21st Century
“Fits”

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Current Disclosures:
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Adult Neurology and Epilepsy

Speaker’s Bureau/Consultant: UCB, Inc.
[ Keppra ® (levetiracetam); Vimpat ® (lacosamide) ]
Overview

- History of Epilepsy
- Seizure and Epilepsy Classification
- Epilepsy Statistics and Risks
- Issues for Women with Epilepsy
- Diagnosis of Epilepsy
- Status Epilepticus
- Pharmacologic Treatment of Epilepsy
- Surgical Treatment of Epilepsy
A Brief History of Epilepsy

- c. 2000 BC – First written description of epilepsy on clay tablets in Babylon. Cause believed to be demons or spirits
- c. 400 BC – “On the Sacred Disease” written, attributed to Hippocrates. Cause believed to be blocked air flow in veins
- 177 AD – Galen delivers lecture “On the Brain” in Rome. Maintains that seizures are caused by pathologic humors or toxins
On the Sacred Disease

“It is thus with regard to the disease called Sacred: it appears to me to be nowise more divine nor more sacred than other diseases, but has a natural cause from which it originates like other afflictions. Men regard its nature and cause as divine from ignorance and wonder, because it is not at all like to other diseases.”
History of Epilepsy

Treatment of Epilepsy in the Middle Ages:

• Even when well intentioned, treatment was medieval

• Included early attempts at epilepsy surgery
History of Epilepsy

The Scientific Era

• 1849 – Robert Bentley Todd develops electrical theory of epilepsy
• Bromide introduced as first true antiepileptic
• 1870 – John Hughlings Jackson describes seizure origin in cerebral cortex
• 1886 - Sir Victor Horsley publishes series of 3 cases of successful (lucky!) brain surgery to relieve epilepsy
History of Epilepsy

20th Century Advances in Epilepsy

• 1912 – Phenobarbital (PB) introduced
• 1929 – Hans Berger develops EEG
• 1938 – Phenytoin (PHT) introduced
• 1950s – Temporal lobe resections for epilepsy
• 1970s – CT scanning becomes available
• 1974 – Carbamazepine (CBZ) approved
• 1978 – Valproic Acid (VPA) licensed in U.S.
• 1980s - MRI scanning becomes available
History of Epilepsy

At the Threshold of the New Millenium:

- 1993 – Felbamate (FBM) approved in US
- 1993 – Gabapentin (GPN) approved
- 1994 – Lamotrigine (LTG) approved
- 1996 – Topiramate (TPM) approved
- 1997 – Vagus nerve stimulation approved
- 1997 – Tiagabine (TGB) approved
- 1999 – Levetiracetam (LEV) approved
- 2000 – Oxcarbazepine (OXC) approved
- 2000 – Zonisamide (ZNS) approved
History of Epilepsy

The 21st Century Begins:

- 2005 - Pregabalin (PGB) approved in US
- 2008 - Rufinamide (RFN) approved
- 2009 - Lacosamide (LCS) approved
- 2009 – Vigabatrin (VGB) approved
- 2009 - NeuroPace® Trial published
- 2010 - Sante DBS Trial published
Seizure and Epilepsy Classification

- International League Against Epilepsy (ILAE) classification scheme
- Latest update 2009
- Older terminology e.g. “Grand Mal” is proving impossible to eradicate
Seizure Classification: ILAE Scheme

**Partial Seizures**
- Focal/local onset

**Generalized Seizures**
- Bilateral onset
International classification of seizures: Partial Onset

- Simple partial seizures: consciousness not impaired
- Complex partial seizures: with impairment of consciousness
- Partial seizures (simple or complex) evolving to secondarily generalized seizures
Seizure Classification: Complex Partial Seizures

- Altered consciousness/awareness
- Duration one half to three minutes

- May occur in clusters
- Semiology varies with site of origin
- EEG: Interictal- sharp waves or spikes; Ictal- focal or bilateral rhythmic sharp
- Amnesia
- Purposeless automatisms
- Especially when of mesial temporal lobe origin, often difficult to control
Seizure Classification: Secondarily Generalized Seizures

- Generalized tonic clonic seizure may be preceded by aura or automatisms
- Distinguishing from primary generalized seizures may help guide therapy
International classification of seizures: Generalized Seizures

- Nonconvulsive (absence) Typical (3/sec spike and slow wave complexes on EEG)
- Atypical (<3/sec spike and slow wave complexes on EEG)
- Convulsive Myoclonic seizures
- Clonic seizures
- Tonic seizures
- Tonic-clonic seizures
- Atonic ("drop attacks")
Seizure Classification: Generalized Tonic-Clonic Seizure

Generalized Tonic-Clonic (grand mal) Seizure
Seizure vs. Epilepsy

SEIZURE:
A sudden, excessive, rapid and local discharge of gray matter

J. Hughlings Jackson

EPILEPSY:
Recurrent unprovoked seizures

John Hughlings Jackson (1835–1911)
Epilepsy Classification

SEIZURES vs. the EPILEPSIES:

• A SEIZURE is a sign or symptom of cerebral paroxysmal discharge.

• The EPILEPSIES are syndromes or diseases characterized by a tendency to have recurrent seizures along with other clinical characteristics.
Epilepsy Classification:
MYOCLONIC EPILEPSY

• Onset childhood to young adulthood
• Sudden jerks, usually bilateral, arms>legs
• One second in duration, often multiple
• May be photic or sensory triggered
• Often maximal on awakening
• EEG: generalized polyspike-wave burst
JUVENILE MYOCLONIC EPILEPSY

- Most common myoclonic epilepsy, genes identified
- Clinical triad of
  - absence seizures (in one third)
  - AM myoclonic jerks (characteristic)
  - tonic-clonic seizures (in majority)
- Age of onset 8 to 26 years, peak at 12-18, persists life long
- Normal neurological state and development
- EEG shows generalized polyspike/wave bursts
- AEDs: valproic acid, lamotrigine, topiramate
ABSENCE EPILEPSY

- Childhood or teenage onset
- Sudden onset, without aura, prompt offset
- Momentary loss of consciousness, eyelid flutter

- 3-15 seconds duration
- Positive Family History
- EEG – 3 Hz spike/wave
- AEDs: ethosuximide, valproic acid, lamotrigine
Complex Partial Epilepsy

- Onset adolescence through adulthood
- Most often of temporal lobe origin
- Can be associated with progressive hippocampal scarring (mesial temporal sclerosis) and cognitive deficits
- AEDs: most any
Psychogenic Nonepileptic Seizures: PNES (older term “Pseudoseizures” is discouraged)
Psychogenic Non-Epileptic Seizures (PNES)

- Considered a conversion disorder
- Typically, patients are not consciously manufacturing symptoms
- 70% Female preponderance
- Accounts for up to 30% of referrals for refractory epilepsy at epilepsy centers
- Most have received AEDs, some have been intubated for presumed status epilepticus
PNES

- High incidence PTSD, hx childhood sexual abuse, other psychiatric comorbidities
- Video/EEG inpatient monitoring is highly sensitive and specific for diagnosis
- Clinical diagnosis of seizures may be misleading
- Caution is required, since many patients exhibit both epileptic seizures and PNES
- Psychiatric treatment is indicated but outcome is variable.
Epilepsy Statistics

• Epilepsy and seizures affect almost 3 million Americans of all ages, at an estimated annual cost of $15.5 billion in direct and indirect costs.
• Approximately 200,000 new cases of seizures and epilepsy occur each year.
• Ten percent of the American population will experience a seizure in their lifetime.
• Three percent will develop epilepsy by age 75.

Source: Epilepsy Foundation of America http://www.epilepsyfoundation.org
Epilepsy prevalence in special populations

- 10 percent of children with mental retardation
- 10 percent of children with cerebral palsy
- 50 percent of children with both disabilities
- 10 percent of Alzheimer patients
- 22 percent of stroke patients
- 8.7 percent of children of mothers with epilepsy
- 2.4 percent of children of fathers with epilepsy
- 33 percent of people who have had a single, unprovoked seizure
Risks of Epilepsy

- Injury from direct and indirect effects of seizures
- Sudden Unexpected Death in Epilepsy (“SUDEP”): varies with severity of epilepsy up to 10 deaths per 1000 patient-years
- Risks of treatment: reproductive and other
- Depression: Suicide risk 3 x control group in one study. FDA required warning placed on all AEDs


- Socioeconomic marginalization due to decreased employability and socialization
- Long term cognitive decline

Cognitive Decline in Severe Intractable Epilepsy Epilepsia 2005 ; 46 (11) 1780 - 1787

- Bone demineralization with long term AED use

Effect of antiepileptic drugs on bone density in ambulatory patients. Neurology 2002; 58:1348-1353
Epilepsy and Driving in Oregon

- New rules adopted state-wide June 2004 (ORS 807.710 and OAR 735-074)
- Requires physicians to report persons over 14 with “Severe and Uncontrollable Impairments” not limited to epilepsy – immunity from civil liability for doing so
- Seizure control for three months on therapy generally required for driving – duty to advise?
AED Long Term Side Effects

Bone Demineralization

• Older AEDs implicated, ?new AEDs also
• Multiple mechanisms, including:
  • Decreased vitamin D levels
  • Reduced calcium absorption
  • Hyperparathyroidism
  • Calcitonin deficiency
Bone Health Treatment Recommendations

- Screen with DEXA after 5 years of AEDs, at baseline in women before starting
- All patients should receive at least 1200 mg/day of calcium
- All patients should receive supplemental vitamin D, at least 400 IU/day – and check levels!
- If there is evidence of osteopenia, more aggressive treatment (biphosphonates, calcitonin)
Issues for Women with Epilepsy
Issues for Women with Epilepsy

• Estimated 500,000 women with epilepsy of childbearing age in US
• 3-5 births per thousand in US are to women with epilepsy
• Some AEDs have unique toxicities for women
• Significant interactions between AEDs and Oral Contraceptive Pills (OCPs)
Teratogenicity of AEDs

- All older AEDs are proven teratogens
- Valproic acid causes up to 10.7% risk of Major Congenital Malformations (MCM); persistently lower IQ in exposed children
- Polytherapy raises birth defect incidence
- Newer AEDs are category C; data is accumulating in AED pregnancy registries
North American AED Pregnancy Registry

- 7,242 women enrolled since 1997
- 1-888-233-2334
- www.aedpregnancyregistry.org
- Encourage all women on AEDs to call!
NA AED Pregnancy Registry:
% MCM on Monotherapy
NA AED Pregnancy Registry: % MCM on Polytherapy

- None
- CBZ+LTG
- CBZ+VPA
- LTG+VPA
NEAD Study of IQ at age 3 for children exposed in utero (p=0.009)
Recommendations for Women

- All women of childbearing potential taking AEDs should take 1mg/day folic acid
- Folic acid 4 mg/day if AED is valproic acid
- Avoid polypharmacy and VPA if possible
- Monitor pregnancy with ultrasonography at 11 and 16 weeks; check alpha fetoprotein
- Vitamin K 10 mg/day in last trimester to prevent newborn hemorrhagic disease
Issues for Women with Epilepsy

Special Risks of Valproic Acid - Polycystic Ovarian Syndrome:

- Affects 7% of all reproductive age women
- Excessive androgen sensitivity
- Signs include hirsutism, obesity, acne, alopecia and anovulatory menstrual cycles
- Metabolic findings include hyperinsulinemia, hyperlipidemia and glucose intolerance
- VPA therapy increases risk of developing metabolic abnormalities similar to PCOS
Recommendations for Women – AED Effect on Oral Contraceptives

No Effect on Low Estrogen OCPs:

- Gabapentin
- Pregabalin
- Lamotrigine (but OCP will lower levels)
- Levetiracetam
- Lacosamide
- Tiagabine
- Zonisamide

Estrogen <35 mcg May be Ineffective for Contraception:

- Barbiturates
- Carbamazepine
- Oxcarbazepine
- Phenytoin
- Topiramate
Diagnosis of Epilepsy
Diagnosis of Epilepsy

- Epileptic seizures or Non-epileptic spells?
- “Not everything that shakes is epilepsy”
- Careful history taking and direct eyewitness reports of events can make a diagnosis or guide further testing
- Try to get description (semiology) of event, not a lay diagnosis (e.g. “petit mal”)
Diagnosis of Epilepsy:
Consider other causes of spells

- Syncope (+/- convulsion): consider cardiac dysrythmia or neurocardiogenic syncope
- Cerebrovascular disease – “Limb Shaking TIA”
- Migraine
- Movement disorders
- Hypoxia, hypoglycemia, toxins/drugs
- Psychiatric (“Pseudoseizure” is now discouraged – prefer “Psychogenic Non-Epileptic Seizure”)

Diagnosis of Epilepsy - EEG

- Routine (interictal) EEG usually performed, sometimes helpful in guiding therapy
- Ambulatory EEG can improve diagnosis of questionable spells, but may be difficult to interpret
- Ictal Video/EEG is the gold standard – but inter-rater reliability is not perfect
Diagnostic Imaging of Epilepsy

- MRI (3 Tesla if available) is preferred over CT, except in acute trauma, and when contraindicated
- MRI can show subtle lesions such as mesial temporal sclerosis (arrow) not apparent on CT scans
Evaluation at the Epilepsy Center

- Invasive monitoring (depth electrodes or subdural grids) for presurgical workup
Magnetoencephalography (MEG)

• Promising and increasingly used in epilepsy centers
• Measures the induced magnetic fields of the brain rather than directly measuring the electrical fields
• Can non-invasively record sources of epilepsy deep in the brain
• Still rather cumbersome
Diagnostic Imaging of Epilepsy - SPECT and SISCOM

- SPECT (Single Photon Emission Tomography) shows areas of hypo- or hyper-metabolism
- Ictal SPECT: IV push of radiolabeled tracer during seizure
- SPECT superimposed on MRI yields ‘SISCOM’ (Subtraction Ictal SPECT Co-registered with MRI)
Pharmacologic Treatment of Epilepsy
Antiepileptic Drug (AED) Selection Guidelines

• Start with a safe AED appropriate for the specific epilepsy syndrome, as monotherapy if possible
• “Start low, go slow” if possible
• Individualize AED to patient characteristics (e.g. obese, female, elderly)
• Consider potential benefits for comorbid conditions (e.g. migraine, mood disorder, pain)
• Consider patient compliance (prefer QD or BID dosing) and drug interactions
AED Selection Guidelines

Primary Generalized Epilepsies:
- Valproic Acid
- Felbamate
- Lamotrigine
- Levetiracetam
- Topiramate
- Phenobarbital
- Zonisamide (may worsen myoclonic epilepsies)

Partial or Secondarily Generalized Epilepsy:
Any AED may be effective except ethosuximide (effective only for absence)

*Note: carbamazepine may worsen absence epilepsy
Benefits of AEDs for Cormorbidities

- Bipolar Disorder: VPA, CBZ, OXC, LTG
- Migraine: TPM, VPA
- Painful Neuropathy: PGB, CBZ, TPM
- Trigeminal Neuralgia: CBZ, PGB, VPA
Cognitive AED Side Effects

- All AEDs can impair cognition
- Some correlation between AED efficacy and cognition (‘strong’ AEDs worse)
- Lamotrigine and levetiracetam in general to cause less impairment.
- Many patients have idiosyncratic cognitive AED side effects
- Some AEDs more associated with psychiatric SEs (levetiracetam, felbamate, tiagabine)
- Suicide risk warning placed on all AEDs
AED by Mechanism of Excretion: Primarily Hepatic vs. Primarily Renal

- Phenobarbital
- Phenytoin
- Carbamazepine
- Valproic Acid
- Felbamate
- Lamotrigine

- (Gapapentin)
- Pregabalin
- Levetiracetam
- Lacosamide
AED selection by Mechanism of Action

- Controversial even among epileptologists……

[Diagram showing AED selection by mechanism of action with categories such as Sodium Channel, Calcium Channel, GABAergic, Glutamate, CA Inhibitor, and Other with specific medications listed under each category.]

AED Selection – pharmacologic considerations

- Hepatic Enzyme inducers vs. non-inducers
- Plasma Protein binding
- Half-life
- Drug-drug interactions: note particularly valproic acid which can markedly inhibit lamotrigine metabolism
Pharmacogenomics

• Promising approach to choosing medication best suited to an individual
• Currently in technological infancy
• Practical application reflected in new black box labeling for carbamazepine
• Increased incidence of Stevens Johnson Syndrome in Asians with HLA-B*1502
• Testing recommended before placing individual of Asian descent on CBZ
Phenytoin Side Effects:

Expected vs. Idiosyncratic

- Ataxia, dizziness
- Gingival hyperplasia
- Hirsuitism, coarsening of facial features
- Cerebellar Degeneration, peripheral neuropathy

- Rash, including Stevens Johnson
- Hepatitis
- Other hypersensitivity reactions
- Lupus like syndrome
- Purple Glove Syndrome
Carbamazepine Side Effects: Expected vs. Idiosyncratic

- Ataxia
- Diplopia
- Dizziness
- Photosensitivity
- Mild neutropenia
- Hyponatremia

- Rash, including Stevens Johnson
- Hepatitis
- Severe Neutropenia
Valproic Acid Side Effects:

**Expected** vs **Idiosyncratic**

- Sedation
- Tremor
- Weight gain
- Change in hair growth
- Mild thrombocytopenia

- Fulminant hepatic failure (mostly infants)
- Pancreatitis
- Valproate encephalopathy
## Felbamate Side Effects:

<table>
<thead>
<tr>
<th>Expected</th>
<th>Idiosyncratic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sleeplessness</td>
<td>Aplastic Anemia (risk 1 in 3000 – 5000)</td>
</tr>
<tr>
<td>Agitation</td>
<td>Fulminant Hepatic Failure</td>
</tr>
<tr>
<td>Headache</td>
<td>Psychosis</td>
</tr>
<tr>
<td>Loss of appetite/</td>
<td></td>
</tr>
<tr>
<td>Weight loss</td>
<td></td>
</tr>
</tbody>
</table>
Lamotrigine Side Effects: Expected vs. Idiosyncratic

- Sedation
- Dizziness
- Diplopia
- Headache (may worsen pre-existing migraines)

- Rash, including Stevens Johnson Syndrome
# Topiramate Side Effects:

**Expected vs. Idiosyncratic**

<table>
<thead>
<tr>
<th>Expected</th>
<th>Idiosyncratic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Extremity paresthesias</td>
<td>Acute angle closure glaucoma</td>
</tr>
<tr>
<td>Altered taste of carbonated bevs</td>
<td>Severe cognitive side effects “zombie”</td>
</tr>
<tr>
<td>Mild cognitive side effects, “spaciness”</td>
<td>Severe metabolic acidosis</td>
</tr>
<tr>
<td>Weight loss</td>
<td></td>
</tr>
<tr>
<td>Mild metabolic acidosis, increased risk of nephrolithiasis</td>
<td></td>
</tr>
</tbody>
</table>
Pregabalin Side Effects: Expected vs. Idiosyncratic

- Sedation
- Dizziness
- Weight Gain
- Pedal edema

- Angioedema
Levetiracetam Side Effects:

**Expected** vs. **Idiosyncratic**

- Drowsiness
- Dizziness
- Mild Irritability
- Severe Mood disorder
- Psychosis
Oxcarbazepine Side Effects:

**Expected vs. Idiosyncratic**

- Headache
- Dizziness
- Nausea
- Diplopia
- Hyponatremia

- Rash, including Stevens Johnson Syndrome
- Severe Hyponatremia
Lacosamide Side Effects: Expected vs. Idiosyncratic

- Dizziness
- Diplopia
- Drowsiness
- Ataxia
- Prolonged P-R interval

- Hepatitis
Dietary Therapy for Epilepsy

- Ketogenic diet has proven track record in children with intractable epilepsy, safety questions remain
- Now efficacy has been demonstrated in adults
- Compliance is problematic
Status Epilepticus

- Defined as seizure activity, either continuous or intermittent, lasting greater than 30 minutes without return to baseline level of consciousness
- Constitutes a medical emergency
- Can result in neuronal cell death, even if blood pressure and oxygenation is maintained
Status Epilepticus Subtypes

• Simple Partial
• Complex Partial
• Generalized Convulsive
• Generalized Non-convulsive
• For a patient presenting with “lights on, nobody home”, EEG required for diagnosis of non-convulsive status epilepticus
Status Epilepticus: Causes

- Approx 1/3 due to exacerbation of pre-existing idiopathic epilepsy, often with medication non compliance
- 1/3 new presentation of epilepsy without other identified cause
- 1/3 due to other: structural, toxic/metabolic, infectious causes
Status Epilepticus: Initial evaluation

- Rule out hypoglycemia and electrolyte imbalance
- Rule out poisoning or overdose (stimulants, TCAs, INH)
- Rule out drug or alcohol withdrawal
- Rule out CNS mass or infection (CT scan and CSF examination)
Status Epilepticus: Standard Treatment

- ABCs and maintain normothermia
- Treat any identified underlying cause
- LORAZEPAM 4mg IV over 2 minutes, repeat if needed in 15 mins (Adults) OR DIAZEPAM 5-10 mg IV load (Adults)
- PHENYTOIN (infuse at<50mg/min) OR FOSPHENYTOIN (up to 150mg/min, preferred) loading dose 15-20mg/Kg
Refractory Status Epilepticus: Old School Approach, still standard

- Standard third line agent: PHENOBARBITAL 15-20mg/Kg IV – likely to cause respiratory depression given after benzodiazepines
- Rapid sequence intubation, EEG monitoring, ICU management as needed
- Standard IV continuous therapy: PENTOBARBITAL 12mg/kg IV load then 5mg/Kg/hr IV, follow EEG monitoring
Status Epilepticus: current trends, (off label use, no RCT data)

- Second line use of any available IV formulated AED – VALPROIC ACID, LEVETIRACETAM, LACOSAMIDE
- Third line use of IV MIDAZOLAM 0.2mg/Kg IV load, then 0.1–0.4 mg/Kg/min drip titrated to clinical effect or EEG
- Third line use of IV PROPOFOL 2mg/Kg IV load, then 0.1 – 0.2 mg/Kg/min IV drip (caution re: acidosis with prolonged use)
Surgical Treatment of Epilepsy
Surgical Treatment of Epilepsy

• Variety of procedures available, two devices currently awaiting approval
• Requires extensive inpatient workup
• Treatment of choice for many patients with pharmacoresistant epilepsy
• Offers chance of epilepsy remission for some refractory patients
Brain Resection Surgery

Successful Outcome Involves many steps

- Accurate diagnosis
- Appropriate patient selection
- Pre-op localization of seizure focus
- Intra-operative seizure recording and functional mapping
The Future is Here!

• Clinical trial completed of Responsive Neuro Stimulation (RNS)
• “Brain Defibrillator”
• Electrodes implanted into seizure focus
• Computer senses and delivers countershock to stop seizure
• Currently awaiting FDA approval
Anterior Thalamic DBS for Epilepsy

- Uses same technology as for Parkinsons
- Awaiting FDA approval
Summary

• The 20\textsuperscript{th} century saw an explosion of new antiepileptic drugs
• The 21\textsuperscript{st} century will see an explosion of high-tech implantable devices and drugs
• Best patient care still begins with a thorough history
• Careful consideration and explanation of risks and benefits is essential
Questions?