Current Diagnosis and Treatment of Epilepsy

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A. Objectives:

1. To learn the two major classes of Seizure types (focal-onset, generalized-onset) and how to recognize the 10 subtypes.
2. To recognize the existence of over 40 spontaneously occurring Epilepsy Syndromes.
3. To understand that antiepileptic drugs (AEDs) benefit, but can worsen, certain seizure types and certain epilepsy syndromes, and that treatment success often depends on matching the correct AED to the patient’s specific seizure type and epilepsy syndrome.
4. To become familiar with the pharmacology of the 23 AEDs.
5. To learn when to order EEGs and EEG-video monitoring to diagnose the Seizure type (including psychogenic or physiologic non-epileptic “seizures”) and Epilepsy Syndrome.
6. To recognize that surgery for epilepsy should be considered early in refractory patients.

B. Epilepsy Diagnosis and Therapy

1. 2010 International Classification of Seizures¹.
Seizures are simply signs and symptoms of either one of the 40+ types of Epilepsy (see below) or a variety of drugs, poisons, fever or other factors affecting the brain. Based on the clinical signs occurring during seizures, and the EEG findings between and during seizures, one can classify seizures according to the International Classification of Seizures:

I. Focal-onset Seizures (formerly “partial”)

A. Focal Seizures Without Impaired Awareness
   Consciousness is normal. Motor or autonomic visible signs, or sensory or psychic symptoms occur as a paroxysmal event in a stereotyped way. These vary greatly between patients depending, in part, on the brain areas involved in the seizure discharge. Patients usually mistakenly call these pre-seizure “auras.” Can be referred to as “focal motor” et cetera. Formerly called, “simple partial seizures.”

B. Focal Seizures With Impaired Awareness
   Often begin as focal seizures without impaired awareness, then progress to altered (not absent) consciousness and often include orolalimentary, hand/arm, trunk or leg automatisms. They are followed by postictal amnesia. Formerly, “psychomotor or complex partial seizures.”

C. Focal seizures evolving to bilateral tonic, clonic or tonic-clonic convulsions
   When a focal seizure spreads to the whole brain, it becomes a convulsion. Rarely, they are hemiclonic. These are known by the archaic colloquialism “grand mal” (“grand maladie” means “big illness” in French). The tonic (increased flexor or extensor “tone”) and clonic (“claw”-like jerking) movements are often asymmetric and asynchronous on the left and right sides.
II. Generalized-onset Seizures (Convulsive and Nonconvulsive)

A. Tonic-Clonic (TCS, “convulsion”)
   The difference from focal-onset TCS is that these begin suddenly without warning and evolve almost perfectly symmetrically and synchronously.

B. Absence seizures (typical and atypical forms)
   i. Typical absence (true “petit mal”) seizures suddenly interrupt movement, speech and behavior causing the child or adult to halt everything as if pushing a pause button on a recorder. The ictal EEG shows 3/sec spike-and-slow-wave complexes diffusely over the brain. The typical absence seizure ends abruptly with resumption of normal behavior. If brief, the patient is usually unaware of the absence.
   ii. Atypical absence seizures are seen in mentally retarded persons along with other seizure types listed below and are associated with slow EEG background frequencies and 1.5-2.5/sec spike-and-slow-wave epileptiform discharges.
      iii. Myoclonic absence.
      iv. Eyelid myoclonia.

Because the term “petit mal” is used too loosely to describe anything less than a “grand mal” convulsion (even to describe SPS and CPS), the terms petit mal and grand mal are abandoned.

C. Myoclonic
   These are sudden, migratory muscular jerks during wakefulness.
      i. Myoclonic.
      ii. Myoclonic atonic.
      iii. Myoclonic tonic.

D. Clonic

E. Tonic
   These are seizures causing sudden increase of tone in trunk or limb muscles. They can be flexor, extensor, or a combination of the two. They occur almost exclusively in mentally retarded patients. They result in falls, and are the most common seizure type causing “drop attacks” in Lennox-Gastaut Syndrome.

F. Atonic
   These are seizures causing sudden loss of tone in all postural muscles. They occur almost exclusively in mentally retarded patients. They result in falls, but are not the most common seizure type causing of “drop attacks.”

III. Unknown onset: Epileptic spasms (formerly, infantile spasms)

2. 2006 Proposed Classification of Epilepsies and Epilepsy Syndromes.
   Based on etiology, family history, seizure type, physical examination, imaging and other studies it is possible to classify >40 syndromes. In many cases, repeated EEGs and EEG-video monitoring are needed for diagnosis. Selected types are:

I. Localization-related syndromes
   A. Idiopathic
      • Benign childhood epilepsy with centrotemporal spikes
   B. Symptomatic (to known cause/lesion)
      • Temporal lobe epilepsies (mesial, lateral)
      • Frontal lobe epilepsies (several locations)
      • Parietal lobe epilepsies
      • Occipital lobe epilepsies
II. Generalized syndromes
   A. Idiopathic (most are hereditary)
      • Benign neonatal familial convulsions (chr. 20q13.3 & 8q24, K+ channel defect)
      • Childhood absence epilepsy (0.1% incidence, glutamate receptor defect)
      • Juvenile absence epilepsy (0.03% incidence, glutamate receptor defect)
      • Juvenile myoclonic epilepsy (chrom. 6p & others, AD, 0.05% incidence)
      • Progressive myoclonic epilepsies: Baltic myoclonus (chr. 21q22.3, cystatin B protein,12 nucleotide repeat expansion); MERRF; Lafora body disease (AR)
      • Generalized epilepsy with febrile seizures plus (chr. 2q24, Na+ channel defect)
   B. Cryptogenic/Symptomatic (hidden/known cause)
      • West syndrome (infantile spasms)
      • Lennox-Gastaut syndrome
      • others: Doose syndrome, Ohtahara syndrome

III. Mixed
   • Continuous spike-waves in slow sleep
   • Acquired epileptic aphasia (Landau-Kleffner syndrome)

IV. Special Situations
   • These do not represent epilepsies: febrile seizures (feb 1-6 genes; chr. 8q, chr. 19p, others; AD; Na+ channel defect), isolated seizures or status epilepticus, and seizures due specifically to other transient medical conditions (alcohol, drugs, eclampsia, toxic/metabolic states, etc.).

3. Approved Antiepileptic Drug (AED) Choices:

   A. Simple and Complex Partial Seizures (with/without Generalization):
      Monotherapy or Adjunctive Therapy:
      • First line: carbamazepine, lamotrigine, oxcarbazepine, phenytoin, topiramate, valproate
      • Second line: phenobarbital, primidone
      • Third line: felbamate
      Adjunctive Therapy Only:
      • First line: ezogabine, lacosamide, levetiracetam, pregabalin, tiagabine, zonisamide
      • Second line: vigabatrin, rufinamide?, clobazam?
      • Less effective: acetazolamide, clorzepate, gabapentin

   B. Absence Seizures:
      • First line: ethosuximide, methsuximide, phensuximide, valproate
      • Second line: acetazolamide, clobazam?, lamotrigine, levetiracetam?, rufinamide?, zonisamide?

   C. Myoclonic Seizures
      • First line: clonazepam, levetiracetam, valproate
• Second line: acetazolamide, clobazam, ethosuximide, lamotrigine, phenobarbital, primidone, rufinamide?, zonisamide

D. Generalized Tonic-Clonic Seizures (in primary generalized epilepsies)
• First line: lamotrigine, levetiracetam, topiramate, valproate
• Second line: phenobarbital, phenytoin, primidone, zonisamide?

D. Juvenile Myoclonic Epilepsy
• First line: clonazepam, levetiracetam, valproate
• Second line: lamotrigine, rufinamide?, topiramate, zonisamide

E. Lennox-Gastaut Syndrome
• First: clobazam*(drop attacks), clonazepam, lamotrigine*, levetiracetam, rufinamide*, topiramate*, valproate, zonisamide
• Second: felbamate*

F. West Syndrome
• First line: ACTH, valproate, vigabatrin

4. Pharmacology of the most commonly used AEDs (alphabetical).

A. Acetazolamide (Diamox™)
Acetazolamide is a sulfonamide whose mechanism of action is to inhibit carbonic anhydrase. It is completely excreted by the kidneys; it has minimal drug interactions. It is 90-95% protein bound. Its $T_{1/2}$ is 10-12 hours. It is a second line drug owing to low efficacy. Indications are absence and generalized tonic-clonic seizures. It may occasionally be helpful with menstrually-related (catamenial) seizures. Tolerance often develops rapidly to the antiepileptic effect. Adverse effects include: rash, transient somnolence, altered taste (carbonation), distal paresthesias, and renal stones. Typical dose range: 250-750 mg/day.

B. Adrenocorticotropic Hormone (ACTH, Acthar® gel)
Injectable adrenocorticotropic hormone 80 U/ml, a porcine extract. Indication: FDA approved 12/2010 for treating epileptic spasms in children under age 2. Effective in unknown and symptomatic cases. Originally approved by FDA in 1952 for MS and nephrotic syndrome. One 1996 study showed 13/15 infants responded to ACTH and 4/14 responded to prednisone. Side effects: Cushingoid appearance, infection, hypertension, irritability, acne. Less with 75 U/m² BID than 150 U/m² daily

C. Carbamazepine (Tegretol™, Tegretol XR™, Carbatrol™)
This drug (CBZ) is related to tricyclic antidepressants. Mechanism of action: enhances rapid inactivation of Na⁺ channels thereby decreasing rapid, repetitive neuronal firing. It also blocks L-type fast Ca²⁺ channels.
It is a classic hepatic enzyme inducer. It is unique in that it undergoes autoinduction (CYP3A4) over 2-3 months necessitating very low starting doses (2-3 mg/kg/d). Like other classic liver-inducing AEDs (PHT, PB) it markedly enhances the metabolism of oral contraceptives, warfarin and other drugs. CBZ metabolism is markedly decreased by some drugs (macrolides, propoxyphene). It is 75% bound to serum proteins. These
factors cause drug interactions. Its $T_{1/2}$ is 14 hours. It is effective for partial seizures which do, or do not secondarily generalize. It can be effective against some primarily generalized seizure types, but can worsen absence and myoclonic seizures in some cases. Dose range: 300-2400mg/day (tid- qid; bid for extended release formulations). Therapeutic range is 4 - 12 $\mu$g/ml, but clinical response is a more important indicator of dosage needs.

D. Clobazam (Onfi™)

Names: Onfi® (U.S.), Urbanyl®, Frisium.® U.S. FDA approval: October 24, 2011 for Lennox-Gastaut Syndrome (LGS). Effective on drop attacks in 2 studies on LGS* at 1.0 mg/kg/day (max 40 mg/day). Used in >100 countries for focal-onset seizures and LGS. GABA receptor agonist – a 1-5 benzodiazepine (hence the name, onfi “one-five”). AEs: sedation, fever, URI, drooling, constipation, cough, UTI, insomnia, aggression, fatigue, irritability, depression, vomiting, trouble swallowing, dyscoordination, bronchitis, and pneumonia.

E. Clonazepam (Klonopin™)

A benzodiazepine which binds to gamma aminobutyric acid type A (GABA-A) receptors containing a gamma subunit. GABA is the main inhibitory neurotransmitter. Binding of GABA to its receptor opens chloride channels on, therefore inhibiting function of, the postsynaptic neuron. Its $T_{1/2}$ is 24 hours. 80% protein bound CZP is effective for myoclonic seizures, but should be used as an adjunct to other AEDs such as valproate or phenytoin. Dose range: 1-20 mg/day (tid). Therapeutic range = 0.04-0.07 $\mu$g/ml. Adverse effects: somnolence, dizziness, depression, fatigue, dependence.

F. Diazepam (rectal Diastat AcuDial™; i.v., p.o. Valium™), lorazepam (Ativan™)

These are also benzodiazepines which bind GABA-A receptors with gamma subunits. They are effective against all seizure types in short-term use only. Lorazepam is preferred for i.v. use in status epilepticus, because it does not undergo redistribution back out of the brain 30 - 60 minutes after injection (as does diazepam). The 2012 RAMPART trial showed mild superiority of i.m. midazolam 10 mg to i.v. lorazepam 4 mg (Silbergleit et al. NEJM 2012). Lorazepam also has a shorter half-life in serum than diazepam due to less uptake into peripheral fatty tissue. Dose range: 2-10 mg/day for DZP, 1-2 mg/day for LZP. Adverse effects: somnolence, dizziness, depression, fatigue, tolerance, dependence. I.V. benzodiazepines may be administered with D5W, unlike hydantoins (phenytoin/fosphenytoin which must be given with saline).

Diatstat AcuDial™ was FDA approved 10/97 for rectal administration. It is a gel formulation with 90% bioavailability which reaches maximal absorption at 1.5 hours. Effective serum levels (>200 ng/ml) are reached in 30 minutes. It is not approved for status epilepticus, but is approved to treat patients age 2 and above who typically have clusters of seizures.

Benzodiazepine relative potency comparisons: diazepam 5 mg ~ lorazepam 2 mg ~ clonazepam 1 mg.

G. Ethosuximide (Zarontin™)

This is the most commonly used succinimide. Mechanism of action: reduces low-threshold T-calcium currents in neurons located in the nuclei of the thalamus. Its $T_{1/2}$ is 40 hours. It has linear pharmacokinetics at lower doses, but may have saturable kinetics in some patients at higher doses. It is mostly metabolized by CYP3A4. It is not
protein-bound, so the concentration in breast milk is close to the mother’s serum level. It is effective virtually only against absence seizures. It is the drug of choice for the absence epilepsies, but needs to be used with drugs effective against GTCS if they are also present. Dose range: 250-1500 mg/day (bid-tid). Therapeutic range = 40-100 µg/ml. Adverse effects: nausea, vomiting, abdominal pain, sedation, ataxia, leukopenia, pancytopenia, rash, Stevens-Johnson Syndrome.

Other succinimides, methsuximide (Celontin™) and phensuximide (Milontin™), are somewhat less effective against absence seizures and side effects are often worse (drowsiness and GI upset), but a few persons tolerate them better than ethosuximide.

H. Ezogabine (Potiga™)

I. Felbamate (Felbatol™)
This carbamate compound, related to meprobamate and carisoprodol was marketed in 8/93, but had its use restricted by the FDA in 8/94. Mechanism of action: may be inhibition of neuronal sodium and calcium channels. It is a hepatic enzyme inhibitor leading to increased levels of coadministered AEDs. Its T½ is 15-20 hours. The most common side effects are: headache, insomnia, abdominal pain or bloating, anorexia, weight loss and nausea. Usual dose range is 1200 -3600 mg/d divided into 3 doses. While approved for monotherapy treatment of partial seizures ages 4+ years, and children Lennox-Gastaut Syndrome in polytherapy, it is a third line agent due to serious toxicity. As of 12/5/96, 31 cases of possible aplastic anemia (AA), 10 fatal; and 16 cases of hepatic failure, 8 fatal, have occurred in well over 100,000 patients. An analysis in 1995 by Boston University suggests that not all reported cases met international criteria for AA, and in only 13 was felbamate possibly or probably etiologic. The mechanism of AA appears to be novel for felbamate. Research is ongoing. The drug is still used with: caution, periodic CBC and LFT monitoring, and after other drugs have failed. Doses of 3600 mg/d often produce levels of 62-104 µg/ml. A urine assay to measure the acid carbamate/mercapturic acid metabolite ratio is being studied as a possible clinical predictive test of those at risk for AA. Normally the ratio is 1-4; one patient with leukopenia had a ratio of 20. HLA antigen testing is also available; some HLA types may be associated with increased risk, and others of decreased risk, of AA.

J. Gabapentin (Neurontin™)
This unique compound was synthesized to mimic the molecular structure of GABA, but it does not act by a GABA-ergic mechanism. Mechanism of action: GBP binds the presynaptic α2-δ subunit of Ca2+ channel, and modulates (not blocks) Ca2+ currents, resulting in lower glutamate, noradrenaline, and substance P release into the synaptic cleft. It is 100% renally excreted. Its t½ = 6 hr. Pharmacokinetics are not linear
because it is carried from the gut and into the brain via an amino acid transport mechanism which is saturable. It undergoes no significant hepatic metabolism and is not protein bound. These features make the drug easy to use because it does not interact with other AEDs/medications. Its serum T1/2 is 6 hours, but CNS effects may be longer. It has been marketed as of 2/94 for adjunctive treatment of partial seizures with or without secondary generalization in patients over age 3 years. It is neither approved for, nor effective in, treatment of primary generalized epilepsies. The most common side effects are drowsiness, ataxia, dizziness, fatigue and nystagmus. Major adverse effects are quite rare at this time. The FDA approved dose range is 300-600 mg TID. These doses often yield serum levels of 4.0 -8.5 µg/ml. Some suggest GBP useful range is 15-25 µg/ml. Higher doses may yield improved seizure control but bioavailability decreases to 34% at 2400 mg/day, so serum levels rise little (zero-order kinetics). It is available as capsules, tablets, and a refrigerated solution.

**K. Lacosamide (Vimpat®)**

FDA approved 10/28/08 for adjunctive treatment of partial-onset seizures age 17 years and above. Lacosamide (LCM), previously known as SPM927 and harkoseride, has a novel proposed mechanism of action: enhancing sodium-channel slow inactivation. The former MOA causes a conformational change in the sodium channel pore and may be how LCM exerts its antiepileptic effect.

Pharmacokinetics are linear. T\( \text{max} \) is 1-4 hrs after oral administration. T\( \frac{1}{2} \) ~13 hrs; steady-state achieved in 3 days. Absolute bioavailability ~100%. Food does not affect rate and extent of absorption. Low inter- and intra-patient variability. No influence of gender or race (Asian, African-American, Caucasian) has been observed. 95% renally-excreted as unchanged drug or as metabolites (metabolized by CYP 2C19 through demethylation). Protein binding is low at <15%. No known drug interactions.

Two European and 1 US study led to approval (*Epilepsia* 2007;48:1308-17, 2009;50:443-453, and 2010;51:958-67). Responder rates were 40-49% at 400 mg/day vs. 18-28% for placebo. I studied it for Monotherapy for focal-onset seizures and the results are pending. I am enrolling patients in the SP982 genetic GTCS study. Some side-effects: diplopia, HA, nausea, dizziness, ataxia, syncope; possibly longer QTc. **Dose:** start at 50 mg BID (or qDay) and ascend to 200-400 mg/day given BID. For renal insufficiency with creatinine clearance <30 mL/min, maximum dose is 300 mg/day. 50% dose supplementation after hemodialysis is recommended. It is not recommended in severe hepatic impairment, or with severe heart disease or cardiac conduction defects. It is also available I.V. for use when oral dosing is not possible, but is not approved for treatment of status epilepticus. The i.v. solution can be mixed all solutions, infused over a minimum of 30 minutes, and has a 1:1 conversion to oral dosing. EKG PR intervals shorten slightly with oral or iv use (Biton et al. *Epilepsia* 2008). It is Schedule V. Useful plasma levels may be 4-8 mcg/ml.

**L. Lamotrigine (Lamictal®, Lamictal XR)**

Lamotrigine (LTG), a triazine compound, has anti-folate properties. **Mechanism of action:** LTG sodium channel rapid-inactivation, thereby decreasing the release of excitatory neurotransmitters, especially glutamate. LTG is hepatically metabolized. It induces valproate (25%) and its own metabolism, but has little effect on phenytoin or carbamazepine. Valproate significantly inhibits LTG metabolism. It is partially protein
bound. LTG has a T\textsubscript{1/2} of 25 hours in monotherapy or when used with VPA plus enzyme inducing AEDs (EIAEDs: PB, PHT, CBZ, PRM), 70 hours when taken with valproate alone, and 13 hrs when taken with EIAEDs. In the third trimester of pregnancy, serum LTG levels can fall 50-70% with large variability between patients; careful monitoring of serum levels is suggested. Oral contraceptives with 30 mcg estradiol and 150 mcg of progestins decrease serum LTG levels by 50%. Conversely LTG produces minimal effects on oral contraceptive levels. OXC and LEV have no effect on LTG clearance, but rifampin increases LTG clearance. Per the FDA, lamotrigine is pregnancy category C. Over 1300 monotherapy pregnancies have been reported to the manufacturer as of 12/08 and the major malformation risk is 2.3-2.6%. Polytherapy with valproic acid yielded a major malformation rate of 12.5% (Neurology 2005; 46 (S1): A119-120).

It is indicated for 1) adjunctive treatment of partial seizures with or without generalization in patients age 2 years and above, 2) treatment of patients with generalized seizures in Lennox-Gastaut Syndrome age 2+ years, 3) conversion to monotherapy in adults with partial seizures taking a single EIAED, and 4) as of 9/22/06, for add-on treatment for primary generalized tonic-clonic seizures (GTCS) in adults and children age 2+ years. Common side effects: dizziness, headache, diplopia, ataxia, nausea, blurred vision, somnolence, rash and vomiting. Above the recommended serum range, diplopia, dizziness, anxiety and insomnia can occur. Serious adverse events include severe, potentially fatal, rash (Stevens Johnson Syndrome, toxic epidermal necrolysis) in 1/1,000 adults and 1/50 - 1/100 children. Fatalities have occurred due to rash or multiorgan failure (these, of course, have occurred with the 4 major older AEDs many times as well). Benign rashes are seen in 10%, but because their course cannot be predicted, LTG should be stopped at the first sign of a rash. The risk of rash increases with concomitant VPA use, with too-rapid dose escalation, and by exceeding the initial dose recommendation. With concomitant use of valproate, the dose must be lowered by at least 50% and there is a higher incidence of rash. Usual dose range is 100-500 mg/d divided bid. This dose produces serum levels in the 1 - 5 µg/ml. Doses of 600-1000 mg and levels of 5-20 µg/ml are often more effective, but not FDA approved. It is available as regular, extended-release, and as chewable-dispersible and orally-disintegrating, tablets.

\textit{M. Levetiracetam (Keppra\textsuperscript{™})}

Levetiracetam (LEV) was approved 12/1/99. It is indicated for: 1. add-on (only) treatment for partial onset seizures ages 4+ years, 2. myoclonic seizures in Juvenile Myoclonic Epilepsy ages 12+ years, and 3. idiopathic (primary) GTCS ages 6+ years. It is a novel drug in the acetamide class related to piracetam. Oddly, it is ineffective in preventing seizures in several animal models of epilepsy (MES, mice kainic acid and pilocarpine), yet it prevents GTC seizures in rats given kainic acid or pilocarpine (mimic TLE). Also, LEV prevents kindling with electroshock or pentylenetetrazol. Animal studies suggest that it is effective against partial and generalized epilepsies. Human add-on studies show an approximate 40% responder rate (50%+ reduction) in partial seizures.

\textit{Mechanism of action:} completely unknown, but it does have a brain-specific synaptic vesicle (SV2A) binding site. It is mostly renally excreted (dose must be reduced in renal impairment), and its hepatic metabolism is not via the CYP450 system (undergoes hydrolysis). Thus, it has no interaction with other AEDs, oral contraceptives, digoxin and warfarin. Pharmacokinetics are linear. T\textsubscript{1/2} is 7 hours. Common side effects are:
somnolence, fatigue, asthenia, dizziness, anger, irritability and infection. Dose range is 1000 – 3000 mg/day, given bid. Useful serum levels appear to be 20-40 µg/ml. The intravenous form was approved for substitution for oral LEV in 2006.

**N. Methsuximide (Celontin™), Phensuximide (Phenurone™):**

Have similar structure and mechanism to ethosuximide. Indication: absence seizures. Side effect profile is worse than ethosuximide.

**O. Oxcarbazepine (Trileptal™)**

FDA approved 1/14/2000 for treatment of partial seizures with or without secondary generalization either as monotherapy in adults and children ≥4 years of age or adjunctive therapy ≥2 years of age. Oxcarbazepine (OXC) is structurally related to carbamazepine, but unlike the latter, which is oxidized to a 10,11- epoxide metabolite, OXC is extensively reduced to 10-monohydroxy derivative (MHD). The 10,11 - epoxide metabolite may account for some of the CNS toxicity sometimes seen with CBZ. MHD and OXC are both pharmacologically active, but because the T₁/₂ of OXC is 2 hours and the T₁/₂ of MHD is about 9 hours, the latter is responsible for most of the anti-seizure effects. **Mechanism of action:** OXC and MHD _in vitro_ produce rapid inactivation of voltage-sensitive Na⁺ channels, resulting in stabilization of hyperexcitable neuronal membranes, inhibition of repetitive neuronal firing, and decreased propagation of synaptic impulses. In addition, OXC increases K⁺ conductance and modulates M- and P/Q-type fast Ca²⁺ channels.

OXC is completely absorbed, and is rapidly reduced to MHD by hepatic cytosolic enzymes. MHD is further metabolized by conjugation with glucuronic acid. Metabolites of OXC are mostly renally excreted. Unlike CBZ, neither OXC nor any of its metabolites undergo autoinduction. The practical effect of this is that the drug can be brought to a maintenance dose much more quickly than can CBZ. Oxcarbazepine induces hepatic metabolism via the cytochrome P450 3A4 isozyme (CYP3A4), but it inhibits CYP2C19. OXC decreases the levels of oral contraceptives by roughly half, possibly rendering them less effective. At a dose of 1200 mg/day, oral contraceptive estrogen levels fall possibly making them less effective. At a dose of 2400 mg/day and above, serum phenytoin concentrations increase about 40%. Strong CYP450 inducers (e.g., carbamazepine, phenobarbital, and phenytoin) decrease OXC levels 29-40%. OXC is 40% plasma protein bound. It has linear pharmacokinetics.

Four randomized, double-blind trials established the efficacy of OXC monotherapy for the treatment of partial-onset seizures by demonstrating significant delays in meeting certain seizure-related exit criteria in patients receiving OXC compared to those receiving placebo, or low dose OXC. Two placebo-controlled, trials in adults and children with partial seizures demonstrated significant efficacy as adjunctive therapy as measured by median percent reduction of seizures. The drop out rate for adverse effects in the high-dose add-on studies was higher than in monotherapy, suggesting that tolerability may be better when OXC is used in initial monotherapy or that OXC may have important pharmacodynamic interactions when given with other AEDs.

The most common adverse effects (>5%) associated with OXC monotherapy have been dizziness, nausea, headache, diarrhea, vomiting, upper respiratory tract infection, constipation, dyspepsia, ataxia, and nervousness. Hyponatremia (<125 mmol/L) has
been observed in 2.5% of patients. Approximately 25-30% of patients with a history of hypersensitivity to carbamazepine will display hypersensitivity to OXC. Monitoring of hepatic function, BUN and complete blood counts is not required (physician discretion).

OXC is not soluble enough to be used intravenously, so only an oral form is currently available. Dosing varies according to age and use of other antiepileptic drugs (AEDs). For adults not receiving AEDs, it is recommended that one start at 300 mg BID for 1 week and then add 600 mg/day at weekly intervals (given BID) until reaching a maximum of 1200-2400 mg BID. TID dosing helps with tolerability in my experience. For adjunctive therapy in children aged 4 to 16 years, an initial dose of 8-10 mg/kg/day given BID (not to exceed 600 mg/day) is recommended. One must refer to the package insert for further dosing guidelines for children, and for adults who will have OXC added to their current AEDs and subsequently transition to OXC monotherapy. No dosage adjustment is required in mild-moderate hepatic impairment. The dose of OXC needs to be adjusted for renal impairment. MHD is not dialyzable, but its metabolites may be. A serum MHD level is available, and it is extremely important to avoid confusion with a CBZ level. If a CBZ level is erroneously measured in a patient receiving OXC, a low CBZ level will likely be reported because of partial cross-reactivity of the assay. Useful serum level appears to be 12-35 µg/ml. It is available as tablets or suspension.

P. Phenobarbital (generic only)

Synthesized in 1912 in Germany, this is the oldest of the currently used AEDs. 
Mechanism of action: all barbiturates bind GABA-A receptors nonspecifically. In this way they keep neuronal chloride channels open longer and inhibit cortical function. It is 45% protein bound in serum. Its T1/2 is 96 hours. PB is a hepatic enzyme inducer, accounting for significant drug interactions. It is hepatically parahydroxyalted and conjugated to glucuronide. Its metabolites are renally-excreted. Elimination is enhanced by diuretics, alkaline urine and activated charcoal, but is reduced by valproic acid.

It is effective for treatment of partial or generalized tonic-clonic seizures. It is the least expensive of all AEDs, but has the greatest side effects and is therefore a second choice agent. Adverse effects: sedation cognitive slowing, depression, rash Stevens-Johnson syndrome, nausea, tolerance, dependence. Therapeutic serum range = 15 - 45 µg/ml.

Q. Phenytoin (Dilantin™ [oral only]), fosphenytoin (Cerebyx™ for i.v., i.m.)

Found to be an AED in 1938. PHT is, by far, the most common of 2 hydantoin in current use; the other is ethotoin (Peganone™). Mephenytoin (Mesantoin) is no longer available in the U.S. Mechanism of action: enhances neuronal sodium channel rapid inactivation, thus preventing dysfunctional neurons from rapidly and repetitively firing to produce the paroxysmal depolarization shift.

Phenytoin is a classic hepatic enzyme inducer (see comments on CBZ), is metabolized by CYP 2C19, and is 90-95% protein bound in serum. These account for much of its drug interactions. Its T1/2 is 22 hours in adults, but is longer at higher doses and serum concentrations due to zero-order kinetics (metabolizing enzyme saturability). The latter causes exponential rises in serum levels at higher doses. Use of 30 mg Kapseals to finely titrate patients in the therapeutic range is indicated. Bioavailability of Kapseals, Infatabs, suspension and generic phenytoin vary. Dose range: 200-600 mg/day (bid-tid). Therapeutic range = 10-25+ µg/ml, but clinical response is what should primarily be used to guide therapy, not strict adherence to this range. It is
effective against partial or generalized tonic-clonic seizures, but is ineffective against absence or myoclonic seizures. Adverse effects: nystagmus, ataxia, dysarthria, cognitive slowing, gingival hyperplasia, hypertrichosis, rash, Stevens-Johnson Syndrome, lymphadenopathy, and pseudolymphoma.

As of 1/1/97, production of i.v. Dilantin ceased. Intravenous phenytoin may not be given i.m., must only be given with normal saline (or it precipitates as crystals requiring an in-line filter), must never be given > 50 mg/min to adults, requires BP and HR monitoring, and can cause thrombophlebitis and, rarely, “purple glove syndrome.” I.V. phenytoin may not be given i.m. because it crystallizes in muscle causing sterile abscesses.

Fosphenytoin, which replaced phenytoin, is the water soluble pro-drug of phenytoin and produces much fewer adverse effects. It can be given to adults at up to 150 mg/min. Because of the latter’s water solubility, it can be given in any i.v. fluids, and it should be remembered that it may also be given i.m.! EKG, and cardiovascular monitoring is still recommended for fosphenytoin, however. Generic phenytoin is still available, but not recommended by our Center. Fosphenytoin is dosed the same as phenytoin, but in mg P.E. (phenytoin equivalent) owing to the phosphate group on the molecule which causes a higher molecular weight. Phosphatase enzymes found widely in the body rapidly cleave the phosphate group leaving the active phenytoin molecule.

R. Pregabalin (Lyrica™)

Pregabalin was FDA approved June 2005 for add-on (adjunctive only) treatment of adult patients with partial seizures or neuropathic pain. Efficacy studies showed a 51% seizure responder rate at the highest dose. Mechanism of action: PGB was synthesized to mimic the molecular structure of GABA, but it does not act by a GABA-ergic mechanism. It binds the presynaptic α2-δ subunit of Ca2+ channel, and modulates (not blocks) Ca2+ currents, resulting in lower glutamate, noradrenaline, and substance P release into the synaptic cleft. It is 100% renally excreted. It is 100% renally excreted. Its t½ = 6 hr. Pharmacokinetics are linear at 75, 150 and 300 BID doses. It is classified as a category V substance. Oral bioavailability is >90% and independent of dose. It is not protein bound, and is renally excreted as unchanged drug. It undergoes negligible hepatic metabolism. It does not inhibit major CYP450 isozymes. It may exacerbate the effects of oxycodone, lorazepam or ethanol on cognitive and gross motor functioning. Common side effects are dizziness, dry mouth, somnolence, decreased attention/concentration, edema, blurred vision, and weight gain. It is available as 25, 50, 75, 100, 150, 200, 225, and 300 mg capsules. It is Schedule V.

S. Primidone (Mysoline™)

Primidone is hepatically metabolized to phenobarbital and both compounds are active. Mechanism of action: appears to bind and inhibit GABA-A receptors nonspecifically. It, too, is a hepatic enzyme inducer, but is <5% protein bound. Its T½ is 12 hours. It is effective against partial or generalized tonic-clonic seizures, but is a second choice for these due to cognitive side effects. Therapeutic range = 6-12 μg/ml (also measure derived phenobarbital).

T. Rufinamide (Banzel™)
FDA approved November 2008 for seizures associated with Lennox-Gastaut Syndrome ages 4 years and above. It is a triazole derivative, structurally unrelated to other drugs. Mechanism of action: enhances rapid-inactivation of sodium channel; no other known effects on receptors or channels. Absorption is slow (Tmax = 4-6 hr) and nonlinear: extent of absorption decreases with higher doses due to limited solubility, but is increased by food. 34% protein bound. It is metabolized by hydrolysis, not hepatic cytochrome P450 system, but it slightly induces CYP3A4. T ½ = 6-10 hours. Valproate increases serum concentration 16-70%. CBZ, PHT, PB and PRM decrease concentrations 19-45%. RUF decreases ethinyl estradiol by up to 22% at dose of 800+ BID. PK profile stable over ages 4-80 years. RUF 022 trial showed efficacy in LGS at 45 mg/kg/day vs. placebo with 32.7% vs. 11.7% median reduction of total seizures and 42.5% reduction vs. 1.4% increase in drop attacks (Glauser et al., Neurology 2008). We conducted an acute monotherapy study in pre-surgical patients, RUF 038. It, and other, studies showed efficacy in partial seizures (Brodie, Epilepsia 8/09), but it is not approved for this. Some more common side effects include: shortening of QT interval, headache, dizziness, fatigue, ataxia, somnolence and nausea. Rare serious AEs are: rash, multi-organ hypersensitivity and status epilepticus. Dosing is 10 mg/kg/day or 400 mg/day increasing to 45 mg/kg/day or 3200 mg/day (whichever is less) given BID. Useful plasma levels may be 5-22 mcg/ml.

U. Tiagabine (Gabitril™)
Approved by the FDA in October 1997 as adjunctive treatment of persons ages 12 and above for partial seizures with or without generalization. Mechanism of action: TGB is a selective GABA reuptake inhibitor (SGRI): inhibits reuptake of GABA from the synaptic cleft into neurons and glia. It is hepatically metabolized (CYP 3A4) with a half-life of 8 hrs in normal volunteers. Its metabolism is induced by PHT, CBZ, PB, and PRM. Doses with these AEDs need to be higher (up to 56 mg/d) than with VPA, GBP or LTG. VPA also causes 40% increase in free TGB concentration, due to high TGB protein binding. Usual dose range = 32-56 mg/day. Side effects are mostly sedation, cognitive slowing, dizziness, tremor, anxiety and nausea. They can be managed by slow upward titration and decreasing the dose. TGB therapeutic level range: 5-70 µg/ml

V. Topiramate (Topamax™)
This sulfamate-substituted monosaccharide, structurally related to fructose, was marketed in the U.S. in February 1997. It is approved for monotherapy ages 10+ years for partial-onset seizures or primary GTCS, and adjunctive-only treatment of adults and children ages 2+ years for: partial seizures with or without generalization, primary GTCS, and the Lennox-Gastaut Syndrome. Mechanisms of action: 1. enhances rapid-inactivation of voltage-activated sodium channels, 2. it enhances GABA-A mediated chloride channels on neurons, 3. is an antagonist at glutamate (excitatory; kainate and AMPA) receptors (kainate/AMPA), 4. modulates L-type Ca²⁺ currents, 5. potentiates K⁺ conductance and 6. functions as a weak carbonic anhydrase inhibitor. Seventy percent is excreted unchanged in the urine, and 30% is metabolized. It is only about 15% bound to plasma proteins. Pharmacokinetics are linear. T ½ is 21 hours, but decreases with enzyme inducing AEDs to about 15 hours. Serum levels are about 33% lower in children, 48% lower with phenytoin, 40% lower with carbamazepine, but no different in the elderly. It has little effect on serum levels of other AEDs, but at doses >200 mg/day it induces the metabolism of the co-administered estrogen component of oral contraceptives. It is recommended that dose initiation be at 25 mg/day with slow
titration up to a maximum of 400 mg/day in adults. Half dose is recommended in renal impairment.

Adverse effects include renal stones in 1.5%, paresthesias, cleft lip/palate in 1.4% of pregnancies (pregnancy category D) dizziness, ataxia, speech problems, nystagmus, nausea, somnolence, psychomotor slowing, nervousness, memory problems, acute angle-closure glaucoma, and blurred vision, decreased sweating, hyperthermia, and hyperchloremic (non-anion gap) metabolic acidosis among others. Serum levels are 15-25 µg/ml in the standard dose range. It is available in 25, 50, 100 and 200 mg tablet sizes, and sprinkle forms. It is recommended that patients drink plenty of fluids, especially in hot weather, to try to avoid some of these side effects.

W. Valproate /Divalproex sodium (Depakene/ Depakote™; i.v. Depacon™)

Mechanism of action: This fatty acid 1) enhances rapid-inactivation voltage-gated sodium channels, 2) affects calcium channels, 3) enhances GABA release, and 4) has other CNS effects. It is one of the AEDs that inhibit hepatic enzymes and it is 80-90% protein bound. Thus, it also has significant drug interactions. Its T1/2 is 15-20 hours. Its main indication is for the treatment of generalized seizures of all types; it is indicated in adults and children over age 9 as monotherapy or adjunctive therapy for the treatment of complex partial seizures with or without generalization. Dose range commonly is 500-6000 mg/day (bid-tid). Therapeutic range = 50 - 100 µg/ml, but at higher serum levels (or in the presence of certain drugs like aspirin) the free valproate percentage may increase dramatically and lead to toxicity.

Adverse effects: nausea, vomiting, abdominal pain, hyperinsulinemia leading to obesity, weight loss, tremor, alopecia, hyperammonemia. Reduced female fertility and polycystic ovaries have been reported. Serious side effects are hepatic failure (microvesicular steatosis with hyperammonemia) and pancreatitis. Several risk factors have been identified for this - see package insert. Major birth malformation rate = 10.7% in North American AED Pregnancy Registry. In the NEAD study (NEJM April 2009) 21% of offspring had subnormal intelligence at age 3 years and median full scale IQ = 92.

An i.v. form (Depacon) was approved May 1997 for short-term parenteral substitution for Depakote. It is used i.v. at the same total daily dose of Depakote, divided 4/day. It should be given i.v. (not i.m.) over 60 minutes (but not faster than 20 mg/min) in D5W, LR, or normal saline. It is not approved for treatment of status epilepticus.

X. Vigabatrin (Sabril™)

FDA approved 8/21/2009 for adjunctive therapy for West Syndrome (infantile spasms; IS) and adults with medically-refractory complex partial seizures (NOT as a first line drug). Numerous trials dating back 20 years showed efficacy in partial-onset seizures. FDA approval was based on two pivotal trials in West Syndrome (Elterman et al., Appelton et al.) and in complex partial seizures (Dean et al. Epilepsia 1999, and French et al. Neurology 1996). Mechanism of action: it is an irreversible inhibitor of GABA-transaminase, the degredative enzyme of GABA. This results in increased levels of GABA in the synaptic cleft. AEs: sedation, weight gain, and irreversible peripheral visual field constriction in 30-40% of patients. The latter is due to toxicity to retinal ganglion cells. Some patients can also experience alteration of central, macular, vision. Infants can show transient increased signal intensities on MRI in the basal ganglia, thalamus, brainstem and cerebellum. These are of unknown origin, and usually subside after drug discontinuation, and sometimes despite continued VGB therapy. Accordingly,
if an infant does not achieve meaningful reduction in infantile spasms within 2-4 weeks and if an adult does not have meaningful reduction of CPS within 3 months, the provider and patient should strongly consider discontinuing vigabatrin in order to potentially avoid further retinal damage. To prescribe, one must enroll in the SHARE program which requires baseline and quarterly visual perimetry and dispensing from a central national pharmacy. It is supplied as 500 mg tablets or powder sachets. Dose is 3000 mg/day, given twice daily. Measurement of plasma levels is not applicable owing to the mechanism of action.

Y. Zonisamide (Zonegran™)

Zonisamide is a non-arylamine sulfonamide derivative, so it is in a class different from the arylamine sulfonamide antibiotics like sulfamethoxazole. It has been used to treat partial and myoclonic seizures at ages 12 and above in Japan since 1989. It was FDA approved on 3/28/2000 for treatment of partial seizures in adults aged 16 years and older. *Mechanisms of action are* 1) enhances rapid-inactivation of sodium channels, 2) decreased voltage-dependent transient inward (T-type) calcium currents, 3) binding the GABA-benzodiazepine ionophore, 4) has mild carbonic anhydrase inhibiting effects, and 5) facilitates dopaminergic and serotonergic, but not GABAergic, transmission. Peak absorption is 2-6 hours; absorption is delayed by food. It block MES tonic seizures and raises the threshold for kindled rat seizures. It decreases the duration of focal seizures due to cortical stimulation. It has no effect on PTZ seizures.

ZNS is hepatically-metabolized via CYP 3A4 reduction to SMAP followed by enzymatic hydrolysis. T ½ is 69 hours in monotherapy, 27-38 hours with EIAEDs, and 46 hours with VPA. Usual dose for adults is 400-600 mg/d, starting at 100 mg/d and increasing by 100 mg/d every 2 weeks (due to long T ½). Serum levels increase disproportionately above 800 mg/d probably due to saturation of binding in RBCs. The useful serum range is 20-30 µg/ml. If the dose is escalated quickly, there is a 20% incidence of CNS side effects. Adverse effects: somnolence, dizziness, fatigue, nausea, anorexia, rhinitis, ataxia, headache, weight loss (10%). Because ZNS is a sulfonamide, severe hypersensitivity reactions, such as Stevens Johnson Syndrome and blood dyscrasias among others, have occurred rarely. There is a 1.2% incidence of symptomatic renal stones. It can cause metabolic acidosis, especially in kids.
## Antiepileptic Drug - useful serum levels

<table>
<thead>
<tr>
<th>AED</th>
<th>mcg/ml</th>
</tr>
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<tbody>
<tr>
<td>carbamazepine</td>
<td>4-14</td>
</tr>
<tr>
<td>clobazam</td>
<td>?</td>
</tr>
<tr>
<td>clonazepam</td>
<td>0.010-0.075</td>
</tr>
<tr>
<td>clorazepate</td>
<td>1.0-2.0 (nordiazepam)</td>
</tr>
<tr>
<td>ezogabine</td>
<td>?</td>
</tr>
<tr>
<td>ethosuximide</td>
<td>40-100</td>
</tr>
<tr>
<td>felbamate</td>
<td>60-180</td>
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<tr>
<td>gabapentin</td>
<td>15-25</td>
</tr>
<tr>
<td>lacosamide</td>
<td>4-20</td>
</tr>
<tr>
<td>lamotrigine</td>
<td>5-20</td>
</tr>
<tr>
<td>levetiracetam</td>
<td>10-50</td>
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<tr>
<td>methsuximide</td>
<td>10-40 (normethsuximide)</td>
</tr>
<tr>
<td>oxcarbazepine</td>
<td>10-35 (monohydroxy derivative)</td>
</tr>
<tr>
<td>phenobarbital</td>
<td>15-40</td>
</tr>
<tr>
<td>phenytoin</td>
<td>10-25</td>
</tr>
<tr>
<td>pregabalin</td>
<td>3-10</td>
</tr>
<tr>
<td>primidone</td>
<td>6-15, also derived phenobarbital</td>
</tr>
<tr>
<td>rufinamide</td>
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<tr>
<td>tiagabine</td>
<td>5-70</td>
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</tr>
<tr>
<td>zonisamide</td>
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</tbody>
</table>

David G. Vossler, MD FAAN - October 4, 2012
5. Surgery.

Surgery for epilepsy needs to be considered early in medically refractory patients with epilepsy. Epilepsy surgery is still vastly underutilized despite being available since the time of the American Civil War! Although retrospective and prospective nonrandomized cohort studies have shown is vast superiority to drug therapy for decades, the first randomized-controlled trial for temporal lobe epilepsy was completed only in 2000. The recently published results conclusively proved that temporal lobectomy should be performed after failure of only a few medications in optimal candidates. Patients with mesial temporal sclerosis with early onset seizures have extremely high seizure free outcome rates (often >75%), in marked contradistinction to the outcome with best medical therapy in two Class I randomized trials.

Combined, long-term EEG-video monitoring is crucial in selecting surgical candidates. Ambulatory EEG monitoring is an inferior technique. The selection and preoperative testing of candidates before surgery requires an Epilepsy Center with a specially-trained multidisciplinary team (epileptologist, functional neurosurgery, neuropsychology, social work, vocational counselor, psychiatrist). Specialized techniques are also required: digital EEG-video monitors with computerized EEG analysis, sphenoidal electrodes, intracerebral depth and subdural strip/grid electrodes, volumetric MRI, SISCOM, PET, intracarotid amobarbital test, specialized neuropsychological test battery.

Surgical techniques include:
A. Focal resection (partial lobectomy or corticectomy).
B. Modified hemispherectomy.
C. Corpus callosotomy.
D. Multiple subpial resection.
E. Vagus nerve stimulation therapy (FDA approved 7/97).

C. Bibliography

D. Related publications by the author


34. VOSSLER DG, Kraemer DLA, Haltiner AM, Morgan JD, Davis B, Rostad S, Kjos BO, Caylor LM. Intracranial EEG in temporal lobe epilepsy: Location of seizure onset relates to degree of hippocampal pathology. Epilepsia 2004;45:497-503.


51. VOSSLER DG, Bell A, Goldeshtein ZF. Patterns of seizure spread in lateral vs. medial temporal lobe epilepsy. J. Clinical Neurophysiology (IN PREPARATION)

Book Chapters:


