Making Sense of Antiepileptic Drugs in 2007

Thomas K. Koch, MD

Spectrum of Seizures

- Status Epilepticus
- Prolonged
- Clusters / Repetitive
- Isolated Seizure
- Recurrent
- Chronic
- Acute

Treatment after 1st seizure

- Seizure recurrence*
  - Risk within 3-5 yrs: 44%
  - Risk Factors
    - EEG abnormality: 56-71%
    - Sleep associated seizure: 55%
    - at 4 yrs
    - Remote symptomatic/MR: 74%

- Daily AEDs
  - Almost never
- Rectal diazepam
- Safety considerations
  - Bathing, swimming
  - Being alone
  - Climbing
  - Driving


Goals of Antiepileptic Treatment

- Control seizures
  - Decrease frequency and intensity
- Minimize side-effects
  - Monotherapy when possible
- Balancing Act:
  - Seizure Control
  - Side-effects
  - Compliance

Therapeutic Selection for Patients with Epilepsy in 2007

- AEDs
- Resective Surgery
- VNS
A wealth of anticonvulsants

Many Never Fully Respond

Seizure-freedom with anticonvulsants

Over one third of patients will never respond to medication alone

Standard Antiepileptic Drugs


Standard Antiepileptic Drug

“Old dogs learn new tricks”

Standard AEDs

New Delivery

Diazepam rectal - Diastat

First line for acute repetitive seizures, clusters

Practical, easily administered

Safety

Adverse respiratory events less than IV

No deaths reported

Rapidly and reliably absorbed

Short onset, longer duration of action

Effective in terminating seizures

Can prevent delays in treatment

Available: 2.5 to 20 mg, increments of 2.5

Standard AEDs

New Prodrug

Phenytoin - Fosphenytoin

First line (with Lorazepam) for status

Phosphate ester prodrug of phenytoin Na

Improved aqueous solubility, neutral pH

Rapidly and completely converted to phenytoin

Rate of Fx (max): 150mg/min vs. 60mg/min

Significantly faster attainment of free phenytoin

Well absorbed IM

Safer delivery - Heart rate, BP, Skin
**Standard AEDs**

**Improved Delivery - BID**

Carbamazepine - Carbatrol, Tegretol XR
- A leading AED for partial seizures
- BUT has an 8 hr half-life

![Carbamazepine Image]

**Standard AEDs**

**New Delivery**

- **Valproate - Depacon**
  - IV formulation
  - **Use:**
    - Oral restriction (NPO)
    - Need for rapid loading
    - Acute seizures (Status)
    - Intractable migraine

- **Adverse event:**
  - Injection site pain and/or redness related to concentration

- **Dosing:** 1:1, IV:PO equivalent q6h
- **Loading Doses:** 10 - 20 mg/kg
- **Infusion Rates:** Infusion: 20mg/min in D5NS or LR
  - Bolus Rx: Suggested 1:1 dilution for site reactions

- **Supplied:** 100 mg/ml of Na Valproate

**New Antiepileptic Drugs**

- **Possible**
  - Felbamate (Felbatol)
  - Gabapentin (Neurontin)
  - Lamotrigine (Lamictal)
  - Levetiracetam (Keppra)
  - Oxcarbazepine (Trileptal)
  - Topiramate (Topamax)
  - Tiagabine (Gabitril)
  - Zonisamide (Zonegran)
  - Vigabatrin (Sabril)**

- **Practical**
  - Lamotrigine
  - Levetiracetam
  - Oxcarbazepine
  - Topiramate
  - Zonisamide
  - Vigabatrin

- *Not currently available in USA

**Lamotrigine (Lamictal)**

- Chemically unrelated to other AEDs
  - a Phenyltriazine
- **Elimination Half-life**
  - monotherapy: 24 hrs
  - with enzyme inducers: 14 hrs
  - with VPA: 60 hrs
  - Increases AE risk
- Linear kinetics
- Metabolism
  - Hepatic - glucuronidation
  - Renal elimination

**Lamotrigine (Lamictal)**

- **Favorable with:** Broad Spectrum
  - Partial seizures
  - Generalized
  - Lennox-Gastaut
  - Absence
- **Drug interactions – significant for VPA**
  - Other AEDs may induce or inhibit lamotrigine metabolism
  - Slow titration*
- **Supplied:**

* Titratin Website: www.lamictal.com/calc1.jsp
**Lamotrigine (Lamictal)**

**Side-effects**

- CNS
  - Headache
  - Nausea
  - Insomnia
  - Dizziness
  - Diplopia
  - Ataxia
  - Tremors/Tics

- **Rash**
  - 1 - 10% risk
  - Greatest on initiation
  - Gradual intro < risk
  - Stevens-Johnson
    - Child: 1:100
    - Adult: 1:1000

* All effects are dose related

**Related to rate of initiation**

**Levetiracetam (Keppra)**

**Pharmacology**

- Chemically unrelated to other AEDs
  - an S-enantiomer of pyrroldine acetamide
- Action: Unknown
- Specific binding site
- Prevents kindling
- Elimination Half-life: 6-8 hrs
- Linear kinetics
- \( P_{450} \) Induction – No
- Metabolism: renal
- Drug interactions - None

**Side-effects**

- CNS
  - Somnolence
  - Asthenia
  - Headache
  - Dizziness
  - Ataxia

- Hematologic
  - Decrease RBC
  - Decrease WBC

- Neurobehavioral
  - Nightmares
  - Agitation
  - Irritability
  - Psychosis
  - Anxiety
  - Lability
  - Depression

**Favorable with:** Broad Spectrum

- Partial seizures & secondarily generalized
- Photosensitive epilepsy
- Brain tumors
- Juvenile Myoclonic Epilepsy

**Supplied:**

**Dosing:**

- **Starting**
  - Child: 10-20 mg/kg/d
  - Adult: 1000 mg/d

- **Maintenance**
  - Child: 60-80 mg/kg/d
  - Adult: 3000 mg/d

- **Interval**
  - BID

**Topiramate (Topamax)**

**Pharmacology**

- Sulphamate-substituted monosaccharide
  - Marked effects on Na\(^+\) channels & GABA\(_A\) receptors
  - Modest effects on glutamate receptors
  - Weak carbonic anhydrase inhibitor
- Elimination Half-life: 20-24 hrs
- \( P_{450} \) Induction – Yes, mild
- Metabolism
  - Hepatic metabolism
  - Renal excretion
- Drug interactions - mild

**Favorable in children:** Broad-Spectrum

- Partial seizures
- Generalized seizures
- Lennox-Gastaut*
- Migraine

**Supplied:**

**Dosing:**

- **Starting**
  - Child: 1 mg/kg/d
  - Adult: 25 mg/d

- **Maintenance**
  - Child: 8-15 mg/kg/d
  - Adult: 100-300 mg/d

- **Interval**
  - BID
**Topiramate (Topamax)**

**Side-effects**
- **CNS**
  - Fatigue / somnolence
  - Cognitive slowing
  - Word finding difficulty
  - Poor concentration
  - Ataxia
  - Anorexia / weight loss
  - Paresthesias
- **Kidney stones**
  - 1.5% adult, 0.6% ped
  - Carbonic anhydrase inhibitor
- **Cognitive slowing**
- **Word finding difficulty**
- **Poor concentration**
- **Dizziness**
- **Ataxia**
- **Anorexia / weight loss**
- **Paresthesias**

**Side-effects**
- **Fatigue**
- **Somnolence**
- **Cognitive slowing**
- **Word finding difficulty**
- **Poor concentration**
- **Dizziness**
- **Ataxia**
- **Anorexia / weight loss**
- **Paresthesias**

**Kidney stones**
- 1.5% adult, 0.6% ped
- Carbonic anhydrase inhibitor
- Avoid Ketogenic diet, Ca++, Ca++

**Oxcarbazepine (Trileptal)**

**Side-effects**
- **CNS**
  - Headache
  - Nausea
  - Ataxia
  - Dizziness
  - Diplopia
  - Somnolence
- **Other**
  - Hyponatremia similar to CBZ – uncommon in children
  - Rash rare, < CBZ
  - No blood dyscrasias or hepatotoxicity

**Oxcarbazepine**

**Supplied**
- 150, 300, 600 mg tabs

**Liquid**
- 300 mg / 5cc

**Dosing**
- **Child**: 10 mg/kg/d
- **Maintenance**: 30-55mg/kg/d
- **Interval**: BID
- **Adult**: 150-300 mg/d
- **Interval**: 2400-3000mg/d
- **Interval**: BID

**Note**: Conversion ratio: CBZ:OXC is 1:1.5

---

**Newer Antiepileptic Drugs**

<table>
<thead>
<tr>
<th>AED</th>
<th>Half-life</th>
<th>Dose / d*</th>
<th>Note 1</th>
</tr>
</thead>
<tbody>
<tr>
<td>Felbamate</td>
<td>14-24 hr</td>
<td>30-45 mg/kg</td>
<td>Fatal AEs – Liver, BM</td>
</tr>
<tr>
<td>Gabapentin</td>
<td>5-7 hr</td>
<td>30-100 mg/kg</td>
<td>Minimal AEs</td>
</tr>
<tr>
<td>Lamotrigine</td>
<td>15-50 hr</td>
<td>5-15 mg/kg</td>
<td>Rash, SJS</td>
</tr>
<tr>
<td>Levetiracetam</td>
<td>4-11 hr</td>
<td>20-80 mg/kg</td>
<td>Nightmares, Psychosis</td>
</tr>
<tr>
<td>Oxcarbazepine</td>
<td>8-10 hr</td>
<td>20-55 mg/kg</td>
<td>Mild AEs, mild inducer</td>
</tr>
<tr>
<td>Tiagabine</td>
<td>4-8 hr</td>
<td>1-2 mg/kg</td>
<td>Mkt AEs – fatigue, confusion</td>
</tr>
<tr>
<td>Topiramate</td>
<td>20-24 hr</td>
<td>4-10 mg/kg</td>
<td>CNS AEs, Renal Stones</td>
</tr>
<tr>
<td>Zonisamide</td>
<td>50-70 hr</td>
<td>4-10 mg/kg</td>
<td>CNS AEs, Renal Stones</td>
</tr>
<tr>
<td>Vigabatrin</td>
<td>5-7 hr</td>
<td>50-150 mg/kg</td>
<td>Not avail in US, ON toxicity</td>
</tr>
</tbody>
</table>

* Maintenance dosing

---

**AED Treatment Options**

**Partial**
- Simple
- Complex
- Secondarily generalized

**Generalized**
- Tonic
- Myoclonic
- Atonic
- Infantile spasms
- Absence

- CBZ, OXC, LTM, LTG, PHT, TPM, GBP, PB, ZNA
- VPA, LTG, TPM, LTM, ZNS, FBM

**Adapted from Pellock J. CNS Spectrums: New Developments in the Treatment of Epilepsy (Monograph). April, 2000.**

OXC (oxcarb), LTM (levetiracetam), LTG (lamotrigine), TPM (topiramate), FBM (felbamate), GBP (gabapentin)
Regardless of Age...

- The chances of becoming seizure-free on AEDs remain below 50% for the **partial epilepsies** (excludes Rolandic).
- The chances of becoming seizure-free on AEDs are only ~25% or less for **symptomatic generalized epilepsies**.

Therapeutic Selection for Patients with Epilepsy

- AEDs
- Resective Surgery
- VNS
- Ketogenic Diet