Overview of Anticonvulsants (AEDs)

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Effectiveness of Antiepileptic Drugs (AEDs)

- Before 1993, drug choices for epilepsy limited
- Since 1993, many new AEDs have been introduced
- More than 50% of those with newly-diagnosed epilepsy become seizure free on medication
- About 75% of those with epilepsy have seizures that are well-controlled by medication

The Anticonvulsants: Established AEDs

- 1912 Phenobarbital
- 1938 Phenytoin (Dilantin)
- 1974 Carbamazepine (Tegretol)
- 1975 Clonazepam (Klonopin)
- 1977 Lorazepam (Ativan)
- 1978 Valproic acid (Depakote)

Anticonvulsant

Spectrum:	Narrow vs Broad
Overview	General impressions / use
Side Effects:	Common or concerning side effects
Dose/Formulations:	Pediatric friendly formulations Typical dosing and serum target range

Phenobarbital

Spectrum:	narrow
Overview	Since 1912! Very low cost, with a long record of experience, efficacy, and safety
Side Effects:	Hyperactivity and inattention in younger children, sedation and cognitive clouding in older
Dose/Formulations:	20mg/5cc; variety of tablet sizes Serum target of 10-20 mcg/ml (4-5 mg/kg /day) IV formulation

Phenytoin (Dilantin)

Spectrum:	narrow
Overview	Effective, low cost, but with erratic absorption in children, a narrow therapeutic range, and concerning side effects (generally not used in children) Good in emergent setting
Side Effects:	gingival hyperplasia, coarsening of facial features, rash
Dose/ Formulations:	IV formulation Target serum levels of 10 to 20 mcg/mL

Valproic acid (Depakote)

Spectrum:	broad
Overview	A very effective medication, particularly for the generalized epilepsy syndromes. Rare but concerning organ toxicities, not a first line agent for young women.
Side Effects:	Tremor, weight gain Increase in insulin, weight gain, polycystic ovary syndrome Platelet abnormalities, bleeding tendencies Pancreatitis, hepatic toxicity Fetal malformations, decrease IQ
Dose/Formulations:	125 mg sprinkle capsules Extended release form IV preparation (Depacon) Start at about 10 mg/kg /day, increase to 30 with serum levels of 50 – 100 mcg/mL

Carbamazepine (Tegretol)

Spectrum:	narrow
Overview	Good efficacy in partial seizures, with fewer cognitive side effects than barbiturates. Enzyme inducing agent
Side Effects:	Somnolence, ataxia, diplopia Rare neutropenia Rash Potential for drug -drug interactions Concern regarding bone health
Dose/Formulations:	Start 5 to 10 mg/kg Maintenance 10 - 30 mg/kg Extended release formulations

Second Generation AEDs

- 1993 Felbamate (Felbatol)
- 1993 Gabapentin (Neurontin)
- 1994 Lamotrigine (Lamictal)
- 1996 Topiramate (Topamax)
- 1997 Tiagabine (Gabitril)
- 1999 Levetiracetam (Keppra)
- 2000 Oxcarbazepine (Trileptal)
- 2000 Zonisamide (Zonegran)
- 2009 Lacosamide (Vimpat)
- 2009 Rufinamide (Banzel)
- 2009 Vigabatrin (Sabril)

Lamotrigine (Lamictal)

Spectrum:	Broad, childhood absence epilepsy
Overview	A good broad spectrum agent, that may be a good alternative to Depakote in the generalized epilepsies. Relatively clean and cognitive profile. Few organ specific toxicities. Concern for rash slow escalation schedule problematic. Mood stabilizer.
Side Effects:	Stevens Johnson syndrome Dizziness, headache, insomnia
Dose/Formulations:	Chewable 5 and 25-mg tablets, 100mg, 200mg Available XR formulation Start at about 0.5 mg/kg per day, increase over a period of 6 weeks to 4 mg/kg/day

Topiramate (Topamax)

Spectrum:	broad
Overview	Thought of as an effective anticonvulsant medication, but with cognitive side effects as a major concern. Good for patients who have obesity or migraine as comorbidities
Side Effects:	Language difficulties, cognitive slowing Weight loss, and appetite suppression paresthesias Kidney stones Anhydrosis and heat stroke
Dose/Formulations:	15 and 25 mg sprinkle capsules start at one to two mg/kg per day, and increase over a period of 3 or 4 weeks to 4 - 5 mg/kg per day

Oxcarbazepine (Trileptal)

Spectrum:	narrow
Overview	Similar to carbamazepine, as effective, and with fewer side effects.(but more expensive)
Side Effects:	hyponatremia dizziness, diplopia, nausea rash, 30% cross-reactivity to carbamazepine
Dose/Formulations:	300 mg /5 ml suspension Started at about 10 mg/kg divided bid, and increase to about 30 mg/kg per day

Levetiracetam (Keppra)

Spectrum:	broad
Overview	A good broad spectrum agent, is also useful in focal seizure disorders. Easy to start quickly, with no drug- drug interactions, and no organs specific toxicities. Renally cleared, and generally well tolerated.
Side Effects:	Agitation, aggression, and behavioral problems
Dose/Formulations:	100 mg/ml suspension Start at 20 mg/kg per day, increase to 60mg/kg/day XR formulation available IV formulation available

Zonisamide (Zonegran)

Spectrum:	broad
Overview	Cousin to Topamax, with perhaps fewer cognitive side effects
Side Effects:	Appetite suppression and weight loss Kidney stones Oligohydrosis with hyperthermia Sulfa moeity
Dose/Formulations:	100 mg caps – can be opened and mixed Start at 2-4 mg/kg/day; increase to 4-8 mg/kg/day

Lacosamide (Vimpat)

Spectrum:	? narrow v broad
Overview	new kid on the block , effective for partial seizures, may have a different mechanism of action than other anticonvulsants
Side Effects:	Dizziness, headache, nausea, double vision, fatigue
Dose/Formulations:	50mg, 100mg tabs 5-15 mg/kg/day divided bid IV formulation available

Runfinamide (Banzel)

Spectrum:	broad
Overview	New agent which works well in Lennox-Gastaut syndrome and other symptomatic generalized epilepsies. Effective for tonic – atonic seizures.
Side Effects:	Usually well tolerated, vomiting and somnolence can be seen if the dose is increased quickly
Dose/Formulations:	200 and 400-mg scored tablets Start at about 10 to 15 mg/kg/day and increase gradually to 30- 50 mg/kg/day Use lower doses in patient taking depakote!

Vigabatrin (Sabril)

Spectrum:	infantile spasms; refractory partial epilepsy
Overview	Approved in UK since 1987; approved in US 2009 Use primarily for infantile spasms (esp with tuberous sclerosis)
Side Effects:	Retinal toxicity and peripheral vision loss (permanent) Tends to occur after 12 months of use All patients must be followed by ophthalmologist Fairly extensive paperwork
Dose/Formulations:	500mg tab Powder for solution

Anticonvulsant Selection

Main Considerations

- Efficacy
- Toxicity
- Drug Interactions
- Administration/Initiation
- Medical History
- Cost

Identify Seizure Type and Epilepsy Syndrome

Primary Generalized Sz

- Lamotrigine
- Levetiracetam
- Valproic acid
- Topiramate
- Zonisamide
- Felbamate
- Rufinamide
- Benzodiazepines

Partial (Focal) Seizures

- Carbamazepine
- Oxcarbazepine
- Phenytoin
- Gabapentin
- Pregabalin
- Lacosamide

Side effects

- Behavioral issues (avoid levetiracetam)
- Concerns re drug-drug interations or liver function – consider levetiractam
- Overweight, female (avoid valproate)
- Concomitant migraine (consider topiramate)
- Underweight/failure to thrive(avoid topiramate)
- Concomitant mood disorder (lamotrigine, valproate)

Side Effects of AEDs Overview

- AED side effects can be unpredictable. Some are dose dependent, while others occur regardless of dose
- Newer medications generally have fewer cognitive side effects
- Long term effects are unclear, but even mild side effects can have a significant impact
- Behavior and mood changes from AEDs are often difficult to sort out and are not necessarily dose-related

Other considerations

- Suicidality:
  - 4/30,000; 0.4% vs 0.2% suicidal thoughts or behaviors
  - probable real increase by overall risk very low
- Brand vs generic:
  - FDA bioequivalent standards 80-125% - ratio of test to reference – ratio usually close to 1
  - Breakthrough seizures reported

Starting a medication

- 15+ seizure medications, who does one choose?
- Keeping the above in mind. . .
- Partial seizures:
  - levetiracetam or oxcarbazepine:
- Generalized seizures
  - Lamotrigine (if I have time), valproate, or levetiracetam