Epilepsy for Primary Care

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Definition of Seizure
- Sudden, excessive, rapid and local discharge of gray matter
- Incidence of a single seizure: 10%
  - Bad Day

Definition of Epilepsy
- A tendency to have recurrent seizures
  - It just takes 2
    - unprovoked
    - Very bad day

Incidence of Acute Symptomatic and Unprovoked Seizures

Magnitude of Epilepsy in the United States
- 150,000 newly diagnosed patients each year
- 2.2 million currently diagnosed with Epilepsy in the US, 65 million worldwide
- Children and older adults are the fastest growing segments of the population with new cases of epilepsy.
- 1 in 26 people in the US will develop epilepsy at some point in their lifetime.
- Epilepsy is the 4th most common neurological disorder after Migraine, Stroke, Alzheimer’s

Institute of Medicine
- IOM report
  - March 2012
  - 409 pages
  - Magnitude of Epilepsy
  - 13 Recommendations presented to improve the lives of people with epilepsy

Free PDFs available: www.iom.edu/epilepsy
Epilepsy Foundation of America, 1999 & 2012

Total estimated costs for all patients: $17.6 Billion
- Direct Medical Costs: ~15% (2.6 Billion)
- Indirect Costs: ~85% (15 Billion)

21-26% of people with controlled seizures were less likely to work than people in the general population.

41-47% of people with uncontrolled seizures were less likely to work than people in the general population.

Economic impact of Epilepsy in the U.S.

Institute of Medicine
Recognize Issues

Living with epilepsy is about much more than seizures. For people with epilepsy, the disorder is often defined in practical terms, such as challenges in school, uncertainties about social and employment situations, limitations on driving a car, and questions about independent living. At the same time, they are faced with health care and community services that are often fragmented, uncoordinated, and difficult to obtain.

Causes of Epilepsy in Children

Causes of Epilepsy in the Adults

Simple Partial
- Seizure onset in a localized region
- No loss of awareness
- Aura
  - Funny feeling, epigastric rising, deja vu, time/space imperceptions, fear

Complex Partial
- Temporal Lobe
  - Aura: Autonomic, Limbic, Psychical
  - Altered consciousness/awareness
  - Automatisms: lip smacking, repetitive swallowing, eye blinking, verbalizations, picking motions
  - Post-ictal period (sleepy, confused)

Idiopathic/
unknown 67%
Congenital 20%
Trauma 5%
Vascular 5%
Neoplastic 1%
Infection 1%
Other 1%

**Complex Partial**

**Frontal Lobe**

- Nighttime Preponderance
- Prominent motor activity:
  - Complex, coordinated but purposeless movements, frenetic.
  - Trembling, Waving, Rotating, Stepping, Cycling, Rocking, Hopping
- Complex vocalizations:
  - Shouting, Screaming, Growling

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**Generalized Tonic-Clonic**

**Old term: Grand mal**

- Loss of Consciousness
- **Tonic** extension of limbs (about 20-40 secs)
- Evolves to rhythmic **Clonic** jerking of extremities (about 30-50 secs)
- Cessation of breathing, tongue biting, incontinence.
- Tiredness and Confusion afterwards (Post-ictal)

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**Absence**

**Old Term: Petit Mal**

- Childhood or teenage onset
- Sudden onset, prompt offset
- Momentary loss of consciousness
- Eyelid flutter (automatism)
- 3-15 seconds duration

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**Myoclonic**

- Sudden, rapid/lighting like isolated or repetitive jerks
- Usually bilateral, usual more upper extremity than lower

**Atonic**

- Sudden loss of muscle tone
- Usually generalized, but may be focal

**Tonic**

- Sudden stiffening
- A few seconds in duration

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**What history is needed?**

- Seizure description:
  - Focality, length, associated sx during, associated sx after. REALLY need to talk to eye witness.
- Circumstances
  - Illness, medications, etoh, sleep deprived, mimicks
- Historical Risks:
  - Family hx, CNS lesion, hx of Meningitis, Febrile sz, birth injury.
- ER workup
  - Prolactin: DON’T PUT STOCK IN THIS
  - Neuroimaging

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**EEG: Electroencephalogram**

- The EEG is the single **most valuable** laboratory test in the evaluation of patients with epilepsy.
- However, A normal EEG **does not** exclude the diagnosis of Epilepsy
Normal EEG

Complex Partial Seizure

Generalized Seizure

Video EEG Monitoring
- Inpatient, 24 hour monitoring with video and EEG telemetry
- Provides direct observation of clinical event and concurrent EEG
- Indications:
  - Diagnosis is uncertain, medications are not working
  - Evaluation for potential epilepsy surgery

Intracranial EEG

MRI
- Required as part of a seizure workup
- 3T vs 1.5T

Normal EEG

Complex Partial Seizure

Generalized Seizure

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Intracranial EEG

MRI
- Required as part of a seizure workup
- 3T vs 1.5T
Structural Lesions that cause Epilepsy

- Stroke
- Tumor
- Meningitis
- Subdural Hematoma
- Intracranial Hemorrhage
- AV Malformation
- Arachnoid Cyst
- Hippocampal Scarring
- Scarring

Structural Lesions that cause Epilepsy

- Cortical Malformations
- Grey Matter Heterotopias

Advanced Neuroimaging

- SPECT
- PET
- DIFFUSION TENSOR IMAGING

New 3-D Color MRI Imaging

Antiepileptic Medications

- Bromides 1857
- Phenobarbital 1912
- Dilantin 1937
- Zantac 1954
- Tegretol 1974
- Depakote 1978
- Felbatol 1993
- Neurontin 1994
- Lamictal 1994
- Topamax 1996
- Gabatril 1997
- Keppra 2000
- Trileptal 2000
- Zonegran 2000
- Lyrica 2005
- Vimpat 2008
- Sabril 2011
- Onfi 2011
- Potiga 2012
Neurophysiology

Nerve Terminal
- GABA, Glutamate, Calcium, Sodium, Potassium

Nerve Terminal

Action Potential: All or None

Antiepileptic Drug Mechanisms of Action
- Calcium channels: (blockers)
  - T-calcium channels have been known to play a role in the 3 per second spike-and-waves discharges of absence seizures. AEDs that inhibit these T-calcium channels are particularly useful for controlling absence seizures.
    - Depakote, ethosuximide, Topamax, Zonegran, Felbatol, "Neurontin?"

- KCN channels
  - Activates / Opens neuronal KCNQ-type K⁺ channels. Increases GABA in brain and affects gaba neurotransmission.
    - Potiga

- Synaptic vesicle protein 2A (SV2A):
  - Prevents binding of the neurotransmitter containing vesicle, preventing conduction across synapses.
    - Keppra

- Sodium Channel Addendum
  - Selective enhancement of slow inactivation of sodium channels and interacts with the neuroplasticity-relevant target-collapsin-response mediator protein-2 (CRMP-2).
    - Vimpat

Antiepileptic Drug Mechanisms of Action
- Sodium channel: (blockers)
  - AEDs that target these sodium channels prevent the return of these channels to the active state by stabilizing the inactive form of these channels. In doing so, repetitive firing of the axons is prevented.
    - Tegretol, Trileptal, Dilantin, Lamictal, Zonegran, Vimpat

- GABA receptors: (~agonistic)
  - When GABA binds to a GABA-A receptor, the passage of chloride, a negatively charged ion, into the cell is facilitated via chloride channels. This influx of chloride increases the negativity of the cell (i.e., more negative resting membrane potential). This causes the cell to have greater difficulty reaching the action potential.
    - phenobarbital, Lyrica (prodrug), Topumex (enhances gaba) Benzodiazepines

- Glutamate: (blocker)
  - Upon binding glutamate, the glutamate receptors facilitate the flow of both sodium and calcium ions into the cell, while potassium ions flow out of the cell, resulting in excitation.
    - Topumex (AMP and kainate), Lamictal (inhibits release of glutamate) Felbatol (NMDA), "Keppra (effect on glycine?)"

Antiepileptic Drug Choice by Seizure Type

Generalized Seizures
- Dilantin, Tegretol, Neurontin, Trileptal, Lyrica, Potiga
- ethanolimide
- ACTH

Partial Seizures
- Depakote, Lamictal, Topamax, Zonegran, Keppra, Felbatol, phenobarbital, Sabrill, Onfi

ACTH
### Antiepileptic Drug Dosing Guide (per Powell)

<table>
<thead>
<tr>
<th>Medication</th>
<th>General Ranges</th>
<th>High Doses</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dilantin / phenytoin</td>
<td>300-600mg</td>
<td>900mg</td>
</tr>
<tr>
<td>Tegretol / carbamazepine</td>
<td>600-1200mg</td>
<td>2000mg</td>
</tr>
<tr>
<td>Depakote / valproic acid</td>
<td>500-3000mg</td>
<td>4000mg</td>
</tr>
<tr>
<td>Neurontin / gabapentin</td>
<td>900-2400mg</td>
<td>4800mg</td>
</tr>
<tr>
<td>Lamictal / lamotrigine</td>
<td>300-400mg</td>
<td>800mg</td>
</tr>
<tr>
<td>Topamax / topiramate</td>
<td>100-400mg</td>
<td>500mg</td>
</tr>
<tr>
<td>Keppra / leviteracetam</td>
<td>1000-3000mg</td>
<td>4500mg</td>
</tr>
<tr>
<td>Zonegran / zonisamide</td>
<td>100-400mg</td>
<td>700mg</td>
</tr>
<tr>
<td>Lyrica / pregabalin</td>
<td>150-300mg</td>
<td>600mg</td>
</tr>
</tbody>
</table>

### Appropriate Incremental Dosing Changes

<table>
<thead>
<tr>
<th>Medication</th>
<th>Dose Increments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dilantin / phenytoin</td>
<td>30mg or 100mg</td>
</tr>
<tr>
<td>Tegretol / carbamazepine</td>
<td>200mg</td>
</tr>
<tr>
<td>Depakote / valproic acid</td>
<td>250-500mg</td>
</tr>
<tr>
<td>Neurontin / gabapentin</td>
<td>300-600mg</td>
</tr>
<tr>
<td>Lamictal / lamotrigine</td>
<td>100mg</td>
</tr>
<tr>
<td>Topamax / topiramate</td>
<td>50-100mg</td>
</tr>
<tr>
<td>Keppra / leviteracetam</td>
<td>250-500mg</td>
</tr>
<tr>
<td>Zonegran / zonisamide</td>
<td>50-100mg</td>
</tr>
<tr>
<td>Lyrica / pregabalin</td>
<td>75-150mg</td>
</tr>
</tbody>
</table>

### Adverse Side Effects - Typical

- **Rash**
  - All of them. However, Dilantin, Tegretol, Lamictal are somewhat more likely
  - Remember Zonegran has a sulfa-like moiety
- **Dizziness / lightheadedness**
  - Tegretol, Dilantin, Trileptal, Lamictal, Vimgat
- **Nausea**
  - Depakote, Topamax, Zonegran, Felbatol
- **Weight change**
  - Increase: Depakote, Neurontin, Lyrica, ~ Tegretol
  - Decrease: Felbatol, Topamax, Zonegran
- **Hair thinning:**
  - Depakote, Topamax

### Adverse Side Effects – Less Typical

- **Bone loss**
  - Dilantin, Tegretol, Depakote, Trileptal, Phenobarbital,
- **Behavior changes**
  - Keppra, Felbatol (and any of the others)
- **Nephrolithiasis**
- **Anhydrosis**
- **Sun Sensitivity**
  - Tegretol, Trileptal, Lamictal
- **Paresthesias**
  - Topamax, fosphenytoin loading

### When to start treatment?

- Treatment of first tonic-clonic seizure does not improve the prognosis of developing epilepsy
- The probability of long-term remission is not influenced by treatment of the first seizure
- Quality of Life is not affected by delay of treatment
- The majority of patients with a first unprovoked seizure will not have a repeat seizure.

### Success Rates of Drug Therapy

<table>
<thead>
<tr>
<th>Drug #</th>
<th>% Seizure Free (&gt;= 1 year)</th>
<th>% of total eventually controlled</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>47.2</td>
<td>73.6</td>
</tr>
<tr>
<td>2</td>
<td>60.2</td>
<td>94</td>
</tr>
<tr>
<td>3 or 2 drug duotherapy</td>
<td>64.0</td>
<td>100</td>
</tr>
</tbody>
</table>

N = 470 Untreated Patients
Expert Approach to the Treatment of Partial Epilepsy

Monotherapy

2nd Monotherapy

2 AEDs  Additional Monotherapy(s)

Begin Evaluation for Epilepsy Surgery


Monotherapy

2nd Monotherapy

2 AEDs  Additional Monotherapy(s)

Begin Evaluation for Epilepsy Surgery


Primary Care Approach to the Treatment of Epilepsy

Monotherapy

2nd Monotherapy

2 AEDs  Additional Monotherapy(s)

Begin Evaluation for Epilepsy Surgery


When to use TROUGH Levels

- New drug
  - Adding or removing an enzyme inhibitor (Depakote)
  - Adding or removing an enzyme Inducer (Tegretol, Dilantin, phenobarbital)
  - Adding a medication to an existing medication known to interact
- Checking for noncompliance
  - Random actually better than trough in this case
- Toxic symptoms
  - Always consider the clinical situation, ex: elderly, meds
- Changing to generic
  - Essentially all antiepileptic medications are available in generics. (except Vimpat and Potiga)
- Pregnancy: levels of all antiepileptics drop during pregnancy

Common Errors

- Clinical decisions based on non-trough levels
- Inappropriate incremental dose changes
  - ex: Dilantin
- Converting doses incorrectly
  - Depakote to Depakote ER (need higher doses of ER)
  - Tegretol to Trileptal (300mg Trileptal per 200mg Tegretol)
  - Neurontin to Lyrica (600mg Neurontin per 100mg Lyrica)
- Ignoring Renal Dosing
  - Topamax, Keppra, Neurontin, Lyrica
- Forgetting interactions
  - Ex: 2 packs and Prozac to Tegretol, Estrogen to Lamictal
  - Adding cytochrome p-450 inducers or inhibitors without dose adjustments, or clinical surveillance

Dilantin Pharmacokinetics

Zero Order Kinetics

First Order Kinetics

Concentration

Dose
**Surgical Options for the treatment of Epilepsy**
- Temporal Lobectomy
- Extratemporal Resection
- Corpus Callosotomy
- Hemispherectomy
- Trephination

**Vagus Nerve Stimulator**

**Devices on the Horizon**
- NeuroPace

Stimulation of the Anterior Nucleus of the Thalamus in Epilepsy (SANTE) trial

**Women with Epilepsy**
- Menstrual Cycle
- Contraception
- Genetic inheritance risks
- Pregnancy
  - Pre-pregnancy treatment
  - Pregnancy monitoring
- Antiepileptic Medications
  - Birth defects risk
  - Breast feeding

**Menstrual Cycle**

<table>
<thead>
<tr>
<th>Estradiol = Epileptogenic</th>
<th>Progesterone = Protective</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lowers seizure thresholds</td>
<td>Elevates seizure thresholds</td>
</tr>
</tbody>
</table>

**Catamenial Epilepsy**

Herzog et al. Epilepsia 1997
Contraception

- Oral contraceptives
  - Progesterone formulations preferred
  - Use high dose estrogens with enzyme inducers
  - Tegretol, Dilantin, Trileptal, Topamax >200mg

- Implants
  - Replace earlier if on enzyme inducers

- IUD’s
  - Mirena-progesterone coated
  - Generalized epilepsies (pseudo contraception)
  - Hypothalamic-Pituitary axis
  - PCOS

Genetic Transmission of Epilepsy

- Generalized Epilepsy
  - 4-6% risk
  - Complicated genetic inheritance

- Partial Epilepsy
  - Uncommon
  - ADNFLE
    - Autosomal dominant nocturnal frontal lobe epilepsy
    - Temporal lobe?

Pre-Pregnancy

- As possible, try to use monotherapy
  - Depakote is essentially contraindicated
- Use lowest dose that will control seizures
- Consider extended-release formulations
- It is **NOT** appropriate to remove antiepileptic medications prior to or during pregnancy. The risk of damage to the fetus from a seizure outweighs the risk of teratogenicity from the medication.
- Folic Acid debate

Antiepileptic Drug Levels-Pregnancy

- Levels of AED’s will **fall** during pregnancy
  - Expansion of Plasma Volume
  - Increased renal elimination due to increased RBF
  - Increased Cardiac output leading to increased Hepatic blood flow, leading to increased metabolism
  - Decreased protein binding (more available for metabolism)

- Consider checking free levels of AED’s associated with protein binding (Tegretol, Dilantin, Depakote, Phenobarb)

- Check Levels at beginning of each trimester and monthly during the last trimester.
  - Especially Lamictal
  - Post-partum: AED levels will rise quickly during the first 1-2 weeks post-partum.

Risk of Congenital Birth Defects

- Risk in general population 2-4%
- Risk in WWE 4-6%
  - Pessimist / The glass is half empty:
    - WWE have twice the risk of birth defects
    - There is a 100% increase in the incidence of birth defects in WWE compared to the general population.
  - Optimist / The glass is half full:
    - only 1 in 50 births will have a risk of congenital birth defects over the risk in the general population.
    - There is a 95% chance that the baby will be entirely normal.
    - Depakote-avoid if at all possible

Breast Feeding

- The American Academy of Neurology & The American Academy of Pediatrics have both approved the use of antiepileptic drugs during breast feeding.
  - Caution with Phenobarbital, monitor for sedation

  - The benefits of breast-feeding outweigh the small risk for adverse effects of anti-epileptic medications
  - The baby has been exposed to the medications for 9 months already!
IOM Recommendations

- Validation and implementation of standard definitions and criteria for epilepsy case ascertainment, health care and community services use and costs, and quality measurement
- Continuation and expansion of collaborative surveillance efforts
- Development and evaluation of prevention efforts for epilepsy and its consequences
- Improvement in the early identification of epilepsy and its comorbid health conditions
- Development and implementation of a national quality measurement and improvement strategy for epilepsy care
- Establishment of epilepsy center accreditation and an Epilepsy Care Network
- Improvement in health professionals' education about the epilepsies
- Improvement in the delivery and coordination of community services
- Improvement in and expansion of educational opportunities for patients and families
- Provision of information to media to improve awareness and eliminate stigma
- Coordination of public awareness efforts
- Continuation and expansion of Vision 20-20 working groups and collaborative partnerships
- Engagement of people with epilepsy and their families in education, dissemination, and advocacy for improved epilepsy care and services

While significant progress has been made in treating some types of epilepsy, much remains to be done to improve quality, access, and value of health care for people with epilepsy. Gaps include delays in diagnosis and referral, disparities in access to care for underserved and rural patients, and challenges in co-management of patients between primary care and specialty providers.

Social Issues: Stigma, QoL, Driving, Dating, Working
- Post-ictal complications
- Mood/psychiatric disorders
- Status Epilepticus/Repetitive Seizures
- Elderly issues
- Developmentally Delayed Population
- Bone loss
- Non-Epileptic/Psychogenic Seizures
- Sudden Death
- Suicide

Institute of Med
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