




Making Sense of Antiepileptic Drugs in 2007

Thomas K. Koch, MD

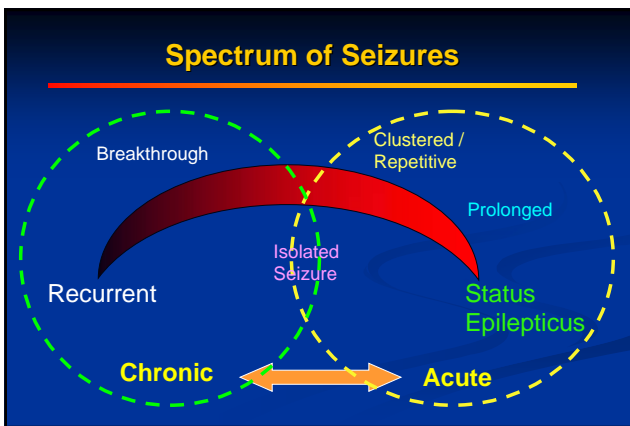
Making Sense of Antiepileptic Drugs

Presented by
Thomas K. Koch, MD

Faculty Disclosure Information

I have a relevant financial relationship to disclose:

- Ortho McNeil Pharmaceuticals
 - ❖ Speakers Bureau
- Abbott Laboratories
 - ❖ Speakers Bureau



Treatment after 1st seizure

- Seizure recurrence*
 - ❖ Risk within 3-5yrs: 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

* Shinnar et al. *Pediatrics*, 1996.

Goals of Antiepileptic Treatment

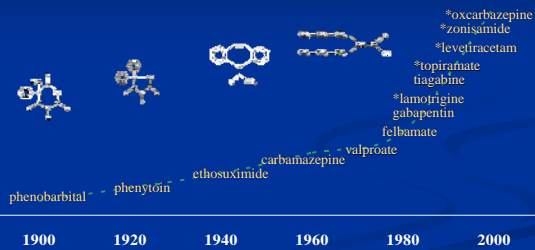
- Control seizures
 - ❖ Decrease frequency and intensity
- Minimize side-effects
 - ❖ Monotherapy when possible
- Balancing Act:

The balancing act is represented by a yellow triangle with 'Seizure Control' at the top vertex, 'Side-effects' at the bottom left vertex, and 'Compliance' at the bottom right vertex. A 'Seizures' icon with a red slash is also present.

Therapeutic Selection for Patients with Epilepsy In 2007

The diagram shows four overlapping circles representing therapeutic options: AEDs (top), Resective Surgery (left), Keto Diet (bottom), and VNS (right). Each circle contains a small image related to that therapy: a pill for AEDs, a brain scan for Resective Surgery, a plate of food for Keto Diet, and an EEG cap for VNS.

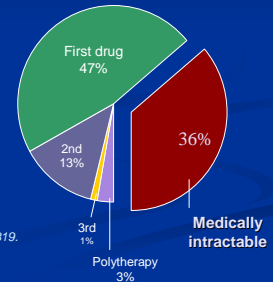
A wealth of anticonvulsants



Many Never Fully Respond

Seizure-freedom with anticonvulsants

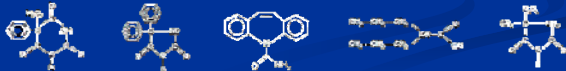
❖ Over one third of patients will never respond to medication alone



Kwan P, Brodie MJ. *N Engl J Med.* 2000;342(5):314-319.

Standard Antiepileptic Drugs

AED	Half-life	Dose / d	Note !
Phenobarbital	30-75 hr	3-5mg/kg	AEs, Inducer
Phenytoin	6-15 hr	3-5mg/kg	Zero order kinetics
Carbamazepine	8-28 hr	20-30mg/kg	Strong inducer, Autoinduction
Valproic Acid	8-15 hr	30-60mg/kg	AEs, Inhibitor, Teratogenic
Diazepam	15-40 hr	0.1-0.3mg/kg	Acute Rx



Standard Antiepileptic Drug

"Old dogs learn new tricks"

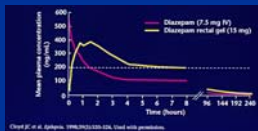
- Phenobarbital
- Benzodiazepines
- Phenytoin
- Carbamazepine
- Valproic Acid



Standard AEDs New Delivery

■ Diazepam rectal - Diastat

❖ First line for acute repetitive seizures, clusters



Cheng J et al. *Epilepsia.* 1998;39(3):520-526. Trial with phenytoin.



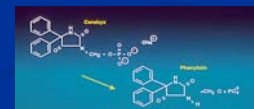
- Practical, easily administered
 - *Pediatric friendly*
- Safety
 - Adverse respiratory events less than IV
 - No deaths reported
- Rapidly and reliably absorbed
- Short onset, longer duration of action
- Effective in terminating seizures
- Can prevent delays in treatment
- Available: 2.5 to 20 mg, 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 Rx (max): **150mg/min** vs. 50mg/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



100mg, 200mg, 300mg

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



Standard AEDs New Delivery

- Valproate - Depakote ER
- ❖ Extended-release (qDay)



Use:

- Epilepsy
- **Migraine**
- Mania

Dosing: q Day at 20-60mg/kg/d

Bioavailability: approx 80+ %

Converting from Depakote: Increase by 20%

Supplied: 250mg, 500mg



New Antiepileptic Drugs

Possible

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

Practical

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

* Not currently available in USA

Lamotrigine (Lamictal) Pharmacology

- 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:**



* Titration Website: www.lamictal.com/cal1.jsp

Lamotrigine (Lamictal) Side-effects

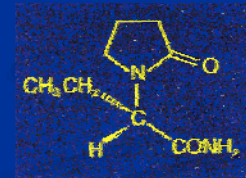
- **CNS***
 - ❖ Headache
 - ❖ Nausea
 - ❖ Insomnia
 - ❖ Dizziness
 - ❖ Diplopia
 - ❖ Ataxia
 - ❖ Tremors/Tics
- **Rash ****
 - ❖ **1 - 10 % risk**
 - Greatest on initiation
 - Gradual intro < risk
 - ❖ **Stevens-Johnson**
 - Child: 1:100
 - Adult 1:1000

* All effects are dose related

** Related to rate of initiation

Levetiracetam (Keppra) Pharmacology

- Chemically unrelated to other AEDs
 - ❖ an S-enantiomer of pyrrolidine acetamide
- Action: Unknown
 - ❖ Specific binding site
 - ❖ Prevents kindling
- Elimination Half-life: **6-8 hrs**
- Linear kinetics
- P₄₅₀ Induction – **No**
- Metabolism: renal
- **Drug interactions - None**



Levetiracetam Keppra

- **Favorable with: Broad Spectrum**
 - ❖ Partial seizures & secondarily generalized
 - ❖ Photosensitive epilepsy
 - ❖ **Brain tumors**
 - ❖ Juvenile Myoclonic Epilepsy

- **Supplied:**



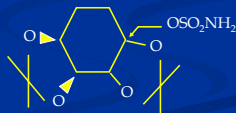
	<u>Starting</u>	<u>Maintenance</u>	<u>Interval</u>
Child:	10-20 mg/kg/d	60-80+ mg/kg/d	BID
Adult:	1000 mg/d	3000 mg/d	BID

Levetiracetam (Keppra) Side-effects

- **CNS**
 - ❖ Somnolence
 - ❖ Asthenia
 - ❖ Headache
 - ❖ Dizziness
 - ❖ Ataxia
- **Hematologic**
 - ❖ Decrease RBC
 - ❖ Decrease WBC
- ✓ **Neurobehavioral**
 - ❖ *Nightmares*
 - ❖ *Agitation*
 - ❖ Irritability
 - ❖ Psychosis
 - ❖ Anxiety
 - ❖ Lability
 - ❖ Depression

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**
- P₄₅₀ Induction – **Yes, mild**
- Metabolism
 - ❖ Hepatic metabolism
 - ❖ Renal excretion
- **Drug interactions - mild**



Topiramate Topamax

- **Favorable in children : Broad-Spectrum**
 - ❖ Partial seizures
 - ❖ Generalized seizures
 - ❖ **Lennox-Gastaut***
 - ❖ **Migraine**

- **Supplied:**



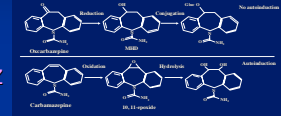
	<u>Starting</u>	<u>Maintenance</u>	<u>Interval</u>
Child:	1 mg/kg/d	8-15 mg/kg/d	BID
Adult:	25 mg/d	100-300 mg/d	BID

Topiramate (Topamax) Side-effects

- **CNS**
 - ❖ Fatigue / somnolence
 - ❖ Cognitive slowing
 - Word finding difficulty
 - ❖ Poor concentration
 - ❖ Dizziness
 - ❖ Ataxia
 - ❖ Anorexia / weight loss
 - ❖ Paresthesias
- **Kidney stones**
 - ❖ 1.5% adult, 0.6% peds
 - ❖ Carbonic anhydrase inhibitor
 - ❖ Avoid **Ketogenic diet**, Ca++
- **Glaucoma / Myopia**
 - ❖ 23/850,000+
 - ❖ Ocular pain
 - ❖ Decreased vision
- **Acidosis**
 - ❖ Carbonic anhydrase inhibitor

Oxcarbazepine Trileptal

- 10-keto analogue of carbamazepine
- **Favorable in children with:**
 - ❖ Partial seizures
 - ❖ Secondary generalized
- **Different metabolism than CBZ**
 - ❖ Acts like a different drug



	OXC	CBZ
Metabolized	Reduction	Oxidation
Epoxide	No	Yes
P₄₅₀ induction	Minimal	YES
Kinetics	Linear	Autoinduce / linear
Autoinduction	No	Yes

Oxcarbazepine Trileptal

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



Liquid: 300 mg / 5cc

	<u>Starting</u>	<u>Maintenance</u>	<u>Interval</u>
Child:	10 mg/kg/d	30-55mg/kg/d	BID
Adult:	150-300 mg/d	2400-3000mg/d	BID

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

Oxcarbazepine (Trileptal) Side-effects – less than CBZ

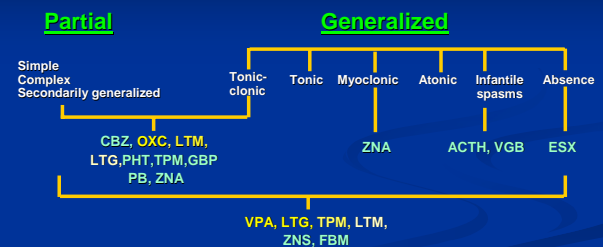
- **CNS**
 - ❖ Headache
 - ❖ Nausea
 - ❖ Ataxia
 - ❖ Dizziness
 - ❖ Diplopia
 - ❖ Somnolence
- **Other**
 - ❖ Hyponatremia similar to CBZ – uncommon in children
 - ❖ Rash rare, < CBZ
 - ❖ No blood dyscrasias or hepatotoxicity

Newer Antiepileptic Drugs

AED	Half-life	Dose / d*	Note !
Felbamate	14-24 hr	30-45 mg/kg	Fatal AEs – Liver, BM
Gabapentin	5-7 hr	30-100 mg/kg	Minimal AEs
Lamotrigine	15-50 hr	5-15 mg/kg	Rash, SJS
Levetiracetam	4-11 hr	20-80 mg/kg	Nightmares, Psychosis
Oxcarbazepine	8-10 hr	20-55 mg/kg	Mild AEs, mild inducer
Tiagabine	4-9 hr	1-2 mg/kg	Mild AEs – fatigue, confusion
Topiramate	20-24 hr	4-10 mg/kg	CNS AEs, Renal Stones
Zonisamide	50-70 hr	4-10 mg/kg	CNS AEs, Renal Stones
Vigabatrin	5-7 hr	50-150 mg/kg	Not avail in US, ON toxicity

* Maintenance dosing

AED Treatment Options



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

