

Updates in Seizures and Epilepsy for the Primary Care Physician

Adam Lipschultz, MD
Assistant Professor
Department of Neurology
University of Minnesota Medical School

Kirby Clark, MD
Assistant Professor
Department of Family Medicine and
Community Health
University of Minnesota Medical School

Disclosures

None

No Consulting fees, no off-label uses of medications, no relationships with ineligible companies



Patient 1

32 y.o. Woman presents to clinic 4 weeks after a hospitalization where she was diagnosed with a generalized tonic clonic seizure (GTC, “Grand Mal”). She has an alcohol use disorder and has been trying to reduce her alcohol intake leading up to starting a new job. On her first day at work she was found on the floor with generalized convulsions and brought to the ED.

She remembers going into work that morning, has a memory lapse and woke in the ED. She describes another seizure in her 20’s associated with alcohol withdrawal and a head injury.

She denies seizures in childhood, a family history of seizures, or any seizures outside of alcohol withdrawal. When she was 25 she had a fall that led to an intracranial hemorrhage and required hospitalization, though no neurosurgical intervention.

Questions: Further workup? Does she have epilepsy? Should you start seizure medications?



What is the Difference Between a Seizure and Epilepsy?

Seizure

- A sudden, uncontrolled burst of electrical activity in the brain
- Can be a single occurrence



What is the Difference Between a Seizure and Epilepsy?

Epilepsy

- Neurological disease with increased risk of developing seizures compared to the general population.
- Diagnostic criteria- at least one of the following:
 1. At least two unprovoked seizures occurring more than 24 hours apart
 2. Diagnosis of an epilepsy syndrome
 3. One unprovoked seizure when the risk of further seizures over the next 10 years is ~60% or greater



Family Physicians Will Encounter Seizure

“It is very common for patients with an unprovoked first time seizure to be seen by a primary care physician or internist; or referred back to a primary care physician if they first present to the Emergency Department.”

-American College of Physicians (ACP Internist Journal)



First Time Seizure Workup - History

- Semiology
 - 3 Phases:
 - Pre-seizure (pre-ictal / prodrome)
 - Seizure (ictal)
 - Post-seizure (post-ictal)
- Duration
 - Status epilepticus?
- Provoked v.s. Unprovoked?
 - Look at all data: History + Exam + Lab + Imaging



First Time Seizure Workup - History

MUST ASK:

- TBI?
- Stroke?
- Brain tumor?
- Febrile seizures (in childhood)?
- Meningitis / Encephalitis?
- Family history?
- Prior personal history of seizure?



First Time Seizure Workup - History

Lowered Seizure Threshold Questions:

- Sleep patterns
- Caffeine use
- Alcohol/benzo use
- Hydration status
- Stress
- Recent changes in medications
- Recreational drug use



First Time Seizure Workup

- Exam:
 - Eyes
 - Tongue
 - Assess for focal neurologic deficits
 - Musculoskeletal: general injuries? Dislocations?
- Imaging / Procedures
 - **MRI Brain** with and without contrast
 - *In pediatrics, brain imaging only needed if there is head trauma, focal neurologic deficits, or history of malignancy
 - **EEG**
- Management
 - **+/- Anti-seizure medications**
 - Truly a first time seizure?
- Counseling
 - No driving for 3 months - state specific



Basic Seizure Types

- Focal
 - Focal onset with secondary generalization
 - Focal seizure with preserved or impaired consciousness
 - More frequent in the adult/ elderly population that has a prior stroke, tumor, resection cavity, etc.
- Generalized
 - Always associated with impaired consciousness
 - Examples: “Grand mal”, Pediatric Absence, Provoked seizure from alcohol intoxication



Primary Generalized Epilepsies

Childhood Absence Epilepsy

- 1 in 1000, onset ages 4-10
- Manifestation: Staring blankly, immediate return to baseline. May have automatisms
- Often misdiagnosed in school as ADHD
- ~90% of patients “grow out of it”

Juvenile Myoclonic Epilepsy

- 0.4 in 1000, onset age 12-18, though diagnosis can be delayed
- Manifestations: myoclonic jerks, GTC, absence
- Triggered by sleep deprivation, alcohol use
- Majority of patients can be controlled on medications, needed lifelong in 80% of pts.

Epilepsy with generalized tonic clonic seizures alone

- Onset age 5-41
- Manifestation is only GTC
- Seizures common upon waking (sleep transition as a trigger is a common in many epilepsies)



Pediatric Febrile Seizures

- Occurs in children 6 months - 5 years, must be associated with fever
- Larger fluctuations in temperature are more likely to lead to seizure
- If classified as “Simple” and without deficit, no further workup is indicated
- Complex febrile seizure:
 - Lasts over 15 minutes, or associated with focal neurologic deficits, resolves within 24 hours
 - Benzodiazepines are indicated for seizures over 5 minutes
 - Further workup is guided by the examination
- These children are likely to have more febrile seizures
- Antiepileptic medications are NOT recommended



Provoked Seizures in Adults

Inciting Factors on Chart Review and History Gathering:

- Alcohol/benzodiazepine withdrawal, amphetamine use disorder
- Acute head injury
- Hyponatremia (is there a threshold?)



Epilepsy in Adults

- Bimodal age distribution
- Adult onset epilepsy is more likely to be focal/ localization related epilepsy from a structural lesion
- Comorbid conditions, and bi-directional comorbidity:
 - 33% of patients with epilepsy have a comorbid psychiatric disorder
 - Risk of depression is 2.7 times the general population
 - Among patients with depression, epilepsy risk is 2.5 X higher
 - Among patients with schizophrenia, epilepsy risk is 2-3 X higher



Return to Patient 1

- Pertinent history
 - 2 lifetime seizures, both in the context of alcohol withdrawal
 - No aura or any type of prodrome
 - Postictal state lasts at least 4 hours
 - No childhood seizures or pertinent family history
 - History of traumatic intracranial bleed
 - Workup: Head CT (MRI), treatment of alcohol withdrawal, outpatient EEG
- Were these seizures provoked by alcohol withdrawal? Is there a cortical lesion from the past injury?



Patient 1 (cont.)

- 2 seizures plus an abnormal head CT
- Is the seizure risk >60% over 10 years?
- EEG showed no seizure, but rare epileptiform discharges arising from the right temporal lobe
- Yes, would diagnose as epilepsy and treat with antiepileptics



Medical Treatment

- $\frac{2}{3}$ of patients will be controlled on one medication
- Upward titration is usually required, so I inform patients of this trial-and-error to find the lowest effective dose
- Maximize one antiepileptic before adding a second medication
- Levetiracetam (Keppra) is usually prescribed up to 2000 mg twice daily
- Lacosamide (Vimpat) usually prescribed up to 200 mg twice daily



Family Physician PEARL -

The effect of additional seizure control diminishes with each successive AED regimen tried

- **1st Antiepileptic Drug (AED) 50 - 60% seizure control**
- 2nd AED provided an additional 11.6%
- 3rd AED additional 4.1%
- 4th AED onwards = additional 1% or less probability of seizure freedom



Drug Levels, What Are They Good For?

- Is the patient taking the medication, yes or no
- Is the patient toxic? In the case of encephalopathy, imbalance, nystagmus
- Levels are therapeutic or mildly supratherapeutic without side effects
 - Levetiracetam, lacosamide, zonisamide ***
- Exceptions- Depakote and phenytoin have well established upper limits of normal, with side effects expected at higher levels
- Does the timing of dose/blood draw matter?
- Pregnancy- will discuss later in this presentation



Non-Pharmacologic Treatments for Epilepsy

- Vagal Nerve Stimulation (VNS)
- Surgical Resection
- Responsive Neurostimulation (RNS)
- Ketogenic Diet
 - Used relatively rarely in cases of intractable epilepsy where the patient's dietary intake is usually under strict control (feeding tube, inability to feed oneself)



Monitor for any breakthrough seizures or other events that could lead to loss of bodily control (syncope, psychogenic spells, etc)

PHYSICIAN MUST COMPLETE THIS SECTION

Note to Reporting Physician: Your report is advisory. Driver and Vehicle Services is responsible for determining eligibility to drive. In accordance with the provision of Minn. Stat. 171.131, a physician is immune from liability as a result of reporting to DVS any physical or mental condition that significantly impairs a person's ability to safely operate a motor vehicle.

1. Number of examinations given (or) length of time under my care: _____
2. Diagnosis: _____ Date of first episode (mm/dd/yy) _____
3. Is the patient cooperating with treatment? Yes No
Long-term prognosis _____
Short-term prognosis _____
4. Is the patient qualified, in all medical respects, to exercise reasonable and proper control over a motor vehicle? Yes No
5. The patient should be required to submit this form every: (*check one*) 4 years 3 years 2 years 1 year 6 months

NOTE: A 6-month or 1-year review is required until episode-free for four years on medication. Leaving this question blank results in a 4-year review, if eligible.

X _____ Date (mm/dd/yy) _____
Signature of Medical Physician

Printed name: _____ **Phone:** (INCLUDE AREA CODE) _____

Address: _____



EEG Report - 3 Reads to Know

- Generalized slowing
 - Medications
 - Toxic metabolic encephalopathy
 - If focal - concern for structural lesion
- Epileptiform discharges - “spike and wave”
 - Increased risk of seizures
 - Epileptiform discharge(s) + clinical history of seizure -> I treat as epilepsy
- Seizure
 - “Generalized spike and wave complexes “consistent with seizure”
 - Electrographic seizure



AAN and AES Guidelines, Seizure Management

- Chance for recurrent seizure is greatest within the first 2 years (level A)
- Patients with a history of stroke, brain trauma, or EEG with epileptiform abnormalities are at increased risk for seizure recurrence (level A)
- Immediate AED therapy reduces the seizure recurrence risk in the first 2 years, though early treatment is unlikely to improve prognosis for sustained seizure remission at 3 years and beyond (level B)
- Risk of treatment with AEDs are predominantly mild and reversible (level B)



Epilepsy in Women

- 1.5 million American women of childbearing age with epilepsy
- Catamenial epilepsy- seizures corresponding to menstrual cycle
 - Reported in 33% of women with epilepsy
 - Estrogens are pro-convulsants, progesterone is anti-convulsive
 - Seizure risk is 4.5 x greater in women using hormonal contraception
 - Greater incidence of reproductive disorders in women with epilepsy (PCOS, infertility, menstrual disorders)



Epilepsy and Contraception

- Enzyme inducing AEDs can lead to contraception failure (carbamazepine, phenytoin, oxcarbazepine, eslicarbazepine
 - Non-hormonal (copper) IUD is more efficacious
- Preferred AEDs without contraception interaction:
 - Levetiracetam (Keppra), Zonisamide (Zonegran), Lacosamide (Vimpat)



Pregnancy and Perinatal Counseling

- Increased seizure frequency in 20-35% of pregnancies in women with epilepsy
 - Higher estrogen to progesterone ratio (weeks 8-16)
 - Sleep deprivation
 - (Self) Discontinuation of AED to prevent exposure to the fetus
 - Reduced AED serum concentration
 - Lamotrigine clearance in particular is 2-3 times higher
- **AAN Practice guideline: Check AED level at baseline and monthly throughout pregnancy**

Chen YH, Chiou HY, Lin HC, Lin HL. Affect of seizures during gestation on pregnancy outcomes in women with epilepsy. Arch Neurol 2009;66(8):979–984



Pregnancy and Perinatal Counseling

- **Preventing seizures during pregnancy is a top priority!**
- **Seizures during pregnancy are associated with increased risk of adverse outcomes**
 - Preterm delivery
 - Small for gestational age (SGA)

Chen YH, Chiou HY, Lin HC, Lin HL. Affect of seizures during gestation on pregnancy outcomes in women with epilepsy. Arch Neurol 2009;66(8):979–984



Risk of Congenital Malformation

- No AEDs 1.6%
- **Valproic acid 10.3%**
- Topiramate 3.9%
- Lamotrigine 2.1%
- Levetiracetam 2.8%
- Lamotrigine 2.9%
- Zonisamide 1.5%

Tomson T, Battino D, Perucca E. Teratogenicity of antiepileptic drugs. *Curr Opin Neurol* 2019;32(2):246–252.



Folic Acid Supplementation

- Guidelines recommend additional folate, though dose is not established
 - 0.4 mg- 5 mg daily starting 3 months before conceiving
 - Children of women with epilepsy who supplemented with folic acid had a higher IQ and lower risk of autism

Bjørk M, Riedel B, Spigset O. Association of folic acid supplementation during pregnancy with the risk of autistic traits in children exposed to antiepileptic drugs in utero. *JAMA Neurol* 2018;75(2):160–168

Meador KJ, Baker GA, Browning N. Fetal antiepileptic drug exposure and cognitive outcomes at age 6 years (NEAD study): a prospective observational study. *Lancet Neurol* 2013;12(3):244–252



Postpartum Care and Breastfeeding

- AED levels will rise, dose adjustments required over the next 3 days- 8 weeks
- With anticipated sleep deprivation, it is reasonable to aim for higher levels than prenatal
- 49% of AEDs are below the limit of detection in breast milk
 - Oxcarbazepine 0.3% of mother's serum in breast milk
 - Zonisamide 44% of mother's serum in breast milk

Pennell PB, Hovinga CA. Antiepileptic drug therapy in pregnancy I: gestation-induced effects on AED pharmacokinetics. *Int Rev Neurobiol* 2008;83:227–240

Birnbaum AK, Meador KJ, Karanam A. Antiepileptic drug exposure in infants of breastfeeding mothers with epilepsy. *JAMA Neurol* 2020;77(4):441–45



Eclampsia – Preeclampsia

- Seizures as a constellation of eclampsia
- Generalized tonic Clonic (GTC)
- Magnesium prophylaxis for preeclampsia/gestational hypertension with severe features
- Magnesium to treat eclamptic seizures
- 20% occur postpartum



Magnesium Seizure Prophylaxis

- Management for preeclampsia with severe features:
- Magnesium sulfate loading dose 4 to 6 grams over 15-20 minutes
- Followed by continuous infusion, 1-2 g/ hr
- Monitor mental status, respiratory status, urine output, reflexes
- Patients with normal renal function do not require routing serum Mg levels (therapeutic range 4 to 8 mg/dL)
- Check Mg levels Q6 hours if decreased renal function, decreased UOP, decreased reflexes
- STOP Mg for resp rate <12, or loss of DTR
- Antidote: 1 gram calcium gluconate IV over 2 minutes



Eclampsia - Seizure Management

- Protect airway, avoid injury
- Magnesium sulfate loading dose 4 to 6 grams over 15-20 minutes
- For patients who already received prophylactic loading dose, an ADDITIONAL 2 to 4g bolus should be administered
 - Other medications not beneficial
 - Maybe Lorazepam 2-4 mg IV for seizures lasting greater than 5 minutes
- Neurology follow up for persistent seizures or deficits, otherwise not indicated



Seizure Mimics

- Commonly occurring, frequently misinterpreted
- Syncope
- Orthostatic hypotension
- Convulsive syncope
- Psychogenic spells, convulsive or otherwise



Psychogenic Non-Epileptic Seizures/ Spells (PNES)

- Confirmatory Testing- video EEG, usually in epilepsy monitoring unit
- Can co-exist with epilepsy
- Increasing doses of antiepileptic medications not helpful
- Type of conversion disorder
- Treatment includes psychological counseling, cognitive behavioral therapy



Thank you!

Questions?

