

Antiseizure Medications (ASM)

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TERMINOLOGY

- historically, medications used in the treatment of epilepsy have been referred to by a variety of terms, such as 'antiepileptic', 'anticonvulsant', or 'antiseizure'. Terminology is important, because using terms which do not reflect accurately the action of specific treatments may result in misunderstanding of their effects and inappropriate use.
- the present ILAE consensus is that these medications should be collectively named as '**antiseizure medications**' (ASMs). This term reflects accurately their primarily symptomatic effect against seizures, and reduces the possibility [of healthcare practitioners, patients or caregivers] having undue expectations, or an incorrect understanding of the real action of these medications.

HISTORY

- 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.

SIDE EFFECTS

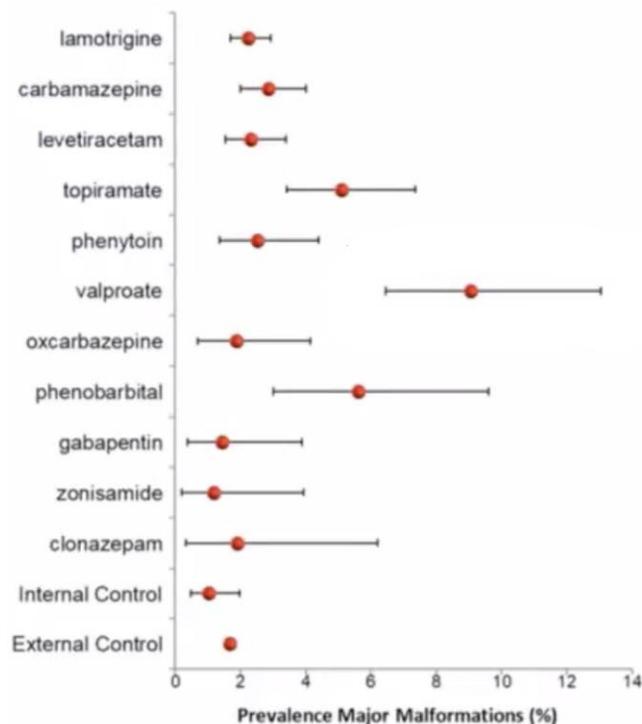
- hyponatremia** - **CARBAMAZEPINE**, **OXCARBAZEPINE**, and occasionally **VALPROATE**, **LAMOTRIGINE**, **LEVETIRACETAM**

All antiepileptics increase risk of **suicidality!**

VALPROIC ACID and PHENYTOIN interfere with **platelet** function!

Enzyme-inducing AEDs (CMZ, PRM, PHT) cause **lipids**↑ (even if on statins) – nobody should be prescribed inducing AEDs

Major Malformations:



CLASSIFICATION (MECHANISM OF ACTION)

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

ESLICARBAZEPINE

PHENYTOIN – the only AED metabolized through nonlinear, zero-order kinetics.

FOSPHENYTOIN

LAMOTRIGINE

ZONISAMIDE

LACOSAMIDE

RUFINAMIDE

2. **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

METHSUXIMIDE

PHENYTOIN also has some Ca²⁺ channel blocking activity.

3. **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)

PERAMPANEL

5. **Unknown mechanisms of action**

LEVETIRACETAM

PREGABALIN

6. **Carbonic anhydrase inhibitors** → intracellular $H^+ \uparrow$ ($pH \downarrow$) → K^+ shifts to extracellular compartment (to buffer acid-base status) → hyperpolarization.

ACETAZOLAMIDE

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):

- 1) increases Cl^- conductance at $GABA_A$ receptors
- 2) attenuates glutamate excitatory response
- 3) alters mRNA for GAD and $GABA_A$ receptor subunits.

N.B. **ESTROGENS** act as proconvulsants:

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

ACTH, PREDNISONE – preferred treatment in **infantile spasms**. see p. E9 >>

Na⁺ channel blockers

N.B. Na-channel blockers (esp. carbamazepine) increase **sudden cardiac death** risk!

CARBAMAZEPINE (CBZ) (Tegretol®, Carbatrol®)

THERAPEUTIC USES

- One of most widely used AEDs in world! (available in USA since 1974)
- 1) highly effective first choice for **all partial seizures** (simple and complex, secondarily generalized, cryptogenic and symptomatic)
 - 2) effective first choice for **tonic-clonic seizures** (not effective for other generalized seizures – may aggravate **absences** and **myoclonic** seizures).
 - 3) **trigeminal neuralgia**
 - 4) occasionally used in **manic-depressive patients**.

PHARMACOKINETICS

- unstable substance (protect from hot or humid conditions).
- absorbed slowly following oral administration; absorption may be erratic! (smaller more frequent doses are preferred)
- 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 (Carbatrol®), elixir (100 mg/5 ml) and **rectal suppositories**.
- **IV form** for use in e.g. status epilepticus is in development
- 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; not to exceed 2000 mg/d (children, 10-40 mg/kg/d).
- **therapeutic blood level**: 4-12 $\mu g/ml$.

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!!!

Less effect on cognitive function than PHT

- 1) *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; hepatitis may be fatal)

Liver function tests monthly

- 2) may aggravate **hyponatremia** by SIADH-like effect
- 3) **stomach irritation**, nausea and vomiting (H: extended-release preparations, e.g. Tegretol XR).
- 4) chronic administration → dose-related **vertigo, ataxia, blurred vision, diplopia, consciousness alterations** (up to coma), **respiratory depression**.
- 5) toxic doses → **breakthrough seizures**.
- 6) **teratogenicity**
- 7) rare **idiosyncratic aplastic anemia**, agranulocytosis, thrombocytopenia, *Stevens-Johnson syndrome*.

All patients should have **CBC** q week x 3 mos, then q month x 3 yrs

- *mild, dose-related leukopenia* is common and does not require drug discontinuation (unless $WBC < 2500/mm^3$ or total granulocyte count $< 750/mm^3$);
- do not start (or discontinue) if: $WBC < 4$, $RBC < 3$, $Hct < 32\%$, platelets < 100 , reticulocytes $< 0.3\%$, $Fe > 150 \mu g\%$.

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.

Significant (40-60%) **cross-reactivity** for rash between CARBAMAZEPINE and PHENYTOIN!

PHENYTOIN (PHT) (Dilantin®)

Available in USA since 1938 (formerly called *diphenylhydantoin*)

- also has Ca^{2+} channel blocking activity.

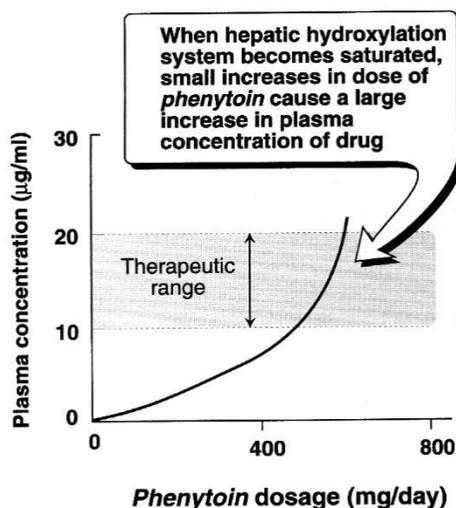
THERAPEUTIC USES

- 1) highly effective first choice for **all partial seizures** (simple and complex, secondarily generalized, cryptogenic and symptomatic) – first choice of seizure prophylaxis in head injury!
- 2) effective first choice for **tonic-clonic seizures** (not effective for other generalized seizures*)
- 3) **status epilepticus**
- 4) 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



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

Metabolized by hepatic microsomal system:

- large **genetic variations** in metabolism rate.
- $T_{1/2}$ = 6-140 hours (dose-dependent);
- **nonlinear kinetics** - as dosage increases, **hydroxylation system becomes saturated** – **1st order kinetics** (elimination proportional to concentration) converts into **zero order kinetics** (elimination at constant rate, i.e. 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

- 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, sterile abscess.
- distribution is rapid and brain concentrations are high.
- 90% protein-bound!
- bioavailability: oral - 90%, IV - 95%
- 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**!

Hold **NG feeding** for 2 hrs before and 1 hour after phenytoin dose to prevent erratic absorption!

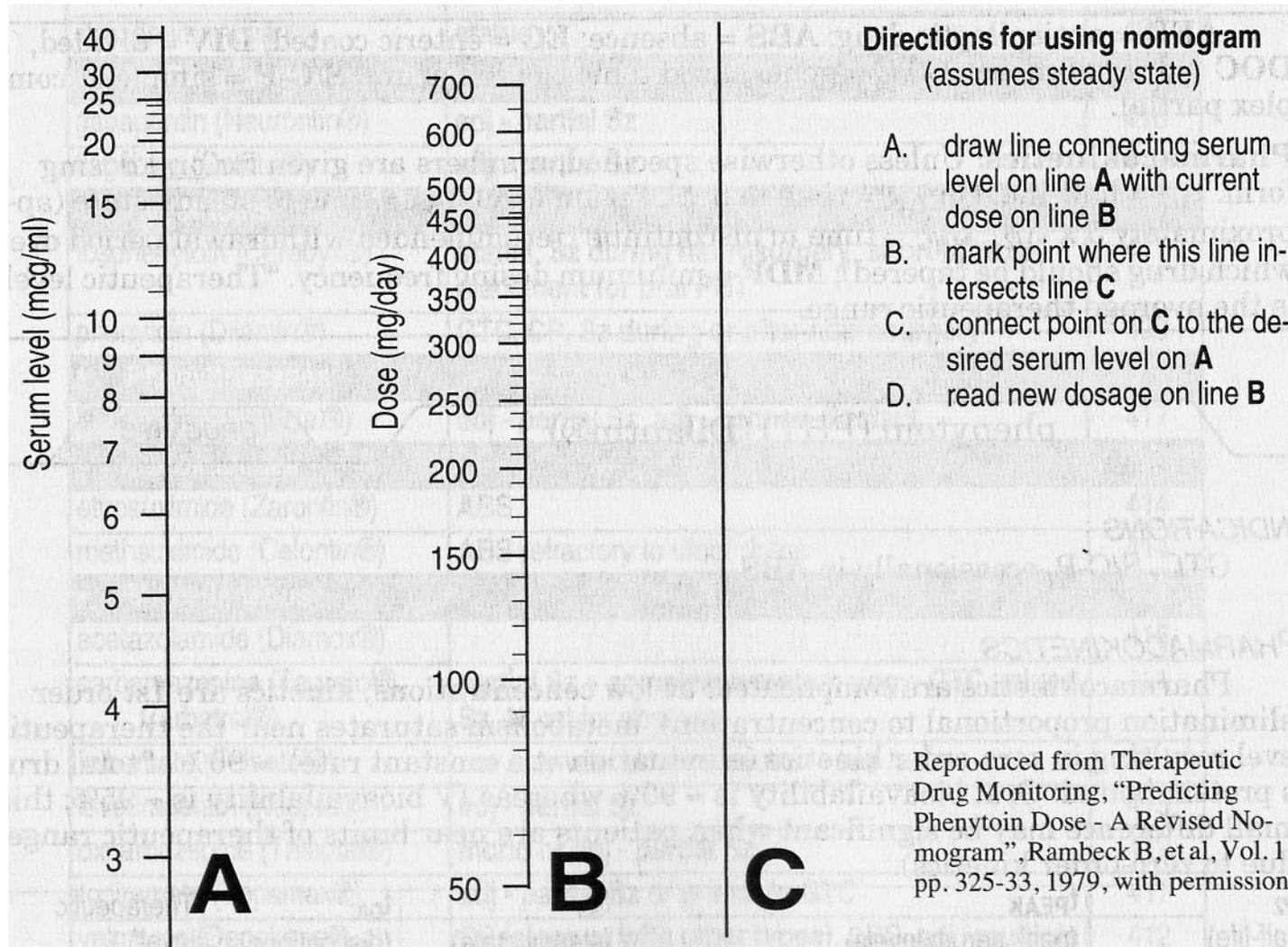
- IV loading dose: 15-20 mg/kg (no faster than 50 mg/min – **negative inotrope** and can cause hypotension).
- oral loading dose 500 mg ×2/d (alt: 300 mg PO q 4 hrs until 17 mg/kg are given); if administered orally, it takes 4-5 days to work.

N.B. maximum PO dose at one time = 400 mg (saturable absorption)

- maintenance dose is 300-600 mg/day (4-12 mg/kg/d in children) divided BID or TID (all available formulations now are ER – may administer x1/d).
- monitor FREE phenytoin levels - therapeutic 1-2 µg/ml (vs. 10-20 µg/ml for TOTAL).

First level 2 – 24 hours after IV load, then again in 2-3 days. No other levels needed unless seizures occur.

$$\text{RELOADING DOSE in mg} = \text{desired change in free conc} \times \text{kg} \times 7$$



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, steroids, oral contraceptives, *quinidine*, *doxycycline*, *cyclosporine*, *mexiletine*, *methadone*, *levodopa*, *digoxin*.
- **RENAL FAILURE:** dosage adjustment not needed (protein binding may be altered in uremia which can obfuscate interpretation of TOTAL serum phenytoin levels).

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 months; 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) **morbilliform rash** (4-5.9%, esp. Asian patients) → stop phenytoin (risk of Stevens-Johnson syndrome, lupus-like syndrome); patient may be rechallenged - often rash will not recur second time.
Phenytoin is associated with the highest rate of rashes (5.9%), followed by lamotrigine (4.8%) and carbamazepine (3.7%)
Significant (40-60%) cross-reactivity for rash between phenytoin and carbamazepine!
- 8) **osteomalacia** (PHT antagonizes 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.
- completely converted in vivo to PHT by organ and blood phosphatases with conversion half-life of 10 minutes, 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 (pH 8.6-9) to veins than PHT (pH 12).
- may be infused with dextrose or saline.
- **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; no liver and hematologic toxicity** (no need to check drug levels).

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).

ESLICARBAZEPINE acetate (Aptiom®)

- FDA approved as add-on medication to treat partial seizures.

- prodrug – in vivo activated to eslicarbazepine (major active metabolite of oxcarbazepine).
- dosage 400 mg once daily $\times 1$ week \rightarrow 800 mg once daily (recommended maintenance dose); max dose 1200 mg/d.

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).

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*)
- 3) **bipolar disorder**

*FDA approved indications

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

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).
- $T_{1/2} = 24-30$ 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 in **monotherapy**: 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:
 - in patients receiving enzyme-inducing AEDs (PHT, CBZ, PHB), start with 50 mg qd $\times 2$ wks \rightarrow 50 mg BID $\times 2$ wks \rightarrow \uparrow by 100 mg/d q week until usual maintenance dose of 200-700 mg/d (divided into 2 doses) is reached.
 - for patients on VPA alone, maintenance dose is 100-200 mg/d (divided into 2 doses), and VPA levels drop by $\approx 25\%$ within few weeks of starting lamotrigine.
 - for patients on both enzyme-inducing AEDs and VA, starting dose is 25 mg qod $\times 2$ wks \rightarrow 25 mg qd $\times 2$ wks \rightarrow \uparrow by 25-50 mg/d q 1-2 wks up to maintenance of 100-150 mg/d (divided into 2 doses).
- **therapeutic blood level**: 1-15 $\mu\text{g/ml}$ (not clearly defined).

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
- **arrhythmias**: in vitro testing showed that Lamictal exhibits Class IB antiarrhythmic activity - could slow ventricular conduction (widen QRS) and induce proarrhythmia, including sudden death - avoid Lamictal in people who have cardiac conduction disorders (e.g., second- or third-degree heart block), ventricular arrhythmias, or cardiac disease or abnormality.
- **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).
- not indicated for use in patients < 16 yrs old due to higher incidence of potentially life-threatening rash in pediatric population
- **hemophagocytic lymphohistiocytosis** - rare but very serious reaction that may lead to death, especially if the reaction is not diagnosed and treated quickly.

ZONISAMIDE (ZNS) (Zonegran®)

- approved in USA in 2000.
- also *blocks T-type Ca²⁺ 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 × 1/d.
- dosage 100 mg/d → up to 600 mg/d.
- **therapeutic blood level**: 5-40 µg/ml.

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 → stabilization of hyperexcitable neuronal membranes → inhibition of prolonged repetitive firing.
- FDA approved:

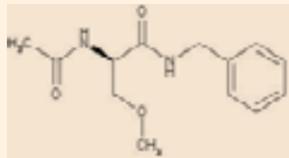
- 1) **monotherapy (!) or adjunctive therapy** for **partial-onset seizures**.
 - 2) **adjunctive therapy** for **primary generalized tonic-clonic seizures** in patients age \geq 4 years
- available in:
 - film-coated **tablets** - 50 mg, 100 mg, 150 mg, 200 mg
 - vial for **IV use** - 200 mg/20 - short term replacement for oral administration.
 - contraindications – none.
 - administered: initiation of treatment - single-loading dose of 200 mg (oral or injection) \rightarrow 12 hours later start 100-mg twice-daily dosing.
 - dosage adjustments are recommended for mild or moderate hepatic impairment or severe renal impairment
 - adverse effects - most commonly - diplopia, headache, dizziness, nausea.

7

Lacosamide (LCM)

Background:

- New chemical enantiomer of the amino acid, L-serine.
- FDA approved 10/29/2008 as adjunctive treatment of partial-onset seizures in patients \geq 17 years of age.



<http://images.rxlist.com/images/rxlist/vimpat1.gif>

Mechanism of Action:

- The only anti-seizure drug which enhances the slow inactivation state of voltage gated (Na_v) channels.
- Binds to the collapsin response mediator protein (CRMP2), but it is unclear if this contributes to the anticonvulsant effect of LCM

Bialer M, et al. *Epilepsy Res.* 2007, 73, 1-52; Stohr T, et al. *Epilepsy Res.* 2007, 74, 147-154; Errington, AC, et al. *Neuropharm.* 2006, 50, 1016-29; Beyrueter BK et al. *CNS Drug Rev.* 2007, 13, 21-42; Bialer M & White HS, *Nature Reviews Drug Discovery* 2010. 9, 68-82; White HS and Rho FM. *Mechanisms of Action of Antiepileptic Drugs*, Professional Communications, Inc., 2010. 1st Edition. West Islip, NY.

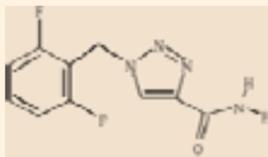
RUFINAMIDE (Banzel®)

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

Rufinamide

Background :

- New triazole structure:



Cheng-Hakimian, A. et al., *Int J of Clin Practice*, 2006. 60(11):1497-1501.

- FDA approved 11/14/2008 as adjunctive for seizures associated with Lennox-Gastaut syndrome in adults and children > 4 years of age.

Mechanism of Action :

- Prolongs the inactivated state of Na_v channels thus limiting sustained, repetitive firing of Na^+ -dependent APs
- Mechanism of Action not fully understood:
 - Preclinical profile suggests may have a broader spectrum of activity than classical sodium channel blocking partial-seizure drugs.

White, HS, et al, *Epilepsia*.2008, 49. 1213-20; Arroyo S. *Neurotherapeutics*, 2007. 4: 155-62; Deeds ED, et al. *CNS Drugs*. 2006. 20; 751-61; Bialer M, et al. *Epilepsy Res*. 2007, 73, 1-52; Bialer M & White HS, *Nature Reviews Drug Discovery* 2010. 9, 68-82.

Ca²⁺ channel inhibitors

ETHOSUXIMIDE (ETX) (Zarontin®)

- blocks T-type Ca^{2+} 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).
- $T_{1/2}$ = 40-70 hours (20-40 hours in children).
- *no significant interactions with other drugs!!!*
- available in 250 mg capsules and syrup (250 mg/5 ml).
- administered \times 1-3/d.
- dosage 500-1500 mg/d (10-75 mg/kg/d in children).
- therapeutic blood level: 40-100 μ g/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).

METHSUXIMIDE (Celontin®)

- indicated for **absence seizures** refractory to other drugs.
- optimum dosage must be determined by trial: start with 300 mg qd → increase by 300 mg PRN at weekly intervals up to 1200 mg/d.
- available in 150 and 300 mg **capsules**.

Activators of voltage-gated K⁺ channels**EZO GABINE**

- FDA approved for partial seizures.
- exact mechanism of action is unknown; may act by reducing excitability through stabilization of neuronal potassium channels in "open" position.
- adverse events - dizziness, fatigue, confusion, vertigo, tremor, problems with coordination, double vision, problems paying attention, memory impairment, and lack of strength.
 - may also cause **urinary retention**, generally within the first 6 months of treatment.
 - **neuropsychiatric symptoms** (confusion, hallucinations, psychotic symptoms) may also occur but typically resolve within a week after discontinuation of the treatment.
 - permanent **skin discoloration**
 - **retina abnormalities** → permanent vision loss

Ezogabine

1:

Background :

- First-in-class KCNQ (Kv7) channel opener for the treatment of epilepsy.
-
- <http://www.axonmedchem.com/ligand-pics/1525retigabine.GIF>
- Approved on 6/10/11 by the FDA as adjunctive treatment for partial seizures and for refractory partial epilepsy.

Mechanism of Action :

- Directly activates low threshold Kv7 potassium channels to enhance the voltage gated M-current.
- Hyperpolarizing effect on neurons reduces neuronal hyperexcitability.
- Enhances GABA_A-activated currents at supratherapeutic concentrations.
- Due to the presence of Kv7.2-Kv7.5 in the bladder urothelium, ezogabine is uniquely associated with urinary retention.

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 $\times 1-3/d$.
- dosage 0,25-12 mg/d (start at 1.5 mg/d divided TID, increase by 0.5-1 mg q 3 d; max 20 mg/d)
- **therapeutic blood level:** 10–80 ng/mL.
- major **ADVERSE EFFECT** is **sedation** + rapid **tolerance**.
 - **children** tolerate much better! (pediatricians use it most often)
 - drug usually works very well for several months, and then tends to become less effective, leaving only sedating effects
- many cases have been reported of **seizures during withdrawal**, including status epilepticus (even in patients with no history of status). **Taper drug over 3-6 months!**

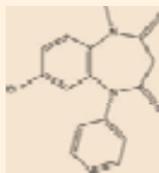
CLOBAZAM (Onfi®)

- 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 $\times 1-2/d$.
- dosage 10-20 mg/d.
- major **ADVERSE EFFECT** is **sedation** + **tolerance**.
- may trigger **Stevens-Johnson syndrome** and **toxic epidermal necrolysis**.

Clobazam

Background :

- 1, 5-benzodiazepine, structurally unique from traditional 1, 4-benzodiazepines (e.g., diazepam):



<http://chembl.blogspot.com/2011/10/new-drug-approvals-2011-pt-xxviii.html>

- Approved by the FDA as adjunctive treatment of seizures associated with Lennox Gastaut syndrome in patients aged ≥ 2 years.

Mechanism of Action :

- Potentiates GABAergic neurotransmission by binding to the benzodiazepine (BZD) site of the GABA_A receptor.
- Less lipophilic and acidic than 1, 4-BZDs, clobazam is better tolerated; may be less sedating and slower to develop tolerance.

gawski MA, et al, Nat Rev Neuro. 5(7):553-64; Bialer M & White HS, Nature Reviews Drug Discovery 2010. 9, 68-82; Buck ML, Pedarmacother, 2011. 17(12): 1-4.

DIAZEPAM (Valium®), **LORAZEPAM** (Ativan®), **MIDAZOLAM** (Versed®, Nayzilam®)

- drugs of choice in **status epilepticus**. see p. E7 >>

- long term use is limited due to rapid tolerance development.

Nayzilam® - nasal spray CIV, FDA approved for the acute treatment of seizure clusters in patients ≥ 12 years.

- contraindicated in patients with **acute narrow-angle glaucoma**
- approval based on randomized, double-blind, placebo-controlled trial (Study 1; NCT01390220) – 5 mg nasal spray was superior to placebo in providing rapid, sustained seizure control when administered to patients experiencing an seizure clusters in the outpatient setting and was associated with a favorable safety profile:
 - termination of seizure(s) within 10 minutes after initial dose of study drug (80.6 versus 70.1%).
 - absence of seizure recurrence between 10 minutes and 6 hours after the initial dose of study drug (58.2 versus 37.3%).
 - smaller proportion of Nayzilam-treated patients experienced the next seizure within 24 hours after the initial blinded dose of study drug (37.3% versus 46.3%).

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)!
About as effective as PHT, but very sedating!

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).
- $T_{1/2}$ = 50-160 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).
- dosage same for oral and parenteral forms; 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 **hyperkinesis 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

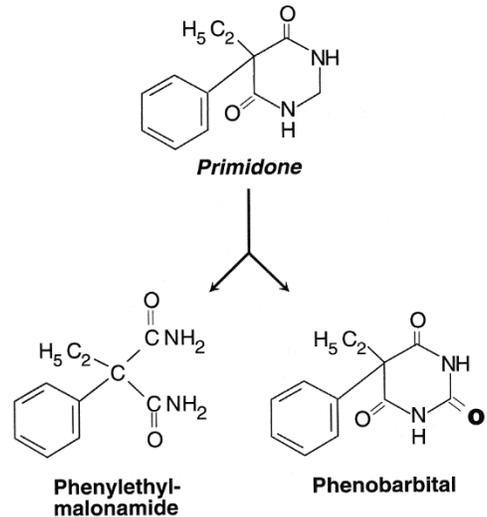
THERAPEUTIC USES

- 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) = 4-18 hrs (pay attention – metabolite PHB $T_{1/2}$ = 50-160 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 $\times 3-4/d$.
- **dosage**: start at 125 mg/d \times 1 wk \rightarrow increase slowly to avoid sedation; average dosage 250-1500 mg/d (peds 10-30 mg/kg/d).
- **[PRM]** 5-12 $\mu\text{g/mL}$ is not useful for monitoring; use **[PHB]**.

ADVERSE EFFECTS

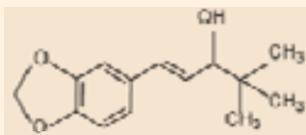
- same as PHB, but PRM initiation is associated with higher incidence of GI distress, dizziness, ataxia, diplopia (H: small initial doses, very slow titration); also loss of libido, rare macrocytic anemia.

STIRIPENTOL (Diacomit®)

Stiripentol

Background :

Stiripentol (STP) is unrelated to other anti-seizure drugs and belongs to a group of aromatic alcohols.



<http://66.197.58.78/stiripentol.htm>

In 2007, the European Medicine Agency (EMA) gave marketing authorization for the orphan drug STP in conjunction with clobazepam and VPA as adjunctive therapy of refractory generalized TC seizures in patients with severe myoclonic epilepsy in infancy (SMEI, Dravet's syndrome) whose seizures are not adequately controlled.

Mechanism of Action :

- Precise mechanism remains unknown.
- Enhances GABAergic neurotransmission in neonatal rat hippocampal slices.
 - At clinically relevant concentrations, has a barbiturate-like effect, increasing the duration of opening of GABA_A receptors.
 - May also increase the central [GABA] by interfering with its uptake and its metabolism
- May have pharmacodynamic interaction with other BZDs, since STP is active in δ -containing recombinant GABA_A receptor which are insensitive to BZDs.
- It also improves the effectiveness of many other anticonvulsants by pharmacokinetic interactions.
 - inhibits cytochrome P450 isozymes (e.g., CYP1A2, CYP2C9, CYP2C19 & CYP3A4) responsible for metabolizing other anti-seizure drugs (e.g., phenobarbital, primidone, phenytoin, carbamazepine, clobazam, and diazepam).

! Nabbout & C. Chiron. Eur J Ped Neurol. 2012. 16:S13-S17; PP Quilichini et al., Epilepsia. 2006. 654:160-5; C. Chiron et al., STILCO study group.

- FDA approved for seizures associated with Dravet syndrome in patients 2 years of age and older taking clobazam.

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).
- supplied in 4, 12, 16 & 20 mg **tablets**
- dosage: 4 mg/d → titration weekly up to 24-64 mg/d.
- administered $\times 2-4/d$.
- **therapeutic blood levels**: 100-200 $\mu\text{g/mL}$.

ADVERSE EFFECTS

- asthenia, nervousness, dizziness, GI upset.

GABA transaminase inhibitors**VIGABATRIN (VGB)** (Sabril®)

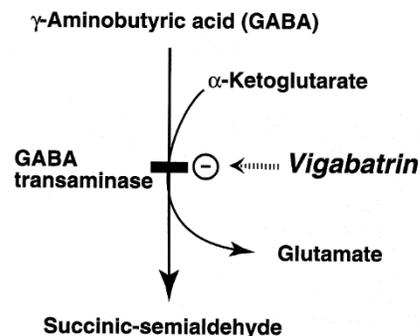
- irreversibly inhibits extracellular **GABA transaminase**.

- 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 up to 4000 mg/d (in children, 40 \rightarrow 100 mg/kg/d).
- poor correlation between plasma levels and clinical effect.

ADVERSE EFFECTS

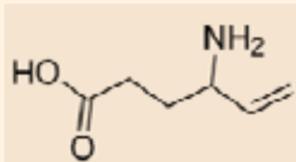
1. Drowsiness, dizziness, **neuropsychiatric symptoms** - depression (5%), agitation (7%), confusion, psychosis.
 - little effect on cognitive function!
2. Irreversible **visual loss** (nasal constriction \rightarrow concentric constriction, with preservation of central vision) in 15-50% of cases.
 - 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.

Vigabatrin

12

Background :

- Analog of γ -amino butyric acid (GABA), gamma vinyl GABA:



http://www.medchemexpress.com/product_pic/Vigabatrin.gif

- FDA Approval on 8/21/09:
 - Adjunctive therapy for refractory complex partial seizures in adults
 - Monotherapy for pediatric patients aged 1 month – 2 years with infantile spasms for whom potential benefits outweigh potential risk of vision loss.

Mechanism of Action :

- Irreversibly inhibits GABA transaminase, the enzyme responsible for catabolism of GABA in presynaptic terminals and glial cells.
- Also inhibit the vesicular GABA transporter and increases extracellular [GABA] in the brain.

Rogawski MA, et al, Nat Rev Neuro. 5(7):553-64; Bialer M & White HS, Nature Reviews Drug Discovery 2010. 9, 68-82.

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®, Depakote®)

Available as **VALPROIC ACID** (Depakene®) and **DIVALPROEX SODIUM** (Depakote®).

(severe GI upset and short half-life make valproic acid much less useful than divalproex sodium)

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** (FDA approved for migraine prophylaxis)

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 µg/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).
- IV dosage: 30 mg/kg IV bolus \rightarrow 3 mg/kg IV over 60 min q6hrs
- **therapeutic blood levels** 50-150 µg/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]**↓ - may be cause of hepatotoxicity!
H: L-carnitine 50-100 mg/kg/d.
- case reports of **hyperammonemia**.
- dose-related **nausea** and **vomiting** (H: enteric-coated preparations).
- hyperphagia, **weight gain**.
- **sedation, ataxia, tremor** (H: β -blocker).
- **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 – important for surgical patients!
- **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!) – correlation between peak VA levels and risk of NTDs has been found (if VA must be used, some experts recommend changing from BID to TID dosing).

GABAPENTIN (GBP) (Neurontin®, Horizant®, Gralise®)

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* (esp. absences).
- has **analgetic** properties in **central pain disorders**.

PHARMACOKINETICS

- bioavailability < 60% (variable absorption depends on L-amino acid transporter); ↓20% 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.
- excreted in urine entirely unchanged; not metabolized, does not induce hepatic enzymes.
- *No drug interactions!*
- $T_{1/2}$ = 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 ×3/d.
- dosage 300 mg/d → titrated to maximum 4800 mg/d.
- **therapeutic blood levels** > 2 µg/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).

- not known to be teratogenic.

GLUTAMATE receptor blockers

FELBAMATE (FLB, FBM) (Felbatol®)

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

Approved in USA in 1993.

- blocks NMDA receptors and voltage-gated **Ca²⁺-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 - **potent metabolic inhibitor**.
 - [felbamate] is significantly increased by VPA!!!
 - felbamate increases [PHT], [VPA], [CBZ] (but increases [epoxide metabolite]) – decrease doses of those by 20-33% (“by third”) if used together with FBM.
- $T_{1/2}$ = 13-30 hours.

- available in **tablets** (400 mg, 600 mg) and **suspension** (600 mg/5 mL).
- administered $\times 2-4/d$.
- dosage 1200 mg/d \rightarrow titration biweekly in 600 mg increments up to 3600 mg/d (max: 45 mg/kg/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** usually discovered after 5-30 wks of therapy (fatalities reported).

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

Due to unacceptably high rate of **aplastic anemia** and **hepatic failure**, FBM should not be used except in those circumstances where benefit clearly outweighs risk (patient should *sign informed consent* release); then, hematologic consultation is recommended by manufacturer.

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) adjunct to other drugs in treating refractory **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% !!!
 - increases [PHT] by up to 25%.
 - 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).

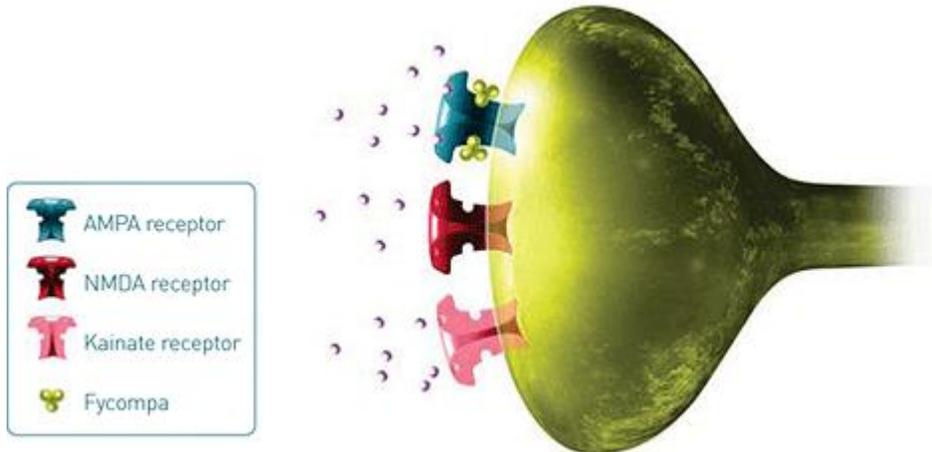
- therapeutic blood level 2-20 $\mu\text{g/mL}$.

ADVERSE EFFECTS

- CNS - impaired concentration, dizziness, ataxia, diplopia, somnolence, nervousness, confusion.
- GI – nausea, appetite suppression → weight loss.
- renal stones (1.5%) – due to carbonic anhydrase inhibition. H: drink plenty of fluids.
- oligohidrosis (reduced sweating) and hyperthermia, primarily in children.
- increased risk of development of cleft lip / cleft palate in infants born to women treated with topiramate during pregnancy (Pregnancy Category D).

PERAMPANEL (Fycompa®)

- highly selective, noncompetitive AMPA receptor antagonist
- FDA approved for partial onset seizures in patients ≥ 12 years.
- at therapeutic levels there is no impact on NMDA or kainate:

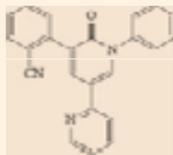


- 30% eliminated in urine, 70% in feces.
- $T_{1/2} \approx 105$ hours.

Perampanel

Background :

First-in-class α -amino-3-hydroxy-5-methyl-4-isoxazole propionic acid (AMPA) ionotropic glutamate receptor antagonist.



Bialer M & White HS, Nature Reviews Drug Discovery, 2010, 9, 68-82.

Approved in the EU, currently under review by FDA for the treatment of partial-onset seizures.

Mechanism of Action :

- Selective, non-competitive antagonist of neuronal AMPA receptors.
- Reduces fast excitatory signaling in the brain critical to generation & spread of epileptic activity.

Bialer M & White HS, Nature Reviews Drug Discovery 2010, 9, 68-82 ; Nat Rev Neurol. 2012; 8(10):534; Kraus GL et al., Neurol. 2012, 78(18): 1408-15; Rogawski MA, Epilepsy Curr. 2011, 11(2):56-63.

CENOAMATE (Xcopri®)

- FDA approved for partial-onset seizures in adults.

5-HT_{2B} Receptor Agonists

FENFLURAMINE (Fintepla®)

6/26/20 FDA approved for the treatment of seizures associated with Dravet syndrome in patients 2 years of age and older.

N.B. there is an association between serotonergic drugs with 5-HT_{2B} receptor agonist activity and **valvular heart disease and pulmonary arterial hypertension**. Echocardiogram is required before, during, and after treatment with FINTEPLA.

Carbonic Anhydrase Inhibitors

Anti-epileptic effect may be due to:

- direct inhibition of CNS carbonic anhydrase (also reduces CSF production)
- slight CNS acidosis: intracellular H^+ \uparrow (pH \downarrow) \rightarrow K^+ shifts to extracellular compartment (to buffer acid-base status) \rightarrow hyperpolarization.

ACETAZOLAMIDE (ACT) (Diamox®)

- adjunctive in refractory seizures:

- centricephalic epilepsies (absence, nonfocal seizures)

b) **catamenial** (i.e. seizure clustering around menstrual period).

- sulfonamide!
- paresthesias - medication should be discontinued.
- dosage: 8-30 mg/kg/d in divided doses (max 1 gm/d, higher doses do not improve control).
- if given with another AED, suggested starting dose is 250 mg once daily → gradually increased.
- supplied: **tablets** 125, 250 mg; also **sustained release capsules** 500 mg (Diamox sequels®); also 500 mg vials for IV use.

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 IP₃-sensitive stores without reducing Ca^{2+} storage.

THERAPEUTIC USES

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

- works well for myoclonic seizures.
- 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, and 1000 mg) and **IV formulation** (5 mL vial contains 500 mg).
- administered $\times 2/d$.
- dosage: 20 mg/kg IV load → 500 mg $\times 2/d$ (up to 3000 mg/d).
- linear pharmacokinetics - **no level monitoring needed**.

ADVERSE EFFECTS

Very well tolerated!

Most significant adverse effects - somnolence, fatigue/asthenia, dizziness, headache, pharyngitis, flu-like syndrome. Rarely – hyponatremia.

BRIVARACETAM (Briviact®)

MECHANISM OF ACTION

- precise mechanism is not known.

- displays high and selective affinity for synaptic vesicle protein 2A (SV2A) in brain - may contribute to anticonvulsant effect.

THERAPEUTIC USES

- indicated as adjunctive therapy in treatment of **partial**-onset seizures in patients ≥ 1 month old.

PHARMACOKINETICS

- available: PO, IV
- rapidly and almost completely absorbed after oral administration - tablets, oral solution, and injection can be used interchangeably.
- metabolized by hydrolysis of amide moiety by hepatic and extra-hepatic amidase.
- excreted in urine.
- terminal plasma $T_{1/2} = 9$ hours.
- dosage: 50 mg twice daily; gradual dose escalation is not required; may be adjusted down to 25 mg twice daily (50 mg per day) or up to 100 mg twice daily (200 mg per day).
 - for all stages of *hepatic impairment*, recommended starting dosage is 25 mg twice daily; maximum dosage is 75 mg twice daily.

ADVERSE EFFECTS

Psychiatric side effect profile is better than with LEV!

- most common adverse reactions - somnolence/sedation, dizziness, fatigue, and nausea/vomiting.
- Pregnancy Category C.

DRUG INTERACTIONS

- **rifampin**: because of decreased BRIVIACT concentrations, increasing BRIVIACT dosage in patients on concomitant rifampin is recommended.
- **carbamazepine**: because of increased exposure to carbamazepine metabolite, if tolerability issues arise, consider reducing carbamazepine dosage in patients on concomitant BRIVIACT.
- **phenytoin**: because phenytoin concentrations can increase, phenytoin levels should be monitored in patients on concomitant BRIVIACT.
- **levetiracetam**: BRIVIACT had no added therapeutic benefit when coadministered with levetiracetam.

PREGABALIN (Lyrica®)

MECHANISM OF ACTION

- *lipophilic structural GABA analogue*.
- does not bind to GABA or benzodiazepine receptors - *not functionally related to GABA* (i.e. does not directly affect GABAergic system).
- binds with high affinity to alpha-2-delta site (auxiliary subunit of **voltage-gated Ca channels**) in CNS tissues \rightarrow reduces (but doesn't block) depolarization-induced Ca^{2+} influx \rightarrow **reduced Ca-dependent release of excitatory neurotransmitters** (e.g. glutamate) \rightarrow *antinociceptive* and *antiseizure* effects.

THERAPEUTIC USES

- potent *anticonvulsant*, *analgesic*, and *anxiolytic* activity.
- FDA approved adjunctive therapy for **partial** seizures (with or without secondary generalization).

- FDA also approved for **neuropathic pain**: *diabetic peripheral neuropathy, postherpetic neuralgia, fibromyalgia, spinal cord injury (traumatic or nontraumatic)*. see p. S20 >>

PHARMACOKINETICS

Very clean pharmacokinetic profile! No significant drug interactions!

- rapidly and extensively absorbed (oral bioavailability > 90%).
- easy diffusion across BBB
- $T_{1/2} = 6$ hours.
- does not bind to plasma proteins.
- not metabolized (does not induce or inhibit liver enzymes) - excreted (> 90% unchanged) by kidneys (decrease dose with renal impairment!).
- dosage: 150-600 mg/d divided $\times 2/d$.

ADVERSE EFFECTS

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

- increased risk for suicidal thoughts or behaviors

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. lollypop, 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).
- oral POTASSIUM CITRATE supplementation may help prevent kidney stones in children who receive ketogenic diet.
- responder rate (50% reduction in seizures):

Type of seizures	VNS	Callosotomy	Ketogenic diet
atonic and/or other generalized seizures	51.7%	53.5%	62.5%
focal seizures	52.9%	55.8%	56%

FISH OIL (N-3 FATTY ACIDS)

DeGiorgio CM "Fish oil (n-3 fatty acids) in drug resistant epilepsy: a randomised placebo-controlled crossover study." J Neurol Neurosurg Psychiatry. 2014 Sep 8.

Low-dose fish oil (3 capsules/day, 1080 mg eicosapentaenoic acid+docosahexaenoic acid) was associated with a **33.6% reduction in seizure frequency compared with placebo**. Low-dose fish oil was also associated with a mild but significant reduction in blood pressure. High-dose fish oil was no different than placebo in reducing seizures or improving cardiac risk factors.

In this phase II randomised crossover trial, low-dose fish oil was effective in reducing seizures compared with placebo. The magnitude of improvement is similar to that of recent antiepileptic drug trials in drug resistant epilepsy (DRE). The results indicate that low-dose fish oil may reduce seizures and improve the health of people with epilepsy.

CANNABIDIOL (CBD) (Epidiolex®)

- nonpsychoactive ingredient in marijuana.

- mechanism of action – unknown.
- FDA-approved indications:
 - 1) tuberous sclerosis complex (TSC) in patients ≥ 1 year
 - 2) Lennox-Gastaut syndrome (LGS)
 - 3) Dravet syndrome (DS)
- reduces seizure rate by about 30% (50% reduction in seizures in 39% of patients); other study - reduction of total number of seizures by median of 38% at 3 months and 31% at 6 months.
- it is just another drug (if adding as a 3rd agent, seizure freedom chances only 4-6%).
- check AST, ALT, total bilirubin – at start, at 1, 3, 6 months.
- T_{1/2} 56-61 hrs
- start at 5 mg/kg/d divided BID for 1 week → increase to 10 mg/kg/d (if needed, may go up to 20).

Patients may be misled by some of the hype surrounding medical marijuana, said Dr. Uliel-Sibony (UCSF): "Patients believe they're getting something natural, something that isn't really a chemical, but CBD is a medicine like any other."

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