

Neurology Updates for the PCP:

**Seizure Medications
(and other therapies)**

**Victoria Wong, MD
Department of Neurology
Portland VA Medical Center
Oregon Health & Science University**

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Disclosures

None

Outline

- Diagnosing a seizure
- Classifying seizures
- Anti-seizure medications
- New medications
- Other treatment modalities
- Status epilepticus
- Epilepsy counseling
- Regional VA EEG/Epilepsy resources

Diagnosing a Seizure

Case:

62-year-old man with treated HTN returns from a trip. That evening, he has a funny feeling then falls and passes out. His wife hears the fall and sees him stiff and shaking for a few seconds. He is agitated for minutes afterwards then gradually recovers. He has bitten his tongue.

Diagnosing a Seizure

- Seizure?
- Syncope?

Other considerations:

- Narcolepsy (cataplexy)
- Migraine equivalent
- Transient ischemic attack (TIA)
- Psychogenic non-epileptic seizure

Diagnosing a Seizure

• Seizure vs Syncope:

- Triggers
- Aura
- Tongue biting
- Urinary incontinence
- Post-ictal state
- Duration

Classifying Seizures

• Outdated terms:

- “Grand mal” = convulsion
 - Focal onset?
 - Generalized onset?
- “Petit mal” = staring spell
 - Complex partial seizure?
 - Absence seizure?

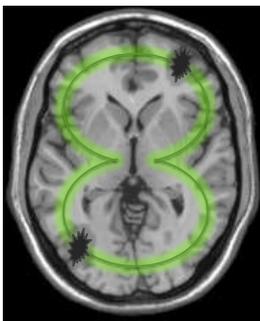
Classifying Seizures

- **Common terms:**
 - **Focal / partial / localization-related:**
 - Originating from a "focus"
 - Networks limited to one hemisphere
 - Can secondarily generalize
 - **Generalized:**
 - Bilaterally distributed networks
 - Does NOT imply "generalized tonic clonic seizure"

Focal Seizure



Generalized Seizure



Generalized seizures	
→ Tonic-clonic (in any combination)	
→ Absence	
Typical	
Atypical	
Absence with special features	
Myoclonic absence	
Eyelid myoclonia	
→ Myoclonic	
Myoclonic	
Myoclonic atonic	
Myoclonic tonic	
Clonic	
Tonic	
Atonic	
Focal seizures	Simple or complex partial
Unknown	Secondarily generalized
Epileptic spasms	

Classification of Seizures

- Under age 10:
 - Generalized epilepsy more common
- After age 10:
 - >50% of all new epilepsy cases are of focal epilepsy

Distinguishing Epilepsy Types

- Clinical history
 - Absence vs complex partial
 - Seizure focality?
- Neurological exam
 - Focal findings?
- EEG
 - “focal” vs “generalized” abnormalities
- Brain imaging (preferably MRI)
 - Lesion?

Classification of Seizures

- **Example of absence seizure:**
 - <http://www.youtube.com/watch?v=H3iLQi6wt94>
 - **Seen in Generalized Epilepsy**

Classification of Seizures

- **Example of a complex partial seizure:**
 - <http://www.youtube.com/watch?v=hyj7MSdaLqw>
 - **Seen in Focal Epilepsy**

Classification of Seizures

- **Example of secondarily generalized tonic-clonic seizure (GTC):**
 - <http://www.youtube.com/watch?v=Nds2U4CzvC4>
 - **Can be seen in Focal or Generalized Epilepsy**
 - **Focal features suggest Focal Epilepsy**

Outline

- Diagnosing a seizure
- Classifying seizures
- **Anti-seizure medications**
- New medications
- Other treatment modalities
- Status epilepticus
- Epilepsy counseling
- Regional VA EEG/Epilepsy resources

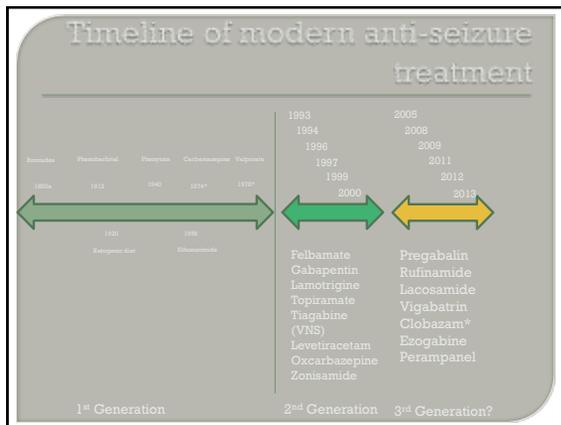
Anti-Seizure Medications

- **AKA:**
 - Anti-epileptic drugs (AEDs)
 - Anti-convulsants

Timeline of modern anti-seizure treatment



Slides courtesy of Paul Motika, MD



How can we organize the AEDs?

Sodium Channel Blocking	GABA Receptor Agonist	GABA reuptake inhibitors	GABA Transaminase inhibitor	Possible GABA activity	Glutamate Blockers	Other	Potassium Channel Openers
Carbamazepine	Clobazam	Tiagabine	Vigabatrin	Gabapentin	Felbamate	Levetiracetam	Ezogabine
Phenytoin	Clonazepam			Pregabalin	Topiramate		
Oxcarbazepine	Phenobarbital			Valproate	Perampnel		
Lamotrigine	Primidone						
Zonisamide							
Lacosamide							
Valproate							

Anti-Seizure Medications

- **Considerations:**
 - Narrow vs broad spectrum
 - Side effect profile
 - Medical comorbidities
 - Drug interactions
 - Formulations
 - Doses per day
 - Cost
- **Goal: No seizures, no side effects!**

Anti-Seizure Medications

- **Narrow-spectrum AEDs:**
 - Effective only in simple partial, complex partial, and secondarily generalized
- **Broad-spectrum AEDs:**
 - Effective in all seizure types

Anti-Seizure Medications

- **Broad-spectrum AEDs:**
 - Effective in all seizure types
- Valproate (Depakote)
- **Lamotrigine (Lamictal)**
- **Levetiracetam (Keppra)**
- Topiramate (Topamax)
- Zonisamide (Zonegran)

Valproic acid (Depakote)

- **Indications:** epilepsy, mania, migraine
- **Hepatic metabolism**
- **Note:**
 - **Regular and delayed release (DR):**
 - 2 to 4 doses per day
 - **Extended release (Depakote ER)**
 - 1 to 2 doses per day

Valproic acid (Depakote)

- Side effects:
 - Nausea/vomiting
 - Weight gain, metabolic syndrome
 - Hair loss
 - Tremor
 - Thrombocytopenia
 - Polycystic ovarian syndrome
 - Transaminitis
 - Acute hepatocellular injury
 - Hyperammonemia
 - Pancreatitis
 - In utero exposure: high risk

Valproic acid (Depakote)

- When used?
 - Healthy young men +/- psychiatric dx
 - Very refractory epilepsy
 - Caution: drug interactions
- Avoid in:
 - Elderly patients
 - Women of child-bearing age
 - Obese patients
 - Patients with hepatic dysfunction
 - Surgical patients

Lamotrigine (Lamictal)

- Indications: epilepsy, bipolar disorder
- Hepatic metabolism
- Interacts with estrogen
- Slow titration is key (avoid Stevens-Johnson)
 - Stop immediately with any rash
 - Temporary benzodiazepines if seizures

Lamotrigine (Lamictal)

- Drug rash



Lamotrigine (Lamictal)

- Stevens-Johnson Syndrome



Lamotrigine (Lamictal)

- Side effects:
 - Rash
 - Nausea
 - Somnolence or insomnia

Lamotrigine (Lamictal)

- When used?
 - Women of childbearing age (but remember estrogen interaction!)
 - Patient with psychiatric comorbidities
- Caution in:
 - Patients with many drug allergies (especially to other seizure medications)

Levetiracetam (Keppra)

- Indications: epilepsy
- Renally cleared
- No drug interactions!
- Rapid titration schedule

Levetiracetam (Keppra)

- Side effects:
 - Somnolence or insomnia
 - Mood disturbance (17%)
 - Other psychiatric effects (2.5%)

Levetiracetam (Keppra)

- **When used?**
 - Women of childbearing age
 - Patients with hepatic dysfunction
 - Patients with a long medication list
- **Avoid in:**
 - Patients with psychiatric comorbidities

Topiramate (Topamax) and Zonisamide (Zonegran)

- **Indications:** epilepsy, migraine (TPM)
- **Hepatic metabolism (partially)**
- **Slow titration due to side effects**
- **ZNM dosed once a day**
- **Weak carbonic anhydrase inhibitor**

Topiramate (Topamax) and Zonisamide (Zonegran)

- **Side effects:**
 - **Weight loss (~6 kg in 1 year on TPM)**
 - **Cognitive impairment**
 - **Paresthesias**
 - **Fatigue**
 - **Mood problems**
 - **Metabolic acidosis**
(average bicarb decrease of 4 meq/L)
 - **Renal stones (1 to 7%)**

Topiramate (Topamax) and Zonisamide (Zonegran)

- When used?
 - Comorbid migraine headaches
 - Desire for weight loss
 - Once daily dosing – zonisamide
- Avoid in:
 - Patients with psychiatric comorbidities
 - Patients with renal stone histories
 - Cognitive impairment

Anti-Seizure Medications

- Narrow-spectrum AEDs:
 - Effective only in simple partial, complex partial, and secondarily generalized
- Phenytoin (Dilantin)
- Phenobarbital (Luminal)
- Carbamazepine (Tegretol)
- Oxcarbazepine (Trileptal)
- Lacosamide (Vimpat)

Phenytoin (Dilantin)

- Indications: epilepsy
- Hepatic metabolism
- May work for all convulsive events (GTCs), but not effective in other types of generalized seizures (e.g., myoclonus, absence)

Phenytoin (Dilantin)

- Pharmacokinetics are NOT first-order
- Half-life increases with higher concentrations
- Highly protein bound
- Conclusion:
 - Follow levels closely
 - Correct for albumin

Phenytoin (Dilantin)

- Side effects:
 - Gingival hypertrophy
 - Body hair increase
 - Rash (Stevens-Johnson)
 - Osteoporosis
 - Sexual dysfunction
 - Neurotoxicity (confusion, slurred speech, double vision, ataxia, neuropathy)

Phenytoin (Dilantin)

- When used?
 - First line after benzos in status epilepticus
- Avoid in:
 - Patients with myoclonus or absence seizures
 - Patients with altered albumin levels (hepatic cirrhosis, nephrotic syndrome)
 - Patients with long medication lists
 - Elderly patients
 - Women of child-bearing age
 - Alcoholics

Phenobarbital (Luminal)

- **Indications: epilepsy**
- **Hepatic metabolism**
- **Use limited by sedation**

Phenobarbital (Luminal)

- **Side effects:**
 - **Sedation, dizziness, confusion**
 - **Depression**
 - **Hematologic effects**
 - **Hypotension (typically with IV form)**
 - **Respiratory depression (with IV form)**

Phenobarbital (Luminal)

- **When used?**
 - **Pediatric neurology**
 - **Once a day dosing desired**
- **Avoid in:**
 - **Most patients unless very refractory**

Carbamazepine (Tegretol) and Oxcarbazepine (Trileptal)

- Similar mechanisms of action
- Indications:
 - CBZ: epilepsy, trigeminal neuralgia, bipolar disorder, neuropathic pain
 - OXC: epilepsy
- Hepatic metabolism
- For CBZ, use extended release for BID dosing

Carbamazepine (Tegretol) and Oxcarbazepine (Trileptal)

- Screening for the HLA-B*1502 allele is recommended prior to starting carbamazepine in patients with Asian ancestry due to the risk of Stevens-Johnson syndrome.

Carbamazepine (Tegretol) and Oxcarbazepine (Trileptal)

- Side effects:
 - Nausea, vomiting
 - Hyponatremia
 - Rash / Stevens-Johnson
 - Sexual dysfunction
 - Dizziness, blurred or double vision
 - Leukopenia (WBC < 3,000/uL)
 - Aplastic anemia

Carbamazepine (Tegretol) and Oxcarbazepine (Trileptal)

- **When used?**
 - **Women of childbearing age (second line after LTG, LEV)**
 - **Patient with psychiatric comorbidities**
- **Caution in:**
 - **Patients hypersensitive to lamotrigine**
 - **Elderly patients**

Lacosamide (Vimpat)

- **Indications: epilepsy**
- **Hepatic metabolism**

Lacosamide (Vimpat)

- **Side effects:**
 - **Dizziness, nausea, vertigo**
 - **Balance problems**
 - **PR interval prolongation**

Lacosamide (Vimpat)

- **When used?**
 - Patients with many non-cardiac medical comorbidities
- **Caution in:**
 - Fall risk
 - Cardiac patients

Pharmacokinetics and drug interactions

Newer AEDs have generally less effects on other AEDs and other medications in general

Liver Enzyme Inducers	Liver Enzyme Inhibitors	Little or no effect
Phenytoin	Valproate	Levetiracetam
Phenobarbital	Felbamate	Lamotrigine
Carbamazepine		Zonisamide
Primidone		Gabapentin
Oxcarbazepine*		Ethosuximide
Topiramate*		Lacosamide
		Pregabalin
		Rufinamide
		Vigabatrin
		Clobazam
		Potiga

Pharmacokinetics and drug interactions

- Some of the drugs that may be affected by enzyme-inducing AEDs:
 - Amiodarone, **propranolol**, metoprolol, nifedipine, felodipine, nimodipine, digoxin, lovastatin, simvastatin, dicumarol, warfarin, quinidine
 - Amitriptyline, nortriptyline, desipramine, clomipramine, citalopram, paroxetine, bupropion, haloperidol, chlorpromazine, clozapine, risperidone, quetiapine
 - Cyclosporine, tacrolimus
 - Oral contraceptives**, prednisone, theophylline, methadone
 - Many of the other seizure medications

General Principles

- If no urgency, start slow for better tolerability
- Monotherapy is best. Maximize one medication before starting a second one.
- Goal: No side effects and seizure freedom.
- If a patient is well-controlled on an older medication, assess long term effects, consider switch.
- Refractory epilepsy: failure of 2+ drugs

Outline

- Diagnosing a seizure
- Classifying seizures
- Anti-seizure medications
- **New medications**
- Other treatment modalities
- Status epilepticus
- Epilepsy counseling
- Regional VA EEG/Epilepsy resources

New and Upcoming Medications

- 2010:
 - Ezogabine (Potiga)
- 2011:
 - Clobazam (Onfi)
- 2012:
 - Perampanel (Fycompa)
 - Oxcarbazepine ER (Oxtellar XR)
- 2013:
 - Topiramate ER (Trokendi XR)
 - Eslicarbazepine (Aptiom)
- Pending
 - Brivaracetam

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Other Treatment Modalities

- In refractory epilepsy patients, consider...
 - Epilepsy surgery – for focal epilepsies
 - The only “cure” for epilepsy
 - Vagus nerve stimulation (VNS)
 - Responsive neurostimulation device (RNS) – NeuroPace
 - Modified Atkins diet
- **Diagnosis of psychogenic non-epileptic seizures?**
 - (25% of veterans admitted to EMU)

Other Treatment Modalities

- Epilepsy surgery:

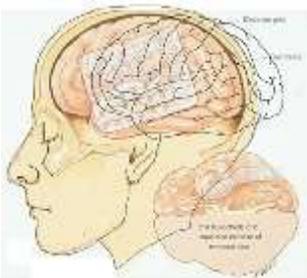


Image from: https://www.epilepsy.com/epilepsynewsletter/july10_surgery

Other Treatment Modalities

- Epilepsy surgery:

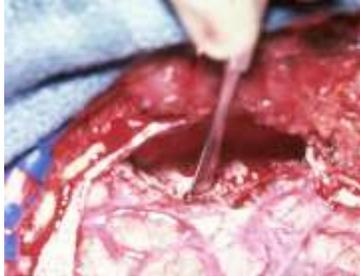


Image from: https://www.epilepsy.com/epilepsynewsletter/july10_surgery

Other Treatment Modalities

- Vagus nerve stimulator (VNS):



Image from: http://www.riversideonline.com/health_reference/Behavior-Mental-

Other Treatment Modalities

- Responsive neurostimulation device (RNS) NeuroPace:

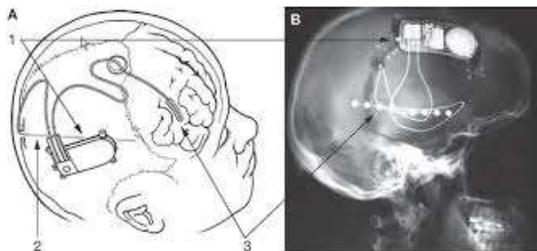
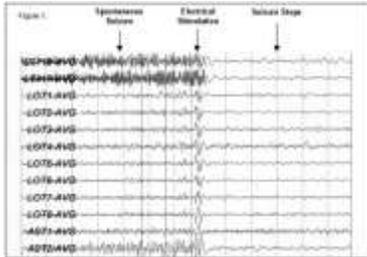


Image from: http://www.nature.com/nrneuro/journal/v4/n4/fig_tab/nrneuro0750_F3.html

Other Treatment Modalities

- Responsive neurostimulation device (RNS) NeuroPace:



Cheng, G.R. et al. Application of an externalizable responsive neurostimulation system (RNS) to patients with intractable epilepsy undergoing intracarotid sodium amobarbital. *Epilepsia*, Vol 43, Suppl 7, 2002

Outline

- Diagnosing a seizure
- Classifying seizures
- Anti-seizure medications
- New medications
- Other treatment modalities
- **Status epilepticus**
- Epilepsy counseling
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Status Epilepticus

- Five or more minutes of continuous clinical and/or electrographic seizure activity

OR

- Recurrent seizure activity without return to baseline between seizures

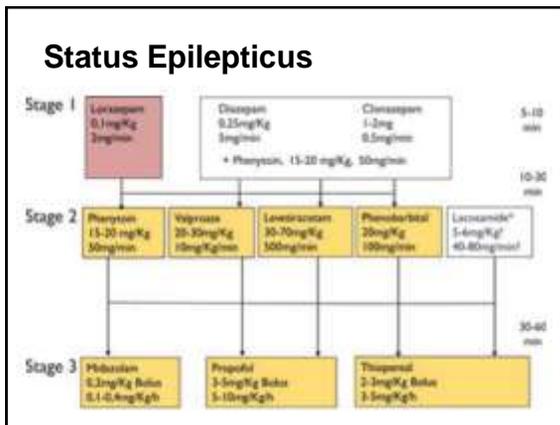
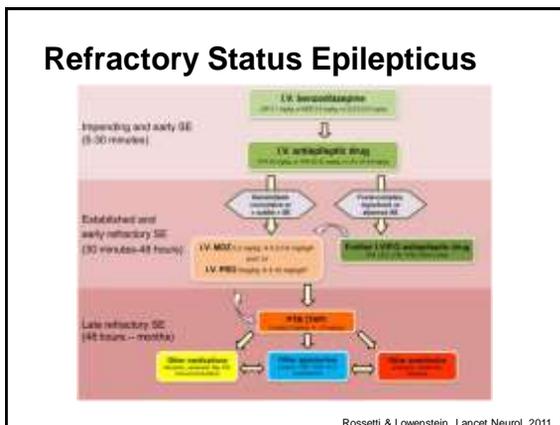


Table 4 Treatment recommendations for SE

Treatment	Class/level of eva
Emergency treatment	
Lorazepam	Class I, level A
Midazolam	Class I, level A
Diazepam	Class Ia, level A
Phenytoin/phenytoin	Class Ib, level A
Phenobarbital	Class Ib, level A
Valproate sodium	Class Ib, level A
Levetiracetam	Class Ib, level C
Supportive treatment	
Valproate sodium	Class Ia, level A
Phenobarbital/phenobarbital	Class Ia, level B
Midazolam (continuous infusion)	Class Ib, level B
Phenobarbital	Class Ib, level C
Levetiracetam	Class Ib, level C
Refractory treatment	
Midazolam	Class Ia, level B
Propofol	Class Ib, level B
Phenobarbital/phenobarbital	Class Ib, level B
Valproate sodium	Class Ia, level B
Levetiracetam	Class Ib, level C
Phenytoin/phenytoin	Class Ib, level C
Lacosamide	Class Ib, level C
Topiramate	Class Ib, level C
Phenobarbital	Class Ib, level C



Refractory Status Epilepticus

- ICU, EEG monitoring absolutely required
 - EEG burst-suppression
- Continue infusions 12-24 hrs then taper & observe (clinical, EEG)
- If ongoing seizures, retreat to burst suppression and reassess 24-48 hrs later; can continue doing this if breakthrough seizures, increasing duration of anesthesia each time

Outline

- Diagnosing a seizure
- Classifying seizures
- Anti-seizure medications
- New medications
- Other treatment modalities
- Status epilepticus
- **Epilepsy counseling**
- Regional VA EEG/Epilepsy resources

Counseling Patients

- Seizure precautions
 - Water safety, heights, heavy machinery
 - Childcare safety
- Driving
 - DMV
- Women with epilepsy
 - Folate, bone health, endogenous and exogenous hormone effects
 - Pregnancy: 6 months advance notice!
 - >90% have normal babies

Counseling Patients

- Prognosis:
 - Generally speaking...
 - 2/3 of epilepsy is easily controlled
 - 1/3 of epilepsy is refractory: refer
 - If you fail 2 medications, you're more likely to fail a 3rd one. And a 4th one. Etc.
 - Psychiatric comorbidity
 - Long term cognitive effects
 - Sudden unexpected death in epilepsy (SUDEP)

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Regional VA EEG/Epilepsy resources



Regional VA EEG/Epilepsy resources

- Portland VA Epilepsy Center of Excellence
- Puget Sound VA Epilepsy Center of Excellence
 - Subspecialty epilepsy care
 - Routine and sleep-deprived EEGs
 - 24-hour ambulatory EEGs
 - Inpatient video EEG monitoring
 - Neuropsychological testing
 - Neuroimaging: MRI, PET, SPECT
 - Vagus nerve stimulator (VNS) services
 - Intracranial EEG monitoring (e.g., subdural grids)
 - Epilepsy surgery

Telehealth Services

- Portland:
 - E-Consults
 - Telehealth at Roseburg, OR VA
 - Telehealth at Boise, ID VA
 - Tele-EEG at Boise, ID VA
 - Telephone visits
- Seattle:
 - E-consults
 - Telehealth at Walla Walla, WA VA
 - Telehealth at Yakima CBOC (coming soon)

Summary

- Seizure identification and classification is essential for management.
- After age 10, most new epilepsy cases are focal/partial epilepsy.
- If seizure/epilepsy type is unknown, start with a broad-spectrum medication. (e.g., Keppra, Lamictal)

Summary

- When choosing a seizure medication, take into account:
 - Epilepsy type
 - Side effect profile
 - Drug interactions
- Monotherapy is best. Maximize one medication before starting a second one.
- If a patient is well-controlled on an older medication, assess long term effects, consider switch.

Summary

- Refractory epilepsy: failure of 2+ drugs
 - Refer to a neurologist
- Within the VA system, feel free to enter an E-consult or refer your patient to an ECoE
- Goal: No seizures, no side effects!

References

- UpToDate
- Handbook of Epilepsy, Browne et al., 4th ed.
- AAN Continuum: Epilepsy, 2010
- Epilepsy.com
- Epilepsyfoundation.org
- International League Against Epilepsy (ILAE)
- Others, as documented on the slides

Acknowledgements

- Paul Motika, MD

Thanks for listening!
