AED selection & Evidence based guidelines to clinical practice:

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Antiepileptic Drug

- A drug which decreases the frequency and/or severity of seizures in people with epilepsy
- Treats the symptom of seizures, not the underlying epileptic condition
- Goal—maximize quality of life by minimizing seizures and adverse drug effects
- Currently no “anti-epileptogenic” drugs available.

Therapy Has Improved Significantly

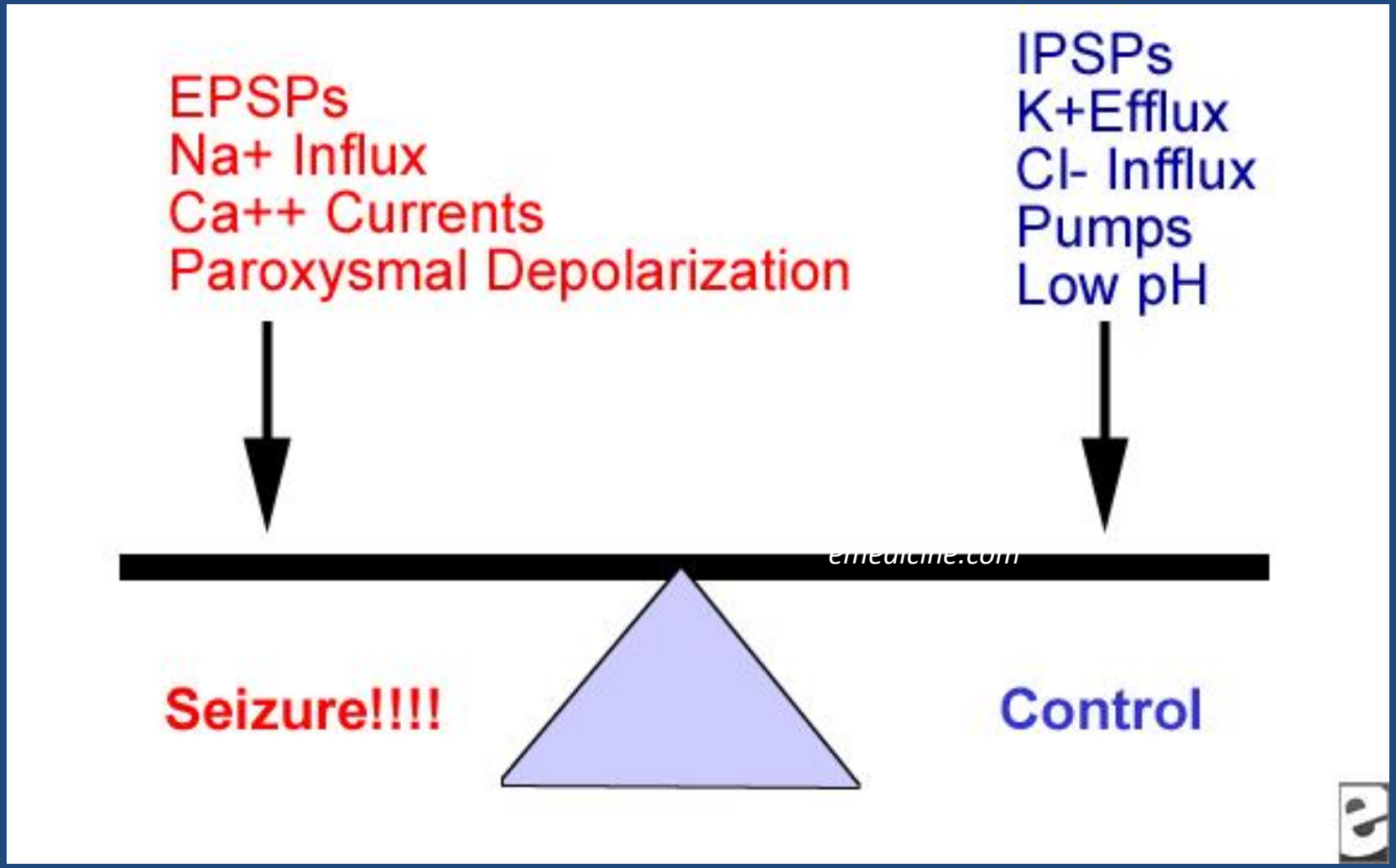
"Give the sick person some blood from a pregnant donkey to drink; or steep linen in it, dry it, pour alcohol onto it and administer this".

– Formey, Versuch einer medizinischen Topographie von Berlin 1796, p. 193

Current Pharmacotherapy

- Approx. 60% of all people with epilepsy can become seizure free with **single drug therapy**
- In another 20% the seizures can be drastically reduced, with **more than one drug.**
- ~ 20% epileptic patients, seizures are refractory to currently available AEDs.

Cellular Mechanisms of Seizure Generation

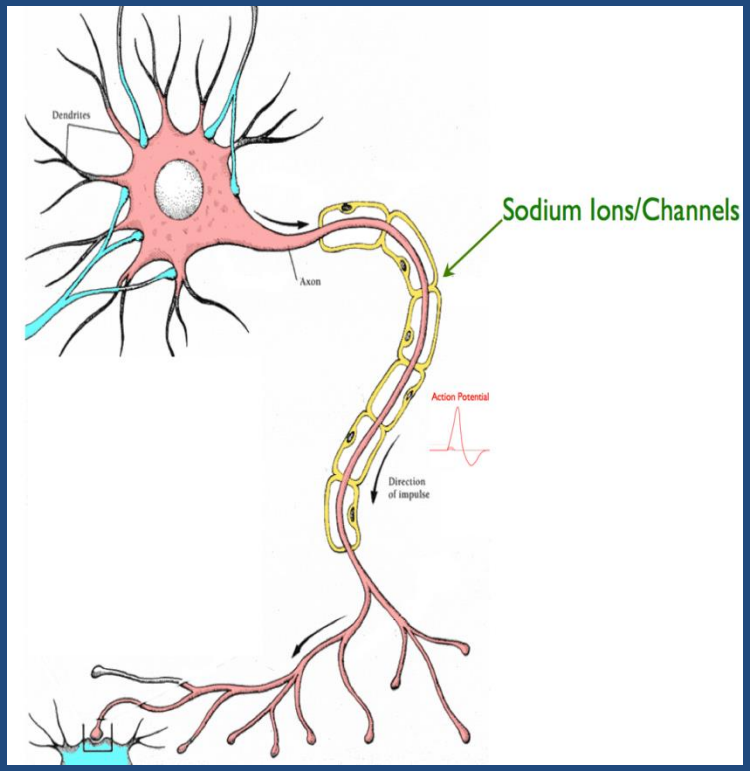


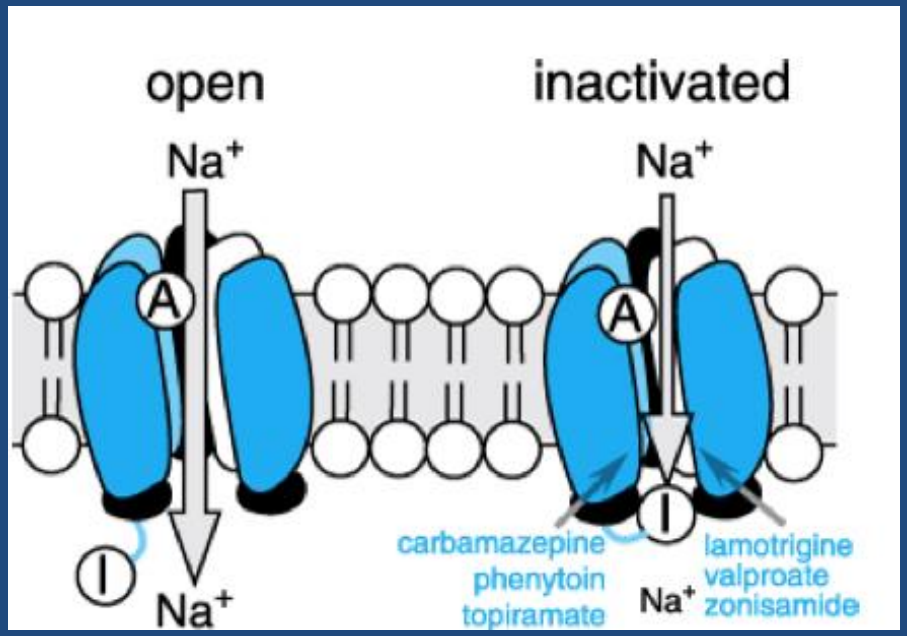
Mechanism of action

3 main categories of therapeutics:

1. Inhibition of voltage-gated Na+ channels to slow neuron firing.
2. Enhancement of the inhibitory effects of the neurotransmitter GABA.
3. Inhibition of calcium channels.

Na+ Channel Inhibitors





blocks voltage-gated sodium channels by selectively binding to the channel in the inactive state and slowing its rate of recovery

Na channel inhibitors

- ✓ Phenytoin (Dilantin, Eptoin)
  - ✓ Fosphenytoin
- ✓ Carbamzepine (Tegretol)
  - ✓ Oxcarbazepine (Trileptal)
- ✓ Valproic Acid (Valproate, Depakote)
- ✓ Lamotrigine (Lamictal)
- ✓ Topiramate (Topamax)
- ✓ Zonisamide (Zonegran)

Phenytoin

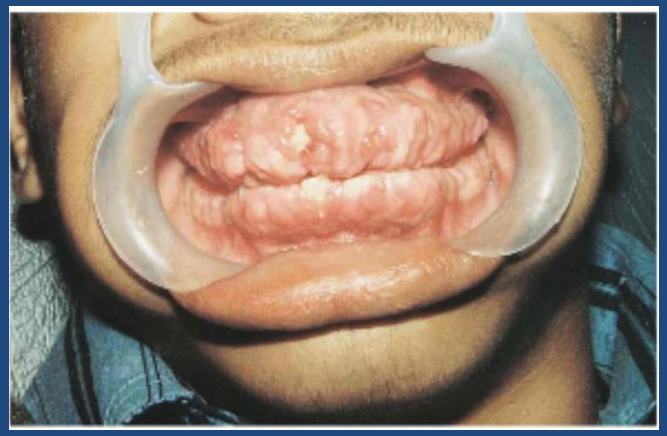
- Oldest non-sedative antiepileptic drug.
  - Indications:
    - First choice for partial and generalized tonic-clonic seizures .
    - Some efficacy in clonic, myoclonic and atonic seizures.
    - status epilepticus
    - No effect on infantile spasms or absence seizures

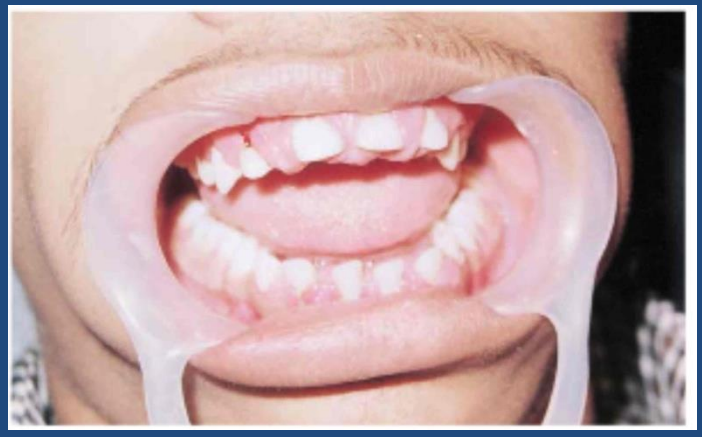
Pharmokinetics

- Potent enzyme inducing properties;
- lowers the level of
  - CBZ, VA, FBT, LTG, TRM, ZNS, and TGB.
  - warfarin, oral contraceptives, and cyclosporine.
- **PHT and Valproate**:
  - PHT is highly protein bound and is displaced from serum proteins by valproate resulting in increase of the free fraction of PHT.
- Elimination is saturable at therapeutic concentrations resulting in a nonlinear relationship between maintenance doses and steady-state concentrations.
- in the upper therapeutic range, small increases in dosage can cause relatively large increases in levels.
- Steady-state levels are achieved in 2 to 3 weeks of a stable maintenance dose.

Side effects:

- Bradyarrhythmia, Hypotension, as well as skin necrosis on i.v.
- Dose related CNS side effects-Nystagmus, ataxia, and lethargy.
- Hypersensitivity reactions
- Gingival hyperplasia, hirsutism, peripheral neuropathy, and bone demineralization





Fosphenytoin

- Prodrug
- rapidly converted to phenytoin in the blood,
- providing high levels of phenytoin within minutes.
- Can also be administered intramuscularly.
- Phenytoin sodium should never be given IM because it can cause tissue damage and necrosis.

Carbamazepine

- ***Was a, not is a*** exclusive drug of first choice for partial and secondarily generalized seizures.
- The elimination kinetics of CBZ is linear.
- ***Autoinduction of its metabolism,***
  - which results in an increase in CBZ clearance during the first weeks of treatment
  - the elimination half-life of CBZ decreases from about 36 hours to 10 to 20 hours.
- ***No parenteral preparation for CBZ***.

SIDE EFFECTS

- ***Dose-related CNS toxicity***
  - is the most common side effect
  - subsides with time,
  - careful titration,
  - closely related to CBZ serum levels.
- Neutropenia, Severe blood dyscrasias, hyponatremia, movement disorders, allergic rashes, and hypersensitivity syndrome are rare ADRs.
- Contraindications:
    - May exacerbate absence or myoclonic seizures.
    - Blood disorders
    - Liver disorders

Oxcarbazepine

- **Prodrug** and is rapidly metabolized to the active compound monohydroxycarbamazepine.
- No parenteral preparation.
- Half-life of 10 to 15 hours.
- level can be reduced by 30% to 40% by PHT, CBZ, or PB.
- OXC is an enzyme inducer, but less so than phenytoin, phenobarbital, or carbamazepine.
- same narrow spectrum of efficacy as carbamazepine, with efficacy limited to partial onset and secondarily generalized seizures.

- **Fewer adverse effects than CBZ, phenytoin.**
- **Hyponatremia is more common with OXC** than with carbamazepine and is more frequent in adults, especially in the elderly.
- The **side effects of OXC are similar** to those of CBZ, although they may be **somewhat milder**.
  - somnolence, dizziness, ataxia, diplopia, and blurred vision.
  - An allergic rash can occur, and cross-reactivity with carbamazepine is at least 25%.

Valproate

- Broad spectrum of activity.
- Other Mechanisms of Action:
    - 1) Some inhibition of T-type Ca2+ channels.
    - 2) Inhibition of GABA transaminase.
- Drug of first choice in patients with primary (idiopathic) generalized epilepsies
- It is also highly effective against absence seizures, generalized tonic-clonic seizures, and myoclonic seizures, infantile spasms and Lennox-Gastaut syndrome

Two types of pharmacokinetic interactions

1. Its **metabolism is accelerated by inducing drugs** such as phenytoin, carbamazepine, phenobarbital, and primidone.
2. VPA **itself can prolong the elimination (and raise the levels) of other drugs**, such as phenobarbital, ethosuximide, lamotrigine, and felbamate.
   - Highly bound to serum proteins and tends to displace other drugs, such as phenytoin.
   - In adults, the half-life is 13 to 16 hours in the absence of inducing drugs; and 9 hours in induced patients.

Adverse Effects

- Weight gain (30-50%)
- Dose-related tremor
- Transient hair loss
- Polycystic ovary syndrome and menstrual disturbances
- Bone loss
- Ankle swelling
- **Fatal hepatotoxicity** and **pancreatitis** are the most serious
- Thrombocytopenia, in conjunction with impaired platelet function, fibrinogen depletion, and coagulation factor deficiencies may cause ***excessive bleeding***.
- The common practice of withdrawing VPA before elective surgery is recommended, although reports have found ***no objective evidence of excessive operative bleeding in neurosurgical patients*** maintained on VPA.
- In women of childbearing age, increased risk for ***neural tube defects*** in the fetus.

Lamotrigine

- Relatively long half-life; Twice a day.
- Other Mechanism of Action:
  - May *inhibit synaptic release of glutamate*.
- Indications:
  - Adjunct therapy (ages 2 & up):
    - Simple & complex partial seizures
    - Generalized seizures of Lennox-Gastaut Syndrome
  - Monotherapy (adults):
    - Simple & complex partial seizures and Absence seizures
- Contraindications:
  - May make myoclonic seizures worse

Topiramate

- Broad-spectrum AED. Other Mechanism of Action:
  - Enhances post-synaptic GABA receptor currents.
- Indications:
  - Adjunct therapy for partial and primary generalized
  - seizures in adults and children over 2.
  - Decreases tonic and atonic seizures in children with Lennox-Gastaut syndrome.

Common side effects

Somnolence, impaired concentration, abnormal thinking, and impaired verbal memory, anorexia, weight loss, and **nephrolithiasis**, as well as metabolic acidosis and decreased sweating in children.

Zonisamide

- Sulfonamide derivative that has a broad spectrum of action
- Other Mechanism of Action:
    - Inhibits T-type Ca2+ currents.
    - Binds to GABA receptors.
    - Facilitates dopaminergic and serotonergic neurotransmission.
- Long half-life of 60 hours once or twice daily.
- Serum levels are lowered by PHT, CBZ , PB, PRM, and VA.
- No known effect on the kinetics of other drugs.

- Indications:
  - Approved for adjunct treatment of partial seizures in adults.
  - Appears to have a broad spectrum:
    - Myoclonic seizures
    - Infantile spasms
    - Generalized & atypical absence seizures
    - Lennox-Gastaut Syndrome
- Side effects

  Psychomotor slowing, behavioral or psychiatric side effects, allergic rash. Metabolic acidosis ,hypohidrosis, **nephrolithiasis (1% to 2%),** paresthesias.

Enhancement of GABA Inhibition

1. Barbiturates

   Phenobarbital and Primidone.

2. Benzodiazepine drugs:
   - Diazepam (Valium).
   - Lorazepam (Ativan).
   - Clonazepam.
   - Clorazepate
3. Tiagabine.

– Mechanism of Action for first two is Increase in the frequency of GABA-A-activated Cl- channel opening.

– While for Tiagabine it is Inhibition of GABA transporter (GAT-1) – reduces reuptake of GABA by neurons and glial cells.

Phenobarbital and Primidone

- The use of PB and PRM for the treatment of seizures has declined steadily
  - ***more sedative and behavioral side effects***
- relatively little systemic toxicity.
- **PB** has excellent pharmacokinetic properties,
  - **can be administered intravenously and intramuscularly**,
- effective in patients with status epilepticus,
- inexpensive.

Other Side effects

- allergic reactions.
- Dupuytren's contracture
- frozen shoulder.

Primidone

- PRM has independent pharmacologic activity
  - probably **is not just a prodrug**.
  - much shorter half-life than PB.
  - Daily dosage requirements of PRM are about five times higher
- Other enzyme-inducing drugs, in particular **phenytoin, accelerate the conversion of PRM to PB**, thereby increasing the PB-to-PRM serum level ratio.
- **Partial and secondarily generalized seizures** as carbamazepine and phenytoin but were found to be associated **with more treatment failures because of mostly early CNS side effects**.

Uses

- Status epilepticus and neonatal seizures,
- Prophylaxis of febrile seizures.
- PB is C/I in absence seizure and PRM is C/I in Porphyria.

Benzodiazepine drugs

- Diazepam and lorazepam are used in treatment of status epileticus.
  - Diazepam is painful to inject
  - lorazepam is more commonly used in acute treatment.
- Only clonazepam & clorazepate approved for long-term treatment.
  - Clorazepate
    - In combination for partial seizures
  - Clonazepam
    - Lennox-Gastaut Syndrome, myoclonic, atonic, and absence seizures
    - Tolerance develops after about 6 months
- Contraindications:
  - Diazepam in children under 9
  - Narrow angle glaucoma

- Adverse Effects:
  - Hypotonia, Dysarthria (Difficulty in articulating words, caused by impairment of the muscles used in speech)
  - Muscle in-coordination (clonazepam)
  - Behavioral disturbances (especially in children)
    - Aggression, Hyperactivity, Irritability and Difficulty concentrating

Tiagabine

- Approved in 1998 as an adjunct therapy for partial seizures in patients at least 12 years old.
- Narrow spectrum of activity and CNS side effects, not found widespread use.
- Contraindications:
    - Absence seizures
- No other pharmacokinetic interactions.
- No severe or potentially life-threatening side effects.
- Difficulty with concentration, nervousness, and emotional lability may be seen.

Calcium Channel Blockers

- Ethosuximide
- Pregabalin.
- Gabapentin.

Ethosuximide

- Mechanism of Action:
  - Reduces low -threshold Ca2+ currents (T currents) in the thalamic neurons.
  - Half-life is ~60 hr in adults; ~30hr in children.
- Indications:
  - First line for absence seizures
- Contraindications:
  - May exacerbate partial & tonic-clonic seizures
- Adverse Effects:
  - Psychotic behavior, Blood dyscrasias, Persistent headaches
  - Anorexia, Hiccups , Lupus-like syndromes
  - Parkinson-like symptoms
  - photophobia

Gabapentin

- Originally designed to be a centrally acting GABA agonist. Selective inhibition of v-g Ca2+ channels containing the α2δ1 subunit.
- Focal onset seizures and Rolandic epilepsy with centrotemporal spikes on EEG.
- Eliminated entirely by the kidneys, has no pharmacokinetic interactions.
- Serious side effects are exceedingly rare. Can exacerbate myoclonic & absence seizures.
- excessive weight gain and behavioral problems in children are common.

Pregabalin

- Very similar to gabapentin in most aspects, except **that PGB has better bioavailability than gabapentin**.
- Half-life of PGB is about 6 hours, twice or three times daily dose.
- Not bound to serum proteins.
- Eliminated mostly unchanged in urine, and has no pharmacokinetic interactions.
    - Approved in 2005 for Adjunct therapy for partial & secondarily generalized seizures
- Other uses:
    - Prescribed for neuropathic pain, fibromyalgia

- Most common side effects
  - Dizziness, somnolence, dry mouth.
  - Peripheral edema, blurred vision, weight gain.
  - difficulty with concentration.
- Because of a slight potential for recreational abuse and dependence, it is a controlled substance .

Miscellaneous AEDs :

Felbamate.

Levetiracetam.

Felbamate

- Potential serious side effects and multiple pharmacokinetic interactions---**used only in special circumstances**. (**drug of third choice** for **Lennox-Gastaut syndrome, focal onset** seizures)
- Raises levels of phenytoin and valproate.
- Common side effects –
  - nausea and vomiting,
  - anorexia and weight loss,
  - somnolence, and insomnia.
  - relatively high incidence of potentially **fatal aplastic anemia** and **hepatic necrosis**
- Multiple proposed mechanisms including :
  - Voltage-dependent sodium channels blockade.
  - competing with the glycine-coagonist binding site on the N-methyl-D-aspartate (NMDA) glutamate receptor
  - Potentiation of GABA actions.

Levetiracetam

- Short half-life of 6 to 8 hours, still used in twice daily dose.
- Linear pharmacokinetics
  - low Protein binding
  - No pharmacokinetic interactions.
- Broad-spectrum antiepileptic drug.
- Indications-
  - Partial and secondarily generalized seizures
  - GTCS in idiopathic general epilepsies, and
  - Myoclonic seizures in JME.
  - Absence seizures,
  - Rolandic epilepsy and
  - Posthypoxic and postencephalitic myoclonus.

- Virtually no serious or life-threatening side effects.
- Side effects-
  - Somnolence, asthenia, dizziness,
  - Emotional lability, depression, and psychosis.
  - Behavioral problems (children).
- Rare-
  - Allergic reactions, liver failure; and
  - Bone marrow suppression.

Selecting an AED

- **Patient factors**
  - Seizure type and syndrome
  - Age
  - Gender
  - Pregnancy potential
  - Comorbidities
  - Comedications
  - Individual lifestyle (once-daily dosing, etc)

AED factor

- Spectrum of efficacy
- Mechanism of action
- Indications (e.g. monotherapy, children, etc)
- Tolerability / safety
- Neuropsychological implications
- Dosing frequency, titration complexity, simplicity of use
- Drug–drug interaction profile
- Teratogenic potential (pregnancy registries)
- Availability, cost, reimbursement

Table 4. Summary of studies and level of evidence for each seizure type and epilepsy syndrome

Seizure type or epilepsy syndrome	Class I studies	Class II studies	Class III studies	Level of efficacy and effectiveness evidence (in alphabetical order)
Adults with partial-onset seizures	4	1	34	Level A: CBZ, LEV, PHT, ZNS Level B: VPA Level C: GBP, LTG, OXC, PB, TPM, VGB Level D: CZP, PRM
Children with partial-onset seizures	1	0	19	Level A: OXC Level B: None Level C: CBZ, PB, PHT, TPM, VPA, VGB Level D: CLB, CZP, LTG, ZNS
Elderly adults with partial-onset seizures	1	1	3	Level A: GBP, LTG Level B: None Level C: CBZ Level D: TPM, VPA
Adults with generalized onset tonic–clonic seizures	0	0	27	Level A: None Level B: None Level C: CBZ, LTG, OXC, PB, PHT, TPM, VPA Level D: GBP, LEV, VGB
Children with generalized-onset tonic–clonic seizures	0	0	14	Level A: None Level B: None Level C: CBZ, PB, PHT, TPM, VPA Level D: OXC
Children with absence seizures	1	0	7	Level A: ESM, VPA Level B: None Level C: LTG Level D: None
Benign epilepsy with centrotemporal spikes (BECTS)	0	0	3	Level A: None Level B: None Level C: CBZ, VPA Level D: GBP, LEV, OXC, STM
Juvenile myoclonic epilepsy (JME)	0	0	1	Level A: None Level B: None Level C: None Level D: TPM, VPA

THANK YOU

What about K+ channels?

- K+ channels have important inhibitory control over neuronal firing in CNS—repolarizes membrane to end action potentials
- K+ channel agonists would decrease hyperexcitability in brain
- So far, the only AED with known actions on K+ channels is valproate
- Retiagabine is a novel AED in clinical trials that acts on a specific type of voltage-dependent K+ channel (M-channel)

Epilepsia, 54(3):551–563, 2013
doi: 10.1111/epi.12074

SPECIAL REPORT

Updated ILAE evidence review of antiepileptic drug efficacy and effectiveness as initial monotherapy for epileptic seizures and syndromes

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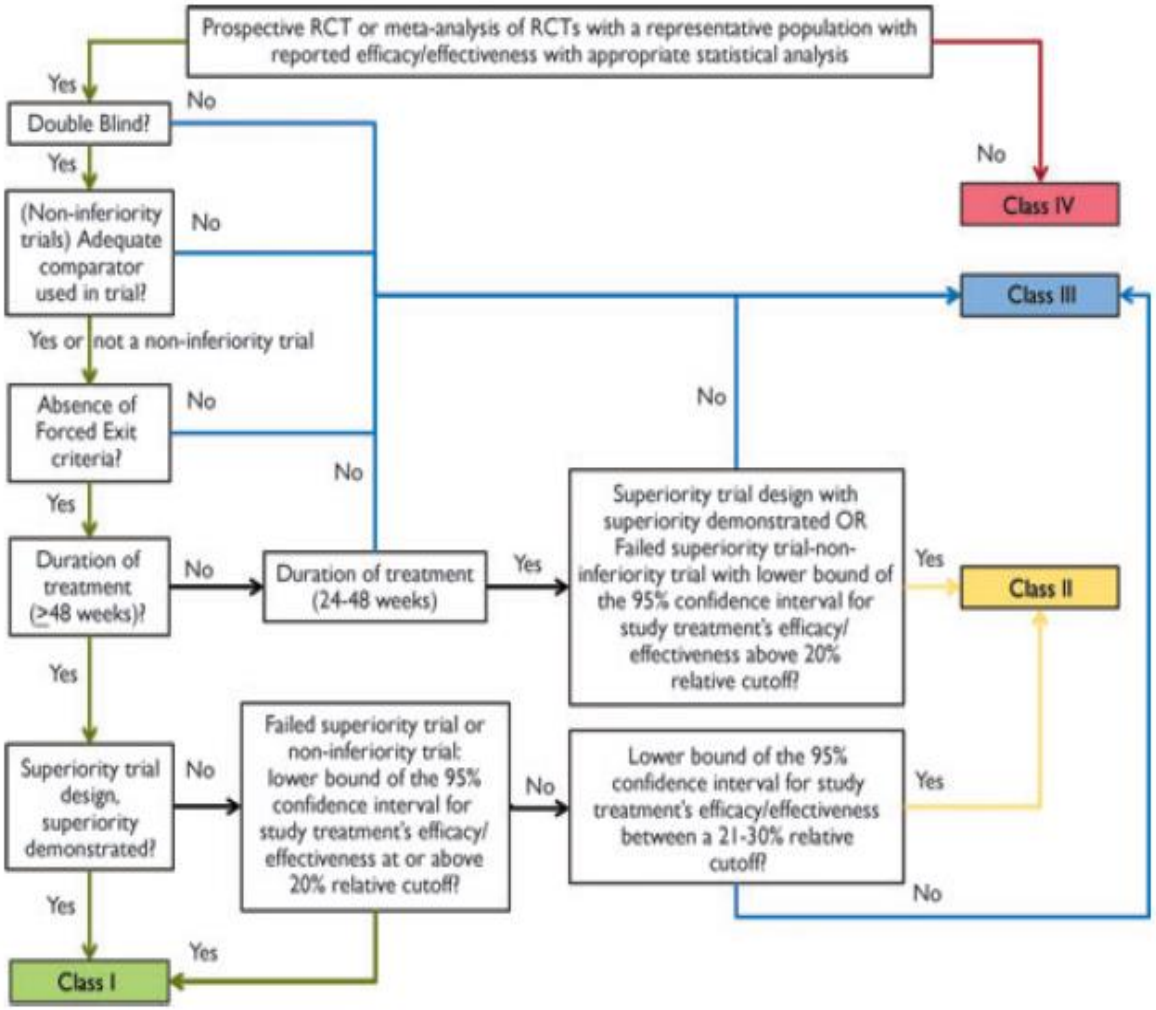

Figure 1.
Application of evidence rating criteria for efficacy/effectiveness studies.
Epilepsia © ILAE

Table 3. Relationship between clinical trial ratings, level of evidence, and conclusions

Combination(s) of clinical trial ratings	Level of evidence	Conclusions
≥ 1 Class I studies or meta-analysis meeting class I criteria sources OR ≥ 2 Class II studies	A	AED established as efficacious or effective as initial monotherapy
1 Class II study or meta-analysis meeting class II criteria	B	AED probably efficacious or effective as initial monotherapy
≥ 2 Class III double-blind or open-label studies	C	AED possibly efficacious or effective as initial monotherapy
1 Class III double-blind or open-label study OR ≥ 1 Class IV clinical studies OR Data from expert committee reports, opinions from experienced clinicians	D	AED potentially efficacious or effective as initial monotherapy
Absence of directly applicable clinical evidence upon which to base a recommendation	E	No data available to assess if AED is effective as initial monotherapy
Positive evidence of lack of efficacy or effectiveness based on class I to IV studies OR Significant risk of seizure aggravation based on class I to IV studies	F	AED established as ineffective or significant risk of seizure aggravation

Principles of AEDs administration

- what seizure type the patient probably has?
- Correctly diagnose the seizure type and syndrome in order to select the most appropriate AED.
- Discuss the possible choices (depending on seizure type) with the patient and make the choice together- efficacy and potential side effects.
- If at all possible, start with slow titration.
- Monitor side effects and communicate with the patient.

- Select the most appropriate initial treatment with not only focusing on seizure freedom, but also considering factors such as: tolerability profile, titration regimen, simplicity of use (once daily) and impact on overall patient outcomes.
- Selection of an appropriate monotherapy should consider the current level of evidence available in conjunction with patient factors and AED characteristics.

- Once the decision is made to use combination therapy, the perceived best combination is one that produces best efficacy with fewest adverse effects.
- •Different AEDs appropriate to the epilepsy syndrome should be added as necessary in sequence, increasing the dose of each slowly to obtain the best response.
- The law of diminishing returns may require patient and doctor to accept the persistence of some seizures once a range of treatment options has failed and no surgically remediable epilepsy detected.

- AEDs generally have good oral absorption and bioavailability.
- Most metabolized in liver but some excreted unchanged in kidneys e.g. Gabapentin.
- Classic and older AEDs generally have more severe CNS sedation than newer drugs (except ethosuximide)

The established, or older, drugs are no longer the drugs of first choice for the majority of seizure types.

Many newer AEDs offer the main advantages of relative safety, favorable pharmacokinetics and interaction profiles, or the absence of need for blood level or other routine laboratory monitoring.

Conclusion about Guidelines

- When selecting a patient`s AED, all relevant variables and not just efficacy and effectivenes should be considered.
- Guidelines or evidence reviews can be seen as additional tool, not the only tool in the clinician armamentarium.
- Absence of evidence does not mean evidence of absence.

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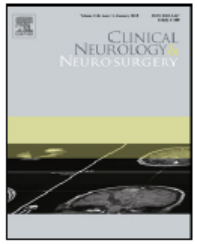

Considerations in prophylaxis for tumor-associated epilepsy: Prevention of status epilepticus and tolerability of newer generation AEDs

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Conclusion:

More than half of GBM patients ultimately developed TAE and 35% of seizure-free patients at diagnosis went on to have at least one seizure. Prophylactic AED therapy did not reduce Post-op TAE but may have prevented SE. Patients with brain tumors were associated with high relative risk of mortality in critically ill patients with refractory status epilepticus; as well as SE can be associated with significant morbidity and higher cost, thus; results would strongly support the use of AED prophylaxis.

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Journal of Clinical Neuroscience

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Clinical Study

Levetiracetam compared to phenytoin for the prevention of postoperative seizures after craniotomy for intracranial tumours in patients without epilepsy

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A total of 235 patients were treated with an antiepileptic drug: 81 patients received LEV, and 154 patients, PHT. Two patients receiving LEV (2.5%) and seven receiving PHT (4.5%) had a seizure despite this treatment but the difference was not significant (p = 0.66). LEV may be a valid option for perioperative anticonvulsant medication in patients with contraindications for PHT who have undergone a craniotomy.

Epilepsy in patients with brain tumours

Lancet Neurol 2007; 6: 421–30

- ✓ A consensus statement has advised discouragement of antiepileptic drugs or their discontinuation after the fi rst operative week in patients with brain tumours who have never had seizures.
- ✓ Enzyme-inducing antiepileptic drugs (CBZ) is discouraged; because of concomitant Chemotherapeutic agents.
- ✓ Existing brain damage from previous surgery or radiotherapy increases the risk of developing side-effects from antiepileptic drugs.
- ✓ Lamotrigine, valproic acid, and topiramate are first-line or second-line antiepileptic agents, although levetiracetam or gabapentin can be used as add-on treatment to a firstline antiepileptic drug.
- ✓ Prefer to start with valproic acid, and to add levetiracetam if needed.

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Journal of Clinical Neuroscience

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Clinical Study

The efficacy of antiepileptic drug prophylaxis in the prevention of early and late seizures following repair of intracranial aneurysms

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The timing of AED prophylaxis had no effect on the incidence of early or late seizures in either group. AED use was associated with an increased rate of early seizures. Postoperative seizures remain important adverse outcomes following aneurysm repair, but despite their traditional role, the routine use of AED should be reconsidered carefully. AED should be used for prophylaxis only when the potential benefit of their use outweighs the likely harm.

Interaction of AEDs with OCPs

AEDs that *decrease the effectiveness* of oral contraceptive steroids

Carbamazepine Oxcarbazepine
Felbamate
Phenobarbital Primidone Phenytoin
Topiramate (doses >200 mg/day)

AEDs that do not decrease the effectiveness of oral contraceptive steroids

Benzodiazepines Gabapentin Tiagabine Zonisamide
Lamotrigine Levetiracetam Valproic acid Vigabatrin