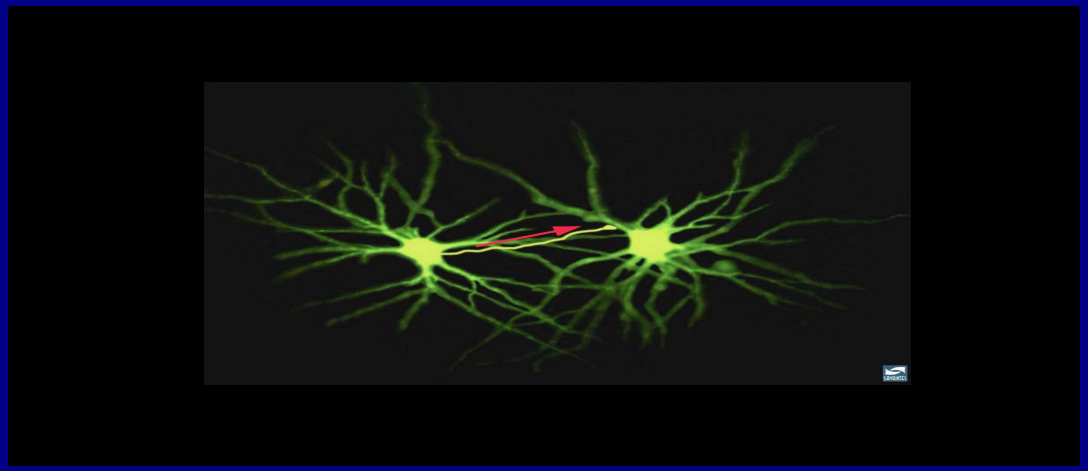
ANTIEPILEPTIC DRUGS

Epilepsy

A group of **chronic** CNS disorders characterized by recurrent **seizures.**

- **Seizures** are sudden, transitory, and uncontrolled episodes of brain dysfunction resulting from abnormal discharge of neuronal cells with associated motor, sensory or behavioral changes.



Causes for Acute Seizures

- Trauma
- Encephalitis
- Drugs
- Birth trauma
- Withdrawal from depressants
- Tumor
- High fever
- Hypoglycemia
- Extreme acidosis
- Extreme alkalosis
- Hyponatremia
- Hypocalcemia
- Idiopathic

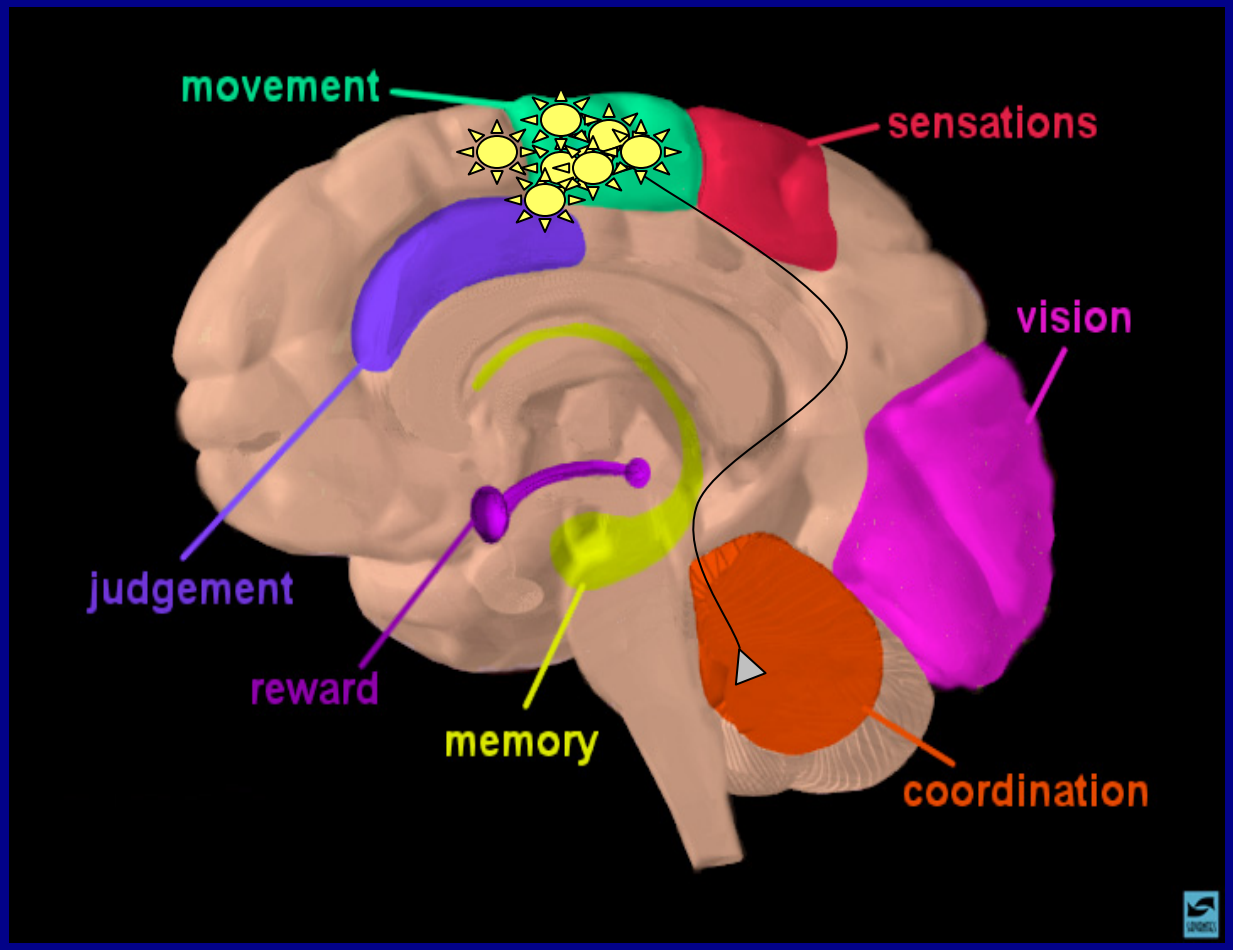
Seizures

- The causes for seizures can be multiple, from infection, to neoplasms, to head injury. In a few subgroups it is an inherited disorder.

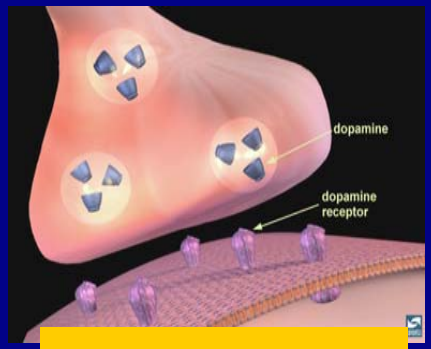
- Febrile seizures or seizures caused by meningitis are treated by antiepileptic drugs, although they are not considered epilepsy (unless they develop into chronic seizures).

- Seizures may also be caused by acute underlying toxic or metabolic disorders, in which case the therapy should be directed towards the specific abnormality.

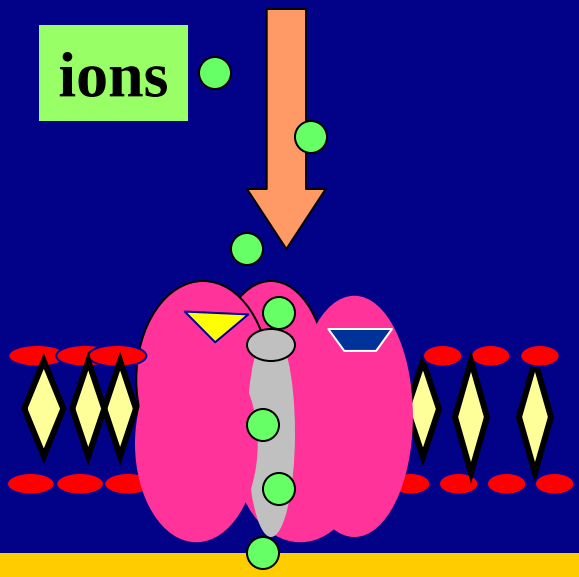
Neuronal Substrates of Epilepsy



The Brain



The Synapse



The Ion Channels/Receptors

Classification of Epileptic Seizures

I. Partial (focal) Seizures
   A. Simple Partial Seizures
   B. Complex Partial Seizures

II. Generalized Seizures
   A. Generalized Tonic-Clonic Seizures
   B. Absence Seizures
   C. Tonic Seizures
   D. Atonic Seizures
   E. Clonic Seizures
   F. Myoclonic Seizures
   G. Infantile Spasms

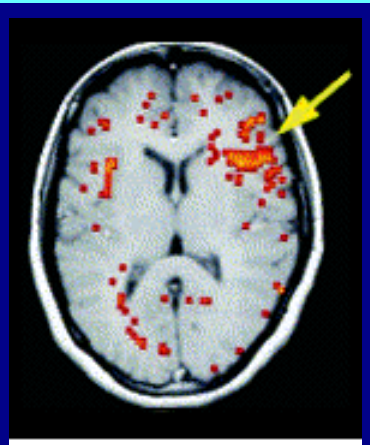
TABLE 20–1. International Classification of Partial and Generalized Seizures

Classification	Characterization
Partial (focal) seizures	Arise in one cerebral hemisphere.
Simple partial seizure	No alteration of consciousness.
Complex partial seizure	Altered consciousness, automatisms, and behavioral changes.
Secondarily generalized seizure	Focal seizure becomes generalized and is accompanied by loss of consciousness.
Generalized seizures	Arise in both cerebral hemispheres and are accompanied by loss of consciousness.
Tonic-clonic (grand mal) seizure	Increased muscle tone is followed by spasms of muscle contraction and relaxation.
Tonic seizure	Increased muscle tone.
Clonic seizure	Spasms of muscle contraction and relaxation.
Myoclonic seizure	Rhythmic, jerking spasms.
Atonic seizure	Sudden loss of all muscle tone.
Absence (petit mal) seizure	Brief loss of consciousness, with minor muscle twitches and eye blinking.

I. Partial (Focal) Seizures

A. Simple Partial Seizures

B. Complex Partial Seizures.



Brain scan of a person with frontal lobe epilepsy. Arrow points to the focus of seizure activity. [Image reproduced with permission from Seeck et al. (1998) Electroenceph. Clin. Neurophys. 106, 508-512.]

I. Partial (Focal) Seizures

A. Simple Partial Seizures (*Jacksonian*)

- Involves one side of the brain at onset.
- Focal w/motor, sensory or speech disturbances.
- Confined to a single limb or muscle group.
- Seizure-symptoms don't change during seizure.
- No alteration of consciousness.

EEG: Excessive synchronized discharge by a small group of neurons. Contralateral discharge.

I. Partial (focal) Seizures

B. Complex Partial Seizures *(Temporal Lobe epilepsy or Psychomotor Seizures)*

- Produces confusion and inappropriate or dazed behavior.
- Motor activity appears as non-reflex actions. Automatisms (repetitive coordinated movements).
- Wide variety of clinical manifestations.
- Consciousness is impaired or lost.

EEG: Bizarre generalized EEG activity with evidence of anterior temporal lobe focal abnormalities. Bilateral.

II. Generalized Seizures

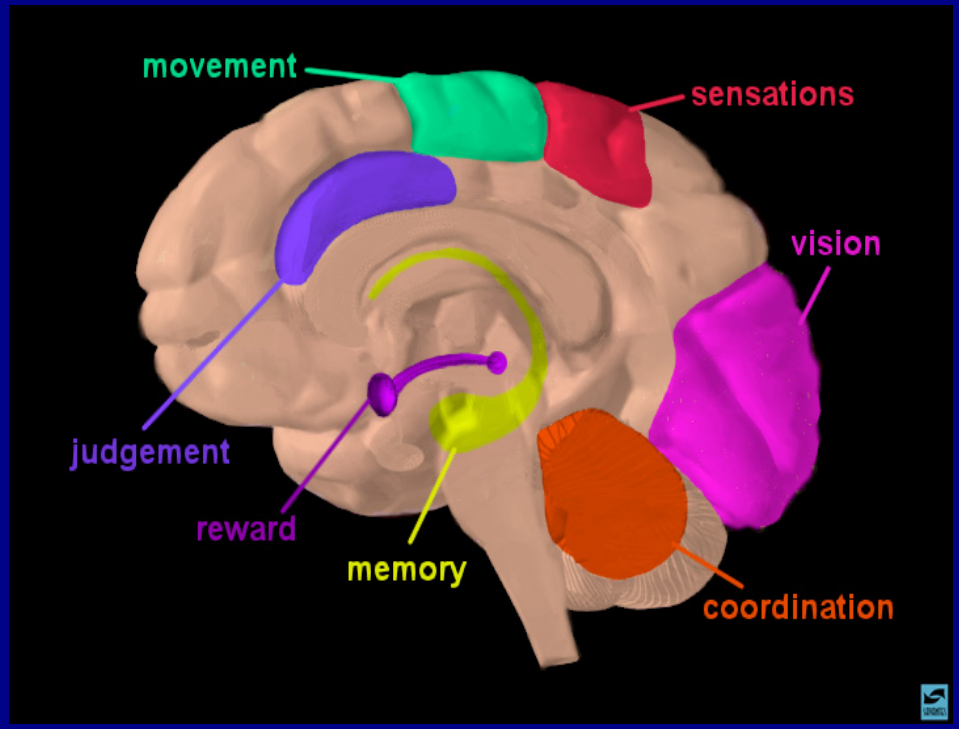
A. Generalized Tonic-Clonic Seizures
B. Absence Seizures
C. Tonic Seizures
D. Atonic Seizures
E. Clonic Seizures
F. Myoclonic Seizures.
G. Infantile Spasms

II. Generalized Seizures

In Generalized seizures, both hemispheres are widely involved from the outset.

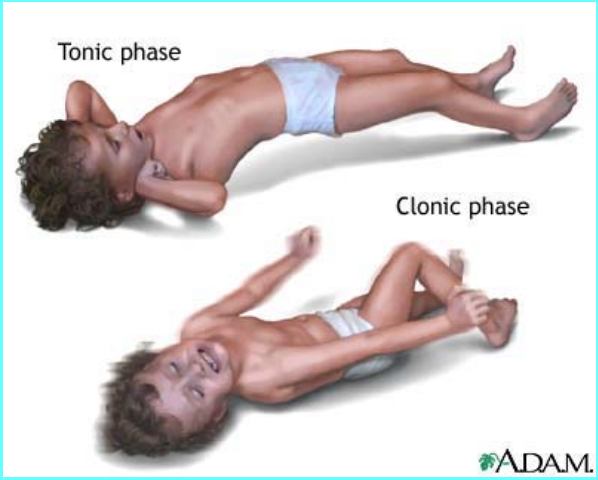
Manifestations of the seizure are determined by the cortical site at which the seizure arises.

Present in 40% of all epileptic Syndromes.



II. Generalized Seizures

A. Generalized Tonic-Clonic Seizures



Major convulsions, usually with two phases:

1) Tonic phase
2) Clonic phase

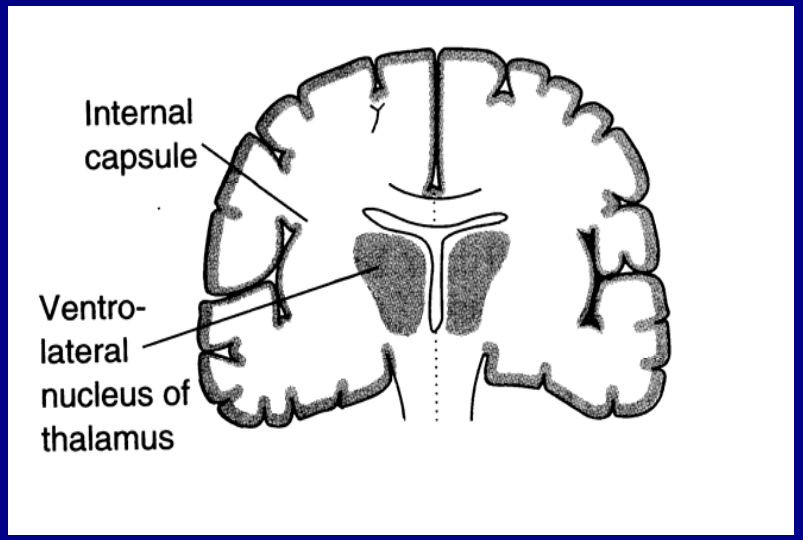
Convulsions:

- motor manifestations
- may or may not be present during seizures
- excessive neuronal discharge

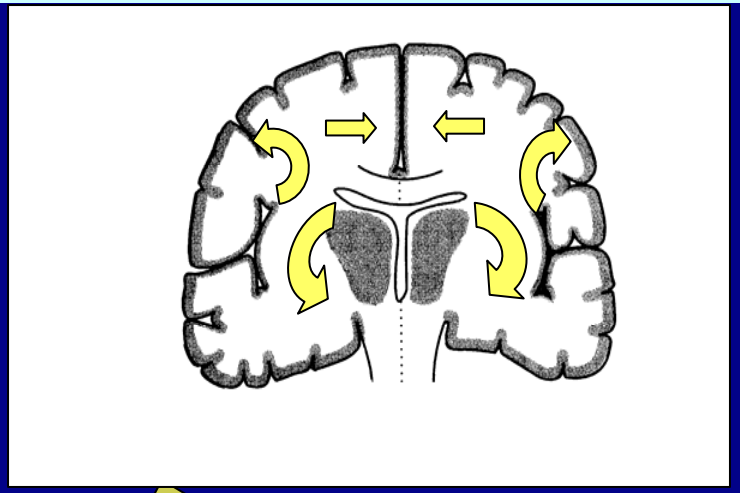
Convulsions appear in Simple Partial and Complex Partial Seizures if the focal neuronal discharge includes motor centers; they occur in all Generalized Tonic-Clonic Seizures regardless of the site of origin.

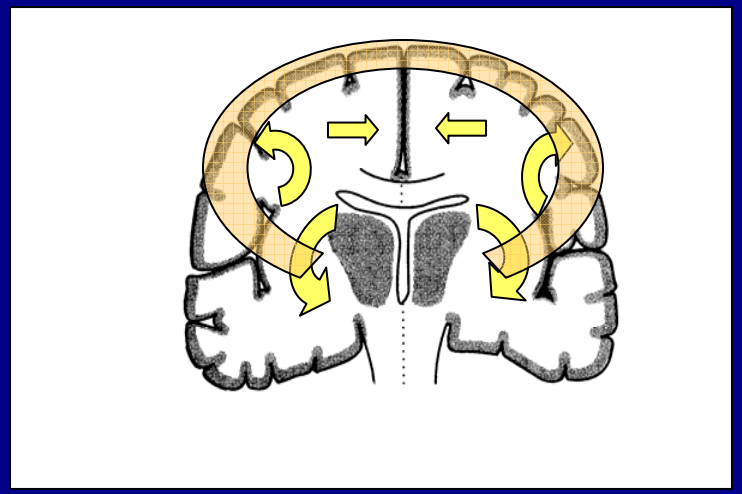
Atonic, Akinetic, and Absence Seizures are non-convulsive

Scheme of Seizure Spread



Generalized Tonic-Clonic Seizures





Both hemispheres are involved from outset

II. Generalized Seizures

B. Absence Seizures (*Petite Mal*)

- Brief and abrupt loss of consciousness, vacant stare.
- Sometimes with no motor manifestations.
- Minor muscular twitching restricted to eyelids (eyelid flutter) and face.
- Typical 2.5 – 3.5 Hz spike-and-wave discharge.
- Usually of short duration (5-10 sec), but may occur dozens of times a day.
- No loss of postural control.

II. Generalized Seizures

B. Absence Seizures (con't)

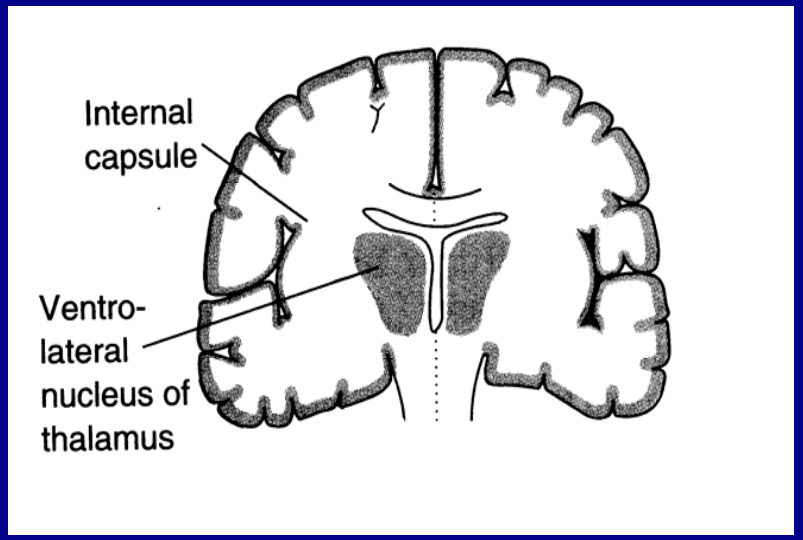
- Often begin during childhood (daydreaming attitude, no participation, lack of concentration).
- A low threshold Ca^{2+} current has been found to govern oscillatory responses in thalamic neurons (pacemaker) and it is probably involve in the generation of these types of seizures.

EEG: **Bilaterally synchronous, high voltage 3-per-second spike-and-wave discharge pattern.**

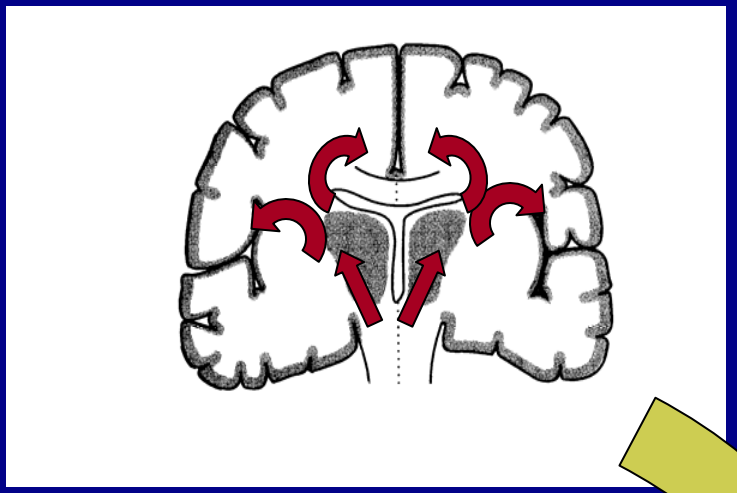
Spike-wave phase:

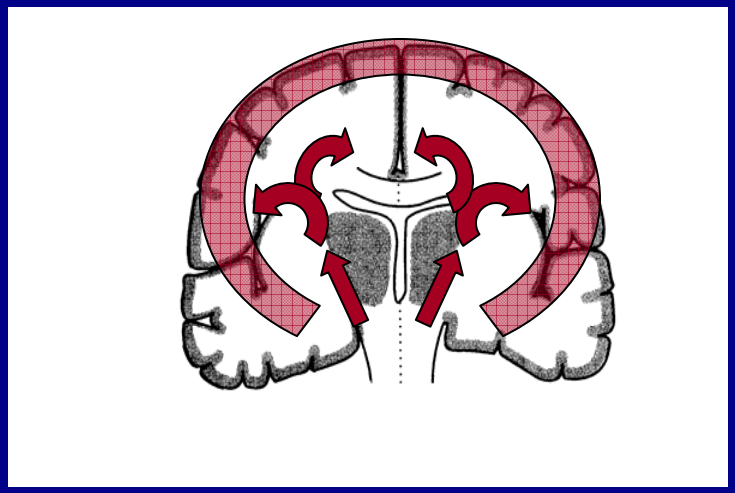
Neurons generate short duration depolarization and a burst of action potentials, but there is no sustained depolarization or repetitive firing of action potentials.

Scheme of Seizure Spread



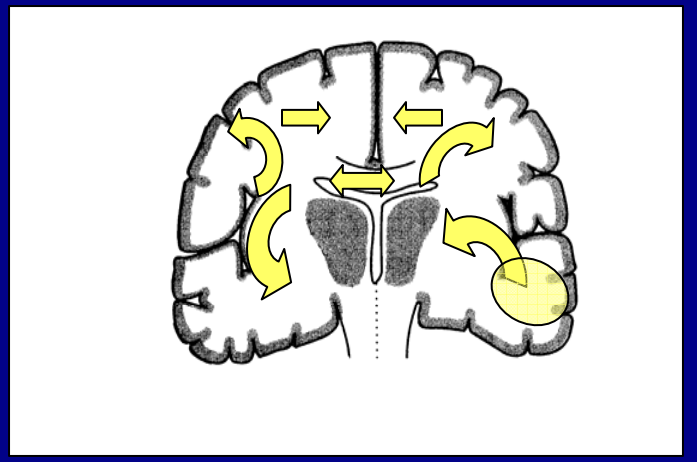
Primary Generalized Absence Seizures

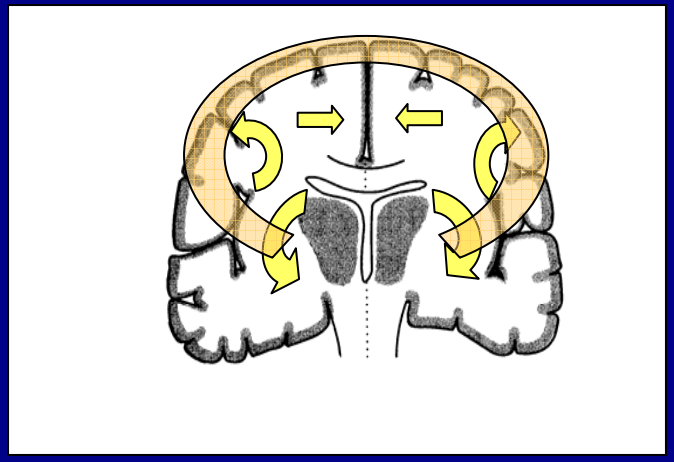


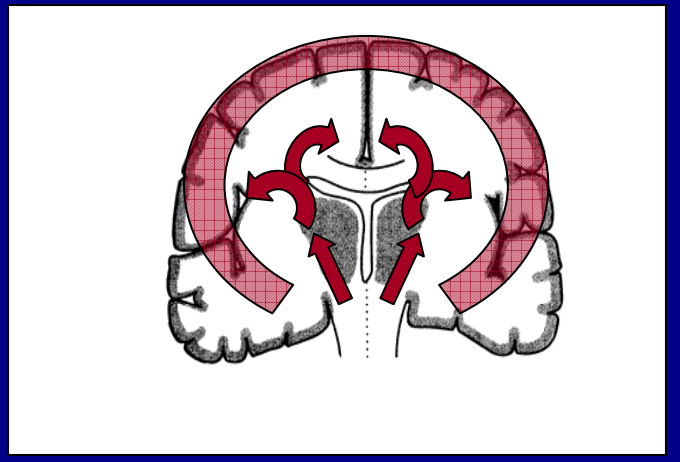


Thalamocortial relays are believed to act on a hyperexcitable cortex

Scheme of Seizure Spread







II. Generalized Seizure

C. Tonic Seizures

- Opisthotonus, loss of consciousness.
- Marked autonomic manifestations

D. Atonic Seizures (*atypical*)

- Loss of postural tone, with sagging of the head or falling.
- May loose consciousness.

II. Generalized Seizure

E. Clonic Seizures

- Clonic Seizures: Rhythmic clonic contractions of all muscles, loss of consciousness, and marked autonomic manifestations.

F. Myoclonic Seizures

- Myoclonic Seizures: Isolated clonic jerks associated with brief bursts of multiple spikes in the EEG.

II. Generalized Seizures

F. Infantile Spasms

- An epileptic syndrome.
- Attacks, although fragmentary, are often bilateral.
- Characterized by brief recurrent myoclonic jerks of the body with sudden flexion or extension of the body and limbs.

Treatment of Seizures

Treatment of Seizures

Goals:

- Block repetitive neuronal firing.
- Block synchronization of neuronal discharges.
- Block propagation of seizure.

Minimize side effects with the simplest drug regimen.

MONOTHERAPY IS RECOMMENDED IN MOST CASES

Treatment of Seizures

Strategies:

- Modification of ion conductances.
- Increase inhibitory (GABAergic) transmission.
- Decrease excitatory (glutamatergic) activity.

Antiseizure drugs

Mechanisms of action

1. **Inhibit glutamate neurotransmission**

   Felbamate, topiramate and valproate

1. **Enhancement of GABA actions**

   -increase GABA actions at receptor (benzodiazepines, phenobarbital)

   -vigabatrin inhibits GABA transaminase

   -tiagabin blocks GABA uptake

2. **Inhibition of sodium channel function**

   -phenytoin, carbamazepine, valproic acid, lamotrigine

3. **Inhibition of Calcium T-type channels (ethosuximide)**

GABAergic SYNAPSE

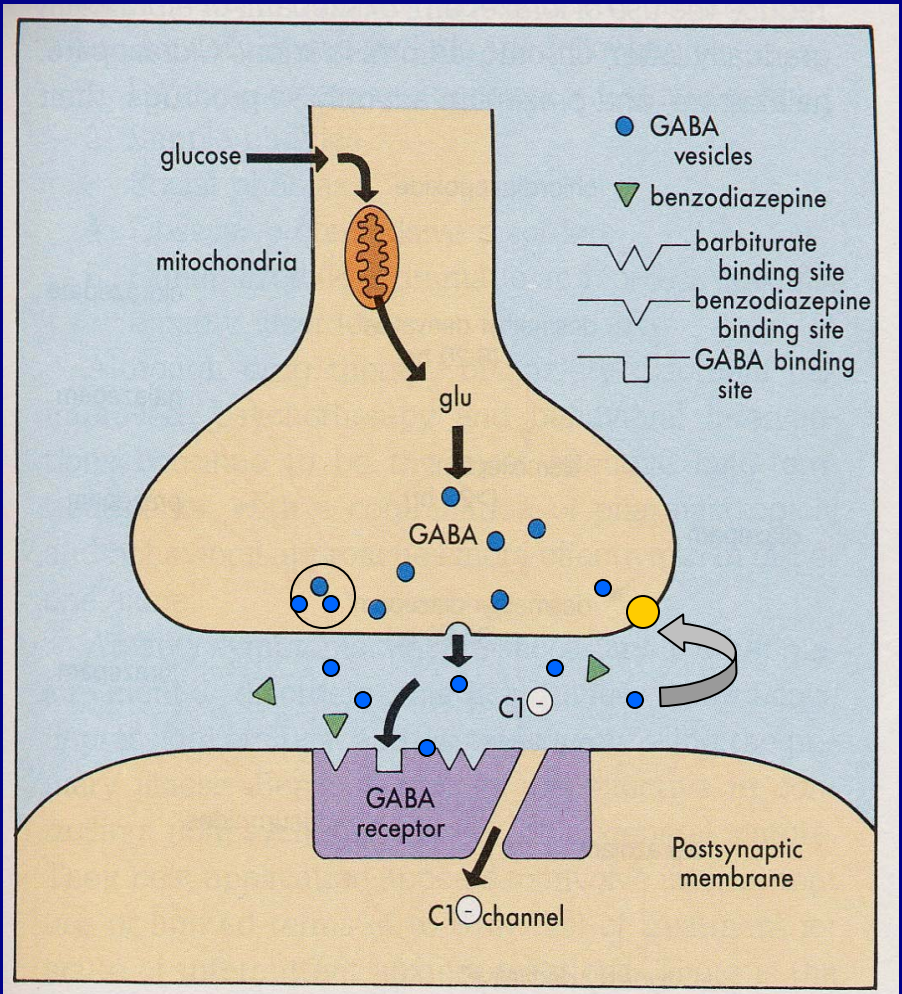


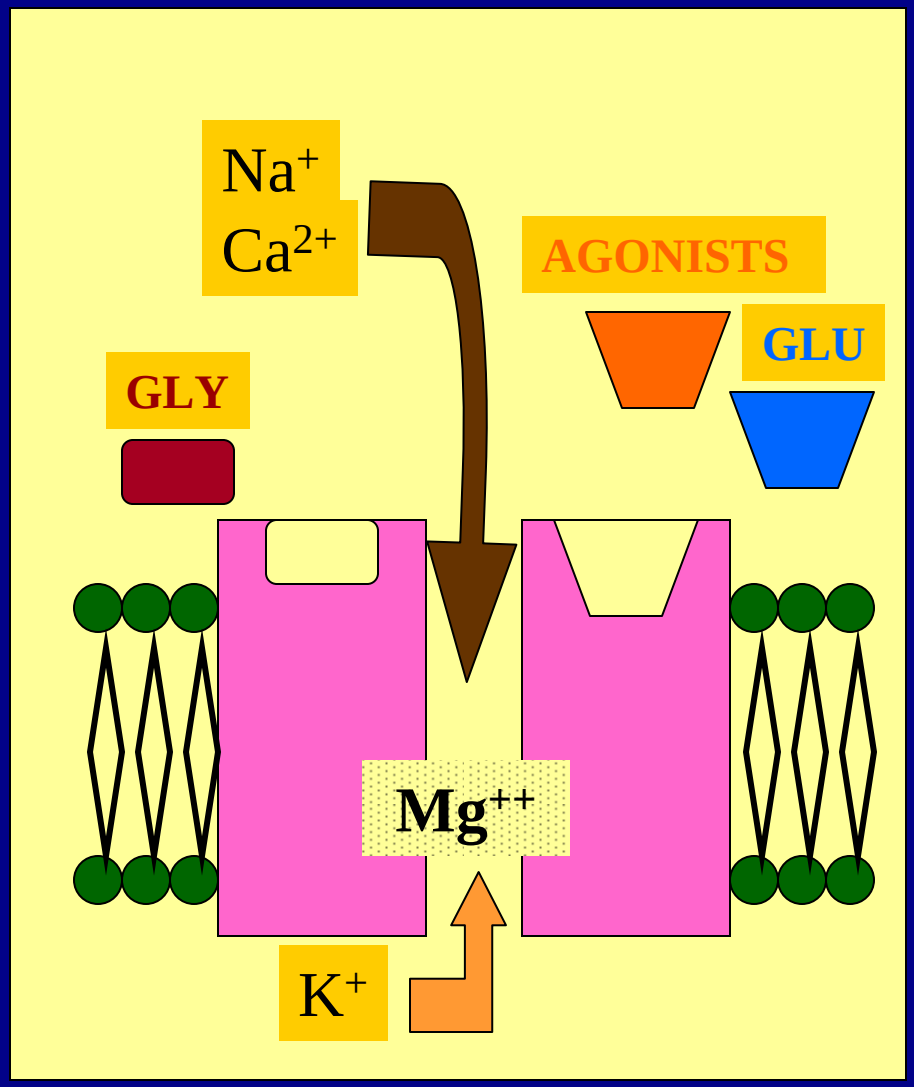
FIGURE 25-2 GABA-benzodiazepine postsynaptic system. Presynaptic system not shown. *Glu*, Glutamic; *GABA*, γ-aminobutyric acid.

Drugs that Act at the GABAergic Synapse

- GABA agonists
- GABA antagonists
- Barbiturates
- Benzodiazepines
- GABA uptake inhibitors

Goal : ↑ GABA Activity

GLUTAMATERGIC SYNAPSE



- Excitatory Synapse.
- Permeable to Na^+, Ca^{2+} and K^+.
- Magnesium ions block channel in resting state.
- Glycine (GLY) binding enhances the ability of GLU or NMDA to open the channel.
- Agonists: NMDA, AMPA, Kianate.

Goal: ↓ GLU Activity

Treatment of Seizures

1) Hydantoins: *phenytoin*
2) Barbiturates: *phenobarbital*
3) Oxazolidinediones: *trimethadione*
4) Succinimides: *ethosuximide*
5) Acetylureas: *phenacemide*
6) Other: *carbamazepine, lamotrigine, vigabatrin, etc.*
7) Diet
8) Surgery, Vagus Nerve Stimulation (VNS).

Treatment of Seizures

PARTIAL SEIZURES (Simple and Complex, including secondarily generalized)

Drugs of choice: Carbamazepine
Phenytoin
Valproate

Alternatives: Lamotrigine, phenobarbital, primidone, oxcarbamazepine.

Add-on therapy: Gabapentin, topiramate, tiagabine, levetiracetam, zonisamide.

Treatment of Seizures

PRIMARY GENERALIZED TONIC-CLONIC SEIZURES (*Grand Mal*)

Drugs of choice: Carbamazepine
Phenytoin
Valproate*

Alternatives: Lamotrigine, phenobarbital, topiramate, oxcartbazepine, primidone, levetiracetam, phenobarbital.

***Not approved except if absence seizure is involved**

Drugs for Partial Seizures and Generalized Tonic-Clonic Seizures

- **Phenytoin – preferentially binds to and prolongs the inactive state of voltage-sensitive Na channels**
- **Carbamazepine –tricyclic compound that blocks voltage-sensitive Na channels and acts presynaptically to decrease synaptic transmission.**

Carbamazepine induces microsomal enzymes leading to an increase in its own clearance after chronic use and several important drug interactions

- **Valproate – blocks voltage-sensitive Na channels and T-type Ca2+ channels, increases GABA synthesis, decreases GABA degradation, may decrease glutamate synthesis**

Adjuncts in the treatment of Partial Seizures

- **Felbamate – blocks glycine activation of NMDA receptors and inhibit initiation of seizures**

- **Gabapentin – despite the fact that Gabapentin has a similar structural relationship to GABA, it does not act on the GABA receptor. Gabapentin may alter GABA metabolism or alter reuptake by presynaptic GABA transporters.**

- **Lamotrigine – blocks voltage-sensitive NA channels and has another mechanism of action (inhibits the release of excitatory amino acids such as glutamate?)**

- **Topiramate - blocks voltage-sensitive NA channels, augments GABA activation of $GABA_A$ receptor, blocks kainate and AMPA glutamate receptors**

Treatment of Seizures

GENERALIZED ABSENCE SEIZURES

Drugs of choice: Ethosuximide

Valproate*

Alternatives: Lamotrigine, clonazepam, zonisamide, topiramate (?).

*** First choice if primary generalized tonic-clonic seizure is also present.**

Treatment of Seizures

ATYPICAL ABSENCE, MYOCLONIC, ATONIC* SEIZURES

Drugs of choice: Valproate**

Lamotrigine***

Alternatives: Topiramate, clonazepam, zonisamide, felbamate.

*** Often refractory to medications.**

****Not approved except if absence seizure is involved.**

***** Not FDA approved for this indication.**

Treatment of Seizures

INFANTILE SPASMS

Drugs of choice: Corticotropin (IM) or
Corticosteroids (Prednisone)
Zonisamide

Alternatives: Clonazepam, nitrazepam, vigabatrin, phenobarbital.

Infantile Spasms

- Infantile spasms are an epileptic syndrome and not a seizure type.
- The attacks although sometimes fragmentary are most often bilateral and are included, for pragmatic purposes, with the generalized seizures.
- Characterized by recurrent myoclonic jerks with sudden flexion or extension of the body and limbs; the form of infantile spasms are, however, quite heterogeneous.
- 90% have their first attack before the age of 1 year.
- Most patients are mentally retarded, presumably from the same cause of the spasms.
- The cause is unknown. Infections, kernicterus, tuberous sclerosis and hypoglycemia have all been implicated.

Drugs for Partial Seizures and Generalized Tonic-Clonic Seizures

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Status Epilepticus

Status Epilepticus

Status epilepticus exists when seizures recur within a short period of time , such that baseline consciousness is not regained between the seizures. They last for at least 30 minutes. Can lead to systemic hypoxia, acidemia, hyperpyrexia, cardiovascular collapse, and renal shutdown.

- The most common, generalized tonic-clonic status epilepticus is life-threatening and must be treated immediately with concomitant cardiovascular, respiratory and metabolic management.

Drugs for Status Epilepticus

- **Diazepam – GABA mediated Cl^- flux**
- **Phenytoin – voltage-sensitive Na channels**
- **Phenobarbital –if necessary**
- **General anesthesia**

DIAZEPAM (Valium) AND LORAZEPAM (Ativan)

- Benzodiazepines.
- Will also be discussed with Sedative hypnotics.
- Given I.V.
- Lorazepam may be longer acting.
- 1° for treating *status epilepticus*
- Have muscle relaxant activity.
- Allosteric modulators of GABA receptors.
- Potentiates GABA function, by increasing the frequency of channel opening.

Toxicity

- Sedation
- Children may manifest a paradoxical hyperactivity.
- Tolerance

Treatment of *Status Epilepticus* in Adults

Initial

- Diazepam, i.v. 5-10 mg (1-2 mg/min)

  repeat dose (5-10 mg) every 20-30 min.
- Lorazepam, i.v. 2-6 mg (1 mg/min)

  repeat dose (2-6 mg) every 20-30 min.

Follow-up

- Phenytoin, i.v. 15-20 mg/Kg (30-50 mg/min).

  repeat dose (100-150 mg) every 30 min.
- Phenobarbital, i.v. 10-20 mg/Kg (25-30mg/min).

  repeat dose (120-240 mg) every 20 min.

Status epilepticus

0-5 min	history, physical examination, intubation?, ECG
5-10 min	start 2 large bore IV saline, dextrose, thiamine, lorazepam or diazapam IV
10-30 min	Phenytoin or phenobarbital IV
30-60 min	If seizures persist after phenytoin, use phenobarbital or vice versa. Admit to CCU, get EEG, consider thiopental, propofol

Drug interactions

- Many antiepileptic drugs interact with other medications
- Carbamazepine and phenytoin induce cytochrome P450 enzymes
- Phenytoin – plasma protein bound
- Valproate inhibits the metabolism of phenobarbital, phenytoin, carbamazepine and ethosuximide

INTERACTIONS BETWEEN ANTISEIZURE DRUGS

With other antiepileptic Drugs:

- Carbamazepine with

phenytoin	**Increased metabolism of carbamazepine**
phenobarbital	**Increased metabolism of epoxide.**

- Phenytoin with

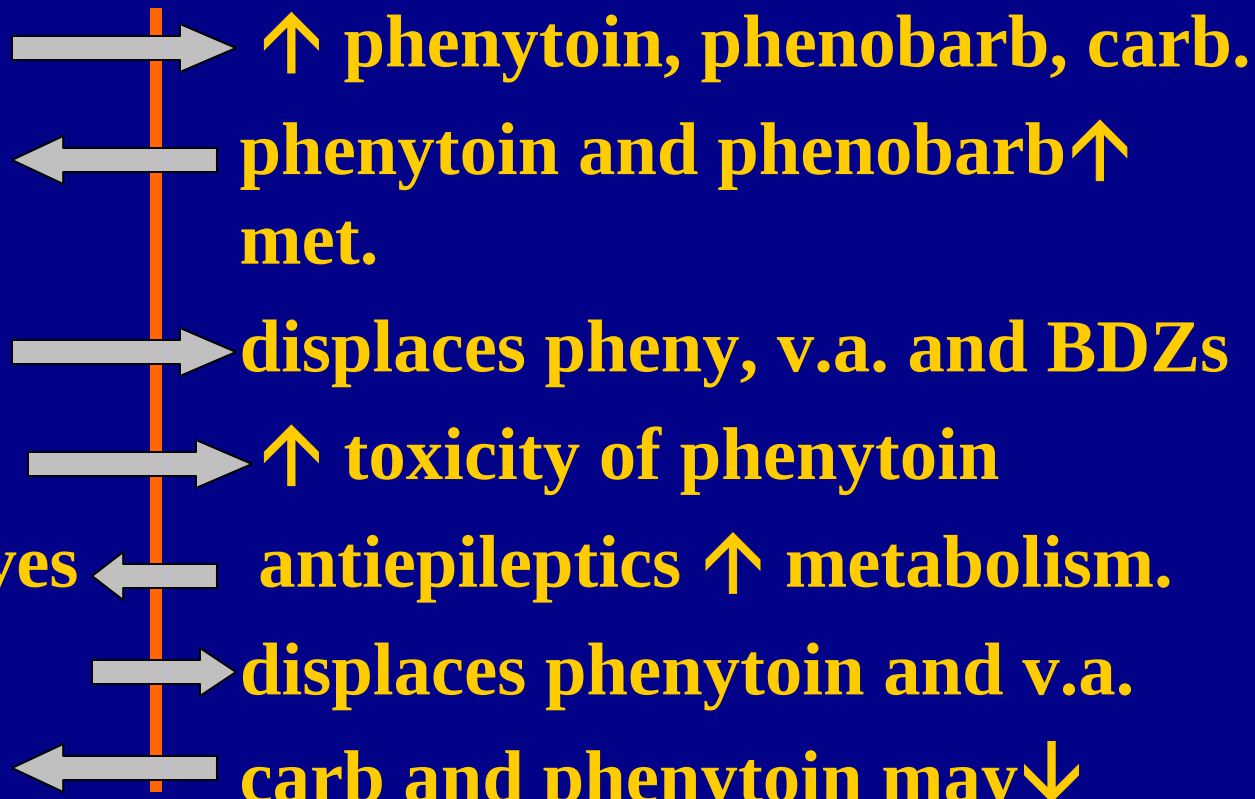
primidone	**Increased conversion to phenobarbital.**

- Valproic acid with

clonazepam	**May precipitate nonconvulsive status epilepticus**
phenobarbital	**Decrease metabolism, increase toxicity.**
phenytoin	**Displacement from binding, increase toxicity.**

ANTISEIZURE DRUG INTERACTIONS

With other drugs:



Side Effects

- **Antiepileptic drugs frequently produce CNS and gastrointestinal side effects**
- **Some antiepileptic drugs infrequently cause severe hematologic or hepatic toxicity**
- **Valproate and phenytoin cause birth defects**

Management of Seizure Disorders

- Start therapy with low dose of single drug
- Increase dose to attain serum concentration
- If single drug is not effective, a second drug may be added or substituted
- Discontinue drug use slowly
- Monitor serum levels to ensure adequate dosage (toxicity, therapeutic failure or non-compliance)

Therapeutic choices

Seizure type	1st choice	alternative or add-on
Tonic-clonic	carbamazepine	clobazam
	phenytoin	lamotrigine
	valproic acid	topiramate
Absence	ethosuximide	clobazam
	valproic acid	lamotrigine
		topiramate
Partial (simple or complex)	carbamazepine	clobazam
	phenytoin	lamotrigine
		valproic acid
		phenobarbital

TABLE 20–2. Mechanisms of Antiepileptic Drugs*

Drug	Effects on Ion Flux	Effects on GABA	Effects on Glutamate
Carbamazepine	Blocks voltage-sensitive sodium channels.	—	—
Clonazepam	—	Enhances GABA-mediated chloride flux.	—
Clorazepate	—	Enhances GABA-mediated chloride flux.	—
Diazepam	—	Enhances GABA-mediated chloride flux.	—
Ethosuximide	Blocks T-type calcium channels.	—	—
Felbamate	—	—	Blocks glycine activation of NMDA receptors.
Gabapentin	—	Increases GABA release.	—
Lamotrigine	Blocks voltage-sensitive sodium channels.	—	—
Lorazepam	—	Enhances GABA-mediated chloride flux.	—
Phenobarbital	—	Enhances GABA-mediated chloride flux.	—
Phenytoin	Blocks voltage-sensitive sodium channels.	—	—
Primidone	Possibly blocks voltage-sensitive sodium channels.	Enhances GABA-mediated chloride flux.	—
Topiramate	Blocks voltage-sensitive sodium channels.	Increases GABA activation of $GABA_A$ receptors.	Blocks kainate and AMPA receptors.
Valproate	Possibly blocks voltage-sensitive sodium channels and T-type calcium channels.	Increases GABA synthesis and inhibits GABA degradation.	Possibly decreases glutamate synthesis.

*AMPA = α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid; GABA = gamma-aminobutyric acid; and NMDA = *N*-methyl-D-aspartate.

Table 1
Proposed mechanisms of antiepileptic drug action

	↓ Na^+ channels	↓ Ca^{2+} channels	↑ K^+ channels	↑ Inhibitory transmission	↓ Excitatory transmission
Established AEDs					
PHT	+++				
CBZ	+++				
ESM		+++			
PB		+		+++	+
BZDs				+++	
VPA	+	+		++	+
New AEDs					
LTG	+++	+			
OXC	+++	+	+		
ZNS	++	++			
VGB				+++	
TGB				+++	
GBP	+	+		++	
FBM	++	++		++	++
TPM	++	++		++	++
LEV		+		+	+

+++, primary action; ++, probable action; +, possible action.

Data from Upton (1994), Schachter (1995), Macdonald & Kelly (1995), Meldrum (1996), Coulter (1997), and White (1999).

Pharmacokinetic Parameters

Effective plasma levels of six antiepileptic drugs [1]

Drug	Effective Level (μg/mL)	High Effective Level[2] (μg/mL)	Toxic Level (μg/mL)
Carbamazepine	4–12	7	> 8
Primidone	5–15	10	< 12
Phenytoin	10–20	18	> 20
Phenobarbital	10–40	35	> 40
Ethosuximide	50–100	80	> 100
Valproate	50–100	80	> 100

PHENYTOIN (Dilantin)

- Oldest nonsedative antiepileptic drug.
- Fosphenytoin, a more soluble prodrug is used for parenteral use.
- "Fetal hydantoin syndrome"
- It alters Na^+, Ca^{2+} and K^+ conductances.
- Inhibits high frequency repetitive firing.
- Alters membrane potentials.
- Alters a.a. concentration.
- Alters NTs (NE, ACh, GABA)

Toxicity:

- **Ataxia and nystagmus.**
- **Cognitive impairment.**
- **Hirsutism**
- **Gingival hyperplasia.**
- **Coarsening of facial features.**
- **Dose-dependent zero order kinetics.**
- **Exacerbates absence seizures.**

Fetal Hydantoin Syndrome

- Pre- and postnatal growth deficiency with psychomotor retardation, microcephaly with a ridged metopic suture, hypoplasia of the nails and finger-like thumb and hypoplasia of the distal phalanges.
- Radiological skeletal abnormalities reflect the hypoplasia and fused metopic suture.
- Cardiac defects and abnormal genitalia.

Teratogenicity of several anticonvulsant medications is associated with an elevated level of oxidative metabolites that are normally eliminated by the enzyme epoxide hydrolase.

CARBAMAZEPINE (Tegretol)

- Tricyclic, antidepressant (bipolar)
- 3-D conformation similar to phenytoin.
- Mechanism of action, similar to phenytoin. Inhibits high frequency repetitive firing.
- Decreases synaptic activity presynaptically.
- Binds to adenosine receptors (?).
- Inh. uptake and release of NE, but not GABA.
- Potentiates postsynaptic effects of GABA.
- Metabolite is active.

Toxicity:

- Autoinduction of metabolism.
- Nausea and visual disturbances.
- Granulocyte supression.
- Aplastic anemia.
- Exacerbates absence seizures.

OXCARBAZEPINE (Trileptal)

- Closely related to carbamazepine.
- With improved toxicity profile.
- Less potent than carbamazepine.
- Active metabolite.
- Mechanism of action, similar to carbamazepine It alters Na^+ conductance and inhibits high frequency repetitive firing.

Toxicity:

•Hyponatremia

•Less hypersensitivity and induction of hepatic enzymes than with carb.

PHENOBARBITAL (Luminal)

- Except for the bromides, it is the oldest antiepileptic drug.
- Although considered one of the safest drugs, it has sedative effects.
- Many consider them the drugs of choice for seizures only in infants.
- Acid-base balance important.
- Useful for partial, generalized tonic-clonic seizures, and febrile seizures
- Prolongs opening of Cl^- channels.
- Blocks excitatory GLU (AMPA) responses. Blocks Ca^{2+} currents (L,N).
- Inhibits high frequency, repetitive firing of neurons only at high concentrations.

Toxicity:

- Sedation.
- Cognitive impairment.
- Behavioral changes.
- Induction of liver enzymes.
- May worsen absence and atonic seizures.

PRIMIDONE (Mysolin)

- Metabolized to phenobarbital and phenylethylmalonamide (PEMA), both active metabolites.
- Effective against partial and generalized tonic-clonic seizures.
- Absorbed completely, low binding to plasma proteins.
- Should be started slowly to avoid sedation and GI problems.
- Its mechanism of action may be closer to phenytoin than the barbiturates.

Toxicity:

•Same as phenobarbital

•Sedation occurs early.

•Gastrointestinal complaints.

VALPROATE (Depakene)

- Fully ionized at body pH, thus active form is valproate ion.
- One of a series of carboxylic acids with antiepileptic activity. Its amides and esters are also active.
- Mechanism of action, similar to phenytoin.
- ⇑ levels of GABA in brain.
- May facilitate Glutamic acid decarboxylase (GAD).
- Inhibits GAT-1. ⇓ $[aspartate]_{Brain}$?
- May increase membrane potassium conductance.

Toxicity:

- Elevated liver enzymes including own.
- Nausea and vomiting.
- Abdominal pain and heartburn.
- Tremor, hair loss,
- Weight gain.
- Idiosyncratic **hepatotoxicity.**
- Negative interactions with other antiepileptics.
- Teratogen: spina bifida

ETHOSUXIMIDE (Zarontin)

- Drug of choice for absence seizures.
- High efficacy and safety.
- VD = TBW.
- Not plasma protein or fat binding
- Mechanism of action involves reducing low-threshold Ca^{2+} channel current (T-type channel) in thalamus.

At high concentrations:

- Inhibits Na+/K+ ATPase.
- Depresses cerebral metabolic rate.
- Inhibits GABA aminotransferase.
  - **Phensuximide = less effective**
  - **Methsuximide = more toxic**

Toxicity:

- Gastric distress, including, pain, nausea and vomiting
- Lethargy and fatigue
- Headache
- Hiccups
- Euphoria
- Skin rashes
- Lupus erythematosus (?)

CLONAZEPAM (Klonopin)

- A benzodiazepine.
- Long acting drug with efficacy for absence seizures.
- One of the most potent antiepileptic agents known.
- Also effective in some cases of myoclonic seizures.
- Has been tried in infantile spasms.
- Doses should start small.
- Increases the frequency of Cl^- channel opening.

Toxicity:

- Sedation is prominent.
- Ataxia.
- Behavior disorders.

VIGABATRIN (γ-vinyl-GABA)

- Absorption is rapid, bioavailability is ~ 60%, $T_{1/2}$ 6-8 hrs, eliminated by the kidneys.
- Use for partial seizures and West's syndrome.
- Contraindicated if preexisting mental illness is present.
- Irreversible inhibitor of GABA-aminotransferase (enzyme responsible for metabolism of GABA) => Increases inhibitory effects of GABA.
- S(+) enantiomer is active.

Toxicity:

- Drowsiness
- Dizziness
- Weight gain

- Agitation
- Confusion
- Psychosis

LAMOTRIGINE (Lamictal)

- Presently use as add-on therapy with valproic acid (v.a. conc. are be reduced).
- Almost completely absorbed
- $T_{1/2}$ = 24 hrs
- Low plasma protein binding
- Also effective in myoclonic and generalized seizures in childhood and absence attacks.
- Suppresses sustained rapid firing of neurons and produces a voltage and use-dependent inactivation of sodium channels, thus its efficacy in partial seizures.

Toxicity:

- Dizziness
- Headache
- Diplopia
- Nausea
- Somnolence
- Rash

FELBAMATE (Felbatrol)

- Effective against partial seizures but has severe side effects.
- Because of its severe side effects, it has been relegated to a third-line drug used only for refractory cases.

Toxicity:

- Aplastic anemia
- Severe hepatitis

TOPIRAMATE (Topamax)

- Rapidly absorbed, bioav. is > 80%, has no active metabolites, excreted in urine. $T_{1/2}$ = 20-30 hrs
- Blocks repetitive firing of cultured neurons, thus its mechanism may involve blocking of voltage-dependent sodium channels
- Potentiates inhibitory effects of GABA (acting at a site different from BDZs and BARBs).
- Depresses excitatory action of kainate on AMPA receptors.
- Teratogenic in animal models.

Toxicity:

- Somnolence
- Fatigue
- Dizziness
- Cognitive slowing
- Paresthesias
- Nervousness
- Confusion
- Urolithiasis

TIAGABINE (Gabatril)

- Derivative of nipecotic acid.
- 100% bioavailable, highly protein bound.
- $T_{1/2}$ = 5 -8 hrs
- Effective against partial and generalized tonic-clonic seizures.
- GABA uptake inhibitor GAT-1.

Toxicity:

- Dizziness
- Nervousness
- Tremor
- Difficulty concentrating
- Depression
- Asthenia
- Emotional lability
- Psychosis
- Skin rash

ZONISAMIDE (Zonegran)

- Sulfonamide derivative.
- Marketed in Japan.
- Good bioavailability, low pb.
- $T_{1/2}$ = 1 - 3 days
- Effective against partial and generalized tonic-clonic seizures.
- Mechanism of action involves voltage and use-dependent inactivation of sodium channels (?).
- May also involve Ca^{2+} channels.

Toxicity:

•Drowsiness

•Cognitive impairment

•High incidence of renal stones (?).

GABAPENTIN (Neurontin)

- Used as an adjunct in partial and generalized tonic-clonic seizures.
- Does not induce liver enzymes.
- not bound to plasma proteins.
- drug-drug interactions are negligible.
- Low potency.
- An a.a.. Analog of GABA that does not act on GABA receptors, it may however alter its metabolism, non-synaptic release and transport.

Toxicity:

- Somnolence.
- Dizziness.
- Ataxia.
- Headache.
- Tremor.