-Arrastia et al. 2000; Marks et al. 1995)

The risk of epilepsy is highest within the first two years following brain trauma

As brain injury severity increases, the period of time for which a survivor is at risk of developing post- traumatic seizures also increases.

Individuals who develop seizures after the first week following TBI have an increased chance of experiencing seizure recurrence; seizures occurring immediately following TBI do not increase the risk of recurrence.

10.3 Clinical Picture of Post-Traumatic Seizures

Wiedemayer et al. (2002) retrospectively analyzed a consecutive series of 1868 adult patients with head injury and found that the first epileptic seizure was generalized in 69 patients (63.3%) and partial in 40 patients (36.7%). Fifty-eight patients (53.2%) experienced a second early seizure during the follow-up period. Based on multiple studies, the incidence by seizure type is as follows: complex or simple partial seizures with secondary generalization, 16%-77% (Di Luca & de Lacerda 2013; Kazemi et al. 2012; Sapina et al. 2014; Zhao et al. 2012); generalized tonic-clonic seizures, 30%-53.6% (Di Luca & de Lacerda 2013; Zhao et al. 2012; Zheng et al. 2013); simple partial seizures, 14%-42.3% (Zhao et al. 2012; Zheng et al. 2013); complex partial seizures, 4.1%-16% (Sapina et al. 2014; Zhao et al. 2012; Zheng et al. 2013); and generalized atonic seizures, 2% (Di Luca & de Lacerda 2013).

There has also been a correlation found between the type and frequency of seizures; those with simple or complex partial seizures experience a higher frequency of seizures (Kazemi et al. 2012). In a study examining 66 individuals who developed LPTS, it was determined that 79% had generalized seizures and 21% had focal seizures (Englander et al. 2003). Another study found focal epilepsy was the most common subtype of PTE, diagnosed in 93% of patients and arising most commonly from the temporal lobes and frontal lobes (Gupta et al. 2014). More specifically, 57% had temporal lobe

epilepsy, 35% had frontal lobe epilepsy, 3% had parietal lobe epilepsy, and another 3% had occipital lobe epilepsy (Gupta et al. 2014).

Seizures following TBI may themselves be a source of significant morbidity and it has been noted that the recurrence of seizures is an important cause of non-elective hospitalization in patients with severe TBI (Cifu et al. 1999). Potential complications include deterioration in cognitive and behavioural functioning and overall functional status, impaired neurological recovery, status epilepticus and death.

10.3.1 Cognitive and Behavioural Function

Post-traumatic seizure disorders may lead to cognitive and behavioural disorders (Yablon & Dostrow 2001). Cognitive problems may arise during the interictal state in the absence of active seizures (Aarts et al. 1984; Binnie & Marston 1992). Patients with PTS can experience persistent behavioural abnormalities and a higher incidence of psychiatric-related hospitalizations even compared to patients with penetrating TBI who do not experience PTS (Swanson et al. 1995).

10.3.2 Influence on Neurologic Recovery

Neurological recovery can be influenced by PTS (Hernandez & Naritoku 1997; Yablon & Dostrow 2001). Yablon and Dostrow (2001) have noted that, in rodent models, brief and infrequent PTS occurring early after brain damage do not appear to impact functional recovery; however, more severe and widespread seizures occurring within the first 6 days post brain injury result in permanent impairments of functional recovery. Seizures occurring after the sixth day result in no change in somatosensory recovery (Hernandez & Naritoku 1997).

10.3.3 Functional Status

Recurrent PTS may exert a negative impact on functional status following TBI, an adverse effect independent of the severity of the injury (Barlow et al. 2000; Schwab et al. 1993). In the case of penetrating TBI, PTS have been reported to be an important and independent factor which affects both employment status and cognitive performance (Schwab et al. 1993). However, in the case of non-penetrating TBI, the impact of PTS on functional prognosis and cognition is less clear (Armstrong et al. 1990; Asikainen et al. 1999). Within a population of individuals with LPTS, Kolakowsky-Hayner and colleagues (2013) discovered that occupational and social integration were the most difficult areas for recovery post-injury. However, Haltiner et al. (1997) found no significant differences at 1 year as a consequence of LPTS in terms of neuropsychological performance and psychosocial functioning when adjusted for injury severity. Asikainen et al. (1999) found that patients with PTS did have poorer outcomes on the Glasgow Outcome Scale. A more recent study found that of individuals with LPTS, 20% were severely disabled, 52% moderately disabled and 28% had a good recovery, as measured by the Extended Glasgow Outcome Scale. No significant differences in employment outcome associated with the presence of PTS have been found (Asikainen et al. 1999). Further Kolakowsky-Hayner et al. (2013) found that among a group on individuals with TBI-LPTS, 40% (7 of 20) of individuals who were driving pre-injury had their license suspended due to their first seizure; 3 were able to re-obtain their license.

10.3.4 Status Epilepticus

Status epilepticus can be defined as either more than 5 minutes of continuous seizure activity or two or more sequential seizures without full recovery of consciousness between seizures. Status epilepticus is regarded as the most serious of the complications of PTS and may actually lead to

additional neurological damage. Simple partial status epilepticus is a subset of status epilepticus characterized as a partial focal seizure that does not cause loss of consciousness or secondary generalization (Hadjigeorgiou et al. 2013). Fortunately, clinically apparent status epilepticus and simple partial status epilepticus are infrequent complications of PTS (Kollevold 1979), with only 0.16% of individuals hospitalized with TBI with status epilepticus (Dhakar et al. 2015).

10.3.5 Mortality

In earlier studies mortality was reported to be high among those who sustain a TBI and develop PTS (Corkin et al. 1984; Walker & Blumer 1989; Walker & Erculei 1970). More recently, Englander et al. (2009) found mortality rates to be higher for patients with TBI who had been diagnosed with LPTS when compared with those who had no recorded history of LPTS. Those in the LPTS group who died tended to be younger than individuals who did not have LPTS. Earlier studies found that patients with penetrating TBIs had a higher risk of dying; however, this is more likely due to the initial trauma rather than PTS (Rish & Caveness 1973; Rish et al. 1983). Yablon and Dostrow (2001) have noted that the complications of a single LPTS are no different than those seen after any seizure, and are generally minimal. However, increased seizure frequency and severity are associated with an increased risk of mortality and morbidity in the form of worsened cognition and overall function.

The risk associated with a single late post-traumatic seizure is minimal and no different than that seen after any seizure.

Following TBI, seizure recurrence can be a significant source of morbidity. Severe and widespread seizure recurrence during the first six days post TBI can be associated with permanent impairments in functional recovery. Those patients with a higher seizure frequency and severity are at increased risk of complications.

Status epilepticus is a rare complication of post-traumatic seizure.

Mortality rates are higher in those patients with TBI diagnosed with post-traumatic seizures, compared to those without seizures.

10.4 Treatment of Post-Traumatic Seizures

Schierhout and Roberts (2001) reported that a seizure occurring soon after head injury may cause secondary brain damage by increasing metabolic demands of the brain, increasing intracranial pressure, and leading to excessive amounts of neurotransmitter release. For this reason, the primary therapeutic objective in the use of anticonvulsant drugs has been the prevention of early seizures in an attempt to minimize the extent of secondary brain damage following TBI.

Some anticonvulsant drugs have been shown to have neuroprotective properties in animal studies. For example, following hypoxia, phenytoin has been linked with reduced neuronal damage in neonatal rats (Vartanian et al. 1996) and in rat hippocampal cell cultures (Tasker et al. 1992). Experimental evidence suggests that the neuroprotective effects of phenytoin are related to a blockage of voltage dependent sodium channels during hypoxia (Tasker et al. 1992; Vartanian et al. 1996) which would be expected to decrease the spread of calcium induced neurotoxicity following hypoxic brain injury. As noted by Schierhout and Roberts (2001), this suggests that anti-epileptics may have beneficial properties which may be independent of their proposed anti-seizure activity.

Conversely, anti-epileptic drugs have shown toxic effects in stable patients, with impaired mental and motor function being the most common adverse effects; serious adverse effects, including deaths as a result of hematological reactions, have been also reported (Reynolds et al. 1998). Schierhout and Roberts (2001) have suggested that the injured brain’s response to anticonvulsants may be such that toxic effects could be more pronounced and neurological recovery may be delayed.

10.4.1 Seizure Prevention or Prophylaxis

Initially, retrospective and nonrandomized clinical trials in humans showed favourable results for the efficacy of anti-epileptic drug prophylaxis; however, prospective investigations of chronic prophylaxis for LPTS have been less impressive. This section summarizes literature exploring the use of various drugs for seizure prevention.

Individual Studies

Table 10.5 Seizure Prevention or Prophylaxis

Phenytoin versus Placebo		
Author/Year/ Country/Study Design/PEDro/N	Methods	Outcome
<p>Dikmen et al. (1991) USA RCT PEDro=6 N_{Initial}=244, N_{Final}=124</p>	<p>Population: Head Injury. <i>Phenytoin Group (n=104):</i> Mean Age=30.9yr; Gender: Male=82, Female=22; Median GCS=11. <i>Placebo Group (n=101):</i> Mean Age=32.9yr; Gender: Male=70, Female=31; Median GCS=9. Treatment: Patients were randomized to receive phenytoin (prophylactic medication) or a placebo for 1yr. Patients were then observed for another 1yr while unmedicated. Outcome Measure: Halstead–Reitan Neuropsychological Test Battery, Katz Adjustment Scale, Sickness Impact Profile.</p>	<ol style="list-style-type: none"> From 1 to 12mo, more participants in the treatment group stopped receiving their assigned drug (p<0.01) due to idiosyncratic reactions and requests. Those severely injured (GCS≤8) and receiving phenytoin did more poorly on most neuropsychological measures than controls determined by the overall rank-sum type test at 1mo (p<0.05). No significant differences were found at 1yr. No significant differences in neuropsychological performance were found between groups for patients with moderate injuries (GCS≥9) at 1mo or 1yr. Changes in neuropsychological measures from 12 to 24mo showed that phenytoin had a small but negative widespread cognitive effect as evidenced by the overall rank-sum type test (p<0.05).
<p>Temkin et al. (1990) USA RCT PEDro=6 N_{Initial}=404, N_{Final}=123</p>	<p>Population: TBI; <i>Phenytoin Group (n=208):</i> Mean Age=34yr; Gender: Male=162, Female=46; GCS ≤10=125. <i>Placebo Group (n=196):</i> Mean Age=34yr; Gender: Male=147, Female=49; GCS ≤10=131. Treatment: Participants were randomized to either the phenytoin (n=208) or placebo group (n=196). Phenytoin group received an initial dose of 20 mg/kg intravenously, then serum levels were maintained at 3–6 μmol/l. Treatment started within 24hr of injury and continued for 1yr. Follow up at 2yr.</p>	<ol style="list-style-type: none"> Cumulative early seizure rates were 3.6% in the phenytoin group and 14.2% in the control group (p<0.001); phenytoin was associated with a decrease of 73% in the risk of early seizures. Late seizure occurrence (day 8 to 2yr) did not differ significantly between the treatment and control groups (27.5% vs 21.2%, p>0.2). More participants in the phenytoin group stopped taking the drug between day 8 and

	Outcome Measure: Occurrence of early (<1wk) and late (>8d) seizures.	1yr, mainly due to idiosyncratic reactions or requests (103 vs 67).
Young et al. (1983) USA RCT PEDro=6 N=244	Population: TBI; <i>Phenytoin Group (n=136)</i> : Mean Age=24.4yr; Gender: Male=110, Female=26. <i>Placebo Group (n=108)</i> : Mean Age=25.8yr; Gender: Male=91, Female=71. Treatment: Patients were administered phenytoin (serum concentration 10-20µg/ml) or placebo, starting within 24hr of injury. Outcome Measure: Occurrence of early seizures (≤1wk of injury).	<ol style="list-style-type: none"> 5 in the phenytoin group and 4 in the control group had early seizures (p=0.75). Mean time from injury to early seizure in the treatment and control group was 3.2 and 4.5d, respectively (p=0.41).
Young et al. (1983) USA RCT PEDro=6 N _{initial} =214, N _{Final} =179	Population: TBI; <i>Phenytoin Group (n=105)</i> : Mean Age=24.1yr; Gender: Male=84, Female=21. <i>Placebo Group (n=74)</i> : Mean Age=26.3yr; Gender: Male=61, Female=13. Treatment: Participants treated with phenytoin (serum concentration 10-20µg/ml) or placebo starting within 24hr of injury. Treated duration 18mo. Patients were switched to phenobarbital if there was a hypersensitivity to phenytoin (n=20). Outcome Measure: Occurrence of late (>7d post injury) seizures.	<ol style="list-style-type: none"> Late seizures occurred in 11 (12.9%) of the phenytoin group, 2 (10%) of the phenobarbital group, and 8 (10.8%) of controls. There were no significant differences between groups in the percentage of late seizures (p=0.75).
McQueen et al. (1983) United Kingdom RCT PEDro=7 N=164	Population: TBI; <i>Phenytoin Group (n=84)</i> : Gender: Male=67, Female=17; Age Range: 5-15yr=29, 16-65yr=55. <i>Placebo Group (n=80)</i> : Gender: Male=63, Female=17; Age Range: 5-15yr=14, 16-65yr=66. Treatment: Patients received either phenytoin or placebo for 1yr. Phenytoin administration for adults was 300mg and for children 5mg/kg. Follow-up continued for 2yr. Outcome Measure: Occurrence of seizures.	<ol style="list-style-type: none"> Only 48% of the treatment group had plasma levels greater than 40µmol/l. 9.1% of participants developed post-traumatic epilepsy within the first 2yr. At 1yr, 6 participants in the treatment group and 5 in the control group developed post-traumatic epilepsy. 8 participants in the treatment group and 7 in the control group developed seizures by 2yr.
Phenytoin versus Levetiracetam		
Author/Year/ Country/Study design/PEDro Score/N	Methods	Outcome
Radic et al. (2014) USA Case Control N=288	Population: Subdural Hematoma; <i>Levetiracetam group (LEV; n=164)</i> : Mean Age=65.96yr; Gender: Male=98, Female=66; Mean GCS=13.5. <i>Phenytoin group (PHT; n=124)</i> : Mean Age=62yr; Gender: Male=85, Female=39; Mean GCS=12.7. Treatment: Patients were retrospectively analyzed. Those who received LEV were compared to those who received PHT for seizure prophylaxis. Outcome Measure: Seizure rate and adverse drug events.	<ol style="list-style-type: none"> There was no significant difference between LEV and PHT in clinical or electrographic seizure risk for patients without a midline shift. In subjects with midline shift >0 mm, LEV was associated with an increased risk of electrographic seizures during hospitalization (p=0.028) and a decreased risk of adverse drug effects (p=0.001), compared with PHT use.
Gabriel & Rowe (2014) USA	Population: TBI; <i>Phenytoin Group (PHT, n=14)</i> : Mean Age=46.8yr; Gender: Male=10, Female=4; Mean GCS=3. <i>Levetiracetam Group (LEV, n=5)</i> :	<ol style="list-style-type: none"> Groups were not similar at baseline in terms of median GCS at presentation (p=0.016) and ICU discharge (p=0.044). The

<p>Cohort N=19</p>	<p>Mean Age=48.8yr; Gender: Male=3, Female=2; Mean GCS=14. Treatment: Participants were divided based on prophylactic treatment: PHT or LEV. Follow-up interview conducted. Outcome Measure: Glasgow Outcome Scale-Extended (GOS-E), occurrence of seizures, medication-related complications.</p>	<p>PHT group, compared to the LEV group, also had a longer period of time between injury and GOS-E assessment (808.8 versus 484.4d, p=0.001). 2. There was no significant difference in the mean GOS-E scores at follow-up (PHT 5.07 versus LEV 5.60, p=0.58). 3. There was no significant difference between groups for occurrence of early or late seizures (both p=0.53). 4. Compared to the PHT group, the LEV group was significantly less likely to experience medication-related complications (p=0.038); the PHT group had a significantly higher rate of days with fever (p=0.014).</p>
<p>Inaba et al. (2013) USA Prospective Controlled Trial N=813</p>	<p>Population: TBI; <i>Levetiracetam Group (LEV, n=406)</i>: Mean Age=51.7yr; Gender: Male=300, Female=106; Mean GCS=12.1. <i>Phenytoin Group (PHT, n=407)</i>: Mean Age=53.6yr; Gender: Male=280, Female=127; Mean GCS=12.6. Treatment: Participants were administered either LEV at 1000mg every 12h or PHT. In the PHT group the loading dose was 20mg/kg then 5mg/kg/d every 8h. Treatment lasted 7d. Outcome Measure: Seizure occurrence.</p>	<p>1. There was no significant difference in seizure rates between groups (1.5% versus 1.5%, p=0.997). 2. There was no significant differences between groups (LEV versus. PHT) in terms of adverse drug reactions (7.9% versus 10.3%, p=0.227), complications (28.3% versus 27.0%, p=0.679) or mortality rates (5.4% versus 3.7%, p=0.236).</p>
<p>Kruer et al. (2013) Retrospective Cohort N=109</p>	<p>Population: TBI; Median GCS=5. <i>Phenytoin Group (PHT, n=89)</i>: Median Age=43.1yr; Gender: Male=76, Female=13. <i>Levetiracetam Group (LEV, n=20)</i>: Median Age=34.1yr; Gender: Male=19, Female=1. Treatment: Retrospective review of patients administered PHT or LEV. Outcome Measure: Occurrence of early seizures.</p>	<p>1. 1 patient from each group seized in the first 7d (p=0.335). 2. Hospital length of stay did not differ significantly between groups (median days, LEV 26.5 versus PHT 11, p=0.134).</p>
<p>Szafarski et al. (2010) USA RCT PEDro=8 N=52</p>	<p>Population: TBI=46; SAH=6. <i>Phenytoin group (PHT; n=18)</i>: Mean Age=35yr; Gender: Male=13, Female=5; Mean GCS=4. <i>Levetiracetam group (LEV; n=34)</i>: Mean Age=44yr; Gender: Male=26, Female=8; Mean GCS=5. Treatment: Patients were randomized within 24h of injury. Patients received either a loading dose of intravenous PHT 20mg/kg, then 5mg/kg/d or intravenous LEV at 20mg/kg, and then 1000mg every 12hr/7d. Outcome Measure: Occurrence of early seizures, Glasgow Outcome Scale (GOS), GOS-Extended (GOSE), Disability Rating Scale (DRS), Resource Utilization Questionnaire.</p>	<p>1. There were no significant differences in the occurrence of early seizures between the PHT and LEV groups (3 versus 5, p=1.0) 2. There were no significant between-group differences in GOS at discharge (p=0.33) and 6mo post discharge (p=0.89). 3. There were no significant differences in the occurrence of fever, increased intracranial pressure, stroke, hypotension, arrhythmia, renal/ liver abnormalities or death between the two groups (p>0.15 for all). 4. Compared to the LEV group, those in the PHT group experienced a significant worsening of their neurological status more often (p=0.024), and experienced anemia less often (p=0.076). 5. Compared to PHT group, the LEV group showed significantly lower DRS at 3 and 6mo (p=0.006 and p=0.037), and higher GOSE at 6mo (p=0.016) in patients who survived.</p>

<p>Steinbaugh et al. (2012) USA <i>Addition to Szaflarski et al. 2010 RCT</i></p>	<p>Addition: Patients received continuous video EEG (cEEG) for up to 72h which was compared to the outcomes collected.</p>	<p>6. The presence of focal slowing, epileptiform discharges, and seizures were not predictive of outcome (GOS-E, DRS). More severe slowing was positively associated with DRS at discharge, 3 and 6mo (p=0.084) and negatively associated with GCS at discharge.</p>
<p>Jones et al. (2008) USA Cohort N=27</p>	<p>Population: Severe TBI; Gender: Male=20, Female=7. Treatment: Patients received Levetiracetam (n=15; 500mg IV every 12h for 7d) administered within 24hr of injury and were compared to a retrospective cohort of patients who received phenytoin (n=12). Outcome Measure: Occurrence of early seizures.</p>	<p>1. There was a significant difference in the occurrence of abnormal EEG findings (seizure or seizure tendency with epileptiform activity) between groups (p=0.003), with the Levetiracetam group having more abnormal findings. 2. There was no significant difference between groups for actual seizures (p=0.556).</p>
<p>Additional Studies of Phenytoin</p>		
<p>Author/Year/ Country/Study design/PEDro Score/N</p>	<p>Methods</p>	<p>Outcome</p>
<p>Bhullar et al. (2014) USA Case-Control N=93</p>	<p>Population: TBI; <i>No Prophylaxis Group (n=43):</i> Gender: Male=28, Female=15. <i>Phenytoin Prophylaxis Group (n=50):</i> Gender: Male=42, Female=8. GCS=3-8. Treatment: Medical records were reviewed and patients were divided into two groups: no prophylaxis and phenytoin prophylaxis. Outcome Measure: Occurrence of early (<7d post injury) seizures, length of stay (LOS), Glasgow Outcome Scale (GOS), modified Rankin Scale (mRS).</p>	<p>1. There was no significant difference in the occurrence of early seizures between the no prophylaxis and phenytoin groups (2.3% versus 4.0%, p=1.0). 2. The phenytoin group, compared to no prophylaxis, had longer hospital stays (36±31 vs 25±16d, p=0.03), and worse functional outcome at discharge (GOS, 2.9±1.0 versus 3.4±1.1, p=0.01; mRS, 3.1±1.5 versus 2.3±1.7, p=0.02).</p>
<p>Dikmen et al. (2000) USA RCT PEDro=8 N_{initial}=279, N_{Final}=107</p>	<p>Population: TBI; Gender: Male=228, Female=51. <i>Group 1 (n=94):</i> Mean Age=37.14yr; Mean GCS=11.3. <i>Group 2 (n=91):</i> Mean Age=36.58yr; Mean GCS=11.23. <i>Group 3 (n=94):</i> Mean Age=35.85yr; Mean GCS=12.11. Treatment: Patients randomized into three groups within 24h of injury: 1) valproic acid (VPA) for 1mo then 5mo of placebo; 2) VPA for 6mo; and 3) phenytoin (PHT) for 1wk then placebo until 6mo post injury. Outcome Measure: A battery of neuropsychological measures.</p>	<p>1. There was a trend towards a higher mortality rate in the VPA groups compared to the PHT group (p=0.07). 2. There were no significant differences at 1, 6 or 12mo on the composite measures based on all the neuropsychological measures, or on only the cognitive measures (0.551<p<0.812). 3. No individual measure showed a significant difference among the treatment groups at 1, 6 or 12 months post injury.</p>
<p>Temkin et al. (1999) USA RCT PEDro=7 N_{initial}=379, N_{Final}=283</p>	<p>Population: TBI; Gender: Male=310, Female=69. <i>Phenytoin Group (n=132):</i> Mean Age=36yr; Mean GCS=11.7. <i>Valproate (1mo, n=120):</i> Mean Age=40yr; Mean GCS=11.6. <i>Valproate (6mo, n=127):</i> Mean Age=36yr; Mean GCS=11.1.</p>	<p>1. There was no significant difference in the number of early seizures between the combined valproate (4.5%) and phenytoin (1.5%, p=0.14) groups.</p>

	<p>Treatment: Patients were divided into three groups within 24h of injury: (1) phenytoin for 1wk (20mg/kg then 5mg/kg/d), placebo until 6mo post injury; (2) Valproate (20mg/kg, then 15mg/kg/d) for 1mo, placebo for 5mo; or (3) valproate for 6mo. Follow-up continued for 2yr.</p> <p>Outcome Measure: Incidence of early and late (>7d post injury) seizures, mortality rates.</p>	<ol style="list-style-type: none"> There was no significant difference between groups ($p=0.19$) in the occurrence of late seizures. Late seizures occurred in 11, 17, and 15 participants in the 1mo and 6mo valproate groups and the phenytoin group, respectively. There were no significant differences in mortality rates between groups (7.2% phenytoin versus 13.4% in the combined valproate group, $p=0.07$). In the phenytoin group, a participant had a rash requiring medication at 1wk and in the valproate (6mo) group a participant had low neutrophil count at 2-4wk, both thought to be treatment related.
<p>Servit & Musil (1981) Czechoslovakia Non-RCT N=167</p>	<p>Population: TBI; Mean Age=30.6yr; Gender: Male=128, Female=39.</p> <p>Treatment: Participants in the treatment group (n=143) were administered phenytoin (160-240mg/d) and phenobarbital (20-60mg/d). The control group (n=24) was treated with conventional methods for 2yr.</p> <p>Outcome Measure: Occurrence of late seizures.</p>	<ol style="list-style-type: none"> Post-traumatic epilepsy occurred in 25% of the control and 2.1% of the treatment group ($p<0.001$).
Additional Medications For Seizure Prevention		
Author/Year/ Country/Study Design/PEDro/N	Methods	Outcome
<p>Formisano et al. (2007) Italy/USA Pre-Post N=137</p>	<p>Population: TBI; GCS<8. <i>Study 1</i> (prospective, n=82): Mean Age=27.1yr; Gender: Male=43, Female=12; Time post Injury=62.1d. <i>Study 2</i> (retrospective, n=55): Mean Age=25.5yr; Gender: Male=59, Female=23; Time Post Injury=55.9d.</p> <p>Treatment: Patients were studied retrospectively and prospectively to determine if anti-epileptic medications were administered and the incidence of late post-traumatic epilepsy (PTE).</p> <p>Outcome Measure: Occurrence of PTE.</p>	<ol style="list-style-type: none"> Within study 1, 18% had late PTE; there was no significant difference in the incidence of PTE between non-treated patients and those treated with prophylactic therapy ($p=0.29$). Within study 2, the occurrence of late PTE was significantly higher in patients treated with an anti-epileptic medication than those not treated (39% vs 0%, $p=0.004$). Out of those treated with medication (n=69), 30 showed epileptic abnormalities on their EEGs.
<p>Watson et al. (2004) USA Cohort N=404</p>	<p>Population: Severe TBI; Gender: Male=309, Female=95.</p> <p>Treatment: Participants who were administered glucocorticoid medications (<1wk post injury; n=125) were compared to those who were not (n=279). 98% of those treated were given dexamethasone. Those in the treatment group were further divided into those administered the drug within 0-1d (n=105) and 2-7d (n=20). Follow-up continued for 2yr.</p> <p>Outcome Measure: Occurrence of late seizures (defined based on order of occurrence as first or second late seizures), mortality.</p>	<ol style="list-style-type: none"> Compared to the untreated group, those treated within 1d were significantly more likely to develop first late seizures ($p=0.04$); an increase of 74% in the risk of first late seizures was seen. Receiving glucocorticoids ≥ 2 days after TBI was not associated with first late seizure development. There was no significant association between receiving glucocorticoids within 1d ($p=0.28$; HR=1.41; CI 95%, 0.75-2.63) or ≥ 2d ($p=0.54$; HR0.63; 95% CI, 0.15-2.74) after TBI and second late seizures.

		<ol style="list-style-type: none"> 4. No significant differences in the number of first (p=0.10) or second late seizures (p=0.41) were found between the treated and not treated groups. 5. There was no cumulative effect found of glucocorticoid exposure on late seizure development (p=0.63; HR=1.16; 95%CI, 0.63-2.16). 6. No difference was noted in cumulative mortality between groups (p=0.57).
<p>Manaka (1992) Japan RCT PEDro=3 N_{initial}=244, N_{Final}=191</p>	<p>Population: Head Injury; <i>Severe Group:</i> Mean Age=38.0yr. <i>Mild Group:</i> Mean Age=29.3yr. Treatment: Patients with severe injuries were divided into two groups: phenobarbital (n=50; 10 – 25 µg/ml) or control (n=76) starting at 4wk post injury for 2yr, tapering off at 3yr. Follow-up continued for 5yr. Participants with mild head injury were in a third group (n=65). Outcome Measure: Occurrence of seizures.</p>	<p><i>*Results of mild head injury group not reported here</i></p> <ol style="list-style-type: none"> 1. At follow-up, 12.7% (n=16) of participants with severe head injury developed epileptic attacks; 8 (16%) in the treatment group and 8 (10.5%) controls.
<p>Wroblewski et al. (1992) USA Case Series N=30</p>	<p>Population: TBI=25, ABI=5; Mean Age=32y; Mean Time Post Injury=14.1mo. Treatment: Chart review of individuals with late post-traumatic seizures treated with Methylphenidate. Majority (n=28) also received an anticonvulsant (carbamazepine or valproic acid). Outcome Measure: Occurrence of seizures.</p>	<ol style="list-style-type: none"> 1. 4 patients had a higher seizure frequency while taking methylphenidate, 13 had a lower frequency of seizures on the medication, and 13 had no change between being on or off the medication. 2. 20 patients had no seizures while taking methylphenidate. 3. There was a trend toward a lesser incidence of seizures in patients during methylphenidate treatment (p=0.063).
<p>Wroblewski & Joseph (1992) USA Case Series N=10</p>	<p>Population: TBI=8, ABI=1, Other=1; Mean Age=32.9yr; Gender: Male=9, Female=1. Treatment: Intramuscular midazolam was administered. Outcome Measure: Cessation of seizures.</p>	<ol style="list-style-type: none"> 1. All patients experienced seizure cessation within minutes of midazolam administration. 2. The only reported side effect was slight to moderate sedation.
<p>Wroblewski et al. (1989) USA Pre-Post N=27</p>	<p>Population: TBI; Mean Age=24yr; Gender: Male=22, Female=5. Treatment: Patients taking phenytoin or phenobarbital had these medications stopped and replaced with carbamazepine. Outcome Measure: Occurrence of seizures.</p>	<ol style="list-style-type: none"> 1. Patients were on the medication due to previous seizures (n=13) or because they were considered high risk for seizures (n=14). 2. For all participants after the medication switch: 10 had a decrease in seizure frequency, 13 had no change, and 4 reported an increase. 3. For the subgroup of participants with previously documented seizures before the medication switch (n=13): 10 had a decrease in seizure frequency, 1 had no change, and 2 had an increase.

PEDro=Physiotherapy Evidence Database rating scale score (Moseley, Herbert, Sherrington, & Maher, 2002).

Table 10.6 Summary of RCTs Studying Prophylaxis for Early and Late Seizures

Authors/Year	N	Methods	Results	
			Early Seizures	Late Seizures
Szaflarski et al. (2010)	52	Phenytoin versus Levetiracetam	ND	NA
Temkin et al. (1999)	379	Phenytoin (1wk) versus Valproate (1mo) versus Valproate (6mo)	ND	ND
Manaka (1992)	191	Phenobarbital versus No treatment	NA	ND
Temkin et al. (1990)	123	Phenytoin versus Placebo	+	ND
Young et al. (1983)a	244	Phenytoin versus Placebo	ND	NA
Young et al. (1983)b	179	Phenytoin versus Placebo	NA	ND
McQueen et al. (1983)	164	Phenytoin versus Placebo	NA	ND

ND=No difference between groups; + = Improvement compared with control; - = Impairments compared with control; NA=Not applicable.

Table 10.7 Summary of non-RCT Studies Studying Prophylaxis of Early and Late Seizures

Authors/Year	N	Methods	Results	
			Early Seizures	Late Seizures
Radic et al. (2014)	288	Phenytoin versus Levetiracetam	ND	NA
Gabriel et al. (2014)	19	Phenytoin versus Levetiracetam <i>*groups were not similar at baseline</i>	ND	ND
Bhullar et al. (2014)	93	Phenytoin versus No prophylaxis	ND	NA
Inaba et al. (2013)	813	Phenytoin versus Levetiracetam	ND	NA
Kruer et al. (2013)	109	Phenytoin versus Levetiracetam	ND	NA
Jones et al. (2008)	27	Phenytoin versus Levetiracetam	ND	NA
Formisano et al. (2007)	137	Anti-epileptic medication versus no medication	NA	-
Watson et al. (2004)	404	Glucocorticoids (within 1d) versus No glucocorticoids	NA	-

ND=No difference between groups; + = Improvement compared with control; - = Impairments compared with control; NA=Not applicable.

Discussion

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

worse functional outcomes at discharge than individuals receiving no treatment (Bhullar et al. 2014). Overall, the evidence for the use of phenytoin for prevention of seizures is not favourable. There was no significant difference in mortality between those treated with antiepileptic drugs (phenytoin and carbamazepam) and control subjects (RR 1.08; 95% CI, 0.79 to 1.46, $p=0.64$) (Thompson et al. 2015).

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

In terms of other medications studied, phenobarbital alone has been shown to have no prophylactic effect on PTE (Manaka 1992). Glucocorticoids given within one day post injury may put patients at an increased risk of developing late seizures (Watson et al. 2004); however, there is no association between late seizures and glucocorticoids if given after the first day post injury (Watson et al. 2004).

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

Conclusions:

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

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

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

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

There is Level 2 evidence that glucocorticoid exposure after brain injury is not associated with a decrease in late seizures, and early exposure (within 1 day post injury) is associated with increased seizure activity.

There is Level 4 evidence that methylphenidate for the treatment of cognitive and behavioral problems can be safely used in brain injured patients at risk for post-traumatic seizures as it is not associated with an increase in seizure frequency.

There is Level 4 evidence that acute intramuscular Midazolam can be used for acute seizure cessation.

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

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

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

Anticonvulsants provided shortly post ABI do not reduce late seizures.

Anticonvulsants have negative consequences on motor tasks.

Intramuscular midazolam may be effective for acute seizure cessation.

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

Glucocorticoid administration increases the risk of developing first late seizures when administered within one day post injury; however, it does not impact late seizures when administered outside that time frame.

10.4.2 Surgical Treatment of Post-Traumatic Seizures

Yablon and Dostrow (2001) noted the recent interest in a subgroup of ABI patients who experience continued PTS despite treatment with multiple antiepileptic drugs. For this special group of patients, surgical treatment may be a viable option.

10.4.2.1 Surgical Excision of the Post-Traumatic Seizure Focus

Some studies have reported a decrease in seizures following surgical resection among a selected group of PTE patients (Diaz-Arrastia et al. 2000; Doyle et al. 1996). The major challenge in this treatment approach is the accurate localization of the exact region responsible for the development of seizures. This is particularly true for patients with severe ABI who frequently show multiple and bilateral sites of brain injury (Diaz-Arrastia et al. 2000).

Individual Studies

Table 10.8 Surgical Treatment of Post-Traumatic Seizures

Author/Year/ Country/Study Design/N	Methods	Outcome
Zheng et al. (2013) USA Case Series N=97	Population: Tumor; Mean Age=51.4yr; Gender: Male=38, Female=59. Treatment: Patients with supratentorial meningioma were retrospectively analyzed after surgical resection for postoperative seizures. Seizures were divided into postoperative early (<1wk) and late (>1wk) occurrence. Outcome Measure: Seizure rates.	<ol style="list-style-type: none"> 62 (63.9%) of the 97 patients were seizure free for the entire postoperative follow-up. 13 (13.4%) of the 97 patients experienced frequent seizures. 14 (14.4%) of the 97 patients experienced early postoperative seizures. 33 (34.0%) of the 97 patients experienced late postoperative seizures include 12 of the 14 patients who experienced early seizures.
Hakimian et al. (2012) USA Case Series N=21	Population: TBI; Mean Age=34.7yr; Gender: Male=12, Female=9; Time Post Injury=12.9yr. Treatment: Retrospective review of patients who had an extratemporal resection (with or without temporal lobectomy) for medically intractable epilepsy. Outcome Measure: Occurrence of seizures (mean follow-up was 7yr).	<ol style="list-style-type: none"> Most patients had both frequent complex partial and generalized tonic-clonic seizures and were unsuccessfully treated with an average of 4.15 antiepileptic drugs. Six patients were seizure-free, six patients had rare seizures (≤ 2/yr), five had a reduction in frequency, and 4 had no benefit from the surgery. Two patients had significant complications (subdural hematomas).
Marks et al. (1995) USA Case Series N=25	Population: Head Trauma; Gender: Male=17, Female=8. Treatment: Participants underwent surgical resection when seizures could be localized. Outcome Measure: Occurrence of seizures.	<ol style="list-style-type: none"> Prior to surgery seizures were localized to the mesial temporal region (Group 1, n=17) and extrahippocampal neocortical area (Group 2, n=8). Nine patients had their seizures successfully localized and underwent a surgical procedure. Afterwards, all were seizure free. 16 patients did not have their seizures adequately localized.

Discussion

Marks et al. (1995) reported that, in a cohort of 25 patients with PTS, it was possible to successfully localize the seizure focus in less than half of the sample. Subsequent surgical excision of the area presumed to be the seizure focus resulted in seizure reduction in all treated patients. In those patients who showed a favourable result, the brain injury lesion was specifically limited to the hippocampus or neocortex (Marks et al. 1995); thus, making the identification and surgical resection more accurate. This study supports that surgical excision of the seizure focus may only be a viable treatment option for a subgroup of ABI patients in whom the site of brain injury can be accurately identified. Therefore patients suffering severe ABI with multiple and bilateral localizations would not be suitable.

In a more recent study, Hakimian et al. (2012) retrospectively examined patients with TBI who had an extratemporal resection for PTE. The resection resulted in 28% of patients being seizure free, 50% had a reduction in seizure frequency, and 19% did not benefit from treatment. Overall, good to excellent outcomes were achieved and the risk of complications was found to be minimal. Zheng et al. (2013)

found that for 63.9% of patients with supratentorial meningioma and preoperative seizures, were seizure free post-surgery.

Conclusions

There is Level 4 evidence that a subgroup of ABI patients (those where the seizure focus can be accurately localized) would benefit from surgical resection for post-traumatic seizures.

There is Level 4 evidence that extratemporal resection is effective in controlling post-traumatic epilepsy.

Surgical resection can reduce seizures if the focus of the seizures can be localized.

10.5 Summary

1. *There is Level 1b evidence to suggest that levetiracetam is as safe and effective as phenytoin in the treatment and prevention of early seizures in individuals in the intensive care unit post ABI.*
2. *There is Level 1b evidence that anticonvulsants given during the first 24 hours post ABI reduce the occurrence of early seizures (within the first week post injury).*
3. *There is Level 1a evidence that anticonvulsants given shortly after the onset of injury do not reduce mortality, persistent vegetative state, or the occurrence of late seizures (>1 week post injury).*
4. *There is Level 1a evidence that seizure prophylactic treatment with either phenytoin or valproate results in similar incidences of early or late seizures and similar mortality rates.*
5. *There is Level 2 evidence that glucocorticoid exposure after brain injury is not associated with a decrease in late seizures, and early exposure (within 1 day post injury) is associated with increased seizure activity.*
6. *There is Level 4 evidence that methylphenidate for the treatment of cognitive and behavioral problems can be safely used in brain injured patients at risk for post-traumatic seizures as it is not associated with an increase in seizure frequency.*
7. *There is Level 4 evidence that acute intramuscular Midazolam can be used for acute seizure cessation.*
8. *There is Level 2 evidence indicating that phenobarbital given post ABI does not reduce the risk of late seizures.*
9. *There is Level 4 evidence that a subgroup of ABI patients (those where the seizure focus can be accurately localized) would benefit from surgical resection for post-traumatic seizures.*
10. *There is Level 4 evidence that extratemporal resection is effective in controlling post-traumatic epilepsy.*

10.6 Reference List

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