ANTISEIZURE DRUGS

(ANTICONVULSANT DRUGS OR ANTIEPILEPTIC DRUGS)

Definition of Epilepsy

- It is a **Chronic** medical condition produced by sudden changes in the electrical function of the brain.

Nature of Epilepsy

- Epilepsy affects about 0.5% of the population.
- The characteristic event is the seizure, which is often associated with convulsion, but may occur in many other forms.
- The seizure is caused by an abnormal high-frequency discharge of a group of neurons, starting locally and spreading to a varying extent to affect other parts of the brain.

Nature of Epilepsy

- The neurochemical basis of the abnormal discharge is not well understood. It may be associated with enhanced excitatory amino acid transmission, impaired inhibitory transmission, or abnormal electrical properties of the affected cells. The glutamate content in areas surrounding an epileptic focus is often raised.

SEIZURE

- PRIMARY SEIZURES
- SECONDARY SEIZURES

Etiology

- **Congenital defects, head injuries, trauma, hypoxia**
- **Infection e.g. meningitis, brain abscess, viral encephalitis**
- **Brain tumors (including tuberculoma), vascular occlusion.**
- **Drug withdrawal, e.g. CNS depressants .**
- **Fever in children (febrile convulsion).**
- **Hypoglycemia**

TRIGGERS:

Fatigue, stress, poor nutrition, alcohol and sleep deprivation.

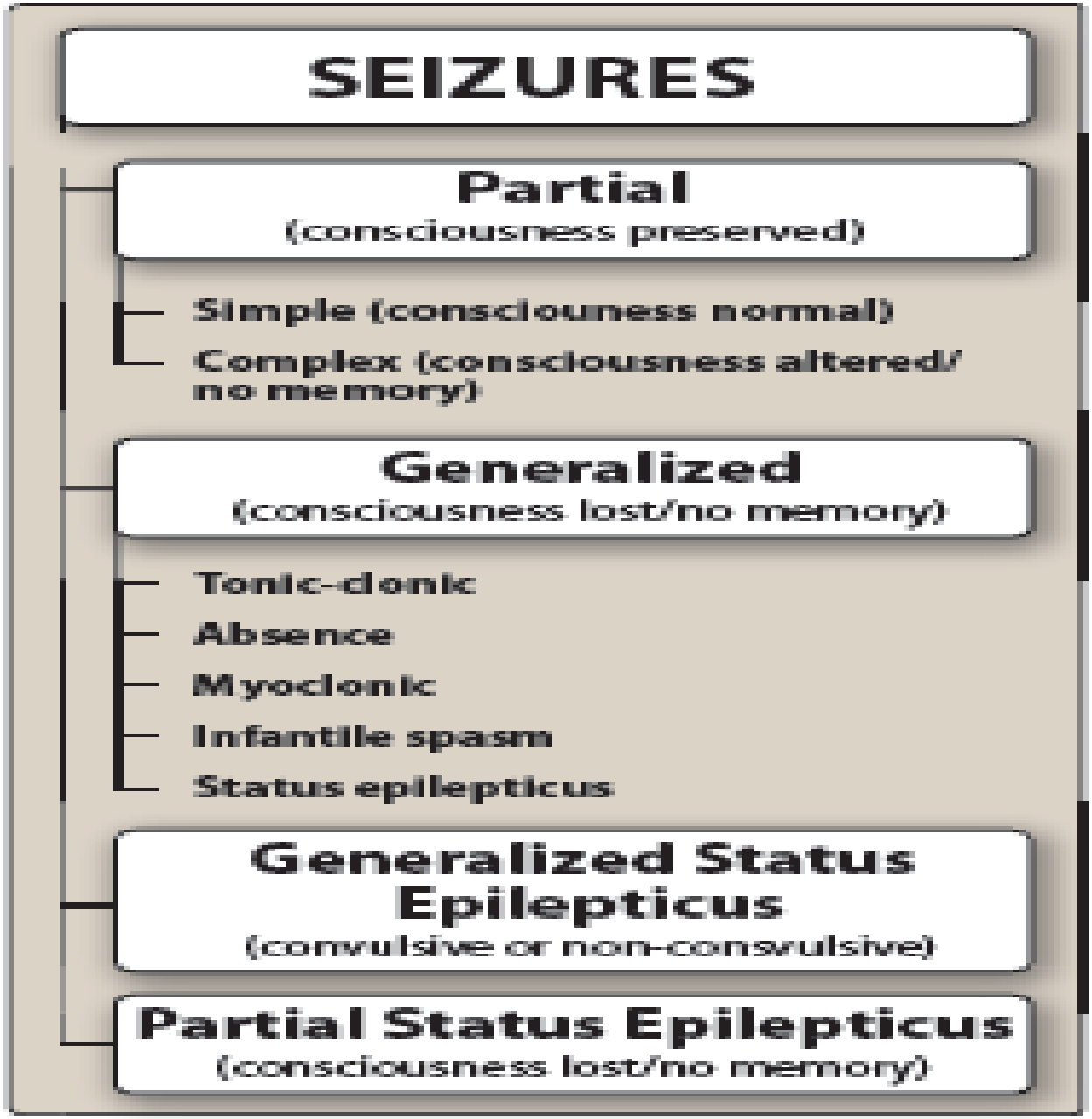
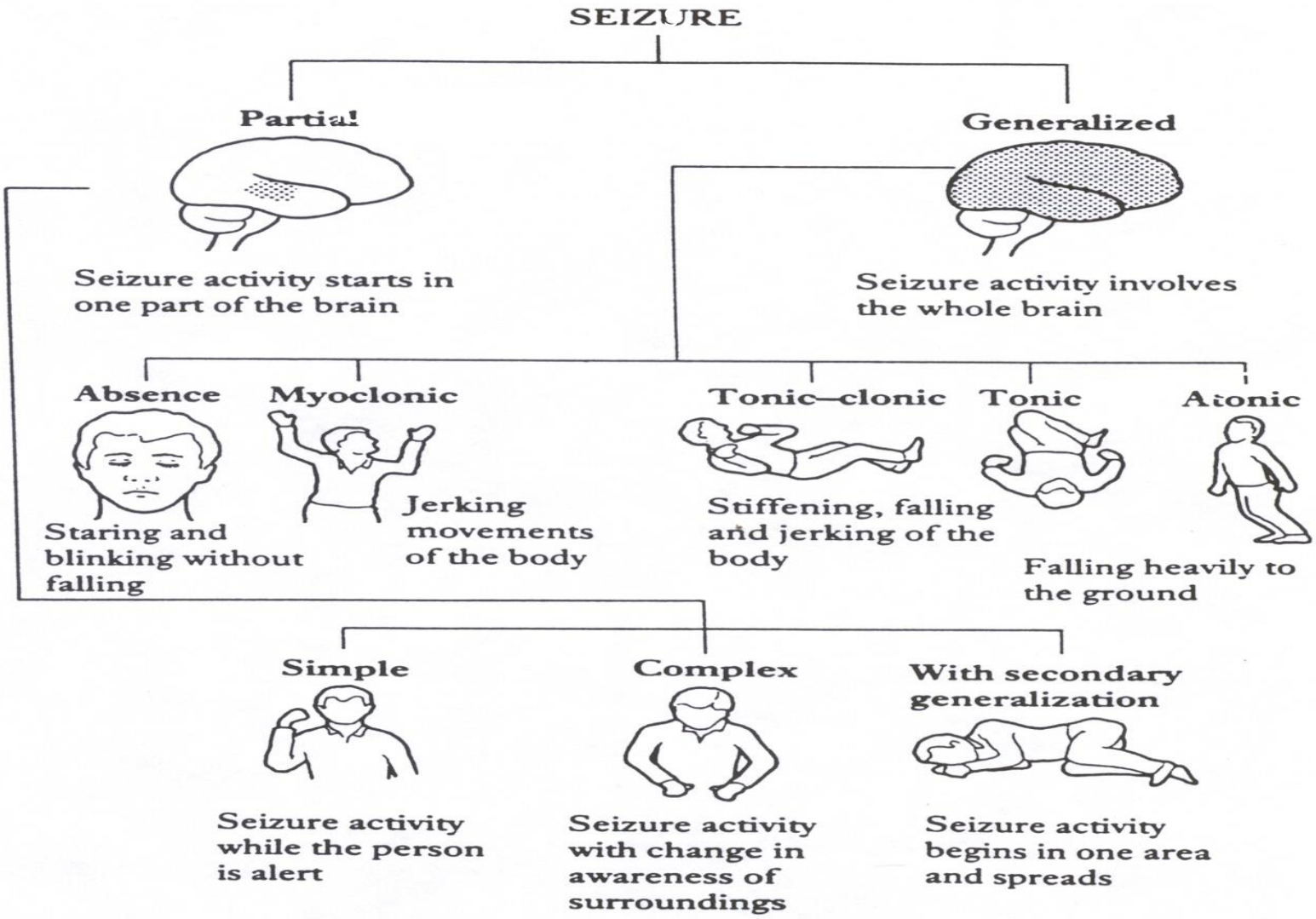


Figure 15.3
Classification of epilepsy.


SEIZURE
Partial
Generalized
Seizure activity starts in one part of the brain
Seizure activity involves the whole brain
Absence
Myoclonic
Tonic–clonic
Tonic
Atonic
Staring and blinking without falling
Jerking movements of the body
Stiffening, falling and jerking of the body
Falling heavily to the ground
Simple
Complex
With secondary generalization
Seizure activity while the person is alert
Seizure activity with change in awareness of surroundings
Seizure activity begins in one area and spreads

CLASSIFICATION OF SEIZURE TYPES

PARTIAL SEIZURES

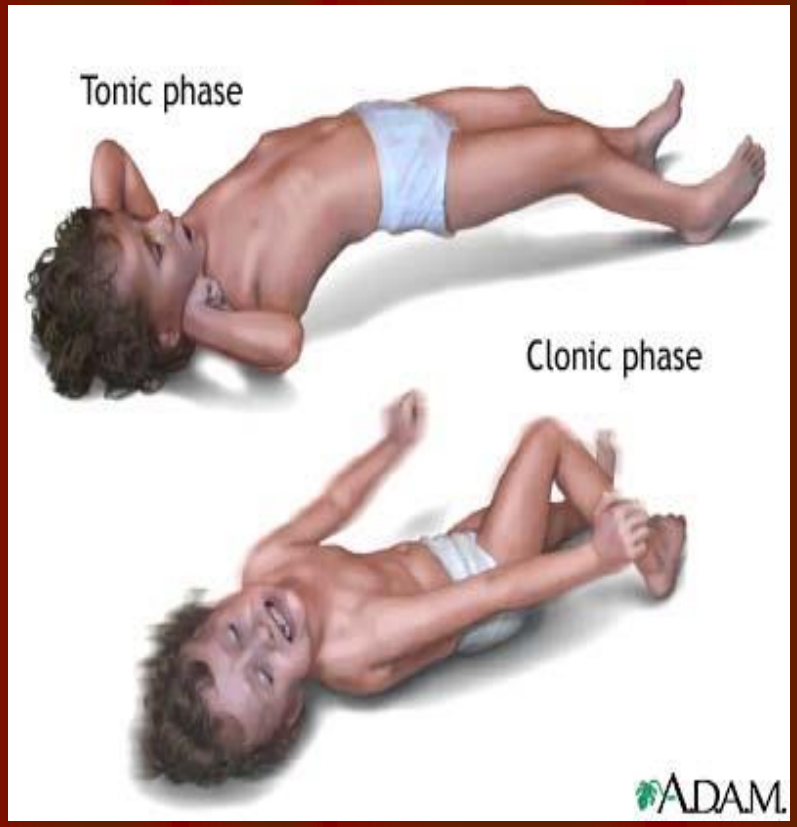
- Simple partial seizures
- Complex partial seizures
- Partial seizures secondarily generalized

CLASSIFICATION OF SEIZURE TYPES

GENERALIZED SEIZURES

- Generalized tonic-clonic (grand mal) Sz
- Absence (petit mal) seizures
- Tonic/ Atonic Seizures
- Clonic & myoclonic seizures
- Infantile Spasms
- Febrile Seizures
- Status Epilepticus

seizure



Carbamazepine TEGRETOL

Diazepam VALIUM

Divalproex DEPAKOTE

Ethosuximide ZARONTIN

Felbamate FELBATOL

Gabapentin NEURONTIN

Lacosamide VIMPAT

Lamotrigine LAMICTAL

Levetiracetam KEPPRA

Lorazepam ATIVAN

Oxcarbazepine TRILEPTAL

Phenobarbital LUMINAL

Phenytoin DILANTIN

Fosphenytoin CEREBYX

Primidone MYSOLINE

Rufinamide BANZEL

Tiagabine GABITRIL

Topiramate TOPAMAX

Vigabatrin SABRIL

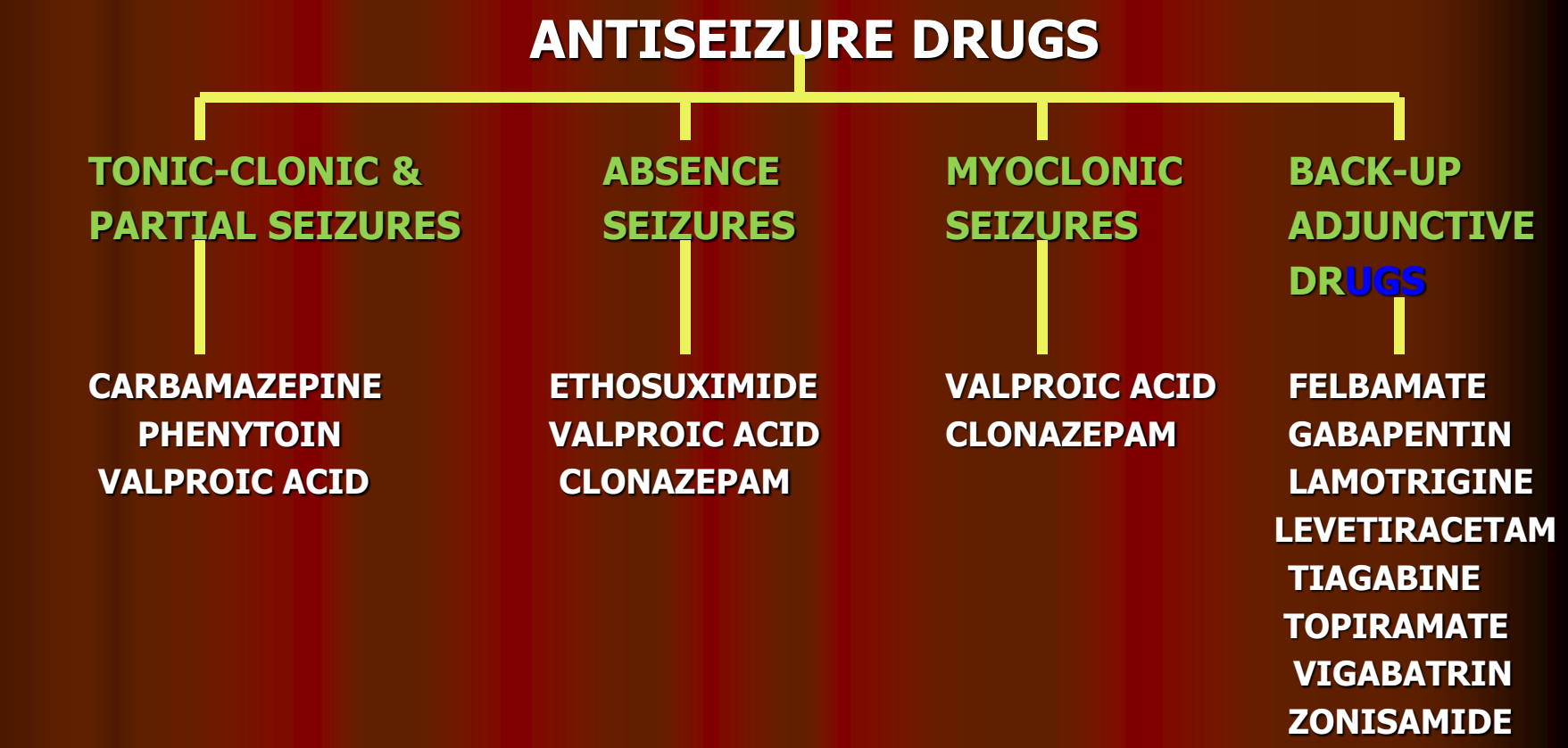
Zonisamide ZONEGRAN

Figure 15.1
Summary of agents used in the treatment of epilepsy. Drugs arranged alphabetically.

Nature of Epilepsy

- Current drug therapy is effective in 70-80% of patients.

ANTISEIZURE DRUGS



Clinical Uses of Antiepileptic Drugs

- *Tonic-clonic (grand mal)* seizures: **carbamazepine** preferred because of low incidence of side-effects, **phenytoin**, **valproate**. Use of single drug is preferred when possible, because of risk of pharmacokinetic interactions.
- *Partial (focal)* seizures: **carbamazepine**, **valproate**; **clonazepam** or **phenytoin** are alternatives.

Clinical Uses of Antiepileptic Drugs

- *Absence seizures (petit mal)*: **ethosuximide** or **valproate**. Valproate is used when absence seizures coexist with tonic-clonic seizures, since most drugs used for tonic-clonic seizures may worsen absence seizures.
- *Myoclonic seizures*: **valproate** or **clonazepam**.
- *Status epilepticus*: must be treated as an emergency, with diazepam intravenously.

Mechanism of Action

- *Current antiepileptic drugs are thought to act mainly by two main mechanisms:*
  - Reducing electrical excitability of cell membranes, possibly through inhibition of sodium channel.
  - Enhancing GABA-mediated synaptic inhibition. This may be achieved by an enhanced pre- or post-synaptic action of GABA, by inhibiting GABA-transaminase, or by drugs with direct GABA-agonist properties.

Mechanism of Action

- A few drugs appear to act by a third mechanism, namely inhibition of T-type calcium channels.
- Newer drugs act by other mechanism, yet to be elucidated.
- Drugs that block excitatory amino acid receptors are effective in animal models, but not yet developed for clinical use.

ANTISEIZURE DRUGS

MECHANISM OF ACTION

A. SODIUM CHANNEL BLOCKADE

- Phenytoin, carbamazepine , valproic acid and lamotrigine
  - Block voltage-gated sodium channels

ANTISEIZURE DRUGS

MECHANISM OF ACTION

B. GABA-RELATED TARGETS

- Benzodiazepines
  - Interact with specific $GABA_A$ receptor-chloride ion channel macromolecular complex
  - Frequency of Cl^- ion channel opening is increased
  - Facilitates the inhibitory effects of GABA

ANTISEIZURE DRUGS

MECHANISM OF ACTION

B. GABA-RELATED TARGETS

- Phenobarbital and other barbiturates
  - Enhance the inhibitory actions of GABA
  - Interact with different receptor site on Cl^- ion channel
  - Increased duration of Cl^- ion channel opening

ANTISEIZURE DRUGS

MECHANISM OF ACTION

B. GABA-RELATED TARGETS

- GABA transaminase
  - An important enzyme in the termination of action of GABA
  - Vigabatrin
    - Irreversibly inactivates the enzyme at therapeutic plasma levels

ANTISEIZURE DRUGS

MECHANISM OF ACTION

B. GABA-RELATED TARGETS

- GABA transaminase
  - Valproic acid
    - Inhibits the enzyme by at very high concentrations

ANTISEIZURE DRUGS

MECHANISM OF ACTION

B. GABA-RELATED TARGETS

- Tiagabine
  - Inhibits reuptake of GABA transporters in neurons and glia

ANTISEIZURE DRUGS

MECHANISM OF ACTION

C. CALCIUM CHANNEL BLOCKADE

- Ethosuximide
  - Inhibits low-threshold (T type) Ca^{2+} currents
  - Valproic acid has similar action

ANTISEIZURE DRUGS

MECHANISM OF ACTION

D. OTHER MECHANISMS

- Valproic acid
  - Neuronal membrane hyperpolarization enhancing K^+ channel permeability
- Phenobarbital
  - Antagonist at some glutamate receptors

ANTISEIZURE DRUGS

MECHANISM OF ACTION

D. OTHER MECHANISMS

- Felbamate
  - Blocks glutamate NMDA receptors
- Topiramate
  - Blocks sodium channels
  - Potentiates the action of GABA
  - May also block glutamate receptors

ANTISEIZURE DRUGS

ANTISEIZURE DRUGS

- Well absorbed orally
- Good bioavailability
- Most drugs metabolized by hepatic enzymes → active metabolites

ANTISEIZURE DRUGS

ANTISEIZURE DRUGS

- DRUG INTERACTIONS are common

1. Drugs that inhibit antiseizure drug metabolism or displace anticonvulsant from plasma protein bindings sites → toxic levels of plasma concentration

ANTISEIZURE DRUGS

ANTISEIZURE DRUGS

- DRUG INTERACTIONS are common

2. Drugs that induce hepatic drug-metabolizing enzymes (e.g., rifampicin) → inadequate levels of plasma concentration

PHENYTOIN

- Diphenylhydantoin
- Non-sedating
- Blocks sodium channels
- USE: partial seizures; generalized tonic-clonic seizures, Antiarrhymic drug
- Oral, IV
- T ½ 12 -36 hrs
- Oral bioavailability is variable
  - Individual differences in first-pass metabolism

PHENYTOIN

Binds extensively to plasma proteins (97-98%)

- Therapeutic concentration (TC) 10-20 mg/ml
  - 5-7 days to reach steady state at low blood concentration
  - 4-6 weeks to reach steady state at high blood concentration
- *Fosphenytoin* is a water-soluble prodrug form that is used parenterally

PHENYTOIN

- Free (unbound) levels in plasma is increased transiently by drugs that compete for binding
  - Sulfonamides
  - Valproic acid

- Metabolism is enhanced in the presence of inducers of liver metabolism
  - Phenobarbital, Rifampicin, carbamazepine, pyridoxine, theophylline

- Metabolism is inhibited by other drugs
  - Cimetidine, chloramphenicol, Isoniazid

PHENYTOIN **decreases** serum levels of:

carbamazepine, chloramphenicol, corticosteroids, haloperidol, quinidine, theophylline, oral contraceptives, warfarin

PHENYTOIN

- Toxic effects
  - Diplopia
  - Ataxia
  - Hirsutism
  - Gingival hyperplasia
  - Idiosyncratic reactions like rashes
  - Hematologic complications

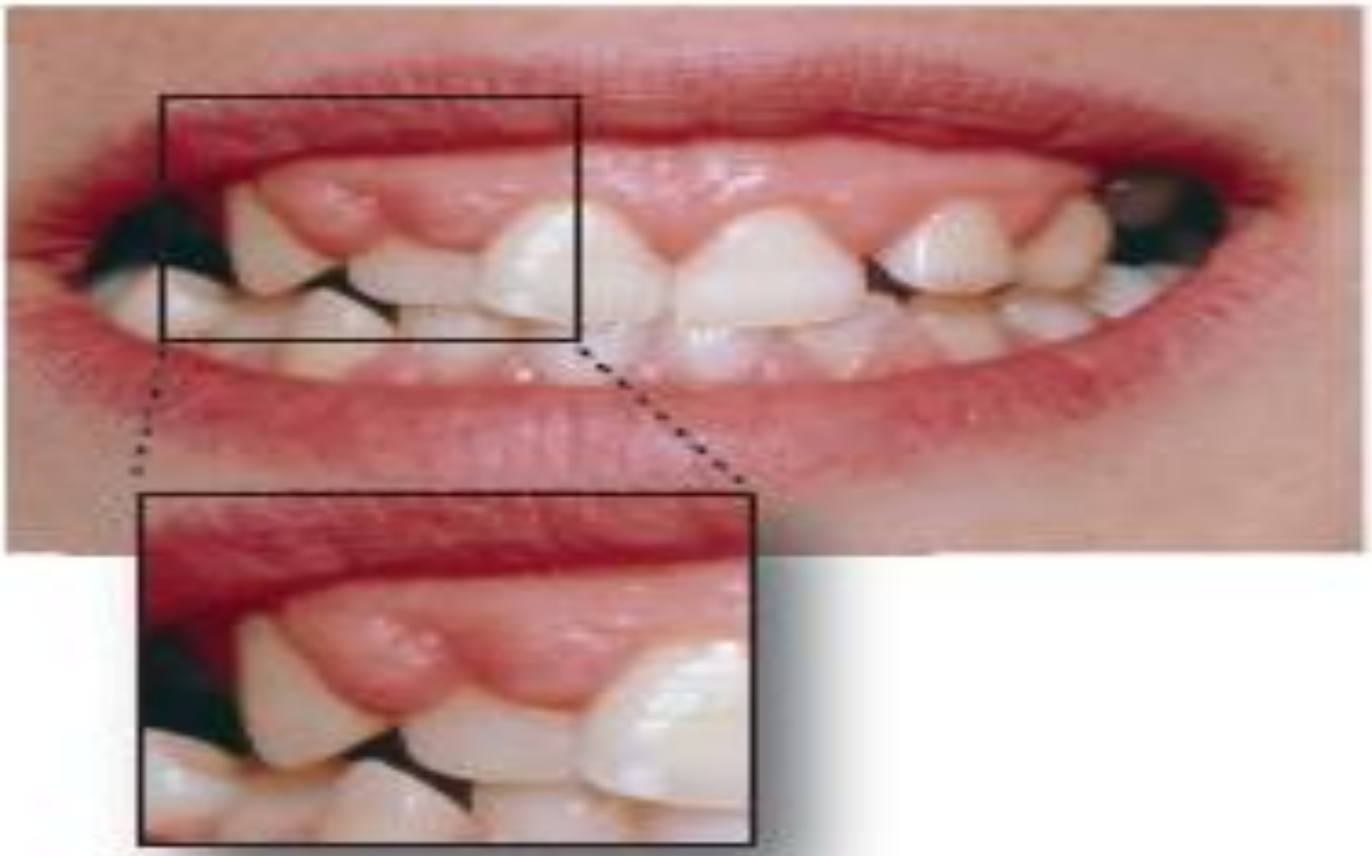


Figure 15.9
Gingival hyperplasia in patient treated with *phenytoin*.

Carbamazepine

- Derivative of tricyclic antidepressants
- Similar profile to that of phenytoin, but with fewer unwanted effects
- Non-sedating
- Blocks sodium channels
- Absorbed orally
- Bound to plasma proteins (70%)
- TC=4-8 microgram/ml

- Effective in most forms of epilepsy (except absence seizures); particularly effective in psychomotor epilepsy;
- Generalized tonic-clonic seizures
- Trigeminal neuralgia
- Mania:bipolar disorders
- Completely metabolized
- CAUSE: diplopia & ataxia, aplastic anemia & agranulocytosis, leukopenia, Rashes

CARBAMAZEPINE DRUG INTERACTIONS

1. I**ncrease** carbamazepine levels via inhibit metabolism: cimetidine, erythromycin, isoniazid
2. **Decrease** carbamazepine levels via increase metabolism: phenytoin, valproic acid
3. Lithium **induces** carbamazepine toxicity.

ANTISEIZURE DRUGS

PHENOBARBITAL

- Barbiturate
- Mephobarbital, methabarbital
- Primidone
  - When metabolize yields phenobarbital
  - Sedating effect
  - For infants

Barbiturates

- Phenobarbital, Luminal: is useful in the treatment of generalized tonic-clonic seizures and status epilepticus.
- Mechanism:(1) block Ca^{2+} currents presynaptic membrane and decrease neurotransmitter release.(2) prolong the openings of the Cl^- channel in postsynaptic membrane and decrease it's response.
- Adverse effects: sedation, depression, drug interaction.
- Tolerance & dependence

PHENOBARBITAL DRUG INTERACTIONS

- **Increase** phenobarbital levels via decrease metabolism; acute ethanol ingestion, chloramphenicol, valproic acid
- Decrease phenobarbital levels via increase metabolism, chronic alcohol ingestion, pyridoxine, rifampin
- Barbiturates **decrease** serum levels: tricyclics, warfarin, beta blockers, oral contraceptives, digitoxin, doxycycline, metronidazole, theophyllline

VIGABATRIN

- Inhibits GABA transaminase
- Partial seizures & 'WEST syndrome
- In patients unresponsive to conventional drugs
- Rapid absorption
- T ½ 6 -8 hrs
- CAUSES: drowsiness, behavioral & mood changes, weight gain, visual field defect

LAMOTRIGINE

- Inhibits sodium channels
- Partial seizures
- Absense seizures
- Completely absorbed
- T ½ of 24 hours
- Broad therapeutic profile
- CAUSES: hypersensitivity rxns, diplopia, ataxia, headache, dizziness, life threatening skin disorders, hematotoxicity

FELBAMATE

- MOA is unknown
- For partial seizures
- Broad therapeutic profile
- T ½ is 20 hrs
- CAUSES: severe hypersensitivity rxs aplastic anemia, hepatotoxicity
- Increase plasma phenytoin & valproic acid
- Decrease carbamazepine levels

GABAPENTIN

- MOA: alters GABA metabolism, its nonsynaptic release or its reuptake by GABA transporters
- Also binds to the α2δ subunit of voltage sensitive calcium channels
- FOR PARTIAL & GENERALIZED SEIZURES
- SATURABLE ABSORPTION

CAUSE: dizziness, ataxia, headache & tremor

TOPIRAMATE

- Complex action: GABA effect, blocks voltage dependent sodium channels
- Similar to phenytoin with lower side effects & simpler pharmacokinetics
- Risk of teratogenesis
- Sedation, mental dulling, renal stones, weight loss

TIAGABINE

- Nicotinic acid derivative
- GABA uptake inhibitor in both neurons & glia
- Partial seizures
- Dizziness, tremor, difficulty in concentration, psychosis

ETHOSUXIMIDE

- Succinimide
- Phenosuximide
- Inhibits calcium channels
- Inhibits NA/K/ ATPase, depresses the cerebral metabolic rate & inhibits GABA aminotransferase
- uses for absense seizures

ETHOSUXIMIDE

- Absorption is complete
- Completely metabolized
- Toxic effects
  - Gastric and hematological abnormalities
  - Skin rashes

- DI: valproic acid inhibits its metabolism

VALPROIC ACID

- calcium channel blockade
- Increased levels of GABA via inhibits GABA transaminase & succinic semialdehyde dehydrogenase
- Sodium channel blockade
- Activates potassium channels

VALPROIC ACID

- Well absorbed;
- Bioavailability > 80%
- T ½ is 9 -18 hrs
- CAUSES: nausea, vomiting, pain & heart burn, sedation uncommon, fine tremors, weight gain, increase in appetite & hair loss, hepatotoxicity, thrombocytopenia,

Valproate

- Valproate is very effective against absence seizure.
- Mechanism: facilitate glutamic acid decarboxylase; inhibit GABA-transaminase; enhance synaptic responses. some effect on sodium channels
- Relatively few unwanted effects: anorexia, nausea, teratogenicity, liver damage (rare, but serious)

VALPROIC DRUG INTERACTIONS

- Decrease valproic acid levels from increase metabolism with carbamazepine
- Increase valproic acid levels with antacid (increase absorption)
- salicylates (displacements from binding sites)
- When used with clonazepam may precipitate absence status

BENZODIAZEPINES

- Diazepam, lorazepam, clonazepam, clorazepate, Nitrazepam, clobazam
- Well absorbed, widely distributed
- Extensively metabolized with many active metabolites
- May cause sedation, tolerance

Benzodiazepine

- Diazepam: preferred drugs for Status epilepticus.
- Nitrazepam: petit mal ,especially myoclonic seizures and infantile spasms.
- Clonazepam: is one of the most effective in some cases of myoclonic seizures. Used in petit mal and status epilepticus

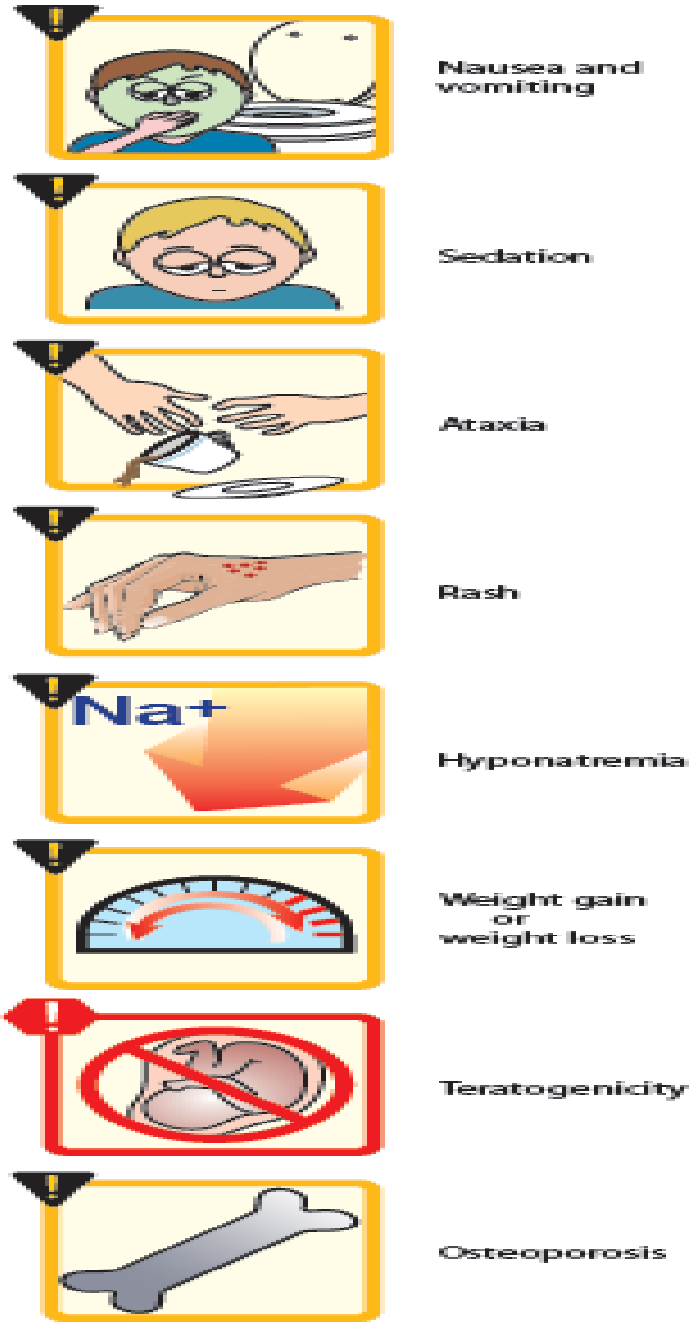


Figure 15.6
Notable adverse effects of anti-seizure medications.

STATUS EPILPETICUS

- DIAZEPAM
- LORAZEPAM
- PHENYTOIN
- PHENOBARBITAL

Antiepileptics and Pregnany:

- Seizure very harmful for pregnant women.
- Monotherapy usually better than drugs combination.
- Folic acid is recommended to be given for every pregnant women with epilepsy
- Phenytoin, sodium valproate are absolutely contraindicated and oxcarbamazepine is better than carbamazepine.
- Experience with new anticonvulsants still not reliable to say that are better than old ones.

Attentions

- Selection of an appropriate antiseizure agent
- Use of single drug
- Withdrawal
- Toxicity
- Fetal malformations