Choosing AEDs

• Lennox-Gastaut Syndrome

• Best evidence/FDA indication*:
  - Topiramate, Felbamate, Clonazepam, Lamotrigine, Rufinamide
  - * FDA approval is for adjunctive treatment for all except clonazepam

• Also effective:
  - Valproate

• Some evidence of efficacy:
  - Zonisamide, Levetiracetam

AEDs and Evidence base

✿ Evidence-based guidelines of AEDs therapy

<table>
<thead>
<tr>
<th>Seizure type</th>
<th>1st line drug</th>
<th>2nd line drug</th>
<th>Drug to be avoided</th>
</tr>
</thead>
<tbody>
<tr>
<td>Generalized Tonic-Clonic (GTC)</td>
<td>CBZ, LTG, VPA, TPM, LEV</td>
<td>CBZ, LEV, OXC</td>
<td>TGB, VGB</td>
</tr>
<tr>
<td>Absence</td>
<td>ESM, LTG, VPA</td>
<td>CBZ, CLZ, TPM</td>
<td>CBZ, GBP, OXC, TGB, VGB</td>
</tr>
<tr>
<td>Myoclonic</td>
<td>VPA, TPM, LEV</td>
<td>CBZ, CLZ, LTG, LEV, TPM, phenytoin</td>
<td>CBZ, GBP, OXC, TGB, VGB</td>
</tr>
<tr>
<td>Tonic</td>
<td>LTG, VPA</td>
<td>CBZ, CLZ, LEV, TPM</td>
<td>CBZ, OXC, PHT</td>
</tr>
<tr>
<td>Atonic</td>
<td>LTG, VPA</td>
<td>CBZ, CLZ, LEV, TPM</td>
<td>CBZ, OXC, PHT</td>
</tr>
<tr>
<td>Partial</td>
<td>CBZ, LTG, OXC, VPA, TPM, LEV</td>
<td>CBZ, GBP, LEV, PHT</td>
<td>TGB</td>
</tr>
</tbody>
</table>

* Principle of AED selection related to seizure types which is difficult to apply to the model of patient-oriented practice.
**AEDs common adverse effects**

- Often dose-related:
  - Dizziness
  - Fatigue
  - Ataxia
  - Diplopia
  - Irritability
    - levetiracetam
  - Word-finding difficulty
    - topiramate
  - Weight loss/anorexia
    - topiramate, zonisamide, felbamate
  - Weight gain
    - valproate
      - carbamazepine, gabapentin, pregabalin

**AEDs serious adverse effects**

- Typically idiosyncratic:
  - Renal stones
    - topiramate, zonisamide
  - Hyponatremia
    - carbamazepine, oxcarbazepine
  - Aplastic anemia
    - felbamate, zonisamide, valproate, carbamazepine
  - Agranulocytosis
    - carbamazepine
  - Hepatic Failure
    - valproate, felbamate, lamotrigine, phenobarbital
  - Anhydrosis, heat stroke
    - topiramate
  - Acute closed-angle glaucoma
    - topiramate
Stevens-Johnson Syndrome (SJS) and
Toxic Epidermal Necrolysis (TENS)
severe life threatening allergic reaction
blisters and erosions of the skin, particularly palms/soles and mucous membranes
fever and malaise
rare: severe risk roughly 1-10/10,000 for many AEDs
rapid titration of lamotrigine especially in combination with valproate increases risk

Drugs rarely associated with rash
Valproate
Gabapentin
Pregabalin
Levetiracetam
Topiramate
AEDs; ADR: Rash

- ▲▲ = rash rate significantly greater than average of all other AEDs (p<0.003)
- ▼▼ = rash rate significantly lower than average of all other AEDs (p<0.003)
- ▲ = trend towards significantly higher than average rash rate of all other AEDs (0.003<p<0.05)
-▼ = trend towards significantly lower than average rash rate of all other AEDs (0.003<p<0.05)

FDA alert 12/2007

- Risk of "dangerous or even fatal skin reactions" (SJS and TEN) are more common in those with HLA-B*1502
- This allele is almost exclusively found in Asians
  - In 10-15% of population in China, Thailand, Malaysia, Indonesia, the Philippines, and Taiwan
  - 2-4% in India
  - <1% in Japan and Korea

- 59/60 Asian patients w/ SJS/TEN had this allele vs 4% of cbz tolerant patients
- Estimated absolute risk for those with the allele: 5%
- Asians "should be screened for the HLA-B*1502 allele before starting treatment with carbamazepine"
- These patients may also be at risk with other AEDs
  - Use drugs not typically associated with rash
AEDs and Comorbidities

• Osteoporosis
  Mostly worsened by the enzyme inducers: phenytoin, phenobarbital, primidone. Carbamazepine data equivocal. Equivocal data with valproate, unavailable for other non-inducers. Take calcium 1000-1500/d; Vit D 400-4000/d

• Depression
  Can be exacerbated by levetiracetam (and less so zonisamide)
  Can be helped by lamotrigine and possibly gabapentin, pregabalin (and vagus nerve stimulator)

• Migraine
  Consider topiramate, valproate

• Obesity
  Weight loss with topiramate and zonisamide
  Weight gain with valproate > gabapentin/pregabalin, carbamazepine

AEDs and Suicidal risk

• Recent FDA alert (1/2008):
  Meta-analysis of 199 placebo-controlled add-on tx trials
  – (44,000 patients)
  Suicidality with adjunct AEDs than adjunct placebo:
  0.43% vs 0.22%
  Extra 2.1 patients per 1000 more patients will have suicidality
  4 suicides with AEDs vs 0 with placebo
  "generally consistent across the 11 AEDs"

• Data analysis is controversial and overall difference is very small
• Further investigation is needed
• Clinicians should be aware of potential risk and screen for depression/suicidality

www.fda.gov
Emerging Rational Polytherapy

Concepts
- **Combination of low to moderate doses of AEDs** is more effective than high-/maximum tolerable dose monotherapy

Principle
- **Combination of drugs for synergistic pharmacodynamic interactions**
  - better efficacy and/or less toxicity

Methods
- (i) **different mechanism of action**
  - principle of pharmacotherapy in medicine
- (ii) **no or less pharmacokinetic interactions**
  - avoid enzyme inducing drugs (Cramer et al., 2002)
- (ii) avoid drugs having similar AE-profiles

A Mechanistic Assessment of Pharmacodynamic AED Interactions in Animal Models

<table>
<thead>
<tr>
<th>AEDs Combined</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Na+ blocker + Na+ blocker</td>
<td>Additive efficacy or antagonism</td>
</tr>
<tr>
<td>Na+ blocker + AED with multiple actions</td>
<td>Variable and unpredictable</td>
</tr>
<tr>
<td>AED with multiple actions + AED with multiple actions</td>
<td>Synergistic efficacy</td>
</tr>
<tr>
<td>Gabapentin + Any other AED</td>
<td>Synergistic efficacy</td>
</tr>
<tr>
<td>Levetiracetam + Other AEDs</td>
<td>Additive or synergistic efficacy</td>
</tr>
</tbody>
</table>

Rational Polytherapy: Current status

- No Class I/II evidence supporting its clinical value

- Clinical evidence (class III/IV) for specific mechanistic combinations
  - Better efficacy by combination of Na-channel blocker
  - (CBZ, LTG) + multiple actions (VPA, TPM)
  - SZ free rate: 36% vs 7% (p=0.05; Kwan & Brodie, 2000)
  - VPA/ESM in absence epilepsy (Rowan, 1983)
  - VPA/LTG: RR (64%) vs CBZ/LTG (41%), PHT/LTG (38%): Brodie et al., 1997
  - VPA/LTG: SF in 30% of pts failed to monotherapy of both drugs: Pisani et al., 1999

- Experimental evidence of synergism (isobolographic analysis)
  - LTG/TPM &LEV/TPM: most effective combination (Luszczki et al., 2002, 2006)

Rational Polytherapy: Pharmocodynamic

- Problem: very little evidence in humans
  - probably synergism: VPA + LTG, VPA + ESM (in absences)
    - VPA + TPM ?, LEV + TPM ?
  - no synergism: VPA + CBZ
  - increased toxicity: + Barbiturates + Benzodiazepines
“Therapeutic Range” of AED Serum Concentrations

A guide not a goal
• Limited data
• Broad generalizations
• Individual differences
• Useful in:
  – Providing initial target in patients with infrequent seizures
  – Understanding unexpected seizures or side effects, especially with polypharmacy
  – Verifying compliance

Dose Initiation and Monitoring

• Discuss likely and unlikely but important adverse effects
• Discuss likelihood of success
• Discuss recording/reporting seizures, adverse effects, potential precipitants
Evaluation After Seizure Recurrence

- Progressive pathology?
- Avoidable precipitant?
- If on AED
  - Problem with compliance or absorption?
  - Increase dose?
  - Change medication?
- If not on AED
  - Start AED?

Discontinuing AEDs

- Seizure freedom for ≥ 2 years implies overall >60% chance of successful withdrawal
- Favorable factors
  - Control achieved easily on one drug at low dose
  - No previous unsuccessful attempts at withdrawal
  - Normal neurologic status and EEG?
  - Primarily generalized seizures only?
  - “Benign” syndrome
- Consider relative risks/benefits (e.g., driving, pregnancy)
Non-Drug Treatment/
Lifestyle Modifications

• Adequate sleep
• Avoidance of alcohol, stimulants, etc.
• Stress reduction — specific techniques
• Adequate diet

Common Epilepsy Treatment Path

- First Monotherapy
- Seizure-freedom
- Alternative Monotherapy
- Seizure-freedom
- Polytherapy
- Seizure-freedom
- Surgery
- Pharmacoresistance
Definition of refractory epilepsy

- Inability to achieve acceptable seizure control despite adequate trials with a sufficient number of drugs at doses that are associated with no side effects or with acceptable side effects only

Refractory epilepsy: clinical practice

- After the drug of first choice ineffective, a second-line treatment should be chosen. Monotherapy is the ideal but cannot always be achieved.

- Combinations of AEDs usually prescribed for those unresponsive to monotherapy.

- When epilepsy remains uncontrolled, it is considered to be “refractory” or “pharmacoresistant.”

- Some of these patients are offered epilepsy surgery or a vagal nerve stimulator.
It has long been recognized that seizures will be or will become refractory to pharmacotherapy >30% of patients.

- Early positive response to treatment implies a good prognosis.
- Conversely, it seems intuitive that individuals prone to refractory epilepsy will be less responsive to AEDs.
- More seizures, the more likely the epilepsy will be refractory.

**Management Paradigm**

- **Newly Diagnosed Epilepsy**
  - 1st Drug: 47% Seizure-free
  - 2nd Drug: 13% Seizure-free
  - 40% "Difficult-to-treat"
  - "Rational" polytherapy
  - Surgical assessment
To remove the epileptogenic lesion aims to make the patients become seizure free or reducing the number of seizure

Epilepsy syndrome not responsive to medical management
- Unacceptable seizure control despite maximum tolerated doses of 2-3 appropriate drugs as monotherapy

Epilepsy syndrome amenable to surgical treatment
Evaluation for Surgery

- History: consistency, localization of seizure onset and progression
- Exam: may have no or only subtle abnormalities
- MRI: 1.5 mm coronal cuts with sequences sensitive to gray-white differentiation and to gliosis
- EEG: ictal and interictal, special electrodes
- Neuropsychological battery
- Psychiatric evaluation
- Social work evaluation
- Intracarotid amobarbital test

Surgical Treatment

- Potentially curative
  - Resection of epileptogenic region ("focus") without causing significant new neurologic deficit
- Palliative
  - Partial resection of epileptogenic region
  - Disconnection procedure to prevent seizure spread — corpus callosotomy
### Epilepsy Surgery Outcomes

| Temporal Lesional Hemispheric Callosotomy |
|-----------------|-----------------|-----------------|-----------------|
| Seizure Free    | 68              | 45              | 66              | 45              | 8               |
| Improved        | 23              | 35              | 22              | 35              | 61              |
| Not improved    | 9               | 20              | 12              | 20              | 31              |
| Total           | 100             | 100             | 100             | 100             | 100             |


<table>
<thead>
<tr>
<th>Countries</th>
<th>Population (million)</th>
<th>Epilepsy surgery program</th>
<th>Prevalence of pts requiring surgery</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Available Pediatric service</td>
<td>No of case/yr</td>
</tr>
<tr>
<td>Hong Kong</td>
<td>6.8</td>
<td>Y</td>
<td>Y</td>
</tr>
<tr>
<td>India</td>
<td>1.000.0</td>
<td>Y</td>
<td>N</td>
</tr>
<tr>
<td>Indonesia</td>
<td>210.0</td>
<td>Y</td>
<td>N</td>
</tr>
<tr>
<td>Japan</td>
<td>120.0</td>
<td>Y</td>
<td>Y</td>
</tr>
<tr>
<td>Korea</td>
<td>47.0</td>
<td>Y</td>
<td>Y</td>
</tr>
<tr>
<td>Mongolia</td>
<td>2.5</td>
<td>N</td>
<td>N</td>
</tr>
<tr>
<td>Philippines</td>
<td>82.0</td>
<td>Y</td>
<td>Y</td>
</tr>
<tr>
<td>Singapore</td>
<td>4.2</td>
<td>Y</td>
<td>Y</td>
</tr>
<tr>
<td>Taiwan</td>
<td>23.0</td>
<td>Y</td>
<td>Y</td>
</tr>
<tr>
<td>Thailand</td>
<td>50.0</td>
<td>N</td>
<td>N</td>
</tr>
<tr>
<td>Vietnam</td>
<td></td>
<td></td>
<td></td>
</tr>
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</tbody>
</table>
In 1995, Regis et al in Marseille performed selective amygdalo-hippocampal radiosurgery for MTS.

- Approximately 7-ml volume target irradiated, dose 25 Gy that caused target necrosis of amygdala and hippocampus.
- 1st case had sz free immediately and the second case had a latency a year later.
Gamma knife in Temporal Lobe Epilepsy (2005)

- 6 cases were done
  - 3 cases with benign tumor mesial temporal lobe – class Ia
  - 2 cases with hippocampal atrophy – class IV
  - 1 case with dual pathology (CD and HS) – class Ia
  - One case has eyes opsoclonus post radio-surgery

Ketogenic Diet

- Anti-seizure effect of ketosis, acidosis
- Low carbohydrate, low protein, high fat after fasting to initiate ketosis
- Main experience with children, especially with multiple seizure types
- Long-term effects unknown
• Intermittent programmed (e.g., 30 sec. on, 5 min. off) electrical stimulation of left vagus nerve
• Option of patient-triggered stimulation (auras)
• Adverse effects local, related to stimulus (hoarseness, throat discomfort, dyspnea)
• Mechanism unknown
Brain stimulation

Direct Brain Stimulation?

- Cerebellum, caudate not reproducibly successful
- Thalamus:
  - Centromedian and subthalamic nucleus only moderate benefits
  - Anterior nucleus perhaps more attractive...

Brain stimulation

Anterior Nucleus of Thalamus

- 5 patients with seizure reduction (2002)
- Recently completed SANTE trial sponsored by Medtronics, Inc.
  - Ages 18-65; 6 partial seizures per month
  - Controlled (5 vs. 0 volts)
  - 157 patients randomized as of December 2007
    - 110 implanted

Reproduced with permission of Dr. Robert Fisher
Brain stimulation

Cortical Stimulation

- NeuroPace™
- Implanted into the skull with electrodes over the region(s) of interest
- Can detect and then electrically disrupt epileptiform activity
- Responsive

Open Loop Neurostimulation

Stimulation delivered continuously or on a clock cycle

Examples: VNS and DBS*

*DBS is not FDA approved for epilepsy

Responsive Neurostimulation

Stimulation delivered in response to detected epileptiform activity

Examples: RNS™ System*

*The RNS™ System is not FDA approved for epilepsy
Brain stimulation

The RNS™ System

<table>
<thead>
<tr>
<th>Year</th>
<th>Author</th>
<th># Patients</th>
<th>Study Type</th>
<th>Seizure Reduction</th>
</tr>
</thead>
<tbody>
<tr>
<td>2002</td>
<td>Theodore (US)</td>
<td>24</td>
<td>Randomized Controlled</td>
<td>16%</td>
</tr>
<tr>
<td>2005</td>
<td>Kinoshita (Japan)</td>
<td>7</td>
<td>Prospective Open-label</td>
<td>19%</td>
</tr>
<tr>
<td>2006</td>
<td>Fregni (Brazil)</td>
<td>21</td>
<td>Randomized Controlled</td>
<td>53%</td>
</tr>
<tr>
<td>2007</td>
<td>Cantello (Italy)</td>
<td>43</td>
<td>Randomized Controlled</td>
<td>15%</td>
</tr>
<tr>
<td>2007</td>
<td>Joo (South Korea)</td>
<td>35</td>
<td>Randomized Prospective</td>
<td>14%</td>
</tr>
<tr>
<td>2008</td>
<td>Santiago-Rodriguez (Mexico)</td>
<td>12</td>
<td>Prospective Open-label</td>
<td>50%</td>
</tr>
</tbody>
</table>
• Definition
  – More than 30 minutes of continuous seizure activity
    or
  – Two or more sequential seizures spanning this period without full recovery between seizures

• A medical emergency
  – Adverse consequences can include hypoxia, hypotension, acidosis and hyperthermia
  – Know the recommended sequential protocol for treatment with benzodiazepines, phenytoin, and barbiturates
  – Goal: stop seizures within 60 minutes
**Status Epilepticus Treatment**

<table>
<thead>
<tr>
<th>Time post onset</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Onset</td>
<td>Ensure adequate ventilation/O2</td>
</tr>
<tr>
<td>2-3 min.</td>
<td>IV line with NS, rapid assessment, blood draw</td>
</tr>
<tr>
<td>4-5 min.</td>
<td>Lorazepam 4 mg (0.1 mg/kg) or diazepam 10 mg (0.2 mg/kg) over 2 minutes via second IV line</td>
</tr>
<tr>
<td>7-8 min.</td>
<td>Thiamine 100 mg, 50% glucose 25 mg IV</td>
</tr>
<tr>
<td></td>
<td>Phenytoin or fosphenytoin 20 mg/kg IV at ≤ 50 mg per minute phenytoin or 150 mg/kg per minute fosphenytoin (≤ 0.75 mg/kg/min)</td>
</tr>
<tr>
<td></td>
<td>Pyridoxine 100-200 mg IV in children under 18 mo.</td>
</tr>
</tbody>
</table>

10 min. Can repeat lorazepam or diazepam if seizures ongoing.

30-60 min. EEG monitoring unless status ended and patient waking up.

40 min. Phenobarbital 20 mg/kg at ≤ 5 mg per minute (0.75 mg/kg per minute).

70 min. Pentobarbital 3-5 mg/kg load, 1 mg/kg per hour infusion, increase to burst-suppression (or midazolam 0.15-0.20 mg/kg load, 0.05-0.30 mg/kg per hour infusion).
**Differential Diagnosis of Paroxysmal Behavioral Event**

- Seizure
- Syncope
- Migraine
- Cerebral ischemia
- Movement disorder
- Sleep disorder
- Metabolic disturbance
- Psychiatric disturbance

**Psychogenic Nonepileptic Seizures**

- 10-45% of refractory epilepsy (referral centers)
- Females > males
- Psychiatric mechanism — dissociation, conversion
- Association with physical, sexual abuse
Psychogenic Nonepileptic Seizures

- Represent genuine psychiatric disease
- Once recognized, approximately 50% respond well to specific psychiatric treatment
- Epileptic and nonepileptic seizures may co-exist
- Video-EEG monitoring often helps clarify the diagnosis

Syncope

- Characteristic warning, usually gradual (except with cardiac arrhythmia)
- Typical precipitants (except with cardiac arrhythmia)
- Minimal to no postictal confusion/somnolence
- Convulsive syncope — tonic-clonic manifestations, usually < 30 sec; usually from disinhibited brainstem structures (only rarely from cortical hypersynchronous activity)
Epilepsy and Pregnancy

- Most pregnancies in epileptic mothers produce normal children
- Fetal anomalies (up to 10% of pregnancies) are multifactorial
  - Drug effects
  - Consequences of the mother's underlying diseases
  - Consequence of maternal seizures during pregnancy
- All antiepileptic drugs carry teratogenic risks

Epilepsy and Pregnancy
Major malformation and AEDs

Most available data on risk of AEDs comes from pregnancy registries.
Main outcome variable of most registries are major congenital malformations (MCM)
MCM = malformation that affects physiologic function or requires surgery
  - Neural tube defects
  - Cardiac defects
  - Genitourinary defects
  - Oral clefts
MCMs are more common with AED exposure
  - MCM risk in general population 1.6-2.1%
  - MCM risk with AED monotherapy 4.5% (OR 2.6)
  - MCM risk with Polytherapy 8.6% (OR 5.1)

Epilepsy and Pregnancy
Major malformation and AEDs

• Valproate consistently associated with poorer outcomes
  MCM rate with valproate monotherapy 6.2-13.2% across 5 registries
  Most studies show dose-related increase in risk with doses > 1000mg/day
  Polytherapy regimens including valproate also substantially increased risk of MCM
  Valproate associated with lower IQs in exposed children

• Phenobarbital probably also poses higher risk of MCM
• compared with other monotherapy regimens.

Meador et al. Neurology 2007; 68 (suppl 1): A337
Meador et al. Neurology 2008; 71:1109-1117

Epilepsy and Pregnancy
Major malformation and AEDs

• MCM rate similar among other studied AEDs in monotherapy, but not enough data to show significant difference between them
  Levetiracetam
  Early data promising (0% in monotherapy, 2.7% in polytx)
  Carbamazepine (2.2-3.9%)
  Substantial data available, relatively good track record
  Lamotrigine (1.4-4.4%)
  Increased risk (5.4%) with doses > 400/day
  Gabapentin (0-3.2%)
  Topiramate (0-4.8%)
  Phenytoin (3.2-6.7%)
  Zonisamide, Pregabalin
  No substantial data on monotherapy

Meador et al. Neurology 2007; 68 (suppl 1): A337
Meador et al. Neurology 2008; 71:1109-1117
Pregnancy and Epilepsy (cont.)

- Effects on pregnancy on epilepsy
  - Risk of increased seizures (low if compliance maintained, doses adjusted upward to maintain free levels)
  - Risk of seizures during delivery (impaired absorption, sleep deprivation, exhaustion)
- Effects of epilepsy on pregnancy
  - Genetic factors in some cases
  - Risks of convulsive seizures
  - Risks of AEDs

Pregnancy and Epilepsy Guidelines

- Risk of fetal malformation is increased twofold to threefold
- Prenatal diagnosis should be discussed
- Seizures may be deleterious to the fetus
- Adequate folate should be ensured (at least 1 mg/day)
- Monotherapy should be used if possible, with the lowest effective dose
Breastfeeding should be encouraged unless clear risk posed

Probably safe:
- Carbamazepine
- Phenytoin
- Valproate
- Lamotrigine

“Use with caution” in lactating women:
- Primidone
- Phenobarbital
- Ethosuximide

Regulation varies state by state regarding:
- Reporting requirements
- Required seizure-free period
- Favorable/unfavorable modifiers

Insurance issues
Employment issues
First Aid Tonic-Clonic Seizure

• Turn person on side with head inclined toward ground to keep airway clear, protect from nearby hazards

• Transfer to hospital needed for:
  – Multiple seizures or status epilepticus
  – Person is pregnant, injured, diabetic
  – New onset seizures

• DO NOT put rigid object in mouth or restrain