Antiepileptic Drugs
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Objectives
• Define the scope of the problem
• Review seizure types and diagnosis
• Describe the limitations of old AEDs
• Outline benefits and important adverse effects of newer antiepileptic drugs
• Consider AED selection factors
• List some of the parameters for stopping AEDs

Abbreviations
• AED: antiepileptic drug (best not to call them anticonvulsants)
• Sz: seizure
• AEs: adverse effects
• DDI: drug to drug interaction
• TBI: traumatic brain injury
• DD: developmental disability

Epilepsy: So What?
• Seizures affect behavior
• Stigma
• Prevalence
• Effects of early treatment

Epilepsy: Considerations
• The mainstay of diagnosis is history
• The primary treatment is pharmacotherapy
• Epilepsy is a chronic problem, usually requiring chronic treatment
• Early diagnosis and aggressive treatment improve outcome

What Is Epilepsy?
• Definition: recurrent, unprovoked seizures
• Epilepsy is not a clearly defined single disease or disorder, but rather a symptom of an underlying cerebral problem
• Manifestations: disordered electrical discharges in the brain which may or may not spread (“brainstorm”)
  – May become a clinical seizure
  – May occasionally result in no clinical symptoms

Epilepsy: So What?
• Seizures affect behavior
• Stigma
• Prevalence
• Effects of early treatment
**What Is Epilepsy?**

- Clinical seizures have many forms
  - Tonic-clonic activity is the most widely recognized
  - But staring episodes are considerably more common
  - Other forms of seizures (e.g. “drop”) may occur, especially in DD patients
- Not all seizures are due to epilepsy (hypoglycemic seizures, EtOH withdrawal seizures, etc.)

**Frequency**

Epilepsy is very common:

- Prevalence: 0.6%-2%, with a bimodal distribution: more common in young children and persons over 65 years old
- > 25% in severe TBI
- 10% of people will have a seizure at some point in life

**Spectrum**

- Anyone can have a seizure or seizures, given the right conditions
- Some patients have only occasional seizures, or Sz only when ill
- Occasional patients have many seizures per month, regardless of Tx
- Epilepsy is materially more common in pt.’s with mental illness, DD

**Factors Causing Sz**

- Sz susceptibility for an individual determined by three sets of factors:
  - Basic makeup (endogenous factors)
  - Acquired factors
  - Daily variables

**Etiology**

Infancy and childhood

- Prenatal/perinatal injury
- Inborn errors of metabolism
- Congenital malformations

Childhood and adolescence

- Idiopathic/genetic syndromes
- CNS infections
- Trauma

**Etiology (Cont.)**

Adolescence and young adults

- Traumatic brain injury
- Drug intoxication and withdrawal*

“Older” adults

- Stroke
- Brain tumors
- Acute metabolic disturbances*
- Neurodegenerative disorders (e.g. AD)

* causes of acute symptomatic (provoked) seizures, not epilepsy
Seizure Precipitants
• Sleep deprivation
• AED reduction or inadequate AED treatment
• Stimulant/other proconvulsant use/abuse
• Sedative/ethanol withdrawal
• Metabolic and electrolyte imbalance
• Hormonal variations
• Stress
• Fever or systemic infection
• Concussion/TBI

Seizure Precipitants (cont.)
Stimulants/Other Pro-convulsant Intoxication
• Cocaine
• Amphetamines
• Ephedrine
• IV drug abuse
• Some CAM/herbal remedies
• AED/benzodiazepine reduction

Seizure Precipitants (cont.)
Other potentially proconvulsant medications
• Antidepressants: bupropion, tricyclics
• Antipsychotic agents: phenothiazines, clozapine
• Theophylline
• Isoniazid
• Meperidine
• Penicillins/carbapenems
• Cyclosporin

Sz History Is Important
• History obtained determines:
  – Sz type, frequency, precipitants, etc
• Needed to craft pt.-specific restrictions and recommendations
• The primary determinant of AED choice
• An observer is important
• Sz calendars: help identify patterns
• Tests are helpful but typically not diagnostic (except video/EEG monitoring)

Seizure Classification
• Partial
  – Seizure starts in limited (focal) area of cortex
  – May or may not spread, sometimes rapidly
  – Consciousness may be partially preserved
• Generalized
  – Begins in entire cortex simultaneously
  – Consciousness is always lost
  – No aura (warning)
  – Convulsive or nonconvulsive

Complex Partial
• Most common seizure type in adults
• Often manifested as staring spells
• Impairment or loss of consciousness; typically memory impairment
• Auras and automatisms
• Previously called “psychomotor” or “temporal lobe”
• Occasional postictal agitation/aggression
  (more common in institutionalized/DD)
Simple Partial

- Less common type of partial Sz
- No alteration in consciousness
- No aura or postictal confusion
- May be motor, sensory or, rarely, other types

Sz Classification: Generalized

- Myoclonic
- Tonic
- Atonic

Sz Classification: Generalized

Tonic-clonic (Grand Mal)

- Rhythmic, repetitive jerking movements of limbs
- No focal onset
- Possible incontinence
- Usually postictal confusion, fatigue, or headache

Seizure Classification

Secondarily generalized

- Can start as simple partial or complex partial
- May generalize very rapidly, making identification of focal onset difficult
- Distinguish rapidly secondarily generalized partial seizures by history and careful observation

Sz Classification: Generalized

Absence ("petit mal")

- Brief (10-15 sec.) Staring spells
- No aura or postictal impairment
- Almost exclusively in children and adolescents
- But occasionally persist into adulthood, most commonly in DD patients
- Characteristic EEG

Complex Partial v. Absence

- CP
  - Aura, postictal confusion are common
  - 60-90 sec.
  - Common in adulthood

- Absence
  - No aura
  - 5-15 sec.
  - Common in childhood; rare in adulthood
  - No postictal confusion
**Carbamazepine (Carbatrol, Tegretol, Tegretol XR)**

- NTI
- Slow, erratic absorption (much moreso the old formulations)
- 75% protein bound (largely not to albumin)
- Half-life 6-20 hours; less with polytherapy
- The good: linear kinetics
- The bad:
  - Autoinduction of metabolic enzymes
  - Active metabolites

**Phenytoin (Dilantin, Phenytek):**

- NTI
- Phenytoin is not easy to use
- Slow, highly variable absorption (100, 30 mg. Kapseals), decreased with antacids
- 90% protein bound (albumin)
- Saturable elimination kinetics
  - Small dose changes can produce enormous changes in levels
- Adverse effects problematic: not a first (or 2nd, or 3rd) line drug in 2011

**Carbamazepine: DDIs**

- Autoinduction; epoxide metabolite
- CYP 3A4 substrate
- Strong CYP 2C9, 3A4 inducer
  - “Statin” agents
- PGP substrate: PPIs, etc
- Complex AED interactions
- Warfarin, clarithromycin, diltiazem, azoles, antipsychotics...

**Carbamazepine**

- Must use name brand
  - Many generics, with much variability
  - Impairment of Sz control well demonstrated
- Long acting forms much superior, and can be given b.i.d.
  - I only use Carbatrol, XR (except with TF)
- Dosage schedule:
  - b.i.d. therapy works well with ER forms
  - I.R. forms must be given at least t.i.d. or, preferably, q.i.d.; Tx adherence suffers

**Phenytoin**

- Dosage considerations:
  - Oral or parenteral loading
  - Some patients must take b.i.d., but many do well with q.d. dosing (with ER formulations)
  - Often, no titration necessary
- Forms:
  - Only true extended absorption are 30, 100 mg. Parke-Davis “Kapseals,” and Phenytek
  - Give 50s at least b.i.d.
  - Suspension poorly soluble, especially with antacids and NGT feedings, and highly variable: avoid

**Carbamazepine**

- Idiosyncratic adverse effects:
  - Rash
  - Aplastic anemia (rare)
  - Hepatic
- Dose-related adverse effects
  - Mild neutropenia (benign!)
  - Blurred vision/diplopia
  - Nausea
  - Dizziness/ataxia
  - SIADH (occasional: primarily older, DD or institutional patients)
Phenytoin
Idiosyncratic adverse effects (long list, at least in part since it's an older drug)

• Rash
• Osteoporosis/Bone loss
• Gingival hyperplasia
• Lymphadenopathy
• Hirsutism
• Lupus-like syndrome
• Neuropathy
• Acne

Phenytoin: DDIs

• Strong hepatic enzyme inducer
• AED interactions complex
• Numerous other interactions, including “statins,” oral contraceptives, erythromycin
• Disulfiram, paroxetine may greatly increase PHT levels
• Displaced by and displaces multiple other drugs, since highly protein bound

Phenytoin
Dose-related adverse effects

• Cerebellar toxicity: diplopia, nystagmus, ataxia
• Memory difficulties
• Other cognitive effects (especially prominent in older patients)

Divalproex Sodium/Valproic Acid (Depakote/ER/Depakene):

• Slow absorption of enteric format (Depakote): about six hours
• 90% protein bound – But less functional impact C/W PHT
• Active metabolites
• Half-life < 15 hours
• IV formulation
• Teratogenicity

Other AEs
Osteoporosis is important

• Older patients
• DD
• WC patients
• Fractures in young epilepsy clinic patients >2x controls

Divalproex

• Indications:
  – Primary generalized seizures, including absence
  – “Second line” drug for CPSD
  – Relatively wide spectrum of AED activity

• Best used as monotherapy: drug-drug interactions a major problem with VPA
Divalproex

Idiosyncratic adverse effects:

• Hepatitis
• Pancreatitis (not as bad as “black box” implies)
• Nausea
• Thrombocytopenia
• Hyperammonemia
• Especially teratogenic

Divalproex

Dose-related adverse effects (Some ? less common with divalproex, VPA ER)

• Weight gain
• Nausea
• Tremor
• Alopecia
• ? PCOS

Divalproex: Interactions

• Hepatic enzyme blocker
• Numerous interactions, especially AED’s
• Sometimes rapid increases in PB levels
• VPA levels reduced dramatically by most other AEDs
• Carbapenem ABx induce metabolism
• Works best as monotherapy

Phenobarbital/primidone

• Definitely last line agents due to AEs
• Long half-life (100-120 hours in adults): weeks to steady state
• Dosage considerations: b.i.d. only for large doses, otherwise all at h.s.
• Drug interactions:
  – Very strong hepatic enzyme inducer
  – Numerous interactions, including Ocs
• Efficacy: lost over time due to tolerance
• Take Home Message: avoid phenobarbital

Phenobarbital

Idiosyncratic Adverse Effects:

• Not less than other AEDs
• Rash
• Hepatic
• Hematologic

Phenobarbital

Dose-related adverse effects: many, and often severe

• Sedation
• Memory deficits, cognitive impairment
• Motor impairment
• Behavioral changes, hyperactivity and irritability (primarily children)
• Depression
• Dependence (GABA receptor changes)
Advantages and Disadvantages

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<tr>
<th>Drug</th>
<th>Advantages</th>
<th>Disadvantages</th>
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<tbody>
<tr>
<td>CBZ</td>
<td>b.i.d. (long acting forms) Linear</td>
<td>Hepatic enzyme inducer</td>
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<tr>
<td>PHT</td>
<td>q D cheap</td>
<td>Very hard to use: kinetics Cosmetic adverse effects</td>
</tr>
<tr>
<td>VPA</td>
<td>Wide spectrum of action ? Less sedating</td>
<td>Weight gain Cost</td>
</tr>
<tr>
<td>PB</td>
<td>None (cheap?)</td>
<td>Many serious adverse effects Addiction/tolerance</td>
</tr>
</tbody>
</table>

Gabapentin

- About 60% absorbed: variable
  - Dose-dependent absorption at higher doses
- Half-life about six hours
- Must be taken t.i.d. or, preferably, q.i.d.
- Drug levels not generally useful
- >>95% of Rx in 2010 for non-epilepsy indications

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Felbamate (Felbatol)

- Not “taken off the market”: still available, but basically used only by epileptologists
- Serious adverse effects limit its use. As of 12/06 (last formal report):
  - Aplastic anemia: 33 cases, 14 died
  - Hepatic failure: 18 cases, 9 died
- Periodic CBC, LFTs
- Very effective

Lamotrigine (Lamictal)

- Multiple mechanisms of action
- Long half-life
- Hepatic metabolism: inducible, “blockable”
- Dosing: scored tablets, in many sizes
- Dose-related AEs:
  - Minimal cognitive toxicity (Neuropsychological studies: normal persons, pt.’s)
  - Headache
  - Otherwise, the usual AEs

Gabapentin (Neurontin)

- Structurally related to GABA
- Does not act primarily at GABA receptor
- Does not bind to serum proteins
- No hepatic metabolism
- Basically no drug interactions
- But: AED effects not so robust
- Behavioral problems in children, DD, psychiatric pt.’s common

Lamotrigine

Idiosyncratic adverse effects:

- Rash (up to 10% if also taking divalproex)
- Some data suggest higher incidence of such rash in children
- European data strongly support much lower rash rates with slow titration
- Rx must be begun at low dose, titrated slowly
Topiramate (Topamax)

- Multiple (but different than LTG) mechanisms
- Wider spectrum of action than some other agents
- Not highly protein bound; Linear kinetics; Partially renal elimination
- Idiosyncratic adverse effects:
  - Renal lithiasis: likely should avoid agent if previous Hx; Hydrate well
  - Oligohidrosis

Oxcarbazepine (Trileptal)

- Mechanism: = CBZ
- Metabolism: no epoxide intermediate
- OXC is a “pro-drug” (MHD metabolite)
- Idiosyncratic AEs: rash, SJS (“black box”); + cross-reactivity
- Dose-related AEs
  - Hyponatremia: more likely in DD, older patients; ? > CBZ
  - Dizziness
  - GI

Topiramate

- Dose-related AEs:
  - Cognitive impairment, primarily slowed language processing (can be severe)
  - Weight loss
  - Paresthesias
- Drug interactions: inducible; OCs; (PHT)
- Slow titration, with 15-25 mg. starting dose, largely eliminates unacceptable adverse effects in most patients

Oxcarbazepine

- Like CBZ, only different:
  - Lower WBC drop
  - SIADH worse
  - Some enzyme induction (< CBZ)
  - OC problems similar or slightly < CBZ
- Problems obtaining and interpreting MHD plasma levels
- ? useful in women of childbearing potential (compared to CBZ)

Tiagabine

- GABA reuptake inhibition: first true GABA drug
- b.i.d. or t.i.d. despite 7-9 hour half-life
- Dose-related adverse effects
  - Dizziness and “asthenia”
  - Cognitive, behavioral and psychiatric effects
- SE in patients with atypical absence Sz
  - New Sz in isolated non-epilepsy pt.’s
- Not as effective for pain as mfr. suggests

Oxcarbazepine: More On DDIs

- OXC, MHD inhibit CYP 2C19
- MHD quite inducible: almost 50% decrease with PHT, CBZ
  - Also decreased with VPA
- May cause large increase in PHT serum levels
- OCs: 50% EE reduction
### Zonisamide (Zonegran)
- Broad spectrum, based on mechanisms
  - Some overlap with TPM
- Often dosed b.i.d.: $T_{1/2}$ actually > 60 hours in MonoTx; I Rx q day
- Not highly protein bound
- Inducible: PHT, PB, CBZ double rate of elimination
- Serum levels generally not useful

### Levetiracetam
- AEs: somnolence, dizziness, ataxia, headache most common; otherwise not unlike other AEDs
- Psychosis, hallucinations and other psychiatric Sx > placebo
  - Depression
- H/H, WBCs occasionally decreased: ? obtain baseline CBC
- My experience: depression, psychosis, anemia can be problems

### Zonisamide
- ZNS is a sulfonamide
  - But cross-reaction with ABx limited
- SJS: 7 deaths in 11 years in Japan
- Renal lithiasis
- Dose-related AEs: similar to TPM but ? lower magnitude
  - Drowsiness, cognitive impairment, weight loss

### Pregabalin (Lyrica)
- MOA similar to GBP
- Linear kinetics: b.i.d. dosing
- Smaller pills and less expensive
- CP Sz adjunctive indication only (in epilepsy)
- Post-marketing efficacy data still limited: not widely used for epilepsy

### Levetiracetam (Keppra)
- MOA remains unclear
- High therapeutic index in animal studies
- Not significantly protein bound
- 2/3 renally excreted
- Half life 6-8 hours (but dosed b.i.d.)
- No clear drug interactions
- Can be titrated more rapidly than some other agents
- IV formulation

### Lacosamide (Vimpat)
- UCB
- Approved 29 Oct. 2008
- Adjunctive Tx of refractory partial Sz; Painful diabetic neuropathy
- MOA: enhances Na+ channel inactivation
- Elimination $T_{1/2}$ 13 h.
- Not highly protein bound (<15%)
- ? inducible
### Rufinamide (Banzel)
- Novartis/Eisai
- Approved 14 Nov. 2008
- Refractory partial epilepsy, LGS
- MOA: ? Na⁺ channels
- LGS study: n=138; 42.5% median reduction in atonic Sz
- QT abnormalities; Hypersensitivity
- Otherwise the usual AEs

### LEV ER (Keppra XR)
- UCB
- Approved 15 Sept. 2008
- Adjunctive Tx of CPS in pt.’s > 15 y.o.
- C<sub>max</sub>, AUC equivalent
- Linear PK from 1g-3g
- AEs similar
- Cost (750 mg.): 12x

### Vigabatrin (Sabril)
- Lundbeck
- Indicated for infantile spasms (monoTx, Refractory CPS (adjunctive))
- Visual field constriction a prominent AE
- Only available through a registration program: not at retail; many forms
- Limited to refractory patients; Generally only Rx by Epilepsy Centers

### LTG XR
- GSK
- Approved 1 June 2009
- Adjunctive and monoTx indications in pt.’s > 12 y.o.
- AEs similar
- Cost (200 mg): 22x

### Ezogabine (retigabine)
- GSK
- Approved 10 June 2011
- Not yet available
- Indication: CPS
- Novel MOA: potassium channels
- Urinary retention in trials (rare)

### Choosing AEDs

#### Monotherapy for Partial Seizures

Best evidence, FDA indication: carbamazepine, oxcarbazepine, phenytoin, topiramate
Similar efficacy, but likely better tolerated: lamotrigine, gabapentin, levetiracetam
Also demonstrated effective: valproate, phenobarbital, felbamate, lacosamide
Limited data but commonly used: zonisamide, pregabalin

Choosing AEDs (cont.)

Monotherapy for Generalized-Onset Tonic-Clonic Seizures

Best evidence and FDA Indication: valproate, topiramate

Also shown to be effective:
- Zonisamide, Levetiracetam
- Phenytoin, Carbamazepine (may exacerbate absence, myoclonic Sz)
- Lamotrigine (may exacerbate myoclonic Sz)

Choosing AEDs (cont.)

Absence seizures

Best evidence:
- Ethosuximide (limited spectrum, absence only)
- Valproate

Also shown to be effective: lamotrigine

May be considered as second-line: zonisamide, levetiracetam, topiramate, felbamate, clonazepam

Antiepileptic Drug Monotherapy

- Simplifies treatment; Reduces DDIs
- Reduces adverse effects
- Conversion to monotherapy
  - Eliminate sedating agents first
  - Withdraw AEDs slowly, often over several months

AEs of AEDs Revisited: Common

Typically dose-related
- Dizziness, fatigue, ataxia, diplopia: all AEDs
- Irritability: levetiracetam, gabapentin
- Word-finding difficulties: topiramate
- Weight loss/anorexia: topiramate, zonisamide, felbamate
- Weight gain
  - Valproate (also associated with polycystic ovarian syndrome)
  - Carbamazepine, gabapentin, pregabalin

AE of AEDs: Serious

Typically Idiosyncratic
- Rash: phenytoin, carbamazepine, lamotrigine, zonisamide
- Aplastic anemia: felbamate, zonisamide, valproate, carbamazepine
- Hepatic Failure: valproate, felbamate, phenobarbital, phenytoin, carbamazepine

AE of AEDs: Serious (Cont.)

Agranulocytosis: carbamazepine
- Hyponatremia: carbamazepine, oxcarbazepine
- Renal stones: topiramate, zonisamide
- Anhydrosis, heat stroke: topiramate
- Acute closed-angle glaucoma: topiramate
- Peripheral vision loss: vigabatrin
More on Rashes

- 15.9% patients experienced a rash attributed to an AED
- Average rate of AED-related rash for a given AED 2.8%, 2.1% causing AED discontinuation.
- Predictors significant in multivariate analysis: occurrence of another AED-rash


Cellular Mechanisms of Sz

- Excitation: increase = Sz
  - Ionic-inward Na⁺, Ca²⁺ currents
  - Neurotransmitters: glutamate, aspartate
- Inhibition: decrease = Sz
  - Ionic-inward Cl⁻, outward K⁺ currents
  - Neurotransmitter: GABA

Rash: Yet More

Drugs rarely associated with rash:

- Valproate/divalproex
- Gabapentin
- Pregabalin
- Levetiracetam
- Topiramate

Nonpharmacologic Therapy

- Epilepsy surgery
  - Resective
  - Callosotomy
- VNS
- Ketogenic diet

Summary: Mechanisms

Hepatic Metabolism and AEDs

- Excitation: increase = Sz
- Ionic-inward Na⁺, Ca²⁺ currents
- Neurotransmitters: glutamate, aspartate
- Inhibition: decrease = Sz
- Ionic-inward Cl⁻, outward K⁺ currents
- Neurotransmitter: GABA

After: White HS. Pediatric Epilepsy: Diagnosis and Therapy. 2001:301-316

Hepatic Metabolism and AEDs

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<tr>
<th>AED</th>
<th>CYP3A4</th>
<th>CYP2C9</th>
<th>CYP2C19</th>
<th>UGT</th>
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After: White HS. Pediatric Epilepsy: Diagnosis and Therapy. 2001:301-316
### Epilepsy Treatment Options

- No treatment
- Acute treatment only
- Begin chronic AED treatment

### Efficacy: GTC

- Carbamazepine
- Phenytoin
- VPA
- Felbamate
- Topiramate
- Lamotrigine
- Zonisamide
- Oxcarbazepine
- Levetiracetam

### Efficacy: Partial

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<thead>
<tr>
<th>Treatment Options</th>
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<td>Carbamazepine</td>
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<td>Levetiracetam</td>
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<td>Pregabalin</td>
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### Efficacy: Myoclonic

- VPA
- Clonazepam
- Lamotrigine (may exacerbate some pts)
- Topiramate
- Zonisamide
- Levetiracetam

### Efficacy: Absence

- Ethosuximide
- VPA
- Lamotrigine
- Topiramate
- Zonisamide
- Levetiracetam

### Sz Aggravation

- Myoclonic: PHT, CBZ, GBP, PGB, ? OXC, ? LTG
- Absence: PHT, CBZ, GBP, TGB, OXC, ? PGB
- GTC: TGB, GBP, ? PGB
- JME: CBZ, PHT, ? TGB, ? OXC
  - LTG: myoclonus
Also Consider:

Mitigation of adverse effects with:

- Multivitamin
- And an additional folate (1 mg., 4 mg.)
  - Women of childbearing age
- Ca++/vitamin D

Life Modifications

- Driving: depends on local laws/reg.'s
- Consider swimming, bicycle riding, etc.
- Ladders and climbing
- Bath v. shower
- Cooking and sharp objects
- Important to carefully balance safety v. independence

First Seizure: Questions

- Seizure or not?
- Provoked? (i.e. metabolic precipitant?)
- Seizure type? (focal v. generalized)
- Evidence of interictal CNS dysfunction?
- Syndrome type?
- Which studies should be obtained?
- Should treatment be initiated?
- If so, with which AED?

Stopping AEDs

- Seizure freedom for > 2 years implies overall >60% chance of successful withdrawal in some epilepsy syndromes
- Favorable factors
  - Control with one drug at low dose
  - No previous unsuccessful W/D attempts
  - Normal neurologic exam and EEG
  - Primary generalized seizures (except JME)
  - “Benign” syndrome
- Risks/benefits (e.g., driving, pregnancy)

To Tx or not to Tx?

Whether to treat first seizure is controversial

- 16-62% of unprovoked seizures will recur within 5 years
- Relapse rate may be reduced by AEDs
- Factors increasing relapse rate:
  - Abnormal imaging/neurological examination/EEG
  - Positive family history
  - Quality of life issues are important (i.e. driving)

Norwegian AED W/D Study

- RCT; 12 mo.; Sz-free x 2 years; W/D:
  n=81, not: n=79
- 12 mo. relapse: 15% W/D, 7% not; RR 2.46 (95% CI: 0.85–7.08; p = 0.095)
- Overall relapse 27% after median 41 mo.
- Full nl neuropsychological battery: increase from 11% to 28%
- Predictors: nl exam, CBZ use
FDA, 1/08:

• “FDA ALERT [1/31/2008]: The FDA has analyzed reports of suicidality... from placebo-controlled clinical studies of [11 AEDs]... In the FDA’s analysis, patients receiving [AEDs] had approximately twice the risk of suicidal behavior or ideation (0.43%) compared to patients receiving placebo (0.22%)... observed as early as one week... continued through 24 weeks. The results were generally consistent among the eleven drugs.... there did not appear to be a specific demographic subgroup...”

AAN Position Statement

• “The AAN opposes generic substitution of anticonvulsant drugs for the treatment of epilepsy without the attending physician’s approval.”
  – “Unlike other diseases, a single breakthrough seizure due to change in delivered medication dose can have devastating consequences, including loss of driver’s license, injury, and even death.”
• “The AAN supports the use of newer-generation anticonvulsant drugs in the treatment of epilepsy.”
• “The AAN opposes prior authorization requirements by public and private formularies.”

Analysis: FDA Pronouncement

• The FDA contention: “class Effect”
• Data set not revealed
• Aggregation problems
• Clear consensus among epileptologists: FDA comments far overreaching
• Published registration trials, as well as other RCTs, show large differences in depression, suicide risk

AES Position Statement

“...physicians and patients, in several surveys including one performed of AES members in 2007, express a majority opinion that the various formulations of the same AED are not always therapeutically equivalent in every patient. Positions taken by several organizations including the American Academy of Neurology, the Epilepsy Foundation and the International League Against Epilepsy (French Chapter) reflect this equipoise and advocate for physician and patient consent prior to switching formulations. The AES recognizes that controlled, prospective data on therapeutic equivalence of different AED formulations in people with epilepsy is not available because appropriate studies have not been conducted.

Generic AEDs Available

• Basically all, except extended release formulations
• Levetiracetam the most recent
• Problems reported with some of these products

The Problem

• Driving is one of the most necessary activities for working, &c
  – A major contributor to QOL
  – Especially in the US, where public transportation is typically not good
• The paroxysmal nature of epilepsy makes driving sometimes unsafe
• Seizures are the most common paroxysmal problem resulting in MVCs
Regulations

- States generally base restrictions on seizure-free intervals
- State legislatures can be unnecessarily restrictive in their rules
- Rules vary widely:
  - 19 states: determined by MD or medical advisory board: flexible
  - Specific Sz-free periods:
    - 3 months: 7 states
    - 6 months: 14 states
    - 12 months: 7 states

Epilepsy And Driving: N.C. Law

- 6-12 mo. seizure free
- Exceptions considered
  - Sz after Rx change
  - Nocturnal
  - No alteration in consciousness
  - Prolonged aura
- May request MD report
- Reviewed annually (or less at DMV discretion)
- Not a mandatory MD reporting state

Driving: Relative Risk of MVC

<table>
<thead>
<tr>
<th>Condition</th>
<th>RR</th>
<th>CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Epilepsy</td>
<td>1.33</td>
<td></td>
</tr>
<tr>
<td>Hearing</td>
<td>1.19</td>
<td>1.02-1.4</td>
</tr>
<tr>
<td>Cardiac</td>
<td>1.23</td>
<td>1.05-1.43</td>
</tr>
<tr>
<td>Diabetes</td>
<td>1.56</td>
<td>1.31-1.85</td>
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<td>Psychiatric</td>
<td>1.72</td>
<td>1.48-1.99</td>
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<tr>
<td>Alcoholism</td>
<td>2.0</td>
<td>1.89-2.12</td>
</tr>
<tr>
<td>Rx effects</td>
<td>1.58</td>
<td>1.45-1.73</td>
</tr>
</tbody>
</table>

After European Driving Consensus, 2005, NHTSA

Conclusions

- Epilepsy is a chronic problem
- Dx is based on history
- Seizure type determines AED Tx
- AEDs have varying AE profiles
  - Phenobarbital is bad; PHT not much better
- Stopping AEDs is done carefully
- Driving with epilepsy may be a problem

Resources

The Epilepsy Foundation of North Carolina
1920 West 1st Street, Suite 5541A
Winston Salem, NC  27104
Phone: 800.642.0500

- An important resource for more information, support groups, advice regarding employment, etc.
- All patients with epilepsy should be given this number and encouraged to call