Antiseizure 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 2/3^{rds}).**
- **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.**

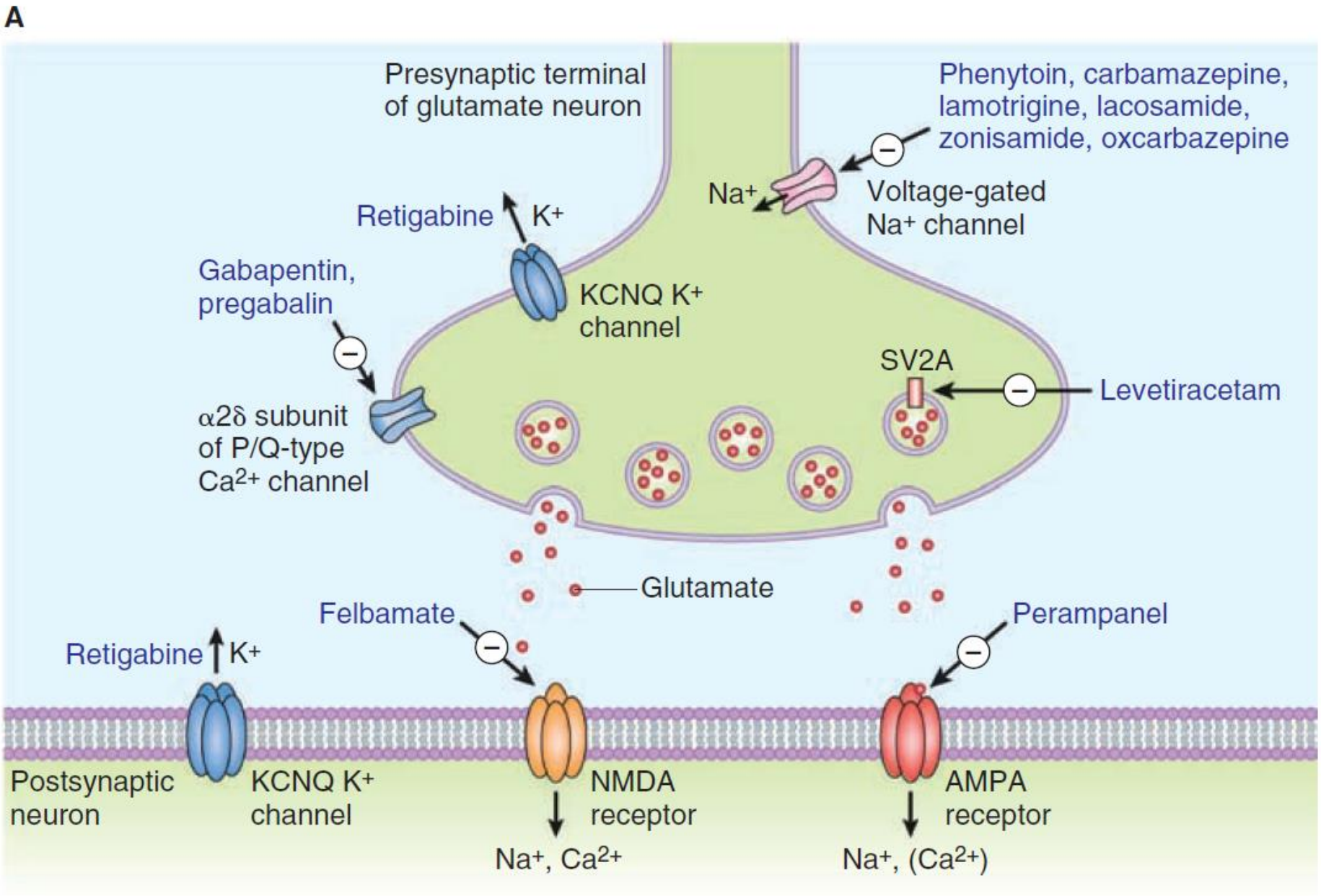
TABLE 24–1 International League Against Epilepsy classification of seizure types.

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)

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
Presynaptic terminal of glutamate neuron
Phenytoin, carbamazepine, lamotrigine, lacosamide, zonisamide, oxcarbazepine
Na+
Voltage-gated Na+ channel
Retigabine
K+
KCNQ K+ channel
Gabapentin, pregabalin
α2δ subunit of P/Q-type Ca2+ channel
SV2A
Levetiracetam
Glutamate
Felbamate
Perampanel
Retigabine
K+
Postsynaptic neuron
KCNQ K+ channel
NMDA receptor
Na+, Ca2+
AMPA receptor
Na+, (Ca2+)

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.**

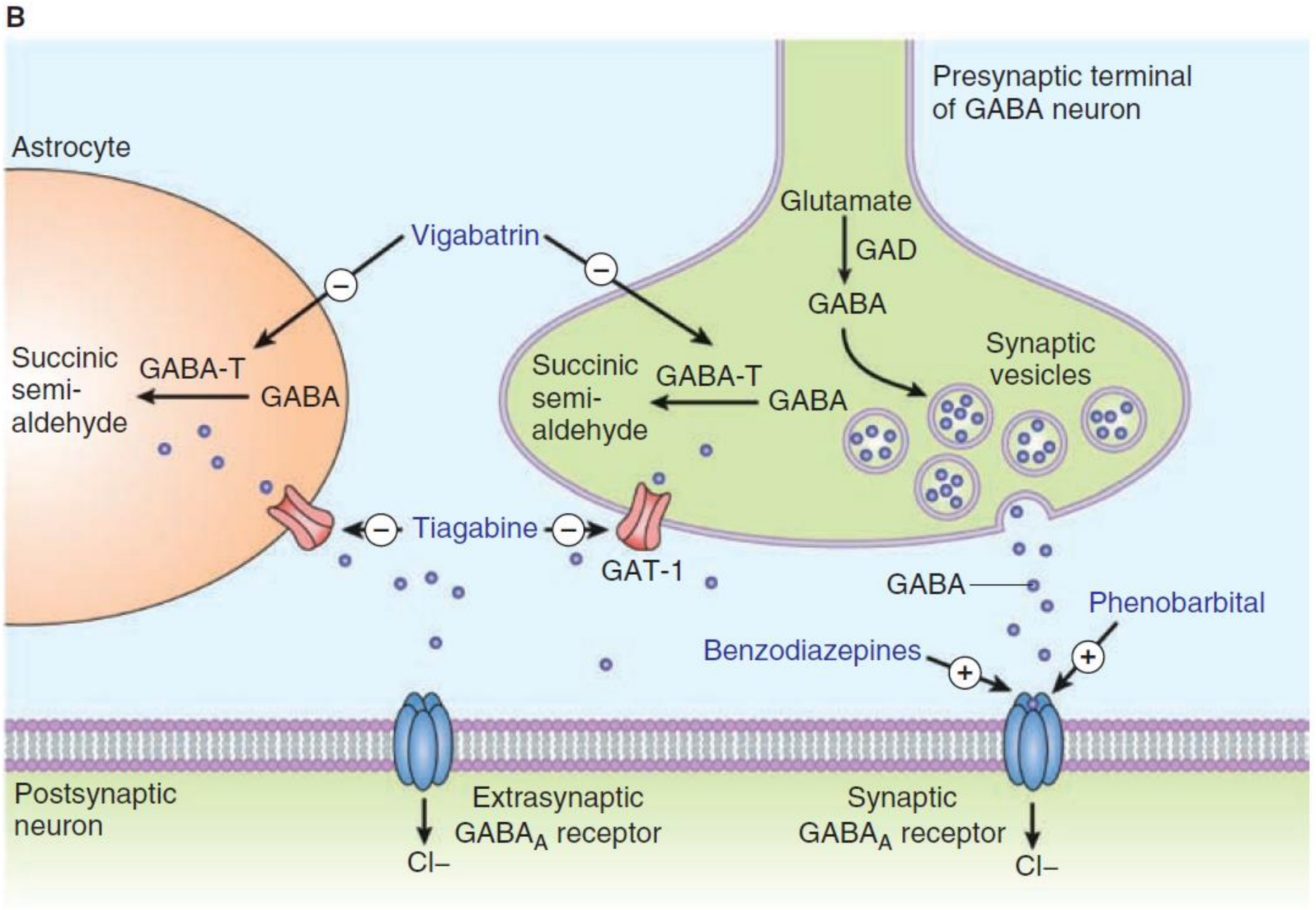

B
Presynaptic terminal of GABA neuron
Astrocyte
Glutamate
GAD
GABA
Vigabatrin
Vigabatrin
Succinic semi-aldehyde
GABA-T
GABA
Succinic semi-aldehyde
GABA-T
GABA
Synaptic vesicles
Tiagabine
Tiagabine
GAT-1
GABA
Phenobarbital
Benzodiazepines
Postsynaptic neuron
Extrasynaptic GABA$_A$ receptor
Cl–
Synaptic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

Phenytoin

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

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
2. Generalized tonic-clonic seizures (1° or 2°).

Pharmacokinetics:

- Absorption is highly dependent on the formulation of the 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.**

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

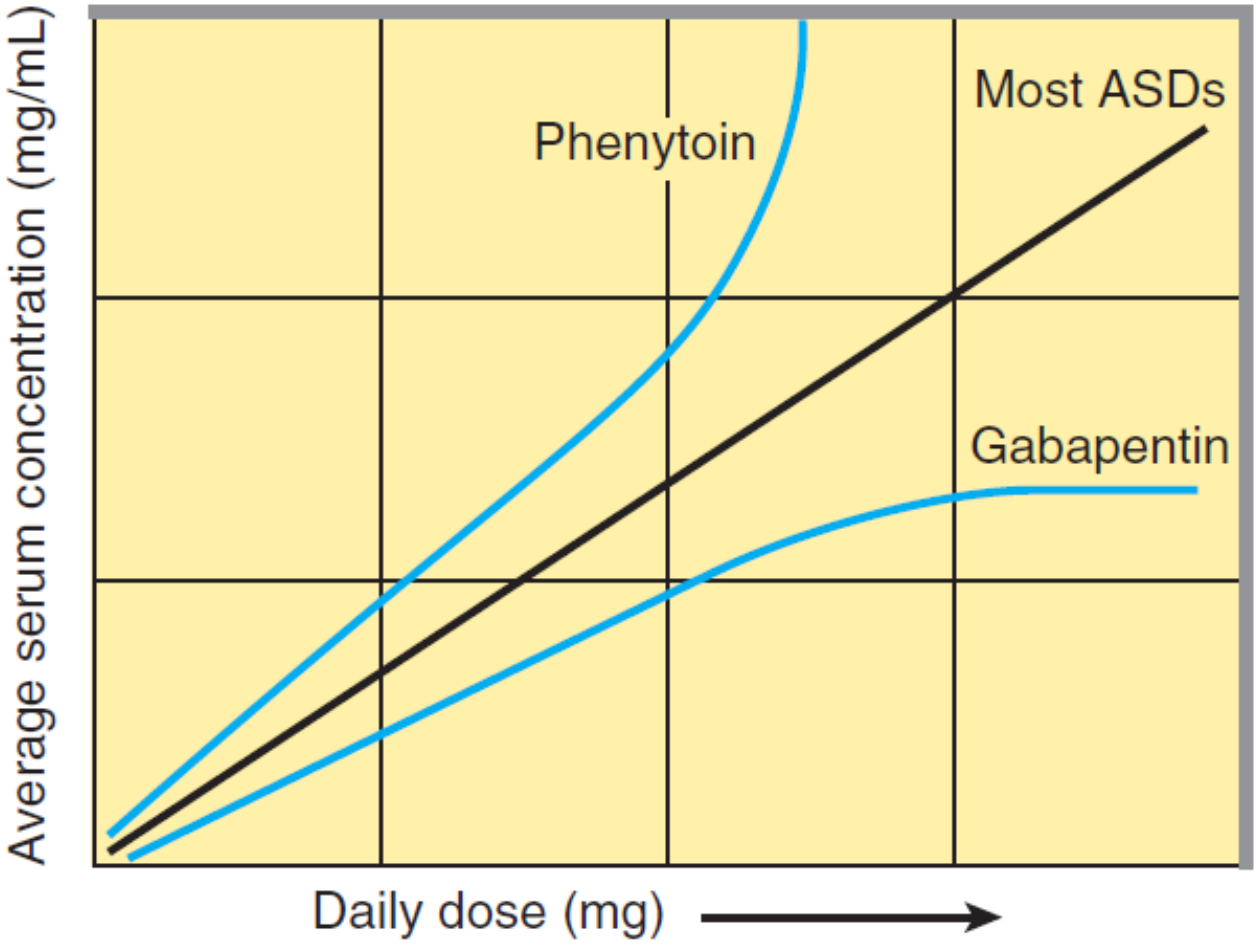

Average serum concentration (mg/mL)
Phenytoin
Most ASDs
Gabapentin
Daily dose (mg)

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.**

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.**

Phenytoin

5. Hirsutism
6. Long-term use is associated with:

   a. coarsening of facial features

   b. mild peripheral neuropathy

   c. osteomalacia due to altered vitamin D metabolism.

   d. megaloblastic anemia secondary to low folate levels.

Phenytoin

7. **Idiosyncratic reactions:**
   - **a. hypersensitivity reaction and skin rash.**
   - **b. fever.**
   - **c. exfoliative skin lesions.**
   - **d. lymphadenopathy (pseudolymphoma).**
   - **e. agranulocytosis.**

- **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**
2. **Generalized tonic-clonic seizures**
3. **Trigeminal neuralgia**
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.

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).**

Carbamazepine

Drug interactions:

- **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 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.**
- **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.**

Valproic Acid

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

Therapeutic uses:

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

Valproic Acid

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.**
3. **Other reversible adverse reactions include increased appetite, weight gain, and Loss of hair.**
4. **Thrombocytopenia (idiosyncratic).**

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.**

Ethosuximide

- **Ethosuximide is a first-line drug for the treatment of generalized absence seizures.**
- **It can be used as monotherapy unless generalized tonic-clonic seizures are also present, in which case valproate is preferred.**

Ethosuximide

Mechanism of Action:

- **It inhibits low-voltage activated T-type calcium channels in thalamocortical neurons that underlie the 3-Hz spike-wave discharges of generalized absence seizures.**
- **Thus, It has narrow spectrum of activity.**

Ethosuximide

- **Other ion channels affected include voltage-gated sodium channels, calcium-activated potassium channels, and inward rectifier potassium channels. These actions may contribute to the efficacy of ethosuximide in absence epilepsy.**

Ethosuximide

Pharmacokinetics:

- Complete absorption.
- Not protein bound.
- 80% metabolized to inactive products by CYP3A.
- t½ ~ 40 (18-72) hours.
- Linear kinetics.

Ethosuximide

- Therapeutic concentration is ~ 40-100 µg/mL.
- Valproic acid inhibits its metabolism → decreased clearance.

Adverse Effects:

1. The most common is gastric distress – pain, nausea, and vomiting.
2. Transient lethargy and fatigue.
3. Headache, dizziness, hiccup, and euphoria.

Lamotrigine

Mechanism of Action:

- **The action of lamotrigine on voltage-gated sodium channels is similar to that of carbamazepine.**

Pharmacokinetics:

- **Almost completely absorbed.**
- **Linear kinetics.**
- **Metabolized primarily by glucuronidation.**

Lamotrigine

- **Metabolism is inhibited by valproate.**
- **Its dose should be reduced if given in combination with valproic acid.**

Lamotrigine

Therapeutic Uses:

1. **Monotherapy for focal seizures.**
2. **Primary generalized tonic-clonic seizures**
3. **Generalized seizures of the Lennox-Gastaut syndrome.**
4. **Absence epilepsy (less effective than ethosuximide and valproate).**

Lamotrigine

Adverse Effects:

1. Dizziness, headache, diplopia, nausea, insomnia, somnolence.
2. Hypersensitivity reaction: skin rash.
3. Serious rash occurs in approximately 0.3–0.8% of children age 2–17 years, and in 0.08–0.3% of adults. This rash is increased if given in combination with valproate.

Topiramate

- **Topiramate is a broad-spectrum antiseizure drug.**
- **It a sulfamate-substituted monosaccharide derived from d-fructose.**

Pharmacokinetics:

- **It is rapidly absorbed, moderate metabolism, primarily excreted in the urine (50–80% is unchanged).**

Topiramate

Mechanism of Action:

- It acts through several cellular targets, which may account for its broad-spectrum activity in epilepsy and migraine.

1. Voltage-gated sodium channels.
2. $GABA_A$ receptor subtypes.
3. AMPA or kainate receptors.

- It is a weak inhibitor of carbonic anhydrase → metabolic acidosis.

Topiramate

Therapeutic Uses:

1. Treatment of focal seizures in adults and children.
2. Primary generalized tonic-clonic seizures.
3. Lennox-Gastaut syndrome
4. May be effective in juvenile myoclonic epilepsy, infantile spasms
5. Childhood absence seizures.

Topiramate

Adverse Effects:

1. **Cognitive adverse effects are common and are a frequent reason for drug discontinuation.**

- **Include: impaired expressive language function (dysnomia and diminished verbal fluency), impaired verbal memory, and a general slowing of cognitive processing without sedation or mood change.**

Topiramate

2. Paresthesias, Somnolence, fatigue, dizziness, nervousness and confusion – dose related.
3. Acute myopia and angle closure glaucoma may require prompt drug withdrawal.
4. Decreased sweating (oligohydrosis) and an elevation in body temperature may occur during exposure to hot weather, mostly in children.

Topiramate

5. **Urolithiasis.**
6. **Long-term use is associated with significant weight loss, due to fat loss.**
7. **Teratogenic – oral cleft formation.**

Drug Interactions:

- **Birth control pills may be less effective in the presence of topiramate**

Gabapentin & Pregabalin

- **Gabapentin and pregabalin are amino acid analogs of GABA, but do not act through GABA mechanism.**

Gabapentin & Pregabalin

Mechanism of Action:

- **They bind to α2δ, a protein that serves as an auxiliary subunit of voltage-gated calcium channels but may also have other functions.**
- **The precise way in which binding of gabapentinoids to α2δ protects against seizures is not known, but may relate to a decrease in glutamate release at excitatory synapses.**

Gabapentin & Pregabalin

Pharmacokinetics:

- These drugs are not metabolized and do not induce hepatic enzymes.
- They are eliminated by the kidney unchanged.
- Both drugs are absorbed by the l-amino acid transport system in the upper small intestine.
- The oral bioavailability of gabapentin decreases with increasing dose because of saturation of this transport system.

Gabapentin & Pregabalin

- **Pregabalin exhibits linear absorption within the therapeutic dose range.**
- **Elimination kinetics are linear.**
- **Not bound to plasma proteins.**
- **No significant drug interactions.**

Gabapentin & Pregabalin

Therapeutic Uses:

1. Focal seizures (less effective than other drugs).
2. Non-epilepsy conditions, such as neuropathic pain (postherpetic neuralgia and painful diabetic neuropathy).
3. Restless legs syndrome
4. Anxiety disorders.

Gabapentin & Pregabalin

5. **Pregabalin is also approved for the treatment of fibromyalgia.**

- **Gabapentin may aggravate absence seizures and myoclonic seizures.**

Adverse Effects:

- **Somnolence, dizziness, ataxia, headache tremor, weight gain, and peripheral edema.**

Levetiracetam

- **Levetiracetam is a broad-spectrum antiseizure agent.**
- **Commonly prescribed because:**

1. **Favorable adverse effect profile (??).**
2. **Broad therapeutic window.**
3. **Favorable pharmacokinetic properties.**
4. **Lack of drug-drug interactions.**

Levetiracetam

Mechanism of Action:

- **It binds selectively to SV2A, a synaptic vesicle integral membrane protein, which may facilitate synaptic vesicle exocytosis.**
- **The drug accesses the luminal side of recycling synaptic vesicles by vesicular endocytosis.**
- **The result is reduction of the release of the excitatory neurotransmitter glutamate.**

Levetiracetam

Therapeutic Uses:

1. Focal seizures in adults and children
2. Primary generalized tonic-clonic seizures
3. Myoclonic seizures of juvenile myoclonic epilepsy.

- Oral absorption is complete, rapid and unaffected by food.

Levetiracetam

Adverse Effects:

1.Somnolence, asthenia, ataxia, infection (colds), and dizziness.

2.Less common but more serious are behavioral and mood changes (irritability, aggression, agitation, anger, anxiety, apathy, depression, and emotional lability).

Levetiracetam

Pharmacokinetics:

- Oral absorption of levetiracetam is rapid and nearly complete.
- Food slows the rate of absorption but does not affect the amount absorbed.
- Kinetics are linear. t½ ~ 6-8 hours.
- Protein binding is low.
- Two thirds excreted unchanged, the rest is metabolized in the blood.

Vigabatrin

- **Is gama-vinyl-GABA (analog of GABA)**
- **It is an irreversible inhibitor of GABA transaminase, the enzyme responsible for the degradation of GABA → an increase in the amount of GABA at synapse.**

Vigabatrin

Therapeutic uses:

1. Infantile spasms, especially when associated with tuberous sclerosis.
2. Focal seizures.

Vigabatrin

Adverse effects:

1. **The most important adverse effect of is irreversible retinal dysfunction.**

- **Patients may develop permanent bilateral concentric visual field constriction**
- **It can damage the central retina.**
- **The onset of vision loss weeks months of starting treatment.**

Vigabatrin

- **Therefore, it is used only in patients refractory to other drugs.**

2. **Somnolence, headache, dizziness, and weight gain.**
3. **Agitation, confusion, and psychosis.**

- **Preexisting mental illness is a relative contraindication.**

Lacosamide

- An amino acid-related compound.

Mechanism of action:

- It binds selectively to the fast inactivated state of sodium channels.

Therapeutic Uses:

- Focal onset seizures in patients age 17 years and older.

Lacosamide

Adverse effects:

- **Dizziness, headache, nausea, and diplopia.**
- **Negligible drug interactions.**

Zonisamide

- **Zonisamide is a broad-spectrum antiseizure drug that is effective for:**

1. **Focal and generalized tonic-clonic seizures in adults and children.**
2. **May be effective in some myoclonic epilepsies and in infantile spasms.**
3. **May improveme generalized onset tonic-clonic seizures and atypical absence seizures.**

Zonisamide

Mechanism of Action:

- **There is little information on its mechanism of action.**
- **It does block voltage-gated sodium channels, but other actions may also contribute to its antiseizure activity.**
- **Carbonic anhydrase inhibition.**

Zonisamide

Adverse effects:

- Drowsiness, cognitive impairment, renal stones, and potentially serious skin rashes.
- Weight loss.
- Kidney stones.
- Oligohydrosis

Drug Interactions:

- Carbamazepine, phenytoin, and phenobarbital increase its clearance.

Benzodiazepines

- First-line acute treatment for seizures, either in status epilepticus or acute repetitive seizures.
- Two prominent aspects of benzodiazepines limit their usefulness in the chronic therapy of epilepsy: sedation and tolerance.

Diazepam:

- Given intravenously is a first-line treatment for status epilepticus.
- Used in a rectal gel formulation for the treatment of acute repetitive seizures.

Benzodiazepines

Lorazepam:

- **It is more commonly used in the treatment of status epilepticus because it has a more prolonged duration of action after bolus intravenous injection.**
- **Lorazepam is more effective and longer-acting, because it binds more tightly to GABA receptors and has a longer distribution half-life (2-3 hours vs 15 min for diazepam which is much more lipid soluble).**

Benzodiazepines

Clonazepam:

- **Long-acting, with documented activity against absence, atonic, and myoclonic seizure.**

Nitrazepam:

- **Used for infantile spasms and myoclonic seizures.**

Benzodiazepines

Clorazepate dipottasium:

- **Adjunct treatment of focal seizures. Drowsiness and lethargy are common.**