

# ERABI

EVIDENCE-BASED REVIEW  
of moderate to severe  
ACQUIRED BRAIN INJURY

## Clinical Guidebook

### 7. Post-Traumatic Seizures Following an Acquired Brain Injury

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## Post-Traumatic Seizures Following Acquired Brain Injury

**By the end of this module you should be able to:**

- Know the different types of seizures which can occur post-ABI
- Identify the risk factors for developing post-traumatic seizures
- Be able to recognize the clinical presentation of post-traumatic seizures
- Know the most common pharmacological and non-pharmacological interventions for post-traumatic seizures

### 7.1 Introduction

Post-traumatic seizures (PTS), although identified as a serious consequence of traumatic brain injury (TBI), remains an understudied problem (Ferguson et al., 2010). This Clinical Guidebook chapter will cover the clinical presentation of PTS, as well as the incidence, risk factors, assessment and management of this specific brain injury sequela.

**Q1. Define the following terms:**

#### **Seizure**

Discrete clinical events that reflect a temporary physiologic dysfunction of the brain characterized by excessive and hypersynchronous discharge of cortical neurons.

#### **Epilepsy**

Epilepsy is a condition characterized by recurrent unprovoked seizures.

#### **Post-Traumatic Seizure**

An initial or recurrent seizure episode not attributable to another obvious cause after penetrating or non-penetrating TBI. The term *post-traumatic seizure* is preferred over *post-traumatic epilepsy* because the former encompasses both single and recurrent events.

#### **Post-Traumatic Epilepsy**

A disorder characterized by recurrent late seizure episodes not attributable to another obvious cause in patients following TBI. Although the term *post-traumatic epilepsy* commonly has designated single or multiple seizures including early seizures, the term should be reserved for *recurrent*, late PTS.

#### **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.

**Non-epileptic Seizure**

Episodic behavioral events that superficially resemble epileptic attacks but are not associated with paroxysmal activity within the brain.

Brain Injury Special Interest Group of the AAPM&R (1998)

## 7.2 Clinical Presentation of Post-Traumatic Seizures

Similar classification is used to describe the onset of both post-traumatic and non-traumatic related seizures. PTS may present as either generalized or partial seizures. Generalized seizures are bilaterally symmetric in origin without focal onset. Partial seizures, also known as focal seizures, originate in a localized area of one cerebral hemisphere. Partial seizures without any change in level of consciousness are known as simple partial seizures; partial seizures with any change in level of consciousness are termed complex partial seizures. Both simple and complex partial seizures may develop into generalized seizures; this is known as a partial seizure with secondary generalization. In a prospective case series of 94 patients with moderate-severe brain injuries, Vespa et al. (1999) found that 52% of PTS were non-convulsive in nature in the first 14 days post-TBI. Wiedemayer et al. (2002) retrospectively analyzed a consecutive series of 1868 adult patients with head injury and found that 5.8% (109 patients) had an early seizure. Of those 109 patients, 69 (63.3%) had a generalized early PTS and 40 patients (36.7%) had a partial early PTS. Table 7.1 shows the frequency of seizure type in those with PTS. The studies referenced are predominantly retrospective reviews that selected all patients with TBI that developed PTS/PTE and calculated rates of seizure type from that sub-population.

**Table 7.1 Frequency of Seizure Type in PTS.**

Seizure Type	Incidence	Reference
Complex or simple partial 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	30-53.6%	(Di Luca & de Lacerda, 2013; Zhao et al., 2012; Zheng et al., 2013)
Simple partial	14-42.3%	(Zhao et al., 2012; Zheng et al., 2013)
Complex partial	4.1-16%	(Sapina et al., 2014; Zhao et al., 2012; Zheng et al., 2013)
Generalized atonic	2%	(Di Luca & de Lacerda, 2013)

### 7.2.1 Incidence of Post-Traumatic Seizures

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 much as 18%), which likely 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 and colleagues (2012) found that when seizures occurred post-TBI, 0.4% were immediate, 0.5% were early, and 88.7% were late.

**Table 7.2 Incidence of unprovoked PTS in 4541 individuals with TBI (Annegers et al., 1998).**

Type	Definition	5-year risk of developing PTE
Mild	LoC /PTA <30 min with no skull fracture	0.7%
Moderate	LoC /PTA 30 min-24 hours and/or skull fracture	1.2%
Severe	LoC/PTA >24 hours and/or brain contusion/intracranial hematoma	10%

## 7.2.2 Risk Factors for Post-Traumatic Seizures

### **Q2. What factors are predictive of patients with ABI that are at high risk of seizures?**

1. Patient characteristics: Increased age, chronic alcohol use, family history of seizures.
2. Injury Characteristics: Bone/metal fragments, depressed skull fracture, focal contusions/injury, focal neurological deficits, dural penetration, intracranial hemorrhage, increased injury severity.
3. Early post-traumatic seizures.

There are several patient and injury characteristics that increase the risk of developing a post-traumatic seizure, both short and long term. These risk factors are presented in Table 7.3, along with references. Mild head injury (head injury without skull fracture and LoC/PTA less than 30 minutes) does not increase the risk of PTS from the general population (Hanaya & Arita, 2016) Identifying patients at a high PTS risk is important for determining when to use prophylactic medications in the acute setting, as well as for guiding history/physical examination focus in the chronic follow-up setting.

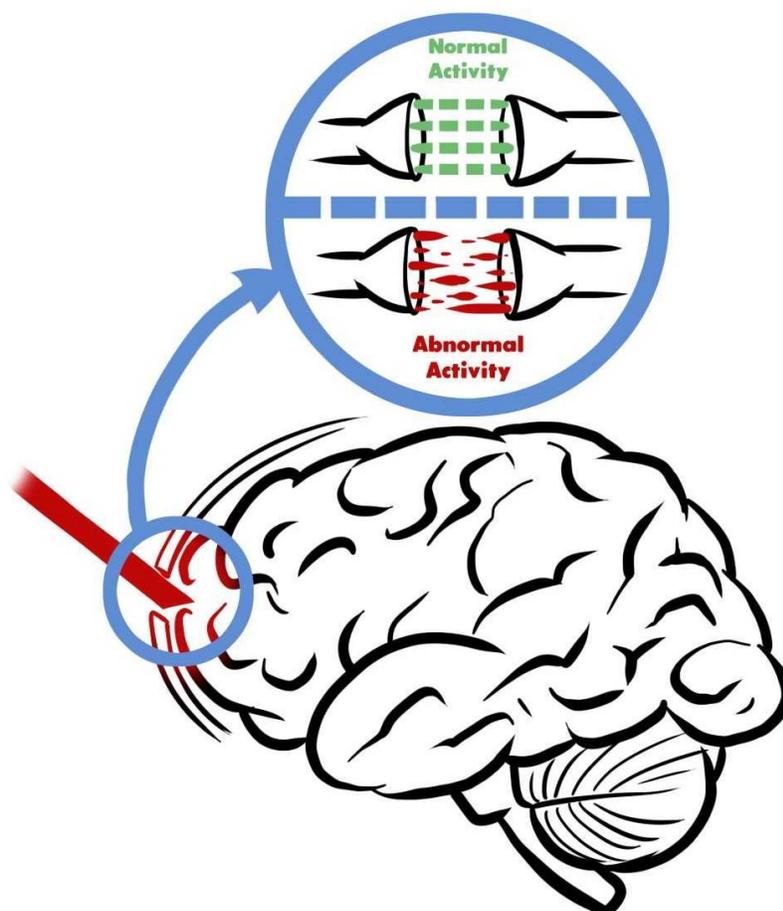
**Table 7.3 Risk Factors for Developing Post-Traumatic Seizures Following ABI**

Risk Factor	Key Factors	Reference
<b>Patient Characteristics</b>		
Age	Rates of PTS are highest between patients aged 30-69 years old. Early PTS rates are highest in children <7 years old.	(Annegers et al., 1980; Asikainen et al., 1999; Hahn et al., 1988; Kollevold, 1979)
Gender	Males are at an increased risk of developing PTS.	(Xu et al., 2017)
Alcohol use	Alcohol use increases the risk of developing PTS, especially in males.	(Evans, 1962; Heikkinen et al., 1990; Japan Follow-up Group for

		Posttraumatic Epilepsy, 1991; Kollevold, 1978)
<b>Injury Characteristics</b>		
Bone/metal fragments	Fragmented material in the cranium increases the risk of PTS.	(Ascroft, 1941; Salazar et al., 1985; Walker & Yablon, 1959)
Depressed skull fracture	Having a depressed skull fracture increases the risk of PTS.	(Hahn et al., 1988; Jennett B, 1975; Phillips, 1954; Wiederholt et al., 1989)
Focal contusions/injury	Focal injuries are associated with higher rates of PTS.	(da Silva et al., 1992; De Santis et al., 1992; Eide & Tysnes, 1992; Glötzner et al., 1983; Heikkinen et al., 1990)
Focal neurologic deficits	Focal neurologic deficits increase the risk of PTS.	(da Silva et al., 1992; Jennett B, 1975; Salazar et al., 1985)
Dural penetration	With each procedure or injury the risk of PTS increases with repeated dural penetration.	(Caveness & Liss, 1961; Evans, 1962; Salazar et al., 1985)
Intracranial hemorrhage	Intracranial hemorrhages increase the risk of PTS.	(Glötzner et al., 1983; Hahn et al., 1988; Japan Follow-up Group for Posttraumatic Epilepsy, 1991)
Injury severity	Loss of consciousness and decreased GCS increase the risk of developing PTS.	(Evans, 1962; Jennett B, 1975; Salazar et al., 1985; Walker & Yablon, 1961)
<b>Other</b>		
Early post-traumatic seizures	20-30% of patients who experience an EPTS will have a LPTS.	(Heikkinen et al., 1990; Jennett, 1975; Salazar et al., 1985)
Intracranial surgery	Craniotomy/craniectomy is one of the most predictive risk factors for PTS.	(Ritter et al., 2016)

### Penetrating Injuries

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). Ritter et al. (2016) found cranial surgeries to be among the strongest predictors for PTS.



**Figure 7.1 Penetrating injuries increase the risk of post-traumatic seizures as a result of abnormal electrophysiological activity in the brain at the site of injury.**

### Timeline

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) noted that 50-66% of individuals who suffer PTS will experience seizure onset within the first 12 months. Further, 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.

After 5 years, adults with mild TBI no longer have a significantly increased risk of developing seizures relative to the general population (Annegers et al., 1998) whereas patients with moderate or severe TBI or penetrating TBI remain at increased risk for more than 5 years post-injury (Annegers et al., 1998; da Silva et al., 1992; Pagni, 1990; Salazar et al., 1985).

## Age

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).

## Genetics

Diamond et al. (2014) 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 $\beta$  (a potential biomarker for epilepsy) ratios were associated with an increased risk of PTE (Diamond et al., 2014). More studies are needed before firm conclusions can be made.

### 7.2.3 Recurrence of Post-Traumatic Seizures

The risk of seizure recurrence after an early PTS is around 25% (Lamar et al., 2014; Lucke-Wold et al., 2015; Yablon & Dostrow, 2001). Comparatively, the risk of recurrence is much higher (86% at 2 years) following a late PTS (Haltiner et al., 1997).

Seizure recurrence is an important factor in the determination of disability, likelihood of employment, quality of life, ability to drive and health care costs (Baker et al., 1997; Van Hout et al., 1997; Yablon & Dostrow, 2001).

**Table 7.4 Features of Recurrent Seizures in TBI Populations.**

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)



#### Clinical Tip!

Study mnemonic risk factors for PTS:  
*E – Early PTS (Immediate PTS do NOT increase risk)*  
*P – Penetrating head injuries*  
*I – Intracranial hematoma (SDH, EDH, ICH)*  
*L – Length of coma/PTA (>24 hours for either)*  
*E – EtOH abuse*  
*P – Presence of intracranial foreign bodies*  
*S – Surgical procedures (intracranial, craniotomy)*  
*Y – Youth (increased risk of early PTS but not late PTS)*

## 7.2.4 Clinical Consequences of Post-Traumatic Seizures

Seizures following TBI may 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.

## 7.2.5 Cognitive and Behavioural Function

Post-traumatic epilepsy 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).

## 7.2.6 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 does 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).

## 7.2.7 Functional Status

Recurrent PTS may lead to negative impacts on functional status following TBI, 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 as 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. In contrast, 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 had poorer outcomes on the Glasgow Outcome Scale (GOS). To date, no significant differences in employment outcomes have been observed with the presence of PTS (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.

## 7.2.8 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 complication of PTS and may lead to additional neurological damage. Simple partial status epilepticus, is a subset of status epilepticus, characterized as a partial 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).

### 7.2.9 Mortality

Mortality has been reported to be high among those who sustain a TBI and develop PTS (Corkin et al., 1984; Walker & Blumer, 1989; Walker & Erculei, 1970). Englander et al. (2009), similarly, 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 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 generally minimal, similar to those who experience a non-trauma related seizure. Increased seizure frequency and severity, however, are associated with an increased risk of mortality and morbidity in the form of worsened cognition and overall function.

#### ***Q3. List some of the complications of post-traumatic seizures.***

1. Deterioration in cognitive and behavioural functioning
2. Deterioration in overall functional status
3. Negative impact on neurological recovery
4. Status epilepticus
5. Death
6. Non-elective hospitalization
7. Accidental injuries
8. Loss of driving privileges

## 7.3 Criteria for Diagnosis of Post-Traumatic Seizures/Epilepsy

The diagnosis of a seizure, post-traumatic or otherwise, can be quite difficult and relies on a combination of thorough history, physical examination and investigations. The gold standard diagnosis requires continuous video electroencephalography (Rao & Parko, 2015). Patients may not be aware of the various presentation types that seizures can take. Psychogenic non-epileptic seizures (PNES) are common after TBI and are an important consideration in order to avoid unnecessary hospitalization and medication treatment. Diagnosis of PNES relies on careful clinical history and should be a diagnosis of exclusion after PTS/PTE has been ruled out (Hung & Chen, 2012).

## 7.4 Assessment of Post-Traumatic Seizures

Once a seizure has been identified, further workup is warranted. The table below outlines various seizure precipitants that should be considered in any patient presenting with a seizure. Detailed history and physical examination can guide further investigations required to rule out potential causes. Consideration should be given to neuroimaging. All patients presenting with seizure should undergo EEG. Comatose patients with a traumatic brain injury should undergo continuous EEG to rule out nonconvulsive seizures (Zimmermann et al., 2017).



### Clinical Tip!

#### Seizure presentation/screening questions for patients:

- Premonitory aura
- Episodes of unresponsiveness or altered awareness
- Déjà vu or jamais vu
- Involuntary motor activity (automatisms, clonic movements)
- Dysphagia
- Amnesia or periods of lost time
- Olfactory or gustatory hallucinations
- Unexplained nocturnal injuries or nocturnal incontinence

**Table 7.5 Potential Seizure Precipitants (Ahmed & Spencer, 2004; Pohlmann-Eden et al., 2006).**

Structural	- Hydrocephalus - Mass occupying lesions (hemorrhage, abscess – especially in penetrating injuries)
Metabolic	- Electrolyte abnormalities (Na, Mg, Ca) - Hypoglycemia - Uremia - Hepatic encephalopathy
Infectious	- Sepsis/fever - Encephalitis/meningitis
Illicit substances	- Alcohol, Cocaine, Ecstasy, Amphetamines (rare at therapeutic doses), Caffeine (high doses)
Medications	- Tricyclic antidepressants, Clozapine, antibiotics (imipenem, quinolones, cephalosporins), Wellbutrin, narcotics

## 7.5 Management and Treatment of Post-Traumatic Seizures

### 7.5.1 Rationale for Early Seizure Prevention & Prophylactic Treatment

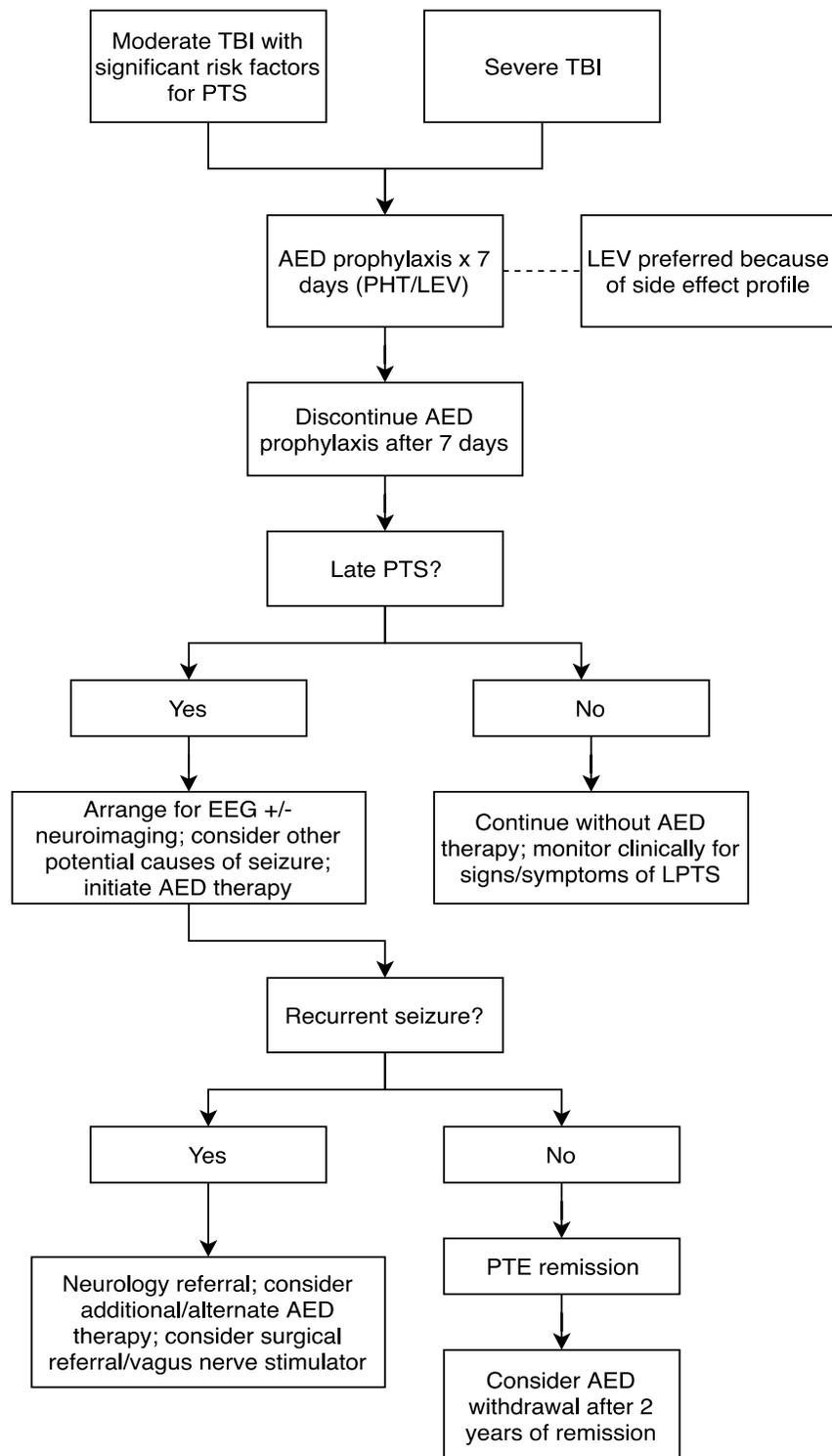
Schierhout and Roberts (2001) reported that early post-traumatic seizures may cause secondary brain damage as a result of increased metabolic demands of the recovering brain, excessive amounts of neurotransmitter release, and increased intracranial pressure. As such, antiepileptic drugs (AEDs) are used in the acute period for those at high risk for early seizures in an attempt to reduce the potential for secondary brain damage following the initial injury.

## 7.5.2 Pharmacologic Management and Prophylaxis of PTS/PTE

### **Q4. What evidence is there to support the prophylactic use of anticonvulsants after ABI?**

1. Based on meta-analysis and the findings of this review, there is Level 1 evidence that anticonvulsants given during the first 24 hours post-TBI reduce the occurrence of early seizures (i.e. seizures within the first week post-injury).
2. There is Level 1 evidence that anticonvulsants given shortly after the onset of injury do not reduce mortality, persistent vegetative state or the occurrence of late seizures (i.e. seizures occurring more than one-week post-injury).

Table 7.6 summarizes the most common pharmacologic interventions to be found in the ERABI evidence, for ABI specific populations. Overall, the majority of interventions have conflicting results and depend on multiple factors. In the TBI population, phenytoin is the most widely studied drug. The beneficial effects of this drug for the prophylactic treatment of PTS are largely mixed, with one larger RCT demonstrating a positive effect. However, the negative side-effects of phenytoin have been consistently reported and for this reason the majority of patients asked to be removed from the drug (Dikmen et al., 1991; Temkin et al., 1990; Young et al., 1983). Recently, both levetiracetam and lacosamide have been investigated for use in the TBI population. Similar to phenytoin, the results are mixed. Both levetiracetam and lacosamide do not appear to be any more effective than phenytoin at reducing early PTS. However, the lower rate of adverse events makes them more appealing for clinical use (Javed et al., 2016; Khan et al., 2016; Kwon et al., 2019; Sapina & Ratkovic, 2017). The algorithm below highlights the appropriate care pathway/indications for investigation and management of PTS/PTE.



**Figure 7.2 A potential assessment and management strategy for post-traumatic seizures following an ABI.**

Table 7.6 Pharmacologic Interventions for the Prevention and Treatment of PTS.

Intervention	Description	Level of evidence	Reference
<b>Phenytoin</b>	<p><b>Route:</b> IV, PO</p> <p><b>Dosing:</b></p> <ul style="list-style-type: none"> <li>- Loading Dose: 10-15 mg/kg IV</li> <li>- Maintenance: 10-20 µg/mL IV or 160-300 mg/day divided TID</li> </ul> <p><b>Mechanism of Action:</b> Likely enhances sodium efflux from neurons in the cortex</p> <p><b>Adverse Events:</b></p> <ul style="list-style-type: none"> <li>- Common: ataxia, nystagmus, confusion, rash, constipation, nausea/vomiting</li> <li>- Serious: Stevens-Johnson, toxic epidermal necrosis, cardiac arrest, agranulocytosis, pancytopenia, hepatotoxicity, nephrotoxicity, suicidality</li> </ul> <p><b>Clinical Notes:</b> Phenytoin administration in the first week post-TBI appears to be beneficial for the prevention of early seizures, but not late seizures. Many patients ask to be taken off of phenytoin due to side-effects. Serum phenytoin level should be monitored during dosage changes or when side effects present. Monitor CBC, BUN/Cr, LFTs.</p>	<p>Level 1b evidence that phenytoin reduces rates of early seizures</p> <p>Conflicting level 1b evidence whether or not phenytoin reduces the rates of long-term seizures.</p>	<p><a href="#">Dikmen et al. (1991)</a>  <a href="#">Temkin et al. (1990)</a>  <a href="#">Young et al. (1983)</a>  <a href="#">Young et al. (1983)</a>  <a href="#">McQueen et al. (1983)</a>  <a href="#">Bhullar et al. (2014)</a>  <a href="#">Servit &amp; Musil (1981)</a>  <a href="#">Yang et al. (2016)</a></p>
<b>Levetiracetam</b>	<p><b>Route:</b> IV, PO</p> <p><b>Dosing:</b></p> <ul style="list-style-type: none"> <li>- Loading Dose: 20-30 mg/kg IV infused at 5 mg/kg/min (second line)</li> <li>- Maintenance: 250-500 mg/day initially, target typically 1000-4000 mg/day (may be divided BID) – both IV and PO</li> </ul> <p><b>Mechanism of Action:</b> Unknown</p> <p><b>Adverse Events:</b></p> <ul style="list-style-type: none"> <li>- Common: decreased BMD, anorexia, dizziness, headache, irritability, fatigue</li> <li>- Serious: Stevens-Johnson, toxic epidermal necrosis, pancytopenia, hepatotoxicity, suicidality, somnolence</li> </ul>	<p>Level 1b evidence that levetiracetam may not be more effective than phenytoin.</p>	<p><a href="#">Javed et al. (2016)</a>  <a href="#">Khan et al. (2016)</a>  <a href="#">Radic et al. (2014)</a>  <a href="#">Gabriel &amp; Rowe (2014)</a>  <a href="#">Inaba et al. (2013)</a>  <a href="#">Kruer et al. (2013)</a>  <a href="#">Szaflarski et al. (2010)</a>  <a href="#">Jones et al. (2008)</a>  <a href="#">Yang et al. (2016)</a></p>

	<p><b>Clinical Notes:</b> Overall, there is conflicting evidence as to the efficacy of this treatment, with it being slightly less effective than phenytoin; however, rates of side-effects are also reduced. Monitor creatinine at initiation. May worsen irritability if present.</p>		
<b>Lacosamide</b>	<p><b>Route:</b> IV, PO</p> <p><b>Dosing:</b></p> <ul style="list-style-type: none"> <li>- Maintenance: 50-100 mg BID initially; titrate to 100-200 mg BID – both IV and PO</li> </ul> <p><b>Mechanism of Action:</b> Unknown; appears to control neural hyperexcitability through selective sodium channel inactivation</p> <p><b>Adverse Events:</b></p> <ul style="list-style-type: none"> <li>- Common: nausea, dizziness, headache, diplopia</li> <li>- Serious: atrial fibrillation/flutter, first degree AV block, suicidality</li> </ul> <p><b>Clinical Notes:</b> Lacosamide was no more effective at reducing early seizures than phenytoin; however, it may have a lower rate of side effects and more tolerable side effect profile. Baseline ECG should be checked prior to initiation.</p>	Level 3 evidence that lacosamide may not be more effective than phenytoin at reducing early seizures.	<p><a href="#">Sapina &amp; Ratkovic (2017)</a></p> <p><a href="#">Kwon et al. (2019)</a></p>
<b>Glucocorticoids (Dexamethasone)</b>	From one cohort study, there was no evidence that glucocorticoid administration, compared to no treatment, was effective at reducing the incidence of early or late seizures.	Level 3 evidence that glucocorticoids are not effective for reducing seizure activity.	<a href="#">Watson et al. (2004)</a>
<b>Methylphenidate</b>	Some patients experienced reduced seizure rate during methylphenidate treatment, while others did not.	Level 4 evidence suggests that methylphenidate may be an effective anti-seizure medication for some individuals.	<a href="#">Wroblewski et al. (1992)</a>
<b>Phenobarbital</b>	Phenobarbital was administered in doses between 10-25µg/mL. No prophylactic benefits have been shown in ABI specific populations.	Level 1b evidence that phenobarbital does not reduce rates of seizures.	<a href="#">Manaka (1992)</a>

### 7.5.3 Length of Prophylaxis and Maintenance Treatment of PTS/PTE

The American Academy of Neurology (Chang & Lowenstein, 2003) recommend AED prophylaxis for the first seven days after injury and discontinuing prophylaxis thereafter as early treatment does not appear to reduce late PTS/PTE. In retrospective reviews, Zaman et al. (2017) and Cranley et al. (2016) both showed that adherence to these guidelines appears to be quite variable with 10-42% receiving prophylactic treatment for longer than one week without indication. Continuing prophylactic treatment longer than one week has not been shown to reduce late PTS/PTE and may result in adverse events.

When determining length of treatment for maintenance therapy, there is less of a consensus. Once PTE remission has been achieved, continuing AED therapy is dependent on several factors including patient age, medication tolerability, and patient preference. Most consider AED withdrawal after two years of PTE remission, but others continue maintenance therapy for four years prior to discontinuing (Rao & Parko, 2015).

### 7.5.4 Non-Pharmacologic Treatment of PTS/PTE

Relative to pharmacologic treatments for seizures, relatively few studies have examined the efficacy of surgical excision in PTE (Hakimian et al., 2012; Marks et al., 1995; Zheng et al., 2013). In general, there is evidence to support that surgical excision for the treatment of PTS can be effective for carefully selected patients with an identified seizure focus on EEG. Vagus nerve stimulator (VNS) is used more frequently as a treatment option for partial onset seizures (Elliott et al., 2011; Englot et al., 2012). 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 VNS (Englot et al., 2012). Table 7.7 outlines the evidence behind both surgical excision and VNS. For patients that develop PTS/PTE, it is important to discuss the appropriate lifestyle modifications that can be made to help prevent seizure recurrence.

**Table 7.7 Non-Pharmacologic Interventions for the Prevention and Treatment of PTS.**

Intervention	Description	Level of evidence	Reference
<b>Surgical excision of PTS focus</b>	Retrospective studies show that surgical excision of the seizure focus, when it can be identified, may be effective for patient populations that have been unresponsive to other measures.	Level 4 evidence supports the use of surgical excision for PTS when other measures have failed.	<a href="#">Esquenazi et al. (2016)</a> <a href="#">Zheng et al. (2013)</a> <a href="#">Hakimian et al. (2012)</a> <a href="#">Marks et al. (1995)</a>
<b>Vagus Nerve Stimulator</b>	VNS was approved for the treatment of partial onset seizures in 1997. Retrospective studies show that VNS reduces the rate of seizures in the TBI population. VNS are usually well tolerated; patients may experience voice alteration, cough, dyspnea, or dysphagia. Complications include pain, wound infections, electrode malfunction, cardiac arrhythmia during testing, and transient vocal cord paralysis.	Level 4 evidence that VNS reduces seizure frequency in those with partial onset seizures.	<a href="#">Englot et al. (2012)</a> <a href="#">Elliot et al. (2010)</a>

**Table 7.8 Additional lifestyle modifications recommended for those with PTE (Hung & Chen, 2012).**

Category	Description
Diet	The ketogenic diet is occasionally used in the treatment of refractory seizures, especially in children. Currently, however, there is no published literature on the use of the ketogenic diet in the TBI population in humans. AEDs commonly affect appetite and weight; both should be monitored while patients are on AEDs.
Sleep	Sleep deprivation is a known seizure trigger. Altered sleep-wake cycle is a common finding in the TBI population. Special care should be given to ensuring an appropriate sleep schedule is maintained.
Exercise	Patients with epilepsy are likely at increased risk of becoming sedentary with a reduced exercise capacity. Safety planning is important when determining an exercise program (special consideration for water sports, motor sports, etc.).
Caffeine, drug abuse, alcohol	Caffeine, alcohol and recreational drug abuse are known seizure triggers in the non-traumatic seizure population and are likely triggers of PTE as well, though this has not been studied specifically. Appropriate counselling and education are important where applicable.
General safety	Special counselling should be provided to patients with PTS/PTE regarding safety around swimming, bathing, cooking, occupational risks, and climbing to heights/use of ladders.
Driving	Clinicians should review their local laws regarding when to report to the appropriate regulatory bodies when patients have a PTS or when AEDs are initiated/discontinued.
Pregnancy	Many AEDs are known teratogens. Some AEDs are also known to lower serum levels of oral contraceptive pills. Special consideration and counselling should be given to women of child bearing age on AEDs.

## 7.6 Case Study

### Patient Snapshot:

#### Mr. LL...

Is a 55 year-old male who was involved in a motor vehicle collision. He sustained a right temporal bone fracture, epidural hemorrhage, diffuse sub-arachnoid hemorrhage, with retained intracerebral fragments of glass. On arrival to hospital his GCS level is 6, he is emergently taken to the OR for a hemi-craniectomy and evacuation of hemorrhage/retained products. He has had no witnessed seizure events since admission.

**Lifestyle Factors:** Mr. LL has a history of alcohol and amphetamine abuse. He is currently employed as a commercial truck driver.

**Medical History:** Mr. LL has no other medical history.

While Mr. LL is being moved into the recovery room post-operatively, his treating physician confirms he has had no witnessed seizure events since coming into hospital 6 hours ago. The treating physician asks if any AEDs are recommended. What do you suggest?



Given Mr. LL has a severe TBI he should be started on AED prophylaxis immediately with a loading dose of either phenytoin (10-15 mg/kg IV) or levetiracetam (20-30 mg/kg IV; infused at 5 mg/kg/min) followed by standard maintenance dosing. You suggest levetiracetam given its preferred side effect profile over phenytoin.

**Q1. What are some of Mr. LL's risk factors for developing PTS/PTE?**

1. Severe TBI
2. Skull fracture
3. Epidural/sub-arachnoid hemorrhage
4. Age
5. Penetrating injury
6. Retained intracerebral fragments
7. GCS level
8. Craniectomy
9. History of alcohol/drug abuse

**Q2. What lab investigations are required when initiating phenytoin and levetiracetam?**

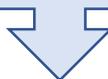
**Phenytoin:**

1. CBC
2. BUN/Cr.
3. Liver enzymes
4. Phenytoin level

**Levetiracetam:**

1. BUN/Cr

**The treating physician starts Mr. LL on phenytoin. Four days later the nurse reports that Mr. LL has started to have difficulty with transfers, whereas he had been improving until that point. What should you do next?**



With any change in recovery trajectory, it is important to identify and treat potentially reversible causes. It is important to complete a detailed history and physical examination to determine if there has been any neurologic change/deterioration. Consideration should be given to repeat neuroimaging. Careful assessment of medications and medication changes is important. Consideration should also be given to potential sources of infection or metabolic abnormalities that may contribute to the decompensation. Phenytoin toxicity may lead to ataxia, which could explain Mr. LL's acutely worsening transfers. A phenytoin level should be checked.

### Q3. What are the features of phenytoin toxicity?

#### Neurotoxicity:

1. Ataxia
2. Nystagmus
3. Confusion
4. Hallucinations
5. Neuropathy
6. Movement disorders

#### Cardiotoxicity:

1. SA/AV nodal block
2. Infusion rates over 50 mg/min may lead to: bradycardia, hypotension and asystole

#### Epidermal:

1. Stevens-Johnson Syndrome
2. Toxic Epidermal Necrosis

#### Other:

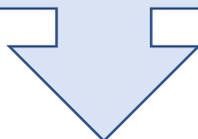
1. Gingival hyperplasia
2. DRESS syndrome
3. Purple Glove syndrome

**7 days after the MVC, the treating physician asks if Mr. LL should be continued on AED prophylaxis because of his significant number of risk factors for late PTS/PTE. What do you suggest?**



There is currently no evidence that AED prophylaxis reduces the rate of late PTS/PTE. Continuing patients on AED prophylaxis past the recommended 7 days potentially exposes them to unnecessary adverse events. The AED prophylaxis should be discontinued.

**One month later, Mr. LL is admitted to your inpatient rehabilitation ward. During a physiotherapy session, Mr. LL briefly becomes unaware of his surroundings while continually picking at his shirt. After 30 seconds of this behaviour he develops whole body convulsions which terminate spontaneously after 90 seconds. He remains stable, your colleague monitors him acutely. He is quite lethargic and confused for 60 minutes afterwards with newfound left arm weakness which resolves after 8 hours. What are your next steps?**



A careful history and physical examination should be carried out. Focus should be given to ruling out potential causes of seizures as well as assessment of the left arm weakness. Provoking causes

(hypoglycemia, electrolyte abnormality, recurrent hemorrhage, infection etc.) should be managed as indicated. AED therapy should be initiated.

**Q4. What type of seizure did Mr. LL experience?**

Mr. LL experienced a complex partial seizure with secondary generalization. The continual picking at clothing is in keeping with an automatism which can be seen in partial seizures. The loss of awareness (change in level of consciousness) indicates it was complex rather than simple (in which level of consciousness remains unaffected). The development of whole-body convulsions indicates secondary generalization of the seizure.

**Q5. What is the cause of the left arm weakness after the seizure?**

The left arm weakness is potentially Todd's paresis, which is a brief period of paresis/paralysis following a seizure. The paresis/paralysis resolves spontaneously (typically within 12-36 hours). Todd's paresis may affect one or both sides of the body and can affect both the upper and/or lower extremities. Other potential causes of the focal weakness should be ruled out (stroke, abscess, hemorrhage, etc.).

**Q6. What investigations should be done?**

1. Bloodwork: CBC, BUN/creatinine, glucose, electrolytes (Na, Mg, Ca), consider liver enzymes
2. EEG
3. Consider neuroimaging
4. Consider infectious workup if clinical concern for infection
5. Consider tox screen if clinical concern for alcohol/drug use
6. Consider potential medication contributions to lowering seizure threshold and check serum levels where appropriate. If Mr. LL had already been on an AED – a serum level should be checked to rule out a subtherapeutic level, if available.

No provoking cause of Mr. LL's seizure is found. After starting Mr. LL on Levetiracetam he does well and has no further seizures while in hospital. Prior to discharge he asks about when he will be able to return to work as a commercial driver.



**Q7. What factors need to be considered before Mr. LL can return to driving?**

Return to driving is a complex issue and legal requirements vary by jurisdiction. It is important to follow local laws when considering a return to driving. The following is a helpful mnemonic outlining issues to consider when patients inquire about driving safety.

**D – Drugs:** Consider medications that may impair alertness (opiates, THC, AEDs, neuroleptics, etc.)

**R – Reaction time:** Reaction time testing should be completed with an occupational therapist

**I – Intellect:** Impaired cognition may inhibit return to driving; consider neuropsychological testing

**V – Vision:** Visual field and visual acuity requirements vary by jurisdiction; consider optometry referral

**E – Epilepsy:** Local laws vary for mandatory reporting after a seizure or medication

initiation/change/discontinuation; it is important to be familiar with the reporting process in your area

**S – Safety record:** Consider previous driving record (accidents, near misses, tickets, reckless driving, etc.)

**A – Attention/Executive Function:** Trail Making A/B provide helpful information; consider neuropsychological testing and/or formal on road testing.

**F – Family concerns:** Involving patient families in the discussion may provide meaningful insight

**E – EtOH:** Careful EtOH/drug use histories are important; consider referral to substance abuse program

**R – Range of Motion:** Assess physical ability (strength, ROM, proprioception/sensation, etc.); consider need for adaptive controls

You continue to follow Mr. LL as an outpatient. He is eventually titrated off of levetiracetam after a seizure free period of two years. You correctly checked local laws for whether you were required to report Mr. LL to the appropriate regulatory body when the medication was withdrawn. Given Mr. LL's previous alcohol and substance abuse, you also remember to ask about alcohol and drug use in follow-up. In follow-up, you remain vigilant to look for any change in level of functioning which could be a sign of recurrent PTE.

## 7.7 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.
- Ahmed, S. N., & Spencer, S. S. (2004). An Approach to the Evaluation of a Patient for Seizures and Epilepsy. *WMJ-MADISON-*, *103*(1), 49-55.
- 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. *Arch Phys Med Rehabil*, *71*(2), 156-160.
- Ascroft, P. B. (1941). Traumatic Epilepsy After Gunshot Wounds of the Head. *Br Med J*, *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. *Arch Phys Med Rehabil*, *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. *J Head Trauma Rehabil*, *27*(6), E36-44.
- Caveness, W. F., & Liss, H. R. (1961). Incidence of Post-traumatic Epilepsy. *Epilepsia*, *2*(2), 123-129.
- Caveness, W. F., Meironsky, 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.
- Chang, B. S., & Lowenstein, D. H. (2003). Practice parameter: antiepileptic drug prophylaxis in severe traumatic brain injury: report of the Quality Standards Subcommittee of the American Academy of Neurology. *Neurology*, *60*(1), 10-16.
- 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. *Arch Phys Med Rehabil*, *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.

- Cranley, M. R., Craner, M., & McGilloway, E. (2016). Antiepileptic prophylaxis following severe traumatic brain injury within a military cohort. *J R Army Med Corps*, *162*(2), 109-114.
- 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., Sganzerla, E., Spagnoli, D., Bello, L., & Tiberio, F. (1992). Risk factors for late posttraumatic epilepsy. *Acta Neurochir Suppl (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.
- Tempo de Intervalo Entre o Traumatismo Cranio-Encefalico e Epilepsia Pos-Traumática. *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., 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.
- 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.
- Elliott, R. E., Morsi, A., Tanweer, O., Grobelny, B., Geller, E., Carlson, C., Devinsky, O., & Doyle, W. K. (2011). Efficacy of vagus nerve stimulation over time: review of 65 consecutive patients with treatment-resistant epilepsy treated with VNS > 10 years. *Epilepsy & Behavior*, *20*(3), 478-483.
- 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. *Arch Phys Med Rehabil*, *84*(3), 365-373.
- Englander, J., Bushnik, T., Wright, J. M., Jamison, L., & Duong, T. T. (2009). Mortality in late post-traumatic seizures. *J 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.
- 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.
- 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.

- 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. *Neurosurg Focus*, 32(3), E10.
- Haltiner, A. M., Temkin, N. R., & Dikmen, S. S. (1997). Risk of seizure recurrence after the first late posttraumatic seizure. *Arch Phys Med Rehabil*, 78(8), 835-840.
- Hanaya, R., & Arita, K. (2016). The New Antiepileptic Drugs: Their Neuropharmacology and Clinical Indications. *Neurol Med Chir (Tokyo)*, 56(5), 205-220.
- Heikkinen, E. R., Rönty, H. S., Tolonen, U., & Pyhtinen, J. (1990). Development of Posttraumatic Epilepsy. *Stereotactic and Functional Neurosurgery*, 54(1-8), 25-33.
- Hernandez, T. D., & Naritoku, D. K. (1997). Seizures, epilepsy, and functional recovery after traumatic brain injury: A reappraisal. *Neurology*, 48(4), 803-806.
- Hung, C., & Chen, J. W. (2012). Treatment of post-traumatic epilepsy. *Current treatment options in neurology*, 14(4), 293-306.
- 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. *J Trauma Acute Care Surg*, 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, V. D. S. 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. *Neurosurg 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. *Arch Phys Med Rehabil*, 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., Zadrán, K. K., Alam, S., & Aurangzeb, A. (2016). Comparison Of Efficacy Of Phenytoin And Levetiracetam For Prevention Of Early Post Traumatic Seizures. *J Ayub Med Coll 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.

- 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. *J Crit Care*, *28*(5), 883.e889-813.
- Kwon, S. J., Barletta, J. F., Hall, S. T., Mangram, A. J., Dzandu, J. K., Abdulhamid, M., & Zach, V. (2019). Lacosamide versus phenytoin for the prevention of early post traumatic seizures. *Journal of critical care*, *50*, 50-53.
- 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.
- 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. *Jpn J Psychiatry Neurol*, *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 concussive 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.
- 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., Beghi, E., Camfield, C., & Camfield, P. (2006). The first seizure and its management in adults and children. *Bmj*, *332*(7537), 339-342.
- 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. *Neurocrit Care*, *21*(2), 228-237.
- Rao, V. R., & Parko, K. L. (2015). *Clinical approach to posttraumatic epilepsy*. Paper presented at the Seminars in neurology.
- 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.
- Ritter, A. C., Wagner, A. K., Fabio, A., Pugh, M. J., Walker, W. C., Szaflarski, J. P., Zafonte, R. D., Brown, A. W., Hammond, F. M., Bushnik, T., Johnson-Greene, D., Shea, T., Krellman, J. W., Rosenthal, J. A., & Dreer, L. E. (2016). Incidence and risk factors of posttraumatic seizures following traumatic brain injury: A Traumatic Brain Injury Model Systems study. *Epilepsia*, *57*(12), 1968-1977.

- 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. *Coll Antropol*, *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.
- 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. *Anaesth 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. *Neurocrit Care*, *12*(2), 165-172.
- 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.
- Van Hout, B., Gagnon, D., Souëtre, E., Ried, S., Remy, C., Baker, G., Genton, P., Vespignani, H., & McNulty, P. (1997). Relationship between seizure frequency and costs and quality of life of outpatients with partial epilepsy in France, Germany, and the United Kingdom. *Epilepsia*, *38*(11), 1221-1226.
- Vespa, P. M., Nuwer, M. R., Nenov, V., Ronne-Engstrom, E., Hovda, D. A., Bergsneider, M., Kelly, D. F., Martin, N. A., & Becker, D. P. (1999). Increased incidence and impact of nonconvulsive and convulsive seizures after traumatic brain injury as detected by continuous electroencephalographic monitoring. *Journal of neurosurgery*, *91*(5), 750-760.
- 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. *J Neurosurg*, *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.
- 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 Res*, *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.
- 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.
- 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. *J Clin 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 Behav*, *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. *Arch Phys Med Rehabil*, *74*(9), 983-1001.
- 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.
- Zaman, A., Dubiel, R., Driver, S., Bennett, M., Diggs, V., & Callender, L. (2017). Seizure prophylaxis guidelines following traumatic brain injury: An evaluation of compliance. *J Head Trauma Rehabil*, *32*(2), E13-E17.
- 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.
- Zimmermann, L. L., Martin, R. M., & Girgis, F. (2017). Treatment options for posttraumatic epilepsy. *Curr Opin Neurol*, *30*(6), 580-586.