When to start & How to select AEDs

Pasiri Sithinamsuwan, MD
Division of Neurology, Phramongkutklao Hospital

Concepts of medical treatments

Treatment Initiation

- Consider other options if seizures are provoked
- Balance risks between recurrent seizures and adverse events of AEDs
  - Frequency of seizures and risk of recurrent
  - Psychosocial consequences of further seizures
  - Avoid AEDs when diagnosis is in doubt
- AED do not prevent development of epilepsy
- Expectations should be modest (50%)

First seizure, evaluate high recurrence risk

- A very high risk of recurrence
  - Examples
    - A single seizure occurring at least a month after a stroke
    - A child with a single seizure conjoined with a structural or remote symptomatic epilepsy and an epileptiform EEG study
    - A patient in whom diagnosis of a specific epilepsy syndrome associated with persistent threshold alteration can be made after the occurrence of a single seizure
    - A first seizure might present present as status epilepticus

Consider (a case-by-case basis)

- Seizure type, syndromic form
- Patient characteristics; age, gender, comorbidities
- Efficacy and side effect profile
- Dosing schedule, drug interaction
- Medical expertise
- Cost, ED drug (national formulary)

Ideal properties for an easy-to-use antiepileptic drug

- Broad spectrum
- High efficacy
- Good tolerability
- No risk of allergic or idiosyncratic reactions including teratogenicity
- Low interaction potential
- Low variability in dosage requirements
- No tolerance
- No withdrawal seizures
- Favorable pharmacokinetics (linear kinetics, T1/2 for 1-2 daily dosing)
- Fast and easy dose escalation rate
- Availability of convenient formulation (syrup, parenteral)
- Low cost, ED

ILAE 2014
Old (standard) AEDs
- Phenobarbital
- Phenytoin
- Carbamazepine
- Valproate
- Benzodiazepines

New and newer drugs
- Levetiracetam
- Lamotrigine
- Topiramate
- Gabapentin
- Pregabalin
- Oxcarbazepine
- Lacosamide
- Brivaracetam
- Carisbamate
- Eslicarbazepine
- Fluorofeltbamate
- Lacosamide
- Retigabine
- Rufinamide
- Perampanel
- Stiripentol

A new antiepileptic medication
- To change of epileptic drug target
- In poly-therapy: try using multiple actions
- Using in chronic epilepsy (> 5yr)
  - 17%: seizure freedom
  - 25%: seizure 50-99% reduction

Main mechanisms of AEDs
- “A decrease in neuronal excitability”
  - Increased GABAergic
  - Decreased glutamatergic neurotransmission
  - Inhibition of voltage-gated ion channels
  - Modifications of intracellular signaling pathways

French JA. Neurology 2004

A new antiepileptic medication
- Evidence level A
- Levetiracetam (1,000-3,000 mg/d)
- Lamotrigine (300-500 mg/d)
- Topiramate (300-1,000 mg/d)
- Gabapentin (600-1,800 mg/d)
- Zonisamide (100-400 mg/d)

French JA. Neurology 2004

Newer medications: drug profiles
- Many mechanism of action (board spectrum)
- Same or better efficacy
- Better drug profile
- Less bound form
- Less side effect
- Less drug interaction
Antiepileptic Drugs and their Molecular Targets

<table>
<thead>
<tr>
<th>Drug</th>
<th>Sodium Channels</th>
<th>Calcium Channels</th>
<th>GABA System</th>
<th>Glutamate Receptors</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Group A (Ion Channel)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Phenytoin</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Carbamazepine</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lamotrigine</td>
<td></td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Group B (Mixed Mechanisms)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Zonisamide</td>
<td>X</td>
<td>1-Type</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vip掐อด</td>
<td>X</td>
<td>1-Type</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lamotrigine</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Levetiracetam (1,5-DA)</td>
<td>X</td>
<td>GABA_B, R</td>
<td>AMPA</td>
<td></td>
</tr>
<tr>
<td>Ethosuximide</td>
<td>X</td>
<td>1-Type</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Group C (GABA-ergic)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gabapentin</td>
<td></td>
<td>GABA_B</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pregabalin</td>
<td></td>
<td>GABA_B</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vigabatrin</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Legend**
- HVA: High voltage activated

ADVERSE EFFECTS OF AEDs

**Early-Onset Adverse Effects**

<table>
<thead>
<tr>
<th>CBZ</th>
<th>CLB</th>
<th>CLB</th>
<th>ETS</th>
<th>GBP</th>
<th>LEV</th>
<th>LCG</th>
<th>PHT</th>
<th>PHG</th>
<th>PHT</th>
<th>PRO</th>
<th>VPA</th>
<th>VGB</th>
<th>ZNS</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

- Somnolence
- Sizness
- Seizure aggravation
- GI
- Liver failure
- Rash

Miminally Increased risk in clinical use
Risk higher than minimal for AEDs as shown above in clinical use
Highest risk among AEDs in clinical use


**Late-Onset Adverse Effects**

<table>
<thead>
<tr>
<th>CBZ</th>
<th>CLB</th>
<th>ETS</th>
<th>GBP</th>
<th>LEV</th>
<th>LCG</th>
<th>PHG</th>
<th>PRO</th>
<th>VPA</th>
<th>VGB</th>
<th>ZNS</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

- Somnolence
- Sizness
- Seizure aggravation
- GI
- Liver failure
- Rash

Miminally Increased risk in clinical use
Risk higher than minimal for AEDs as shown above in clinical use
Highest risk among AEDs in clinical use


Therapeutic considerations

- First lines for generalized epilepsy and partial epilepsy
- Partial Seizures:
  - Newer AEDs as efficacious as traditional AEDs (except GBP), but more tolerable and less enzyme inducing
  - Generalized S:\:
    - Valproic acid, lamotrigine, levetiracetam, topiramate, clobazam
    - Ethosuximide (absence only)
    - GBP, CBZ, OXC, PH may induce myoclonic seizures

The Treatment of Epilepsy (Simon Shorvon), Third edition, 2009
Evidence-Based Guidelines for the Treatment of Epileptic Seizures with AEDs

- Optimal initial monotherapy for patients with newly diagnosed or untreated epilepsy
- ILAE multi-countries Team
  - Epileptologists
  - Clinical pharmacologists
  - Statistician
  - Methodologist

Recommendation (Based on efficacy and effectiveness data only)

<table>
<thead>
<tr>
<th>Evidence Level</th>
<th>Conclusions</th>
<th>Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>AED established as efficacious or effective as initial monotherapy</td>
<td>First line monotherapy</td>
</tr>
<tr>
<td>B</td>
<td>AED probably efficacious or effective as initial monotherapy</td>
<td>First line monotherapy</td>
</tr>
<tr>
<td>C</td>
<td>AED possibly efficacious or effective as initial monotherapy</td>
<td>Alternative firstline monotherapy</td>
</tr>
<tr>
<td>D</td>
<td>AED potentially efficacious or effective as initial monotherapy</td>
<td>Weak efficacy</td>
</tr>
<tr>
<td>E</td>
<td>No data available to assess if AED is effective as initial monotherapy</td>
<td>No data</td>
</tr>
<tr>
<td>F</td>
<td>AED established as ineffective or significant risk of seizure aggravation</td>
<td>Should not be used for initial monotherapy</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Class I criteria</th>
<th>Level of evidence</th>
<th>Conclusions</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 Class I studies or meta-analysis meeting class I criteria sources OR</td>
<td>AED established as efficacious or effective as initial monotherapy</td>
<td></td>
</tr>
<tr>
<td>2 Class II studies</td>
<td>B</td>
<td>AED probably efficacious or effective as initial monotherapy</td>
</tr>
<tr>
<td>3 Class III studies</td>
<td>C</td>
<td>AED possibly efficacious or effective as initial monotherapy</td>
</tr>
<tr>
<td>4 Class IV studies</td>
<td>D</td>
<td>AED potentially efficacious or effective as initial monotherapy</td>
</tr>
<tr>
<td>5 Evidence from nonrandomized, prospective, controlled or uncontrolled studies, case series, or expert reports</td>
<td>E</td>
<td>No data available to assess if AED is effective as initial monotherapy</td>
</tr>
<tr>
<td>6 Evidence from randomized, placebo-controlled clinical trials, or large scale post-approval studies</td>
<td>F</td>
<td>AED established as ineffective or significant risk of seizure aggravation</td>
</tr>
</tbody>
</table>

A prospective, randomized, controlled clinical trial (RCT) or meta-analysis of RCTs, in a representative population that meets all six criteria:
- Primary outcome variable: efficacy or effectiveness
- Treatment duration: ≥ 48 weeks
- Study design: double blind
- Design: For superiority trials: superiority demonstrated. For noninferiority trials or failed superiority trials: the study treatment’s efficacy/effectiveness lower limit (95% confidence interval) is above a 20% lower boundary relative to the adequate comparator’s point estimate of efficacy/effectiveness using a per-protocol study population (for age/seizure type subgroups). The study treatment is not inferior to the adequate comparator by a predetermined number of treatment emergent seizures. Appropriate statistical analysis.

An RCT or a meta-analysis meeting all the class I criteria except that:
- Treatment duration: ≥ 24 weeks but <48 weeks OR
  - Design: For noninferiority trials or failed superiority trials: the study treatment’s efficacy/effectiveness lower limit (95% confidence interval) is between the 21% and 30% lower boundary relative to the adequate comparator’s point estimate of efficacy/effectiveness using a per-protocol study population (for age/seizure type subgroups)

AEDs for:
- Adults with partial-onset seizures
- Elderly with partial-onset seizures
- Adults with generalized-onset tonic-clonic seizures
- JME
Optimal initial monotherapy for patients with newly diagnosed or untreated epilepsy

**Partial Seizures: Adults recommendations**

<table>
<thead>
<tr>
<th>Level</th>
<th>AEDs</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>CBZ, PHT, LEV, ZNS</td>
</tr>
<tr>
<td>B</td>
<td>VPA</td>
</tr>
<tr>
<td>C</td>
<td>GBP, LTG, OXC, PB, TPM, VGB</td>
</tr>
<tr>
<td>D</td>
<td>CZP, PRM</td>
</tr>
<tr>
<td>E</td>
<td>Others</td>
</tr>
<tr>
<td>F</td>
<td>None</td>
</tr>
</tbody>
</table>

**Partial Seizures: Elderly recommendations**

<table>
<thead>
<tr>
<th>Level</th>
<th>AEDs</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>GBP, LTG</td>
</tr>
<tr>
<td>B</td>
<td>None</td>
</tr>
<tr>
<td>C</td>
<td>CBZ</td>
</tr>
<tr>
<td>D</td>
<td>TPM, VPA</td>
</tr>
<tr>
<td>E</td>
<td>Others</td>
</tr>
<tr>
<td>F</td>
<td>None</td>
</tr>
</tbody>
</table>

**Generalized onset Tonic Clonic Seizures: Adults Recommendations**

<table>
<thead>
<tr>
<th>Level</th>
<th>AEDs</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>None</td>
</tr>
<tr>
<td>B</td>
<td>None</td>
</tr>
<tr>
<td>C</td>
<td>None</td>
</tr>
<tr>
<td>D</td>
<td>GBP, LEV, VGB</td>
</tr>
<tr>
<td>E</td>
<td>Others</td>
</tr>
<tr>
<td>F</td>
<td>None</td>
</tr>
</tbody>
</table>

**Juvenile Myoclonic Epilepsy: Adult Recommendations**

<table>
<thead>
<tr>
<th>Level</th>
<th>AEDs</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>None</td>
</tr>
<tr>
<td>B</td>
<td>None</td>
</tr>
<tr>
<td>C</td>
<td>None</td>
</tr>
<tr>
<td>D</td>
<td>TPM, VPA (ZNS, CZP, LTG*, LEV)</td>
</tr>
<tr>
<td>E</td>
<td>Others</td>
</tr>
<tr>
<td>F</td>
<td>CBZ*, GBP, OXC*, PHT*, TGB, VGB</td>
</tr>
</tbody>
</table>

*may aggravate myoclonic seizure types, should be used with caution

**Concepts of medical treatment**

- Minimally effective dose → Maximally tolerated dose
- Sequential monotherapy
  - Ability of seizure control
  - Tolerability, toxicity, drug interaction
  - Compliance, cost
- Polytherapy (adjunctive treatment)
  - Same or “different” mechanisms of action
- Rational polytherapy
- Special considerations
  - Young, elderly, females, conceptual age, pregnancy, specific medical conditions
Monotherapy

47% of the newly diagnosed epileptic patients achieved 100% reduction in seizure frequency with their first AED.

The chance to be seizure free with

- 1st AED: 61.8%
- 2nd AED: 41.7%
- 5th AED: 16.6%
- 6th AED: 0%

Follow up plans

- Efficacy: seizure frequency (seizure diary)
- Side effects (tolerability)
- Quality of life
- Monitoring: blood level, EEG, CBC, Na, Cr, LFT
  - Beware “phenomenon of regression to the mean”
  - Wide fluctuations in seizure frequency over time
  - Exacerbation-spontaneous amelioration

Prognostic groups

1) Spontaneous remission (20-30%)
   - Benign epilepsy of childhood with centrotemporal spikes (BECT)
   - Childhood absence epilepsy (CAE)

2) Remission on AEDs (20-30%)
   - Most focal epilepsy
   - Juvenile myoclonic epilepsy (JME)**

3) Persistent seizure with AEDs (30-40%)
   - Refractory patients
     - An increased risk of psychosocial and medical morbidities and mortality

Concerns

Administration

- Enteral: tablet, capsule, syrup
- Parenteral: IM, IV
- Other routes: buccal, intranasal, per-rectal
- Half-life, frequency of treatment
- Control released formulation
- Generic or original

Kwan P, Brodie MJ. Early identification of refractory epilepsy. NEJM 2000

Schiller Y. Neurology 2008

Administration

- Oral: tablet, capsule, syrup
- Parenteral: IM, IV
- Other routes: buccal, intranasal, per-rectal
- Half-life, frequency of treatment
- Control released formulation
- Generic or original

Precipitating factors

- Identify and avoid precipitating factors
  - Miss tablets (poor compliance)
  - Excessive sleep deprivation
  - Some photosensitive epilepsies
    - Intermittent flashing lights, certain video games
  - Excessive alcoholic drinking
  - Stress, fever, etc.

Precaution

- Driving
- Swimming
- Heights
- Some work environments
- Bath as opposed to shower

Summary

- The most important is to diagnose correctly
- Plans of initial management both pharmacological and non-pharmacological approaches are essential
- Evaluation and prompt treatments including using either standard or new AEDs should be done on a case-by-case basis
- Identify refractory epilepsy case and consider refer to Epilepsy centers at the proper time
- Some special conditions need to consider