Neurology Updates for the PCP:

Seizure Medications
(and other therapies)

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April 4, 2014
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

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- Outdated terms: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”
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

![Timeline of modern anti-seizure treatment](image)

Slides courtesy of Paul Motika, MD
Timeline of modern anti-seizure treatment

<table>
<thead>
<tr>
<th>Year</th>
<th>Medication</th>
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<tr>
<td>1850s</td>
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<tr>
<td>2012</td>
<td>Rufinamide</td>
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<tr>
<td>2013</td>
<td>Lacosamide</td>
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How can we organize the AEDs?

<table>
<thead>
<tr>
<th>Category</th>
<th>GABA Receptor Agonist</th>
<th>GABA Receptor Inhibitor</th>
<th>Sodium Channel Blocker</th>
<th>Potassium Channel Opener</th>
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</table>

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**

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<thead>
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<th>Enzyme Inducer</th>
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<td>Primidone</td>
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<td>Evening primrose</td>
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<td>Phenobarbital</td>
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- 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/epilepsy-newsletter/july10_surgery]

Other Treatment Modalities

• Vagus nerve stimulator (VNS):

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

Other Treatment Modalities

• Responsive neurostimulation device (RNS) NeuroPace:

[Image from: http://www.nature.com/nrneurol/journal/v4/n4/fig_tab/ncpneuro0750_F3.html]
Other Treatment Modalities

- Responsive neurostimulation device (RNS) NeuroPace:

Outline

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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
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

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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!