Epilepsy Pharmacotherapy: Epidemiology & Clinical Presentation

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Definitions

- Seizure: the clinical manifestation of an abnormal, excessive excitation and synchronization of a population of cortical neurons

- Epilepsy: recurrent seizures (two or more) which are not provoked by systemic or acute neurologic insults

Epidemiology of Seizure / Epilepsy

- ~ 10% population – single seizure during lifetime
- ~ 4-5% population – epilepsy – two or more unprovoked seizures in lifetime
- ~1-2% population – epilepsy now
  - 30% intractable
  - 30% occasional seizures
  - 40% controlled on medications

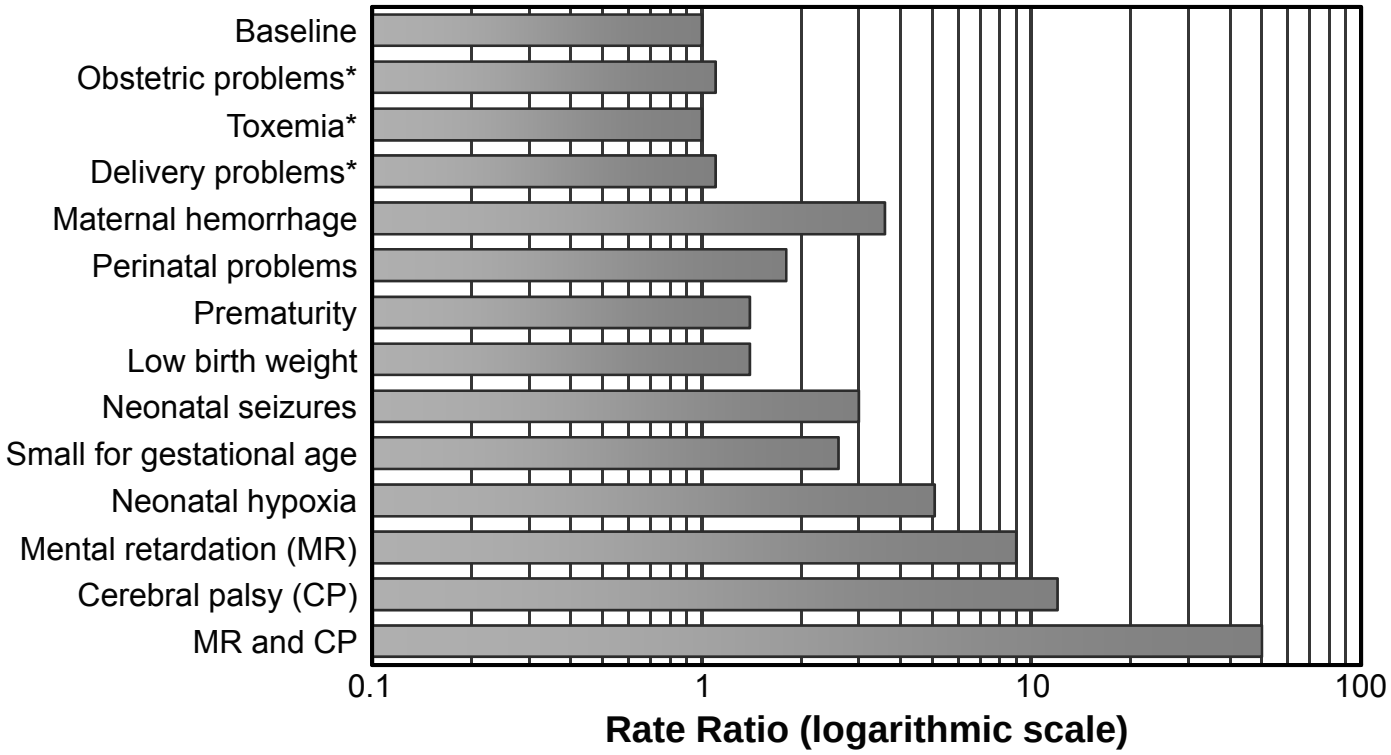
Incidence and Prevalence of Epilepsy in the United States

Community incidence[1]: Rochester, Minn (1935–1984)

- Epilepsy affects more than 3 million people[2]
- 200,000 new cases of epilepsy diagnosed annually[2]

1. Hauser WA et al. *Epilepsia.* 1993;34:453–468. Adapted with permission of *Epilepsia*.
2. Epilepsy Foundation. Epilepsy Fact Sheet. http://www.epilepsyfoundation.org/about/factsfigures.cfm. Accessed June 2, 2009.

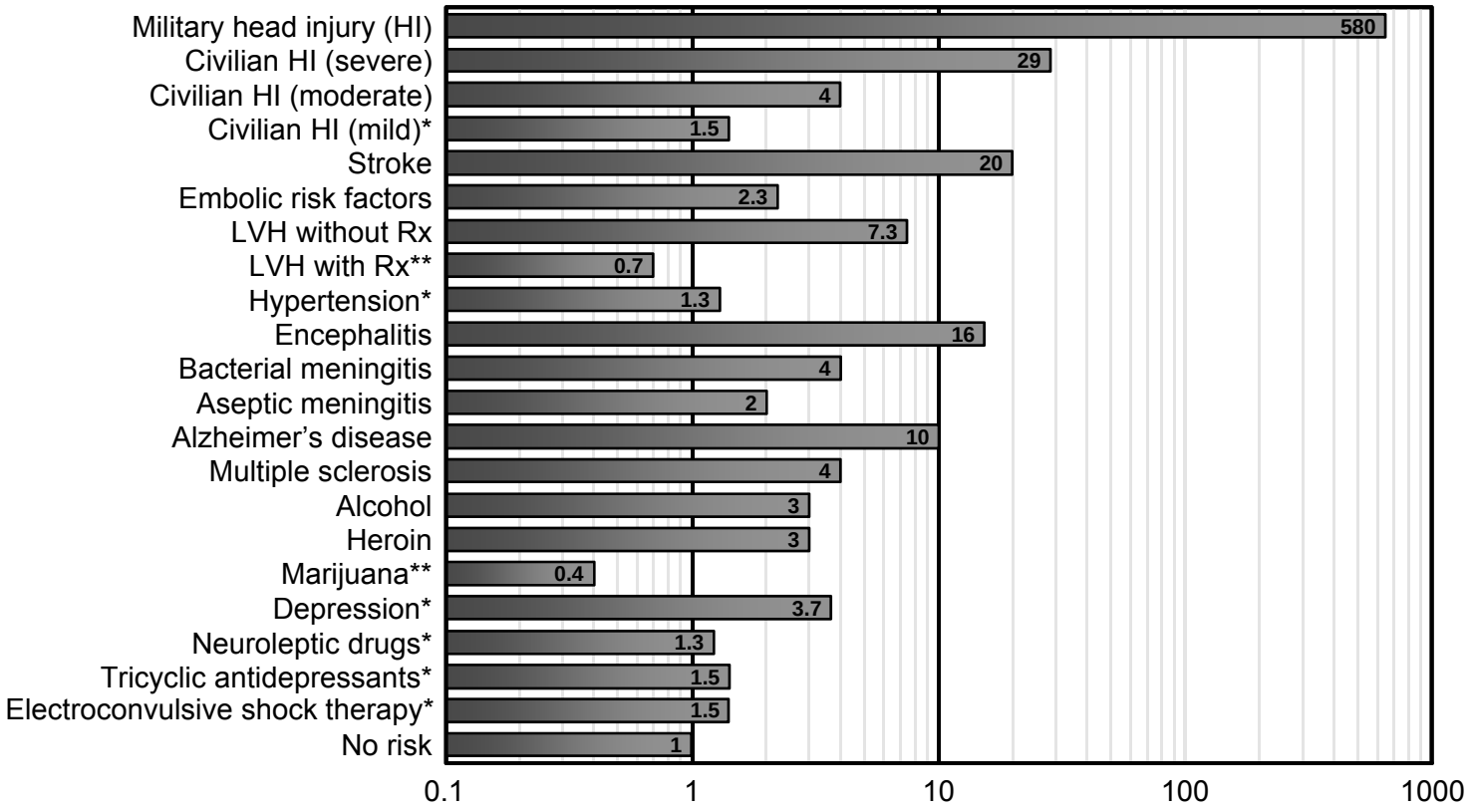
Risk for Epilepsy: Prenatal and Perinatal Factors



*Not statistically significant.

Adapted with permission from Hessdorffer DC, et al. *Epilepsy: A Comprehensive Textbook*. Philadelphia, Pa: Lippincott-Raven Publishers: 1997:59-67.

Adult Risk Factors for Epilepsy



*Not significant; **Protective; LVH – Left ventricular hypertrophy.

Adapted with permission from Hessdorffer DC, et al. *Epilepsy: A Comprehensive Textbook.* Philadelphia, Pa: Lippincott-Raven Publishers; 1997:59-67.

Epilepsy and Other Chronic Convulsive Diseases

‘ Every fit, slight or severe, is in some degree
the effect of those which precede it,
the cause of those that follow it.’

William Gowers, M.D.,1881

Molecular, Synaptic, and Cellular Effects of Seizures

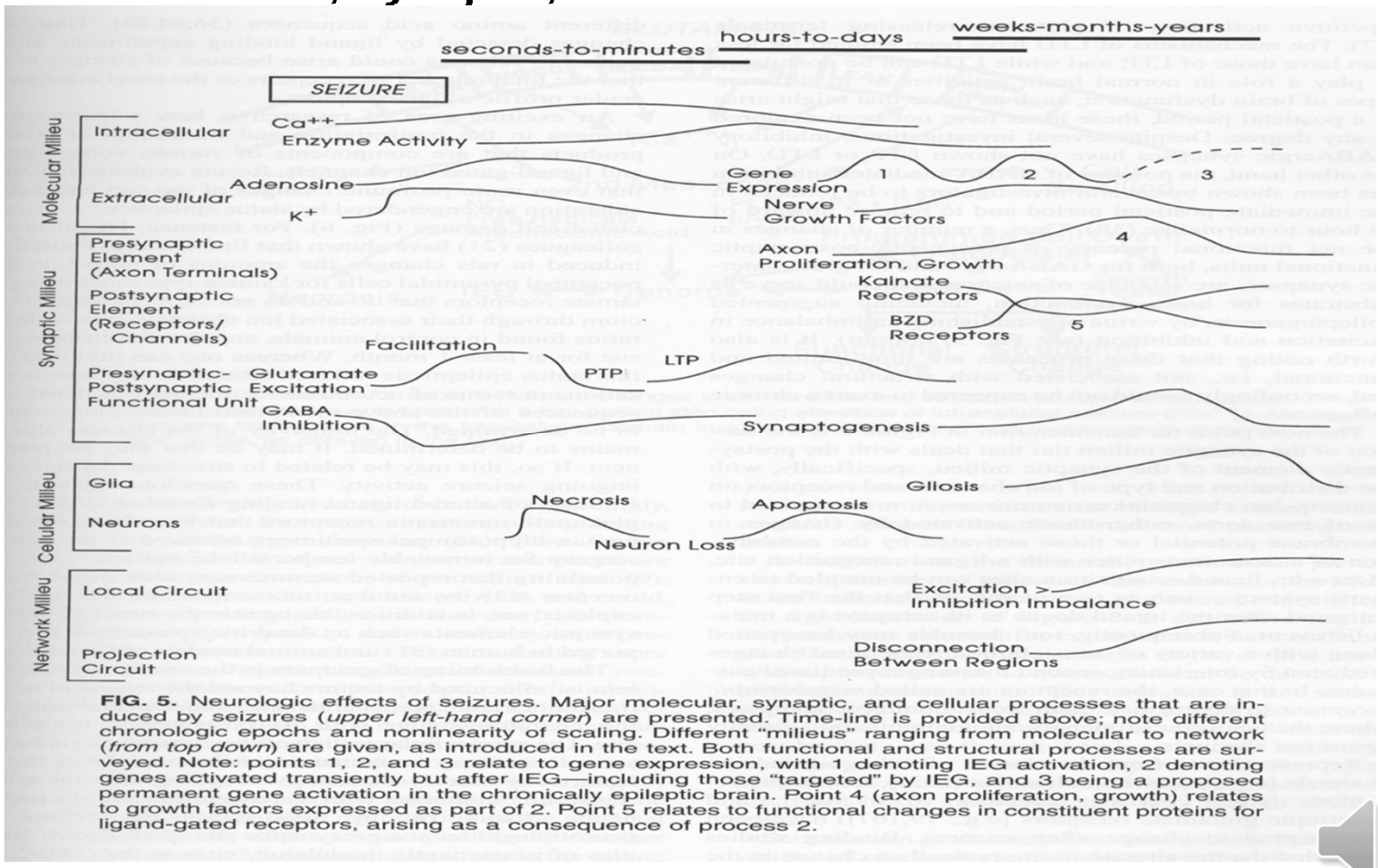
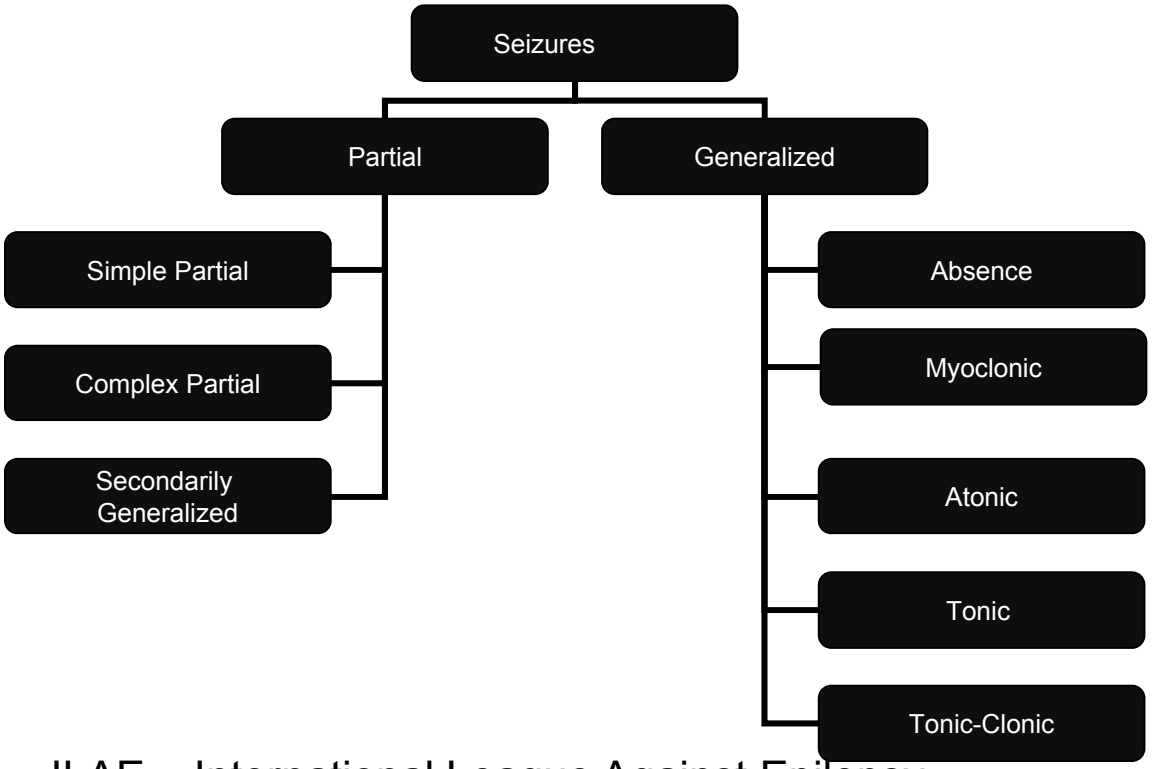


FIG. 5. Neurologic effects of seizures. Major molecular, synaptic, and cellular processes that are induced by seizures (*upper left-hand corner*) are presented. Time-line is provided above; note different chronologic epochs and nonlinearity of scaling. Different "milieus" ranging from molecular to network (*from top down*) are given, as introduced in the text. Both functional and structural processes are surveyed. Note: points 1, 2, and 3 relate to gene expression, with 1 denoting IEG activation, 2 denoting genes activated transiently but after IEG—including those "targeted" by IEG, and 3 being a proposed permanent gene activation in the chronically epileptic brain. Point 4 (axon proliferation, growth) relates to growth factors expressed as part of 2. Point 5 relates to functional changes in constituent proteins for ligand-gated receptors, arising as a consequence of process 2.

Lotham E, 1997

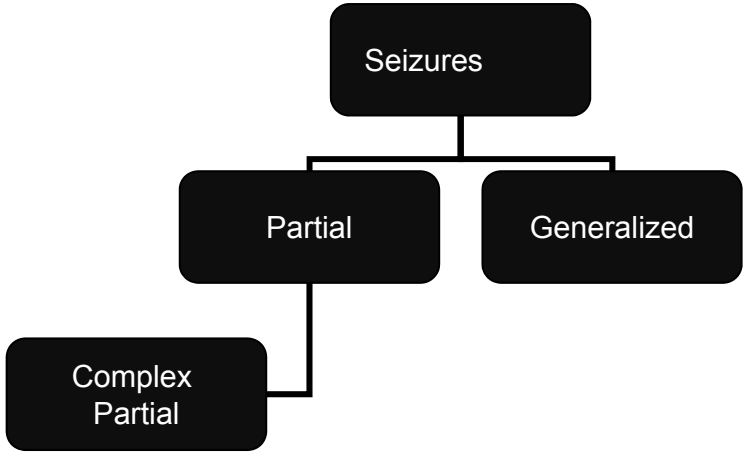
ILAE Classification of Seizures



ILAE – International League Against Epilepsy

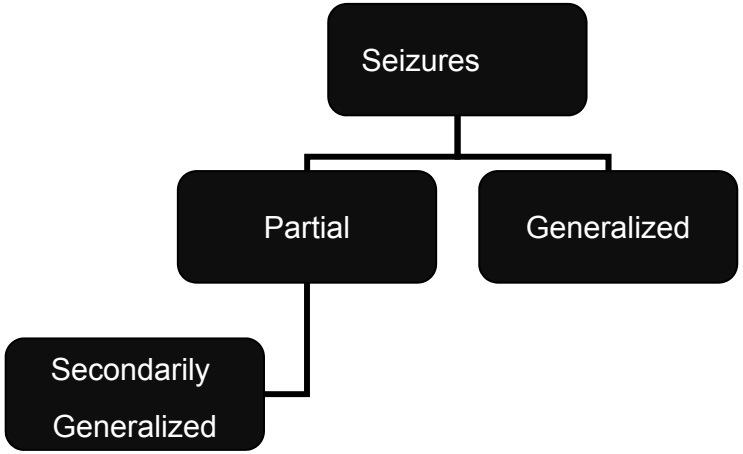
Complex Partial Seizures

- Impaired consciousness
- Clinical manifestations vary with site of origin and degree of spread
  - Presence and nature of aura
  - Automatisms
  - Other motor activity
- Duration typically < 2 minutes

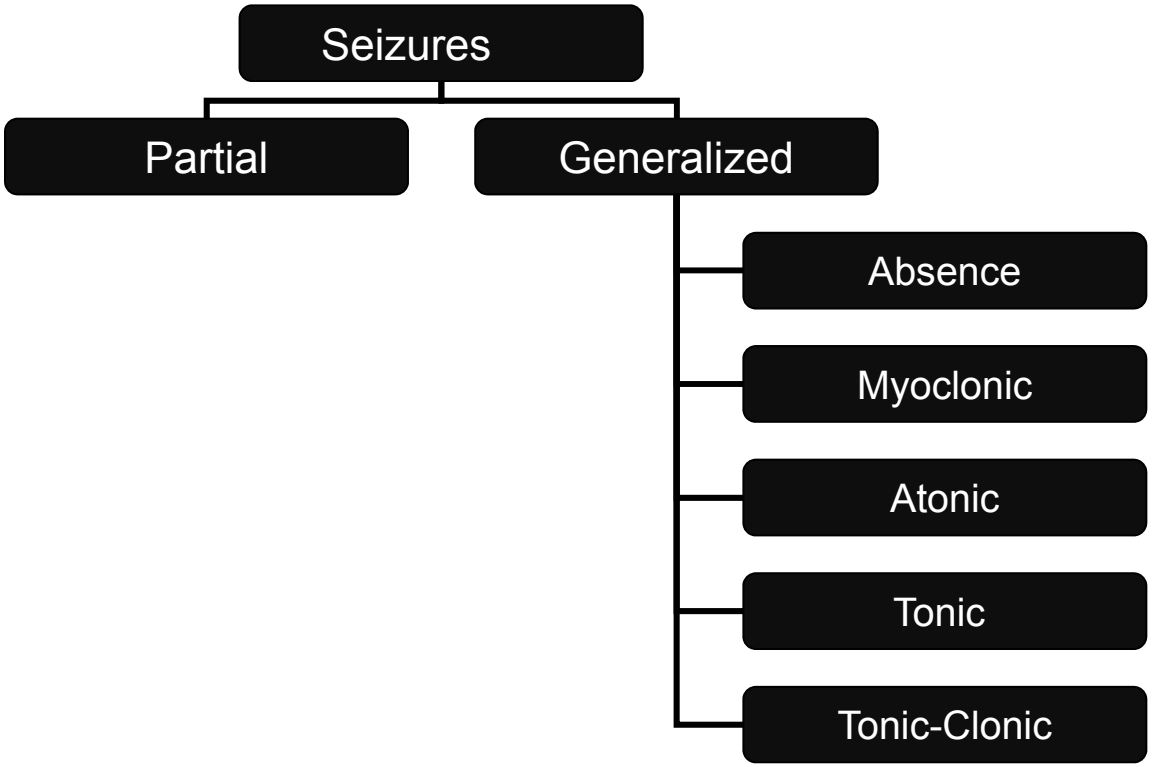


Secondarily Generalized Seizures

- Begins focally, with or without focal neurological symptoms
- Variable symmetry, intensity, and duration of tonic (stiffening) and clonic (jerking) phases
- Typical duration 1-3 minutes
- Postictal confusion, somnolence, with or without transient focal deficit

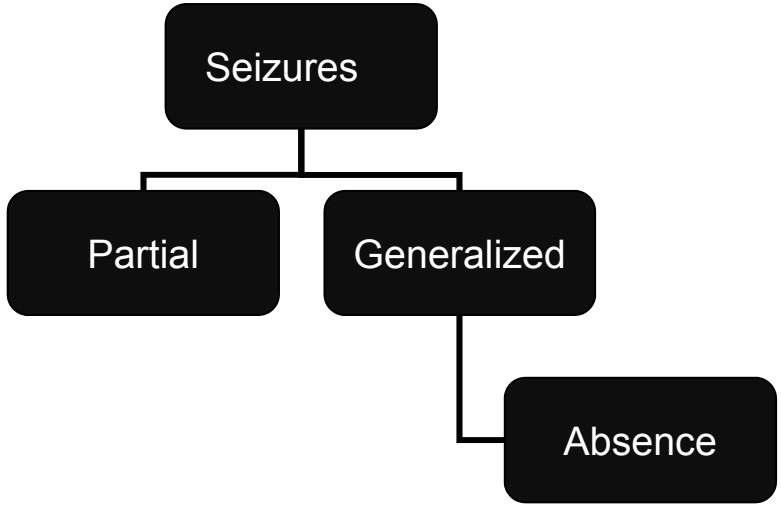


ILAE Classification of Seizures



Typical Absence Seizures

- Brief staring spells ("petit mal") with impairment of awareness
  - 3-20 seconds
  - Sudden onset and sudden resolution
  - Often provoked by hyperventilation
  - Onset typically between 4 and 14 years of age
  - Often resolve by 18 years of age
- Normal development and intelligence
- EEG: Generalized 3 Hz spike-wave discharges



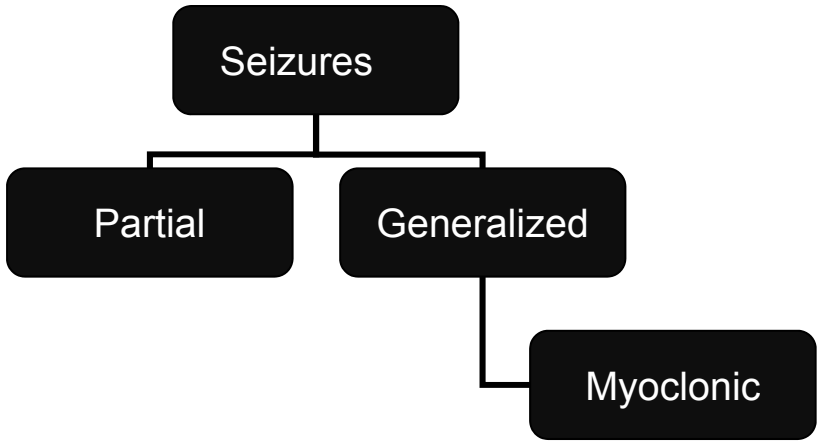
Atypical Absence Seizures

- Brief staring spells with variably reduced responsiveness
  - 5-30 seconds
  - Gradual (seconds) onset and resolution
  - Generally not provoked by hyperventilation
  - Onset typically after 6 years of age
- Often in children with global cognitive impairment
- EEG: Generalized slow spike-wave complexes (<2.5 Hz)
- Patients often also have Atonic and Tonic seizures

Myoclonic Seizures

Epileptic Myoclonus

- Brief, shock-like jerk of a muscle or group of muscles
- Differentiate from benign, nonepileptic myoclonus (e.g., while falling asleep)
- EEG: Generalized 4-6 Hz polyspike-wave discharges



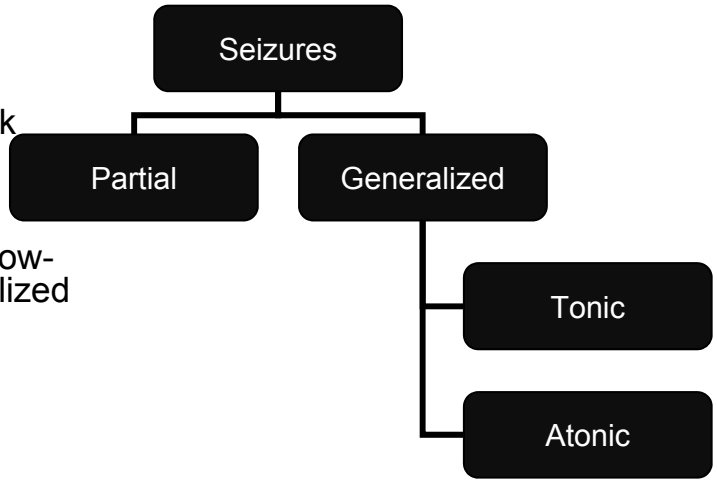
Tonic and Atonic Seizures

Tonic seizures

Symmetric, tonic muscle contraction of extremities with tonic flexion of waist and neck

Duration - 2-20 seconds.

EEG – Sudden attenuation with generalized, low-voltage fast activity (most common) or generalized polyspike-wave.



Atonic seizures

Sudden loss of postural tone

- When severe often results in falls
- When milder produces head nods or jaw drops.

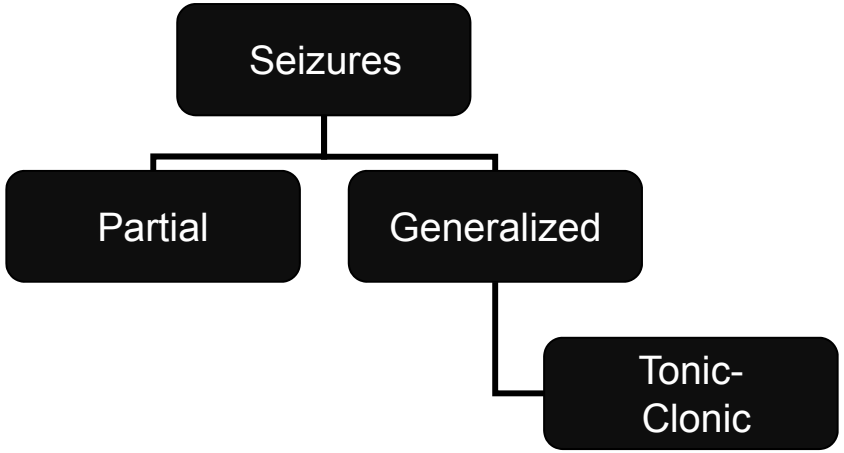
Consciousness usually impaired

Duration - usually seconds, rarely more than 1 minute

EEG – sudden diffuse attenuation or generalized polyspike-wave

Generalized Tonic-Clonic Seizures

- Associated with loss of consciousness and post-ictal confusion/lethargy
- Duration 30-120 seconds
- Tonic phase
  - Stiffening and fall
  - Often associated with ictal cry
- Clonic Phase
  - Rhythmic extremity jerking
- EEG – generalized polyspikes



Seizure Precipitants

- Metabolic and Electrolyte Imbalance
- Stimulant/other proconvulsant intoxication
- Sedative or ethanol withdrawal
- Sleep deprivation
- Antiepileptic medication reduction or inadequate AED treatment
- Hormonal variations
- Stress
- Fever or systemic infection
- Concussion and/or closed head injury

Seizure Precipitants (cont.)

Metabolic and Electrolyte Imbalance

- Low blood glucose
  (or high glucose, esp. w/ hyperosmolar state)
- Low sodium
- Low calcium
- Low magnesium

Seizure Precipitants (cont.)

Stimulants/Other Pro-convulsant Intoxication

- IV drug use
- Cocaine
- Ephedrine
- Other herbal remedies
- Medication reduction

Seizure Precipitants (cont.)

Medications that can lower seizure threshold

- Antidepressants:
  - Bupropion
  - Tricyclics
- Neuroleptics
  - Phenothiazines
  - Clozapine
- Theophylline
- Isoniazid
- Penicillins
- Cyclosporin
- Meperidine

Choosing an Antiepileptic Drug (AED)

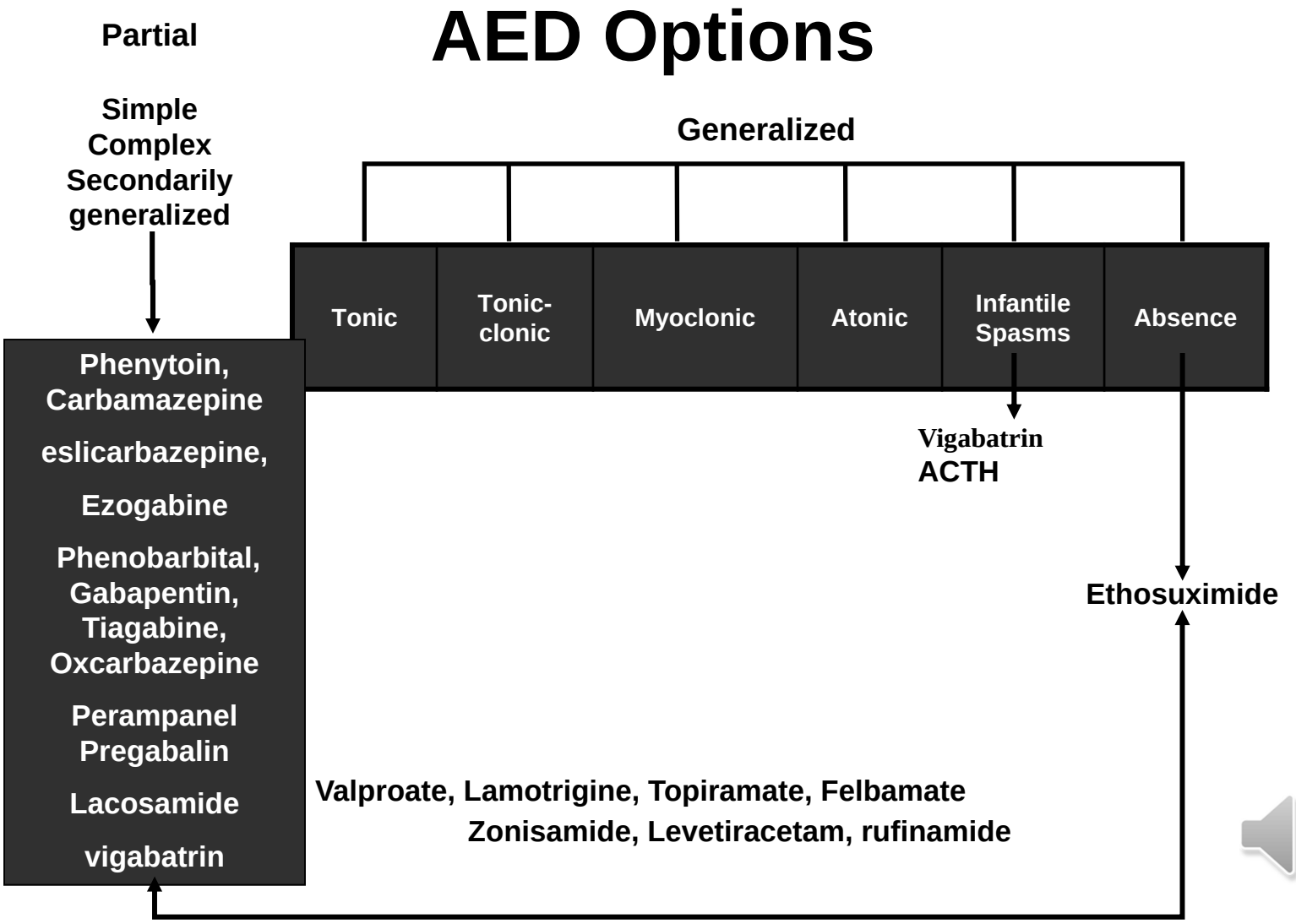
- Seizure type
- Epilepsy syndrome
- Drug Mechanism of Action (MOA)
- Pharmacokinetics
  - Drug interactions
  - formulation
- Concomitant medical/psychiatric conditions
- Adverse effects
- Cost

Currently Available AEDs: Generic Names & Trade Names

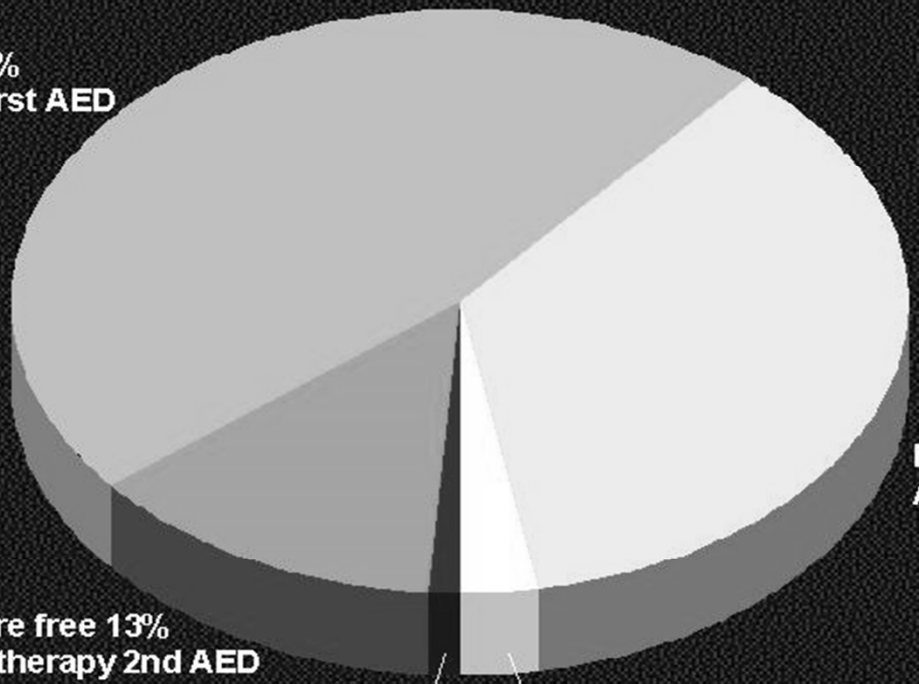
Generic	Trade
Carbamazepine (CBZ)	Carbatrol, Tegretol
Eslicarbazepine (ESL)	Aptiom
Ezogabine (EZG)	Potiga
Ethosuximide (ETH)	Zarontin
Felbamate (FBM)	Felbatol
Fosphenytoin (FOS)	Cerebyx
Gabapentin (GBP)	Neurontin
Lamotrigine (LTG)	Lamictal
Levetiracetam (LEV)	Keppra
Oxcarbazepine (OXC)	Trileptal

Generic	Trade
Perampanel (PER) Phenobarbital (PB)	Fycompa
Phenytoin (PHT)	Dilantin
Pregabalin (PGB)	Lyrica
Primidone (PRM)	Mysoline
Tiagabine (TGB)	Gabitril
Topiramate (TPM)	Topamax
Valproate (VPA) Vigabatrin (VGB)	Depakote Sabril
Zonisamide (ZNS) Lacosamide (LCM) Vigabatrin (VGB)	Zonegran Vimpat Sabril

AED Options


Partial
Simple
Complex
Secondarily generalized
Generalized
Tonic
Tonic-clonic
Myoclonic
Atonic
Infantile Spasms
Absence
Phenytoin,
Carbamazepine
eslicarbazepine,
Ezogabine
Phenobarbital,
Gabapentin,
Tiagabine,
Oxcarbazepine
Perampanel
Pregabalin
Lacosamide
vigabatrin
Vigabatrin
ACTH
Ethosuximide
Valproate, Lamotrigine, Topiramate, Felbamate
Zonisamide, Levetiracetam, rufinamide

Success in AED regimens



Kwan and Brodie. *N Engl J Med*. 2000.

When Monotherapy Fails…….

Seizure Freedom* with Adjunctive Therapy or Substitution Monotherapy in Patients with Inadequate Seizure Control on First Well-Tolerated AED

- Adjunctive AED therapy may be more effective when initiated immediately after failure of first AED vs after failure of second AED

*Seizure freedom=no seizures of any type for ≥1 year.

Graph adapted from: Kwan P, et al. *Seizure*. 2000;9:464-468. Used with permission.

Choosing an AED

- Do the pharmacokinetics match my patient?

AED Drug Interactions

- **Broad Spectrum Inducers**
  - **Carbamazepine**
  - **Phenytoin**
  - **Phenobarbital**
- **Selective 3A4 Inducers**
  - **Felbamate**
  - **Topiramate**
  - **Oxcarbazepine**
- **Inhibitors**
  - **VPA (CYP 2C19, UGT)**
  - **Felbamate, Topiramate, Oxcarbazepine**
    - **(CYP 2C19)**

Choosing an AED

- Adverse effects matter!

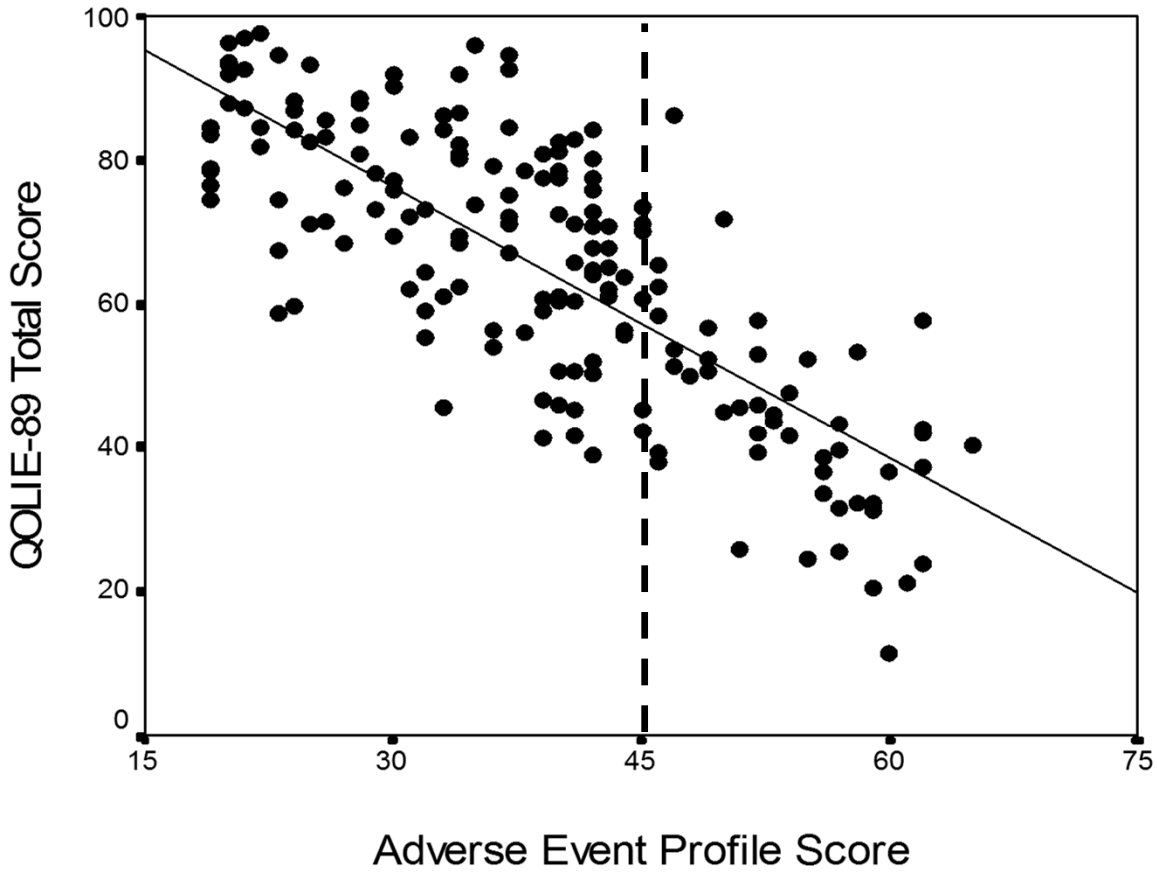
VA Cooperative Trial I:

Reason for AED Failure

	CBZ	PB	PHT	PRM	All Patients
	N=101	N=101	N=110	N=109	N=421
Toxicity alone	12	19	18	36	85
Toxicity plus seizures	30	33	29	35	127
Seizures alone	3	4	1	3	11
Total Failures	45	56	48	74	233

Mattson et al, *NEJM*, 1985

AED Toxicity and Quality of Life



(n=200, r = -0.78, p< 0.0001) Gilliam et al, *Neurology* 58 (suppl5): S9-19, 2002

Epilepsy Adverse Effects: Cognition and Behavior

- Most AEDs can influence cognitive function
- Monotherapy better than polypharmacy
- AEDs may amplify or ameliorate behavior
- AEDs may exacerbate certain seizure types
- Seizure frequency may significantly affect cognition/behavior transiently and permanently
- Some research shows that:
  - Intractability of the seizure disorder does not seem to be an independent risk factor for occurrence of depression*
  - There is no relationship between severity of depression and monthly seizure rate*
- Chronic disease state may significantly alter development and behavior – managing uncertainty about seizures, stigma, impact on others, managing treatments

Attarian H, et al. *Epilepsy & Behavior* 2003;4:298-301.