The new landscape of antiepileptic drugs

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WSNS Annual Meeting, Oct 13, 2012

Outline
• Seizure types
• 2010 nomenclature
• AED choices based on seizure type or epilepsy syndrome
• Status epilepticus – 2012 guidelines
• Individual AEDs
• Strategies for AED resistance

1981 Classification of Seizures*

I. Partial (Focal, Local) Seizures
   A. Simple Partial Seizures (SPS) ("aura", "focal motor", etc.)
      Normal consciousness.
      Signs/symptoms: motor, somatosensory, special sensory, autonomic, or psychic (vary greatly between patients depending upon the brain area involved in the seizure).
   B. Complex Partial Seizures (CPS) ("psychomotor")
      Consciousness is impaired. May begin as SPS. Automatisms +/-.
   C. Partial seizures evolving to generalized seizures
      When SPS or CPS evolve, they usually progress to secondarily generalized tonic-clonic seizures (SGTCS). Rarely, they are hemi-clonic or incomplete GTCS.

*International League Against Epilepsy Epilepsia 1981;22:489-501

Homunculus

2010 ILAE system of terminology and concepts for organization of seizures and epilepsies*

• The 2006 classification of epilepsy syndromes was unchanged, except the “focal” & “generalized” dichotomy is abandoned*
• Changed many of the 1981 seizure names
  – Removes “simple and complex partial” seizures
  – Adds "epileptic spasms" and removes neonatal seizures
• Clarifies generalized and focal seizure onset modes
• Etiologies are now: genetic, structural/metabolic, unknown

*ILAE Commission on Classification and Terminology. Epilepsia 2010;51:676-85

1981 Classification of Seizures* (cont.)

II. Generalized Seizures (convulsive and nonconvulsive)
   A. Absence seizures (typical and atypical) ("petit maladie")
   B. Myoclonic
   C. Clonic
   D. Tonic
   E. Generalized tonic-clonic (GTCS) ("grand maladie")
   F. Atonic
III. Unclassified seizures (incomplete data)

*International League Against Epilepsy Epilepsia 1981;22:489-501
Table 1* - Classification of seizures

- **Generalized Seizures**
  - Tonic-clonic (in any combination)
  - Absence
    - Typical
    - Atypical
    - Myoclonic absence
    - Eyelid myoclonia
  - Myoclonic
    - Myoclonic
    - Myoclonic atonic
    - Myoclonic tonic

- **Focal Seizures**
  - Unknown: epileptic spasms

*ILAE Commission, *Epilepsia* 2010;51:676-85

Table 2* - Descriptors of focal seizures

- Without impairment of consciousness or awareness
  - With observable motor or autonomic components
  - Subjective sensory or psychic phenomena only
- With impairment of consciousness or awareness
- Evolving to a bilateral, convulsive seizure (involving tonic, clonic or tonic-clonic features)

*ILAE Commission, *Epilepsia* 2010;51:676-85

Selection of AEDs by seizure type or epilepsy syndrome

Evidence–based, using head-to-head comparison trials when available

Yellowstone National Park, Wyoming

Current U.S. AEDs

Comparison trials of older AEDs

![Graph showing the timeline of AEDs usage from 1900 to 2020](image)
Comparison trials of older AEDs

VA cooperative study #1
VA cooperative study #2

Standard and New Antiepileptic Drugs (SANAD) Studies

- Multicenter studies in UK; age > 4 years
- Two head-to-head randomized, open-label trials:
  - CBZ, GBP, LTG, OXC, TPM for focal sz (SANAD-A)
  - VPA, LTG, TPM for generalized-onset sz (SANAD-B)
- Primary outcome measures:
  1. Retention (time to treatment failure due to inadequate seizure control or intolerable side effects)
  2. Seizure control (time to 1-year seizure remission)


SANAD-A: Retention

Probability of staying on-drug
N = 1721

Years from randomization


SANAD-A: Seizure Control

Probability of 12-month remission

Years from randomization


Recommended AEDs for Focal Seizures*

- Monotherapy:
  - First: carbamazepine, lamotrigine, oxcarbazepine, phenytoin, topiramate, valproate (none vastly superior)
  - Second: phenobarbital, primidone
  - Third: felbamate
- Adjunctive therapy only:
  - First: ezogabine, lacosamide, levetiracetam, tiagabine, pregabalin, zonisamide
  - Second: vigabatrin, rufinamide, clobazam?
  - Less effective: gabapentin, clonazepate, acetazolamide

*Based on: ILAE Treatment Guidelines Epilepsia 2006;47:1094-1120, FDA approval RCTs, and extensive recent literature

Generalized-onset Epilepsy

SANAD-B: Retention

Probability of staying on drug
N = 716

Time from randomization (mo)

Recommended AEDs for Generalized-onset Seizures*

- **Absence:**
  - First: ethosuximide, meth- or phensuximide, valproate
  - Second: acetazolamide, clobazam?, lamotrigine, levetiracetam?, rufinamide?, zonisamide?

- **Myoclonic:**
  - First: clonazepam, levetiracetam, valproate
  - Second: AZM, clobazam?, ESM, lamotrigine, PB, PRM, rufinamide?, zonisamide?

- **GTCS:**
  - First: LTG, LEV, topiramate, valproate
  - Second: PB, phenytoin, PRM, zonisamide?

*Based on: ILAE Treatment Guidelines Epilepsia 2006;47:1094-1120, FDA approval RCTs, and extensive recent literature

AEDs for Specific Syndromes

- **Juvenile Myoclonic Epilepsy**
  - First: clonazepam, levetiracetam*, valproate,
  - Second: lamotrigine?, rufinamide?, TPM?, zonisamide?

- **Lennox-Gastaut Syndrome**
  - First: clonazepam*(drop attacks), clonazepam, lamotrigine*, levetiracetam, rufinamide*, topiramate*, valproate
  - Second: felbamate*

- **West Syndrome (epileptic spasms)**
  - ACTH*, valproate, vigabatrin*

*FDA approved for syndrome specifically

Based on: ILAE Treatment Guidelines Epilepsia 2006;47:1094-1120, FDA approval RCTs, and extensive recent literature

Focal-onset epilepsy syndromes

1. Temporal lobe epilepsies (67%)
2. Frontal lobe epilepsies (20%)
3. Occipital lobe epilepsies (8%)
4. Parietal lobe epilepsies (5%)

*Based on: ILAE Treatment Guidelines Epilepsia 2006;47:1094-1120, FDA approval RCTs, and extensive recent literature

Status epilepticus

1. Convulsive: GTCS lasting > 5 min, or repeated seizures without recovery of consciousness between*
2. Non-convulsive
   1. Absence
   2. Focal w/ altered awareness
   3. Focal motor

*Glauser and AES Guidelines Committee. JAMA 2012; in press
Convulsive status epilepticus*

- **Step 1:**
  - ABCs and obtain bloodwork
  - Infuse normal saline and 100 mg thiamine
  - Then, give one ampule of D50 (adult) or 2 ml/kg of D25 (children) if glucose < 60 mg/dl

- **Step 2:**
  - i.v. lorazepam 4 mg (2 mg for weight 13-40 kg) (not diazepam) or i.m. midazolam 10 mg (5 mg for 13-40 kg)*
  - be ready to place on ventilator
  - give NO muscle relaxants (except short-acting to intubate)


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Convulsive status (cont.)

- **Step 3:**
  - give i.v. fosphenytoin (Cerebyx) 18 mg/kg P.E. load (not faster than 150 mg/min) may repeat up to 30 mg/kg (i.v. or i.m.)
  - monitor BP and heart rate
  - i.v. phenytoin causes bradycardia, hypotension, and thrombophlebitis. NEVER give phenytoin i.m., in anything other than saline, or >50 mg/min!

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AED Choice by Seizure Type

- **Focal-onset**
  - Simple
  - Complex
  - Secondary generalized

- **Generalized-onset**
  - Tonic
  - Tonic-clonic
  - Myoclonic
  - Atonic
  - Epileptic status

- Actions:
  - topiramate? valproate?
  - vigabatrin

- Ethosuximide

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Older Antiepileptic Drugs (AEDs)

- 1857 bromide salts
- 1912 phenobarbital
- 1938 phenytoin
- 1954 primidone
- 1960 ethosuximide
- 1968 diazepam
- 1974 carbamazepine
- 1975 clonazepam
- 1978 valproic acid
**Newer AEDs**

1993 felbamate  
1994 gabapentin  
1995 lamotrigine  
1996 fosphenytoin  
1997 topiramate, tiagabine, vagus nerve stimulator  
1999 levetiracetam  
2000 oxcarbazepine, zonisamide  
2005 pregabalin  
2009 lacosamide, rufinamide, vigabatrin  
2010-12 ACTH gel, ezogabine, clobazam  
2013+, brivaracetam, perampanel, eslicarbazepine, remacemide  

**ACTH**

- Injectable adrenocorticotropic hormone (H.P. Acthar® gel) 80 U/ml, a porcine extract  
- One 1996 study showed 13/15 infants responded to ACTH and 4/14 responded to prednisone.  
- Side effects: Cushingoid appearance, infection, hypertension, irritability, acne. Less with 75 U/m² BID than 150 U/m² daily  

**Carbamazepine**

- **Indication:** focal-onset seizures. Can reduce some genetic GTCS, but can worsen absence and myoclonic seizures  
- **Pharmacokinetics:**  
  - hepatic enzyme inducer  
  - Undergoes autoinduction over 2-3 months → need low starting doses (2-3 mg/kg/d) and build up gradually over 3 months  
  - 75% bound to serum proteins  
  - $T_{1/2}$ 14 hrs  

**Carbamazepine (cont.)**

- **MOA:** enhance rapid Na⁺ channel inactivation, modulate L-type Ca²⁺ channels  
- **Dose:** 300-2400 mg/day (given tid-qid; bid for extended release forms)  
- **Range:** 4 - 12 μg/ml; check CBC monthly at first  
- **Adverse Effects:** diplopia, ataxia, nausea, rash, Stevens Johnson Syndrome, aplastic anemia (<1/65,000), SIADH  
- **Names:** Tegretol™, Tegretol XR™, Carbatrol™

**Clobazam**

- **Names:** Onfi®  
- **U.S. FDA approval:** 10/2011 for Lennox-Gastaut Syndrome (LGS) age ≥22 years  
- Effective on drop attacks in 2 studies on LGS* at 1.0 mg/kg/day (max 40 mg/day)  
- **MOA:** GABA receptor agonist – 1.5 benzodiazepine  
- **Dose:** 10-40 mg daily (given BID)  
- Used in >100 countries also for focal-onset seizures  
- **AEs:** sedation, fever, URI, drooling, constipation, cough, UTI, insomnia, aggression, fatigue, irritability, depression, vomiting, trouble swallowing, dyscoordination, bronchitis, and pneumonia

**Clonazepam**

- **Indication:** myoclonic, typical absence, atypical absence (Lennox-Gastaut Syndrome) seizures  
- **MOA:** binds GABA-Ay receptors → enhances Cl⁻  
- **Pharmacokinetics:** hepatic metabolism. 80% protein bound. $T_{1/2}$ is 24 hrs.  
- **Dose:** 0.5-6 mg/day (divided tid)  
- **Range:** 0.04-0.07 μg/ml  
- **Adverse Effects:** somnolence, dizziness, depression, fatigue, dependence  
- **Name:** Klonopin™

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*Ng et al. Neurology 2011;77:1473-81*
### Diazepam & Lorazepam

- **Class**: 1,4 benzodiazepines
- **Indication**: frequent focal sz or GTCS (acute therapy only); can cause absence status.
- **Lorazepam** is preferred for iv use in status epilepticus because, unlike diazepam, there is no redistribution back out of the brain 30 - 60 minutes later. Lorazepam has a shorter half-life in serum than diazepam due to less uptake into peripheral fatty tissue. Can be given with any iv fluids.

### Diazepam and Lorazepam (cont.)

- **MOA**: binds GABA-Aγ receptors → enhances Cl⁻
- **Pharmacokinetics**: hepatic metabolism.
  Tolerance and dependence develop
- **Dose equiv**: 5 mg diazepam = 2 mg lorazepam = 5 mg midazolam = 1 mg clonazepam
- **Rectal diazepam gel** for cluster seizures
- **Adverse Effects**: somnolence, dizziness, depression, fatigue, tolerance, dependence
- **Names**: Valium ™, rectal Diastat ™, Ativan ™

### Ethosuximide

- **Indication**: absence (? myoclonic) seizures
- **MOA**: modulates slow T-type Ca channels
- **Pharmacokinetics**: hepatic metabolism. 0% bound to serum proteins. T₁/₂ is 40 hrs
- **Dose**: 250-1500 mg/day (given bid-tid)
- **Range**: 40 - 100 µg/ml
- **Adverse Effects**: nausea, abdomen pain, sedation, ataxia, leukopenia, pancytopenia, Stevens-Johnson
- **Name**: Zarontin ™

### Ezogabine

- **Indication**: adjunctive for partial seizures in adults
- **MOA**: Potassium channel opener, increasing M-current, which in turn stabilizes the resting and sub-threshold membrane potential (Kᵥ7.2-5)
- **Pharmacokinetics**: glucuronidation → renal
- **Dose**: 600-1200 total daily, given TID
- **Range**: ? µg/ml
- **Adverse Effects**: urinary retention (3%), dizziness, blurred vision, neuropsychiatric effects, 7 msec QT prolongation, increased digoxin & alcohol levels
- **Names**: Potiga®, (retigabine outside U.S.)
- **FDA approval**: 10/11, final 3/2012

### Felbamate

- **Indication**: partial seizures; Lennox-Gastaut Syndrome
- **MOA**: enhance rapid Na channel inactivation, ↓ Ca²⁺ channels
- **Pharmacokinetics**: hepatic metabolism; enzyme inhibitor. T₁/₂ is 15-20 hrs
- **Dose**: 1200-3600 mg/day (given TID)
- **Range**: 60-100 µg/ml; check CBC, LFTs monthly
- **Adverse Effects**: Fatal aplastic anemia (31/10,000), fatal hepatic failure (16/10,000), insomnia, headache, anorexia/weight loss
- **Name**: Felbatol ™

### Gabapentin

- **Indication**: adjunctive - partial seizures, > age 12
- **MOA**: modulates Ca channel at α2-δ subunit
- **Pharmacokinetics**: renal excretion. 0% bound to serum proteins. T₁/₂ = 6 hrs. Bioavailability = 60% at lower doses but falls to 30% at higher doses
- **Dose**: 900-1800 mg/day (bid-tid) (occ. more)
- **Range**: 4-8.5 µg/ml
- **Adverse Effects**: drowsiness, ataxia, dizziness; no serious organ toxicity
- **Name**: Neurontin ™
**Lacosamide**

- **Indication:** adjunctive, adult, focal-onset seizures
- **MOA:** enhances sodium-channel slow inactivation,
- **Pharmacokinetics:** linear; partially renally-excreted and partially metabolized by CYP 2C19. No known drug interactions. 15% protein bound
- **AEs:** diplopia, HA, nausea, dizziness, ataxia, syncope, longer PR and QTc
- **Dose:** 200-400 mg/day (given BID), Also available I.V.
- **Name:** Vimpat®
- I have a genetic GTCS study open (SP982)

_Epilepsia_ 2007;48:1308-17 and 2009;50:443-453

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**Physiology of Voltage-Gated Sodium Channels**

- **Carbamazepine, lamotrigine, oxcarbazepine, phenytoin, rufinamide**
- **Inactivated state**
  - fast (within ms)
- **Repolarization**
- **Resting potential**
- **Open state**


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**Lamotrigine**

- **Indication:** focal seizures, primary GTCS, and Lennox-Gastaut Syndrome ≥ age 2
- **MOA:** enhances rapid inactivation of Na⁺ channel
- **Pharmacokinetics:** hepatic metabolism. 0% bound to serum proteins. \( T_{1/2} = 25 \) hrs alone; 13 hrs with enzyme inducing AEDs (PB, PHT, CBZ, PRM) oral contraceptives or rifampin; 70 hrs with inhibitor (valproate). Serum levels fall by 67% in third trimester of pregnancy
- **Dose:** 100-500 mg/day (bid); up to 1000 mg/day
- **Range:** 4-20 µg/ml
- **Adverse Effects:** dizziness, blurred vision, vomiting, <0.1% Stevens-Johnson or TENS, rare multi-organ failure
- **Name:** Lamictal™

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**Levetiracetam**

- **Indication:** adults & kids: adjunctive for partial seizures, myoclonic seizures in JME, and genetic GTCS
- **MOA:** unknown
- **Pharmacokinetics:** renal excreted, liver hydrolyzed; <10% bound to serum proteins \( T_{1/2} = 7 \) hrs
- **Dose:** 1000-3000 mg/day (bid)
- **Range:** 20-40 µg/ml
- **Available:** oral or i.v. forms
- **Adverse Effects:** somnolence, fatigue, asthenia, dizziness, infection, irritability, depression
- **Name:** Keppra™

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**Oxcarbazepine**

- **Indication:** partial seizures over age 3
- **MOA:** enhance rapid Na⁺ channel inactivation, modulate N- and P-type Ca²⁺ channels
- **Pharmacokinetics:** hepatic reduction to MHD then renal excretion. No autoinduction. 40% bound to serum proteins. \( T_{1/2} = 9 \) hrs; shorter w/ EIAEDs. OC estrogen falls at 1200 mg/d
- **Dose:** 1200-2400 mg/day (bid-tid); up to 3 g/d
- **Range:** 12-35 µg/ml (MHD - watch lab error)
- **Adverse Effects:** dizziness, nausea, ataxia, hyponatremia (2.5%)
- **Name:** Trileptal™

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**Phenobarbital and Primidone**

- **Indication:** partial and generalized seizures. PRM helps myoclonic seizures
- **MOA:** bind GABA-A receptors nonspecifically --- enhances CI conductance
- **Pharmacokinetics:** hepatic enzyme inducers. PR is 50%, PRM is <5%, bound to serum proteins. \( T_{1/2} = 96 \) hrs for PB, 12 hrs for PRM. PB -> PRM
- **Dose:** 60-180 mg/day for PB, 250-2000 mg/day for PRM
- **Range is 15-45 (PB), 6-12 (PRM) µg/ml
- **Adverse Effects:** sedation, cognitive slowing, depression, rash, Stevens-Johnson, nausea, tolerance, dependence
- **Names:** phenobarbital; Mysoline™

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**Epilepsia** 2007;48:1308-17 and 2009;50:443-453
Phenytoin & fosphenytoin

- **Indication:** partial and generalized tonic-clonic seizures
- **MOA:** enhance rapid Na+ channel inactivation
- **Pharmacokinetics:** hepatic enzyme inducer. 90-95% bound to serum proteins. T1/2 is 22 hrs in adults - longer at higher doses due to zero-order kinetics, longer in elderly/neonates
- **Dose:** 200-600 mg/day (q day-tid) p.o.; fosphenytoin i.m./i.v. 200-800 mg/day P.E. (given q8h).
- **Therapeutic range is 10-20+ µg/ml
- **Adverse Effects:** nystagmus, ataxia, dysarthria, cognitive slowing, gingival hyperplasia, hypertrichosis, rash, Stevens-Johnson, lymphadenopathy, pseudolymphoma, osteomalacia
- **Names:** Dilantin™; for i.m./i.v.= Cerebyx™

Pregabalin

- **Indication:** adjunctive - partial szs in adults
- **Mechanisms:** binds α2-δ unit of Ca2+ channel, modulates Ca2+ current, glutamate, noradrenaline, and substance P
- **Pharmacokinetics:** 100% renal excretion; T1/2 = 6 hr, Cmax = 1 hr; 90% bioavailability
- **Dose:** 150-600 mg/d (given tid). Category V.
- **Adverse effects:** dizziness, dry mouth, somnolence, decreased attention/concentration, edema, blurred vision, weight gain
- **Name:** Lyrica™

Rufinamide

- **Rufinamide (Banzel®)
  - **Indication:** seizures in Lennox-Gastaut Syndrome, age 4+
  - **MOA:** enhances rapid inactivation of Na+ channel
  - **Pharmacokinetics:**
    - Absorption is slow and nonlinear: extent of absorption decreases with higher doses, but is enhanced by food
    - T ½ = 6-10 hours
    - AEs: sedation, fatigue, dizziness, ataxia, dizziness, nausea, shorter QTc interval
    - Dose: 400-3200 mg/day (divided BID)

Neurology 2008;70:1950-58, Epilepsia Aug 2009

Tiagabine

- **Indication:** adjunctive - partial seizures age 12+
- **MOA:** selective GABA reuptake inhibitor (SGRI)
- **Pharmacokinetics:** hepatic metabolism. 0% bound to serum proteins; displaced by VPA. T1/2 is 40 hrs; shorter with EIAEDs
- **Dose:** 32-56mg/day (bid-qid)
- **Range:** 5-70 µg/ml
- **Adverse Effects:** sedation, cognitive slowing, dizziness, tremor, anxiety, nausea
- **Name:** Gabitril™

Topiramate

- **Indication:** monotherapy for partial seizures, GTCS, and Lennox-Gastaut Syndrome
- **MOA:** ↑ rapid Na+ channel inactivation, ↑ GABA-A, modulate L-type Ca2+ channels, ↓ glutamate, inhibit carbonic anhydrase
- **Pharmacokinetics:** 71% renal excretion. 15% bound to serum proteins. T1/2 is 21 hrs (15 hr with EIAEDs); induces phenytoin 25% and oral contraceptives at 200 mg/d
- **Dose:** 200-400 mg/day (given bid-tid)
- **Range:** 15-25 µg/ml
- **Adverse Effects:** renal stones (1.5%), glaucoma, tingling, word-finding difficulties, cognitive slowing, metabolic acidosis
- **Name:** Topamax™

Valproate

- **Indication:** partial; absence, myoclonic and GTCS
- **MOA:** ↑ rapid Na+ channel inactivation, ↑ GABA-A, modulate L-type Ca2+ channels
- **Pharmacokinetics:** hepatic enzyme inhibitor. 80-90% bound to serum proteins – displaced by ASA. T1/2 is 15-20 hrs in adults
- **Dose:** 500-6000 mg/day (divided bid-tid)
- **Range:** 50-150 µg/ml
- **Adverse Effects:** nausea, vomiting, abdominal pain, hyperinsulinemia -> obesity, weight loss, tremor, alopecia, hyperammonemia, hepatic failure, sedation
- **Names:** Depakene, Depakote™; i.v. = Depacon™
Vigabatrin

- **Indication**: infants ages 1 mo – 2 years with infantile spasms, and for adults with refractory complex partial seizures
- **MOA**: GABA transaminase inhibitor - irreversible
- **Pharmacokinetics**: Renal excretion.
- **Dose**: 3000-6000 mg/day, given BID
- **AEs**: sedation, weight gain, anemia, peripheral neuropathy
- **Serious AE**: visual field constriction due to irreversible retinal cell damage in 30% of patients; infants may get MRI T2 white matter changes
- **Name**: Sâbril®
- **FDA approved**: 8/21/09

Zonisamide

- **Indication**: partial seizures age 16 and above
- **MOA**: enhance rapid Na+ inactivation, ↓ T-type Ca2+ current, ↓ GABA, inhibit carbonic anhydrase
- **Pharmacokinetics**: hepatic metabolism. T 1/2 = 69 hr monoRx; 27-38 hr w/ EIAEDs, 46 hr w/ VPA
- **Dose**: 400-600 mg/day (given daily or bid)
- **Range**: 20-30 μg/ml
- **Adverse effects**: sufa: Stevens-Johnson or blood dyscrasia; somnolence, dizziness, nausea, rhinitis, ataxia, HA, weight loss (10%), renal stones (<4%)
- **Name**: Zonegran™

Treatment – new definitions*

- “Treatment failure” = sz recurrence after adequate Rx
- “Drug resistance” = failure of 2+ AEDs to achieve seizure freedom
- “Seizure free” = freedom of all sz for either 3X longest pre-Rx sz-free interval or 12 months (whichever is longer)


Surgical Treatment

- Anterior (medial) temporal lobectomy
- Lesionectomy
- Focal Cortical Resection
- Multiple Subpial Transections
- Corpus Callosotomy
- Hemispherectomy
- Vagus Nerve Stimulation
- Research only: Responsive and Deep Brain Stimulation, stereotactic radiosurgery

Comparative Efficacies

<table>
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<tr>
<th>Treatment</th>
<th>Age</th>
<th>Indication</th>
<th>Efficacy</th>
<th>Adverse Effects</th>
</tr>
</thead>
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<tr>
<td>Antiepileptic Drugs</td>
<td>Children Adults</td>
<td>Specific AEDs for specific seizure types</td>
<td>65% or freedom with first 3 AED-therapy trials*</td>
<td>Varied by AED, often CNS-related</td>
</tr>
<tr>
<td>Ketogenic Diet</td>
<td>Children Adults</td>
<td>All seizure types</td>
<td>Rarely seizure-free; 24% pts &gt;50% seizure reduction at 3 months</td>
<td>Lipid disorders, ketoneurias</td>
</tr>
<tr>
<td>Surgical Resection (TLE)</td>
<td>Children Adults</td>
<td>Pharmacoresistant partial epilepsy</td>
<td>85% seizure freedom, improved quality of life</td>
<td>Cognitive effects, surgery-related risks</td>
</tr>
<tr>
<td>VNS</td>
<td>12 and older</td>
<td>Pharmacoresistant partial epilepsy</td>
<td>Rarely seizure-free; 43% of pts &gt;20% seizure reduction at 3 years</td>
<td>Voice alteration, cough, dyspnea, infection, high cost for rare or freedom</td>
</tr>
</tbody>
</table>


TLE surgery - results

- ERSET study seizure-freedom:*
  - 0% medical group vs.
  - 85% surgical group (O.R. = ∞)

*Treatment failure” = sz recurrence after adequate Rx

VNI Epilepsy Center

- David Vossler MD FAAN, neurology & neurophysiology
- Baburaj Thankappan MD, neurology & neurophysiology
- Kevin Joseph DO, pediatric neurology & sleep medicine
- Erica-Brandling-Bennett PhD, neuropsychology
- Peter Balousek MD, neurosurgery
- Carole Burton RN, clinical research
- Tony Bell, Zoé Goldeshtein, Amarjit Kaur, R EEG/EP T
- Vicki Murphy MSW, social work
- Heather Shimamoto PharmD, pharmacy

425-656-4004 or 888-686-4964 (4WNI)
www.valleymed.org/neuro

Future AEDs

- Seeking US FDA approval:
  - Brivaracetam
  - Eslicarbazepine
  - Perampanel
- Still in research
  - Carabersat, remacemide
- Rejected by FDA:
  - Carisbamate


Eslicarbazepine

- BIA 2-093, Zebenix®, a dibenzapine like CBZ, OXC
- **Indication:** adjunctive for partial-onset seizures
- **MOA:** enhance rapid Na⁺ channel inactivation, modulate N- and P-type Ca²⁺ channels
- **Pharmacokinetics:** not metab. by inducible CYP 450
- **Dose:** 800 – 1200 mg qDay
- **Range:** ? μg/ml
- **Adverse Effects:** headache, dizziness, diplopia, nasopharyngitis*
- We are conducting adjunctive (BIA 304) and monotherapy trials (BIA 045) – excludes HLA-B 1502

* Halasz et al. *Epilepsia* 2010;51:1963-9

Brivaracetam

- Brivaracetam
  - Effective in partial-onset seizures*
  - 2-pyrrolidinone derivative
  - Analogs of levetiracetam (Keppra), seletracetam and piracetam (Nootropil®)
  - Like LEV, it binds synaptic vesicle protein 2A (SV2A)
  - It also inhibits voltage-dependent Na⁺ currents#, and it reverses the inhibition of GABA- and glycine-induced currents
  - UCB Pharma

*French et al. *Neurology* 2010;75:519-25
#Zona et al. *Epilepsy Research* 2010;88:46-56

Perampanel

- Perampanel (E2007)
  - Doses of 8 & 12 mg effective in 2 RCTs (Eisai 304, 305)
  - Glutamate (AMPA) antagonist

*Big Sky Mountain, Montana*