

Role of the New Antiepileptic Drugs

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Epilepsy

- Incidence: 0.5% - 1.0% of U.S. population
 - Peak incidence of onset:
 - first 2 years of life, ages 5-7 years, early puberty and elderly.
 - 125,000 new cases/year
- 30% < 18 year Generalized > partial
25% > 65 year Partial > Generalized

SEIZURES

SITUATIONAL

- As part of an acute illness or temporary cause
- Not expected to recur when cause resolves
- Examples
 - Febrile seizures, substance withdrawal

EPILEPSY

- Recurrent Seizures over time
- Usually spontaneous
- Cause may be known or unknown

INTERNATIONAL CLASSIFICATION OF SEIZURES

- **PARTIAL ONSET**
Seizures begin in a focal area of brain as defined clinically or by EEG. Patient may be aware of onset (“aura”)
- **GENERALIZED ONSET**
Seizures appear to begin in brain everywhere at once, bilateral EEG discharges, immediate loss of consciousness

INTERNATIONAL CLASSIFICATION OF SEIZURES

- **PARTIAL ONSET**
 - Simple Partial
 - Complex Partial
 - Complex Partial - 2° generalization
- **GENERALIZED ONSET**
 - Generalized tonic-clonic
 - Absence
 - Atypical Absence
 - Myoclonic
 - Atonic

History of AEDs in U.S.

- 1910's: Phenobarbital
- 1930's: Methobarbital Phenytoin
- 1940's: Trimethadione Mephentoin Paramethadione
- 1950's: Phenacemide Metharbital Phensuximide Primidone Methsuximide Ethotoin
- 1960's: Ethosuximide Diazepam
- 1970's: Carbamazepine Valproate
- 1990's: Felbamate Gabapentin Lamotrigine Topiramate Tiagabine
- 2000's: Zonisamide Levetiracetam Oxcarbazepine
- Pending: Remacemide Pregabalin Rufinamide

Drugs of Choice

<u>Seizure Type</u>	<u>Drugs of Choice</u>	<u>Alternatives</u>
Partial: Simple/Complex	Carbamazepine Phenytoin Valproic acid	Lamotrigine Gabapentin Phenobarbital Primidone Topiramate Tiagabine Levetiracetam Oxcarbazepine Zonisamide

Drugs of Choice

<u>Seizure Type</u>	<u>Drugs of Choice</u>	<u>Alternatives</u>
GTC	Carbamazepine Phenytoin Valproic acid	Lamotrigine Phenobarbital Primidone Topiramate
Absence	Ethosuximide Valproic Acid	Lamotrigine Clonazepam
Atypical Absence, Atonic, Myoclonic	Valproic acid	Clonazepam Felbamate

Limitations of Older AEDs

- Efficacy: limited efficacy in complex partial, atypical absence, myoclonic, atonic seizures
- Adverse Effects: similar neurotoxicity, idiosyncratic reactions

Limitations of Older AEDs

- Teratogenicity
- Pharmacokinetics: nonlinearity, low aqueous solubility, hepatic metabolism
- Drug Interactions:
 - Enzyme induction: CBZ, PHT, PB
 - Enzyme inhibition: VPA

What is the Role of the New AEDs??

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- Different MOA → TX of refractory seizures
- Rational polytherapy
- Different (less ?) adverse effects
- Less drug interactions

EFFICACY

Interpretation of Clinical Trials on Newer AEDs

- Patients with refractory partial seizures
- Primarily “add-on” trials (adjunctive)
- Strict test of AED efficacy/safety
- Older AEDs □ seizure frequency 15-20% in similar trials
- Adverse effects complicated by adjunctive therapy

Prognosis for total control of complex partial and secondarily generalized tonic clonic seizures. Department of Veterans Affairs Epilepsy Cooperative Studies No. 118 and No. 264 Group
Mattson et al *Neurology* 1996; 47:68-76

- Re-analyzed two VA studies
 - Prognosis based on seizure type:
 - Evaluated 12 month seizure free rate
- Conclusions
 - Overall prognosis for control of seizures
 - GTC only (55 % and 48 %)
 - CPS only (23 % and 26 %)
 - Mixed (32 % and 25 %)

ODDS OF 100% CONTROL BY SEIZURE TYPE

- Absence 80%
- Tonic-clonic 65%
- Complex partial 40%

RATIONAL POLY THERAPY

- Combining drugs with different mechanism of action for synergism of anticonvulsant effect
- Avoid drugs with similar adverse effects

Wilder Neurology 1995;45:S7-S11

Lamotrigine-Valproate: Pharmacodynamic Interaction

- *Lancet* 1993;341:445
 - 2 patients (7 and 14 yr.): refractory atypical absence
 - LTG 25-50 mg/day
 - Seizure-free ONLY with combination
- *Lancet* 1993;341:1224
 - 7 adult patients with refractory complex partial seizures.
 - LTG: 200-500 mg/day VPA: 400-800 mg/day
 - 3 pts w/ 2,3 and 17 seizures/month became seizure free
 - 4 pts decreased from 4-45 seizures/month to 1-2/month

Lamotrigine Substitution Study: Evidence for Synergism with Sodium Valproate?

Brodie et al: Epilepsy Res 1997;423-432.

- 357 patients with uncontrolled seizures treated with VPA (117), CBZ (129), PHT (92), PB (9)
- Added Lamotrigine
- Results: Percent Responders
 - Valproate+LTG: 64%
 - Carbamazepine +LTG: 41%
 - Phenytoin + LTG: 38%
- True for patients with partial as well as GTC seizures.

The Efficacy of Valproate-Lamotrigine Co-medication in Refractory Complex Partial Seizures: Evidence for a Pharmacodynamic Interaction *Pisani et al. Epilepsia 1999;40:1141-46*

- N=20 adults w/ refractory CPS
- No previous exposure to VPA or LTG
- 3 consecutive add-on treatments w/ VPA, LTG or LTG+VPA
- Results: > 50% reduction in seizures
 - VPA: 3/20
 - LTG: 4/17
 - LTG+VPA: 4/13 seizure free, 4/13 >50% reduction [LTG] and [VPA] were lower in combination

Lamotrigine and Topiramate may be a useful combination. *Stephen et al. Lancet: 1998;351:958-963*

- Two cases reported
 - Patient with GTC
 - Patient with partial and GTC
 - Both seizure free with a combination of a dose of lamotrigine (375 mg/day, 800 mg/day) and a small dose of topiramate (50 mg/day, 75 mg/day)

ADVERSE EFFECTS

Incidence of Adverse Effects in 392 Pediatric Outpatients *Epilepsia 1988;29:794-804*

Best Tolerated	Carbamazepine
Least Tolerated	Phenytoin
Behavioral disorders	Phenobarbital
Neurological Disorders	Phenytoin
GI	Valproate
Other	Phenytoin

Incidence of Adverse Effects in 392 Pediatric Outpatients *Epilepsia 1988;29:794-804*

Drug	Any ADR	Serious ADR
Phenytoin	71 %	10 %
Phenobarbital	64 %	4 %
Carbamazepine	43 %	3 %
Valproate	43 %	8 %
Primidone	29 %	8 %

Sedation

- One of the most commonly reported ADRs
- 33-42% incidence reported in monotherapy
- Older AEDs such as CBZ, PHT, PB, PRM, VPA may be particularly troublesome
- AED effects on alertness may be more common with polytherapy

Mattson et al NEJM 1992;327:765-71

Sedation



More Prominent		Less Prominent
Phenobarbital	Levetiracetam	Gabapentin
Carbamazepine	Valproate	Lamotrigine
Phenytoin		
Topiramate		
Tiagabine		
Oxcarbazepine		

Sedation

- Drowsiness may contribute to patient complaints of cognitive impairments and potentially mood

Cognition

- Patients with epilepsy tend to have impaired cognitive performance as compared to healthy individuals
- Cognitive impairment is multifactorial and involves seizure etiology, type, frequency and severity
- AEDs tend to reduce neuronal excitability and synaptic function, and thereby may impair cognition

Cognition

- All currently marketed AEDs *may* impair cognition in individual patients
- Polytherapy and high serum levels increases this risk
- Differential effects of older AEDs is controversial (e.g. CBZ vs PHT vs VPA)
- Most convincing evidence implicates benzodiazepines, barbiturates & topiramate

Lamotrigine vs. Carbamazepine

Brodie et al. Epilepsy Res. 1999;37:81-87

- N=150 elderly patients
- LTG vs. CBZ in newly diagnosed epilepsy
- Rash rate: LTG 3 % vs. CBZ 19 %
- Somnolence: LTG 12 % vs. CBZ 29 %
- Drop-out rate adverse effects:
LTG 18% vs. CBZ 42%
- Efficacy Results
 - No difference in time to first seizure
 - Pts. seizure free for 16 wks. LTG 39% CBZ 21%
 - Patients continued on therapy: LTG 71 % CBZ 42%

Differential effects of Carbamazepine and Gabapentin

Meador et al. Epilepsia 1999;40:1279-1285

- N=35 healthy subjects
- Cross-over study x 5 week treatment periods
- Gabapentin 2400 mg/d
- Carbamazepine dose adjusted to maintain CBZ concentrations in therapeutic range (mean 8.3 µg/ml)
- Results:
 - Gabapentin caused significantly less impairment than carbamazepine on 5 of 31 variables of a neuropsychological test battery
 - Gabapentin had better performed on variables of attention, reaction time, reading speed, vigor and memory for stories (p< 0.05)

Cognitive effects of topiramate, gabapentin, and lamotrigine in healthy young adults.

Martin et al. *Neurology* 1999;52:321-327

- Randomized single blind study
- Topiramate 2.8 mg/kg (n=6)
- Gabapentin 17 mg/kg (n=6)
- Lamotrigine 3.5 mg/kg (n=5)
- Results:
 - Topiramate causes a significant decrease in verbal fluency and attention compared to baseline. LTG and GBP no effect.

AEDs & Weight Change Valproate

- Weight gain seen frequently in both children & adults:
 - 44 - 71% of patients experience excessive weight gain (≥ 4 kg)
 - Mean gains of 7 - 20kg have been reported
 - Weight gain typically appears within 1st 3-6 months of treatment
 - Weight gain frequently resistant to dietary interventions
 - Baseline weight not necessarily predictive

Dinesen et al *Acta Neurol Scand* 1984;70:65
Coman et al *Can J Neurol Sci* 1997;24:240
Novak et al *J Child Neurol* 1999;14:490

Weight Change and New AEDs

Weight Gain

- Gabapentin (15-20% pts)

Weight Loss

- Felbamate (2-75%)
- Topiramate (10-20%)
- Zonisamide (20-50%)

Weight Neutral

- Lamotrigine
- Levetiracetam

Gidal, et al *Ann Pharmacother* 1995;29:1048
Detolado et al *Ther Drug Monit* 1997;19:394

Bergin, et al *Clin Neuropharm* 1995;18:23
Jones, et al *Can J Neurol Sci* 1998;25:13

Rash with Other AEDs

- Phenytoin: 7-10%
- Carbamazepine: 6 - 17%
- Valproic acid: 0%
- Phenobarbital: 7-10%
- Lamotrigine: 5 - 10%

Risk of serious cutaneous disorders after initiation of use of phenytoin, carbamazepine, or sodium valproate

Neurology 1997;49:542-6

- RXN that occurred w/ 60 days of 1 or 2 Rx
 - PHT: 8 out of 8,888 = 2.3-4.5/10,000
 - CBZ: 6 out of 9,738 = 1-1.4/10,000
 - VPA: 0 out of 1,504 = 0

Cross sensitivity of skin rashes with antiepileptic drugs

Can J Neurol Sci 1997;24:245-249

- N=633 patients exposed 1,875 to 14 AEDs
 - If had a PHT rash: 58% had rash with CBZ
 - If had a CBZ rash: 40% had rash with PHT
 - If had a PB rash: 4/5 had rash to CBZ or PHT or both
 - No rash with VPA or clobazam

Lamotrigine Skin Rash

- Maculopapular and/or erythematous eruptions are common
- Onset within 4-6 weeks
- Usually mild to moderate but can progress
- Frequency higher in children than adults
- Frequency enhanced by VPA, higher starting doses and rapid dose escalation

Lamotrigine Rash: Risk Factors

- High initial starting dose and/or rapid titration
- Concomitant VPA
- Children
- Limited post-marketing data suggest increased risk in patients experiencing rash from other AEDs

French JA, Morris G. *Epilepsia* 1996;37:203

Lamotrigine Skin Rash: Effect of dose, dosing rate & other AEDS

Starting Dose	Enzyme Inducing	VPA + inducer	VPA
25 mg qod	-----	0.5%	7.8%
50 mg qod	-----	0%	12%
50 mg qd	1.1%	0.9%	5.7%
50 mg bid	1.4%	4.5%	40%
> 50 mg bid	2.8%	18.2%	-----

Oxcarbazepine: Skin Rash

- Lower incidence of rash with oxcarbazepine compared to carbamazepine? (4-12%)
- Less severe rash ---- no reported SJS
- Estimated 20% - 30% incidence of cross-reactivity in patient who develop a rash with carbamazepine therapy

Epilepsia 1987;34:163-5
Neurology 2000;54:2245-51

Drug Interactions



AED Inducers

- Broad Spectrum Inducers:
 - Carbamazepine Phenytoin
 - Phenobarbital
- Selective CYP3A Inducers:
 - Felbamate Topiramate
 - Oxcarbazepine
- Selective UGT Inducers:
 - Lamotrigine Oxcarbazepine

AED Inhibitors

■ Valproate

- Inhibits: UDP glucuronosyltransferase (UGT)
 - plasma concentrations of Lamotrigine, Lorazepam, AZT
- Inhibits: CYP2C19
 - plasma concentrations of Phenytoin, Phenobarbital

■ Felbamate Oxcarbazepine Topiramate

- Inhibits: CYP2C19
 - plasma concentrations of Phenytoin, Phenobarbital

New AEDs and Drug Interactions

	Inducer	Inhibitor
Gabapentin	No	No
Lamotrigine	Yes UGT	No
Topiramate	Yes CYP3A4	Yes CYP2C19
Tiagabine	No	No
Levetiracetam	No	No
Oxcarbazepine	Yes CYP3A4 UGT	Yes CYP2C19
Zonisamide	No	No

Women and Epilepsy

Seizure frequency and severity can be altered:

- at puberty
- menstrual cycle (catamenial seizures)
- pregnancy
- menopause

Hormonal Influences

■ Estrogen

- Pro-convulsive



■ Progesterone

- Anticonvulsive

Women with Epilepsy

Are more likely to have:

- anovulatory menstrual cycles
- abnormal pituitary LH release
- altered ovarian steroid concentrations
- polycystic ovary disease (valproate)
- lower fertility rates



Role of AEDs vs. Epilepsy

- Carbamazepine, Phenytoin, Phenobarbital and Valproic acid alter endogenous steroid hormones.
- Newer drugs: Lamotrigine and Gabapentin do not alter levels of steroid hormones and may have some advantages in women.
- Levetiracetam and Zonisamide may also have advantage in women as they are both are non-inducing AEDs

Oral Contraceptives

- No evidence that OC's worsen seizures
- Use of OC's with enzyme inducing AEDs can result in birth control failure
 - Phenytoin, Carbamazepine, Primidone, Phenobarbital
 - Topiramate, Oxcarbazepine, Felbamate

Oral Contraceptives

Recommendations

- Non-inducing AED
 - Valproic acid Lamotrigine Gabapentin Levetiracetam Zonisamide
- Or if using an Enzyme Inducing AED, use at least an OC containing $\geq 50 \mu\text{g}$ of estrogen
 - Warn patients that mid-cycle bleeding indicates possible OC failure
 - or use an alternative method of birth control

Teratogenicity

- Incidence in mothers using AEDs is 2-3X baseline.
- Monotherapy results in significantly lower risk
- Similar incidence with all traditional AEDs except for added 1-2% increase in risk of neural tube defects with valproic acid and carbamazepine.
- Increased risk with increased dose (or concentration) found with valproic acid and phenytoin

New AED Teratogenicity:

Animal studies

- Intrauterine growth retardation and delayed skeletal ossification with both old and new AEDs
 - not a clear link with teratogenicity
- Orofacial, cardiovascular, neural tube and urogenital defects observed with old AEDs have not been observed with new AEDs
 - except Topiramate: craniofacial defects

Lamotrigine: 9/92 - 3/99

- 1 birth defect in 47 prospective reports of pregnancy with LTG monotherapy in first trimester
 - 2.1% [95% CI: 0.1% - 12.7%]
- 10 birth defects in 142 with either LTG mono or polytherapy
 - 7.0% [95% CI: 3.6% - 12.9%]
 - no consistent pattern of birth defects
 - Does not suggest an increased risk of birth defects with lamotrigine as found with other AEDs.

Role of New AEDs?

- Generally considered second/third line therapy
- Evidence of rational polytherapy for refractory patients
- Decreased vs. different adverse effects
- Less drug interaction potential
- Potential advantages in the use of Women with epilepsy