Epilepsy
Medical Treatment

Mahmoud Benour R3

Dr. N. Jette

- Special Thanks to Dr Jette for valuable presentations and articles.

Outline of presentation

- Definition of epilepsy
- Epidemiology and etiology
- Classification
- Seizure types
- Treatment
  - Medical
  - Alternative therapies for epilepsy

Outline of presentation

- AED in special situations:
  - Women, pregnancy
  - Elderly
  - Liver toxicity
  - Renal disease
  - Brain tumors
  - Traumatic brain injury

Definition of Epilepsy

Definition of Epilepsy

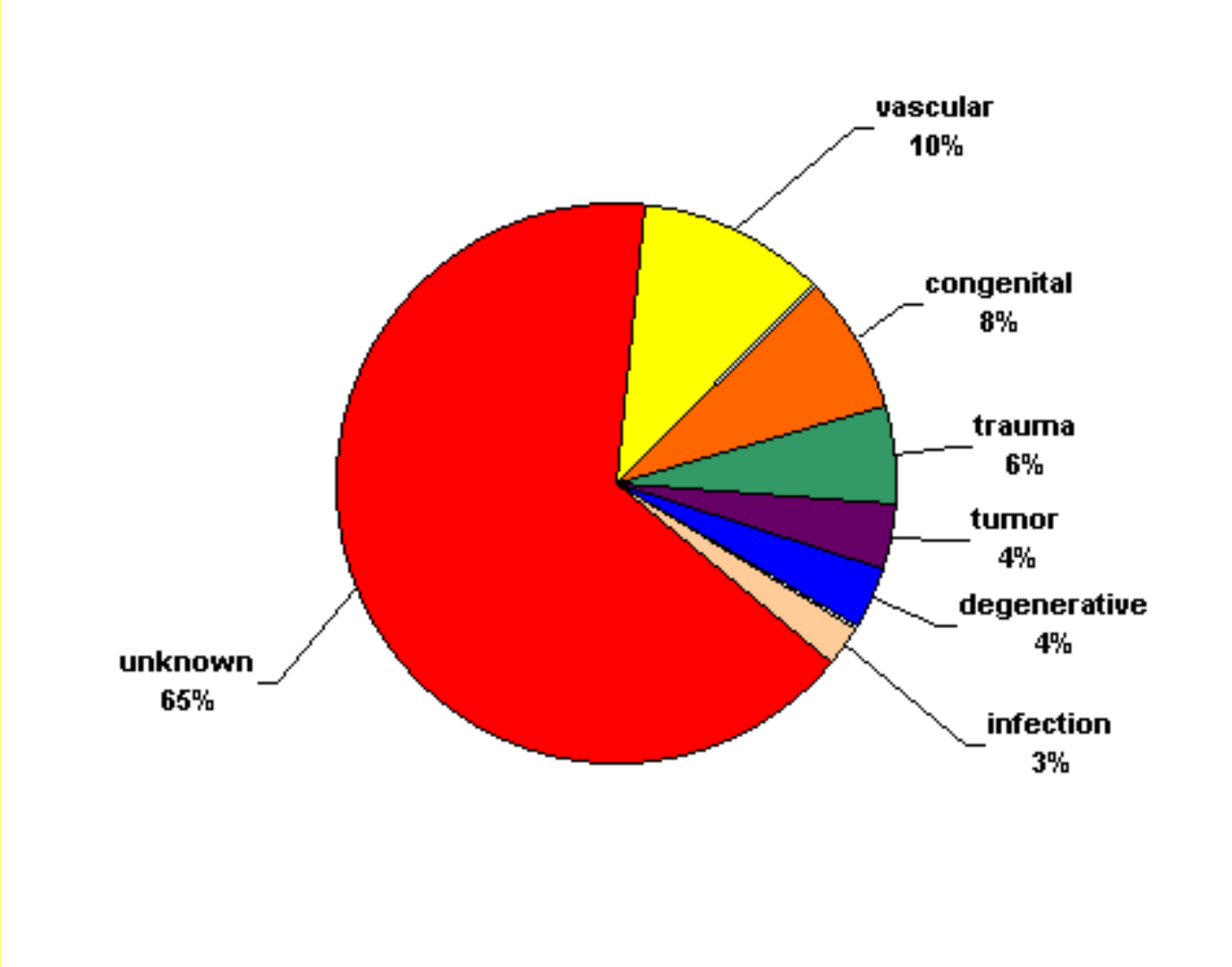
- Epilepsy is:
  - A chronic condition of various etiologies characterized by a predisposition to recurrent, spontaneous epileptic seizures.
  - A single seizure does not (usually) constitute epilepsy.
- An epileptic seizure is:
  - Abnormal and excessive discharge of brain neurons involving hypersynchrony, accompanied by some behavior change.

Epidemiology of Epilepsy

Epidemiology of Epilepsy

- 3rd most common neurologic disorder, following stroke and dementia.
- Prevalence: 1-2% of the population has active epilepsy.
- Incidence of epilepsy (Hauser et al 1993)
  - 44 per 100,000 person years
  - Higher in developing countries
- The chance of having at least 1 seizure during a person's lifetime is approximately 8-10%.

Etiology of Epilepsy

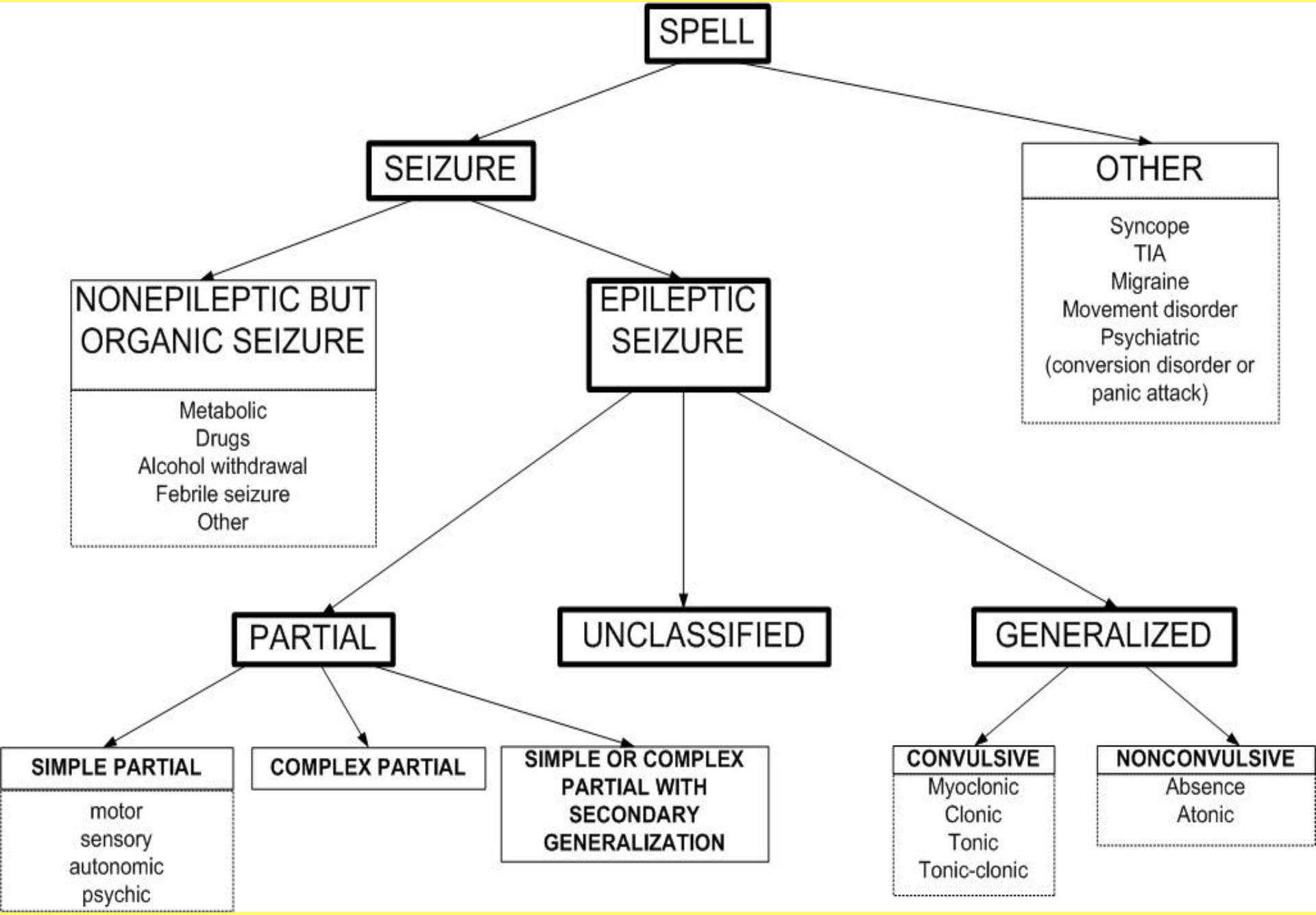


Hauser WA in Epilepsy: A Comprehensive Textbook (1997)

Precipitating Factors for Seizures

- Sleep deprivation
- Alcohol
- Flashing lights
- Stress
- Menstruation
- Recreational drugs
- Infection/fever
- Non-compliance with antiepileptic drugs
- Medication withdrawal (barbiturate or benzodiazepine withdrawal)

Classification of Seizures and Epilepsy Syndromes


SPELL
SEIZURE
OTHER
Syncope
TIA
Migraine
Movement disorder
Psychiatric
(conversion disorder or
panic attack)
NONEPILEPTIC BUT ORGANIC SEIZURE
Metabolic
Drugs
Alcohol withdrawal
Febrile seizure
Other
EPILEPTIC SEIZURE
PARTIAL
UNCLASSIFIED
GENERALIZED
SIMPLE PARTIAL
motor
sensory
autonomic
psychic
COMPLEX PARTIAL
SIMPLE OR COMPLEX PARTIAL WITH SECONDARY GENERALIZATION
CONVULSIVE
Myoclonic
Clonic
Tonic
Tonic-clonic
NONCONVULSIVE
Absence
Atonic

Epilepsy Syndrome

- Localization-related epilepsies and syndrome
  - e.g. Benign childhood epilepsy with centrotemporal spikes, temporal lobe epilepsies
- Generalized epilepsies and syndromes
  - e.g. Childhood absence epilepsy, juvenile myoclonic epilepsy, Lennox-Gastaut syndrome
- Undetermined epilepsies and syndromes
  - e.g. neonatal seizures, acquired epileptic aphasia (Landau-Kleffner syndrome)
- Special syndromes
  - e.g. febrile seizures, seizures occurring only when there is an acute metabolic or toxic event (alcohol, drugs, eclampsia, nonketotic hyperglycemia)

Examples of Seizures

1) Temporal Lobe Seizures

- Often preceded by an aura
  - Rising epigastric sensation, nausea, fear, etc.
- Prominent autonomic sx
  - Flushing, pupillary dilation, pallor, arrest of respiration, etc
- Often with automatisms (oral, manual or pedal)
  - Manual automatisms usually ipsilateral to epileptic focus in the brain, but can also be contralateral.
- May have dystonia (i.e. sustained muscle contractions that produce twisting or abnormal postures)
  - Dystonia of a limb is contralateral to epileptic focus in the brain
- Postictal cough or nose wiping (usually ipsilateral to focus)

2) Frontal Lobe Seizures

- Typically nocturnal
- Many seizures (tend to cluster)
- Short duration
- Vocalization can occur.
- Prominent motor manifestations
  - Bizarre bimanual/bipedal activity
  - Adversive head or eye deviation may occur.
- Minimal or no postictal confusion
- EEG frequently normal, even ictally (i.e. during a seizure).

3) Absence Seizures

- Typical onset ages 3-10
- Duration: 10-20 seconds
- Complete loss of consciousness
- Abrupt onset and offset
- Often multiple attacks in one day
- Up to 50% also get generalized tonic-clonic seizures
- May be associated with eyelid fluttering
- Childhood absence epilepsy usually remits in adolescence and typically responds well to treatment.

4) Myoclonic Seizures

- Sudden, brief, shocklike contractions
- Generalized or focal
- May be subtle or may make patient fall; patient may often drop things
- May be mistaken for tics
- Most commonly seen in patient with juvenile myoclonic epilepsy

Juvenile Myoclonic Epilepsy

- Inherited condition
- Myoclonic jerks, tonic-clonic seizures +/- absence seizures.
- Seizures usually occur after awakening in the morning.
- Usually responds well to treatment but lifelong treatment typically necessary.
- EEG shows a characteristic pattern with 4-6 Hz spike and wave pattern and multiple spike and wave complexes that may be precipitated by photic stimulation and sleep deprivation.

Generalized Tonic-Clonic Seizures

- Begins suddenly without warning (primary generalized epilepsy) or may be preceded by a warning (aura) if partial seizure with secondary generalization.
- Patient cries out (tonic contraction of trunk muscles causes forced expiration) → tonic phase (generalized stiffening) → clonic phase → end of seizure +/- incontinence
- Usually associated with increase in heart rate and blood pressure and lasts 1-2 minutes
- +/- tongue biting
- Confusion and fatigue always occur immediately after the seizure lasting generally about 5-10 minutes but may last longer (hours or days) in some.

CHARACTERISTIC	SYNCOPE	SEIZURE
Position	Usually upright (vasodepressor)	Any
Diurnal pattern	Daytime	Daytime or night-time
Colour	Pallor	Normal or cyanotic
Aura	Dizziness, nausea, visual blurring, light-headedness	Possible specific aura (e.g. rising epigastric sensation)
Onset	Gradual	Sudden or brief aura
Autonomic features	Common	May occur
Duration	Brief	Brief or prolonged
Injury	Rare	Can occur (tonic-clonic, atonic, myoclonic, tonic)
Urinary incontinence	Rare	More common
Disorientation (post-ictally)	Rare	Can occur with tonic-clonic, complex partial
Motor activity	Occasionally brief tonic seizure or clonic jerks (convulsive syncope)	Myoclonic, tonic-clonic, clonic
Automatisms	None	Can occur with complex partial seizures or rarely with absence seizures
EEG	Normal	Frequently abnormal, may be normal

.

Medical Management of Epilepsy

When to Start AEDs

- Consider seizure related risks:
  - Sudden death of epilepsy
  - Direct physical injury
  - Vehicular accidents
  - Brain damage
  - Secondary epileptogenesis

Consider Treatment:

- Abnormal EEG
- Known cause (tumor, stroke)
- Generalized tonic clonic seizure
- Risk occupation (driver, pilot, etc)
- No disease interfering with drugs

Do not treat

- Alcohol withdrawal
- Drug abuse
- Acute illness
- Post impact seizure
- Specific benign epilepsy syndrome
- Seizure from excessive sleep deprivation

List of AEDs

- phenobarbital 1912
- mephobarbital (Mebaral) 1935
- phenytoin (Dilantin) 1938
- trimethadione (Tridione) 1946
- mephenytoin (Mesantoin) 1947
- paramethadione (Paradione)* 1949
- phenthenylate (Thiantoin)* 1950
- phenacemide ((Phenurone) 1951
- metharbital (Gemonil)* 1952
- benzchlorpropamide (Hibicon)* 1952
- phensuximide (Milontin) 1953
- primidone (Mysoline) 1954
- methsuximide (Celontin) 1957
- Ethotoin (Peganone) 1957
- Ethosuximide (Zarontin) 1960

- diazepam (Valium) 1968
- carbamazepine (Tegretol) 1974
- clonazepam (Klonopin) 1975
- valproate (Depakene) 1978
- clorazepate (Tranxene) 1981
- felbamate (Felbatol) 1993
- gabapentin (Neurontin) 1993
- lamotrigine (Lamictal) 1994
- fosphenytoin (Cerebyx) 1996
- topiramate (Topamax) 1996
- tiagabine (Gabitril) 1997
- levetiracetam (Keppra) 1999
- zonisamide (Zonegran) 2000
- oxcarbazepine (Trileptal) 2000

*withdrawn from the market

Indication for AEDs

Partial seizures and GTCs

- phenobarbital
- phenytoin (Dilantin)
- carbamazepine (Tegretol, Carbatrol)
- gabapentin (Neurontin)
- tiagabine (Gabitril)
- oxcarbazepine (Trileptal)

Broad spectrum

- valproic acid (Depakote)
- felbamate (Felbatol)
- lamotrigine (Lamictal)
- topiramate (Topamax)
- zonisamide (Zonegran)
- levetiracetam (Keppra)
- Clobazam (Frisium)

Newer AEDs Indications

Preferred first-line AEDs for treatment of new-onset and refractory epilepsy in adults[a]

New-onset epilepsies	Refractory epilepsy
Partial epilepsies	
Carbamazepine	Pregabalin
Gabapentin	Zonisamide
Lamotrigine	Clobazam
Levetiracetam	
Oxcarbazepine	
Topiramate	
Valproate	
Idiopathic generalized epilepsies	
Lamotrigine	Clobazam
Topiramate	Levetiracetam
Valproate	

Recent evidence showing effectiveness in new onset epilepsy

Reproduced with permission from Elger C.E. and Schmidt D. Epilepsy and Behavior, 2008 (in press)

Side Effects of Newer AEDs

AED	Serious	Nonserious
Felbamate (Felbatol)	Aplastic anemia,* hepatotoxicity*	Anorexia, insomnia
Gabapentin (Neurontin)	None	Sedation, weight gain
Lamotrigine (Lamictal)	Stevens-Johnson syndrome*	Insomnia
Topiramate (Topamax)	Kidney stones, oligohidrosis, glaucoma	Parasthesias, cognitive impairment, weight loss
Tiagabine (Gabatril)	Spike-wave stupor	Tremor, sedation, impaired concentration
Levetiracetam (Keppra)	None	Sedation, behavioral changes
Oxcarbazepine (Trileptal)	Hyponatremia, rash	Ataxia, diplopia
Zonisamide (Zonegran)	Kidney stones, oligohidrosis, rash	Parasthesias, weight loss
Pregabalin (Lyrica)	None	Sedation, weight gain

*Black-box warning.

LaRoche, The Neurologist 13(3):2007

Clobazam: no known serious side effect. Nonserious side effects include sedation, behavioral changes, weight gain and rarely depression.

Most older AEDs = association with bone loss (carbamazepine, phenobarbital, phenytoin, valproate). There is not enough information regarding whether there is an association between the new AEDs and bone loss. Consider calcium and vitamin D supplementation in persons with epilepsy on AEDs.

A guide to AED selection…

Choice of AEDs to consider for different patient profiles, if possible[a]

Feature	Consideration
Efficacy for individual seizure and epilepsy syndrome	Prefer efficacious first-line agents (I)
Tolerability of AED? Any issues to be discussed	Prefer well tolerated first-line agents (I)
Older than 65 years	Prefer GBP or LTG over CBZ (I)
Male hypogonadism	Prefer GBP, LTG, OXC, and TPM over enzyme-inducing AEDs such as CBZ (III)
Body mass index > 25 kg/m^2	Prefer weight-neutral AEDs such as CBZ, LTG, and OXC over VPA, GBP, or PGN, or prefer TPM for weight loss (III)
Depression	Prefer CBZ, GBP, LTG, VPA, and TPM over PHT, PHB, or VGB (III)
Anxiety	Prefer GBP and PGB over LEV, PHT, PHB, or VGB (III)
Mood disorders	Prefer CBZ, GBP, LTG, VPA, and TPM over PHT, PHB, or VGB (III)
Cognition issues	Prefer CBZ, GBP, LTG, VPA, and OXC over PHB or PRM (III)
Lipid profile	Prefer OXC and TPM over CBZ (III)
Osteoporosis	Prefer GBP, LTG, and OXC over enzyme-inducing AEDs such as CBZ and VPA, which may activate osteoclastic activity
Current or future comedication	Prefer non-enzyme-inducing agents (III)
History of idiosyncratic reactions	Prefer AEDs that do not cause such reactions, such as GBP (I)

Enzyme inhibiting

Reproduced with permission from Elger C.E. and Schmidt D. Epilepsy and Behavior, 2008 (in press)

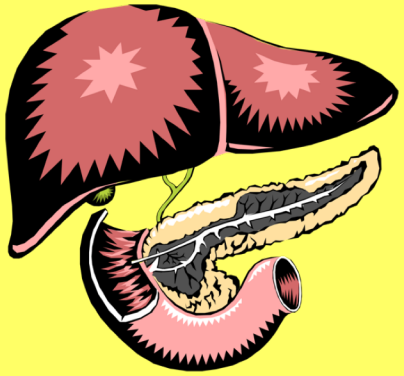
Pharmacokinetic Properties of AEDs

Drug	Protein binding (%)	Enzymatic activity	Will induce metabolism of OCP	Half life (hr)	Elimination route (%)	
					Renal	Liver
Carbamazepine	75	Broad spectrum inducer	Yes	9-15	1	99
Clobazam	83	Induces epoxidation	No	10-30	<5	>90
Clonazepam	85	Induces CYP2B	No	20-60	<5	>90
Ethosuximide	0	None	No	30-60	<20	>80
Felbamate	25	Induces CYP3A4 Inhibits CYP2C19	Yes	13-22	50	50
Gabapentin	0	None	No	5-7	100	0
Lamotrigine	55	Induces UGTs	Yes, minimally, progesterone component only	12-62	10	90
Levetiracetam	<10	None	No	6-8	100	0
Oxcarbazepine	40	Induces CYP3A4, UGTs Inhibits CYP2C19	Yes	9	1	99
Phenobarbital	45	Broad spectrum inducer	Yes	75-110	25	75
Phenytoin	90	Broad spectrum inducer	Yes	9-36	5	95
Pregabalin	0	None	No	5-7	100	0
Tiagabine	96	None	No	7-9	2	98
Topiramate	15	Induces CYP3A4 Inhibits CYP2C19	Only at doses > 200 mg/day	12-24	65	35
Valproate	90	Broad spectrum inhibitor	No	6-8	2	98
Vigabatrin	0	None	No	5-8	100	0
Zonisamide	40	None	No	63	35	65

Bolded drugs are considered the newer AEDs

AEDs and the liver

- Many antiepileptic drugs (AEDs) affect liver metabolism, and thus affect the way the P450 system works.
- AEDs can increase, decrease or have no effect on the P450 cytochrome system of the liver.



Enzyme inducing AEDs → Increase P450 function → Eliminate birth control faster = risk of birth control failure

AEDs and the oral contraceptive pill (OCP) – Bottom line

Use an OCP with at least 50 µg of ethinylestradiol in women on an enzyme inducing drug which has been found to interact with hormonal birth control.

Consider intrauterine device if too much interactions.

Lamotrigine, OCP and pregnancy

- OCPs and pregnancy induce lamotrigine metabolism (Level I and II evidence) = ↑ risk of seizures:
  - OCP: 84% increase in lamotrigine clearance compared to baseline
  - Pregnancy: 94-230% increase in lamotrigine clearance compared to baseline

- The above effects immediately revert within a few days postpartum or after stopping OCP (pill free week) = lamotrigine toxicity

- Lamotrigine dose adjustments are often needed in the above situations. Carefully monitor for seizures or side effects.

Christensen et al, *Epilepsia* 2007;48(3):484-489. Pennell, *Epilepsy Currents* 2008;8(1):8-10

Interactions between AEDs and other non AED drugs

Drug	Protein binding (%)	Enzymatic activity	Will induce metabolism of OCP or other drugs metabolized by the liver	Elimination route (%)		Will be metabolized faster if used with enzyme inducing drug
				Renal	Liver	
Carbamazepine	75	Broad spectrum inducer	Yes	1	99	Yes
Clobazam	83	Induces epoxidation	No	<5	>90	Minimally
Clonazepam	85	Induces CYP2B	No	<5	>90	Minimally
Ethosuximide	0	None	No	<20	>80	Yes
Felbamate	25	Induces CYP3A4 Inhibits CYP2C19	Yes	50	50	Minimally
Gabapentin	0	None	No	100	0	No
Lamotrigine	55	Induces UGTs	Yes, minimally, progesterone component only	10	90	Yes
Levetiracetam	<10	None	No	100	0	No
Oxcarbazepine	40	Induces CYP3A4, UGTs Inhibits CYP2C19	Yes	1	99	Yes
Phenobarbital	45	Broad spectrum inducer	Yes	25	75	Yes
Phenytoin	90	Broad spectrum inducer	Yes	5	95	Yes
Pregabalin	0	None	No	100	0	No
Tiagabine	96	None	No	2	98	Yes
Topiramate	15	Induces CYP3A4 Inhibits CYP2C19	Only at doses > 200 mg/day	65	35	Minimally
Valproate	90	Broad spectrum inhibitor	No	2	98	Yes
Vigabatrin	0	None	No	100	0	No
Zonisamide	40	None	No	35	65	Yes

Liver function and hepatotoxicity during AED therapy

- Most of the newer AEDs are not eliminated by the liver except for a few exceptions. An ↑ in liver enzymes is often noted with the use of enzyme inducing AEDs in the absence of hepatic pathology.
    - A more than 2-3 fold increase in liver enzymes during AED therapy may indicate coexistent liver disease → work up for liver disease and consider switching to an alternative AED.

Ahmed and Siddiqi, *Seizure* 2006;15;156-164

Renal Disease and AEDs

- Many of the newer AEDs are primarily renally eliminated.
- Their dose will need to be adjusted in individuals with ↓ renal dysfunction (depending on creatinine clearance).
- Hemodialysis (HD) affects many of the AEDs → thus the need for administering a supplementary dose of AED post HD in most patients on an AED
- See Lacerda et al: Optimizing therapy of seizures in patients with renal or hepatic dysfunction, *Neurology* 2006;67(suppl 4):S28-S33 for more info.

Epilepsy and the Elderly

VA Cooperative Study (Ramsey et al.)

- Target doses (2-6 weeks titration):
  - Carbamazepine 600 mg, Gabapentin 1500 mg, Lamotrigine 150 mg.
- Results:
  1. Both lamotrigine and gabapentin retained patients better at one year than carbamazepine.
  2. Trend toward lamotrigine being better than gabapentin.
  3. More patients were seizure free on carbamazepine (64.9%) than on gabapentin (51.4%) and lamotrigine (51.9%).

Bone Health in Persons Taking Antiepileptic Drugs

- Women and men with epilepsy on antiepileptic drugs (AEDs) may be at higher risk for bone disease.
- The severity of abnormalities is correlated with the duration of AED exposure, the number of AEDs used, and use of enzyme-inducing AEDs.

AEDs Most Commonly Associated with Altered Bone Disease and Decreased Bone Density

- Phenobarbital
- Primidone
- Phenytoin
- Carbamazepine

Conclusion

1. Most new AEDs do not interact with other drugs or interact only minimally.

2. Older AEDs, mostly the enzyme inducers, are associated with bone loss → discuss calcium and vitamin D supplementation with your patients. Effects of new AEDs on bone are unknown.

3. Enzyme-inducing AEDs will increase birth control clearance → use higher dose of ethinylestradiol (minimum 50 µg) in women on enzyme inducers

Conclusion

4. Hormonal birth control and pregnancy will significantly increase the metabolism of lamotrigine.

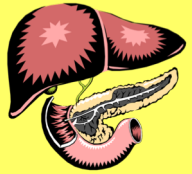
   – Recognize that LTG level will increase up to 84% during the pill free week, and may result in toxicity.

   – Have a low threshold to increase LTG dose during pregnancy if seizures occur or ↑ in frequency.

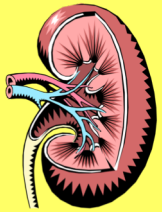
   – Any women with epilepsy considering pregnancy or who is pregnant should be referred to a neurologist, preferably an epilepsy specialist.

Conclusion

5. Increases in liver enzymes (up to two-three fold) are common in patients who are on an enzyme inducing AEDs → higher increases need to be investigated and alternative AED considered.



6. Many of the newer AEDs are primarily or only renally eliminated and their doses will need to be adjusted in those with renal failure based on the individual's creatinine clearance.



7. Most AEDs are eliminated by hemodialysis resulting in the need for a supplementary

Antiepileptic drugs for preventing seizures in people with brain tumors

[Review]

Antiepileptic drugs for preventing seizures in people with brain tumors

IW Tremont-Lukats, BO Ratilal, T Armstrong, MR Gilbert

Cochrane Database of Systematic Reviews 2008 Issue 2 (Status: *New*)

DOI: 10.1002/14651858.CD004424.pub2 This version first published online: 16 April 2008 in Issue 2, 2008

This record should be cited as: Tremont-Lukats IW, Ratilal BO, Armstrong T, Gilbert MR. Antiepileptic drugs for preventing seizures in people with brain tumors. *Cochrane Database of Systematic Reviews* 2008, Issue 2. Art. No.: CD004424. DOI: 10.1002/14651858.CD004424.pub2.

- Up to 60% of people with brain tumors may present with seizures, or may have a seizure for the first time after diagnosis.
- The risk of a seizure varies with the tumor type and its location in the brain.
- Seizures are an added burden with a negative impact on quality of life, affecting activities of daily living, independence, work, and driving.

Result

- The five randomised controlled trials identified by the review authors from the medical literature looked at the antiepileptic drugs phenytoin, phenobarbital, and divalproex sodium.
- There was no difference between treatment with these antiepileptic drugs and placebo, or observing the patient, in preventing a first seizure
- The risk of an adverse event was higher for those on antiepileptic drugs
- Side effects include nausea, skin rash, sore gums, myelosuppression, vertigo, blurred vision, tremor, and gait unsteadiness.

Post-traumatic seizure prophylaxis

- Prophylaxis for PTS refers to the practice of administering anticonvulsants to patients following traumatic brain injury to prevent the occurrence of seizures
- PTSs are classified as early, occurring within 7 days of injury, or late, occurring after 7 days following injury.

Incidence of PTS

- The incidence of seizures following penetrating injuries is about 50% in patients followed for 15 years
- In TBI studies that followed high-risk patients up to 36 months, the incidence of early PTS varied between 4% and 25%, and the incidence of late PTS varied between 9% and 42% in untreated patients

Risk Factors

- Glasgow Coma Scale (GCS) Score <10
- Cortical contusion
- Depressed skull fracture
- Subdural hematoma
- Epidural hematoma
- Intracerebral hematoma
- Penetrating head wound
- Seizure within 24 h of injury

Summary of evidences

- The majority of studies do not support the use of the prophylactic anticonvulsants prevention of late PTS.
- Routine seizure prophylaxis later than 1 week following TBI is, therefore, not recommended.
- If late PTS occurs, patients should be managed in accordance with standard approaches to patients with new onset seizures.
- Phenytoin has been shown to reduce the incidence of early PTS.
- Valproate may also have a comparable effect to phenytoin on reducing early PTS but may also be associated with a higher mortality.

JOURNAL OF NEUROTRAUMAVolume 24, Supplement 1, 2007 © Brain Trauma Foundation Pp. S-83–S-86 DOI: 10.1089/neu.2007.9983

Alternative Therapies for Epilepsy

- Ketogenic Diet and Atkins Diet
- EEG biofeedback/neurofeedback
- Yoga
- Acupuncture
- Complementary and herbal remedies
- Seizure alert dogs

Syncope, seizure, epilepsy and driving

Event	Comment	Class	Drive after
1. Syncope or single seizures	Syncope: no neurological or cardiac cause and for seizure CT and EEG normal.	5 or6	3m
		1-4	12m
2. Auras (simple partial seizures)	Non disabling sensory or motor	5 or 6	0
		1-4	12m
3. Epilepsy	On treatment and sz free	5 or 6	6m -12m
		1-4	5 yrs on or off AEDs
4. Seizures	Only in sleep or awakening, awake EEG normal	5 or 6	0
		1-4	5 yrs on or off AEDs
5. AED w/d szs	Initial w/d no szs	5 or 6	3m
	Seizures recur	5 or 6	6m*
		1-4	5 yrs on or off AEDs
6. Etoh seizures	Etoh and sz free, completed rehabilitation program	Any	12m
1. CMA Determining medical fitness to drive 6th ed. 2000. 2. CCMTA Medical standards for drivers. July 2004 (modified by Dr. N. Pillay)			