

10. Post-Traumatic Seizure Disorder Following Acquired Brain Injury

Robert Teasell MD FRCPC
Shannon Janzen MSc
Heather MacKenzie MD
Pavlina Faltynek MSc
Shawn Marshall MSc MD FRCPC
Nora Cullen MSc MD FRCPC

Key Points

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

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

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

First generation anti-epileptic drugs are as effective as new generation anti-epileptic drugs in reducing post-traumatic seizures.

Glucocorticoid administration may increase seizure frequency.

Injections of midazolam may reduce active seizure activity.

Carbamazepine may be effective in reducing seizure recurrence.

Methylphenidate may be effective in reducing rate of post-traumatic seizures.

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

There is no difference in effectiveness between early craniectomy versus craniotomy for the reduction of the frequency of seizures.

Table of Contents

10.0 Introduction	1
10.1 Incidence of Post-Traumatic Seizures.....	1
10.2 Risk Factors for Post-Traumatic Seizures and Post-Traumatic Epilepsy	2
10.2.1 Onset	3
10.2.2 Recurrence	4
10.3 Clinical Presentation of Post-Traumatic Seizures	5
10.3.1 Influence on Neurologic Recovery.....	5
10.3.2 Cognitive and Functional Status	5
10.3.3 Status Epilepticus	6
10.3.4 Mortality	6
10.4 Treatment of Post-Traumatic Seizures	6
10.4.1 Seizure Prophylaxis	7
<i>10.4.1.1 Phenytoin</i>	<i>7</i>
<i>10.4.1.2 Miscellaneous Medications for Post-Traumatic Seizures.....</i>	<i>13</i>
10.4.2 Surgical Management of Post-Traumatic Seizures	16
<i>10.4.2.1 Surgical Management of Post-Traumatic Seizures.....</i>	<i>16</i>
10.5 Conclusions	18
10.6 Summary	19
10.7 References	20

This review has been prepared based on the scientific and professional information available up to December 2018. The ERABI information is provided for informational and educational purposes only. If you have or suspect you have a health problem, you should consult your health care provider. The ERABI contributors shall not be liable for any damages, claims, liabilities, costs, or obligations arising from the use or misuse of this material.

Teasell R, Janzen S, MacKenzie H, Faltynek P, Marshall S, Cullen N. (2019). Post-Traumatic Seizure Disorder Following Acquired Brain Injury. In Teasell R, Cullen N, Marshall S, Janzen S, Faltynek P, Bayley M, editors. Evidence-Based Review of Moderate to Severe Acquired Brain Injury. Version 13.0: p1-27.

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

Post-Traumatic Seizure Disorder Following Acquired Brain Injury

10.0 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. This module is intended to provide insight into the frequency and clinical presentation of PTS, as well as any evidence-based interventions that exist.

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

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% (Bushnik et al., 2012; Zhao et al., 2012). Zhao and colleagues (2012) found that when seizures occurred post injury, 88.7% were diagnosed as late seizures; with the majority of those (66%) occurring between 10 days and three years post-injury. 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 13-50% (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 (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 (GCS) 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, being male, 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. 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 to explore genetic 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 (p.310; Yablon & Dostrow, 2001)

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 B, 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 B, 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 B, 1975; Salazar et al., 1985; Walker & Yablon, 1961)
Other	
Early post-traumatic seizures	(Heikkinen et al., 1990; Jennett, 1975; Salazar et al., 1985)

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 or 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).

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

Table 10.3 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 B, 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)

10.3 Clinical Presentation 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 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 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).

10.3.2 Cognitive and Functional Status

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).

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 Glasgow Outcome Scale Extended. 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 of individuals with TBI-LPTS, 40% (7 of 20) of individuals who were driving prior to injury had their license suspended due to their first seizure, and 3 were able to re-obtain their license.

10.3.3 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).

10.3.4 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.

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 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 the literature to date which has explored the use of various drugs for seizure prevention.

10.4.1.1 Phenytoin

Table 10.4 Seizure Prophylaxis Using Phenytoin

Author Year Country Research Design PEDro Sample Size	Methods	Outcome
Dikmen et al. (1991) USA RCT PEDro=6 N _{Initial} =244, N _{Final} =124	Population: Head Injury; <i>Phenytoin Group</i> (n=104): Mean Age=30.9yr; Gender: Male=82, Female=22; Median GCS=11. <i>Placebo Group</i> (n=101): 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.	<ol style="list-style-type: none"> 1. From 1 to 12mo, more participants in the treatment group stopped receiving their assigned drug (p<0.01) due to idiosyncratic reactions and requests. 2. Those severely injured (GCS≤8) and receiving phenytoin did more poorly on most neuropsychological measures than controls determined by the overall rank-sum type test at 1mo (p<0.05). No significant differences were found at 1yr. 3. No significant differences in neuropsychological performance were found between groups for patients with moderate injuries (GCS≥9) at 1mo or 1yr. 4. 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).
Temkin et al. (1990) USA	Population: TBI; <i>Phenytoin Group</i> (n=208): Mean Age=34yr; Gender: Male=162, Female=46; GCS	<ol style="list-style-type: none"> 1. Cumulative early seizure rates were 3.6% in the phenytoin group and 14.2% in the

<p>RCT PEDro=6 N_{Initial}=404, N_{Final}=123</p>	<p>≤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. Outcome Measure: Occurrence of early (<1wk) and late (>8d) seizures.</p>	<p>control group (p<0.001); phenytoin was associated with a decrease of 73% in the risk of early seizures. 2. Late seizure occurrence (day 8 to 2yr) did not differ significantly between the treatment and control groups (27.5% vs 21.2%, p>0.2). 3. More participants in the phenytoin group stopped taking the drug between day 8 and 1yr, mainly due to idiosyncratic reactions or requests (103 vs 67).</p>
<p>Young et al. (1983) USA RCT PEDro=6 N=244</p>	<p>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 10–20 μg/ml) or placebo, starting within 24hr of injury. Outcome Measure: Occurrence of early seizures (≤1wk of injury).</p>	<p>1. Five in the phenytoin group and 4 in the control group had early seizures (p=0.75). 2. Mean time from injury to early seizure in the treatment and control group was 3.2 and 4.5d, respectively (p=0.41).</p>
<p>Young et al. (1983) USA RCT PEDro=6 N_{Initial}=214, N_{Final}=179</p>	<p>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 10–20 μg/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.</p>	<p>1. Late seizures occurred in 11 (12.9%) of the phenytoin group, 2 (10%) of the phenobarbital group, and 8 (10.8%) of controls. 2. There were no significant differences between groups in the percentage of late seizures (p=0.75).</p>
<p>McQueen et al. (1983) United Kingdom RCT PEDro=7 N=164</p>	<p>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.</p>	<p>1. Only 48% of the treatment group had plasma levels greater than 40 μmol/l. 2. Nine percent of participants developed post-traumatic epilepsy within the first 2yr. 3. At 1yr, 6 participants in the treatment group and 5 in the control group developed post-traumatic epilepsy. 4. Eight participants in the treatment group and 7 in the control group developed seizures by 2yr.</p>
<p>Bhullar et al. (2014) USA Case Control N=93</p>	<p>Population: TBI, GCS=3–8; <i>No Prophylaxis Group (n=43)</i>: Gender: Male=28, Female=15. <i>Phenytoin Prophylaxis Group (n=50)</i>: Gender: Male=42, Female=8. Treatment: Medical records were reviewed and patients were divided into two groups: no prophylaxis and phenytoin prophylaxis. Outcome Measure: Occurrence of early (<7d post injury) seizures, length of stay (LOS), Glasgow Outcome Scale (GOS), modified Rankin Scale (mRS).</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>

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

Author Year Country Research Design PEDro Sample Size	Methods	Outcome
Younus et al. (2018) Pakistan RCT PEDro= 6 N = 140	Population: Phenytoin Group (<i>N</i> =69): Mean GCS= 11.23. Levetiracetam group (<i>N</i> =73): Mean GCS=11.17. Overall: 117 males, 23 females; Mean Age= 29.48±16.24y Intervention: TBI patients admitted to the hospital were randomized into the Phenytoin medication group, or the Levetiracetam group. Both groups received medication for 7 days. No statistical differences between groups at baseline Outcomes: Abnormal EEG, Seizure activity (7-10 days), Glasgow Coma Scale (GCS).	<ol style="list-style-type: none"> 1. The number of abnormal EEGs was found to be significantly different between the two groups ($p=0.002$) showing the Levetiracetam group had fewer individuals with abnormal EEG. 2. The amount of seizure activity at follow-up was significantly different between groups ($p=0.014$), showing the Levetiracetam group had fewer instances of seizures. 3. There was no significant difference between GCS scores at follow-up between the two groups.
Szaflarski et al. (2010) USA RCT PEDro=8 N=52	Population: TBI=46; SAH=6; Phenytoin group (PHT; n=18): Mean Age=35yr; Gender: Male=13, Female=5; Mean GCS=4. Levetiracetam group (LEV; n=34): Mean Age=44yr; Gender: Male=26, Female=8; Mean GCS=5. 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.	<ol style="list-style-type: none"> 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. 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.
Steinbaugh et al. (2012) USA Addition to Szaflarski et al. 2010 RCT	Addition: Patients received continuous video EEG (cEEG) for up to 72h which was compared to the outcomes collected.	
Khan et al. (2016) Pakistan Cohort N=154	Population: Mean Age=24.15yr; Gender: Males=115, Females=29; Mean GCS: 59.1% (8-13), 40.9% (3-7). Intervention: Group A received Phenytoin (5 mg/kg/day), group B received Levetiracetam (10-20 mg/kg/day). Outcome Measure: Incidence of post-traumatic seizures, efficacy of drug on moderate vs severe TBIs.	<ol style="list-style-type: none"> 1. There were no significant differences between groups in terms of the drug efficacy of Phenytoin vs Levetiracetam. 2. There was no significant difference in how each drug impacted moderate vs severe TB and seizure rates.

Javed et al. (2016) Pakistan Cohort N=100	<p>Population: Group 1 (n=50): Mean Age=31.16yr. Group 2 (n=50): Mean Age=34.96.</p> <p>Intervention: Group 1: received IV phenytoin and Levetiracetam (35 mg/kg three times daily). Group 2: EEG monitoring.</p> <p>Outcome Measure: Incidence of post-traumatic seizures.</p>	<ol style="list-style-type: none"> 1. There were no significant differences between the number patients in each group which had post-traumatic seizures.
Radic et al. (2014) USA Case Control N=288	<p>Population: Subdural Hematoma; Levetiracetam group (LEV; n=164): Mean Age=65.96yr; Gender: Male=98, Female=66; Mean GCS=13.5. Phenytoin group (PHT; n=124): Mean Age=62yr; Gender: Male=85, Female=39; Mean GCS=12.7.</p> <p>Treatment: Patients were retrospectively analyzed. Those who received LEV were compared to those who received PHT for seizure prophylaxis.</p> <p>Outcome Measure: Seizure rate and adverse drug events.</p>	<ol style="list-style-type: none"> 1. There was no significant difference between LEV and PHT in clinical or electrographic seizure risk for patients without a midline shift. 2. In subjects with midline shift >0 mm, LEV was associated with an increased risk of electrographic seizures during hospitalization (p=0.028) and a decreased risk of adverse drug effects (p=0.001), compared with PHT use.
Gabriel & Rowe (2014) USA Cohort N=19	<p>Population: TBI; Phenytoin Group (PHT, n=14): Mean Age=46.8yr; Gender: Male=10, Female=4; Mean GCS=3. Levetiracetam Group (LEV, n=5): Mean Age=48.8yr; Gender: Male=3, Female=2; Mean GCS=14.</p> <p>Treatment: Participants were divided based on prophylactic treatment: PHT or LEV. Follow-up interview conducted.</p> <p>Outcome Measure: Glasgow Outcome Scale-Extended (GOS-E), occurrence of seizures, medication-related complications.</p>	<ol style="list-style-type: none"> 1. Groups were not similar at baseline in terms of median GCS at presentation (p=0.016) and ICU discharge (p=0.044). The PHT group, compared to the LEV group, also had a longer period of time between injury and GOS-E assessment (808.8 versus 484.4d, p=0.001). 2. There was no significant difference in the mean GOS-E scores at follow-up (PHT 5.07 versus LEV 5.60, p=0.58). 3. There was no significant difference between groups for occurrence of early or late seizures (both p=0.53). 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).
Inaba et al. (2013) USA Prospective Controlled Trial N=813	<p>Population: TBI; Levetiracetam Group (LEV, n=406): Mean Age=51.7yr; Gender: Male=300, Female=106; Mean GCS=12.1. Phenytoin Group (PHT, n=407): Mean Age=53.6yr; Gender: Male=280, Female=127; Mean GCS=12.6.</p> <p>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.</p> <p>Outcome Measure: Seizure occurrence.</p>	<ol style="list-style-type: none"> 1. There was no significant difference in seizure rates between groups (1.5% versus 1.5%, p=0.997). 2. There was no significant differences between groups (LEV versus. PHT) in terms of adverse drug reactions (7.9% versus 10.3%, p=0.227), complications (28.3% versus 27.0%, p=0.679) or mortality rates (5.4% versus 3.7%, p=0.236).
Kruer et al. (2013) USA Retrospective Cohort N=109	<p>Population: TBI; Median GCS=5. Phenytoin Group (PHT, n=89): Median Age=43.1yr; Gender: Male=76, Female=13. Levetiracetam Group (LEV, n=20): Median Age=34.1yr; Gender: Male=19, Female=1.</p> <p>Treatment: Retrospective review of patients administered PHT or LEV.</p> <p>Outcome Measure: Occurrence of early seizures.</p>	<ol style="list-style-type: none"> 1. One 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).

Jones et al. (2008) USA Cohort N=27	Population: Severe TBI; Gender: Male=20, Female=7. Treatment: Patients received Levetiracetam (n=15; 500mg IV every 12h for 7d) administered within 24hr of injury and were compared to a retrospective cohort of patients who received phenytoin (n=12). Outcome Measure: Occurrence of early seizures.	<ol style="list-style-type: none"> 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 ($p=0.556$).
--	---	---

Table 10.6 Phenytoin Compared to Other Medications for Seizure Prophylaxis

Author Year Country Research Design PEDro Sample Size	Methods	Outcome
Dikmen et al. (2000) USA RCT PEDro=8 N _{Initial} =279, N _{Final} =107	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 were 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.	<ol style="list-style-type: none"> 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.
Temkin et al. (1999) USA RCT PEDro=7 N _{Initial} =379, N _{Final} =283	Population: TBI; Gender: Male=310, Female=69. Phenytoin Group (n=132): Mean Age=36yr; Mean GCS=11.7. Valproate (1mo, n=120): Mean Age=40yr; Mean GCS=11.6. Valproate (6mo, n=127): Mean Age=36yr; Mean GCS=11.1. 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. Outcome Measure: Incidence of early and late (>7d post injury) seizures, mortality rates.	<ol style="list-style-type: none"> 1. There was no significant difference in the number of early seizures between the combined valproate (4.5%) and phenytoin (1.5%, $p=0.14$) groups. 2. There was no significant difference between groups ($p=0.19$) in the occurrence of late seizures. 3. Late seizures occurred in 11, 17, and 15 participants in the 1mo and 6mo valproate groups and the phenytoin group, respectively. 4. There were no significant differences in mortality rates between groups (7.2% phenytoin versus 13.4% in the combined valproate group, $p=0.07$). 5. In the phenytoin group, a participant had a rash requiring medication at 1wk and in the valproate (6mo) group a participant had low neutrophil count at 2-4wk, both thought to be treatment related.
Servit & Musil (1981) Czechoslovakia Cohort N=167	Population: TBI; Mean Age=30.6yr; Gender: Male=128, Female=39. Treatment: The treatment group (n=143) were administered phenytoin (160-240mg/d) and phenobarbital (20-60mg/d). The control group (n=24) received conventional methods for 2yr. Outcome Measure: Occurrence of late seizures.	<ol style="list-style-type: none"> 1. Post-traumatic epilepsy occurred in 25% of the control and 2.1% of the treatment group ($p<0.001$).

Discussion

When the administration of phenytoin is compared to a placebo, its effect on the occurrence of early seizures is not encouraging; several studies did not find phenytoin to be effective (Bhullar et al., 2014; Temkin et al., 1990; Young et al., 1983). However, one RCT by Temkin et al., (1990) did find that phenytoin reduced the rate of early seizures only compared to placebo. A systematic review by Thompson et al. (2015) found that the traditional antiepileptic drugs, phenytoin or carbamazepine, decreased the risk of early seizures compared to controls (RR 0.42; 95% CI, 0.23 to 0.73, $p=0.003$); however, the evidence was low quality. Moreover, phenytoin was found to be no more effective than placebo in preventing late seizures (McQueen et al., 1983; Temkin et al., 1990; Young et al., 1983). In fact, Formisano et al. (2007) found that the occurrence of late seizures was significantly higher in patients treated with anti-epileptic medications than those who were not. It should be noted that phenytoin has been shown to have a negative impact on recovery. Further, those taking phenytoin had longer hospital stays and worse functional outcomes at discharge than individuals receiving no treatment (Bhullar et al., 2014). Overall, the evidence for the use of phenytoin for the prevention of seizures is not favorable. There was no significant difference in mortality between those treated with antiepileptic drugs (phenytoin and carbamazepine) and control subjects (RR 1.08; 95% CI, 0.79 to 1.46, $p=0.64$) (Thompson et al., 2015).

When phenytoin was compared to levetiracetam, many studies have shown the two drugs to be comparable in terms of seizure rates (Inaba et al., 2013; Javed et al., 2016; Jones et al., 2008; Kruer et al., 2013; Radic et al., 2014), complications, adverse drug reactions, mortality rates (Inaba et al., 2013), and length of hospital stay (Kruer et al., 2013). A randomized controlled trial (RCT) by Szaflarski et al. (2010) found similar results in terms of there being no difference for early seizure rates, death, or adverse events between the two drugs; however, the authors found that those on levetiracetam performed significantly better on the Disability Rating Scale at 3 and 6 months ($p=0.042$), and the GOS at 6 months ($p=0.039$) post intervention compared to the phenytoin group. A large RCT by Younus et al. (2018) found that individuals on levetiracetam has a significant decrease in seizure activity at follow-up, and fewer abnormal EEGs compared to those on phenytoin. Furthermore, upon differentiation Radic et al. (2014) found that individuals with any evidence of a midline shift were at a higher risk for electrographic seizures and a lower risk for adverse drug reactions on levetiracetam compared to phenytoin. Overall, a meta-analysis by Zafar et al. (2012) concluded that there was no superiority of either drug at preventing early seizures.

When examining the effects of phenytoin compared to valproate Temkin et al. (1999) found no significant differences in rates of early seizures, late seizures, or mortality. Dikmen et al. (1991) found that severely injured individuals receiving phenytoin performed no more poorly on neuropsychological measures than those taking valproic acid and valproate. The following year (12 to 24 months later), phenytoin was shown to have a small but negative effect on cognition (Dikmen et al., 1991).

Conclusions

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

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

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

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

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

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

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

10.4.1.2 Miscellaneous Medications for Post-Traumatic Seizures

Table 10.7 Studies examining miscellaneous medications for post-traumatic seizures

Author Year Country Research Design PEDro Sample Size	Methods	Outcome
Sapina & Ratkovic (2017) Croatia Cohort N=226	Population: <i>Post-Traumatic Epilepsy Group (n=113):</i> Gender: Males=67, Females=46). <i>Complex Partial Seizures, Control Group (n=113):</i> Gender: Males=20, Females=93. Intervention: Patients were either administered conventional anti-epileptic drugs (AED) or new generation AEDs. Outcome Measure: EEG severity, time to remission of seizures.	<ol style="list-style-type: none"> Both groups significantly reduced EEG severity with treatment over a five-year period regardless of drug ($p<0.05$). There were no significant differences in EEG severity based on drug given between groups. Patients in the standard AED group with comorbid psychiatric disorders had a significantly longer time to remission ($p<0.05$) than those in the new generation AED group with comorbid psychiatric disorders.
Formisano et al. (2007) Italy/USA Pre-Post N=137	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. Treatment: Patients were studied retrospectively and prospectively to determine if anti-epileptic medications were administered and the incidence of late post-traumatic epilepsy (PTE). Outcome Measure: Occurrence of PTE.	<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.

Glucocorticoid Medications		
Watson et al. (2004) USA Cohort N=404	<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"> 1. 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. 2. Receiving glucocorticoids ≥ 2 days after TBI was not associated with first late seizure development. 3. 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. 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 ($p=0.57$).
Phenobarbital		
Manaka (1992) Japan RCT PEDro=3 N _{Initial} =244, N _{Final} =191	<p>Population: Head Injury; <i>Severe Group:</i> Mean Age=38.0yr. <i>Mild Group:</i> Mean Age=29.3yr.</p> <p>Treatment: Patients with severe injuries were divided into two groups: phenobarbital (n=50; 10 – 25 $\mu\text{g/ml}$) 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).</p> <p>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.
Servit & Musil (1981) Czechoslovakia Cohort N=167	<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"> 1. Post-traumatic epilepsy occurred in 25% of the control and 2.1% of the treatment group ($p<0.001$).
Methylphenidate		
Wroblewski et al. (1992) USA Case Series N=30	<p>Population: TBI=25, ABI=5; Mean Age=32y; Mean Time Post Injury=14.1mo.</p> <p>Treatment: Chart review of individuals with late post-traumatic seizures treated with Methylphenidate. Majority (n=28) also received an anticonvulsant (carbamazepine or valproic acid).</p> <p>Outcome Measure: Occurrence of seizures.</p>	<ol style="list-style-type: none"> 1. Four 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. Twenty patients had no seizures while taking methylphenidate. 3. There was a trend toward a lesser incidence of seizures in patients during methylphenidate treatment ($p=0.063$).

Midazolam		
Wroblewski & Joseph (1992) USA Case Series N=10	Population: TBI=8, ABL=1, Other=1; Mean Age=32.9yr; Gender: Male=9, Female=1. Treatment: Intramuscular midazolam was administered. Outcome Measure: Cessation of seizures.	<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.
Carbamazepine		
Wroblewski et al. (1989) USA Pre-Post N=27	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.	<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.

Discussion

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. 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. In terms of the efficacy between first generation and new generation anti-epileptic drugs, no significant differences were found (Sapina & Ratkovic, 2017), indicating that the use of first generation drugs may still be appropriate.

Conclusions

There is level 2 evidence that there is no difference in the ability, between first generation and new generation anti-epileptic drugs, in reducing the rate of post-traumatic seizures.

There is level 2 evidence that glucocorticoid administration within 1 day may put patients at a higher risk of late seizure development.

There is level 4 evidence that methylphenidate may be an effective anti-convulsant medication.

There is level 4 evidence that an intramuscular injection of midazolam may be effective in stopping active seizure activity.

There is level 4 evidence that carbamazepine may reduce seizure activity.

First generation anti-epileptic drugs are as effective as new generation anti-epileptic drugs in reducing post-traumatic seizures.

Glucocorticoid administration may increase seizure frequency.

Injections of midazolam may reduce active seizure activity.

Carbamazepine may be effective in reducing seizure recurrence.

Methylphenidate may be effective in reducing rate of post-traumatic seizures.

10.4.2 Surgical Management of Post-Traumatic Seizures

Yablon and Dostrow (2001) reported on 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 Management of Post-Traumatic Seizures

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). Accurate localization of the exact region responsible for the development of seizures is important but can be a challenge. This is particularly true for patients with severe ABI who frequently show multiple and bilateral sites of brain injury (Diaz-Arrastia et al., 2000).

Table 10.8 Studies Examining Surgical Treatment of Post-Traumatic Seizures

Author Year Country Research Design PEDro Sample Size	Methods	Outcome
Won et al. (2017) Germany Cohort N=139	Population: (<i>subdural hematoma</i>): Mean Age=72.7yr; Gender: Males=94, Females=45; GCS: ≤8=73, >8=66. Intervention: Patients either received a craniotomy or a craniectomy. Outcome Measure: Risk factors for seizure incidence, seizure frequency, functional outcome at 3 mo.	<ol style="list-style-type: none">1. A GCS score of ≤8 was seen as a significant predictor of post-traumatic seizures (p=0.03). Additionally, having a GCS score of ≤8 24hr post-op was also seen to significantly predict post-traumatic seizures (p=0.008).2. There was no significant difference in terms of seizure frequency between those who received a craniotomy compared to a craniectomy (p=0.06).3. There was no significant difference in functional outcomes between groups.

Author Year Country Research Design PEDro Sample Size	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"> 1. Sixty-two (63.9%) of the 97 patients were seizure free for the entire postoperative follow-up. 2. Thirteen (13.4%) of the 97 patients experienced frequent seizures. 3. Fourteen (14.4%) of the 97 patients experienced early postoperative seizures. 4. Thirty-three (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"> 1. Most patients had both frequent complex partial and generalized tonic-clonic seizures and were unsuccessfully treated with an average of 4.15 antiepileptic drugs. 2. 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. 3. 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"> 1. Prior to surgery seizures were localized to the mesial temporal region (Group 1, n=17) and extrahippocampal neocortical area (Group 2, n=8). 2. Nine patients had their seizures successfully localized and underwent a surgical procedure. Afterwards, all were seizure free. 3. 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 supported surgical excision of the seizure focus as a viable treatment option for a subgroup of patients with ABI in whom the site of brain injury can be accurately identified. Patients suffering severe ABI with multiple and bilateral localizations where the seizure focus cannot be accurately identified are not suitable candidates for this surgical approach.

Hakimian et al. (2012) retrospectively examined patients with TBI who had an extratemporal resection for PTE. After the resection 28% of patients were seizure free, approximately 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. In another study, Zheng et al. (2013)

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

Won et al. (2017) retrospectively examined how a craniotomy compared to a craniectomy could influence seizure occurrence and management. It was found that of the cohort examined, 21 out of 53 individuals had preoperative post-traumatic seizures following a subdural hematoma; while 34 had postoperative (two individuals had both). For those with preoperative seizures, 90% saw an elimination of seizures for three months following surgery regardless of craniotomy or craniectomy (Won et al., 2017). However, the majority of individuals who experienced seizures experienced them after surgery. Ultimately, there were no significant differences between groups to suggest a craniectomy or craniotomy reducing the incidence of seizures following an ABI.

Conclusions

There is level 2 evidence that craniectomies are not more effective in reducing the frequency of seizures than craniotomies in TBI populations when performed within the first few days of injury.

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

There is level 4 evidence that extratemporal resection may be effective for controlling post-traumatic epilepsy in patients with TBI.

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

There is no difference in effectiveness between early craniectomy versus craniotomy for the reduction of the frequency of seizures.

10.5 Conclusions

PTS is relatively common post ABI, however there are limited evidence for effective interventions. This does not mean that they are not effective, but most traditional pharmacological prophylactic interventions and newer drugs which show more promise have not been subjected to rigorous evaluation. Surgical interventions, in general, appear to be effective in treating PTS in patients who have failed pharmacological treatment.

10.6 Summary

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

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

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

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

There is level 2 evidence that there is no difference in the ability, between first generation and new generation anti-epileptic drugs, in reducing the rate of post-traumatic seizures.

There is level 2 evidence that glucocorticoid administration within 1 day may put patients at a higher risk of late seizure development.

There is level 4 evidence that methylphenidate may be an effective anti-convulsant medication.

There is level 4 evidence that an intramuscular injection of midazolam may be effective in stopping active seizure activity.

There is level 4 evidence that carbamazepine may reduce seizure activity.

There is level 2 evidence that craniectomies are not more effective in reducing the frequency of seizures than craniotomies in TBI populations when performed within the first few days of injury.

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

There is level 4 evidence that extratemporal resection may be effective for controlling post-traumatic epilepsy in patients with TBI.

10.7 References

- Aarts, J. H. P., Binnie, C. D., Smit, A. M., & Wilkins, A. J. (1984). Selective cognitive impairment during focal and generalized epileptic form EEG activity. *Brain*, 107(1), 293-308.
- Andelic, N., Hammergren, N., Bautz-Holter, E., Sveen, U., Brunborg, C., & Roe, C. (2009). Functional outcome and health-related quality of life 10 years after moderate-to-severe traumatic brain injury. *Acta Neurologica Scandinavica*, 120(1), 16-23.
- Annegers, J. F. (1996). The epidemiology of epilepsy. In E. Wyllie (Ed.), *The treatment of epilepsy: principles and practice* (2 ed., pp. 165-172). Baltimore: Williams & Wilkins.
- Annegers, J. F., Grabow, J. D., Groover, R. V., Laws, E. R., Jr., Elveback, L. R., & Kurland, L. T. (1980). Seizures after head trauma: a population study. *Neurology*, 30(7 Pt 1), 683-689.
- Annegers, J. F., Hauser, W. A., Coan, S. P., & Rocca, W. A. (1998). A population-based study of seizures after traumatic brain injuries. *New England Journal of Medicine*, 338(1), 20-24.
- Armstrong, K. K., Sahgal, V., Bloch, R., Armstrong, K. J., & Heinemann, A. (1990). Rehabilitation outcomes in patients with posttraumatic epilepsy. *Archives of Physical Medicine and Rehabilitation*, 71(2), 156-160.
- Ascroft, P. B. (1941). Traumatic Epilepsy After Gunshot Wounds of the Head. *British Medical Journal*, 1(4193), 739-744.
- Asikainen, I., Kaste, M., & Sarna, S. (1999). Early and late posttraumatic seizures in traumatic brain injury rehabilitation patients: Brain injury factors causing late seizures and influence of seizures on long-term outcome. *Epilepsia*, 40(5), 584-589.
- Baker, G. A., Nashef, L., & Van Hout, B. A. (1997). Current issues in the management of epilepsy: The impact of frequent seizures on cost of illness, quality of life, and mortality. *Epilepsia*, 38(SUPPL. 1), S1-S8.
- Barlow, K. M., Spowart, J. J., & Minns, R. A. (2000). Early posttraumatic seizures in non-accidental head injury: Relation to outcome. *Developmental Medicine and Child Neurology*, 42(9), 591-594.
- Bhullar, I. S., Johnson, D., Paul, J. P., Kerwin, A. J., Tepas 3rd, J. J., & Frykberg, E. R. (2014). More harm than good: Antiseizure prophylaxis after traumatic brain injury does not decrease seizure rates but may inhibit functional recovery. *Journal of Trauma & Acute Care Surgery*, 76(1), 54-61.
- Binnie, C. D., & Marston, D. (1992). Cognitive correlates of interictal discharges. *Epilepsia*, 33(SUPPL. 6), S11-S17.
- Bontke, C. F., Don Lehmkuhl, L., Englander, J., Mann, N., Ragnarsson, K. T., Zasler, N. D., Graves, D. E., Thoi, L. L., & Jung, C. (1993). Medical complications and associated injuries of persons treated in the traumatic brain injury model systems programs. *Journal of Head Trauma Rehabilitation*, 8(2), 34-46.
- Brain Injury Special Interest Group. (1998). Practice parameter: antiepileptic drug treatment of posttraumatic seizures. *Archives of Physical Medicine and Rehabilitation*, 79(5), 594-597.
- Bushnik, T., Englander, J., Wright, J., & Kolakowsky-Hayner, S. A. (2012). Traumatic brain injury with and without late posttraumatic seizures: what are the impacts in the post-acute phase: a NIDRR Traumatic Brain Injury Model Systems study. *Journal of Head Trauma Rehabilitation*, 27(6), E36-44.
- Caveness, W. F. (1963). Onset and Cessation of Fits Following Craniocerebral Trauma. *Journal of Neurosurgery*, 20, 570-583.
- Caveness, W. F., & Liss, H. R. (1961). Incidence of Post-traumatic Epilepsy. *Epilepsia*, 2(2), 123-129.

- Caveness, W. F., Meirowsky, A. M., Rish, B. L., Mohr, J. P., Kistler, J. P., Dillon, J. D., & Weiss, G. H. (1979). The nature of posttraumatic epilepsy. *Journal of Neurosurgery*, 50(5), 545-553.
- Cifu, D. X., Kreutzer, J. S., Marwitz, J. H., Miller, M., Hsu, G. M., Seel, R. T., Englander, J., High Jr, W. M., & Zafonte, R. (1999). Etiology and incidence of rehospitalization after traumatic brain injury: A multicenter analysis. *Archives of Physical Medicine and Rehabilitation*, 80(1), 85-90.
- Cohen, M., & Groswasser, Z. (1991). Epilepsy in traumatic brain-injured patients. *Epilepsia*.
- Corkin, S., Sullivan, E. V., & Carr, F. A. (1984). Prognostic factors for life expectancy after penetrating head injury. *Archives of Neurology*, 41(9), 975-977.
- da Silva, A. M., Nunes, B., Vaz, A. R., & Mendonça, D. (1992). Posttraumatic epilepsy in civilians: clinical and electroencephalographic studies. *Acta Neurochirurgica, Supplement*, 55, 56-63.
- da Silva, A. M., Vaz, A. R., Ribeiro, I., Melo, A. R., Nune, B., & Correia, M. (1990). Controversies in posttraumatic epilepsy. *Acta Neurochirurgica, Supplement*, 50, 48-51.
- De Santis, A., Cappricci, E., & Granata, G. (1979). Early post traumatic seizures in adults. Study of 84 cases. *Journal of Neurosurgical Science*, 23(3), 207-210.
- De Santis, A., Sganzerla, E., Spagnoli, D., Bello, L., & Tiberio, F. (1992). Risk factors for late posttraumatic epilepsy. *Acta Neurochirurgica, Supplement (Wien)*, 55, 64-67.
- Dhakar, M. B., Sivakumar, S., Bhattacharya, P., Shah, A., & Basha, M. M. (2015). A retrospective cross-sectional study of the prevalence of generalized convulsive status epilepticus in traumatic brain injury: United States 2002-2010. *Seizure*, 32, 16-22.
- Di Luca, D. G., & de Lacerda, G. C. B. (2013). Time interval between traumatic brain injury and Post Traumatic Epilepsy. *Revista Neurociencias*, 21(2), 222-228.
- Diamond, M. L., Ritter, A. C., Failla, M. D., Boles, J. A., Conley, Y. P., Kochanek, P. M., & Wagner, A. K. (2014). IL-1beta associations with posttraumatic epilepsy development: a genetics and biomarker cohort study. *Epilepsia*, 55(7), 1109-1119.
- Diaz-Arrastia, R., Agostini, M. A., Frol, A. B., Mickey, B., Fleckenstein, J., Bigio, E., & Van Ness, P. C. (2000). Neurophysiologic and neuroradiologic features of intractable epilepsy after traumatic brain injury in adults. *Archives of Neurology*, 57(11), 1611-1616.
- Dikmen, S. S., Machamer, J. E., Winn, H. R., Anderson, G. D., & Temkin, N. R. (2000). Neuropsychological effects of valproate in traumatic brain injury: a randomized trial. *Neurology*, 54(4), 895-902.
- Dikmen, S. S., Temkin, N. R., Miller, B., Machamer, J., & Winn, H. R. (1991). Neurobehavioral effects of phenytoin prophylaxis of posttraumatic seizures. *Journal of the American Medical Association*, 265(10), 1271-1277.
- Doyle, W. K., Devinsky, O., Perrine, K., Pacia, S., Vasquez, B., & Luciano, D. (1996). Surgical management of post-traumatic epilepsy who underwent surgical management. *Epilepsia*, 37(supp 5), 185.
- Eide, P. K., & Tysnes, O. B. (1992). Early and late outcome in head injury patients with radiological evidence of brain damage. *Acta Neurologica Scandinavica*, 86(2), 194-198.
- Englander, J., Bushnik, T., Duong, T. T., Cifu, D. X., Zafonte, R., Wright, J., Hughes, R., & Bergman, W. (2003). Analyzing risk factors for late posttraumatic seizures: a prospective, multicenter investigation. *Archives of Physical Medicine and Rehabilitation*, 84(3), 365-373.
- Englander, J., Bushnik, T., Wright, J. M., Jamison, L., & Duong, T. T. (2009). Mortality in late post-traumatic seizures. *Journal of Neurotrauma*, 26(9), 1471-1477.

- Englot, D. J., Rolston, J. D., Wang, D. D., Hassnain, K. H., Gordon, C. M., & Chang, E. F. (2012). Efficacy of vagus nerve stimulation in posttraumatic versus nontraumatic epilepsy. *Journal of Neurosurgery*, 117(5), 970-977.
- Evans, J. (1962). Post-traumatic epilepsy. *Neurology*, 12, 665-674.
- Feeney, D. M., & Walker, A. (1979). The prediction of posttraumatic epilepsy: A mathematical approach. *Archives of Neurology*, 36(1), 8-12.
- Ferguson, P. L., Smith, G. M., Wannamaker, B. B., Thurman, D. J., Pickelsimer, E. E., & Selassie, A. W. (2010). A population-based study of risk of epilepsy after hospitalization for traumatic brain injury. *Epilepsia*, 51(5), 891-898.
- Formisano, R., Barba, C., Buzzi, M. G., Newcomb-Fernandez, J., Menniti-Ippolito, F., Zafonte, R., Vinicola, V., & Spanedda, F. (2007). The impact of prophylactic treatment on post-traumatic epilepsy after severe traumatic brain injury. *Brain Injury*, 21(5), 499-504.
- Gabriel, W. M., & Rowe, A. S. (2014). Long-Term Comparison of GOS-E Scores in Patients Treated With Phenytoin or Levetiracetam for Posttraumatic Seizure Prophylaxis After Traumatic Brain Injury. *Annals of Pharmacotherapy*, 48(11), 1440-1444.
- Glötzner, F. L., Haubitz, I., Miltner, F., Kapp, G., & Pflughaupt, K. W. (1983). Seizure prevention using carbamazepine following severe brain injuries. *Neurochirurgia*, 26(3), 66-79.
- Grafman, J., Jonas, B., Salazar, A. (1992). Epilepsy following penetrating head injury to the frontal lobes. In D.-E. A. Chauvel D, Halgren E, Bancaud J, (Ed.), *Advances in neurology* (Vol. 57 pp. 369-378). New York: Raven Press.
- Gupta, P. K., Sayed, N., Ding, K., Agostini, M. A., Van Ness, P. C., Yablon, S., Madden, C., Mickey, B., D'Ambrosio, R., & Diaz-Arrastia, R. (2014). Subtypes of post-traumatic epilepsy: Clinical, electrophysiological, and imaging features. *Journal of Neurotrauma*, 31(16), 1439-1443.
- Hadjigeorgiou, G. F., Petsanas, A., Anagnostopoulos, C., Chamilos, C., Vranos, G., & Spyridakis, P. (2013). Treatment of refractory simple partial status epilepticus by the addition of oral lacosamide in neurosurgical patients. Report of 3 cases. *Epilepsy and Behavior Case Reports*, 1(1), 69-70.
- Hahn, Y. S., Fuchs, S., Flannery, A. M., Barthel, M. J., & McLone, D. G. (1988). Factors influencing posttraumatic seizures in children. *Neurosurgery*, 22(5), 864-867.
- Hakimian, S., Kershenovich, A., Miller, J. W., Ojemann, J. G., Hebb, A. O., D'Ambrosio, R., & Ojemann, G. A. (2012). Long-term outcome of extratemporal resection in posttraumatic epilepsy. *Neurosurgical Focus*, 32(3), E10.
- Haltiner, A. M., Temkin, N. R., & Dikmen, S. S. (1997). Risk of seizure recurrence after the first late posttraumatic seizure. *Archives of Physical Medicine and Rehabilitation*, 78(8), 835-840.
- Heikkinen, E. R., Rönty, H. S., Tolonen, U., & Pyhtinen, J. (1990). Development of Posttraumatic Epilepsy. *Stereotactic and Functional Neurosurgery*, 54(1-8), 25-33.
- Hendrick, E., Harris, L. (1968). Post-traumatic epilepsy in children. *Journal of Trauma*, 8, 547-556.
- Hernandez, T. D., & Naritoku, D. K. (1997). Seizures, epilepsy, and functional recovery after traumatic brain injury: A reappraisal. *Neurology*, 48(4), 803-806.
- Inaba, K., Menaker, J., Branco, B. C., Gooch, J., Okoye, O. T., Herrold, J., Scalea, T. M., Dubose, J., & Demetriades, D. (2013). A prospective multicenter comparison of levetiracetam versus phenytoin for early posttraumatic seizure prophylaxis. *Journal of Trauma & Acute Care Surgery*, 74(3), 766-771; discussion 771-763.
- Japan Follow-up Group for Posttraumatic Epilepsy. (1991). The factors influencing posttraumatic epilepsy: multicentric cooperative study. *No Shinkei Geka*, 19(12), 1151-1159.

- Javed, G., Waqas, M., Qadeer, M., Bari, E., & Murtaza, G. (2016). Use of Levetiracetam in Prophylaxis of Early Post-Traumatic Seizures. *Turk Neurosurg*, 26(5), 732-735.
- Jennett, B. (1975). *Epilepsy after non-missile head injuries*. Chicago: William Heinemann.
- Jennett B, Van De Sande, J. (1975). EEG prediction of post-traumatic epilepsy. *Epilepsia*, 16, 251-256.
- Jones, K. E., Puccio, A. M., Harshman, K. J., Falcione, B., Benedict, N., Jankowitz, B. T., Stippler, M., Fischer, M., Sauber-Schatz, E. K., Fabio, A., Darby, J. M., & Okonkwo, D. O. (2008). Levetiracetam versus phenytoin for seizure prophylaxis in severe traumatic brain injury. *Neurosurgical Focus*, 25(4), E3.
- Kalisky, Z., Morrison, D. P., Meyers, C. A., & Von Laufen, A. (1985). Medical problems encountered during rehabilitation of patients with head injury. *Archives of Physical Medicine and Rehabilitation*, 66(1), 25-29.
- Kazemi, H., Hashemi-Fesharaki, S., Razaghi, S., Najafi, M., Kolivand, P. H., Kovac, S., & Gorji, A. (2012). Intractable epilepsy and craniocerebral trauma: analysis of 163 patients with blunt and penetrating head injuries sustained in war. *Injury*, 43(12), 2132-2135.
- Khan, S. A., Bhatti, S. N., Khan, A. A., Khan Afridi, E. A., Muhammad, G., Gul, N., Zadran, K. K., Alam, S., & Aurangzeb, A. (2016). Comparison Of Efficacy Of Phenytoin And Levetiracetam For Prevention Of Early Post Traumatic Seizures. *Journal of Ayub Medical College Abbottabad*, 28(3), 455-460.
- Kolakowsky-Hayner, S. A., Wright, J., Englander, J., Duong, T., & Ladley-O'Brien, S. (2013). Impact of late post-traumatic seizures on physical health and functioning for individuals with brain injury within the community. *Brain Injury*, 27(5), 578-586.
- Kollevold, T. (1978). Immediate and early cerebral seizures after head injuries. Part III. *Journal of the Oslo city hospitals*, 28(6), 77-86.
- Kollevold, T. (1979). Immediate and early cerebral seizures after head injuries. Part IV. *Journal of the Oslo city hospitals*, 29(4), 35-47.
- Krause-Titz, U. R., Warneke, N., Freitag-Wolf, S., Barth, H., & Mehdorn, H. M. (2016). Factors influencing the outcome (GOS) in reconstructive cranioplasty. *Neurosurgical Review*, 39(1), 133-139.
- Kruer, R. M., Harris, L. H., Goodwin, H., Kornbluth, J., Thomas, K. P., Slater, L. A., & Haut, E. R. (2013). Changing trends in the use of seizure prophylaxis after traumatic brain injury: a shift from phenytoin to levetiracetam. *Journal of Critical Care*, 28(5), 883.e889-813.
- Lamar, C. D., Hurley, R. A., Rowland, J. A., & Taber, K. H. (2014). Post-traumatic epilepsy: Review of risks, pathophysiology, potential biomarkers. *The Journal of Neuropsychiatry and Clinical Neurosciences*, 26(2), 108-113.
- Lucke-Wold, B. P., Nguyen, L., Turner, R. C., Logsdon, A. F., Chen, Y.-W., Smith, K. E., Huber, J. D., Matsumoto, R., Rosen, C. L., Tucker, E. S., & Richter, E. (2015). Traumatic brain injury and epilepsy: Underlying mechanisms leading to seizure. *Seizure*, 33, 13-23.
- Mahler, B., Carlsson, S., Andersson, T., Adelöw, C., Ahlbom, A., & Tomson, T. (2015). Unprovoked seizures after traumatic brain injury: A population-based case-control study. *Epilepsia*, 56(9), 1438-1444.
- Malav, R. A., Anil Chandra, B. K. O., Singh, S. K., Srivastava, C., Chandra, N., Srivastava, S., & Gupta, A. (2015). Outcome of penetrating brain injury in civilian practice. *Indian Journal of Neurotrauma*, 12(2), 122-127.
- Manaka, S. (1992). Cooperative prospective study on posttraumatic epilepsy: risk factors and the effect of prophylactic anticonvulsant. *Japanese Journal of Psychiatry and Neurology*, 46(2), 311-315.

- Marks, D. A., Kim, J., Spencer, D. D., & Spencer, S. S. (1995). Seizure localization and pathology following head injury in patients with uncontrolled epilepsy. *Neurology*, 45(11), 2051-2057.
- McCrory, P. R., Bladin, P. F., & Berkovic, S. F. (1997). Retrospective study of convulsive convulsions in elite Australian rules and rugby league footballers: phenomenology, aetiology, and outcome. *BMJ*, 314(7075), 171-174.
- McQueen, J. K., Blackwood, D. H. R., Harris, P., Kalbag, R. M., & Johnson, A. L. (1983). Low risk of late post-traumatic seizures following severe head injury: Implications for clinical trials of prophylaxis. *Journal of Neurology Neurosurgery and Psychiatry*, 46(10), 899-904.
- Moseley, A. M., Herbert, R. D., Sherrington, C., & Maher, C. G. (2002). Evidence for physiotherapy practice: a survey of the Physiotherapy Evidence Database (PEDro). *Australian Journal of Physiotherapy*, 48(1), 43-49.
- Pagni, C. A. (1990). Posttraumatic epilepsy. Incidence and prophylaxis. *Acta Neurochirurgica, Supplement*, 50, 38-47.
- Phillips, G. (1954). Traumatic Epilepsy after Closed Head Injury. *Journal of Neurology, Neurosurgery, and Psychiatry*, 17(1), 1-10.
- Pohlmann-Eden, B., & Bruckmeir, J. (1997). Predictors and dynamics of posttraumatic epilepsy. *Acta Neurologica Scandinavica*, 95(5), 257-262.
- Radic, J. A., Chou, S. H., Du, R., & Lee, J. W. (2014). Levetiracetam versus phenytoin: a comparison of efficacy of seizure prophylaxis and adverse event risk following acute or subacute subdural hematoma diagnosis. *Neurocritical Care*, 21(2), 228-237.
- Reynolds, P. S., Gilbert, L., Good, D. C., Knappertz, V. A., Crenshaw, C., Wayne, S. L., Pillbury, D., & Tegeler, C. H. (1998). Pneumonia in dysphagic stroke patients: Effect on outcomes and identification of high risk patients. *Journal of Neurologic Rehabilitation*, 12(1), 15-21.
- Rish, B. L., & Caveness, W. F. (1973). Relation of prophylactic medication to the occurrence of early seizures following craniocerebral trauma. *Journal of Neurosurgery*, 38(2), 155-158.
- Rish, B. L., Dillon, J. D., & Weiss, G. H. (1983). Mortality following penetrating craniocerebral injuries. An analysis of the deaths in the Vietnam Head Injury Registry population. *Journal of Neurosurgery*, 59(5), 775-780.
- Salazar, A. M., Jabbari, B., Vance, S. C., Grafman, J., Amin, D., & Dillon, J. D. (1985). Epilepsy after penetrating head injury. I. Clinical correlates: A report of the Vietnam Head Injury Study. *Neurology*, 35(10), 1406-1414.
- Sapina, L., & Ratkovic, M. (2017). Treatment of posttraumatic epilepsy with new generation antiepileptic drugs (AEDs) - our experience. *Med Glas (Zenica)*, 14(1), 126-131.
- Sapina, L., Vuletic, V., Lojen, G., Janjetovic, Z., & Vukovic-Arar, Z. (2014). Head trauma and posttraumatic epilepsy in Slavonski Brod, East Croatia, 1988-2008. *Collegium Antropologicum*, 38(3), 1077-1079.
- Sazbon, L., & Groswasser, Z. (1990). Outcome in 134 patients with prolonged posttraumatic unawareness. Part 1: Parameters determining late recovery of consciousness. *Journal of Neurosurgery*, 72(1), 75-80.
- Schierhout, G., & Roberts, I. (2001). Anti-epileptic drugs for preventing seizures following acute traumatic brain injury. *Cochrane database of systematic reviews (Online)*(4).
- Schwab, K., Grafman, J., Salazar, A. M., & Kraft, J. (1993). Residual impairments and work status 15 years after penetrating head injury: Report from the Vietnam head injury study. *Neurology*, 43(1), 95-103.
- Servit, Z., & Musil, F. (1981). Prophylactic treatment of posttraumatic epilepsy: Results of a long-term follow-up in Czechoslovakia. *Epilepsia*, 22(3), 315-320.

- Steinbaugh, L. A., Lindsell, C. J., Shutter, L. A., & Szaflarski, J. P. (2012). Initial EEG predicts outcomes in a trial of levetiracetam vs. fosphenytoin for seizure prevention. *Epilepsy & Behaviour*, 23(3), 280-284.
- Sundararajan, K., Milne, D., Edwards, S., Chapman, M. J., & Shakib, S. (2015). Anti-seizure prophylaxis in critically ill patients with traumatic brain injury in an intensive care unit. *Anaesthesia & Intensive Care*, 43(5), 646-651.
- Swanson, S. J., Rao, S. M., Grafman, J., Salazar, A. M., & Kraft, J. (1995). The relationship between seizure subtype and interictal personality: Results from the Vietnam head injury study. *Brain*, 118(1), 91-103.
- Szaflarski, J. P., Sangha, K. S., Lindsell, C. J., & Shutter, L. A. (2010). Prospective, randomized, single-blinded comparative trial of intravenous levetiracetam versus phenytoin for seizure prophylaxis. *Neurocritical Care*, 12(2), 165-172.
- Tasker, R. C., Coyle, J. T., & Vornov, J. J. (1992). The regional vulnerability to hypoglycemia-induced neurotoxicity in organotypic hippocampal culture: Protection by early tetrodotoxin or delayed MK-801. *Journal of Neuroscience*, 12(11), 4298-4308.
- Temkin, N. R. (2001). Antiepileptogenesis and seizure prevention trials with antiepileptic drugs: Meta-analysis of controlled trials. *Epilepsia*, 42(4), 515-524.
- Temkin, N. R., Dikmen, S. S., Anderson, G. D., Wilensky, A. J., Holmes, M. D., Cohen, W., Newell, D. W., Nelson, P., Awan, A., & Winn, H. R. (1999). Valproate therapy for prevention of posttraumatic seizures: A randomized trial. *Journal of Neurosurgery*, 91(4), 593-600.
- Temkin, N. R., Dikmen, S. S., Wilensky, A. J., Keihm, J., Chabal, S., & Winn, H. R. (1990). A randomized, double-blind study of phenytoin for the prevention of post-traumatic seizures. *New England Journal of Medicine*, 323(8), 497-502.
- Thompson, K., Pohlmann-Eden, B., Campbell, L. A., & Abel, H. (2015). Pharmacological treatments for preventing epilepsy following traumatic head injury. *Cochrane Database Syst Rev*(8), Cd009900.
- Vartanian, M. G., Cordon, J. J., Kupina, N. C., Schielke, G. P., Posner, A., Raser, K. J., Wang, K. K. W., & Taylor, C. P. (1996). Phenytoin pretreatment prevents hypoxic-ischemic brain damage in neonatal rats. *Developmental Brain Research*, 95(2), 169-175.
- Walker, A. E., & Blumer, D. (1989). The fate of World War II veterans with posttraumatic seizures. *Archives of Neurology*, 46(1), 23-26.
- Walker, A. E., & Erculei, F. (1970). Post-traumatic epilepsy 15 years later. *Epilepsia*, 11(1), 17-26.
- Walker, A. E., & Yablon, S. A. (1959). A follow-up of head injured men of World War II. *Journal of Neurosurgery*, 16, 600-610.
- Walker, A. E., & Yablon, S. A. (1961). *A follow-up study of head wound in World War II. Veterans administration medical monograph*. Washington DC: US Government Printing Office.
- Walker, W. C., Ketchum, J. S., 3rd, Marwitz, J. H., Kolakowsky-Hayner, S. A., McClish, D. K., & Bushnik, T. (2015). Global Outcome and Late Seizures After Penetrating Versus Closed Traumatic Brain Injury: A NIDRR TBI Model Systems Study. *Journal of Head Trauma Rehabilitation*, 30(4), 231-240.
- Wang, H., Xin, T., Sun, X., Wang, S., Guo, H., Holton-Burke, C., & Pang, Q. (2013a). Post-traumatic seizures--a prospective, multicenter, large case study after head injury in China. *Epilepsy Res*, 107(3), 272-278.
- Wang, H., Xin, T., Sun, X., Wang, S., Guo, H., Holton-Burke, C., & Pang, Q. (2013b). Post-traumatic seizures-A prospective, multicenter, large case study after head injury in China. *Epilepsy Research*, 107(3), 272-278.

- Watson, N. F., Barber, J. K., Doherty, M. J., Miller, J. W., & Temkin, N. R. (2004). Does glucocorticoid administration prevent late seizures after head injury? *Epilepsia*, 45(6), 690-694.
- Weiss, G. H., Feeney, D. M., Caveness, W. F., Dillon, D., Kistler, J. P., Mohr, J. P., & Rish, B. L. (1983). Prognostic factors for the occurrence of posttraumatic epilepsy. *Archives of Neurology*, 40(1), 7-10.
- Wiedemayer, H., Triesch, K., Schäfer, H., & Stolke, D. (2002). Early seizures following non-penetrating traumatic brain injury in adults: Risk factors and clinical significance. *Brain Injury*, 16(4), 323-330.
- Wiederholt, W. C., Melton, L. J., 3rd, Annegers, J. F., Grabow, J. D., Laws, E. R., Jr., & Ilstrup, D. M. (1989). Short-term outcomes of skull fracture: a population-based study of survival and neurologic complications. *Neurology*, 39(1), 96-102.
- Wilson, D. A., & Selassie, A. W. (2014). Risk of severe and repetitive traumatic brain injury in persons with epilepsy: a population-based case-control study. *Epilepsy & Behaviour*, 32, 42-48.
- Won, S. Y., Dubinski, D., Herrmann, E., Cuca, C., Strzelczyk, A., Seifert, V., Konczalla, J., & Freiman, T. M. (2017). Epileptic Seizures in Patients Following Surgical Treatment of Acute Subdural Hematoma-Incidence, Risk Factors, Patient Outcome, and Development of New Scoring System for Prophylactic Antiepileptic Treatment (GATE-24 score). *World Neurosurg*, 101, 416-424.
- Wroblewski, B. A., Glenn, M. B., Whyte, J., & Singer, W. D. (1989). Carbamazepine replacement of phenytoin, phenobarbital and primidone in a rehabilitation setting: effects on seizure control. *Brain Injury*, 3(2), 149-156.
- Wroblewski, B. A., Leary, J. M., Phelan, A. M., Whyte, J., & Manning, K. (1992). Methylphenidate and seizure frequency in brain injured patients with seizure disorders. *Journal of Clinical Psychiatry*, 53(3), 86-89.
- Xu, T., Yu, X., Ou, S., Liu, X., Yuan, J., Huang, H., Yang, J., He, L., & Chen, Y. (2017). Risk factors for posttraumatic epilepsy: A systematic review and meta-analysis. *Epilepsy & Behavior*, 67, 1-6.
- Yablon, S., & Dostrow, V. (2001). Post-traumatic seizures and epilepsy. *Brain injury medicine: principles and practice*, 443.
- Yablon, S. A. (1993). Posttraumatic seizures. *Archive of Physical Medicine and Rehabilitation*, 74(9), 983-1001.
- Yeh, C.C., Chen, T.L., Hu, C.-J., Chiu, W.T., & Liao, C.C. (2013). Risk of epilepsy after traumatic brain injury: A retrospective population-based cohort study. *Journal of Neurology, Neurosurgery & Psychiatry*, 84(4), 441-445.
- Young, B., Rapp, R. P., Norton, J. A., Haack, D., Tibbs, P. A., & Bean, J. R. (1983). Failure of prophylactically administered phenytoin to prevent early posttraumatic seizures. *Journal of Neurosurgery*, 58(2), 231-235.
- Younus, S. M., Basar, S., Gauri, S. A., Khan, A. A., Imran, M., Abubakar, S., Sheikh, D., Shehbaz, N., & Ashraf, J. (2018). Comparison of Phenytoin versus Levetiracetam in Early Seizure Prophylaxis after Traumatic Brain Injury, at a Tertiary Care Hospital in Karachi, Pakistan. *Asian journal of neurosurgery*, 13(4), 1096-1100.
- Zafar, S. N., Khan, A. A., Ghauri, A. A., & Shamim, M. S. (2012). Phenytoin versus Leviteracetam for seizure prophylaxis after brain injury—A meta analysis. *BMC Neurology*, 12.
- Zhao, Y., Wu, H., Wang, X., Li, J., & Zhang, S. (2012). Clinical epidemiology of posttraumatic epilepsy in a group of Chinese patients. *Seizure*, 21(5), 322-326.

Zheng, Z., Chen, P., Fu, W., Zhu, J., Zhang, H., Shi, J., & Zhang, J. (2013). Early and late postoperative seizure outcome in 97 patients with supratentorial meningioma and preoperative seizures: A retrospective study. *Journal of Neuro-Oncology*, 114(1), 101-109.