# PHARMCOLOGY

SHEET NO. 8

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# Antiseizure Drugs

we just target the electrical activity of the brain

so we don't call them antiepileptic drugs

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# Antiseizure Drugs

- ~ 1% of the world population has epilepsy.
- Standard therapy permits control of only ~ 80% of seizures (adequate in only 2/3rds).
- Epilepsy is a heterogeneous symptom complex, and a chronic disorder characterized by recurrence.
- Seizures are finite episodes of brain dysfunction resulting from abnormal discharge of cerebral neurons.

# Antiseizure Drugs

- A fraction of epileptic population is resistant to all available drugs, which may be due to increased expression of the multidrug transporter, P-glycoprotein.
- In children, some severe seizures associated with progressive brain damage are very difficult to treat.

– not curable Disease
– Good percentage of individuals are not well controled 20-30%

# TABLE 24–1 International League Against Epilepsy classification of seizure types.

| |
|---|
| **Focal onset (formerly *partial onset*) seizures** |
| Focal aware seizure (formerly *simple partial seizure*) |
| Focal impaired awareness seizure (formerly *complex partial seizure*) |
| Focal-to-bilateral tonic-clonic seizure (formerly *partial seizure secondarily generalized* or *grand mal seizure*) |
| **Generalized onset seizures** |
| Generalized tonic-clonic seizure (formerly *primary generalized tonic-clonic seizure* or *grand mal seizure*) |
| Generalized absence seizure (formerly *petit mal seizure*; occurs, for example, in absence epilepsy) |
| Myoclonic seizure (occurs, for example, in juvenile myoclonic epilepsy and Dravet's syndrome) |
| Atonic seizure (*drop seizure* or *astatic seizure*; occurs, for example, in the Lennox-Gastaut syndrome) |
| Epileptic spasms (as in infantile spasms also known as West's syndrome) |

The Doctor asked to memorize those



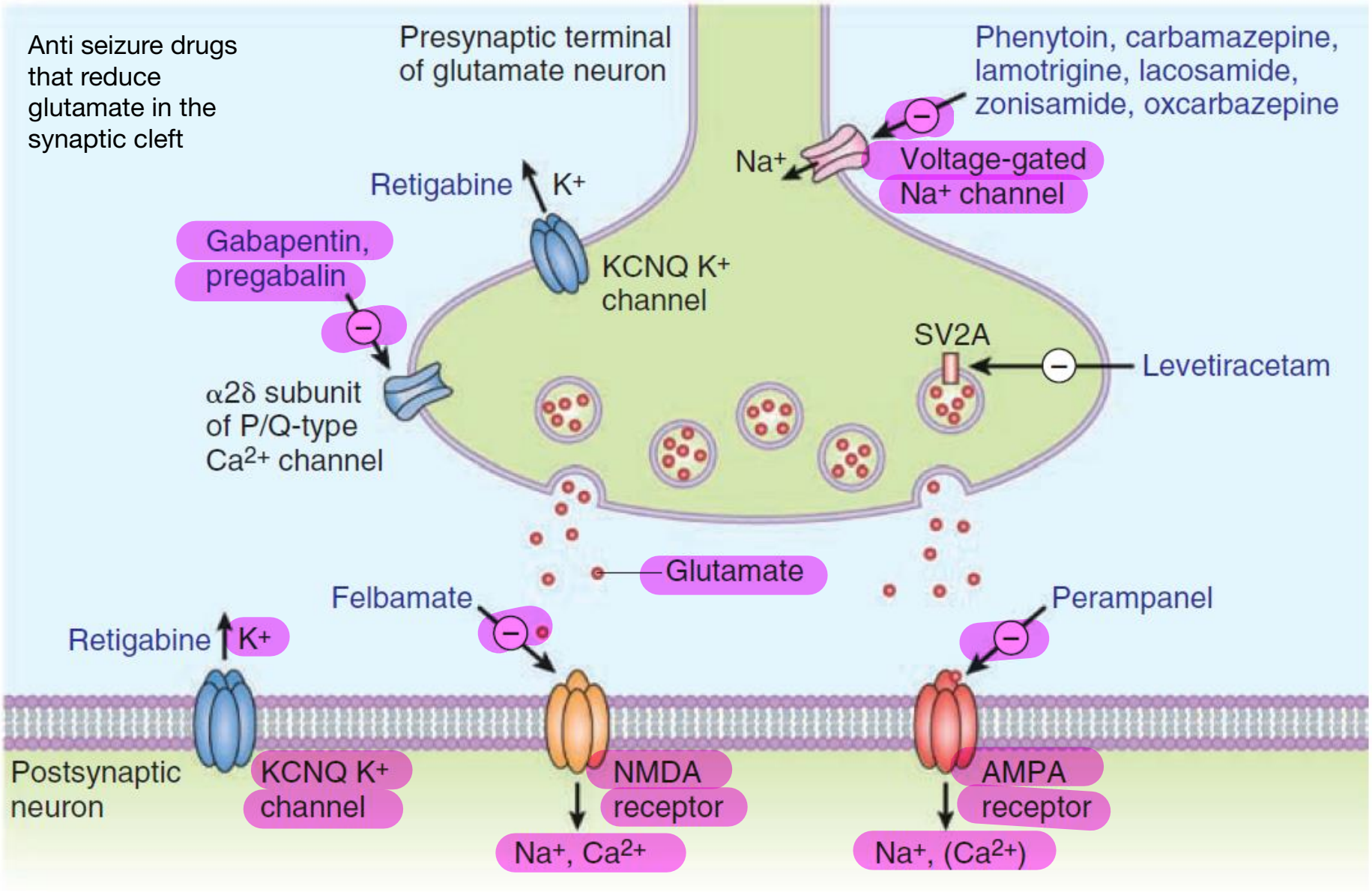
Lennox-Gastaut syndrome, Dravet's syndrome, and juvenile myoclonic epilepsy are epilepsy syndromes in which there are multiple different seizure types.

# Molecular Targets for Antiseizure drugs at the Excitatory Glutamatergic Synapse

- Presynaptic targets diminishing glutamate release include Nav voltage-gated sodium channels (carbamazepine, monohydroxy derivative[MHD], phenytoin, lamotrigine, and lacosamide), Kv7 voltage-gated potassium channels (retigabine [ezogabine]), and α2δ (gabapentin and pregabalin).
- Postsynaptic targets at excitatory synapses are AMPA receptors (perampanel), T-type Cav voltage-gated calcium channels ethosuximide, dimethadione), and Kv7 voltage-gated potassium channels (retigabine [ezogabine]).

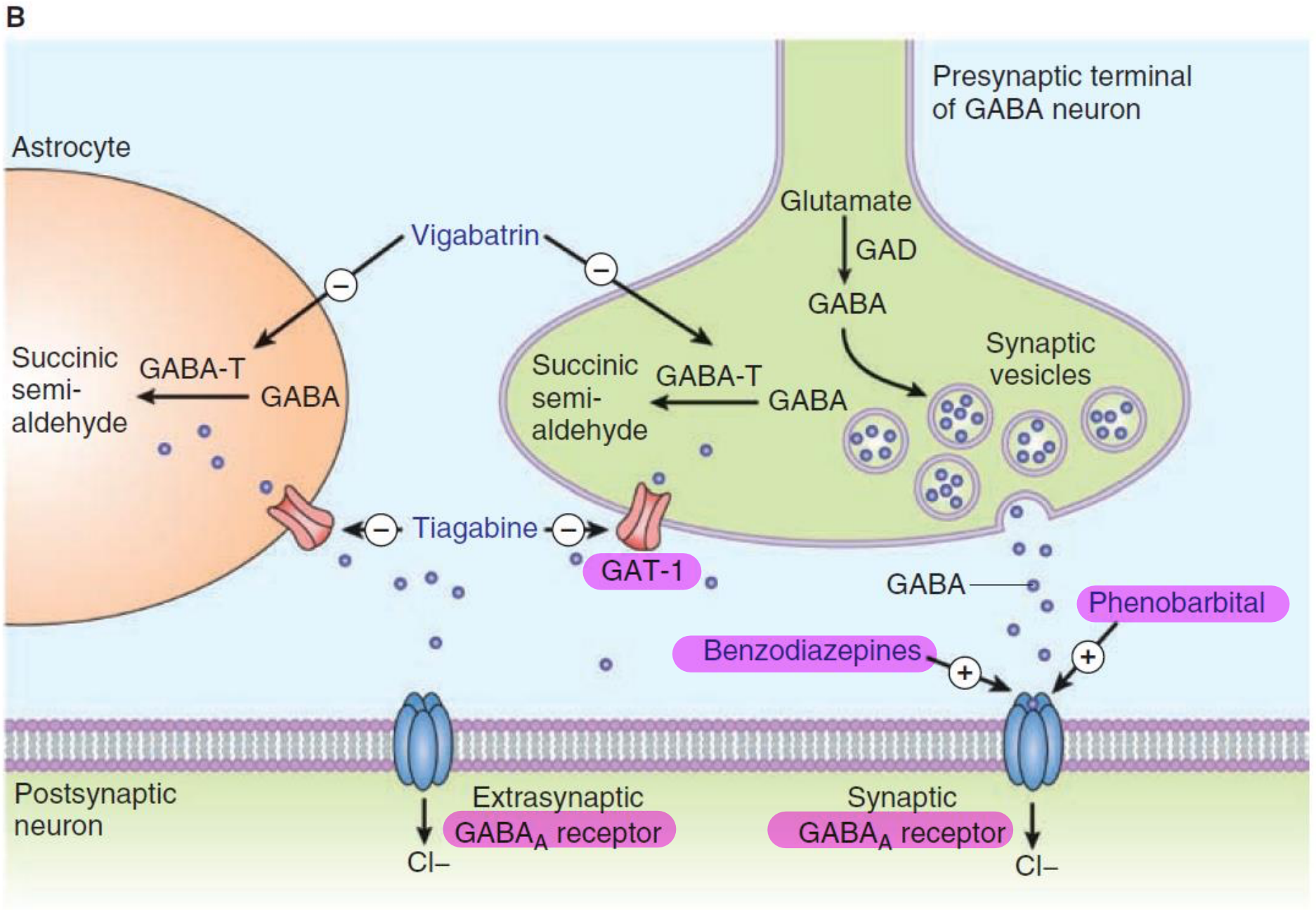
A

Anti seizure drugs that reduce glutamate in the synaptic cleft



# Molecular Targets for Antiseizure Drugs at the Inhibitory GABAergic Synapse

- **At inhibitory synapses and in astrocytes, vigabatrin inhibits GABA-transaminase (GABA-T) and tiagabine blocks GABA transporter 1 (GAT-1).**
- **Phenobarbital, primidone (via metabolism to phenobarbital), and benzodiazepines are positive allosteric modulators of synaptic $GABA_A$ receptors; high GABA levels resulting from blockade of GABA-T may act on extrasynaptic GABAA receptors.**
- **www.webofpharma.**


B
Presynaptic terminal of GABA neuron
Astrocyte
Glutamate
GAD
GABA
Vigabatrin
Succinic semi-aldehyde
GABA-T
GABA
Succinic semi-aldehyde
GABA-T
GABA
Synaptic vesicles
Tiagabine
GAT-1
GABA
Phenobarbital
Benzodiazepines
Postsynaptic neuron
Extrasynaptic
GABA$_A$ receptor
Cl–
Synaptic
GABA$_A$ receptor
Cl–

## TABLE 24–2 Molecular targets of antiseizure drugs.

| Molecular Target | Antiseizure Drugs That Act on Target |
|---|---|
| **Voltage-gated ion channels** | |
| Voltage-gated sodium channels ($Na_v$) | Phenytoin, fosphenytoin[1], carbamazepine, oxcarbazepine[2], eslicarbazepine acetate[3], lamotrigine, lacosamide; possibly topiramate, zonisamide, rufinamide |
| Voltage-gated calcium channels (T-type) | Ethosuximide |
| Voltage-gated potassium channels ($K_v7$) | Retigabine (ezogabine) |
| **GABA ~~inhibition~~** facilitation | |
| $GABA_A$ receptors | Phenobarbital, primidone, benzodiazepines including diazepam, lorazepam, and clonazepam; possibly topiramate, felbamate, ezogabine |
| GAT-1 GABA transporter | Tiagabine |
| GABA transaminase | Vigabatrin |
| **Synaptic release machinery** | |
| SV2A | Levetiracetam, brivaracetam |
| $\alpha 2\delta$ | Gabapentin, gabapentin enacarbil[4], pregabalin |
| **Ionotropic glutamate receptors** | |
| AMPA receptor | Perampanel |
| **Mixed/unknown**[5] | Valproate, felbamate, topiramate, zonisamide, rufinamide, adrenocorticotropin |

We have to know that the new developed seizure drugs are not more effective

# Phenytoin

- The oldest nonsedative antiseizure drug (1938).
- Fosphenytoin is a soluble prodrug of phenytoin (phosphate ester). reducing the effect

## Mechanism of Action:

- At therapeutic concentrations, the major action of phenytoin is to block sodium channels and inhibit the generation of rapidly repetitive action potentials.

# Phenytoin

## Therapeutic uses:

1. Partial seizures /Focal seizures
2. Generalized tonic-clonic seizures (1° or 2°).
   ↳ convulsions

## Pharmacokinetics:

- Absorption is highly dependent on the formulation of the dosage form.

You can't generalize that the drug is poorly or well absorbed because it depends on the dosage
If you control a pt on a specific formulation don't change that dosage form

- Particle size and pharmaceutical additives affect both the rate and extent of absorption.

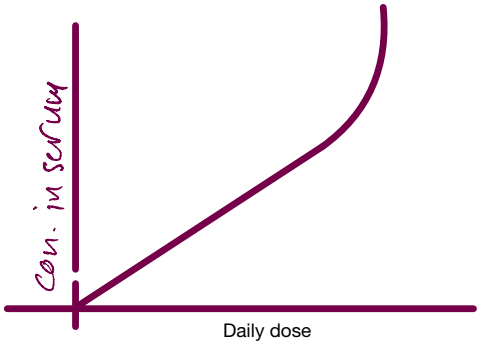
# Phenytoin

- Absorption of phenytoin Na from the GIT is almost complete, the time to peak ranges from 3-12 hours.
- Absorption after IM injection is unpredictable, since some drug precipitation in the muscle occurs (not recommended route).
- In contrast, fosphenytoin (a more soluble phosphate prodrug) is well absorbed after IM administration.

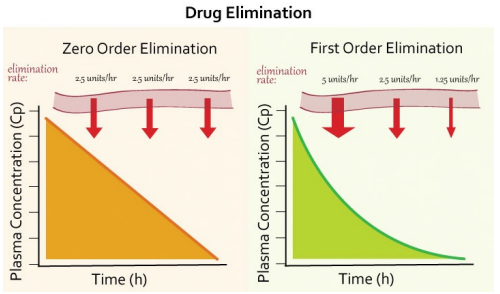
We know that the acting particle of the drug is free portion of it not the bounded to plasma proteins part
If there was a displacement we'll face two problems:
1. The free fraction will increase so it will increase the chance to have toxicity
2. More free fractions more elimination of the fractions so the total plasma concentration of the drug will be decreased
But the free fraction could still adequate

# Phenytoin

- **It is highly bound to plasma proteins.**
- **The total plasma level decreases when the percent bound decreases, as in uremia or hypoalbuminemia.**
- **Drug concentration in CSF is proportional to the free plasma level.**
- **It accumulates in brain, liver, muscle and fat**
- **It is metabolized to inactive metabolites.**




# Phenytoin




- **The elimination of phenytoin is dose-dependent: At very low dose levels, phenytoin metabolism follows first-order kinetics.**
- **However, as blood levels rise within the therapeutic range, zero-order (saturation) kinetics prevail.**
- **Small increases in dosage may produce very large changes in phenytoin concentrations.**

# Phenytoin

- In such cases, the half-life of the drug increases markedly, and steady state may not be achieved.
- Half-life ranges from 12-36 hours in patients with low to mid therapeutic range, and much higher at higher concentrations.
- At low levels it takes 5-7 days to reach steady-state. (At higher doses 4-6 weeks are needed to reach SS).

# Phenytoin

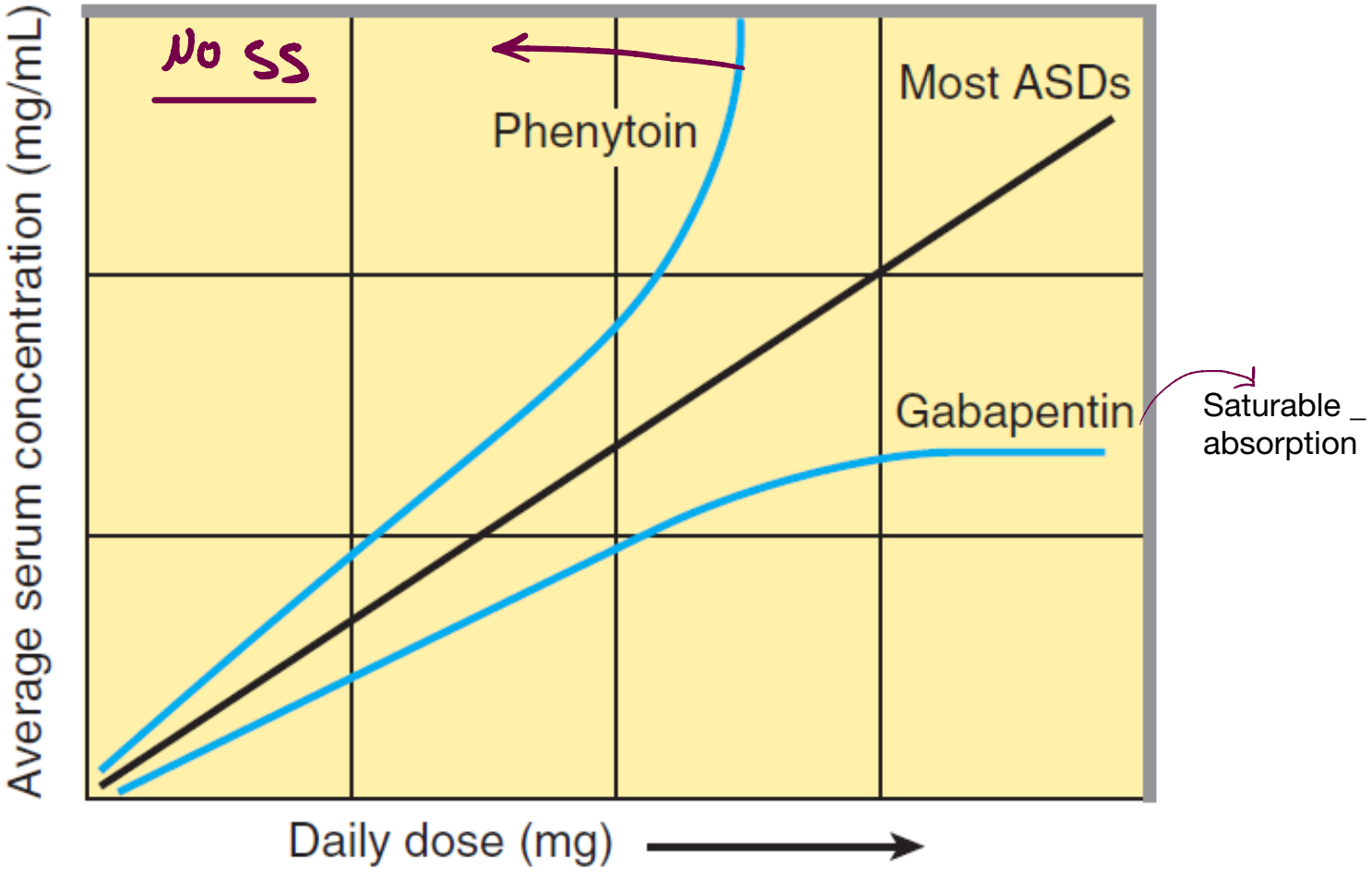

No SS
Phenytoin
Most ASDs
Gabapentin
Saturable _ absorption
Average serum concentration (mg/mL)
Daily dose (mg)

**FIGURE 24–4** Relationship between dose and exposure for antiseizure drugs (ASDs). Most antiseizure drugs follow linear (first-order) kinetics, in which a constant fraction per unit time of the drug is eliminated (elimination is proportional to drug concentration). In the case of phenytoin, as the dose increases, there is saturation of metabolism and a shift from first-order to zero-order kinetics, in which a constant quantity per unit time is metabolized. A small increase in dose can result in a large increase in concentration. Orally administered gabapentin also exhibits zero-order kinetics, but in contrast to phenytoin where metabolism can be saturated, in the case of gabapentin, gut absorption, which is mediated by the large neutral amino acid system L transporter, is susceptible to saturation. The bioavailability of gabapentin falls at high doses as the transporter is saturated so that increases in blood levels do not keep pace with increases in dose.

# Phenytoin

- **Therapeutic total plasma level is between 10-20 µg/mL.**

**Drug Interactions:**

1. **Phenylbutazone and sulfonamides can displace phenytoin from binding sites to plasma proteins.**
2. **Hypoalbuminemia results in decreased total plasma drug concentration but not the free concentration.**

# Phenytoin

- In these 2 cases intoxication may occur if total drug levels are increased by increasing the dose.

3. The drug has affinity for thyroid-binding globulin which confuses some tests for thyroid function.
4. Phenytoin induces many drug metabolizing enzymes.
5. Phenobarbital and carbamazepine induce the metabolism of phenytoin.

Never give these three drugs together

# Phenytoin

6. Isoniazid inhibits the metabolism of phenytoin.

**Adverse effects:**

1. Nystagmus.
2. Diplopia and ataxia are the most common dose-related adverse effects, requiring dose reduction.
3. Sedation only occurs at high levels (??).
4. Gingival hyperplasia. Duration dependent

# Phenytoin

5. **Hirsutism** Duration dependent / females
6. **Long-term use is associated with:**
   - **a. coarsening of facial features**
   - **b. mild peripheral neuropathy**
   - **c. osteomalacia due to altered vitamin D metabolism.** It interfere with the absorption of vitamin D and folic acid
   - **d. megaloblastic anemia secondary to low folate levels.**

# Phenytoin

7. **Idiosyncratic reactions:** Not dose dependent
   - **a. hypersensitivity reaction and skin rash.**
   - **b. fever.**
   - **c. exfoliative skin lesions.** Steven Johnson syndrome
   - **d. lymphadenopathy (pseudolymphoma).**
   - **e. agranulocytosis.**

For carbamazepine

- **Therapeutic drug level is ~ 4-8 µg/mL.**

# Carbamazepine

- **A tricyclic compound related to imipramine.**

## Mechanism of Action:

- **It blocks sodium channels, like phenytoin.**

## Therapeutic uses:

1. **Partial seizures** / Focal
2. **Generalized tonic-clonic seizures**
3. **Trigeminal neuralgia** → Pain in the distribution of trigeminal nerve
4. **Bipolar manic-depressive disorder**

# Carbamazepine

## Pharmacokinetics:

- There is interindividual variation in oral absorption.
- Absorption is slowed if given after meals.
- It is completely metabolized to several metabolites. One, carbamazepine-10,11-epoxide, has anticonvulsant activity.

Should be given before meals

# Carbamazepine

- **Induces microsomal drug metabolizing enzymes.**
- **Induces its own metabolism (autoinduction) → t½ after initial dose is ~ 36 hours, and after continuous therapy becomes ~ 8-12 hours (dose adjustment is needed within 1 week of therapy).**

Tolerance in the drug is due to auto induction

# Carbamazepine

**Drug interactions:**

Not given in combination with these drugs

- **It increases the metabolism of primidone, phenytoin, ethosuximide, valproic acid, and clonazepam.**
- **Propoxyphene, troleandomycin, and valproic acid may inhibit carbamazepine clearance and increase its steady-state levels.**
- **Phenytoin and phenobarbital decrease SS concentration of carbamazepine by enzyme induction.**

# Carbamazepine

## Adverse effects:

1. The most common dose-related adverse effects are diplopia and ataxia.
2. Mild GIT upset.
3. Unsteadiness and drowsiness.
4. Hyponatremia and water intoxication.
5. Idiosyncratic reactions: aplastic anemia and agranulocytosis, leukopenia, erythematous skin rash and hepatic dysfunction.

# Phenobarbital

- **Is the oldest of the currently available antiseizure drugs.**
- **Pharmacodynamics have been discussed under "sedative-hypnotics".**
- **The drug of choice for responsive seizures only in infants (especially febrile seizures).**

# Primidone

- It is 2-desoxyphenobarbital
- It is metabolized to phenobarbital and phenylethylmalonamide (PEMA).
- All 3 compounds are anticonvulsants but PEMA is weak.
- The mechanism of action of primidone may be more like phenytoin.
- Therapeutic uses are partial seizures (→ focal) and generalized tonic-clonic seizures.

# Valproic Acid & Sodium Valproate

- A fatty carboxylic acid.
- The active form is the valproate ion.

## Mechanism of Action:

- It is not very well known.
- It has broad-spectrum aniseizure activity.
- Anticonvulsant activity appears to be poorly correlated with blood or tissue level of the parent drug.

# Valproic Acid

## Pharmacokinetics:

- **Well absorbed after oral administration.**
- **Food may delay absorption.** Before Food
- **It is 90% bound to plasma proteins, binding is saturable, and the free fraction is increased at plasma levels in the upper end of the therapeutic range, resulting in an increase in the plasma free fraction of valproate from 10% at levels up to 75 µ/mL to 30% at levels greater that 150 µ/mL.**

Just like phenytoin

# Valproic Acid

- t½ ~ 9-18 hours. Metabolized by conjugation
- 20% eliminated as a direct conjugate.

## Therapeutic uses:

1. Absence seizures.
2. Myoclonic seizures.
3. Tonic-clonic seizures.
4. Atonic attacks – few patients respond.

Extremely difficult to treat

# Valproic Acid

focal

5. **Partial seizures.**
6. **Bipolar disorders.**
7. **Migraine prophylaxis.**

- **Therapeutic levels ~ 50-100 µg/mL.**

# Valproic Acid

**Drug Interactions:**

1. **It displaces phenytoin from plasma proteins.**
2. **It inhibits the metabolism of phenobarbital, phenytoin, carbamazepine, and other drugs.**

# Valproic Acid

## Adverse Effects:

1. The most common dose-related adverse effects are nausea, vomiting, abdominal pain and heart burn. Gradual starting avoids them.
2. Fine tremor, at high plasma levels. (toxic)
3. Other reversible adverse reactions include increased appetite, weight gain, and Loss of hair.
4. Thrombocytopenia (idiosyncratic). (Not dose related)

# Valproic Acid

5. **Hepatotoxicity (idiosyncratic).**

- **Can be severe and fatal (Most fatalities within 4 months after initiation of therapy).**
- **Risk is more in patients under the age of 2 years, and those taking multiple medications.**

# Valproic Acid

6. **It can cause lethargy associated with increased blood ammonia concentrations.**

- **Fatal hyperammonemic encephalopathy has occurred in patients with genetic defects in urea metabolism.**
- **The drug is contraindicated in these patients.**

# Valproic Acid

8. **Teratogenicity (neural tube defects including spina bifida, cardiovascular, orofacial and digital abnormalities).**

- **cognitive impairment in offspring has been reported.**