Pediatric Epilepsy and Seizure Management:

A Primary Care Perspective

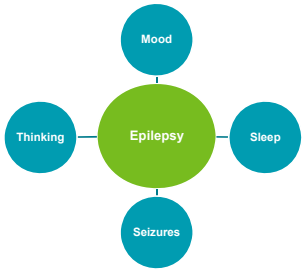
Disclosures

- Eisai Speakers Bureau
- No other disclosures

Objectives

- Describe the general characteristics of epilepsy, seizures, and non-epileptic seizures
- Discuss treatment and side effect management of antiepileptic medications, diet, and surgical options
- Describe psychosocial aspects of epilepsy care, including stigma, learning issues, and driving

Epilepsy is More Than Seizures



Comorbidities

- ADHD: 30-40% people with epilepsy
  - If don't meet criteria, many still have inattention and executive function deficits
- Depression symptoms: 25%
- Suicidal ideation: 20%
- Anxiety symptoms: 30%

- Smith, Plueger, and Wagner, 2019

Seizure

- Dysfunction of the brain involving paroxysmal and disorderly depolarization of neurons and spread of the resulting neuronal discharge through brain tissue
- A sudden surge of electrical activity on the surface of the brain

- https://www.epilepsy.com/learn/about-epilepsy-basics/what-seizure, accessed 8/5/19

Epilepsy

- A variety of disorders characterized by chronic recurrent seizures of **central nervous system** origin
  - Imbalance between cerebral excitation and inhibition
    - Excitation: Glutamate, AMPA, kainate, NMDA
    - Inhibition: GABA

Epilepsy Syndrome

- A collection of signs and symptoms that are grouped together:
  - Type of seizure
  - Age of onset
  - Presence or absence of other neurological problems
  - Characteristic EEG findings
  - Etiology
  - Other associated clinical features

Seizure and Epilepsy Relationship

- **Single** unprovoked seizure
  - **30%** chance of a second seizure
    - **3-10%** provoked; **30-50%** unprovoked
- **Second** unprovoked seizure
  - Nearly **100%** chance of another
- Usually (not always) wait for second seizure before diagnosing epilepsy

- Camfield, P., and Camfield, C. (1993). J of Pediatrics
- Bernd, Camfield,C and Camfield, P (2004) BMJ

Epilepsy Prevalence

- **10%** of people experience at least one seizure in their lifetime
- Approximately **1-4%** (1 in 26) of people develop epilepsy
- In United States, 3.4 million people have active epilepsy (2017); 64 million worldwide
- 400,000 U.S. children develop epilepsy yearly

- MMWR Morb Mortal Wkly Rep. 2017;66(31):821-25

Seizure Control: New Onset

- First year after diagnosis
  - 50-60% seizure free with first medicine
  - Additional 11-20% seizure free with second medicine
  - 25% adults develop uncontrolled epilepsy
- Children
  - New onset, **74% seizure free** within 2 years
  - Uncontrolled epilepsy in 9%

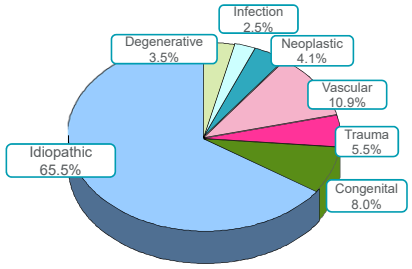
- Kwan and Brody, 2001; Begley et al., 2000; Del Felice et al. 2010

Seizure Control: Overall

- 60-70% may get control of seizures after several years
- 30% at any given time may be having seizures
  - Unsure if complete control
  - No data on side effects

- Fisher et al., 2000, Epilepsy Research

Epilepsy Etiology



Hauser, 1992. Epilepsia 33 (suppl. 4), S6-S14.

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Outgrowing Epilepsy

- **70%** patients outgrow their epilepsy
- **Two year seizure free period**
- EEG findings at two year seizure free interval help with decision to wean medicine
- Specific epilepsy syndrome can affect decision (JME)

- Camfield, P. & Camfield C. (1993). J of Pediatrics

Cincinnati Children's

CLASSIFICATION

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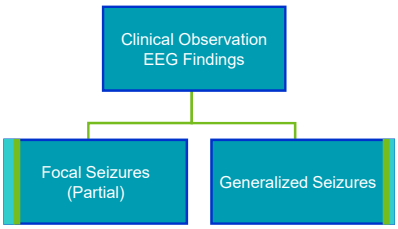
Classification Background

- **Common language** aids communication
  - Epilepsy care providers
  - Epilepsy research
  - People with epilepsy (PWE)
- **Guides** testing, treatment, and prognosis
  - Medications designed for specific types of seizures

Classification Evolution

- Seizure **appearance**
  - Grand mal, petit mal
- **All** brain vs. **part** of brain
  - Partial, generalized
- **Networks**
  - Focal seizures in localization-related epilepsy
  - Aspirational

International League Against Epilepsy (ILAE)



Focal Seizures

- Symptom of **localization-related** epilepsy
- Also known as partial seizures
- Usually impairment of consciousness
- Most common type of seizure in both children and adults

Focal Seizure Appearance

- **Varies** with location of seizure focus
  - Motor Onset
    - Automatisms
    - Tonic, clonic, atonic, myoclonic
  - Nonmotor Onset
    - Autonomic
    - Behavior arrest
    - Emotional, cognitive, sensory

Generalized Epilepsy

- Seizure crosses **both hemispheres** of the brain
- More commonly found in pediatrics than adults
  - No identifiable reason
  - Normal development
  - Relatively self-limited
  - Responsive to medication
  - Genetic predisposition

Generalized Seizures

- **Absence:** stares,≤ 30 sec, may see eye blinks or flutters
- **Myoclonic:** single jerk, usually extremities
- **Clonic:** rhythmic jerks
- **Tonic:** stiffening (increased tone), often with falls
- **Tonic-clonic (GTC):** stiff, then rhythmic jerks
- **Atonic:** " drop attacks" loss of tone, often with falls
  - Causes the most injuries

Other Categories

- Unknown
  - Onset of seizure cannot be determined
- Unclassified
  - Inadequate information
  - Inability to place in other category

THE WORKUP

Seizure Workup

- **History**
  - event, personal, family
  - Exact description, especially start of seizure
    - Duration, repetitive motor movements, triggers
    - Any premonitions (focal seizure)
  - Alteration of awareness
  - Stereotypical?
  - Confusion, tiredness after event?

Diagnose the Seizure

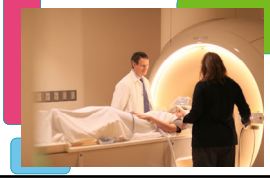
- Focal vs. Generalized
  - Physical exam
  - Neurological exam
  - EEG
  - Imaging (MRI)
  - Referral if needed (cardiology, sleep, psychiatry)
  - Goal setting with patient
  - Treatment plan

Electroencephalogram (EEG)

- Hyperventilation
- Photic stimulation
- Sleep deprivation ?
- **Confirms**, not diagnostic

Imaging Studies (MRI)

- MRI with "seizure protocol"
  - May find likely cause (brain bleed, dysplasic lesions, errors in brain development (e.g., heterotopias)
  - Focus on areas prone to seizures (surface of brain)



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Pathways in Diagnosis

- Epilepsy: **Two** unprovoked seizures >24 hours apart and/or EEG evidence
- **Single** seizure
  - Prescribe rescue medicine
  - Return if second seizure
- Unsure/normal EEG
  - Further workup
    - Video EEG
    - Neuropsych testing

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PSYCHOGENIC NON-EPILEPTIC SEIZURES (PNES)

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Differential: Paroxysmal Episodes

- **Organic** causes
  - Migraine
  - Syncope
  - Transient ischemic attacks (TIA)
  - Tics
  - Cardiac arrhythmias
- **Psychogenic** causes
  - **PNES**

Psychogenic Nonepileptic Seizures (PNES)

- Psychogenic illness common to all medical specialties
- Manifestation of psychological distress
- **True** disorder
  - Probable conversion reaction
  - Females at higher risk than males
- Normal EEG

- Benabis, S.R. (2004). Epilepsy and Behavior

PNES

- Diagnosed in 20-30% of patients referred to epilepsy centers with refractory epilepsy
  - Can be in patients with epilepsy
  - Can be only manifestation (non-epilepsy)

- General population prevalence
  - 2-33/100,000
  - Benbadis, 2018, Medscape

PNES Event Features

- Seizure differences
  - Pelvic thrusting
  - Head shaking
  - Crying
  - Asynchronized convulsive activity
  - Absent post-ictal confusion, tiredness
  - EEG is **gold standard** to diagnose
- Correct approach with families is **critical**!

Differential

- **Conversion**
  - Somatic symptom disorder
    - Common to other disease states
- **Malingering**
  - Reason for deception is tangible
  - Reason is rationally understandable
  - Not a mental illness
- **Factitious**
  - Pathologic need for sick role

- Benbadis, 2018, Medscape

Family Approach

- Great news…it isn't epilepsy
- The spells/events are **real**
- Guide family into recognition the body is converting stress into physical symptoms
- Risk is family won't accept and go elsewhere for same issue
- Meds don't help with PNES!

Terminology Matters

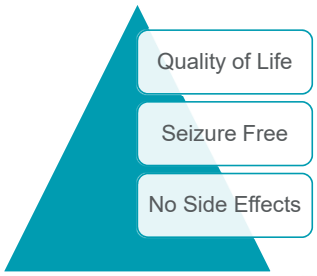
- Former names
  - Pseudoseizures
  - Nonepileptic seizures
  - Nonepileptic events
  - Psychogenic seizures
- May want to use terms like “attacks” or “events” rather than seizure

TREATMENT OPTIONS

Seizure Treatment

- Antiepileptic drugs (AEDs)
- Surgery
  - Neurostimulation
- Ketogenic diet

Goals of Therapy



First Line Therapy: AEDs

- Seizure classification
- Guidelines
- Randomized double blind controlled studies for best evidence
- Mechanisms of Action (MOA) of drugs
  - Basis for rational polypharmacy
- Side effect profiles
- Dosing frequency
- Cost

FDA Extrapolation Pathway

- Monotherapy indication for **focal** (partial) onset epilepsy
  - September 2016 General Advice letter to drug manufacturers
    - "**Acceptable to extrapolate the efficacy and safety**"… of previously approved adjunctive therapy meds
    - Analysis of monotherapy and adjunctive therapy drugs show similar side effects, dosing range
    - **Pellock, 2017, Epilepsia**

Extrapolation Implications

- Will see more monotherapy indications listed over next few years
- Not likely to see for AEDs past patent life
- Not for generalized onset seizures

AED Mechanisms of Action

- Sodium channel
- Calcium channel
- GABAergic
- Glutamate
- Carbonic anhydrase inhibitors
- Unknown/hormones

General AED Dosing Guidelines

- Start low, go slow
- For **first** antiepileptic drug
  - Titrate to toxicity
  - If ineffective
    - Titrate second drug
    - Wean first drug
- **Two drugs is limit**
  - Surgical evaluation

Monotherapy

- Preferred option
  - Easier to use
  - May improve **adherence**
  - Decreases costs
  - Reduces drug-drug interaction risk
  - Decreases potential side effects

AED Selection: Comorbidities

- Migraine
  - valproate, topiramate, gabapentin
- Obesity
  - zonisamide, topiramate, felbamate
- Affective disorder
  - valproate, lamotrigine, oxcarbazepine, topiramate, carbamazepine
- Oncology, Immunotherapy, HIV+
  - Avoid enzyme-inducing AEDs
    - Phenobarb, phenytoin, carbamazepine

AED Selection: Properties

- **Inducers:** drugs that increase (induce) the metabolism of other drugs (phenytoin, carbamazepine, oxcarbamazepine)
- **Inhibitors:** drugs that decrease metabolism of other drugs (e.g., valproic acid, felbatol)
- **Implications:**
  - drug-drug interactions common
  - Titration takes time

AED Efficacy

- **Effectiveness**
  - How well an AED **stops seizures**
  - Effectiveness is the same across all AEDs
- **Side effects**
  - How significant the side effects are
  - Side effects **lessened** the newer the drug is
    - Less likely to need levels

AED Suicide Risk: Class Effect

- FDA meta analysis
  - 199 placebo-controlled trials
  - 44,000 patients
  - Effect noted with 11 AEDs ➡ class effect
    - **0.43%** on AEDs had suicidal thoughts
    - **0.24%** on placebo had suicidal thoughts
- Important: screen for depression
- **FDA alert: 2008**

Over 25 AEDs on the Market

- **Oldest**
  - Phenobarbital 1912
  - Phenytoin 1938
  - Primidone 1954
  - Ethosuximide 1958
- **Last Quarter 20th Century**
  - Carbamazepine 1974
  - Valproic acid 1978
  - Felbatol 1993
  - Gabapentin 1993
  - Lamotrigine 1994
  - Topiramate 1996
  - Tiagabine 1997

Over 25 AEDs on the Market

- **2000s**
  - Oxcarbazepine 2000
  - Zonisamide 2000
  - Rufinamide 2008
  - Lacosamide 2008
  - Vigabatrin 2009
- **Current decade**
  - Clobazam 2011
  - Ezogabine 2011
  - Perampanel 2012
  - Eslicarbazepine 2013
  - Brivaracetam 2016
  - Retigabine 2017
  - **EPIDIOLEX** 2018

Medication (AED) Safety

- Drug naïve patients just starting therapy and those on multiple AEDs more likely to have side effects
  - Detailed, **updated medication history** critical
    - Especially with ED visits, admissions
  - If **CNS** side effects present
    - **Manage fall risk** if dizziness, ataxia, unsteadiness are side effects

AED Side Effects

- Effectiveness is similar among all AEDs
- Types of side effects
  - **Common**
    - Dose-**dependent**
    - Often CNS or GI systems
  - **Chronic**
    - **Delayed** presentation
    - Years of exposure
  - **Idiosyncratic**
    - Unpredictable
    - Dose-**independent**

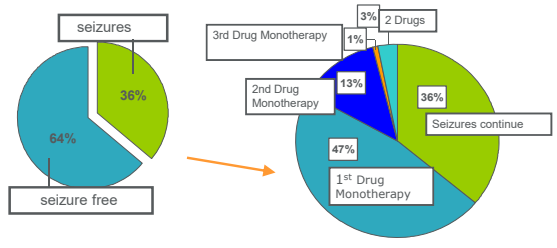
Common Side Effects

- **Central Nervous System**
  - Tiredness
  - Sleepiness
  - Dizziness/gait issues
  - Slowed processing speed
  - Irritability
  - Memory impairment
  - Insomnia
- **Gastrointestinal System**
  - Nausea
  - Vomiting
  - Constipation
  - Stomach upset

Chronic and Idiopathic Side Effects

- **Chronic**
  - Weight gain
  - Bone loss
  - Hirsuitism
  - Facies change
  - Vitamin deficiencies
  - Acne
  - Libido loss
- **Idiosyncratic**
  - Rash (Stevens-Johnson Syndrome)
  - Blood disorders (aplastic anemia)
  - Liver failure
  - Psychosis
  - Depression

Response to AED Therapy



Kwan P. & Brodie, M.J., (2000). NEJM 342, 314-319.

Epilepsy Surgery Workup

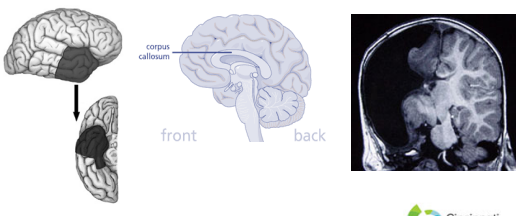
- Evaluate need after **two trials** of appropriately selected AED
- Epilepsy Monitoring Unit admission
- Phase I or Phase II pre-surgical evaluations

Epilepsy Surgery

- Resective (-ectomy)
  - Hemispherectomy
  - Lobectomy
  - Corticoectomy
  - Lesionectomy
- Disconnective (-otomy)
  - Hemispherotomy
  - Corpus Callosotomy
  - Multiple subpial transections

Surgical examples

Lobectomy | **Corpus Callosotomy** | **Hemispherectomy**



Neurostimulation

- VNS
  - Vagal Nerve Stimulation
- RNS
  - Responsive Neuro Stimulation
- DBS
  - Deep Brain Stimulation

Vagal Nerve Stimulator (VNS)

- Electrical impulses through left vagus nerve
  - 80% efferent
- Local, not systemic, side effects
  - Cough, hoarseness
  - Usually temporary
- Unknown mechanism of action
- Takes extended time to assess efficacy
- https://www.epilepsy.com/learn/treating-seizures-and-epilepsy/surgery/types-epilepsy-surgery#MST

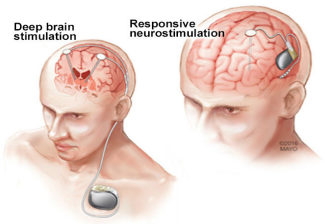
Vagus Nerve Stimulator

RNS vs. DBS

- RNS
  - Approved 2013
  - Adults 18+ years
  - Device in bone
  - Pacemaker-like
    - Monitors brain waves
    - Detects seizures
    - Provides stimulation
- DBS
  - Approved 2018
  - Adults 18+ years
  - Device in chest
  - Pacemaker-like
    - Delivers regular stimulation

- https://www.epilepsy.com/learn/treating-seizures-and-epilepsy/surgery/types-epilepsy-surgery#MST

Deep Brain Stimulation (DBS)



Ketogenic Diet

- **Background**: People with epilepsy during famine often have improved seizure control
- **Ketogenic diet**: high fat, moderate protein, low carb, in use since 1921
  - Acidosis may decrease neuronal excitability
  - Mimics fasting state
  - Butter, mayonnaise, heavy cream, oils
  - Calorie, protein carb restricted

Ketogenic Diet Efficacy

- Effectiveness
  - 50-60% children have seizure reduction
  - Up to 33% have 90% reduction
  - >10% seizure free
- Commitment
  - At least 3-6 month trial

Diet Side Effects

- Abdominal pain
- Bone density loss
- Constipation
- Dehydration
- Diarrhea
- Hyperlipidemia
- Hypoglycemia
- Kidney stones
- Reflux

- Smith, Plueger, &Wagner, 2019

Ketogenic vs. Modified Adkins Diet (MAD)

- Ketogenic
  - Glut-1 or PDHD
  - Multiple daily seizures
  - Tube fed
  - Motivated caregivers
  - Likes keto foods
- MAD
  - Middle/high school or adult
  - Eats by mouth
  - Seizures mostly controlled on AEDs
  - Better tolerated!

PRIMARY CARE

APRN Priorities

- **Patient Education**
- Self-Management
- Comorbidity Assessment

- Smith, Plueger, Wagner, 2019, American Nurse Today

Patient Education: Disease

- Seizure first aid
- Epilepsy syndrome, if known
- Treatment side effects
  - When to call provider
- SUDEP: Sudden Unexplained Death in Epilepsy

Seizure First Aid

- **Focal** seizures
  - Supportive care until seizure ends
  - May be confused with behavior problems or drug use
- Generalized seizures
  - Stay calm
  - Time seizure
  - Call 911 if seizure lasts >5 minutes
  - Clear sharp objects from surroundings
  - Turn on side during and after seizure
  - Nothing in mouth

Seizure First Aid

Rescue Medications

- Diazepam (Diastat®)
  - Rectal gel
  - Administer after 5 minutes

Rescue Medications

- Midazolam (Versed)
  - Nasal administration
  - Administer after 5 minutes

Post Seizure Care

- Reorient patient
- Ask about premonitions (formerly aura)
- Assess for injuries
- Allow time to rest or sleep

SUDEP

- >1:1000 people with epilepsy die annually
  - >SIDS deaths/year
- Highest risk: uncontrolled epilepsy
- **Not** higher risk
  - Myoclonic
  - Absence
  - https://www.epilepsy.com/learn/early-death-and-sudep/sudep/sudep-faq
- Theories
  - Heart arrhythmia
  - Breathing
    - Apnea after seizure
    - Obstruction
  - Brain 'decoupling'
  - All of these
  - None of these

SUDEP: Risk and Mitigation

- Poor Adherence
- Young adult
  - 20-40 years
- Suddenly stopping medicines
- Cognitive impairment
  - IQ <70

- How to lower risk
  - Adherence
  - Consider surgery or diet if still seizing
  - Avoid triggers
  - Educate family and friends on first aid

- https://www.epilepsy.com/learn/early-death-and-sudep/sudep/sudep-faq

Patient Education: Life-based

- **Family**
  - Affects family dynamics
    - Vulnerable child
- **School**
  - Processing delays
  - Working memory issues
  - IEP, 504 plans
- **Driving**
  - State rules vary

- **Activities**
  - Camp, sleepovers, sports
- **Relationships**
  - Loss of independence
  - Social isolation
  - Mood issues
- **Work**
  - Disclosure?
  - Stress, **stigma**

Tristate Driving Rules

- Ohio
  - No report; no set seizure free period
- Kentucky
  - No report; **3 months** or more seizure free
- Indiana
  - No report: no set seizure free period

APRN Priorities

- Patient Education
- **Self-Management**
- Comorbidity Assessment

- Smith, Plueger, Wagner, 2019, American Nurse Today

Self Management

- Promote self- and family management
  - Improve quality of life
  - Improve health outcomes
  - Management
    - Treatment
    - Seizure
    - Lifestyle

  - Smith, Plueger, Wagner, 2019, American Nurse Today

Self Management Themes

- **Treatment** management
  - Medication schedules
  - Keep clinic appointments
  - Communication with health care providers
- **Seizure** management
  - Recognize/avoid triggers
  - Track seizures
  - Look for patterns

  - Smith, Plueger, Wagner, 2019, American Nurse Today

- **Lifestyle** management
  - Adequate sleep
  - Reduce stress
  - Maintain social connections

APRN Priorities

- Patient Education
- Self-Management
- **Comorbidity Assessment**

- Smith, Plueger, Wagner, 2019, American Nurse Today

Comorbidity Assessment

- Identify Comorbidities **before** treatment
  - Differentiate from AED side effects
- **Behavioral**
  - Inattention, depression, anxiety, **suicidal ideation**, neuropsychological findings
- **Physical**
  - Weakness, poor coordination, migraine, fertility, sleep
- **Social isolation**
  - Stigma (2nd only to HIV)

- Smith, Plueger, Wagner, 2019, American Nurse Today

Health Promotion Approach

- **Tier 1**: cognitive, behavioral health screen and self-management abilities
  - Refer to websites or local advocacy group
  - Refer to mental health professional if needed
- **Tier 2**: more comprehensive assessments for those at risk for self-management challenges
  - Refractory epilepsy
  - Behavioral health, neurodevelopmental, adherence issues

- Smith, Plueger, Wagner, 2019, American Nurse Today

Health Promotion Approach (cont'd)

- **Tier 3**: patients with known comorbid, neurodevelopmental, behavioral health issues or nonadherence
  - Refer for indicated services
  - Consider meds for ADHD, depression, anxiety
  - Consider psychological-based treatments
    - Skills-based
    - Emphasize coping, cognitive restructuring, problem-solving, mood-enhancing behaviors

- **Smith, Plueger, Wagner, 2019, American Nurse Today**

Resources

- American Academy of Pediatrics: national Coordinating Center for Epilepsy
  - aap.org/en-us/advocacy-and-policy/aap-health-initiatives/Coordinating-Center-on-Epilepsy/Pages/default.aspx
- Centers for Disease Control and Prevention-Epilepsy-- You Are Not Alone: Resource Guide
  - http://cdc.gov/epilepsy/toolkit/resource_guide.htm
- Epilepsy Foundation
  - epilepsy.com

Resources (cont'd)

- Managing Epilepsy Well Network
  - http://managingepilepsywell.org
- Epilepsy Alliance Ohio
  - www.epilepsy-ohio.org