Clinical Management of Post-Traumatic Epilepsy

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Objectives

- Definition and Types of TBI
- Epidemiology of TBI and PTE
- Pathophysiology of TBI and Post-Traumatic Epilepsy(PTE)
- Types of seizures in TBI and PTE
- Management of seizures and PTE
- Management of psychosocial and cognitive comorbidities in PTE

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TBI

- Traumatic brain injury (TBI) is an acquired condition from an external force/mechanical, which can cause significant effects to the brain vasculature and neighboring neuronal cells.
- The traumatic brain injury (TBI) is the leading cause of death and severe disability among affected people.
- Over 55 million people have TBI internationally. About 1.7 million people in the U.S. sustain a TBI each year. About 5%–30% of adult patients with TBI develop posttraumatic seizures.
- Epidemiology of TBI: Younger patients are more likely to suffer TBI as the result of motor vehicle accidents (most common cause), sports, or battlefield exposure to blast waves; whereas the elderly population is generally affected by falls (neurogenic or cardiogenic in origin).

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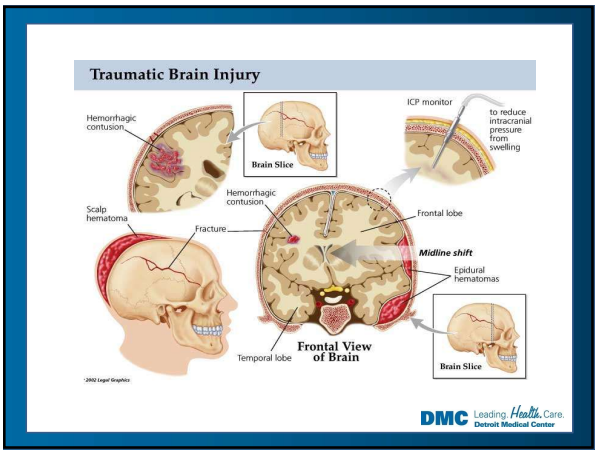


TBI Types and Classifications

Two anatomical types of TBI:

1- Closed head injury

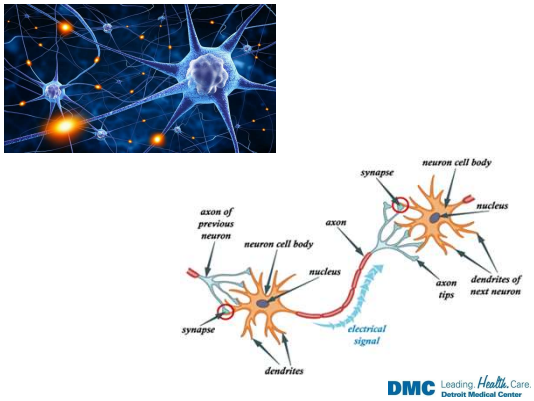
2- Penetrating head injury

ALSO TBI can be classified into:

1- Focal injury causes brain contusion (impact TBI; **Acute primary phase**),

2- Diffuse/generalized injury (Blast injury; **Subacute secondary phase**) causes diffuse axonal shearing {DAI means diffuse axonal tear/diffuse separation of axons from neuron cell bodies}, and damage brain small blood vessels.

3-Chronic phase: Tau kinase/phosphatase imbalance leads to hyperphosphorylation of tau. The Tau hyperphosphorylation forms neurofibrillary tangles near perivascular regions; promoting neurodegenerative disease and cognitive decline. In addition, Increased amyloid precursor protein promotes the toxic oligomerization of amyloid beta, causing cognitive decline.



TBI is classified depending on the level of severity into:

1-Mild (unnoticed initially or exhibit SDH, but might develop later emotional and cognitive impairment), the incidence ratio for the occurrence of PTE is 1.5 in mildly injured patients.

2-Moderate, the incidence ratio for the occurrence of PTE is 2.9 in moderately injured patients.

3-Severe (can cause SAH; Severe TBI is often life-threatening and requires immediate care, its effects are more likely irreversible in both the short-term and the long-term). The incidence ratio for the occurrence of PTE is 17.0 in severely injured patients.

TBI is classified clinically into:

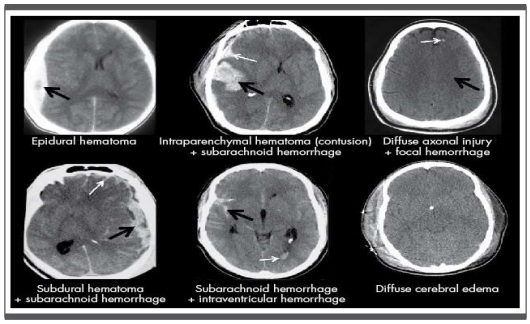
1-Sub-concussive injury can have no initial symptoms,

2-Concussive injury (acute) presents with dizziness, confusion or seeing stars, having loss of consciousness or having post-traumatic amnesia.

3-Post-concussive syndrome involves **concussive symptoms(**cognitive, emotional, headache, dizziness/vertigo, and sleep symptoms) **lasting >3 months**, and **chronic traumatic encephalopathy (common also with repeated mild TI) , and years later**, might followed by onset of neuropsychiatric symptoms.

-TBI has a predilection for the frontal and temporal lobes.

Axial computed tomography scans from patients with Glasgow Coma Scale scores < 8, highlighting the heterogeneity of pathologies among persons with similar clinical presentations.



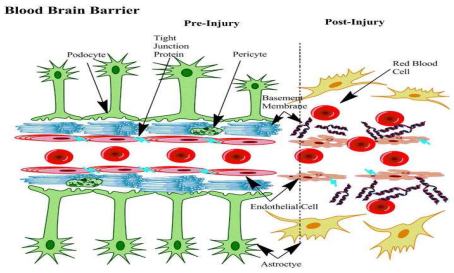
Pathogenesis of TBI and PTE

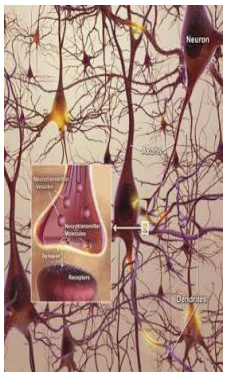
1-primary acute phase
2-secondary subacute phase
3-chronic phase

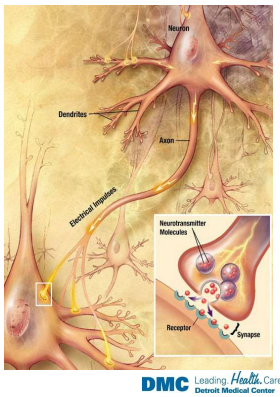
- The physical forces of TBI can cause acute immediate 1ry effects (response with in few hours) such as shear axons apart from the neuron bodies, break down plasmalemma(BBB), and rupture brain microvessels (this will release cytotoxic levels of iron into the brain parenchyma).
- The Iron promotes Ca^{2+}-dependent mechanisms, which can stimulate cell survival, or trigger cell death depending on severity and duration of iron exposure, this will LEAD TO subacute delayed 2ry effects (response within hours >7 hrs to days) as the neurons/astrocytes can rapidly depolarize, increase glutamate extracellular (Reduced glutamate uptake activates NMDA receptors) causing Glutamate Excitotoxicity, and activate voltage gated Ca^{2+} channels;

- Thereby, increasing intracellular Ca^{2+}, then will bind to calmodulin forming calpain kinase that cleaves normal p35 into toxic unfolded p25, causes energy failure and formation of toxic reactive oxygen species(ROS) due to damage of important cell organelles such as the endoplasmic reticulum (the main source of normal protein formation), and mitochondria (the main source of fat metabolism and energy production) respectively,
- This will lead to irreversible cell damage and neuron cell death in lesional and peri-lesional areas, which in turn lead to long-term changes in neural network organization, particularly in the hippocampus and neocortex .

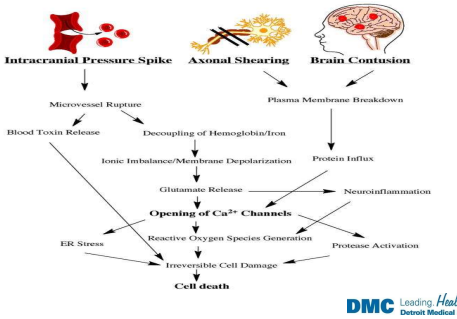
The Effects of Traumatic Brain Injury on the Blood-Brain-Barrier. TBI can cause disruptions of tight junction proteins connecting endothelial cells. Astrocytes can undergo astrogliosis and the basement membrane can become disrupted. Ultimately these changes increase the likelihood of red blood cell extravasations.







Pathophysiology of Neuronal Cell Death Following Traumatic Brain Injury. An intracranial pressure spike, axonal shearing, and brain contusion contribute to secondary mechanisms that lead to an increase in Ca^{2+}channel opening. The generation of reactive oxygen species can ultimately contribute to cell death



- Brain edema leading to an expansion of brain volume has a crucial impact on morbidity and mortality following traumatic brain injury (TBI) as it increases intracranial pressure, impairs cerebral perfusion and oxygenation, and contributes to additional ischemic injuries.
- Classically, two major types of traumatic brain edema exist: First “cytotoxic/cellular” due to sustained intracellular water collection.
- Then vasogenic” due to blood–brain barrier (BBB) disruption resulting in extracellular water accumulation.
- And a third type, “osmotic” brain edema is caused by osmotic imbalances between blood and tissue.

- The chronic phase of TBI has been shown to hyperphosphorylate tau protein, and produce amyloid beta proteins.
- These neurodegenerative factors are activated immediately following TBI and can advance profoundly over time.
- Cortical tissue loss and white matter atrophy resulting from TBI are associated with cognitive deficits.

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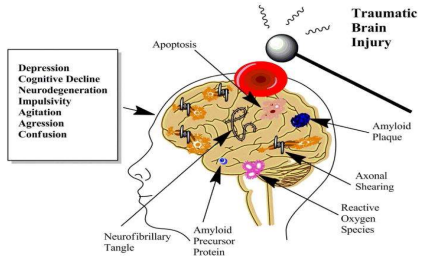
The Chronic Effects of Traumatic Brain Injury. Some individuals experiencing TBI are more susceptible to chronic effects than others. Environmental and genetic factors play a role. Pathologic changes that may develop include neurofibrillary tangles, axonal shearing, and amyloid plaques to name a few. Neuropsychiatric symptoms may also develop such as depression, impulsivity, cognitive decline, and confusion. This area of chronic deficits following TBI is a topic of growing importance receiving renewed research focus and funding



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Post-traumatic epilepsy (PTE)

- Post-traumatic epilepsy (PTE) is a serious and disabling delayed consequence of a traumatic brain injury (TBI).
- Immediate Seizures occur within first 24 hrs of TBI and are provoked, with incidence of 1-4%, and might occur due to transient dysregulation of inhibitory function in the brain due to injury-related cell loss.
- Early Seizures occur within first week (1-7d) of TBI; they are considered provoked, with incidence of 4-25%.
- Late PTS occur at any time after first week of TBI and are characterized by one or more **unprovoked** seizures and **determine** the occurrence of **PTE** with incidence of 9-42%.

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- PTE is one of the most common types of acquired (or secondary) epilepsies. These seizures appear to reflect the development of longer-term, and possibly permanent, aberrant neuronal network function..
- People with PTE commonly experience a latent or silent period of at least 6 months, and sometimes up to 20 years, between the causative injury and the onset of seizures.

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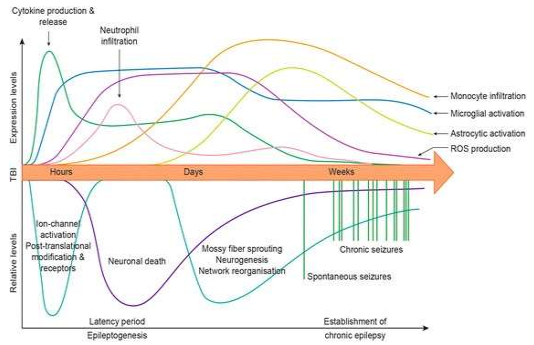

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The types of seizures experienced by people with PTE are:

- Focal onset seizures with or without secondary generalization to bilateral tonic-clonic convulsive activity,
- Focal nonconvulsive seizures only,
- Subclinical seizures are common as well, and are even higher in penetrating injuries than in non-penetrating injuries.

- Early seizures are often of the generalized tonic-clonic convulsive type in comparison to late seizures, which are mostly focal and nonconvulsive in nature.
- The risk of PTE is the highest within the first 2 years of TBI. However, the risk of developing PTE is still high for more than 10 years later in people with moderate TBI, and more than 20 years later in people with severe TBI.
- There is stronger evidence for a high risk of seizure recurrence subsequent to the first late seizure: 47% within a month after TBI, and 86% after 2 years following TBI.
- Intractable PTE develops in a minority of patients, 13.3%, despite aggressive anticonvulsant treatment

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Risk factors of early PTS

- Glasgow coma scale < 10
- Penetrating brain injuries
- Acute intracerebral hematoma
- Acute subdural hematoma
- Younger age
- Loss of consciousness
- Post traumatic amnesia lasting > 30 min
- Chronic alcoholism

Risk factors for late PTS/PTE

- Early PTS
- Acute intracerebral hematoma
- Brain contusion
- Loss of consciousness
- Post traumatic amnesia lasting > 24 h
- Age > 65 at the time of injury
- Residual cortical neurological deficits.
- Persistent focal abnormalities on EEG more than 1 month after injury.

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Management of Seizures and Post Traumatic Epilepsy (PTE)

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Seizure prophylaxis protocol in neuro-ICU

Seizure prophylaxis

- Definitive prophylaxis
- Probable prophylaxis
- Possible/no prophylaxis

Conditions

- Severe TBI (7 days)
- Unsecured aneurysm in SAH
- Elevated intracranial pressure (ICP) and concern for poor compliance
- ICH
- AVM
- Cavernoma
- Brain neoplasm
- Malignant ischemic stroke
- Postoperative craniotomy
- Meningitis
- Cerebral venous sinus thrombosis (CVST)
- PRES

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Current Prophylactic Treatment Options

Medication	Mechanism of Action	Adverse Reactions
Phenytoin	Stabilize inactive form of sodium channel	Fever, nystagmus leukocytosis, rash, hypersensitivity
Carbamazepine	Stabilize sodium channels in inactive state	Aplastic anemia, pancytopenia, Stevens Johnson Syndrome
Phenobarbital	Activate GABA receptors, inhibit calcium channels	Dizziness, fatigue, ataxia, aplastic anemia
Valproate	Inhibit sodium channels and GABA transaminase Activate GABA-synthetic enzyme glutamic acid decarboxylase Alter the conductance of calcium and potassium	Thrombocytopenia, hypofibrinogenemia, pancytopenia, hair loss

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MANAGEMENT OF PTE IN ADULTS

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Medication	Mechanism of action	Protein binding	Elimination	Drug-drug interactions
Lamotrigine	Prolongs voltage-sensitive sodium channel inactivation, inhibits synaptic glutamate release	55%	Hepatic conjugation	Does not appear to significantly affect other AEDs, although anecdotal evidence suggests that levels of the 10,11-epoxide of carbamazepine may be increased when LTG is added. OXC, CBZ, PHT, and PB decrease LTG levels, and VPA increases LTG levels.
Topiramate	Inhibits voltage-dependent sodium channels and glutamatergic AMPA receptor-mediated sodium currents, potentiates GABA receptor-associated chloride currents, mildly inhibits carbonic anhydrase	13%	Renal excretion, hepatic oxidation	Slows metabolism and increases levels of PHT, and has minor effects on other AEDs. Enzyme inducers (CBZ, PHT, PB) decrease TPM levels.
Zonisamide	Blocks excitatory T-type calcium channels (thalamus), prolongs sodium channel inactivation, somewhat inhibits carbonic anhydrase	38%–49%	Hepatic conjugation, oxidation	May increase CBZ and PHT levels. Enzyme-inducing AEDs (CBZ, PHT, PB) decrease ZNS levels.
Oxcarbazepine	Blocks voltage-sensitive sodium channels by active 10-monohydroxy metabolite	40%	Hepatic conjugation, renal excretion	Increases PHT (40%) and PB (15%) levels. Enzyme-inducing AEDs (CBZ, PHT, PB) lower serum levels of OXC.
Levetiracetam	Alters synaptic release and trafficking of excitatory neurotransmitters	Minimal	Renal excretion, hepatic hydrolysis	No known interactions with other AEDs.

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Medication	Mechanism of action	Protein binding	Elimination	Drug-drug interactions
Pregabalin	Modulates calcium channel function; Minimal Renal excretion			No known interactions with other AEDs.
Lacosamide	Enhances slow inactivation of voltage-gated sodium channels			No known interactions with other AEDs.
Gabapentin	Uncertain; may modulate GABA and glutamate synthesis			No known interactions with other AEDs.
Phenytoin	Acts on voltage-dependent sodium channels			
Carbamazepine	Acts on voltage-dependent sodium channels; its principal metabolite, carbamazepine-10,11-epoxide, also has anticonvulsant activity			Induces its own hepatic metabolism, requiring dose adjustments to maintain serum levels during early period of treatment with CBZ. Interacts with many other AEDs

Note: AED = antiepileptic drug; AMPA = ±-amino-3-hydroxy-5-methyl-4-isoxazole-propionate; CBZ = carbamazepine; GABA = ≥-aminobutyric acid; LTG = lamotrigine; OXC = oxcarbazepine; PB = phenobarbital; PHT = phenytoin; TPM = topiramate; VPA = valproic acid; ZNS = zonisamide.

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Pharmacotherapy: Common side effects & risks associated with anticonvulsant medications

Medication	Comments
Topiramate	May cause cognitive impairment (especially word-finding difficulties, memory impairment), psychosis, dizziness, fatigue, weight loss, nausea, urolithiasis, paresthesias Increases insulin efficacy.
Zonisamide	May cause somnolence, impaired attention, dizziness, anorexia, nausea, urolithiasis, paresthesias, and alterations in taste. Severe hypersensitivity reactions (rash, Stevens-Johnson syndrome) may occur and are likely related to sulfa moiety.
Oxcarbazepine	Has relatively few adverse cognitive effects; may cause headache, dizziness, fatigue, and ataxia. May cause hyponatremia (which occurs more frequently during treatment with OXC than with CBZ and is more common in elderly persons). Severe hypersensitivity reactions (rash, Stevens-Johnson syndrome) may occur. There is a 25%–30% cross-reactivity with CBZ.
Levetiracetam	Has relatively few adverse cognitive effects; may cause somnolence, an effect that does not appear to be dose related; may cause anxiety, depression, emotional lability, psychosis, and agitation; may cause weight gain; and may cause transient leukopenia, and the elderly. Absorption improved if taken with an empty stomach.

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Pregabalin	Dose-related somnolence, dizziness, and ataxia; may cause peripheral edema, weight gain, blurred vision, and PR interval prolongation on ECG. Abrupt withdrawal may cause increase in seizure frequency, necessitating gradual tapering (over at least 1 week). Combining pregabalin with thiazolidinedione antidiabetic agents can cause fluid retention. Lower dosages recommended for patients with renal impairment and for elderly patients.
Lacosamide	May cause nausea, dizziness, ataxia, and diplopia; may cause cardiac rhythm or conduction abnormalities, especially among patients with known heart disease or diabetes. Slower titrations may improve initial drug tolerability.
Gabapentin	May impair attention and processing speed; may have anxiolytic effects; commonly causes somnolence and dizziness; somnolence risk increases at dosages of > 600 mg/day; may cause weight gain; may cause peripheral edema, especially in the elderly.
Phenytoin	Adverse cognitive effects are well established among adults with epilepsy and among persons with TBI receiving PHT prophylactically; somnolence, psychomotor slowing; Long-term use may cause hirsutism, gingival hyperplasia, peripheral neuropathy, osteopenia, cerebellar dysfunction.

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The following surgical options for treatment of post-traumatic epilepsy are available, depending on presurgical evaluation:

- Surgical resection
- Implantation of:
  - RNS
  - DBS
  - VNS

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Responsive Neurostimulator/RNS

- Open-loop studies on the effect of electrical stimulation on induced after discharges (ADs) have shown that ADs can be aborted (Lesser et al., 1999).
- External responsive neurostimulation studies have shown that closed-loop stimulation can significantly affect duration of spontaneously occurring electrographic seizure activity (Peters et al., 2001; Murro et al., 2002, 2003).
- Early seizure detection and stimulation of multiple contacts in the immediate vicinity of the seizure focus have improved the frequency of suppression of epileptiform activity.

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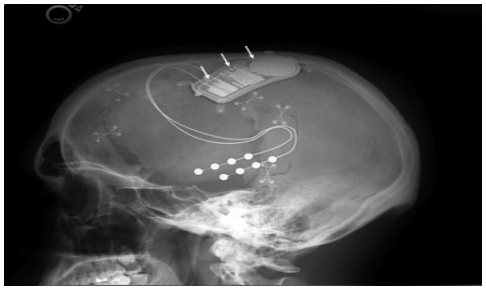
Example of RNS with two 4-contact subdural strip electrodes implanted over the left superior and middle temporal gyri. The three arrows left to right point to the connector port, microchip, and battery of the IPG (Implantable Pulse Generator).



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- Closed-loop systems are “intelligent” brain devices that can produce bursts of stimulation that react to and terminate physiological changes such as epileptiform activity (Litt, 2003).
- These stimulators may provide comparable or even more effective seizure suppression than their “blind,” “open-loop” counterparts (described above) that stimulate continuously or intermittently without reacting to any physiological changes.
- Penfield and Jasper (1954) were the first to apply focal electrical stimulation to a human’s brain and successfully terminated spontaneous seizures detected by electrocorticography during resective surgery.
- Closed-loop devices are more efficient and should be better tolerated than an open-loop modality because of lower daily doses of stimulation (Osorio et al., 2001).
- “Intelligent” detection may be less toxic than intermittent and continuous stimulation.

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Deep Brain Stimulator/DBS

- Approximately one-third of patients with epilepsy will have persistent seizures despite maximal antiepileptic drug (AED) therapy (Juul-Jensen, 1986; Sander, 1993; Sillanpaa and Schmidt, 2006).
- Resective brain surgery is typically indicated for patients with refractory partial seizures and can result in at least a 90% reduction in seizure frequency, though permanent neurologic deficits or death can occur in nearly 4% of cases (ILAE Commission Report, 1997).
- At least 50% of patients are not candidates for resection or choose not to undergo such an invasive procedure. Some of these patients might have a vagus nerve stimulator (VNS) placed as an adjunct to medical therapy, associated with up to a 50% reduction in seizure frequency (Vagus Nerve Stimulation Study Group, 1995).

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- However, most of these patients will not be seizure-free. Thus, due to the success of deep brain stimulation (DBS) for movement disorders (Krack et al., 2003; Halpern et al., 2007) combined with its advantages of adjustability, reversibility, and less risk of permanent neurologic deficits then surgical ablation (Schuurman et al., 2000), there has been an explosion of research into implantable devices for treating pharmaco-resistant epilepsy.
- The mechanism by which DBS may diminish seizures is not completely understood.
- Evidence from subthalamic nucleus (STN) DBS suggests that high frequency stimulation may block epileptiform activity in the cortex (Monnier et al., 1960, M. Velasco and F. Velasco, 1982; Lado et al., 2003), whereas low frequency stimulation may drive or synchronize cortical activity.

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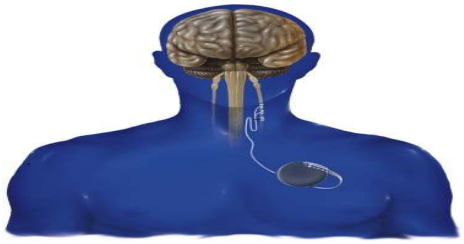
Vagus Nerve Stimulator/VNS



Schematic representation of VNS therapy. A pulse generator inserted in the subcutaneous tissues of the upper left chest delivers intermittent electrical stimulation to the cervical vagus nerve trunk via a bifurcated helical lead

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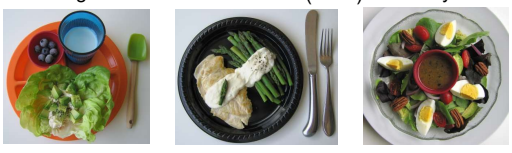
DIETARY THERAPIES

Ketogenic | Modified Atkins (MAD) | Low Glycemic



- All are considered medical therapies and should be monitored by professionals (dietitian and neurologist)
- Ketogenic diet is most restrictive, easier to use in children
- Evidence of benefits in adults is growing
- MAD and low glycemic are less restrictive, easier to manage

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Post Traumatic Psychological Disorders

- Survivors of traumatic brain injury (TBI) often develop chronic neurological, neurocognitive, psychological, and psychosocial deficits that can have a profound impact on an individual’s wellbeing and quality of life.
- Around 60% of people experience a psychiatric illness in the 12-months following a TBI, with affective disorders such as depression and anxiety the most common presentation.
- After TBI, a psychological process of grief and adjustment can occur in response to sudden changes in personal circumstance caused by the injury. Such psychosocial changes can be temporary or permanent.

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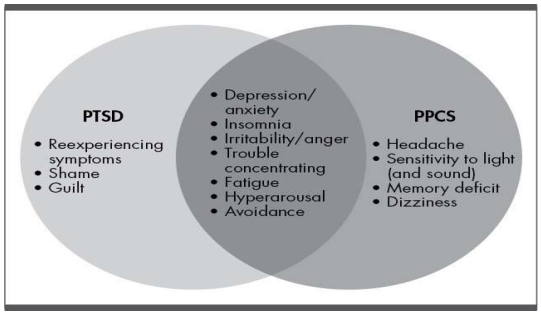
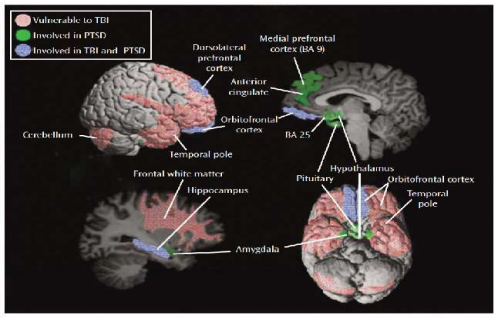
Overlap between posttraumatic stress disorder (PTSD) and persistent post concussive symptoms (PPCS).



Relationship between regional alterations of brain structure associated with posttraumatic stress disorder (PTSD) and traumatic brain injury (TBI).



Psychological & Cognitive Comorbidity in PTE

Psychological
- Mood Disorders
- Anxiety Disorders
- Psychotic Disorders

Cognitive
- Memory impairment
- Attention deficits
- Executive function disorder
- Slowed processing speed
- Language difficulties
- Specific learning disabilities related to seizure focus or injury location

Psychological Comorbidity in PTE: Contributing Factors

Epilepsy Treatment-related	Epilepsy-related	TBI-related
• Medication side effects (direct & indirect effects) • De novo psychiatric disorders or exacerbation of existing ones after epilepsy surgery	• Postictal symptoms (depression, psychosis) • Psychological trauma from seizures (resulting in PTSD & PNES) • Fear of seizures	• Psychological trauma from events surrounding TBI – (leading to PTSD & PNES) • Structural & pathophysiologcial changes to relevant brain regions (e.g. limbic system)
	• Activity restriction & loss of independence • Stigma & social isolation	

Cognitive Comorbidity in PTE: Contributing Factors

Epilepsy Treatment-related	Epilepsy-related	TBI-related
• Medication side effects (direct & indirect effects) • Functional deficits after epilepsy surgery	• Postictal memory dysfunction • Interictal epileptiform discharges • Additional brain injury from seizure-related falls or status epilepticus	• Structural and pathophysiologcial changes to relevant brain regions (e.g. hippocampus & memory; frontal lobe & attention/executive function
	• Sleep disorders • Mood & anxiety disorders	

Medical and Behavioral Interventions to promote emotional and cognitive wellbeing

Medical Interventions	Behavioral Interventions
• Sleep study to identify possible sleep disorder • Neuropsychological evaluation • Treatment changes to improve seizure control and/or reduce interictal epileptiform discharges • Med changes to reduce side effects • Meds for ADHD • Meds for anxiety/depression	• Sleep hygiene • Physical activity • Social activity, support groups • Stress management, relaxation techniques • Healthy diet • Health coaching (motivational interviewing, goal setting) • Cognitive behavioral therapy and other counseling approaches • Cognitive rehabilitation

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