

Post-Traumatic Epilepsy and Treatment

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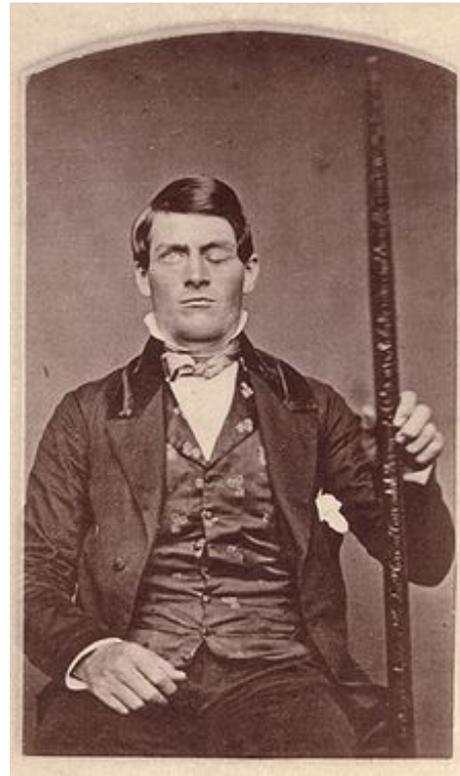
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Phineas P. Gage: PTE and SE



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Introduction of PTE

- ❑ a major long-term complication of traumatic brain injury (TBI)
 - ❑ usually develops within 5 years of head injury
 - ❑ may not be present during the initial rehabilitation
 - ❑ risk for developing post-traumatic epilepsy (PTE) varies with the type of TBI
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Risk of Developing PTE

- between 10-25% in combat associated closed-head trauma with positive brain imaging
 - about 5% in moderately severe closed-head injury without imaging finding
 - about 53% in Korean and Vietnam War veterans with penetrating brain injuries
 - unknown risk for OIF/OEF veterans with minimal TBI due to blast exposure, but could be around 1%
 - unknown whether repeated minimal TBI increases the risk of PTE
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Important Issues of PTE

- ❑ d/d of complex partial seizure vs. Posttraumatic stress disorder
 - ❑ Accidents: drowning, burning, aspiration, fractures
 - ❑ medical complications: pneumonia, hypertension, hypoxia, cardiac arrhythmias
 - ❑ SUDEP, sudden unexpected death in epilepsy
 - ❑ seizures becomes refractory to medical treatment years after TBI.
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Social Consequences of PTE

- social stigma that compromises patients' re-integration into society
- driving issue and maintaining employment
- optimal seizure control is essential to the physical and emotional health of patients with TBI

Definition of PTE

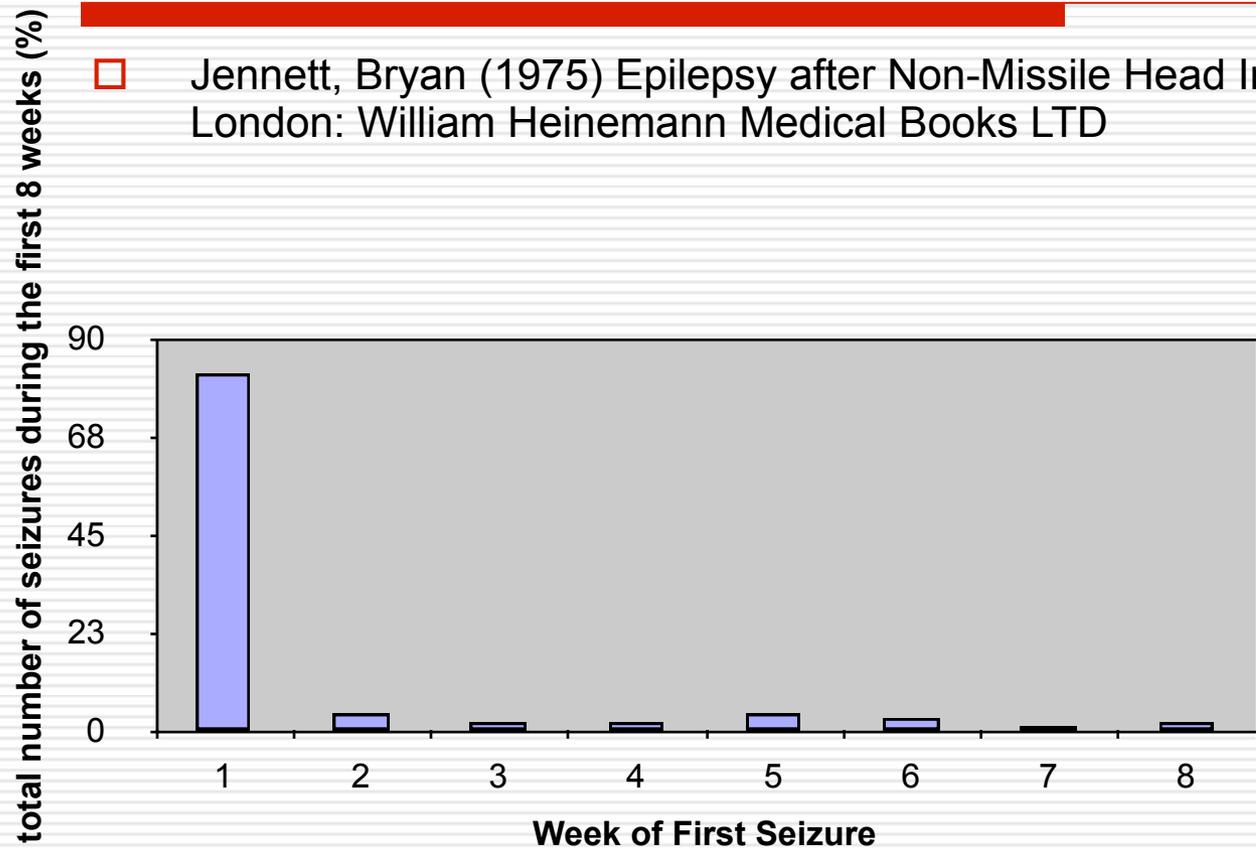
- two or more unprovoked seizures after a head injury
 - seizures that occur within the first 7 days after TBI are defined as provoked seizures
 - The pathogenesis, clinical presentation and long-term outcome of provoked and unprovoked seizures may be different.
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Definition of PTE

- many published articles define PTE as one or more **unprovoked** late seizure after head injury
 - 86% of patients with one late posttraumatic seizure had a second seizure within 2 years
 - advantage of allowing the initiation of anticonvulsant treatment early
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Definition-Why "1 week"?

- Jennett, Bryan (1975) Epilepsy after Non-Missile Head Injuries. Second Edition. London: William Heinemann Medical Books LTD



Risk of PTE after TBI

- significantly correlated with the severity of injury
 - mild TBI: loss of consciousness [LOC], posttraumatic amnesia for < 30 min, no skull fracture
 - moderate TBI: LOC, posttraumatic amnesia lasting 30 min to 24 h or skull fracture
 - severe TBI: brain contusion or intracranial hematoma or LOC or posttraumatic amnesia >24 h.
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Risk of PTE after TBI

5-year cumulative probability of seizures

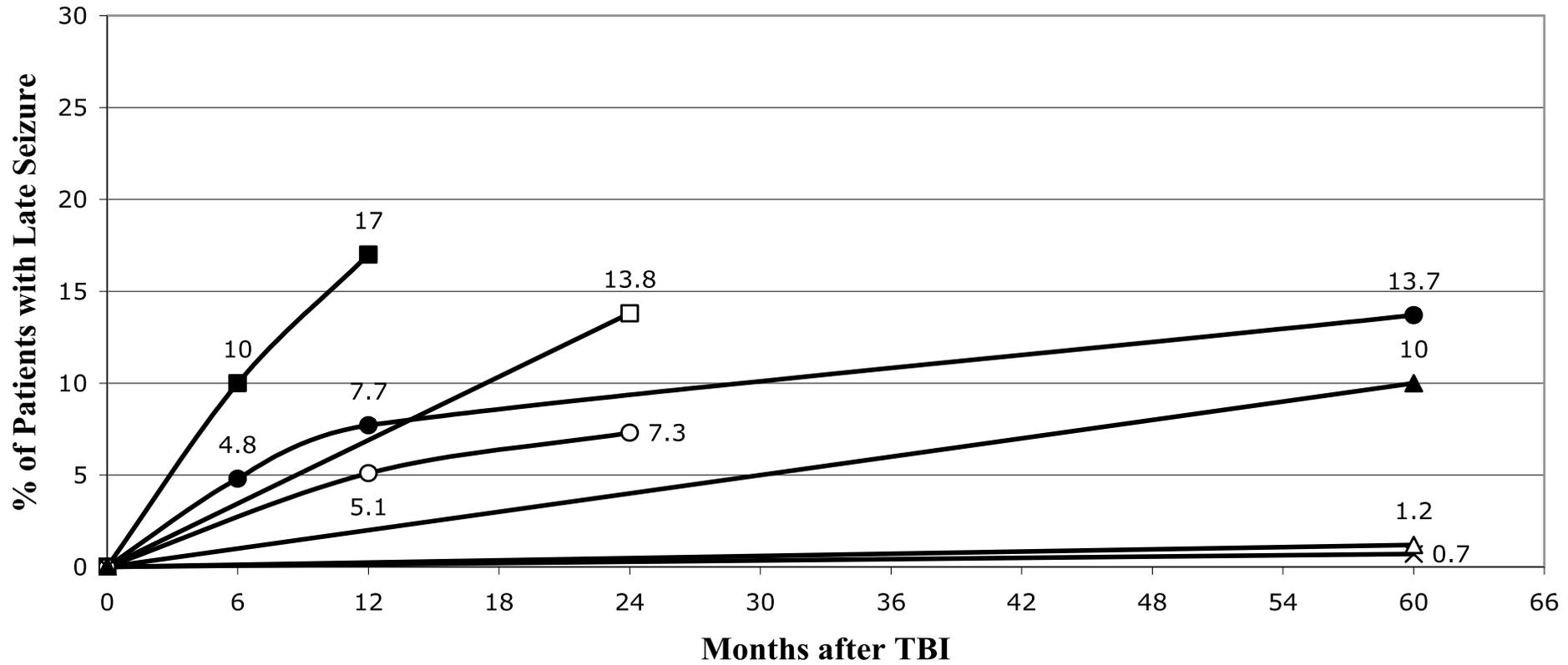
Mild TBI: 0.7%

Moderate TBI: 1.2%

Severe TBI: 10.0%

Annegers et al., 1998

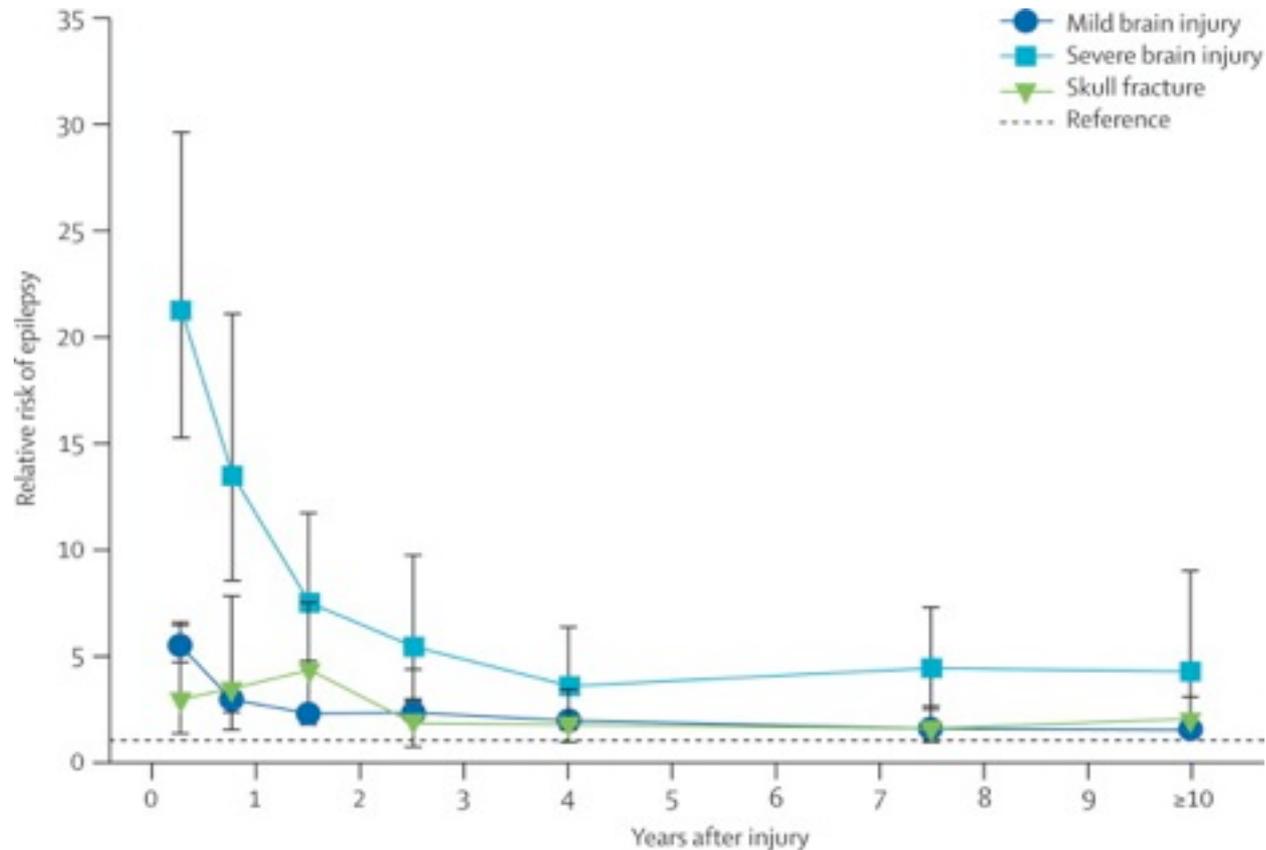
Cumulative Probability of Late Seizure after TBI



- Asikainen et al
- Angeleri et al
- Englander et al
- Jennett et al., peds included
- × Annegers et al., Mild TBI, peds included
- △ Annegers et al., Moderate TBI, peds included
- ▲ Annegers et al., Severe TBI, peds included

Chen et al, 2009

Epidemiology



Christensen J, Pedersen MG, Pedersen CB, Sidenius P, Olsen J, Vestergaard M. Long-term risk of epilepsy after traumatic brain injury in children and young adults: a population-based cohort study. *Lancet*. 2009 Mar 28;373(9669):1105-10. Epub 2009 Feb 21.

High Risk Factors

- depressed skull fracture
- brain contusion
- intracranial hemorrhage
- coma duration
- low Glasgow Coma Scale
- older age

The presence of early seizures did not increase risk of PTE in mild TBI.

Risk Parameters not Studied

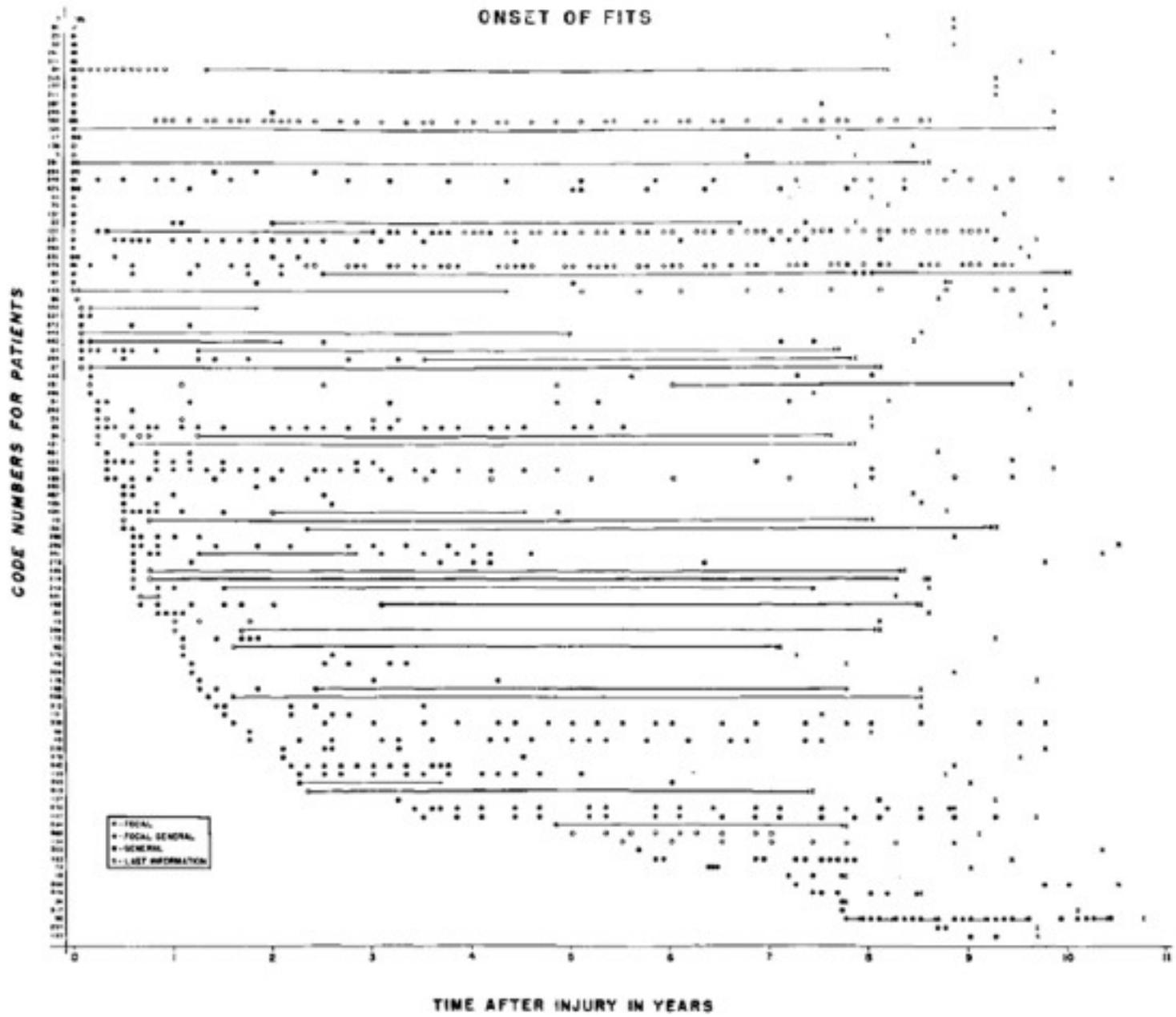
- Modern methods such as MRI, PET scan or diffusion tensor imaging, which visualize the brain, are far superior to simple skull X-rays in detecting traumatic brain hemorrhage, axonal injury and other types of TBI, but have not yet been used in large, long-term prognostic studies for identifying risk factors.
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Risk of PTE in Veterans with TBI

- ❑ PTE in veterans with combat-related TBI in the WWI, WWII and the Korean war were 35-45% (Caveness et al., 1962).
- ❑ In the Vietnam head injury study (Salazar et al., 1985), 53% of veterans with penetrating head injury developed at least one seizure.
- ❑ In Korea, no treatment was provided, while in Vietnam, PHT was given to all penetrating TBIs for 6 months, without any effort to monitor compliance. The incidence of PTE was not reduced.
- ❑ The type of injury differed (mostly shrapnel wounds in Vietnam, bullet wounds in Korea) and survival after severe injuries was much higher in Vietnam.

Timing of Developing PTE

- In about 50% of patients, the first seizure occurred within one year of TBI, but about 15% of patients developed PTE more than 5 years later.
 - PTE could develop 35 years after combat head injury (Raymont et al., *Neurology*, 2010).
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Caveness WF. Onset and Cessation of Fits Following Craniocerebral Trauma. J Neurosurg. 1963 Jul;20:570-83.

Prognosis of PTE

- ❑ In the Korean war study, 39% of the veterans had 1-3 seizures during a 10-year follow up period, while 38% had > 30 seizures (Caveness, 1976).
 - ❑ seizure remission rates: about 25-40% (Jennett, 1979) in non-penetrating head injury
 - ❑ 13% becomes refractory to AED therapy (Schierhout and Roberts, 1998).
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Etiology of Epilepsy and Intractability

Etiology	> 1yr seizure free (%)
Idiopathic generalized	82
Cryptogenic partial	45
Symptomatic partial	35
Extratemporal partial	36
Head injury	30
Dysgenesis	24
Temporal lobe (TLE)	20
TLE with HS	11
TLE without HS	31
Dual pathology	3

Semah et al, Neurology 1998; (51)

Socioeconomic Cost of PTE

- ❑ a social stigma that compromises veterans' re-integration into society
 - ❑ People with uncontrolled epilepsy are not able to hold a driving license.
 - ❑ They have difficulty obtaining or maintaining employment.
 - ❑ Accidents (drowning, burning, aspiration, fractures) and medical complications (pneumonia, hypertension, hypoxia, cardiac arrhythmias) commonly occur during seizures.
 - ❑ SUDEP
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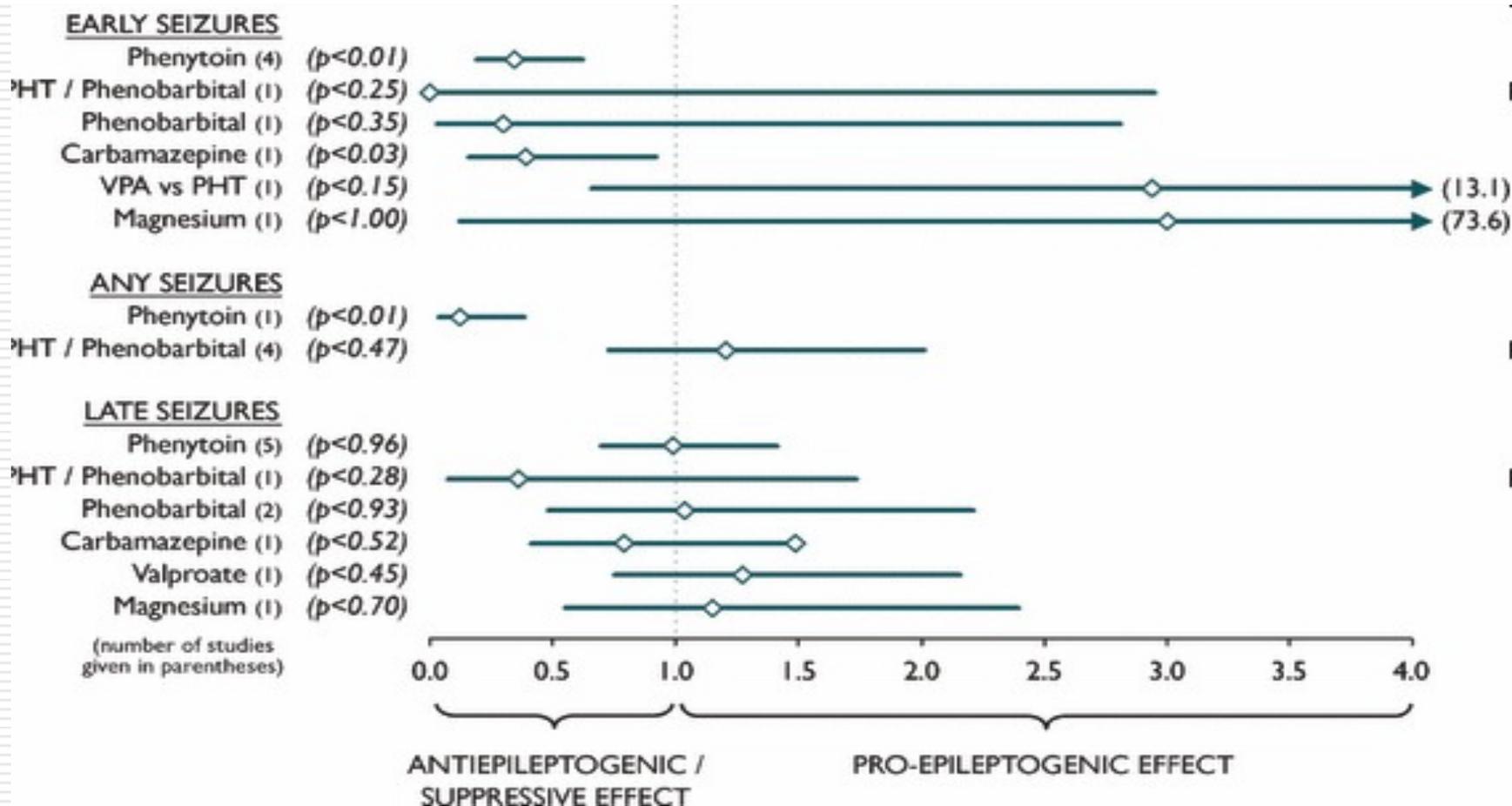
Preventing PTE: Observational Studies

- ❑ PB+PHT (Servit and Musil, 1981); PHT (Wohns and Wyler, 1979; Young et al., 1979), PB (Murri et al., 1992) and VPA (Price, 1980)
 - ❑ 62 to 390 patients per study
 - ❑ follow-up periods from 6 months to 13 years
 - ❑ a trend toward a reduced probability of seizures in the treated groups, 0-10% vs. 2-50% in untreated groups
 - ❑ PB+PHT (Servit and Musil, 1981) showed a marked difference of 2% vs. 25%
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Preventing PTE: Randomized Clinical Trials

- ❑ No beneficial effects of prophylactic treatment with AEDs in several randomized trials using PHT, PHT+PB or Carbamazepine (CBZ)
 - ❑ Follow up periods of 3 months to 5 years
 - ❑ Three studies showed a higher incidence of PTE in patients receiving PHT or PB (Young et al., 1983; Temkin et al., 1990; Manaka, 1992).
 - ❑ One unblinded study (Annegers et al., 1998) showed beneficial effects of PHT
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Treatment of PTE



Epilepsia. 2009 Feb;50 Suppl 2:10-3. Preventing and treating posttraumatic seizures: the human experience. Temkin NR.

Preventing PTE: Randomized Clinical Trials

- ❑ Cochrane review using meta-analysis pooled the data from 10 randomized controlled clinical trials with a total of 2036 patients (Schierhout and Roberts, 1998: prophylactic treatment with PHT or CBZ)
 - ❑ It was only effective in reducing the risk of early provoked seizures after TBI, but showed no beneficial effect in the prevention of PTE.
 - ❑ The treated groups seem to suffer from higher incidence of AED side effects.
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The Role of AEDs after TBI

- AED prophylaxis seems to be effective in controlling the early provoked seizures.
- AED is not effective in preventing PTE.

Potential Pitfalls of Using AED Prophylaxis

- ❑ AEDs tend to have a high incidence of CNS side effects, such as cognitive impairment and neurobehavioral problems.
 - ❑ The unwanted CNS side effects could be augmented in patients with TBI.
 - ❑ AEDs might interfere with the recovery of brain function after TBI (Hernandez, 1997).
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Potential Pitfalls of not Using AED Prophylaxis

- ❑ Heterogeneity of patient populations: difficult to match both the severity and locations of TBI between the placebo and the treatment groups
 - ❑ The development of epilepsy is brain region dependent: more likely in hippocampus but not in the cerebellum.
 - ❑ The difficulty in controlling the heterogeneity of the TBI patients in clinical trials might obscure a prophylactic effect of AEDs in a specific subgroup of TBI patients.
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Potential Pitfalls of not Using AED Prophylaxis

- ❑ The timing of AED treatment after TBI is also variable among studies.
 - ❑ The timing of AED treatment might be crucial because in one uncontrolled study (Wohns and Wyler, 1979), 1 gm of PHT was given during the initial resuscitation in the ER, which resulted in a marked difference of the risk of PTE, 10% in the treated vs. 50% in the untreated group.
 - ❑ The heterogeneity issue is further complicated by the different types of seizures that were present.
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Epileptogenesis

- The molecular, cellular and network processes involved in the development of epilepsy
- Hyperexcitability is commonly observed.
- Anatomical changes: mossy fiber sprouting
- Physiological changes: ion channel expressions and kinetics, GABA and NMDA receptors
- Inhibition (or loss) of the GABAergic system is one of the primary reasons that the neuronal network becomes hyperexcitable.
- An injury to the superficial layers of GABAergic neurons in TBI, could tilt the delicate balance between the excitatory and inhibitory neurons toward hyperexcitability, for the provoked seizure.
- During neurogenesis after injury, the imbalance of the excitatory and inhibitory system could be augmented.

Kindling Model in Epileptogenesis

- The graded increase of hyperexcitability has been observed in the kindling models of epilepsy.
- periodic subconvulsive electrical stimulation of the hippocampus could induce the sequential and stepwise development of local hyperexcitability, electrographic seizures and finally full-blown generalized behavior seizures.
- When kindling process is fully established, it tends to be permanent: certain irreversible changes in the anatomical structures and physiological functions from molecular to network levels.

Onset of Epileptogenesis

- PTE prophylaxis is to initiate anti-epileptogenetic therapy before the epileptogenesis process starts, or at least before it escalates into an irreversible stage.
- The exact timing of onset of epileptogenesis is unknown, but it could occur very early, even as early as the onset of TBI.
- Undercut PTE model showed a critical period of 3 days for anti-epileptogenetic effect with TTX (Graber & Prince, 2004).

Epileptogenesis in PTE

Hypothesis: TBI could set the process of epileptogenesis in motion, and many other accessory factors, such as genetic propensity, neurogenesis, repair of the brain tissues, etc., will also determine whether epileptogenesis could complete its course of developing PTE.

PTE prophylaxis

- The timing of initiating anti-epileptic treatment is crucial, and should be optimally started right after TBI or even before the expected TBI.
- Initiation of anti-epileptogenetic treatment

Genetic Propensity for PTE

- genotype/phenotype discordance: the specific genetic defects could be viewed as genetic propensity for developing the phenotype, the epilepsy, when the other co-factors are present.
 - The Vietnam Head Injury Study showed that a family history of epilepsy was not a significant risk factor for PTE.
 - APOE 4: relative risk 2.41 (n=109, Diaz-Arrastia et al.,2003)
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Potential New Treatment

- Many newer AEDs have not been systemically investigated for specific applications in the prevention and treatment of PTE.
 - Gabapentin, Felbamate, Oxcarbazepine, Topiramate, Tiagabine, Vigabatrin, Levetiracetam, Lamotrigine, Pregabalin, Zonisamide, Lacosamide
 - VNS, DBS??
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Issues in the Diagnosis and Treatment of PTE

- 1/ whether diagnostic screening for TBI is adequate to detect PTE
 - 2/ whether mild, moderate or severe TBIs should undergo diagnostic studies to detect PTE (for example, penetrating head injuries, which have an incidence of PTE >50%, would seem to represent a reasonable indication for EEG and other diagnostic studies, but how about blast injuries, for which we do not even have reliable statistics of PTE incidence?)
 - 3/ the indications for pharmacotherapy, criteria for defining pharmacoresistance, criteria for treatment failure
 - 4/ Criteria for surgical evaluation
 - 5/ Surgical indications
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Preliminary Guidelines for Detection and Therapy of PTE

- Early treatment: AED prophylaxis seems to be effective in controlling the early provoked seizures, so early treatment with AEDs up to one week after TBI seems advisable.
 - Long-term AEDs treatment is not recommended after TBI.
 - AED treatment should be initiated as early as possible for PTE.
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EEG and Neuroimaging Studies

- ❑ EEG screening during the first 2 years after TBI?
- ❑ Neuroimaging studies: brain MRI with epilepsy protocol
- ❑ It is unclear whether the patients with only electrographic seizures or interictal discharges without clinical manifestations should receive AED therapy.
- ❑ If AED therapy is initiated, it is also unclear what clinical parameters could be used to guide the continuation or termination of therapy.

Pharmacotherapy of PTE

- If PTE is discovered, AED therapy should be initiated following the general guidelines used for other types of acquired epilepsy.
- Monotherapy
- If clinically indicated following failure of one or two single AEDs, polytherapy with the combination of at least two AEDs of different pharmacological mechanisms should be used.
- aiming for complete freedom from seizures, and of using the least amount of AED to achieve satisfactory seizure control with minimal or no side effects

Epilepsy Surgery for PTE

- Medically refractory cases should receive epilepsy surgery evaluation
 - inpatient video-EEG monitoring, PET scan study and brain MRI
 - depth/grid intracranial electrodes, fMRI, or cortical functional mapping with electrocorticography
 - Wada
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PTE after Blast Injury

- WLA Series, a preliminary result
- Discussion of WLA Experiences
- Epileptic vs. Non-Epileptic Events
- Workup Recommendations
- Treatment