Antiepileptic drugs (AEDs)

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Disclosure

I have no financial relationships to disclose that are relative to the content of my presentation.
FDA-approved AEDs

**old**
- Phenobarbital (Luminal) 1912
- Primidone (Mysoline)
- Phenytoin (Dilantin)
- Methsuximide (Celontin)
- Ethosuximide (Zarontin)
- Clonazepam (Klonopin)
- Carbamazepine (Tegretol, Carbatrol)
- Valproate (Depakote) 1978

**new**
- Felbamate (Felbatol) 1993
- Gabapentin (Neurontin)
- Lamotrigine (Lamictal)
- Topiramate (Topamax)
- Tiagabine (Gabitril)
- Levetiracetam (Keppra)
- Oxcarbazepine (Trileptal)
- Zonisamide (Zonegran)
- Pregabalin (Lyrica)
- Vigabatrin (Sabril)
- Lacosamide (Vimpat)
- Clobazam (Onfi)
- Rufinamide (Banzel)
- Ezogabine (Potiga)
- Perampanel (Fycompa) 2012

Coming soon: Eslicarbazepine, brivaracetam…
Felbamate (FBM)
Felbatol ®

- First approved in 1993. FDA indication: monotherapy or adjunctive therapy for partial epilepsy in adult and pediatric patients, adjunctive therapy for Lennox-Gastaut syndrome (with black box warning)

- MOA: NMDA antagonist, sodium and calcium channel antagonist, ? GABA-A agonist

- Available dosage: 400, 600 mg and oral solution
**FBM- absorption, distribution**

- Oral absolute bioavailability: >90%
- $T_{max} = 2-6$ hours
- Protein binding: ~25%
- $V_d = \sim 0.75$ L/Kg
FBM - metabolism, elimination

- **Metabolism:** hepatic via isozyme CYP3A4 (most metabolites are inactive)
- **Elimination:** mostly renal (40% as metabolites from the liver)
- $T_{1/2} = 23-23$ hours (16 hours in children)
FBM- interactions

- FBM is an inhibitor of CYP enzyme complex causing increased levels of PB, PHT, VPA, and coumadin
- FBM decreases levels of CBZ but increases levels of its epoxide
- FBM decreases levels of OCPs
- Enzyme-inducing AEDs will decrease the level of FBM
FBM- adverse effects

- **Aplastic Anemia** (100-fold increased risk, 20-30% fatality, therapy > 1 month)
- **Hepatic Failure** (risk is 1:26,000 to 1:34,000, 67% risk of death or transplant)
- Sedation
- Weight loss (especially in children)
# FBM- titration & dosing

<table>
<thead>
<tr>
<th>Initiation</th>
<th>Titration</th>
<th>Optimization</th>
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<tbody>
<tr>
<td>600 mg twice daily</td>
<td>Increase dose by 300 mg twice daily every two weeks, depending on seizure control and tolerability</td>
<td>1200 mg twice daily</td>
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<tr>
<td>15 mg/kg/day divided 3 or 4 times daily (in children)</td>
<td>Increase dose by 10-15 mg/kg/day divided 3 or 4 times daily every 2 weeks (in children)</td>
<td>35-45 mg/kg/day divided 3 or 4 times daily (in children)</td>
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</tbody>
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Gabapentin (GBP) Neurontin ®

- First approved in 1994. FDA indication: adjunctive therapy in adult and pediatric (3 years and older) patients for partial epilepsy
- MOA: mostly unknown, binds to $\alpha 2\delta 1$ subunit of voltage-gated Ca channels
- Available dosage: 100, 300, 400, 600, 800 mg and oral solution
GBP- absorption, distribution

- Oral absolute bioavailability is inversely proportional to the dose (bioavailability of is approximately 60%, 47%, 34%, 33%, and 27% following 900, 1200, 2400, 3600, and 4800 mg daily given 3 times daily)

- Tmax = 2-4 hours (delayed when taken with food)

- Protein binding: negligible (~3%)

- $V_d = \sim 0.6 \, \text{L/Kg}$
GBP- metabolism, elimination

- Not appreciably metabolized in humans
- Elimination is mostly renal (unchanged)
- $T_{1/2} = 5-7$ hours (132 hours in anuric patients)
GBP- interactions

- No known interactions with enzyme-inducing or enzyme-inhibiting AEDs
- May potentiate effects of sedatives and alcohol
- Products containing aluminum or magnesium (e.g., Maalox) will decrease GBP bioavailability by 20%
GBP- adverse effects

- Sedation
- Weight gain
- Peripheral edema
- Rash (Drug Reaction with Eosinophilia and Systemic Symptoms or DRESS)
- Emotional lability and hyperkinesia (in children)
- Myoclonus
- Exacerbation of myoclonic seizures
GBP - titration & dosing

**Initiation**
- 300 mg 3 times daily
- 10-15 mg/kg/day divided 3 times daily (in children)

**Titration**
- Increase dose by 300 mg 3 times daily every week, depending on seizure control and tolerability
- Increase dose by 10-15 mg/kg/day divided 3 times daily (in children)

**Optimization**
- 1800 mg 3 times daily
- 35-50 mg/kg/day divided 3 times daily (in children)
Lamotrigine (LTG)  
Lamictal ®

- First approved in 1994- FDA indications: adjunctive therapy for adult and children patients with partial seizures, primary GTC, generalized seizures of LGS and conversion to monotherapy for patients 16 years of age with partial seizure
- MOA: mostly unknown, inhibits voltage sensitive sodium channels (also modulates presynaptic release of glutamate, and weakly inhibits serotonin receptors)
- Available dosage: 25, 100, 150, and 200 mg (IR)- 25, 50, 100, 200, 250, 300 (XR)- and oral solution
LTG- absorption, distribution

- Oral absolute bioavailability >98%
- Tmax = 1.4-4.8 hours (decreased with food)
- Protein binding: ~55%
- $V_d = \sim 0.9-1.3 \text{ L/Kg}$
LTG- metabolism, elimination

- Metabolism: predominantly by glucuronic acid conjugation; the major metabolite is an inactive 2-N-glucuronide conjugate
- Weakly inhibits dihydrofolate reductase (in vitro)
- Elimination: in urine (94%, ~90% as glucuronide conjugates and ~10% unchanged)
- $T_{1/2} = 12-70$ hours (depending on concomitant enzyme-inducing or enzyme-inhibiting medications)
LTG- interactions

- Enzyme-inducing AEDs, OCPs, pregnancy, rifampin decrease LTG levels
- Addition of valproate increases LTG levels
- Addition of LTG increases levels of TPM, may decrease level of VPA
LTG- adverse effects

- Sedation, ataxia, nystagmus
- Rash
- **Stevens-Johnson syndrome** (higher risk with co-administration of valproate, higher doses, and faster titration)
- GI upset
- Headache
- May exacerbate myoclonus in IGE
- Aseptic meningitis
- Mood stabilization (FDA approval for bipolar disorder)
## LTG- titration & dosing

<table>
<thead>
<tr>
<th>Phase</th>
<th>Dosage Details</th>
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<tbody>
<tr>
<td><strong>Initiation</strong></td>
<td>25-50 mg daily (depending on co-administration of enzyme-modulating AEDs)</td>
</tr>
<tr>
<td></td>
<td>0.15-6 mg/kg/day (in children)</td>
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<tr>
<td><strong>Titration</strong></td>
<td>Increase dose by 25-100 mg daily or twice daily over 1-2 weeks (depending on co-administration of enzyme-modulating AEDs) and depending on seizure control and tolerability</td>
</tr>
<tr>
<td></td>
<td>0.3 to 1.2 mg/kg/day (in children)</td>
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<tr>
<td><strong>Optimization</strong></td>
<td>100-250 mg twice daily (depending on co-administration of enzyme-modulating AEDs) daily</td>
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<tr>
<td></td>
<td>5-15 mg/kg/day (in children)</td>
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Topiramate (TPM)  
Topamax®

- First approved in 1995. FDA indication: initial monotherapy for adult and pediatric patients with partial onset or primary GTC seizures, adjunctive therapy for adult and pediatric patients with seizures associated with LGS
- MOA: mostly unknown, likely blocks voltage-dependent sodium channels, augments the activity of GABA, antagonizes the AMPA/kainate subtype of the glutamate receptor, and weakly inhibits the carbonic anhydrase enzyme
- Available dosage: 25, 50, 100, 200 mg (IR or XR)- oral solution
TPM - absorption, distribution

- Oral absolute bioavailability ~80%
- Tmax = 1.5-4 hours
- Protein binding: 15-40%
- Vd = ~0.7 L/Kg
TPM - metabolism, elimination

- Metabolism: moderate hepatic metabolism by P450 enzyme complex.
- Elimination: in urine (70% unchanged)
- $T_{1/2} = 14$-23 hours
TPM- interactions

- Addition of PHT, CBZ, VPA and LTG decrease levels of TPM
- At higher doses (>400 mgs daily), TPM becomes a weak CYP2C19 inhibitor and a weak CYP3A4 inducer
- Addition of TPM may decrease OCP efficacy and coumadin levels,
- Addition of TPM may cause hyperammononemia with VPA, and increase PHT levels
TPM - adverse effects

- Sedation
- Cognitive slowing
- Suicidal ideations, depression
- Kidney stones
- Acute angle closure glaucoma
- Parasthesia
- Oligohydrosis (in children)
- Metabolic acidosis
- Weight loss
- Anti-migrainous effect (FDA indication)
## TPM- titration & dosing

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<thead>
<tr>
<th>Initiation</th>
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<tbody>
<tr>
<td>25 mg twice daily</td>
<td>Increase dose by 25-50 mg twice daily every week depending on seizure control and tolerability</td>
<td>200 mg twice daily</td>
</tr>
<tr>
<td>1-3 mg/kg/day (for children)</td>
<td>Increase dose by 1-3 mg/kg/day every week depending on seizure control and tolerability (for children)</td>
<td>5-9 mg/kg/day (for children)</td>
</tr>
</tbody>
</table>
**Levetiracetam (LEV)**  
**Keppra ®**

- First approved in 1999. FDA indication: adjunctive therapy for adult and children patients with partial onset seizures, generalized tonic-clonic (IGE) and myoclonic seizures (JME)

- MOA: mostly unknown, binds to synaptic vesicle protein SV2A, thought to be involved in the regulation of vesicle exocytosis

- Available dosage: 250, 500, 750, and 1000 mg (for IR)- 500, and 750 mg (for XR)- oral solution- and IV formulation
LEV- absorption, distribution

- Oral absolute bioavailability ~100%
- Tmax = 1-3 hours
- Protein binding: negligible
- V_d = ~0.6 L/Kg
LEV- metabolism, elimination

- No hepatic metabolism, partly hydrolized to inactive compounds
- Elimination is mostly renal (66% unchanged, remaining are inactive metabolites)
- $T_{1/2} = 6-9$ hours (longer for XR)
LEV- interactions

- No known interactions with other medications
LEV- adverse effects

- Sedation
- Headache
- Suicidal ideations
- Irritability and aggression (~ 6.5%, more common in children)- ? Protective role of pyridoxine
**LEV- titration & dosing**

<table>
<thead>
<tr>
<th>Initiation</th>
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<tbody>
<tr>
<td>500 mg twice daily</td>
<td>Increase dose by 500 mg twice daily every 2 weeks depending on seizure control and tolerability</td>
<td>1500 mg twice daily</td>
</tr>
<tr>
<td>10 mg/kg/day divided twice daily (in children)</td>
<td>Increase by 10 mg/kg/day twice daily every 2 weeks depending on seizure control and tolerability (in children)</td>
<td>30 mg/kg/day divided twice daily (in children)</td>
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Zonisamide (ZNS) Zonegran®

- First approved in 2000. FDA indication: adjunctive therapy of adults and children >16 years of age with partial epilepsy
- MOA: mostly unknown, blocks sustained repetitive firing of Na channels, reduces T-type Ca^{2+} currents, and weakly inhibits carbonic anhydrase
- Available dosage: 25, 50, and 100 mg
ZNS- absorption, distribution

- Oral absolute bioavailability: ~100 %
- Tmax = 2-5 hours (lower with food intake)
- Protein binding: ~ 50%
- \( V_d = \sim 0.7 \text{ L/Kg} \)
ZNS- metabolism, elimination

- Hepatic metabolism by acetylation and conjugation with glucuronic acid
- Elimination by excretion in urine (metabolites are inactive)
- $T_{1/2} = 50-68$ hours
ZNS- interactions

- Addition of enzyme-inducing AEDs decrease ZNS levels
ZNS- adverse effects

- Sedation
- Cognitive slowing
- Suicidal ideations, depression
- Kidney stones
- Oligohydrosis (in children)
- Metabolic acidosis
- Weight loss
- Sulfonamide allergy
ZNS- titration & dosing

Initiation

100-200 mg daily

Titration

Increase dose by 100 mg daily every week depending on seizure control and tolerability

Optimization

400 mg daily
Pregabalin (PGB) 
Lyrica ®

- First approved in 2005. FDA indication: adjunctive therapy for adult patients with partial onset seizures
- MOA: mostly unknown, binds to α2δ1 subunit of voltage-gated Ca channels
- Available dosage: 25, 50, 75, 100, 150, 200, 225, and 300 mg, and oral solution
PGB- absorption, distribution

- Oral absolute bioavailability: >90%
- $T_{\text{max}} = 2.5$ hours (decreased with food)
- Protein binding: negligible ($\sim 3\%$)
- $V_d = \sim 0.6 \text{ L/Kg}$
PGB- metabolism, elimination

- Not appreciably metabolized in humans
- Elimination is mostly renal (unchanged)
- $T_{1/2} = 6-9$ hours (prolonged in anuric patients)
PGB- interactions

- No known interactions with enzyme-inducing or enzyme-inhibiting AEDs
- May potentiate effects of sedatives and alcohol
PGB- adverse effects

- Sedation
- Agitation, irritability
- Weight gain (~ 10%)
- Angioedema
- Peripheral edema
- Extremity tingling
- Myoclonus
- Exacerbation of myoclonic seizures
PGB- titration & dosing

**Initiation**

75 mg twice daily

**Titration**

Increase dose by 75 mg twice daily every 7-10 days depending on seizure control and tolerability

**Optimization**

300 mg twice daily
Vigabatrin (VGB) Sabril®

- First approved in 2009. FDA indication: adjunctive therapy of partial seizures in adults who have not responded to several alternative treatments
- MOA: inhibits irreversibly GABA transaminase
- Available dosage: 500 mg- and solution
VGB- absorption, distribution

- Oral absolute bioavailability: ~85%
- Tmax = 1 hour
- Protein binding: negligible
- V_d = ~0.8 L/Kg
VGB- metabolism, elimination

- Metabolism by enzymatic hydrolysis (no hepatic involvement)
- Elimination by excretion in urine (metabolites are inactive)
- $T_{1/2} = 7-9$ hours
VGB- interactions

- VGB is a weak inducer of CYP2C9 isoenzyme
- Addition of VGB decreases PHT levels
VGB - adverse effects

- Sedation
- Suicidal ideations, depression
- **Visual loss** consisting of permanent bilateral concentric visual field constriction in 30% of patients (risk increases with cumulative dosage and therapy duration - withdraw VGB in 3 months if no response)
- MRI changes with increased T2 and DWI (asymptomatic and typically reversible)
VGB- titration & dosing

Initiation

500 mg twice daily

Titration

Increase dose by 500 mg every week depending on seizure control and tolerability

Optimization

1500 mg twice daily (recommended)
Lacosamide (LCM)
Vimpat®

- First approved in 2008. FDA indication: adjunctive therapy for adult patients with partial onset seizures
- MOA: likely enhances slow inactivation of Na channels (in vitro)
- Available dosage: 50, 100, 150, and 200 mg- oral solution- and IV formulation
LCM- absorption, distribution

- Oral absolute bioavailability: ~100%
- Tmax = 1-4 hours
- Protein binding: <15%
- \( V_d = \sim 0.6 \text{ L/Kg} \)
LCM- metabolism, elimination

- Metabolized by biotransformation to inactive metabolites (60%) or remains unchanged (40%)
- Elimination by excretion in urine (95% of which 40% as unchanged drug)
- $T_{1/2} = 13$ hours
LCM- interactions

- No known interactions with other medications
LCM- adverse effects

- Sedation (significant with co-administration of Na-channel blockers)
- P-R interval prolongation
- Suicidal ideations, depression
**LCM- titration & dosing**

**Initiation**
50 mg twice daily

**Titration**
Increase dose by 50 mg twice daily every week depending on seizure control and tolerability

**Optimization**
200 mg twice daily
Rufinamide (RFM)  
**Banzel®**

- MOA: mostly unknown, prolongs the inactive state of Na channels
- Available dosage: 200, and 400 mg- and solution
RFM- absorption, distribution

- Oral absolute bioavailability: ~85%
- $T_{max} = 4-6$ hours (faster with food)
- Protein binding: ~35%
- $V_d = \sim 0.7 \text{ L/Kg}$
RFM- metabolism, elimination

- Metabolism by enzymatic hydrolysis (no hepatic involvement)
- Elimination by excretion in urine (metabolites are inactive)
- $T_{1/2} = 6-10$ hours
RFM- interactions

- Addition of enzyme-inducing AEDs decrease RFM levels
- Addition of VPA increases RFM levels
- RFM decreases OCP efficacy
RFM- adverse effects

- Sedation
- Suicidal ideations, depression
- Short QT interval
- Headache
### RFM- titration & dosing

<table>
<thead>
<tr>
<th>Initiation</th>
<th>Titration</th>
<th>Optimization</th>
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<tbody>
<tr>
<td>200-400 mg twice daily</td>
<td>Increase dose by 200-400 mg twice daily every other day depending on seizure control and tolerability</td>
<td>1600 mg twice daily</td>
</tr>
<tr>
<td>10 mg/kg/day divided twice daily (for children)</td>
<td>Increase dose by 10 mg/kg/day divided twice daily every other day depending on seizure control and tolerability (for children)</td>
<td>45 mg/kg/day divided twice daily (in children)</td>
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</tbody>
</table>
Ezogabine (EZG) Potiga®

- First approved in 2011. FDA indication: adjunctive therapy of partial seizures in adult patients
- MOA: potassium channel agonist (KCNQ) stabilizing resting membrane potentials (GABA effect in vitro)
- Available dosage: 50, 200, 300, and 400 mg
EZG- absorption, distribution

- Oral absolute bioavailability: ~60%
- $T_{max} = 0.5\text{-}2 \text{ hours (with or without food)}$
- Protein binding: ~80% (~45% for N-acteyl metabolite or NAMR)
- $V_d = \sim 2.5 \text{ L/Kg}$
**EZG- metabolism, elimination**

- Extensively metabolized primarily via glucuronidation and acetylation. It is also metabolized to NAMR that is also subsequently glucuronidated. NAMR has a less potent antiepileptic activity (in animal models).

- Elimination: 85% is renal

- $T_{1/2} = 7-11$ for both EZG and NAMR
EZG- interactions

- Enzyme-inducing AEDs such as CBZ or PHT decrease EZG levels

- EZG through NAMR may inhibit transport of coumadin causing increased INR
EZG- adverse effects

- Sedation
- Urinary retention, hesitancy (in first 6 months, 2%)
- Psychosis, confusional states, suicidal ideation
- Prolonged QT interval (dose dependent)
- Hyperactivity/irritability in children
- Retinal or skin discoloration
- Photoreceptor damage
- Weight gain
EZG- titration & dosing

Initiation

100 mg 3 times daily

Titration

Increase dose by 50 mg 3 times daily every week

Optimization

200 to 400 mg 3 times daily (may target higher dose if on enzyme inducing AEDs)
PGB- adverse effects

- Sedation
- Agitation, irritability
- Weight gain (~ 10%)
- Angioedema
- Peripheral edema
- Extremity tingling
- Myoclonus or excaverbation of myoclonic seizures
Perampanel (PRL)
Fycompa ®

- Firs approved in 2012. FDA indication: adjunct therapy for partial seizures in adults and children > age 12
- MOA: noncompetitive AMP (glutamate) receptor antagonist
- Available dosage: 2, 4, 6, 8, 10, and 12 mg
PRL - absorption, distribution

- Oral absolute bioavailability: >70%
- Tmax = 0.5-2.5 hours (delayed when taken with food)
- Protein binding: ~95%
- Vd = ~0.77 L/Kg
PRL- metabolism, elimination

- **Primary route of metabolism through CYP3A4**
- **Elimination in feces (70%) and urine (30%).**
- **$T_{1/2} = 105$ hours in adults, may reach 270 hours in patients with liver failure.**
PRL- interactions

- Addition of known CYP enzyme-inducers including carbamazepine, phenytoin, primidone, oxcarbazepine (rifampin, St John’s wart) decrease PRL levels

- PRL (at dose of 12 mg daily) reduces levonorgestrel by approximately 40%
PRL- adverse effects

- Sedation
- Headache
- GI upset
- **Behavioral changes** including hostility and aggression (up to 20% of patients—regardless of prior psychiatric history) and suicidal/homicidal ideation (up to 0.5%)
- Depression
- Weight gain
- Peripheral edema
- Hyponatremia
### PRL- titration & dosing

<table>
<thead>
<tr>
<th>Initiation</th>
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<tbody>
<tr>
<td>2 mg daily at night (or 4 mg if on enzyme-inducing AEDs)</td>
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<table>
<thead>
<tr>
<th>Titration</th>
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<tbody>
<tr>
<td>Increase dose by 2 mg daily at night every week depending on seizure control and tolerability</td>
</tr>
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</table>

<table>
<thead>
<tr>
<th>Optimization</th>
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<tbody>
<tr>
<td>8-12 mg daily at night (may target higher dose if on enzyme inducing AEDs)</td>
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</table>
Unblinded randomized controlled trial that recruited 1721 patients for whom CBZ was deemed to be standard treatment. Patients were randomly assigned to receive CBZ, GBP, LTG, OXC, or TPM.

Primary outcomes were time to treatment failure, and time to 12-month remission, and assessment was by both intention to treat and per protocol.

For time to treatment failure, LTG was significantly better than CBZ, GBP, and TPM, and had a non-significant advantage compared with OXC.

For time to 12-month remission CBZ was significantly better than GBP and estimates suggest a non-significant advantage for CBZ against LTG, TPM, and OXC.

In a per-protocol analysis, at 2 and 4 years the difference in the proportion achieving a 12-month remission (LTG-CBZ) is 0 (−8 to 7) and 5 (−3 to 12), suggesting non-inferiority of LTG compared with CBZ.

“LTG is clinically better than CBZ, the standard drug treatment, for time to treatment failure outcomes and is therefore a cost-effective alternative for patients diagnosed with partial onset seizures.”
SANAD- Generalized Tonic-Clonic Seizures in Idiopathic Generalized Epilepsy


- Unblinded randomized controlled trial in hospital-based outpatient clinics in the UK.
- 716 patients for whom valproate was considered to be standard treatment [450 had idiopathic generalized epilepsy; 119 (26%) had juvenile myoclonic epilepsy] were randomly assigned to valproate, lamotrigine, or topiramate between Jan 1999, and Aug 2004.
- Follow-up data were obtained up to Jan 2006.
- For patients with idiopathic generalized epilepsy, valproate was significantly better than both lamotrigine and topiramate (better tolerated than topiramate and more efficacious than lamotrigine).
Question 1

Which of the following AED is not known to modulate GABA?

a- Topiramate
b- Tiagabine
c- Pregabalin
d- Vigabatrin
e- None of the above
Question 2

- The blood levels of which AED will not be altered after addition of phenytoin?

a- Felbamate
b- Topiramate
c- Zonisamide
d- Rufinamide
e- None of the above
Question 3

Which AED has the shorter half-life?

a- Phenobarbital
b- Perampanel
c- Lacosamide
d- Zonisamide
e- Phenytoin
Question 4

- All of the following AEDs have negligible protein binding except:
  a- Vigabatrin
  b- Pregabalin
  c- Ezogabine
  d- Levetiracetam
  e- All of the above