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Prevention of Seizures Following Traumatic Brain Injury

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1. Introduction

Traumatic brain injury (TBI) is a devastating and complex disease state. Of the observed complications associated with TBI, the development of seizures following injury can be among the most challenging to manage. In addition to the direct effects on the brain, seizures following TBI lead to significant patient morbidity, with potential limitations on overall independence. Quality-of-life may also be adversely affected as the diagnosis of seizure carries the burden of extended exposure to anti-epileptic drugs. The use of these therapies often entails unfavorable medication related side-effects, frequent laboratory monitoring and dosage adjustments, as well as frequent physician visits. With these factors in mind, identification and prophylaxis of those at risk for post-traumatic seizures may provide significant improvement on patient outcomes.

2. Historical perspective

The association between head injury and seizures has long been observed. In the Hippocratic text, "On *Injuries of the Head*", wounds to the left temporal region were described as being associated with convulsion on the right side of the body. Later, Hippocratic surgeons noted that convulsions following head trauma were often a sign of impending fatality. [1] Interestingly, the reference to seizures was only in the immediate time frame surrounding the injury; chronic seizures were not noted to have been documented in those writings. [2] As medicine and neuroscience progressed, the recognition of the association between head trauma and the development of seizure disorder gradually began to grow. As an example, in the 14th century, the Italian physician Valescus de Tharanta described a patient who suffered a penetrating head wound which infiltrated into the pia mater and subsequently experienced seizures 7 to 8 times a day until death. [3] Approximately 150 years later, Berengarius da Carpi, an Italian physician



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and surgeon, documented that epileptic seizures developed approximately 60 days following a severe head wound which likely is the first documentation of post-traumatic epilepsy, or seizures occurring outside of the immediate post-injury period. This association was further strengthened by the writing of Duretus who reports his observations of a patient suffering a depressed skull fracture who developed seizures 6 years following injury. [1]

Despite the above observations, head injury failed to gain recognition as a *common* cause of epilepsy. Perhaps the first major medical publication noting this connection was book "*Epilepsy and Its Treatment*" in 1904 in which its author William Spratling specifically mentions trauma as an etiology for epilepsy. Spratling writes, "Traumatic lesions of the cranium and the cerebrum cause epilepsy without any predisposition to the disease", and he goes on to describe observed epileptic patterns in significant detail. [4]

The majority of our modern knowledge pertaining to seizures following TBI is derived from military literature. The Second World War, the Korean conflict, and the Vietnam War offered an extensive cohort from which to observe the effects of head trauma. While this data has provided tremendous insight, it does not translate well to head injuries in the civilian sector in regard to mechanism and potential complications. Recently, epidemiologic investigations have examined the impact of TBI and the frequency of post-traumatic seizures in civilians, yielding valuable information for this very different patient population.

3. Definitions

Post-traumatic seizure disorder is a broad term for new-onset seizures following TBI. This terminology fails to capture the distinct differences in etiology, incidence, outcome, and management of these seizures. It is these differences that necessitated the development of a classification system, separating the observed seizures into distinct diagnostic entities based on time of development. The first formal classification of post-traumatic seizures was suggested in 1939 when Elvidge proposed the observed seizures be separated into 3 distinct groups: immediate (within the first few hours following injury), delayed (occurring with 2 weeks of injury), and late (those occurring after a period of time). He further proposed that the immediate and delayed seizures be combined into a group of events termed early epilepsy which was felt to be distinctly different from late epilepsy. [5] This classification has been modified slightly, yet generally remains accepted to this day. The current accepted definitions adopted into practice today are:

- Immediate seizure: Seizures occurring less than 24 hours post injury.
- Early seizures: Seizures occurring less than 1 week post injury.
- Late seizure: Seizures occurring greater than 1 week post injury. [2] These seizures are considered "unprovoked" and are therefore considered epileptic in nature.
- Post-traumatic epilepsy: Recurrent late seizures, with no identifiable cause other then TBI

4. Epidemiology

The burden of post traumatic seizures (PTS) is often underestimated in relation to the overall incidence of epilepsy. A prevalence study by Hauser et al examined several characteristics of epileptic patients in Rochester, MN. Their results showed that approximately 20% of symptomatic disease and 5% of all epilepsies can be attributed to traumatic injury and that in patients less than the age of 65, brain trauma was the most frequently identified risk factor associated with the development of epilepsy. [6] In fact, trauma may be the primary cause of epilepsy in up to 30% of patients between the ages of 15 and 34. [2]

The incidence of seizures following TBI is commonly separated into two distinct categories; early seizures (occurring within 1 week of the index injury) and late (occurring greater than 1 week after the index injury). Each of these categories varies from the other in terms of incidence and risk factors.

The first major publication documenting the incidence of early PTS was presented in 1960. Jennett et al found that among 898 patients admitted with closed head injury, 4.2% experienced seizure within the first 7 days following the injury. [7] Approximately 20 years later, in a retrospective chart review of 2,747 head injury patients experiencing loss of consciousness, Annegers et all found the incidence of early seizure was 2.1%, and of those, 75% occurred in the first 24 hours following injury. [8] Desai et al reviewed the records of 702 patients with any degree of head trauma and found early seizure occurred in 4.1% of patients. [9] Annegers published a second retrospective chart review in 1998 after examining the records of 4,541 pediatric and adult head injury patients. This in-depth review reported the incidence of early PTS to be 2.6%. [10] Asikainen examined a group of 490 TBI patients (approximately 50% of patients studied were under the age of 16) admitted to a TBI rehabilitation facility. Early PTS were observed at an incidence of 16.4%, a number higher than what had been observed previously. The authors comment that there was a statistically significant relationship between the age at time of injury and occurrence of early PTS, as they reported that patients age 7 or younger experience early seizures at a rate of 30.8%, those ages 8 to 16 at a rate of 20%, and patients above the age of 16 at a rate of 8.4%. [11] These results mirrored findings in earlier studies in which pediatric head injury patients were more likely to experience early seizure, independent of the degree of head trauma as compared to adult patients with similar injuries. [7, 8]

Military data is the best source of information when assessing seizure risk following penetrating head injury. The Vietnam Head Injury Study (VHIS) provided valuable information regarding outcomes of patients with penetrating head wounds, including incidence of seizure. In this cohort, early PTS was observed at 4.3%. [12, 13]

While these studies offer useful insight into overall frequency of early PTS, there are limitations that must be addressed. The heterogeneity of the populations being assessed in the available literature makes generalization difficult. In the reports mentioned above, the characteristics of patients observed varies drastically based on severity of head injury, age distribution of the population observed, and mechanism of injury. In addition, the standard of care provided to the head injury patient has evolved and should be considered when assessing the occurrence

of any disease sequelae. It must be noted that very little is mentioned in the epidemiologic literature about therapies provided to these patients. When evaluating the overall incidence of early PTS, these limitations must be taken into consideration.

Despite the above mentioned limitations, some of the most useful data gained from these epidemiologic studies is the identification of risk factors for early PTS. When looking at these risk factors as a whole and considering the various populations evaluated, several factors stand out. Age at the time of injury is associated with risk of early PTS, as younger patients are more likely to experience this complication than older patients. Jennett, as stated above, found that patients < 5 years of age were at increased risk of early PTS at any degree of head injury. Of the 75 patients in this age demographic, 9.4% developed early PTS while patients older than the age of 5 had in incidence rate of 3.8%. [7] Annegers et al. also identified children as being at higher risk of early PTS. The incidence of early PTS in patients <15 years of age was 30% while the rate was 10% in adult patients. [8] Similarly, Desai and Asikainen also found that younger patients had a greater risk of early PTS compared with older patients. [9, 11]

Severity of injury at the time of presentation has also been repeatedly associated with increased risk of early PTS. Early on, duration of post-traumatic amnesia (PTA), a guide to assessing the degree of brain injury as reported by Jennett, was found to be associated with an increased risk of early PTS. Approximately 11.7% of patients with PTA lasting greater than 24 hours were seen to have early PTS while those with shorter durations experienced early seizures at a rate of 2.7%. [7] Desai reported that focal deficit on admission and loss of consciousness (LOC)/PTA of more than 30 minutes following injury greatly increased the likelihood of early PTS. [9] It has also been shown that patients presenting with Glascow Coma Scale (GCS) scores of <10 have an increased risk of early PTS with an incidence as high as 20%. [14] Lee et al and Gilad et al examined the rates of PTS following mild head injury and found no increased incidence of seizure development than in the general population experiencing non-trauma related seizures further supporting the theory that severe head injuries pose a higher risk for PTS development. [15, 16] Skull fracture and penetrating head injury have been repeatedly shown to increase the risk of early PTS. Basilar skull fractures, specifically those that are depressed or in the temporal-parietal region, appear to infer the highest risk. [7, 9]

The presence of intracranial blood on radiographic imaging has also been positively associated with early PTS. It is observed that intracranial hemorrhage (ICH) may precede early PTS in up to 23% of patients while epidural/subdural hematoma and cortical contusion are seen in approximately 16% of such cases. [9, 14] Jennett utilized the presence of bloodstained cerebral spinal fluid (CSF) to infer the presence of ICH as cranial imaging at the time was very limited. In those with bloodstained CSF, early PTS were observed at a rate of 9.7% which is noted to be approximately double the incidence of patients observed in the entire series. [7] Additionally, a survey of approximately 3000 patients with severe closed head injury revealed that ICH was present in 66% of all patients experiencing early PTS. [17]

The incidence and risk factors for late PTS are significantly different than that of early PTS and must be described separately. The lowest incidence of late PTS reported was by Jennett at 10.2% whereas Caveness et al, in the VHIS, reported a rate of 27.9%. [7, 13] Annengers, having collected data on 2,747 patients, was able to compare the incidence of late PTS to the expected

rate of new onset epilepsy. Using the age and sex-specific incidence rates for Rochester, Minnesota as a comparator, there was found to be a 3.6 fold increase in the risk of developing seizure disorder following head trauma. [8]

Several authors have assessed the duration of risk for the onset of late PTS and a strong trend has emerged from that data. The time-frame for the development of late PTS potentially extends several years post-injury. Salazar et al, utilizing data from the VHIS, found that 7% of all patients with late PTS reported their first seizure 10 or more years post injury while Annegers reports that in patients with moderate to severe TBI, the risk for late PTS extends as far as 20 years post injury. [10, 12] With the awareness of the extended risk for late PTS, it must be noted that more than half of all seizures occur within the 1 year following TBI and approximately 80% occurring within 2 years. [7, 12, 13, 18, 19]

Early PTS are found to be an important predictor of late PTS as Jennett reports a four-fold increase in late PTS if the patient seizes within 7 days of injury. [7] Annengers also found that in patients with moderate or severe TBI, early PTS were associated with an increased likelihood of late PTS. This was found not to be true in pediatric patients, mirroring the findings of Asikainen, who reported increasing age as predisposing factor for late onset seizures. [8, 11] Temkin and Englander report that the presence of intracranial blood, be that SDH or ICH, increases the risk of late seizure development some 400 times the expected rate seen in the general population. [14] Several investigators also report the severity of head injury, as stratified by GCS or an extended duration (most commonly > 24 hours) of PTA, exhibits a positive correlation with late PTS. [7, 10, 11, 13, 14, 19, 21]

Study Author	Population	N	Early Seizure %	Risk Factors Identified	Late Seizure %	Risk Factors Identified
Jennett and Lewin ⁷	All admitted patients	896	4.2	Age<5, PTA >24 hours, skull fracture, ICH	10.2	Early PTS, PTA >24 hours, Depressed Skull fracture
Annengers et al. 1980 ⁸	General population	2747	2.1	Age <15, severe injury	1.9	Moderate/ Severe TBI
Desai et al. 9	All admitted patients	702	4.1	Age <16, focal defecit, LOC/ PTA >30 minutes, skull fracture, ICH	Not assessed	Not assessed
Annegers et al. 1998 ^[10]	Gerneral population	4541	2.6	Not assessed	2.1	Early PTS, Cortical Contusion/ SDH, PTA >24hours
Asikainen et al. [11]	TBI Rehab	490	16.4	Age <8	24.8	Coma >24 hours
Englander et al. ^[20]	Severe TBI	647	3	Not Assessed	10.2	Early PTS, cortical contusion, dural penetration, multiple intracranial procedures, >5mm midline shift, evacuated SDH

Table 1. Incidence and Risk Factors for PTS



5. Pathophysiology

The exact mechanisms surrounding the pathogenesis of PTS are still highly debated. Despite extensive animal modeling and basic science bench work, an accurate replication of human TBI has yet to be created. With the lack of an accurate model, the hypotheses found regarding PTS development must be taken in such context. [22]

The pathology surrounding the development of PTS is likely different based on the time of seizure onset, with different mechanisms playing a role in the development of early PTS and late PTS. Early PTS are often considered injury-induced or "provoked" and therefore cannot be considered epileptic. Following the initial insult of tissue deformation and compression, a cascade of events begins to take place almost immediately. Vascular damage and increased permeability of the blood brain barrier (BBB) are noted. [22, 23] Inflammatory cascades are drastically up-regulated leading to neuronal and glial swelling. Glial swelling may lead to impaired neuronal oxygen delivery and subsequent energy depletion leading to cellular death. Glutamate, an excitatory neurotransmitter, is released in high quantities. High concentrations of extracellular glutamate may stimulate ion channel activation and an intracellular flooding of calcium, followed by eventual cell death. [22, 23, 24] In any type of penetrating injury, direct neuronal damage due to cortical laceration, contusion, imbedded bone fragments, or retained foreign bodies becomes extraordinarily irritating to the injured brain and a potential focus for seizure activity. Also, the presence of intracranial blood has been found to predispose the TBI patient to early PTS. When extravasated blood undergoes hemolysis, hemoglobin is engulfed by macrophages which degrade the hemoglobin into hemosiderin and biliverdin. Hemosiderin is deposited into neuronal tissue. These pathogenic deposits initiate lipid peroxidation, damaging cell membranes, and inhibiting Na-K ATPase. [25, 26] The combination of these factors is profoundly pro-excitatory and likely predisposes the post TBI patient to seizures proximal to the time of injury.

The pathology of late PTS is considerably different and more controversial. There are three core theories of epileptogenesis in this setting, the kindling model, the fluid-percussion model, and the synaptic plasticity model. Each of these models attempts to describe the changes taking place in the brain during the latent period between the time of injury and onset of first late seizure.

The kindling theory of epileptogenesis is well validated in several animal models. Briefly, weak electrical stimulation is applied to specific, susceptible regions of the brain in rodents until a seizure occurrs. It has been found that over time, less stimulation was needed to initiate a seizure and this reduced threshold is a change that appears permanent over the remaining life of the animal. In the post-TBI human brain, it is thought that subclinical seizures due to structure changes or brain lesions will reduce the seizure threshold to a point in which epileptogenesis occurs. [27, 28] While this is well described in several animal models, the findings do not completely translate into human patients. Additionally, compounds traditionally assumed effective in controlling kindling type epilepsy (phenytoin, carbamazapime) have been shown to be ineffective preventing late PTS. [29]

The fluid-percussion model may more accurately help depict epileptogensis following TBI in humans. In animal-based experiments, a small hole is drilled into the skull of the animal, followed by the delivery of a fluid-wave percussion against the intact dura initiated by a pendulum impact on a fluid column. The seizures following this type of injury appear after a latent period, much like is seen in late PTS. Sustained hyperexcitability was also observed in the region surrounding the injured neocortex and this excitability was associated with intense glial reactivity. [30] This reactivity may impair glutamate metabolism, exposing injured neurons to potentially toxic concentrations of this excitatory neurotransmitter. [31] This also mirrors late PTS in humans, as epileptiform activity seems to generate from the injured, hyperexcitable region of brain. [30]

The brain has the ability to adapt to injury through both changes in function and structural reorganization. [32, 33, 34] These changes are termed synaptic plasticity and are found to be an adaptive mechanism aiding in neurologic recovery. [35] During the recovery process, compensatory axons sprout, forming new adaptive neural pathways. While generally beneficial to recovery, these sprouts may, in some settings, become a focus for epileptic activity and may allow a seizure to impact relatively distant regions of the brain. [36] This "maladaptive plasticity" after TBI makes management of this potential pathology very challenging as not all plasticity is harmful. In using therapies that target the sprouting axons, there may be significant impairment in neurological recovery as "adaptive plasticity" would be targeted as well. [37, 38]

6. Impact

Post-traumatic seizures have a broad, sweeping impact on the lives of post-TBI patients. In addition to loss of independence from seizure restrictions (restricted driving privileges); psychological health, employment, quality of life, and mortality may also suffer.

Recurrent seizures are identified as an important cause of hospital readmission among patients with severe TBI. [39, 40] These readmissions are not always directly related to PTS as psychologically related admissions are seen to increase as well. It is understood that TBI patients often suffer from mood disturbances and behavioral abnormalities. Patients with PTS are increasingly sensitive to these disorders and there is a significant increase in the number of psychiatric related hospitalizations among patients with PTS as compared to those without. [41] Addi-

tionally, it has been found that irritability and aggressive, disinhibited behavior were observed to be more frequent and severe in rehabilitation patients with PTS as opposed to those not experiencing seizures. [41]

Post-traumatic seizures have been found to correlate with poorer outcomes and quality of life. In the *VHIS*, seizures following penetrating head injury were 1 of 7 impairments that were independently predictive of poor employment status. [42] Also, Asikainen reports that patients with PTS have inferior outcomes per Glasgow Outcome Scale (GOS) scores when compared to those without PTS. These results were mirrored by the findings of Mazzini, who also notes that PTS correlated with poorer GOS scores as well as several other neurobehavioral scales in TBI patients 1 year post injury. [11, 43]

Mortality is seen to be higher in patients with PTS in multiple reports, although it is unknown if there is a direct correlation. [44, 45, 46, 47] It is highly possible that the increase in the incidence of death is more likely related to the severity of the injury as opposed to the development of seizures. [48, 49]

7. Prevention of post-traumatic seizures

With the evolution of the association between head injury and seizure activity, as well as the recognition of the above discussed repercussions, came considerable efforts to develop preventative strategies against epileptic activity post TBI. Early studies, some dating back to the late 1940's, examined the use of anti-epileptic medication in patients with a variety of head injuries. Rapport and Penry noted that in three distinct series of head injured patients, the use of anti-epileptic medication seemed to reduce the incidence of seizure activity when compared to those not receiving such treatment. Their survey of American board certified neurosurgeons found that, at the time, only 14% of those polled typically used PTS prophylaxis. There were no specific professional recommendations for prophylactic treatment and most physicians at the time felt the evidence was considerably sparse. In fact, the most common reasoning for not treating prophylactically was uncertainty of appropriate indication for treatment. When a PTS prophylaxis regimen was initiated, the use of diphenylhydantoin was by far the most commonly used medication, followed the combination of phenobarbitol + diphenylhydantoin. [50]

Phenytoin, the most commonly utilized agent in the hydantoin class, is the most extensively studied PTS prophylaxis medication. Phenytoin is available intravenously (IV) and because of its high (80-90%) bioavailability, can be given orally (PO) as well. [51] The drug enters the brain rapidly and is redistributed throughout the body, being disbursed well throughout all tissues. [52] Phenytoin has a complex, and not yet fully understood, mechanism of action. It appears that the primary site of action for phenytoin is the motor cortex, where it inhibits the spread of seizure activity. Phenytoin has been observed to promote sodium efflux from neurons, stabilizing the neuron and increasing the cell's threshold against hyperexcitability caused by excessive stimulation or environmental changes capable of reducing membrane sodium gradient. [53] Phenytoin is complex kinetically, saturating its metabolism at clinically utilized

dosing ranges. Consequently, small changes in dose can translate to large changes in plasma concentration, potentially leading to toxicity or loss of efficacy. Extensively bound to albumin, phenytoin plasma levels must be interpreted in the context of the patient's serum albumin concentration and if necessary, corrected for. Phenytoin levels are appropriately drawn as a "trough", approximately 30 minutes prior administering a dose and the optimal concentration maximizing efficacy and minimizing toxicity is between 10-20mcg/mL. [53]

The impact of phenytoin on the occurrence of PTS has been investigated repeatedly with variable results depending on trial design and outcome assessed. Wohns and Wyler investigated the effect of phenytoin for PTS prophylaxis as compared to no treatment in the seriesz in 62 patients with severe head injury. The dosing of phenytoin was not standardized, but most patients received a 1g load with a maintenance dose of 400mg/day. Therapy was continued for 1 year in the 50 patients managed with phenytoin and plasma concentrations were maintained between 10-20mcg/mL. There were no early PTS observed in this series but a marked difference in the incidence of late PTS was observed. Of the 50 patients treated with phenytoin for seizure prophylaxis, 10% had EEG confirmed late PTS, while those without prophylaxis experience late PTS at a rate of 50%. There was no statistical assessment of this data, but the authors hypothesized that phenytoin may offer some degree of protection from late PTS. [54]

Young et al was not able to confirm the findings of Wohns and Wyler. In a study assessing the effectiveness of phenytoin prophylaxis in preventing late PTS, patients at high risk (>15%) of developing late PTS were assigned to receive either PTS prophylaxis with phenytoin or matching placebo for a minimum of 18 months. There was no measurable difference in the rate of late PTS between groups, however; all patients in the phenytoin arm whom developed PTS had plasma concentrations <12mcg/mL, potentially explaining the lack of efficacy. [55]

The landmark trial demonstrating the efficacy of phenytoin in PTS prophylaxis was published by Temkin et al in 1999. Patients with severe TBI were randomized to receive phenytoin or placebo for 12 months unless adverse drug reactions necessitated early discontinuation. Those receiving phenytoin were loaded with 20mg/kg via IV infusion within 24 hours of injury. The follow-up dosing was not standardized, but an unblinded study-staff member followed frequent blood levels and adjusted phenytoin dosing as need to maintain high therapeutic serum concentrations. The effect of phenytoin on both early and late PTS was evaluated as patients were followed for a total of 24 months (12 months post discontinuation of study medication). Early PTS occurred at a rate of $3.6\% \pm 1.3$ in those receiving phenytoin versus $14.6\% \pm 2.6$ in the placebo group (p<0.001). This effect was seen in spite of early serum phenytoin concentrations being less than desired. Unfortunately, the rate of late PTS was unaffected by phenytoin therapy with no significant difference in the number of PTS events when compared with placebo after both 1 year ($21.2\% \pm 3.6$ vs. $15.7\% \pm 3.2$; p>0.2) and 2 years $(27.5\% \pm 4 \text{ vs. } 21.\%1 \pm 3.7; \text{ p>0.2})$ of treatment. No difference in mortality was observed and treatment was generally well tolerated, although more patients in the phenytoin group needed to therapy discontinued secondary to medication related adverse events. [56]

A follow-up study, looking at the same data set, attempted to determine if PTS prophylaxis with phenytoin following TBI had any effect on neurocognitive and psychosocial recovery. All patients, independent of treatment arm, (phenytoin or placebo for 1y post TBI) received neuropsychological and psychosocial testing 1, 12, and 24 months post injury. Interestingly, at 1 month post injury, those treated with phenytoin performed significantly worse than those receiving placebo across most neuropsychological parameters. The difference seemed to vanish at the 1 year assessment, but it was noted that at the 2 year assessment, there was a small but widespread negative effect seen in patients treated with phenytoin. Additionally, the negative trend was also seen in patients receiving placebo that developed PTS and were subsequently started on phenytoin for the remainder of the study period. [57]

The above mentioned data set was utilized a third time in order to assess if treatment with phenytoin for 1 or 2 weeks as prophylaxis of early PTS was associated with changes in mortality or morbidity due to adverse drug events. Rash was the most commonly observed drug reaction. Hypersensitivity was rarely seen, occurring only in 0.6% of patients during the first week of therapy and increasing to 2.5% at the end of the second week. Of note, very few adverse reactions were reported in the first week of therapy, with no reports of fever and only one report of leukocytosis. No difference in mortality was observed between patients receiving phenytoin and those receiving placebo, but it was noted that if the patient experienced early PTS, the risk of death increased significantly independent of the treatment arm (p=0.03 RR 2; 95% CI 1.1-3.7). [58] While this may again encourage the use of phenytoin as prophylaxis against early PTS, it is important to note that the analysis was not powered to assess a mortality benefit and when corrected for severity of injury, the mortality benefit was no longer observed. Considering the risk-benefit ratio for 1 week of therapy and considering the two previous investigations, a recommendation limiting PTS prophylaxis to 7 days post injury was put forth.

Phenytoin, while potentially efficacious as prophylaxis against early PTS, is a potentially toxic medication. The side-effect profile of this drug is well documented and while these effects are rarely seen in a 7 day treatment period, they must be none-the-less considered. Severe, cutaneous hypersensitivity reactions associated with phenytoin are well documented and potentially life-threatening. [52, 59, 60] Fever, a significant confounder in the critically ill, and potential cause of secondary neurological injury, is reported frequently as well. [52, 53, 61] Phenytoin is an inducer of CYP450 and the UGT isozyme system potentially leading to multiple drug interactions involving absorption, metabolism, and protein binding which may drastically impact the effect of the drug on physiology. [52, 53] Phenytoin's enteric absorption and bioavailability can also be altered when exposed to a food bolus or continuous enteral tube feeds. [52] Bauer evaluated the impact of continuous tube feeds on phenytoin absorption in 53 neurosurgical patients when administered via enteric route. All patients were found to have subtherapeutic serum phenytoin concentrations and approximately 60% continued to be subtherapeutic even after dosage increase. He notes that hypermetabolism and binding of drug to tubing were unlikely as symptoms of phenytoin toxicity were observed following discontinuation of tube feed. [62] In response to these findings, the investigator held tube feedings for 2 hours prior to and following phenytoin administration and flushed the feeding tube with 60mL of water before restarting. With this intervention, serum phenytoin concentrations became therapeutic with only slight dosage increases. [62] Currently, this practice is widely implemented but also leads to significant nutritional issues. [63] With phenytoin typically requiring thrice daily dosing, continuous tube feeds could potentially be held for 12 hours daily. This strategy is met with much resistance as appropriate nutrition may be significantly hindered.

Fosphenytoin (Cerebyx) was approved by the Food and Drug Administration in 1996 as a potential replacement for phenytoin. Fosphenytoin is a pro-drug, fully converting via phosphatases in the liver, red blood cells, and tissue, to phenytoin within 20 minutes of administration. The most clinically significant benefit of fosphenytoin is the ability to infuse the medication as a more rapid rate. Phenytoin loading is often limited by the risk of extravasation and cardiovascular collapse (hypotenion, bradycardia) and due to these concerns, can only be infused at a maximum rate of 50mg/ min. Dosed in phenytoin equivalents (PE), the use of fosphenytoin allows for faster infusion (100-150mg PE/min) and IM administration when there is a lack of effective IV access. [79]

Due to the above mentioned concerns, much effort has been invested in finding an efficacious treatment alternative to phenytoin. The drug most commonly utilized in place of phenytoin is levetiracetam. Levetiracetam is available in both IV and PO formulations with equal bioavailability. Enteral absorption is rapid and predictable, with peak plasma concentrations occurring less than 1 hour following administration. Levetiracetam does not undergo any significant metabolism, avoiding the CYP system which drastically reduces the incidence of clinically relevant drug interactions. Levetiracetam is excreted primarily by the kidney and dosage reductions are recommended in patients with significant renal impairment. [64] Levetiracetam's mechanism of action is poorly understood, but it is thought that it may be novel in its activity. Animal data seems to suggest that levetiracetam may be protective against the development of epilepsy in certain clinical scenarios, yet this is unproven in human subjects. [52, 64, 65] Levetiracetam is very well tolerated and is associated with very few adverse drug events; however, in several patient populations, levetiracetam has been noted to induce nonpsychotic behavioral disorders and mood instability. [64] Serum levetiracetam concentrations are not affected by enteric feeds and serum drug level monitoring is not recommended although there are some reports of increased clearance in TBI patients. [66, 67]

The first published trial assessing the use of levetiracetam for PTS was published by Jones et al in 2008. In this analysis, 32 patients with severe TBI (GCS 3-8) were given levetiracetam as PTS prophylaxis at a dosage of 500mg IV every 12 hours for the first 7 days following injury. These patients were compared with a historical control of 41 patients with similar injuries. If a clinical seizure was suspected, an EEG was performed and was subsequently interpreted by a blinded neurologist. The EEG results were classified as normal or abnormal, with abnormal being further stratified into status epilepticus, seizure, or seizure tendency. The patients receiving levetiracetam for prophylaxis had 15 EEG examinations with 53% being abnormal. Seizure activity was only seen in 1 patient, while seizure tendency was observed in the 7 other abnormal EEG's. Of the 41 patients receiving phenytoin for prophylaxis, 12 required EEG and

of those 12, none were considered abnormal. The results of this small, non-randomized investigation led the authors to conclude that levetiracetam was as effective as phenytoin in prevention of early PTS. They noted that the observed trend of an increase in seizure tendency required further investigation. [61]

Szalflarski at al completed a prospective, randomized, placebo controlled trial investigating the use of levetiracetam versus phenytoin for PTS prophylaxis. Patients with subarachnoid hemorrhage (SAH) or TBI were randomized in a 2:1 ratio to receive levetiracetam or phenytoin for 7 days following injury. Levetiracetam was loaded at 20mg/kg followed by 1000mg IV q12 hours. Phenytoin was also loaded, followed by twice daily maintenance dosing but no mention of desired blood level or strategy of dose adjustment was noted. Patients were placed on continuous EEG monitoring until awake and following commands or for a maximum of 72 hours. Of the 52 patients enrolled, 34 received levetiracetam while 18 were managed with phenytoin. No difference was observed in the incidence of seizure or overall mortality. Phenytoin use was associated with an increase in the incidence of neurological status decline and gastrointestinal upset while those treated with levetiracetam were devoid of significant adverse drug reactions. In surviving patients, those treated with levetiracetam had significantly better functional outcomes via GOS and the Disability Rating Scale (DRS) at both 3 and 6 months. [68]

The largest investigation to date comparing levetiracetam to phenytoin for early PTS prophylaxis enrolled 813 patients with severe TBI secondary to blunt impact trauma. At the discretion of the providing physician, patients received levetiracetam at a dose of 1g every 12 hours or phenytoin titrated to a serum level of 10-20mcg/mL. No significant difference in the rate of clinical seizures was noted between groups, nor any difference in adverse drug reactions, complications of therapy, or mortality. More patients had therapy discontinue due to medication side effects in the phenytoin group; however, hospital length of stay was increased in the levetiracetam group. [69]

With neither therapy providing a distinct advantage in several individual clinical trials, Zafar at al conducted a meta-analysis attempting to identify any difference in early PTS incidence when levetiracetam or phenytoin were used for prophylaxis. Eight studies (6 observational/2 randomized controlled trials) were included, leading to a total patient population of 990. There was a trend toward increased efficacy with levetiracetam, but this difference did not reach statistical significance even when corrected for heterogeneity. It was noted that levetiracetam may have a more favorable side effect profile, but this meta-analysis was not designed to formally assess adverse drug events. As no difference in efficacy was noted, the authors conclude that cost should be the driving factor in the choice of agent for PTS prophylaxis. [70]

A cost-utility analysis by Cotton et al attempted to determine whether levetiracetam or phenytoin was more cost effective as an early PTS prophylaxis strategy. Using quality-adjusted life years (QALY) as the primary cost-utility determinant, phenytoin was found to be the more cost- effective management strategy. Phenytoin was reported to have a ratio of \$1.58/ QALY versus levetiracetam which had a ratio of \$20.72/QALY. It must be noted that at the time of this analysis, levetiracetam was not available as a generic product. Levetiracetam has been

available via several generic manufactures since May 2010 and the subsequent cost reduction must be taken in consideration when interpreting these results. [71]

Several other treatment modalities have been investigated as preventive strategies for PTS with little benefit derived. Valproate was compared with phenytoin for prevention of PTS in high risk TBI patients. No difference in the incidence of either early or late PTS was noted, but mortality in the valproate group (13.4%) was almost double that seen in those managed with phenytoin (7.2%) leading to the early closure of the investigation. [72] Phenobarbital has been assessed both alone and in combination with phenytoin as a PTS prophylaxis strategy. When used as monotherapy for PTS prophylaxis in severe head injury, no benefit was observed and, due to adverse drug reactions, medication compliance was poor. [73] In combination with phenytoin, there was an observed reduction in seizures, but this difference could have been influenced by the use of phenytoin, and significant concern of toxicity was noted. [74] Magnesium was thought to be potentially neuroprotective, but when higher serum concentrations were targeted with continuous infusion there was an increase in the incidence of hypotension, reduced cerebral perfusion pressure, and a doubling of mortality. Lower magnesium target ranges also failed to provide any benefit. [75] In an observational series, corticosteroids were found to provide no PTS protection and were found to worsen excitotoxicity and oxidative neuronal damage in animal models. [76] There is a theoretic benefit with targeted temperature management as this therapy has several neuroprotective effects such as reduced metabolic rate, reduced inflammatory response, fewer epileptic discharges, and a reduction in the production of reactive oxygen species. This modality has not been formally evaluated for its impact on PTS, but offers a potential area of future research and potential benefit. [77]

As of 2007, the Brain Trauma Foundation guidelines for the management of severe traumatic brain injury consider the use of anti-epileptic medications for early PTS prophylaxis a Level II recommendation and note that prolonged prophylactic therapy (>7days) is not recommended. At the time of publication, phenytoin was the preferred agent for early PTS prophylaxis, but in the time since, a significant amount data surrounding the use of levetiracetam has been published. At this point, the two therapies should be considered equivalent from an efficacy standpoint, but consideration needs to be given to the individual characteristics of each medication and institutional costs associated with their administration. [78]

Traumatic brain injury is a devastating disorder having significant impact on patient morbidity and mortality. Seizures following TBI are a potentially preventable complication if the patients at highest risk are identified quickly and are initiated on a prophylactic regimen. The highest risk patients (penetrating injury, age <16, GCS <10, basilar skull fracture, intracerebral blood) should be started on prophylactic anticonvulsant therapy as soon as possible. Based on the latest evidence, there are two potentially efficacious strategies; phenytoin (or substituted fosphenytoin) and levetiracetam. Phenytoin appears most effective when loaded at a dosage of 10-15mg/kg followed by a regimen of 100mg every 8 hours and should be titrated to a trough total phenytoin concentration of 10-20 mcg/mL. Levetiracetam is an acceptable alternative regimen found to be effective when dosed at 1000mg every 12 hours with no serum drug monitoring being currently recommended. Both phenytoin and levetiracetam should be administered for 7 days following initial injury and when utilized in this manner a significant reduction in early PTS is observed, potentially improving patient outcomes.

Drug Name (Brand)	Phenytoin (Dilantin)	Levetiracetam (Keppra)		
Mechanism of Action	Enhanced sodium efflux from neurons of the motor cortex, stabilizing the threshold against hyperexcitability. Posttetanic potentiation at synapses is then reduced preventing cortical seizure foci from detonating adjacent cortical areas	Inhibition of voltage-dependent N-type calcium channels; facilitation of GABA-ergic inhibitory transmission; reduction of delayed rectifier potassium current; and/or binding to synaptic proteins which modulate neurotransmitter release		
Route of Administration	IV/ PO	IV/ PO		
Typical Loading Dose	10-15mg/kg x1	None recommended		
	Fosphenytoin: 10-20mg PE/kg			
Typical Maintenance Dose	100mg q8hr	500-1000mg q12hr		
	Fosphenytoin: 4-6mg PE/kg			
Elimination Half-Life	7-42 hours	6-8 hours		
		(Metabolite =8.4 hr)		
Metabolism/ Excretion	Metabolism: Hepatic via hydroxylation	Metabolism: enzymatic hydrolysis via liver		
	Excretion: Extensively excreted in bile as well as in urine following gastrointestinal reabsorption	Excretion: 66% unchanged in urine		
Dosing Considerations	Metabolism and excretion may be impaired in renal and hepatic disease. Consider following unbound phenytoin levels for dose adjustment	Consider dosage reduction in patients with renal failure		
Major Adverse Effects	Rash	Pancytopenia		
	Nausea/ vomiting	Thrombocytopenia		
	Ataxia	Liver Failure		
	Confusion	Personality disturbances		
	Fever			
	Stevens-Johnson Syndrome			
	Myelosuppression			
	Nephrotoxicity			
	Hypotension			
	Bradycardia			
	Venous irritation			
Monitoring/ Laboratory Considerations	Monitor trough concentration for efficacy. Toxicity is a clinical diagnosis and must be assess based on patient	No routine monitoring currently recommended		

Table 3. makinji caption

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