SEIZURE DISORDER IN ADULTS

Overview and Definitions\(^1,2\)
1. Seizure – sudden change in behavior that is the consequence of brain dysfunction.
2. Epilepsy – recurrent (two or more), unprovoked seizures resulting from electrical hypersynchronization of neuronal networks in the cerebral cortex caused by a genetically determined or acquired brain disorder.
3. Non-Epileptic Seizure (NES) – provoked seizure occurring in the setting of metabolic derangement, drug or alcohol withdrawal, or acute neurological disorders (i.e. stroke, encephalitis).

Etiology\(^1,2\)
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\text{Epilepsy} & \text{Non-Epileptic Seizures (NES)} \\
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1. <50% of patients have an identifiable cause. & 1. Patients with seizure due to acute medical or neurological illness or injury (i.e. stroke, brain injury, meningitis, anoxic encephalopathy) - Increased risk for future epilepsy (but less than risk assoc with unprovoked seizure). \\
2. Genetically determined cause presumed in most patients. & 2. Patients with acute medical illness such as drug/alcohol withdrawal, drug intoxication/interactions, medications (including bupropion, typical antipsychotics etc…), hypo/hypernatremia, hypomagnesium, hypocalcemia, hypoglycemia, nonketotic hyperglycemia, uremia, hypoxia, hyperthyroidism, porphyria - No increased risk for future epilepsy. \\
3. Other causes: head trauma, brain tumour, stroke, intracranial infection, cerebral degeneration, congenital brain malformation, inborn errors of metabolism. & \text{Other: Psychological Disorder, Sleep Disorder, Paroxysmal Movement Disorder, Migraine, TIA.} \\
4. Elderly: vascular, degenerative, neoplastic causes more common. & \text{Other: Psychological Disorder, Sleep Disorder, Paroxysmal Movement Disorder, Migraine, TIA.} \\
5. Children: congenital brain malformations more common. & \text{Other: Psychological Disorder, Sleep Disorder, Paroxysmal Movement Disorder, Migraine, TIA.} \\
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Diagnostic Considerations\(^1,2\)

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<tr>
<th>History</th>
<th>Investigations</th>
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<td>1. Obtain history from patient and witnesses,</td>
<td>1. Labs: CBC, electrolytes, glucose, calcium, magnesium, phosphate, renal/liver function tests, toxicology.</td>
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<td>2. Circumstances preceding seizure (precipitants/triggers including strong emotions, intense exercise, loud music, flashing lights). Other conditions such as fever, menses, sleep deprivation, new medications, stress which may ↓ seizure threshold.</td>
<td>2. EEG: Demonstrates epileptiform abnormalities in 23% of patients with 1st seizure. Normal EEG does NOT rule out epilepsy. - Sensitivity for detection of epileptiform abnormalities is increased by repeating the EEG, recording for a longer time period, including a sleep recording (i.e. spontaneous, sedative induced, or deprived sleep), and performing an EEG within 1 day of a seizure.</td>
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<td>3. Seizure symptoms and signs during seizure A: Simple partial seizure (auras). Patient experiences symptoms at beginning of seizure. Depends on where seizure originates (e.g., occipital cortex → flashing lights; motor cortex → rhythmic jerking of face/arm/leg). - Consciousness not impaired. Involves part of cortex. Supports diagnosis of epileptic seizure.</td>
<td>3. Neuroimaging: to rule out structural lesion in 1st seizure. MRI preferred over CT.</td>
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<td>B. Complex partial seizure: Most common in epileptic adults. Patient appears awake but may appear to stare into space, motionless, non-responsive. Often display automatisms (grimacing, lip smacking, repeating words, etc.). Lasts &lt;3min. Postictal phase can last hrs. - Consciousness is impaired. Involves part of cortex. Occurs in epileptic/NES.</td>
<td>4. LP: Only if considering an infectious etiology.</td>
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<td>4. Postictal state that occurs and the end of the seizure. Postictal state is the interval of brain recovery back to normal consciousness and function. The patient may be confused and have focal neurological deficits. Lasts seconds to hrs depending on type of seizure, length of seizure, patient age, medications. - Postictal paresis (Todd’s paralysis): transient neurological deficit lasting hours after seizure. Typically moderate weakness of unilateral hand, arm, or leg.</td>
<td>4. LP: Only if considering an infectious etiology.</td>
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<td>5. Other: Medications, PMHx, FHx of seizure</td>
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Differential Diagnosis\(^3\)

Syncope: prodrome of lightheadedness and nausea, associated with pallor and diaphoresis, quick recovery. Unlikely to occur while supine. Tongue-biting is uncommon. Urinary incontinence can occur in both. May have occasional, brief jerking movement.

Other: Psychological Disorder, Sleep Disorder, Paroxysmal Movement Disorder, Migraine, TIA.

Management Considerations\(^1,2\)

1. Driving: legislation varies based on location. Usually patient will not be permitted to drive until seizure free for at least 1 year. For further details:
   - Epilepsy Ontario: http://www.epilepsyontario.org/client/EIO/EOWeb.nsf/web/Epilepsy+$+$+Driving$+$+in$+$+Ontario
   - Canadian Medical Association: Physician’s Guide to Driver Examination
2. Hospitalization: consider if prolonged postictal state/incomplete recovery, systemic illness, status epilepticus, history of head trauma, poor compliance.
3. Pharmacotherapy: If NES treat underlying cause +/- anti-epileptic drugs (AED). The goal of treatment is to achieve a seizure-free status without adverse effects. This goal is accomplished in more than 60% of patients who require treatment with anticonvulsants. However, many people have adverse effects, and some have seizures that are refractory to medical therapy.

Dr. Michael Evans developed the One-Pager concept to provide clinicians with useful clinical information on primary care topics.
*Notes:  a. AED therapy is usually reserved for patients at increased risk of recurrent seizure (ie. dx of epilepsy) and should be based on each individual.
b. AED therapy is also recommended after a single unprovoked seizure associated with a symptomatic cause of epilepsy (ie. stroke, trauma, etc.); epileptiform activity on EEG, abnormality on neuroimaging, or abnormal neurological exam.
c. Individualize therapy based on seizure type/epilepsy syndrome. Need to consider other medications/comorbidities, patient lifestyle/preference/ caregivers ( eg. ethosuximide and valproic acid are considered first line for absence seizures).

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<th>Seizure Type</th>
<th>Antiepileptic Drug</th>
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| **Broad Spectrum: all seizure types** | - valproate, lamotrigine, topiramate  
- Others which may be started by specialist (Felbamate, levetiracetam, rufinamide, zonisamide) |
| **Narrow Spectrum: simple/complex partial/secondary generalized** | - carbamazepine, phenytoin  
- Others which may be started by specialist (Gabapentin, lacosamide, oxcarbazepine, phenobarbital, pregabalin, primidone, tiagabine, vigabatrin) |

4. **Referral:** usually warranted for diagnostic clarification in the case of first time seizures. Typically, an EEG is performed +/- head imaging and more detailed laboratory work-up. Referral is not always required (eg. a child presenting with a typical febrile seizure and the cause has been clearly uncovered and child responds promptly to antipyretics).

**Pharmacotherapy of Selected Drugs**

1. Treat with monotherapy initially. If unsuccessful, switch monotherapy to new drug.
2. In general, enzyme-inducing AEDs (ie. phenytoin, carbamazepine, topiramate, etc.) have the most drug interactions (warfarin, oral contraceptives, anti-infective drugs, anti-cancer drugs, other anti-seizure medications).
3. Caution must be placed with patients who have liver or kidney disease because AEDs are either metabolized by the liver or excreted by the kidneys. Women of childbearing age should also be counseled about teratogenic effects and consider taking folic acid supplementation.
4. Continuing AED therapy should be planned by a specialist. In uncomplicated circumstances, AED therapy can be prescribed in primary care settings.
5. Drug monitoring: routine blood testing is not recommended. Should be done if clinically indicated (eg. determine noncompliance, suspected toxicity, breakthrough seizures, etc.).

### Drug Information

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<th>Drug</th>
<th>Dosing</th>
<th>Contra-indications / Precautions</th>
<th>Drug Interactions</th>
<th>Adverse Effects</th>
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| Phenytoin (Dilantin) | 200-400mg/d  
Target Level: 40 – 80 umol/L (depends on albumin) | Pregnancy | Significant CYP450 induction (↓ levels) interactions – review meds (other antiseizure meds, CCB, FQ, atypical antipsychotics, warfarin, COC, methadone)  
Chronic alcohol decreases phenytoin levels | Gingival hypertrophy, rash  
Rare: agranulocytosis, SJS, aplastic anemia, hepatic failure  
Blood dyscrasias, osteomalacia, suicidal ideation. |
| Valproate (Depakene) | 1000-3000mg/d  
Level: 350 – 700umol/L | Pregnancy, hepatic failure, pancreatitis | Significant CYP450 induction (↓ levels) interactions – review meds (other antiseizure meds, CCB, FQ, atypical antipsychotics, warfarin, COC, methadone)  
Chronic alcohol decreases valproate levels | Weight gain, nausea, vomiting, hair loss, bruising  
Rare: agranulocytosis, SJS, aplastic anemia, hepatic failure  
CNS depression, encephalopathy with toxicity, suicidal ideation, thrombocytopenia |
| Divalproex Sodium (Depakote) | 1250-3500mg/d  
Level: 350 – 700 umol/L | | | |
| Carbamazepine (Tegretol) | 800-1600mg/d  
Level: 17 – 50umol/L | Pregnancy, Hypersensitivity to TCA, bone marrow depression, concomitant MAOI | Significant CYP450 induction (↓ levels) interactions – review meds (other antiseizure meds, CCB, FQ, atypical antipsychotics, warfarin, COC, methadone)  
Induces its own metabolism, so should have 2 levels – 7 days apart when starting to ensure at steady state | Nausea, vomiting, fatigue, hyponatremia, rash pruritus  
Rare: agranulocytosis, SJS, aplastic anemia, hepatic failure  
Blood dyscrasias, CNS depression, skin reaction, psychiatric illness, suicidal ideation |
| Topiramate (Topamax) | 200-400mg/d | Pregnancy, psychiatric illness, glaucoma | Weak inducer of CYP 2C19/3A4 – may affect atypical antipsychotics, antidepressants, warfarin, methadone – check others  
More affected by concomitant use with other antiseizure meds (decreases topiramate by ~50%) | Weight loss, parathesias  
Toxic doses: difficulty concentrating, psychomotor slowing  
Rare: acute myopia and glaucoma  
encephalopathy, renal stones, suicidal ideation |
| Lamotrigine (Lamictal) | 300-400mg/d | Decreased lamotrigine levels by other antiseizure meds by ~50%  
Valproate/ divalproex + lamotrigine – 2 x incidence of rash (use alternate titration schedule to decrease risk) | Rash (increased with valproate coadministration), nausea  
Rare: SJS, hypersensitivity, aseptic meningitis, blood dyscrasias, CNS depression, skin reactions, suicidal ideation.
**Status Epilepticus**

Def’n: Varied. Seizure lasting >5-30min or ≥2 sequential seizures without full recovery of consciousness in between.

Rx: ABC’s. Labs (CBC, electrolytes, extended lytes, glucose, liver/renal function tests, toxicology, ABG, ECG, EEG, AED levels).

1. Early seizure termination w/ IV medication:
   - 1st line: lorazepam 0.02-0.03 mg/kg IV (- alternatives: diazepam 0.1mg/kg, midazolam 0.05mg/kg)
   - wait 1 minute for response then start lorazepam IV PRN (max dose: 0.1mg/kg @ 2mg/min)

2. Phenytoin
   - Add if seizure is continues. Administered through a different IV catheter because can precipitate if done in same IV line as benzodiazepines.
   - Loading Doses: 20mg/kg @ 25-50mg/min

3. If hypoglycemia: 50ml glucose IV and thiamine 100mg (if related to alcohol)

**Bottom Line**

Seizures can be classified into unprovoked and provoked (NES). Epilepsy is defined as recurrent (2 or more), unprovoked seizures. Provoked seizures may be due medical/neurological illness or injury, metabolic derangement, or drug/alcohol withdrawal. A complete and thorough history is essential in the seizure work up for a patient. Lab tests include CBC, electrolytes, extended lytes, glucose, kidney/liver function tests, and toxicology. Other important investigations include neuroimaging and EEG. Treatment involves AED therapy and needs to be individualized by taking into account a patient’s seizure type, co-morbidities, and lifestyle.

References can be found online at http://www.dfcm.utoronto.ca/programs/graduateprograms/One_Pager_ProjectReferences.htm