1 in 26 Americans will be diagnosed with epilepsy within their lifetime.

Epilepsy is the 4th most common neurological condition in the US, after migraine, stroke, and Alzheimer’s disease.
Who Develops Epilepsy?

Hauser, Epilepsia 33:1992
Epilepsy: Etiology vs. Age of Onset

- Perinatal injury
- Metabolic defect
- Congenital malformation
- Infection
- Genetic epilepsy
- Postnatal trauma
- Brain tumor
- Vascular disease

Age (years)

- Birth
- 2
- 3
- 5
- 10
- 20
- 30
- 50
- 70
Distinct Behavioral and Electrical Characteristics Common to All Seizures

✴ Usually discrete, time-limited events with an identifiable onset and termination.

✴ A well-defined and predictable evolution of behavior from beginning to end, often with impaired awareness.

✴ After termination of most seizures there is a progressive recovery of consciousness and/or neurologic function.

✴ Epileptic seizures may be expressed as a variety of behaviors within one seizure type, but epileptic seizures are generally stereotyped within the same individual.
Cross-Cutting Themes

- A common and complex neurological disorder
- Often affects quality of life
- Whole-patient perspective needed
- Effective treatments available but access falls short
- Data needed to improve epilepsy knowledge and care and to inform policy
- Strengthen health professionals’ education
- Bolster education efforts for people with epilepsy and their families
- Eliminate stigma
The Agency for Healthcare Research and Quality (AHRQ), Department of Health and Human Services

- Sponsors, conducts, and disseminates research designed to:
  - improve the outcomes and quality of healthcare
  - reduce healthcare costs
  - address patient safety and medical errors
  - broaden access to effective and efficient services
  - help people make more informed healthcare decisions
AES Press Release Regarding AHRQ Report on Epilepsy Treatment

• Conclusion: “No significant differences in the risk of maintaining seizure freedom” when newer antiepileptic medications were compared versus carbamazepine (CBZ), phenytoin (PHT), and valproate (VPA).

• Leading representatives of the American Epilepsy Society, American Academy of Neurology, and the Epilepsy Foundation have grave concerns about the implications and potential misuse of the AHRQ report.
AES Press Release Regarding AHRQ Report on Epilepsy Treatment

- Study focus fails to recognize different types of epilepsy.

- Study compares effectiveness of old-line anticonvulsants to newer epilepsy drugs irrespective of epilepsy type.

- Medication side effects and potential drug-drug interactions are given relatively little attention.
Pediatric Epilepsy Update
Differences Between Kids & Adults

- Kids are more predisposed to have seizures
  - Many may improve with time, often benign
  - Most are extra-temporal in children
  - Children more likely to have multifocality
- Seizure control can have significant developmental implications in children
  - Need to treat epilepsy quickly
  - Optimize developmental progress
The majority (1/2 to 2/3) of pediatric seizures and epilepsy syndromes are localization-related.

This contrasts to 75% to 90% in adults.

Childhood-onset epilepsy may go into remission

60% to 75% of children seizure free on AEDs for more than 2 years remain so after stopping medication

Childhood-onset epilepsy is associated with adverse social and educational outcomes
Benign vs. Catastrophic Epilepsy in Kids

Benign (Idiopathic Epilepsies):
- Easily treated with medications
- Normal intelligence
- Remission after certain age
- Genetic predisposition
- Gradual disappearance of spikes from EEG with normal background in between spike

Examples:
- febrile, benign Rolandic, absence
Catastrophic (Symptomatic Generalized Epilepsy):
- Usually intractable and refractory to multiple medications
- Often with daily seizures
- Mental retardation
- Possible shortened life expectancy
- EEG has diffuse slowing, multifocal spikes, slow spike-wave, periodic patterns, electrodecrement, multiple seizure types
- Often have symptomatic etiology
Examples of Catastrophic Epilepsy

- Infantile spasms
- Severe encephalopathy epilepsy in early infancy
- Progressive myoclonus epilepsies
- Lennox-Gastaut syndrome
- Landau-Kleffner syndrome or epileptic aphasia
- Can be due to symptomatic etiologies
  - Cortical dysplasia, hemimegalencephaly, Rasmussen’s encephalitis, neurocutaneous syndromes, metabolic illness, Aicardi’s syndrome
Epileptic encephalopathies

Frequent epileptic activity contributes to severe cognitive and behavioral impairment and can worsen over time
Cause of Epileptic Encephalopathies

• Until recently regarded as acquired disorders
• 2001 - Dravet syndrome: 80% SCN1A mutations
• De novo mutations of genes in many cases
• More we know, more complicated it gets!
  – Several genes for an epilepsy syndrome
  – Several syndromes for a gene
Whole new world in infantile epileptic encephalopathies

- Unravelling the genetic architecture
- Many due to *de novo* mutations
- Rapidly increasing number of genes responsible
- Distinctive electroclinical syndromes emerging
  e.g. *STXB P1, CDKL5, KCNQ2, CHD2, SCN1A*
Genetic heterogeneity in EE

- 101 genes
- 622 patients
- 72 (12%) solved

- Novel EE genes
- Known EE genes
- Known genes for related disorders

Carvill et al., 2013, Nat Genet & unpublished
$K^+$ channel
Epileptic Encephalopathies

Neonatal
Infantile

Kobertz et al Biochemistry
2000;39:10347-10352
Benign Familial Neonatal Epilepsy

- Well neonates until seizures begin on day 2 or 3
- Onset by 3 months
- Premature infants delay onset until term
- Seizures – tonic, apnoea, clonic, focal, autonomic
- EEG – normal or multifocal
- Autosomal dominant, 85% penetrance
- 5% febrile seizures
- 11% later epilepsy
**KCNQ2 encephalopathy**

- Tonic seizures beginning in first week of life
- Seizures resolve by 4 years
- EEG at onset: burst suppression, multifocal
- Motor features - spasticity
- Profound – severe intellectual disability
- Early MRI characteristic abnormalities
  - Hyperintensities in basal ganglia and thalamus resolve
- 10% neonatal epileptic encephalopathies including Ohtahara syndrome

*Weckhuysen et al, Ann Neurol 2012; Neurol 2013*
De novo gain-of-function KCNT1 channel mutations cause malignant migrating partial seizures of infancy

- Epilepsy of infancy with migrating focal seizures
- Rare epileptic encephalopathy
  - Onset < 6 months
  - Focal seizures migrating between hemispheres
  - Poor developmental outcome
- 6/12 patients had de novo KCNT1 mutations
Ohtahara syndrome
Early infantile epileptic encephalopathy
with suppression burst

- *STXBP1* mutations in 20/100 (20%)
- 75% evolve to West syndrome
- Variable outcome
  - 12 poor outcome, 3 good (Saitsu 2008, 2010)
  - Seizures resolve (5/5), 4 by 1 yr, EEG normalized (Milh 2011)
- Non epileptic movement disorders prominent
- MRI – frontal atrophy, thin CC, delayed myelination
- Profound impairment
STXBP1 encephalopathy
Disease presentation

- Onset < 6 months
- Seizures: tonic, spasms, focal, myoclonic
- EEG: Burst suppression or lateralized or bilaterally synchronous epileptiform activity
- Movement disorders: stereotypies
- Profound impairment

- Expect 10-20% mutation rate in EIEE & EOEE
- Few % infantile spasms

**CHD2 encephalopathy (6/500, 1.2%)**

- Seizure onset: median 18 mths (12 mths - 3 yrs)
- All had myoclonic seizures, 3 photosensitive
- Intellectual disability: 2 moderate - 4 severe, 2 ASD
- Epilepsy syndromes
  - 2 Epilepsy with Myoclonic Atonic Seizures
  - 1 Lennox-Gastaut Syndrome
  - 3 non-specific epileptic encephalopathy
- *De novo* mutations reported in
  - Patient with ID, absence seizures (*Rauch et al.*, 2012)
  - Patient with ASD (*Neale et al.*, 2012)

*Carvill et al Nat Genet 2013*
Deficiency States
Presentations of Biotinidase Deficiency

- Symptoms usually begin at 2 to 3 months of age and consist of: seizures (which can be generalized tonic-clonic, myoclonic, or infantile spasms), hypotonia, episodic ataxia, respiratory disturbances, high-frequency hearing loss, optic atrophy, and developmental delay dermatitis, alopecia, conjunctivitis, and chronic candidiasis.

- We reported the occurrence of Biotinidase deficiency with infantile spasms and mental delay without rash or other Sxs.

Cerebral Folate Deficiency

- **Etiology:** mutations in the FOLR1 (folate receptor alpha gene), blocking antibodies for folate receptors or secondary to mitochondrial disorders, Rheumatoid arthritis, Rett, autism.
- **Onset:** 4-6 months of age with delay in development, hypotonia, and ataxia, dyskinesias (choreo-athetosis, hemiballismus), spasticity, epilepsy and a times progressive encephalopathy.
- **Treatment** of the condition with folinic acid 0.5-3 mg/kg/day.

(A) Left hemisphere 3-4 Hz spike and wave discharges.
(B) Mild cerebellar
Cerebral Folate Deficiency
Recent Insights

- **Seizures**: myoclonic astatic, tonic, myoclonic, rarely focal
- **EEG**: Generalized 3-4 Hz SSW, multifocal spikes
- We reported occurrence of **infantile spasms** and of electrical status epilepticus, **ESES**, in sleep as epileptic manifestation of cerebral folate deficiency

Pyridoxine Dependent Epilepsy

- Seizures: partial ± generalization, myoclonic, atonic.
- Transient response to AEDs was observed
- An early encephalopathy with an apparent ocular apraxia
- EEG: Suppression burst, Generalized irregular SSW, uni or bilateral EEG szs, multifocal spikes, hysarrhythmia

Pyridoxine Dependent Epilepsy
Recent Insights

- We reported that EEG burst suppression may fluctuate for up to 5 days after start of therapy
- Others reported presence of cerebral atrophy, mega cisterna magna hydrocephalus, FCD and thin posterior CC common (abnormal MRI in half)
- Low lysine diet, folinic acid (folinic responsive szs allelic)

Pyridoxine Responsive Seizures

- The UK survey identified infants and children who responded to pyridoxine and in whom it was later discontinued without recurrence.
- Some children with infantile spasms respond to pyridoxine (12% in largest series).
- Struys et al reported 2 sibs with B6-responsive szs and increased urinary α-AASA. Subsequent studies: molybdenum cofactor deficiency due to homozygous MOCS2 mutation.

Struys EA et al., Pediatrics 2012;130:e1716; Netherlands
Presentations of Glucose Transporter Deficiency

- Microcephaly, MR, ataxia,
- Dystonic choreoathetosis, exercise induced dyskinesia
- Neonatal Seizures
- Infantile myoclonic seizures or infantile spasms
- Early-onset absence
- Myoclonic absence
- Lennox-Gastaut syndrome
- Early onset JME at times with TV screen "attraction"

Presentations of GLUT1 Deficiency New Insights

- Myoclonic epilepsy unresponsive to eight anticonvulsants. Oral steroid treatment achieved dramatic seizure control
- Alternating Hemiplegia of Childhood (only episodes of hemiplegia and delay with improvement in sleep and delay, no dystonia reported)

Other Treatable Etiologies

- **Coenzyme Q deficiency**: of various causes has been associated with and IS and EIME at times with CFC syndrome, nephrotic syndrome and cardiomyopathy, but replacement therapy has not consistently helped.

- **Serine synthesis Defects**: Can present with neonatal seizures and later delay and microcephaly, therapy with L-serine (500 mg/kg/d, and glycine 200 mg/kg/d has been effective.

Conclusions

1) New discoveries in EIEE are resulting from collaboration, NGS, likelihood analysis, network analysis, and MEAs. Novel therapies are likely.

2) Newly recognized entities (e.g. K and Na channel, STXBP1, CHD2, and SYNGAP1 related EIEEs) have distinctive clinical profiles.

3) Multiple amenably entities (e.g. Biotin, thiamine, B6, PLP, and folinic EIEEs, GLUT1 deficiency) have typical and atypical presentations.

4) We can apply all this new knowledge in the clinic.
Clinical Approach

- **Things are not what they seem:** be familiar with the spectrum of presentations typical & atypical.
- **Keep it simple:**
  - Screen for inborn errors of metabolism and vitamin responsive entities that you do not want to miss
  - Target specific genes sequencing to the disorder you are suspecting the most
  - If there are none then resort to gene panel or whole exome sequencing
Workup Targeted to Ruling Out Amenably Treatable Conditions

- **Blood and Urine:** Amino acids, Organic acids, Acyl carnitine profile, carnitine free and total, lactate, pyruvate, ammonia, biotinidase, pipecolic acid, creatine, guanidino acetic acid, alpha amino adipic acid semialdehyde, MRS for creatine peak,

- **CSF:** amino acids, lactate ammonia, routines, neurotransmitter studies, Pyridoxal 5’-phosphate, 5-methyltetrahydrofolate

- **Gene Testing:** Targeted gene testing, or panels, or exome sequencing

Genetic diagnosis & clinical care

• Knowing the genetic diagnosis....
  • Improves prognosis counseling
  • Facilitates discussion of recurrence risk
  • Affects medical management in some cases

• But...we only have a diagnosis in a fraction of cases
### Old Epilepsy Classification

<table>
<thead>
<tr>
<th>Generalized</th>
<th>Idiopathic</th>
<th>Symptomatic or Cryptogenic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Localization Related</td>
<td>IGE</td>
<td>SGE</td>
</tr>
<tr>
<td></td>
<td>ILE</td>
<td>SLE</td>
</tr>
</tbody>
</table>
ILAE Proposal for Revised Terminology for Organization of Seizures and Epilepsies 2010

Classification of Seizures

- Generalized seizures
  - Arising within and rapidly engaging bilaterally distributed networks
    - Tonic-Clonic
    - Absence
    - Clonic
    - Tonic
    - Atonic
    - Atypical
      - Absence with special features
        - Myoclonic absence
        - Eyelid Myoclonia

- Focal seizures
  - Originating within networks limited to one hemisphere
    - Characterized according to one or more features:
      - Aura
      - Motor
      - Autonomic
      - Awareness/Responsiveness: altered (dyscognitive) or retained
    - May evolve to:
      - Bilateral convulsive seizure

- Unknown
  - Insufficient evidence to characterize as focal, generalized or both
    - Epileptic Spasms
    - Other

Changes in terminology and concepts

<table>
<thead>
<tr>
<th>New Term and Concept</th>
<th>Examples</th>
<th>Old Term and Concept</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Etiology</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Genetic: genetic defect directly contributes to the epilepsy and seizures are the core symptom of the disorder</td>
<td>Channelopathies, Glut1 deficiency, etc.</td>
<td>Idiopathic: presumed genetic</td>
</tr>
<tr>
<td>Structural-metabolic: caused by a structural or metabolic disorder of the brain</td>
<td>Tuberous sclerosis, cortical malformations, etc.</td>
<td>Symptomatic: secondary to a known or presumed disorder of the brain</td>
</tr>
<tr>
<td>Unknown: the cause is unknown and might be genetic, structural or metabolic</td>
<td></td>
<td>Cryptogenic: presumed symptomatic</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Terminology</th>
<th>Terms no longer recommended</th>
</tr>
</thead>
<tbody>
<tr>
<td>Self-limited: tendency to resolve spontaneously with time</td>
<td>Benign</td>
</tr>
<tr>
<td>Pharmacoresponsive: highly likely to be controlled with medication</td>
<td>Catastrophic</td>
</tr>
<tr>
<td>Focal seizures: seizure orioleology described according to specific subjective (auras), motor, autonomic, and dyscognitive features</td>
<td>Complex partial</td>
</tr>
<tr>
<td>Evolving to a bilateral convulsive seizure: eg. tonic, clonic, tonic-clonic</td>
<td>Simple partial</td>
</tr>
<tr>
<td>Secondarily generalized</td>
<td></td>
</tr>
</tbody>
</table>

References:
ILAE Proposal for Revised Terminology for Organization of Seizures and Epilepsies 2010

Electroclinical Syndromes and Other Epilepsies Grouped by Specificity of Diagnosis

Electroclinical syndromes

One example of how syndromes can be organized:
Arranged by typical age at onset

Neonatal period
- Benign neonatal seizures
- Benign familial neonatal epilepsy (BFNE)
- Ohtahara syndrome
- Early Myoclonic encephalopathy (EME)

Infancy
- Febrile seizures, Febrile seizures plus (FS+)
- Benign infantile epilepsy
- Benign familial infantile epilepsy (BFI)
- West syndrome
- Dravet syndrome
- Myoclonic epilepsy in infancy (MEI)
- Myoclonic encephalopathy in nonprogressive disorders
- Epilepsy of infancy with migrating focal seizures

Childhood
- Febrile seizures, Febrile seizures plus (FS+)
- Early onset childhood occipital epilepsy (Panayiotopoulos syndrome)
- Epilepsy with myoclonic atonic (previously atactic) seizures
- Childhood absence epilepsy (CAE)
- Benign epilepsy with centropontal spikes (BECTS)
- Autosomal dominant nocturnal frontal lobe epilepsy (ADNFLE)
- Late onset childhood occipital epilepsy (Gastaut type)
- Epilepsy with myoclonic absences
- Lennox-Gastaut syndrome (LGS)
- Epileptic encephalopathy with continuous spike-and-wave during sleep (CSWS)
- Landau-Kleffner syndrome (LKS)

Adolescence – Adult
- Juvenile absence epilepsy (JAE)
- Juvenile myoclonic epilepsy (JME)
- Epilepsy with generalized tonic-clonic seizures alone
- Autosomal dominant epilepsy with auditory features (ADEAF)
- Other familial temporal lobe epilepsies

Variable age at onset
- Familial focal epilepsy with variable foci (childhood to adult)
- Progressive myoclonus epilepsies (PME)
- Reflex epilepsies

Distinctive constellations/surgical syndromes

Mesial temporal lobe epilepsy with hippocampal sclerosis (MTLE with HS)
- Rasmussen syndrome
- Gelastic seizures with hypothalamic hamartoma
- Hemiconvulsion-hemiplegia-epilepsy

Nonsyndromic epilepsies**

Epilepsies attributed to and organized by structural-metabolic causes
- Malformations of cortical development (hemimegalencephaly, heterotopias, etc.)
- Neurocutaneous syndromes (tuberous sclerosis complex, Sturge-Weber, etc.)
- Tumor, infection, trauma, angiomia, antenatal and perinatal insults, stroke, etc

Epilepsies of unknown cause

This Proposal is a work in progress......
We welcome your thoughts on this proposal. Please visit our Classification & Terminology Discussion Group at: http://community.ilae-epilepsy.org/home/ to login and register your comments.
Purposes of Epilepsy Monitoring

- Confirmation of Epilepsy Diagnosis
  - Identification of Interictal Epileptiform Discharges
  - Seizure classification
  - Seizure quantification
- Identification of Imitators of Epilepsy
- Presurgical Evaluation
  - Seizure localization
- Intensive Care Unit Monitoring
- Pharmacologic Monitoring
Classification of Seizures - Focal

- Partial onset seizures
  - Simple partial seizures
  - Complex partial seizures
    - Impaired consciousness at outset
    - Simple partial evolving to lost consciousness
    - Partial seizures evolving to secondary generalized tonic-clonic seizures

1 in 10 people will have a seizure during their life
Classification of Seizures - Generalized

- Absence seizures
- Myoclonic seizures
- Primary generalized tonic-clonic seizures
- Tonic seizures (epileptic spasms)
- Clonic seizures
- Atonic seizures

1 in 10 people will have a seizure during their life
Physiologic Nonepileptic Events

Figure 8–2. Overview of the spectrum of physiological nonepileptic events. Note. TIA = transient ischemic attack.

Gates, 1998
Breath-Holding Spells

- Phenomenon common between 6 months and 6 years
- 76% of the attacks occur between 6 and 18 months of age
- 85% of affected children are free of attacks by age 5 years
- Often confused with tonic seizures
- Historical description of precipitating cause is key
- Child is described as falling
- Followed by tremulousness or convulsive clonic-like movements (especially with longer events)
- Thought to be related to reflex vagal changes, bradycardia, decrease cerebral blood flow

From Engle Epilepsy Comprehensive Text
Breath-Holding Spells - Two Types

- Cyanotic form
  - More common, starting during 2nd or 3rd year of life
  - In response to anger, fear, excitement, or minor injury
  - Child will cry and suddenly stop breathing, often during expiration
  - Cyanosis within seconds, followed by LOC
  - Rapid return to baseline after 1-2 min.

- Pallid form
  - Also often follows minor trauma
  - Child does not cry
Breath-Holding Spells

- Attacks are repetitive and stereotypic
- Treatment
  - Usually behavioral modification
  - No need for medication
- Can also occur in older children and even adults with developmental disorders
- May be a relationship with mental retardation and epilepsy later in life
Psychogenic Nonepileptic Seizures

- 10-45% of patients referred for intractable spells
  - Disassociation, conversion
  - Association with physical, emotional, and sexual abuse
  - Females > males
- Video-EEG monitoring often required for diagnosis
  - Non-ictal pattern on EEG & atypical clinical features
  - 20-40% can have cessation of events (up to 80% of kids)
  - Approximately 50% respond well to specific psychiatric treatment
- Epileptic and nonepileptic seizures may co-exist
Treatment Options

- Medication
- Surgical Treatment
- Implantable Stimulation Devices
- Ketogenic Diet
<table>
<thead>
<tr>
<th>Year</th>
<th>Drug</th>
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<tbody>
<tr>
<td>1857</td>
<td>bromides</td>
</tr>
<tr>
<td>1912</td>
<td>phenobarbital</td>
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<tr>
<td>1932</td>
<td>mephobarbital</td>
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<tr>
<td>1937</td>
<td>phenytoin</td>
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<tr>
<td>1952</td>
<td>acetazolamide</td>
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<tr>
<td>1974</td>
<td>carbamazepine</td>
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<td>1978</td>
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<td>2012</td>
<td>perampanel*</td>
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<tr>
<td>2013</td>
<td>eslicarbazepine*</td>
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**AED Choice by Seizure Type**

- **Focal Onset**
  - Tonic Clonic
    - PHT, CBZ, PB, GBP, TGB, OXC, PGB, LCM, VGB, EZO, PRM

- **Generalized Onset**
  - Tonic
  - Myoclonic
  - Atonic
    - RUF, CBM
  - Infantile Spasms
    - ACTH, VGB
  - Absence
    - ESX

- **VPA, LVT, LTG, TPM, ZNS, FBM, RUF?, LCM?, PRM?**
Factors in Treatment Choice

- Seizure/Epilepsy Type
- Short Term Side Effects and Tolerability
- Rare, Serious and Long Term Side Effects
- Co-morbid Conditions
- Drug Interactions
- Timing and Compliance
- Cost
# Psychiatric Comorbidities

<table>
<thead>
<tr>
<th>Disorder</th>
<th>Prevalence</th>
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<tbody>
<tr>
<td>Anxiety disorders(^1)</td>
<td>19% to 66%</td>
</tr>
<tr>
<td>Major depression(^1)</td>
<td>20% to 57%</td>
</tr>
<tr>
<td>Bipolar symptoms(^2)</td>
<td>12%</td>
</tr>
<tr>
<td>Psychosis(^1)</td>
<td></td>
</tr>
<tr>
<td>- Interictal psychosis</td>
<td>9%</td>
</tr>
<tr>
<td>- Postictal psychosis</td>
<td>6%</td>
</tr>
</tbody>
</table>

Chronic Medical Management

Early Identification of Refractory Epilepsy
Kwan P. & Brodie M.J.
New England Journal of Medicine, 2000

- Prospective series
- 470 previously untreated subjects
- Five year follow-up
- 64% seizure-free:
  - 47% controlled with first drug
  - 14% controlled with second drug
  - 3% controlled with two-drug combination
Delay to Epilepsy Center Referral

- Standard of care
  - Refer if 2-3 drugs in 2-3 years fail to control seizures
  - Actual average time to referral in U.S. over 10 years
- 5-10% of monitored patients may benefit from surgery
- Estimated number of surgeries in U.S.: 3000 per year
- Need may be an order of magnitude greater
Devices if Non-Surgery

- VNS
- RNS
- DBS
- TNS
Outcomes in a subset of 65 patients seen for at least 10 years post-VNS Therapy

- Seizure frequency was significantly reduced from baseline at each of the recorded intervals (P<0.01)

![Mean Seizure Reduction](image)
Cumulative Adjusted Net Healthcare Costs

Net total healthcare cost savings started at 1.5 years post-VNS implant

*Negative net costs indicate lower costs in the Post-VNS quarter relative to the mean quarterly cost in the Pre-VNS period.
Devices if Non-Surgery

- VNS
- RNS - 11/13 approval ~ 39% reduction
- DBS
- TNS
Devices if Non-Surgery

- VNS
- RNS
- DBS - EU only, ~ 39% reduction
- TNS
Devices if Non-Surgery

- VNS
- RNS
- DBS
- TNS - EU, US pending ~ 30% responders
New for Emergencies?
Rapid Anticonvulsant Medication Prior to Arrival Trial - RAMPART STUDY -

- NINDS + Defense Department
- midazolam IM auto-injector vs. lorazepam IV by paramedics
- Primary end point - seizure free on ER arrival
  - 73% for midazolam
  - 63% for lorazepam
- midazolam patient were less likely to require hospitalization
- similarly low rates of recurrent seizures

NEJM, Feb. 16, 2012
Rescue Benzodiazepines

- intranasal midazolam
- intranasal diazepam
- intramuscular diazepam
### Agent | IV Loading Dose | Maintenance | Adverse Effects | Comments
--- | --- | --- | --- | ---
Valproate | 20 mg/kg to 40 mg/kg at 5 mg/kg/min | 4 mg/kg to 6 mg/kg every 6 h | Hepatic toxicity, thrombocytopenia, pancreatitis, induction of autoimmunity | Avoid in pregnancy or after head trauma; numerous drug interactions
Levetiracetam | 1 g to 6 g at 2 mg/kg/min to 5 mg/kg/min | 10 mg/kg to 15 mg/kg every 12 h | Accumulates when creatinine clearance is diminished | Minimal drug interactions
Lacosamide | 200 mg to 400 mg over 15 min to 30 min | 200 mg every 12 h | Somnolence, atrial fibrillation | Interactions with antiretroviral drugs
Topiramate | Not available for IV use; 400 mg enterally every 3 h to 4 h up to 2 g | 300 mg every 6 h | Sedation, metabolic acidosis | Numerous drug interactions

Phenytoin/fosphenytoin is still the only status epilepticus Rx w/ Class I data

Bleck, Thomas P. MD, FAAN, FCCM CONTINUUM: Lifelong Learning in Neurology Volume 18(3) Critical Care Neurology June 2012 p 560–578
<table>
<thead>
<tr>
<th>Agent</th>
<th>Loading Dose</th>
<th>Maintenance Dose</th>
<th>Adverse Effects</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Midazolam\textsuperscript{21}</td>
<td>0.2 mg/kg over 5 min</td>
<td>0.2 mg/kg/h to 2.0 mg/kg/h</td>
<td>Hypoventilation, hypotension</td>
<td>Tachyphylaxis occurs rapidly.</td>
</tr>
<tr>
<td>Propofol</td>
<td>1 mg/kg to 5 mg/kg (depending on blood pressure and other drugs used) over 5 min to 10 min</td>
<td>Up to 15 mg/kg/h (increasing risk of propofol infusion syndrome above 5 mg/kg/h)</td>
<td>Propofol infusion syndrome (acidosis, rhabdomyolysis), hypotension, immune suppression</td>
<td>Lipid vehicle is a substantial calorie source.</td>
</tr>
<tr>
<td>Pentobarbital</td>
<td>5 mg/kg to 10 mg/kg at 50 mg/min; slow infusion for hypotension</td>
<td>0.5 mg/kg/h to 5 mg/kg/h</td>
<td>Acidosis from glycols in vehicle, hypotension, immune suppression, prominent negative inotrope at higher doses</td>
<td>May become unavailable; substitute phenobarbital at a loading dose of 20 mg/kg.</td>
</tr>
<tr>
<td>Ketamine\textsuperscript{22}</td>
<td>1 mg/kg to 3 mg/kg over 2 min to 5 min</td>
<td>0.5 mg/kg/h to 10 mg/kg/h</td>
<td>Hypotension may develop in patients who have exhausted their intravascular catecholamine stores</td>
<td>Raises blood pressure in about 70% of cases. Increased intracranial pressure reported in the past was a consequence of carbon dioxide retention, not an issue with controlled ventilation.</td>
</tr>
<tr>
<td>Isoflurane or desflurane\textsuperscript{23}</td>
<td>Requires assistance of an anesthesiologist</td>
<td></td>
<td></td>
<td>Newer delivery devices may facilitate intensive care unit use.</td>
</tr>
</tbody>
</table>
What’s New With Medications?
Treatment of Catamenial Epilepsy using Natural Progesterone (Herzog et al Neurology 2012)

- NIH-sponsored trial of natural progesterone in women with partial epilepsy
- Multicenter, double-blind, randomized, placebo-controlled
- 2:1 randomization tx vs. placebo
- Treatment arm was progesterone 200 mg lozenge TID days 14-25; 100 mg TID days 26-27; 50 mg TID day 28 and stop
Treatment of Catamenial Epilepsy using Natural Progesterone, cont’d

- Subjects randomized within catamenial or noncatamenial arms
- Subjects showing any catamenial pattern in 2/3 baseline menstrual cycles were randomized to the catamenial arm
- 294 subjects treated; 44% or 130/294 were in catamenial arm
Treatment of Catamenial Epilepsy using Natural Progesterone, cont’d

- **Results**
  - Primary outcome measure of efficacy of 35% in treated arm achieving 50% seizure frequency reduction was not met
  - Post-hoc analysis showed efficacy for catamenial type 1 (premenstrual seizures)
  - Should the approach of hormone treatment for catamenial seizures be more mechanistically based?
Catamenial Seizure patterns

- **C1** Perimenstrual
  - Days -3 to 3
  - 1.69X more seizures during these days than other days of cycle
- **C2** Periovulatory
  - Days 10 to -13
  - 1.83 X more seizures
- **C3** Luteal
  - Days 10 to 3
  - 1.62X more seizures

(Slide courtesy of A. Herzog)
**Recommendations**

C1 Level $\geq 3$

- Progesterone lozenges 200 mg, Days 14-28
  - (Consider taper beginning Day 26)

C1 Level $< 3$

- Clobazam, 20-30 mg/day x 10 days
  - Begin 2 days prior to phase of increased seizures based on individual diary review

- Acetazolamide, 250-500 mg/day, beginning Day -7 to -3 until Day 1

- Continuous oral contraceptive pills without placebo phase

- Increase daily dosage of AEDs (other than PHT) during days of seizure worsening

- Medroxyprogesterone acetate 150mg IM q 10-12 weeks

Pennell & Harden
North American AED Pregnancy Registry Between 1997 And 2011: Percent Mcms And 95% CI With Monotherapy 1st Trimester Exposure (Hernandez-diaz, Et Al. Neurology 2012)

Number of outcomes: CBZ=1033 VPA= 323 LTG= 1562 PHT=416 OXC=182 GBP= 145 PB=199 ZNS= 99 TPM=359 CZP= 64 LVT=450
LACOSAMIDE

- Add-on for partial onset seizures
- Age 17 & older
- 50 mg - 100 mg - 150 mg - 200 mg tabs
- Recommended titration to 100 mg BID in 1 week
- No known drug interactions
- Novel mechanism of action - enhances slow inactivation of voltage-gated Na+ channels
- Watch for dizziness, especially with classic (fast inactivation) Na+ channel drugs in the background
VIGABATRIN

- Initial therapy for infantile spasms
- Add-on for refractory focal seizures (age 12+)
- Binds irreversibly to GABA transaminase
- Time-course of effect dependent upon enzyme re-synthesis
- Not really a new drug, available world-wide since 1989

Ben-Menachem et al., 2011; Faught, 2011
VIGABATRIN

- Peripheral Vision - side effect of special interest
  - Up to 1/3 of patients will develop PERMANENT peripheral visual field constriction
  - May happen at any time but not likely before several months of exposure (dose-dependent)
- Mandatory quarterly vision testing in U.S.A.
- Otherwise relatively well tolerated, usual CNS side effects

Sabril package insert; Ben-Menachem et al., 2011; Faught, 2011
CLOBAZAM

• Add-on for children $\geq 2$ and adults with seizures related to the Lennox-Gastaut syndrome

• Novel mechanism of action, sort of
  • A benzodiazepine that modulates function of GABA receptors
  • 1,5-benzodiazepine unlike the other, 1,4-benzodiazepines
  • Significance not clear but may be less sedating and less prone to habituation

Ng et al., 2011; Ben-Menachem et al., 2011; Sankar 2012
Clobazam

- Not really a new drug, available worldwide since 1974
- Approved for seizures associated with Lennox-Gastaut
  - Tonic-atonic/drop seizures
  - Worldwide experience suggests utility in other seizures
- CNS side effect most prominent
  - Sedation, somnolence, lethargy, drooling, ataxia, aggression
- Need to watch for excessive sedation in combination with other benzodiazepines, such as those used for rescue in seizure clusters

Ng et al., 2011; Ben-Menachem et al., 2011; Sankar 2012
RUFINAMIDE

- Approved as add-on for Lennox-Gastaut syndrome
- Age 4 to adult
- 200 mg & 400 mg tabs, crushable
- Recommended titrate to 3200 mg in 2 weeks
  - Probably far too aggressive
- Does not alter other AEDs but can be altered by them - especially decreased clearance with VPA
- Some interactions with non-AEDs - OCP

Glauser et al., 2008
## RUFINAMIDE

### Adverse Events

<table>
<thead>
<tr>
<th></th>
<th>Rufinamide, n (%)</th>
<th>Placebo, n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total patients studied</td>
<td>74</td>
<td>64</td>
</tr>
<tr>
<td>Total patients with an adverse event</td>
<td>60 (81.1)</td>
<td>52 (81.3)</td>
</tr>
<tr>
<td>Most common adverse events</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Somnolence</td>
<td>18 (24.3)</td>
<td>8 (12.5)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>16 (21.6)</td>
<td>4 (6.3)</td>
</tr>
<tr>
<td>Pyrexia</td>
<td>10 (13.5)</td>
<td>11 (17.2)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>4 (5.4)</td>
<td>7 (10.9)</td>
</tr>
</tbody>
</table>

Glauser et al., 2008
EZOGABINE

• retigabine worldwide but ezogabine in U.S.
• Add-on for adults with refractory focal seizures
• Novel mechanism of action
  • potassium (K+) channel opener - KCNQ (Kv7)
• Efficacious in a broad range of animal models
  • Potential activity for a variety of epilepsy types in humans

Large et al., 2011
EZOGABINE

- CNS side effect most prominent
  - fatigue, somnolence, confusion, dizziness
- Adverse event of special interest
  - Urinary retention occurred in 2%, rarely requiring catheterization
  - Psychiatric side effects, some serious 2%
  - Bluish skin, mucosal, scleral discoloration, rare
  - Bluish retinal pigmentary changes with decreased acuity, rare but REMS in place
- Serum level reduced by hepatic enzyme-inducing first generation AEDs

Large et al., 2011
PERAMAPANEL

- Three phase 3 pivotal trials
  - 2 mg - 20-23%
  - 4 mg - 28.5%
  - 8 mg - 35.3%
  - 12 mg - 35.0%
- Non-competitive AMPA receptor blocker
- Half life ~ 70 hrs
- Tolerability
  - sedation, weight gain, vertigo
  - aggression (homicidal ideation, US only)
- Schedule 3
**ESLICARBAZEPINE**

![Chemical Structures](image)

- ESL
- (S)-licarbazepine [(S)-MHD]
  - OXC: 80%
  - ESL: 95%

- (R)-licarbazepine [(R)-MHD]
  - OXC: 20%
  - ESL: 5%

Nature Reviews | Drug Discovery
Extended Release

- oxcarbazepine
- topiramate