

Antiepileptic Drugs (AED)

Updated: April 25, 2010

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- modern seizure treatment started in 1850 with introduction of **BROMIDES** (based on theory that epilepsy was caused by excessive sex drive).
- in 1910, **PHENOBARBITAL** was found to have antiseizure activity - became drug of choice for many years.
- in 1938, Houston Merrit and Tracy Putnam introduced **animal models** for screening multiple compounds for antiepileptic activity (published in *Journal of American Medical Association*).
- in 1940, **PHENYTOIN** was found to be effective drug - became major first-line antiepileptic drug for partial and secondarily generalized seizures.
- in 1990s, **newer drugs** with good efficacy, fewer toxic effects, better tolerability, and no need for blood level monitoring were developed.

All antiepileptics increase risk of **suicidality!**

Antiepileptic drugs:

- block initiation** of electrical discharge
- prevent spread** of electrical discharge (most current AED)

- Na⁺ channel blockers** - stabilize **inactive state** of Na⁺ channels (prevent return of Na⁺ channels to **active state**) in frequency-dependent manner → prevented rapid, repetitive, sustained firing of axons (normal action potentials are not inhibited!).

Most common and most well-characterized mechanism of currently available AEDs!

- each sodium channel dynamically exists in 3 states:
 - resting state** - allows Na⁺ passage into cell
 - active state** (during action potential) - allows increased Na⁺ influx into cell
 - inactive state** (during refractory period) - does not allow Na⁺ passage.

Na⁺ channels – action potential

- CARBAMAZEPINE**
- OXCARBAZEPINE**
- PHENYTOIN** – the only AED metabolized through nonlinear, zero-order kinetics.
- FOSPHENYTOIN**
- LAMOTRIGINE**
- ZONISAMIDE**
- LACOSAMIDE**
- RUFINAMIDE**

- Ca²⁺ channel inhibitors**
 - Ca²⁺ channels in CNS exist in 3 forms - L, N, T.
 - these channels are small and are inactivated quickly.
 - influx of Ca²⁺ currents in resting state produces partial depolarization of membrane (Ca²⁺ channels function as **“pacemakers” of normal rhythmic brain activity**), e.g. T-calcium channels in thalamus.

Ca²⁺ channels - “pacemakers”, voltage-dependent neurotransmission

- ETHOSUXIMIDE**
- PHENYTOIN** also has some Ca²⁺ channel blocking activity.

- GABA enhancers**
 - GABA binds to GABA_A receptor → Cl⁻ influx → hyperpolarization (repolarization).
 - GABA is produced by **glutamate decarboxylation** (glutamic acid decarboxylase, GAD).
 - GABA is catabolized by **GABA transaminase** (GABA-T).

GABA (inhibitory neurotransmitter) - hyperpolarization

GABA_A RECEPTOR AGONISTS

- Benzodiazepines - **CLONAZEPAM, DIAZEPAM, CLOBAZAM**
- Barbiturates - **PHENOBARBITAL, PRIMIDONE**

GABA REUPTAKE INHIBITORS

TIAGABINE

GABA TRANSAMINASE INHIBITORS

VIGABATRIN

POTENTIAL GABA MECHANISM OF ACTION

- GABAPENTIN**
- VALPROATE**

4. **Glutamate receptor blockers**

- glutamate binds to glutamate receptor → Na⁺ and Ca²⁺ influx → depolarization

Glutamate (excitatory neurotransmitter) - depolarization

FELBAMATE

TOPIRAMATE

LAMOTRIGINE inhibits glutamate release

5. **Unknown mechanisms of action**

LEVETIRACETAM

PREGABALIN

6. **Carbonic anhydrase inhibitors** → intracellular H⁺↑ (pH↓) → K⁺ shifts to extracellular compartment (to buffer acid-base status) → hyperpolarization.

ACETAZOLAMIDE (ACT) (Diamox) - adjunctive in refractory seizures:

- petit mal
- catamenial (i.e. seizure clustering around menstrual period).

TOPIRAMATE and ZONISAMIDE also are weak carbonic anhydrase inhibitors (not important for their antiseizure efficacy).

7. **Hormones**PROGESTERONE is natural *anticonvulsant* (effective for exacerbated **catamenial** seizures):

- increases Cl⁻ conductance at GABA_A receptors
- attenuates glutamate excitatory response
- alters mRNA for GAD and GABA_A receptor subunits.

N.B. ESTROGENS act as *proconvulsants*:

- reduce Cl⁻ conductance
- act as agonist at NMDA receptors in CA1 region (hippocampus).

ACTH, PREDNISON – preferred treatment in **infantile spasms**. see p. E9 >>**Na⁺ CHANNEL BLOCKERS****CARBAMAZEPINE (CBZ) (TEGRETOL[®], CARBATROL[®])****THERAPEUTIC USES**

One of most widely used AEDs in world! (available in USA since 1974)

- highly effective first choice for **all partial seizures** (simple and complex, secondarily generalized, cryptogenic and symptomatic)
- effective first choice for **tonic-clonic seizures** (not effective for other generalized seizures – may aggravate *absences* and *myoclonic* seizures).
- trigeminal neuralgia**
- occasionally used in **manic-depressive patients**.

PHARMACOKINETICS

- unstable substance (protect from hot or humid conditions).
- absorbed slowly following oral administration.
- high lipid solubility - enters brain rapidly.
- available in 200-mg tablets; 100-mg chewable tablets; 100-mg, 200-mg, and 400-mg extended-release capsules, elixir (100 mg/5 ml) and rectal suppositories.
- dosage: 100 mg × 2 on day 1; increase (by 200 mg/d with 100-mg increments q12h prn) to 200-400 mg × 2-4/day (children, 10-40 mg/kg/d); not to exceed 1200-1600 mg/d.
- therapeutic blood level: 4-12 µg/ml.

Metabolized in liver by CYP3A4

- induces its own hepatic metabolism (**autoinduction**) → T_{1/2} shortened by 50% during first few weeks (H: gradual dose titration);
T_{1/2} = 30-32 hrs (when drug is first introduced) → 11-20 hrs (following repeated treatment); also shortens T_{1/2} of other AEDs (e.g. PHENYTOIN) and other drugs (esp. hormonal contraceptives, warfarin, dexamethasone, cyclosporine).
- hepatic metabolism is enhanced by: PHENOBARBITAL, PHENYTOIN, PRIMIDONE, FELBAMATE, VALPROATE.
N.B. active metabolite (carbamazepine-10,11-epoxide) accumulates → neurotoxic effects despite low plasma concentration of parent drug!
- hepatic metabolism is inhibited by (dose adjustment is required!): cimetidine, macrolides, isoniazid, propoxyphene, fluoxetine, verapamil, diltiazem.

ADVERSE EFFECTS

Well tolerated!!!

- potential for serious liver toxicity** – all patients should have **liver function tests** monthly for 3-4 months (5-10% develop asymptomatic elevation of liver enzymes)

Liver function tests monthly

- stomach irritation, nausea and vomiting (H: extended-release preparations, e.g. Tegretol XR).
- chronic administration → dose-related **vertigo**, **ataxia**, **blurred vision**, **consciousness alterations** (up to coma), **respiratory depression**.
- toxic doses → **breakthrough seizures**.
- teratogenicity**
- rare **idiosyncratic** aplastic anemia, agranulocytosis, thrombocytopenia, Stevens-Johnson syndrome – all patients should have **CBC** monthly for 3-4 months.

mild, dose-related leukopenia does not require drug discontinuation (unless WBC < 2500/mm³ or total granulocyte count < 750/mm³).

Dangerous **skin reactions** (Stevens Johnson syndrome, toxic epidermal necrolysis) are significantly more common in patients with **HLA-B*1502 allele**; this allele occurs almost exclusively in patients with ancestry across broad **areas of Asia**, including South Asian Indians - patients with ancestry from these areas should be screened for the HLA-B*1502 allele before starting treatment with CARBAMAZEPINE (if test positive, carbamazepine should not be started); patients who have been taking CARBAMAZEPINE for more than few months without developing skin reactions are at low risk of these events ever developing from CARBAMAZEPINE.

PHENYTOIN (PHT) (DILANTIN[®])Available in USA since 1938 (formerly called *diphenylhydantoin*)

- also has Ca²⁺ channel blocking activity.

THERAPEUTIC USES

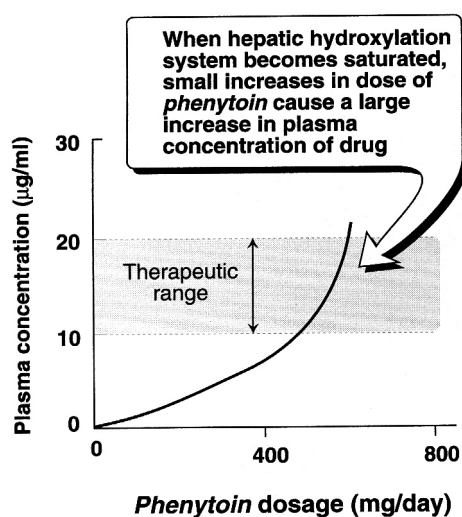
- highly effective first choice for **all partial seizures** (simple and complex, secondarily generalized, cryptogenic and symptomatic) – first choice of seizure prophylaxis in head injury!
- effective first choice for **tonic-clonic seizures** (not effective for other generalized seizures*)
- status epilepticus**
- some **antiarrhythmic** properties

*may even worsen *absence* and *myoclonic seizures*!

- not generalized CNS depressant, but does produce some degree of drowsiness without progression to hypnosis.
- contraindication – bradyarrhythmias.

PHARMACOKINETICS

- absorbed rather slowly in *small intestines* (not absorbed in stomach because of low pH).
- in status epilepticus, is given *intravenously* (infusion > 50 mg/min may cause cardiac arrest!)
- if administered i/m, *drug precipitates in muscle* → tissue necrosis.
- distribution is rapid and brain concentrations are high.
- available as capsules (25 mg, 50 mg, 100 mg, 200 mg), chewable tablets (50 mg), suspension (30 mg/5 mL, 125 mg/5 mL), injection (250 mg/5 mL).
N.B. phenytoin is incompatible (precipitates) with glucose-containing solutions!
- administered ×1-2 /day.
- administered orally, it takes 4-5 days to work; H: loading oral doses (e.g. 500 mg ×2/d).
- maintenance dose is 300-500 mg/day (4–12 mg/kg/d in children).
- IV dosage: 17 mg/kg (no faster than 50 mg/min).
- therapeutic blood level: 10-20 µg/ml.
- 90% protein-bound!



Nonlinear effect of *phenytoin* dosage on plasma concentration of drug.

Metabolized by hepatic microsomal system:

- large *genetic variations* in metabolism rate.
- $T_{1/2}$ = 6-42 hours (dose-dependent);
- **nonlinear kinetics** - as dosage increases, *hydroxylation system becomes saturated* - metabolic rate approaches constant value at high concentrations - relatively small increases in each dose can produce large exponential increases in plasma level (and $T_{1/2}$) - one of main causes of acute phenytoin toxicity!!!
H: careful dose titration using dose increments of 30 mg

One of most problematic drug interaction profiles among all AEDs!!!

- metabolism is inhibited by: FELBAMATE*, *cimetidine*, *chloramphenicol*, *dicumarol*, sulfonamides, *isoniazid*.
* displaces PHT from protein-binding site
- metabolism is enhanced** by: PHENOBARBITAL, CBZ, VALPROATE.
** variable unpredictable effect because same drugs also compete with PHT for liver enzymes
- PHT is strong inducer - enhances metabolism of: other AEDs (CBZ, ETX, felbamate, primidone, tiagabine, phenobarbital), anticoagulants, oral contraceptives, *quinidine*, *doxycycline*, *cyclosporine*, *mexiletine*, *methadone*, *levodopa*.

ADVERSE EFFECTS

Less well tolerated than carbamazepine.

- 1) **GI problems** (nausea, vomiting) are common.
- 2) **behavioral changes** (confusion, hallucination, drowsiness) are common.
- 3) cerebellum and vestibular system depression → **nystagmus** and **ataxia**.
Nystagmus on lateral gaze is good clinical sign that patient is taking medication!
- 4) **megaloblastic anemia** (drug interferes with folate metabolism) - CBC when initiating therapy and at monthly intervals for several mo; H: yeast tablet supplements (folate administration may interfere with anticonvulsant action).
- 5) **gingival hyperplasia** (gums grow over teeth), particularly in children; slowly regresses after drug termination.
- 6) **hirsutism, coarsening of facial features, hyperpigmentation, acne** in girls.
N.B. PHT is not advisable for *young patients*!
- 7) **morbiliform rash** (4%) → stop phenytoin (risk of Stevens-Johnson syndrome, lupus-like syndrome).
- 8) **osteomalacia** (affected vit. D metabolism)!
- 9) **lymphadenopathy**
- 10) inhibition of antidiuretic hormone & insulin secretion → **hyperglycemia** and **glycosuria**.
- 11) **teratogenic effects** (only 11 % fetuses whose mothers take phenytoin during pregnancy - genetic constitution of fetus is important) - "**FETAL HYDANTOIN SYNDROME**" (cleft lip, cleft palate, congenital heart disease, slowed growth, mental deficiency).
- 12) rapid intravenous administration - **hypotension** and **cardiac arrhythmias**! (avoid in patients with bradyarrhythmias)
- 13) "**PURPLE GLOVE SYNDROME**" - progressive edema, discoloration, and pain in limb after IV phenytoin extravasation; rarely can lead to limb amputation.

FOSPHENYTOIN (CEREBYX®)

- **water soluble PHT prodrug (diphosphate ester of phenytoin) for parenteral administration.**

- FDA approved in 1996.
- its active metabolite is PHT, so drug is dosed by PE (phenytoin equivalents).
- antiepileptic effect = PHT.
- completely bioavailable following i/m administration (but i/v route is preferable).
- less irritating to veins than PHT.
- safer and clearly better tolerated than PHT - can be infused 3 times faster than intravenous PHT - indicated for **status epilepticus** treatment. see p. E7 >>
- much more expensive than PHT.
- **adult dose**: loading 15-20 mg PE/kg (100-150 mg PE/min) → maintenance 4-6 mg PE/kg/d (150 mg PE/min to minimize risk of hypotension and cardiac arrest).
- **pediatric dose**: loading 15-20 mg PE/kg → initial dose: 5 mg PE/kg/d → maintenance 4-8 mg PE/kg
if > 6 years, may require minimum adult dose (max 300 mg PE/d).

OXCARBAZEPINE (OXC) (TRILEPTAL®)

- **CBZ analog** – retains CBZ benefits while avoiding autoinduction and drug interaction properties.

PHARMACOKINETICS

- absorbed completely on oral administration (can be taken with food!).
- readily crosses BBB.
- metabolized in liver to **10-monohydroxy metabolite (MHD)** - active compound responsible for pharmacologic effects of OXC!
does not produce epoxide metabolite (which is largely responsible for CBZ adverse effects)!
- $T_{1/2}$ of MHT = 8-10 hours.
- induces / inhibits some cytochrome P-450 enzymes (CYP3A4/5 and CYP2C19), but other cytochrome enzymes are unaffected; **drug interactions** (fewer than CBZ):
 - reduces efficacy of *oral contraceptives* (H: additional non-hormonal contraception).
 - no effect on warfarin, cimetidine, erythromycin, verapamil, dextropropoxyphene.
 - no autoinduction!

- increases [PHT].
- strong P450 inducers (CBZ, PHT, PHB) decrease [MHT].
- available as **tablets** (150 mg, 300 mg, 600 mg) and **oral suspension** (300 mg/5 ml).
- administered $\times 2/d$.
- initial dose 300-600 mg/d with titration up to 2400 mg/d; recommended 1200 mg/d (children 10 \rightarrow 30 mg/kg/d).

THERAPEUTIC USES

- **partial** and **secondary generalized** seizures (monotherapy or adjunctive therapy).
- worsens juvenile **idiopathic generalized epilepsies** (esp. myoclonic and absence)
- substitution for CBZ can be made abruptly with OXC-to-CBZ ratio of 300:200.

ADVERSE EFFECTS

Better tolerability than CBZ!

- 1) dose-related CNS effects (main cause of OXC intolerance) - **somnolence, headache, dizziness, ataxia**.
- 2) **GI disturbances**
- 3) **hyponatremia** (H: fluid restriction), weight gain
- 4) alopecia
- 5) **idiosyncratic reactions** less common than with CBZ, but 25-30% patients hypersensitive to CBZ, also show hypersensitivity to OXC (esp. skin reactions).

LAMOTRIGINE (LTG) (LAMICTAL[®])

- very effective, broad spectrum and well-tolerated!

- approved in USA in 1994.
- also *inhibits glutamate release*.
- weak *antifolate effect* unrelated to antiseizure efficacy (LTG was developed as antifolate agent based on theory that mechanism of some AEDs is related to their antifolate property).

PHARMACOKINETICS

- oral bioavailability close to 100%.
- metabolized by liver;
 - no active metabolites;
 - does not induce or inhibit hepatic enzymes (at higher doses produces slight auto-induction).
 - $T_{1/2} = 25-30$ hours.
 - VPA, *sertraline* increase [LTG] and $T_{1/2}$ up to 70 hrs.
 - hepatic enzymes inducers (CBZ, PHT, PHB) reduce [LTG] and $T_{1/2}$ up to 14 hrs.
- available in 25, 100, 150, 200 mg **tablets**.
- administered $\times 2/d$.
- dosage 75–300 mg/d \rightarrow 150-800 mg/d (children 1-5 mg/kg/d).
- in *adjunctive therapy*, dosage depends on co-administration of other AED.
- **therapeutic blood level**: 1-15 $\mu\text{g/ml}$ (not clearly defined).

THERAPEUTIC USES

- 1) **partial onset*** (first-choice drug in elderly!) and **secondarily generalized** tonic-clonic seizures*
- 2) **primary generalized** seizures (absence seizures, atypical absence seizures, primary generalized tonic-clonic seizures, tonic/atonic seizures, Lennox-Gastaut syndrome*).

*FDA approved indications

N.B. can worsen **myoclonic seizures** in *juvenile myoclonic epilepsy* or *myoclonic epilepsy of infancy*!

ADVERSE EFFECTS

Few CNS side effects!!! Not sedating! (preferred in elderly patients)

LAMOTRIGINE - one of preferred treatments during pregnancy (low incidence of congenital malformations!!!)

- *low incidence of congenital malformations* (preferred during pregnancy*)!!!
 - *preliminary information from North American Antiepileptic Drug Pregnancy Registry: babies exposed to Lamictal during first trimester may have higher chance of cleft lip / cleft palate
- **rash is main concern** (occurs in 5% patients and is associated with rapid titration), up to fatal Stevens-Johnson syndrome.
 - if patient has stopped LTG and then has seizure*, restarting LTG at prior dose may precipitate rash even if patient did not have one before. H: starting at appropriate initial dose, then titrate up slowly (starting another AED during time that LTG dose is being raised may be necessary).

ZONISAMIDE (ZNS) (ZONEGRAN[®])

- approved in USA in 2000.
- also *blocks T-type Ca^{2+} channels*.
- also has weak *carbonic anhydrase inhibiting* activity.
- also has *neuroprotective effects* (free radical scavenging).
- contraindication – sulfonamide hypersensitivity (ZNS is sulfonamide).

THERAPEUTIC USES

- effective *adjunctive therapy* for **partial seizures** in patients > 12 years.
- very effective for myoclonus (esp. juvenile myoclonic epilepsy).

PHARMACOKINETICS

- absorbed quickly and completely when administered orally.
- high affinity for binding to RBCs and 40% protein-binding capacity.
- partially metabolized by liver (70%) - P-450 system, followed by glucuronidation.
- does not induce P-450 system.
- $T_{1/2} = 60-63$ hours.
- PHT, CBZ, PHB, VPA decrease $T_{1/2}$ to 27-46 hours.
- ZNS does not affect levels of other drugs.
- available in 100 mg **capsules**.
- administered $\times 1/d$.
- dosage 100 mg/d \rightarrow up to 600 mg/d.

ADVERSE EFFECTS

- most commonly - **somnolence** and **fatigue, dizziness, ataxia, anorexia, headache**, confusion, speech abnormalities, irritability, tremor, weight gain, depression, psychosis.
- **renal stones** (in 1.5% patients).
- **oligohidrosis and hyperthermia** in children (due to effect on carbonic anhydrase).
- rare **idiosyncratic skin reactions**.

LACOSAMIDE (VIMPAT[®])

- selectively enhances slow inactivation of voltage-gated Na^+ channels \rightarrow stabilization of hyperexcitable neuronal membranes \rightarrow inhibition of repetitive firing.

- FDA approved as **adjunctive** therapy for **partial-onset seizures**.
- **available** in:
 - film-coated **tablets** - 50 mg, 100 mg, 150 mg, 200 mg
 - vial for **IV use** - 200 mg/20 - short term replacement for oral administration.
- **contraindications** – none.
- administered 50 mg ×2/d → increase to 100-200 mg ×2/d (recommended therapeutic dose).

ADVERSE EFFECTS

- most commonly - diplopia, headache, dizziness, nausea.

RUFINAMIDE (BANZEL®)

- acts by regulating activity of Na⁺ channels.
- **FDA approved** as adjunctive treatment in **Lennox-Gastaut syndrome**.
- **contraindicated** in familial short-QT syndrome.

Ca²⁺ channel inhibitors

ETHOSUXIMIDE (ETX) (ZARONTIN®)

- blocks **T-type Ca²⁺ channels**.
- first choice in **absence seizures**; not used in other seizures!
- approved in USA in 1960.

PHARMACOKINETICS

- well absorbed orally.
- not bound to plasma proteins.
- 25% excreted unchanged in urine; 75% metabolized in liver by P-450 system (ETX does not induce P-450).
- T_{1/2} = 60 hours (30 hours in children).
- *no significant interactions with other drugs!!!*
- **available** in 250 mg **capsules** and **syrup** (250 mg/5 ml).
- administered × 1-3/d.
- **dosage** 750-1500 mg/d (10-75 mg/kg/d in children).
- **therapeutic blood level**: 40-100 µg/ml.

ADVERSE EFFECTS

- **stomach irritation** (nausea and vomiting on chronic administration).
- **CNS effects** - drowsiness, dizziness, agitation, anxiety, hiccup, parkinsonism.
- **idiosyncratic reactions** (Stevens-Johnson syndrome, leukopenia, thrombocytopenia, aplastic anemia).

GABA_A receptor agonists

BENZODIAZEPINES

- safest and most free from severe side effects of all AEDs!!! see p. Rx1 >>

Chronic treatment – **CLONAZEPAM**, **CLOBAZAM**, **CLORAZEPATE**;
Terminating status epilepticus – **DIAZEPAM** (drug of choice), **LORAZEPAM**.

CLONAZEPAM (KLO) (KLONOPIN®)

- potent chronic treatment of **absence** and **myoclonic** seizures;
- **effective against all other types of seizures** (*generalized seizures* and, to lesser extent, *partial seizures*); also effective for *subcortical myoclonus*.
- useful in patients with concomitant *anxiety disorder*.
- very high affinity for GABA_A receptors.
- plasma levels and antiepileptic effects are not correlated.
- acetylated in liver (metabolic rate depends on genetic acetylator function); metabolites have no clinical relevance; [KLO] is decreased by CBZ, PHB.
- T_{1/2} = 20-80 hrs.
- **available** as tablets (0.5 mg, 1 mg, 2 mg), also can be given IV or rectally.
- administered × 1-3/d.
- **dosage** 0,25-12 mg/d.
- **therapeutic blood level**: 10–80 ng/mL.
- major **ADVERSE EFFECT** is **sedation** + rapid **tolerance**.
- N.B. children tolerate much better! (pediatricians use it most often)
- withdrawal may induce status epilepticus.

CLOBAZAM

- potent anticonvulsant for **partial epilepsy**.
- useful in **intermittent treatments** (e.g. catamenial epilepsy), **situational prophylaxis** (in traveling, celebrations, etc).
- not available in USA.
- no available IV or IM preparations.
- metabolized in liver.
- T_{1/2} = 10-50 hrs.
- administered × 1-2/d.
- **dosage** 10-20 mg/d day.
- major **ADVERSE EFFECT** is **sedation** + **tolerance**.

DIAZEPAM (VALIUM®), LORAZEPAM (ATIVAN®), MIDAZOLAM (VERSED®)

- drugs of choice in **status epilepticus**. see p. E7 >>
- long term use is limited due to rapid tolerance development.

BARBITURATES

- **very potent** anticonvulsants, but **significant adverse effects** - used as second-line drugs for chronic treatment. see p. Rx2 >>

PHENOBARBITAL (PHB) (LUMINAL®), BARBITA®)

- most commonly prescribed AED of 20th century! (cheap + effective in wide variety of seizures)

Oldest currently available AED (first marketed in USA in 1912)!

THERAPEUTIC USES

- first choice for **febrile seizures** in children!!!
N.B. PHB can depress cognitive performance in children.
- first-line drug for **status epilepticus!!!** (esp. in children)

- also used for **simple partial seizures** (not very effective for complex partial seizures), recurrent **tonic-clonic seizures**.
- not effective for **absences**, **myoclonic** seizures.

PHARMACOKINETICS

- well absorbed orally, freely penetrates brain (brain penetration is much faster during status epilepticus because of increased blood flow and acidosis).
- $T_{1/2}$ = 75-120 hrs (in infants – up to 400 hrs; in children > 6 months – 70 hrs).
- 75% inactivated by hepatic microsomal P-450 system.
 - Phenobarbital is **potent P-450 inducer** (but no autoinduction)!!! → increased metabolism of estrogen, steroids, warfarin, CBZ, diazepam, KLO, VPA (effect on PHT is unpredictable).
 - PHB metabolism is inhibited by PHT, VPA, felbamate, dextropropoxyphene.
 - PHB metabolism is increased by enzyme inducers (e.g. rifampin).
- **available** in **tablets** (15 mg, 30 mg, 50 mg, 60 mg, 100 mg), **elixir** (4 mg/mL), **injections** (200 mg/mL).
- starting **dose** 30-60 mg ×1/d → slowly titrated up to 240 mg/d, in children 3-6 mg/kg/d (as ×1-2/d). antiepileptic doses are lower than those that cause pronounced CNS depression.
- **therapeutic blood levels**: 15-40 µg/mL.
- exercise precautions during parenteral administration! see p. E7 >>

ADVERSE EFFECTS

- **sedation**, **cognitive performance**↓ (→ IQ↓ in children), behavioral changes (e.g. paradoxical **hyperkinesia in children**!!!), **physical dependence**, **withdrawal seizures** (H: very slow withdrawal over months). see p. Rx2 >>
- long-term use → **connective tissue disorders** (facial features coarsening, osteomalacia, Dupuytren contractures).
- **folate deficiency**, **megaloblastic anemia**, and idiosyncratic **skin reaction** are rare.
 - H: vitamin supplementation; routine blood work is not indicated.

PRIMIDONE (PRM) (MYSOLINE®)

available in USA since 1954

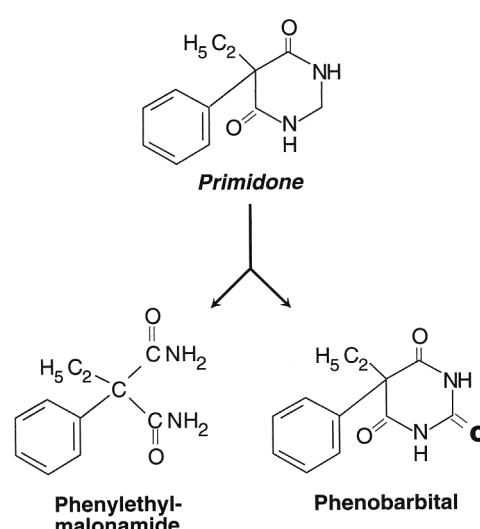
THERAPEUTIC USES

- efficacy comes from metabolites which have longer half-lives:

Phenobarbital (PHB) - **tonic-clonic** and **simple partial** seizures

Phenylethylmalonamide (PEMA) - **complex partial** seizures.

- ineffective in **absences**.
- often used with CBZ and PHT, allowing smaller doses.
- low doses used in treatment of *essential tremor*.



PHARMACOKINETICS

- well absorbed orally.
- $T_{1/2}$ (of primidone) = 5-18 hrs.
- metabolized by cytochrome oxidase system; affected by enzyme inducers, including PHB itself.
- **available** in **tablets** (50 mg, 125 mg, 250 mg), **suspension** (50 mg/mL).

250 mg of PRM = 60 mg of PHB

- administered ×3-4/d.
- average **dosage** 500-1500 mg/d (10-25 mg/kg/d).
- [PRM] 5-12 µg/mL is not useful for monitoring; use [PHB].

ADVERSE EFFECTS

- same as PHB, but PRM initiation is associated with higher incidence of GI distress, dizziness, ataxia, and diplopia (H: small initial doses, very slow titration).

GABA reuptake inhibitors

TIAGABINE (TGB) (GABITRIL®)

- reversibly inhibits GABA reuptake transporter-1 (GAT-1).

- available in USA since 1998

THERAPEUTIC USES

- second-line adjunctive therapy in **refractory partial** or **secondarily generalized** seizures.
- can worsen **absence** epilepsy or **partial** epilepsy **with generalized spike wave** – can cause absence status or status epilepticus!

PHARMACOKINETICS

- well absorbed orally.
- extensively (96%) bound to plasma proteins.
- extensively metabolized by P-450 system
- $T_{1/2}$ = 4.5-13 hrs;
 - ↓ down to 3.8 hrs in patients co-medicated with enzyme-inducing drugs.
 - ↑ in liver impairment (contraindicated in severe hepatic impairment).
- **dosage**: 4 mg/d → titration up to 24-64 mg/d.
- administered ×2-3/d.
- **therapeutic blood levels**: 100-200 µg/mL.

ADVERSE EFFECTS

- asthenia, nervousness, dizziness, GI upset.

GABA transaminase inhibitors

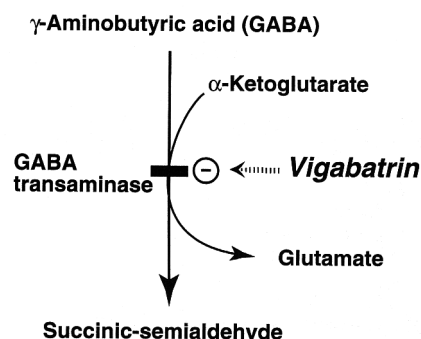
VIGABATRIN (VGB) (SABRIL®)

- irreversibly inhibits extracellular **GABA transaminase**.

- GABA transaminase requires 3-6 days to be resynthesized.
- not licensed in USA because of **visual toxicity**.

THERAPEUTIC USES

- **refractory complex partial** seizures; very effective in **infantile spasms** (esp. in tuberous sclerosis).
- less effective against primarily generalized tonic-clonic seizures.
- may worsen **myoclonic** and **absence** seizures (can cause absence status!).



PHARMACOKINETICS

- rapidly absorbed orally.
- $T_{1/2} = 4-8$ hrs.
- eliminated unchanged in urine.
 - *Minimal drug interactions!!!* (can reduce [PHT] by 25%)
- administered $\times 2/d$.
- dosage 1000 \rightarrow 4000 mg/d (in children, 40 \rightarrow 100 mg/kg/d).
- poor correlation between plasma levels and clinical effect.

ADVERSE EFFECTS

1. Drowsiness, dizziness, **neuropsychiatric symptoms** - depression (5%), agitation (7%), confusion, psychosis.
 - little effect on cognitive function!
2. Irreversible **visual loss** (nasal constriction \rightarrow concentric constriction, with preservation of central vision) in 15-50% of cases.
 - loss of vision appears after months of therapy and does not begin, progress, or reverse after drug is discontinued.
 - site of injury is **retina** (drug is more effectively transported into retina than into brain).
 - do **visual field testing** at baseline and at 6 months.

Potential GABA mechanism of action

Possible mechanisms of action:

- 1) enhanced GABA synthesis by **GAD enzyme**.
- 2) competitive inhibition of **GABA-T enzyme** (**GABAPENTIN**).
- 3) block of **Na⁺ channel** during rapid sustained repetitive firing (**VALPROATE**).

VALPROATE (VPA) (DEPAKENE®)

One of most commonly used AEDs around world!

- approved in USA since 1978
- used in different forms (do not differ significantly) - enteric-coated DIVALPROEX sodium (Depakote®), MAGNESIUM salt, CALCIUM salt, VALPROMIDE.

THERAPEUTIC USES

- - very potent AED **effective against all types (generalized and partial) of seizures!**
- most effective agent for **myoclonic** seizures!!!
- drug of choice in **idiopathic generalized epilepsy**.
- first-line drug in **photosensitive epilepsy** and **Lennox-Gastaut syndrome**.
- second choice for **absence** seizures (because of hepatotoxic potential), **infantile spasms**.
- also reduces **partial** seizures (simple > complex).
- useful in patients with *concomitant migraine headache*.

PHARMACOKINETICS

- rapidly absorbed orally.
- *highly bound to plasma proteins*, but binding is concentration dependent and nonlinear (e.g. doubling plasma concentration from 75 to 150 $\mu\text{g/ml}$ can result in 6-fold rise in free drug concentration) - *as dose is increased, side effects may worsen rapidly!!!*
- reaches brain by active saturable transport process.
- 97% converted to active metabolites by liver; VPA does not induce P-450 enzymes.
 - VPA increases levels of PHB, PHT, CBZ, LTG.
 - [VPA] is decreased by enzyme-inducing drugs.
 - [VPA] is increased by felbamate and clobazam.
- $T_{1/2} = 4-20$ hrs (enzyme-inducing AEDs reduce $T_{1/2}$ to 9 hours).
- available in **delayed-release tablets** (125 mg, 250 mg, 500 mg), **sprinkle capsules** for mixture with food (125 mg, 250 mg), **syrup** (250 mg/5 mL), **IV form*** (Depacon®).
 - *not associated with hemodynamic changes! (as are PHT and PHB).
- administered $\times 2-4/d$.
- dosage 250 mg/d \rightarrow rapid titration up to 3000 mg/d (in children, 10 \rightarrow up to 70 mg/kg/d).
- **therapeutic blood levels** 50-150 $\mu\text{g/ml}$ - poor correlation with clinical effect and significant daily fluctuations (adverse effects also fluctuate!).

ADVERSE EFFECTS

- idiosyncratic, genetically determined **hepatic toxicity** - microvesicular steatosis with necrosis (due to hepatotoxic 4-ene metabolite), esp. in patients < 2 years.
 - N.B. tend do not to occur until after several months of symptom-free therapy - hepatic enzymes should be monitored frequently!
- inhibition of plasmalemmal carnitine uptake \rightarrow **serum [carnitine]** \downarrow - may be cause of hepatotoxicity! H: L-carnitine 50-100 mg/kg/d.
- dose-related **nausea** and **vomiting** (H: enteric-coated preparations).
- hyperphagia, **weight gain**.
- **sedation**, **ataxia**, **tremor**.
- **coma** may result from hyperammonemia (typically with normal liver function tests).
- **rash** and **alopecia** (H: baby shampoo and multivitamin supplement).
- **thrombocytopenia** and inhibition of platelet aggregation.
- **endocrine effects** - insulin resistance, anovulatory cycles, amenorrhea, polycystic ovary syndrome.
- rare **bone marrow suppression**.
- rare but potentially fatal **acute pancreatitis**.
- **teratogenic** effects! (esp. neural tube defects!)

GABAPENTIN (GBP) (NEURONTIN®)

Approved in USA in 1993.

- increases brain GABA levels.
- may reduce brain glutamate levels.
- structure similar to GABA; however, *no action on GABA receptors*.

THERAPEUTIC USES

- - only modest efficacy in **partial** and **secondarily generalized** tonic-clonic seizures.
- ineffective in most *generalized seizures*.
- has **analgetic** properties.

PHARMACOKINETICS

- bioavailability < 60% (variable absorption depends on L-amino acid transporter); further \downarrow by antacids; doses > 1200 mg produce only modest increases in bioavailability.
- readily crosses BBB and achieves **plasma-to-CSF ratio 1:10**.
- not bound to plasma proteins.
- not metabolized. does not induce hepatic enzymes.
 - *No drug interactions!*
- excreted in urine entirely unchanged.

- $T_{1/2}$ = 5-9 hours (does not change with chronic administration, nor is it influenced by concomitant medications!).
- available as **capsules** (100 mg, 300 mg, 400 mg, 600 mg) and **tablets** (800 mg).
- administered $\times 3/d$.
- dosage 300 mg/d \rightarrow titrated to maximum 4800 mg/d.
- **therapeutic blood levels** $> 2 \mu\text{g/ml}$ (not necessary to monitor).

ADVERSE EFFECTS

Well tolerated! - relatively minor adverse effects in high doses (somnolence, dizziness, ataxia, nystagmus, headache, tremor, fatigue, diplopia, rhinitis, nausea or vomiting).

GLUTAMATE receptor blockers

FELBAMATE (FLB) (FELBATOL[®])

- potent, very **effective against all seizure types!**

Approved in USA in 1993.

- blocks NMDA receptors and voltage-gated Ca^{2+} -channels.
- modulates Na^+ -channel conductance.
- no effect on GABA receptors.
- has **neuroprotective** effect on hypoxic-ischemic injuries.

THERAPEUTIC USES

- **restricted*** to **severe refractory partial epilepsy** or **Lennox-Gastaut syndrome**.

*potentially fatal toxic effects (aplastic anemia, hepatic failure).

PHARMACOKINETICS

- well absorbed orally.
- extensively metabolized in liver.
 - [felbamate] is significantly increased by VPA!!!
 - felbamate increases [PHT] and reduces [CBZ] (but increases [epoxide metabolite])
- $T_{1/2}$ = 13-30 hours.
- available in **tablets** (400 mg, 600 mg) and **suspension** (600 mg/5 mL).
- administered $\times 3-4/d$.
- dosage 1200 mg/d \rightarrow titration up to 3600 mg/d.
 - N.B. to avoid drug interactions, concomitant AEDs should be reduced by 20-30% when felbamate is initiated.
- **therapeutic blood level** 20-100 $\mu\text{g/mL}$.

ADVERSE EFFECTS

Well tolerated!

- common adverse effects - insomnia, weight loss, nausea, dizziness, fatigue, ataxia, lethargy.
- fatal **hepatic failure** (in 14 of 110,000 treated patients within 6 months of therapy initiation).
- **aplastic anemia** (31 cases with 10 fatalities).

H: monthly monitoring of **liver function studies**, **CBC**, **reticulocyte count**.

TOPIRAMATE (TPM) (TOPAMAX[®])

- very potent, highly effective anticonvulsant, chemical relative of fructose (was developed as antidiabetic drug).

- approved in USA in 1996.
- has several actions:
 - 1) blockade of **AMPA subtype** of **glutamate** receptors.
 - 2) blockade of voltage-gated Na^+ -channels
 - 3) increased **GABA** activity at GABA_A receptors (topiramate modulates phosphorylation of Cl^- channel \rightarrow increased frequency of channel openings).
 - 4) weak inhibitor of **carbonic anhydrase**
 - 5) **neuroprotective** in animal studies

THERAPEUTIC USES

- 1) **partial** onset and secondarily generalized tonic-clonic seizures
- 2) primary **generalized tonic-clonic** seizures
- 3) Lennox-Gastaut syndrome.

PHARMACOKINETICS

- oral bioavailability 80-100%.
- 15-30% is metabolized in liver (remaining is excreted unchanged in urine).
 - decreases [ethinyl estradiol] by 30%!!!
 - PHT and CBZ decrease [TPM] by 50%.
- $T_{1/2}$ = 16-30 hours.
- available as **tablets** (25 mg, 50 mg, 100 mg, 200 mg) and **sprinkle** (15 mg, 25 mg).
- administered $\times 2/d$.
- dosage 25 mg/d \rightarrow titrated slowly up to 600 mg/d (in children, 0.5-1 \rightarrow 9-11 mg/kg/d).
- **therapeutic blood level** 2-20 $\mu\text{g/mL}$.

ADVERSE EFFECTS

- **CNS** - impaired concentration, dizziness, ataxia, diplopia, somnolence, nervousness, confusion.
- **GI** - nausea, appetite suppression \rightarrow weight loss.
- **renal stones** (1.5%) - due to carbonic anhydrase inhibition. H: drink plenty of fluids.

UNKNOWN MECHANISMS OF ACTION

LEVETIRACETAM (LEV) (KEPPRA[®])

- potent AED, PIRACETAM (S-enantiomer pyrrolidone) derivative.

- mechanism of action unknown; **neuroprotective effect** in animal studies.
- brain-specific stereo-selective binding site for LEV has been identified (effect on this site still is unknown).
- inhibits Ca^{2+} release from IP_3 -sensitive stores without reducing Ca^{2+} storage.

THERAPEUTIC USES

- adjunctive therapy in **partial** onset seizures in adults.

- one of preferred AEDs in *elderly patients*.
- potential agent for **epilepsy prevention** (e.g. in traumatic brain injury).

PHARMACOKINETICS

- oral bioavailability $\approx 100\%$.
- $< 10\%$ protein-bound.
- minimally ($\approx 27\%$) metabolized; **no drug interactions!!!**
- $T_{1/2}$ = 6-8 hours (in renal insufficiency, up to 24 hours).

- available in **tablets** (250 mg, 500 mg, 750 mg, 1000 mg) and **IV formulation**.
- administered $\times 2/d$.
- dosage 1000 mg/d \rightarrow 3000 mg/d.

ADVERSE EFFECTS

Very well tolerated!

Most significant adverse effects - somnolence, asthenia, dizziness, headache, pharyngitis, flu-like syndrome.

PREGABALIN (LYRICA®)

- lipophilic structural GABA analogue (easy diffusion across BBB).

- not functionally related to GABA (does not directly affect GABAergic system).
- **α -2- δ ligand** - reduces (but doesn't block) depolarization-induced Ca^{2+} influx \rightarrow reduction in release of excitatory neurotransmitters (e.g. glutamate).

THERAPEUTIC USES

- adjunctive therapy for **partial** seizures (with or without secondary generalization) approved in USA in 2005.

- potent **anticonvulsant**, **analgesic**, and **anxiolytic** activity.
- in 2004 FDA approved for **neuropathic pain** (postherpetic neuralgia, diabetic peripheral neuropathy).

PHARMACOKINETICS

Very clean pharmacokinetic profile! No significant drug interactions!

- rapidly and extensively absorbed (oral bioavailability $> 90\%$).
- $T_{1/2} = 6.3$ hours.
- does not bind to plasma proteins.
- not metabolized (does not induce or inhibit liver enzymes) - excreted unchanged by kidneys (decrease dose with renal impairment!).
- administered $\times 2-3/d$.

ADVERSE EFFECTS

Most commonly CNS related - dizziness (28%), somnolence, ataxia, asthenia, weight gain.

KETOGENIC DIET

- strict **high-fat, low-protein, very low-carbohydrate** diet (i.e. most calories provided as fat).

- indication - **refractory generalized** seizures (esp. children with complex myoclonic epilepsy with associated tonic-clonic convulsions).
- initiated with fast to achieve ketosis.
- mechanism of action unknown (may increase GABA), but efficacy in some cases is unquestionable (some patients may reduce or eliminate concomitant AEDs).
- seizures decrease in frequency shortly after diet initiation (some patients may not respond for months).
- **poorly tolerated**:
 - 1) fatty unpalatable
 - 2) demands precise weighing of foodstuffs and is time consuming to prepare.
- any small carbohydrate intake (e.g. lollipop, piece of candy) resets ketone metabolism for 2 weeks, eliminating antiseizure efficacy.
- unsuitable for teenagers or adults (unless all of their intake is being delivered via gastric tube).
- some children respond to **LIBERALIZED KETOGENIC DIET** (medium-chain triglycerides substituted for high-fat content).

BIBLIOGRAPHY for ch. "Epilepsy and Seizures" \rightarrow follow this [LINK](#)