Pharmacology Lectures by

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Antiseizure drugs

- Tonic-clonic & partial seizures
  - Carbamazepine
  - Lamotrigine
  - Phenytoin
  - Valproic acid

- Absence seizures
  - Clonazepam
  - Ethosuximide
  - Valproic acid

- Myoclonic seizures
  - Clonazepam
  - Lamotrigine
  - Valproic acid

- Back-up & adjunctive drugs
  - Felbamate
  - Gabapentin
  - Lamotrigine
  - Levetiracetam
  - Phenobarbital
  - Tiagabine
  - Topiramate
  - Vigabatrin
  - Zonisamide
**Seizures** Finite episodes of brain dysfunction resulting from abnormal discharge of cerebral neurons

**Partial seizures, simple** Consciousness preserved; manifested variously as convulsive jerking, paresthesias, psychic symptoms (altered sensory perception, illusions, hallucinations, affect changes), and autonomic dysfunction

**Partial seizures, complex** Impaired consciousness that is preceded, accompanied, or followed by psychological symptoms

**Tonic-clonic seizures, generalized** Tonic phase (less than 1 min) involves abrupt loss of consciousness, muscle rigidity, and respiration arrest; clonic phase (2–3 min) involves jerking of body muscles, with lip or tongue biting, and fecal and urinary incontinence; formerly called grand

**Absence seizures, generalized** Impaired consciousness (often abrupt onset and brief), sometimes with automatisms, loss of postural tone, or enuresis; begin in childhood (formerly, petit mal) and usually cease by age 20 yrs

**Myoclonic seizures** Single or multiple myoclonic muscle jerks

**Status epilepticus** A series of seizures (usually tonic-clonic) without recovery of consciousness between attacks; it is a life-threatening emergency
Single-photon-emission-coherence tomography (SPECT) can be used to measure regional blood flow in the brain. The image shows an increased blood flow in the left temporal lobe associated with the onset of a seizure in the same area.
SEIZURES

Partial
(consciousness preserved)
- Simple (consciousness normal)
- Complex (consciousness altered/no memory)

Generalized
(consciousness lost/no memory)
- Tonic-clonic
- Absence
- Myoclonic
- Infantile spasm
- Status epilepticus

Generalized Status Epilepticus
(convulsive or non-convulsive)

Partial Status Epilepticus
(consciousness lost/no memory)
Newly diagnosed epilepsy
- Consider starting therapy after the second seizure.

First-choice drug
- Choose drug appropriate for the patient's type of seizure.
  - Consider toxicities of the agent
  - Consider characteristics of the patient
- Gradually titrate the dosage to that which is maximally tolerated and/or produces optimal seizure control.

Seizures persist

Seizure free

Second-choice drug
- The second drug is titrated to a therapeutic level that controls seizures before tapering and discontinuing the original antiseizure agent.
- If the first drug is associated with significant adverse effects, it should be tapered while the second drug is added.

Seizures persist

Seizure free

Rational combination of two drugs

Seizures persist

Seizure free

Consider vagal nerve...
Nausea and vomiting

Drowsiness - sedation

Ataxia

Rash

Hyponatremia

Weight gain or Weight loss
<table>
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<th>Enzyme</th>
<th>Substrates</th>
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<tr>
<td>CYP1A2</td>
<td>Carbamazepine</td>
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<tr>
<td>CYP2C8</td>
<td>Carbamazepine</td>
</tr>
<tr>
<td>CYP2C9</td>
<td>Carbamazepine, Divalproex, Phenobarbital, Phenytoin</td>
</tr>
<tr>
<td>CYP2C19</td>
<td>Divalproex, Felbamate, Phenobarbital, Phenytoin, Zonisamide</td>
</tr>
<tr>
<td>CYP3A4</td>
<td>Carbamazepine, Ethosuximide, Tiagabine, Zonisamide</td>
</tr>
<tr>
<td>UDP-glucuronosyltransferases</td>
<td>Divalproex, Lamotrigine, Lorazepam</td>
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When the hepatic hydroxylation system becomes saturated, small increases in the dose of phenytoin cause a large increase in the plasma concentration of the drug.
Figure 15.9
Gingival hyperplasia in patient treated with phenytoin.
In utero exposure to valproate, when compared with other commonly used antiepileptic drugs, is associated with an increased risk of impaired cognitive function at 3 years of age. Valproate should not be used in women of childbearing potential.
A

1. An implanted pulse generator connects to electrodes that coil around the vagus nerve.

2. The vagal nerve stimulator generates an electrical pulse that stimulates the vagus nerve.

3. This electrical stimulation prevents the abnormal electrical activity that can cause a seizure.

4. The patient activates the stimulator when they anticipate a seizure.

B

Biscuit

Spaghetti strands
Fig. 31.1  Action of antiepileptic drugs (from Duncan et al., 2006).
Propagated action potential

Retigabine

K+ channel

Voltage-gated Na+ channel

Depolarization

Sericabazine acetate

Phenytoin

Carbamazepine

Oxcarbazepine

Eslicarbazepine acetate

Lamotrigine

Lacosamide

Zonisamide

Levetiracetam

Ethosuximide

GabaPentin

Pregabalin

K+ channel

αδ-subunit of Ca2+ channel

Gabapentin

Pregabalin

Tiagabine

GABA

Glutamate

Perampanel

K+ channel

T-type Ca2+ channel

Postsynaptic neuron

Inhibitory synapse

Excitatory synapse

GABA receptor

AMPA receptor

KCNQ K+ channel

Not illustrated:
- Vigabatrin → GABA degradation
- Drugs with multiple mechanisms:
  - Valproate → GABA turnover, Na+ channels, NMDA receptors
  - Topiramate → Na+ channels, AMPA/kainate receptors, GABA receptors
  - Felbamate → Na+ channels, GABA receptors, NMDA receptors
AEDs: Mechanisms of Action

GABA

elevates GABA levels by irreversibly inhibiting its main catabolic enzyme, GABA-transaminase

Vigabatrin

Interferes with GABA reuptake

Tiagabine

Inhibitory presynaptic terminal

Succinic semi-aldehyde

Glutamate

GAD

GABA

GABA-T

Succinic semi-aldehyde

GAT-1

GABA

Benzodiazepines

Felbamate, topiramate, zonisamide

Barbiturates

Postsynaptic neuron

GABA_A receptor

Cl⁻
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<tr>
<th>DRUG</th>
<th>MECHANISM OF ACTION</th>
<th>ADVERSE EFFECTS AND COMMENTS</th>
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<tr>
<td>Carbamazepine</td>
<td>Blocks Na⁺ channels</td>
<td>Hyponatremia, drowsiness, fatigue, dizziness, and blurred vision. Drug use has as been</td>
</tr>
<tr>
<td>Divalproex</td>
<td>Multiple mechanisms of action</td>
<td>Weight gain, easy bruising, nausea, tremor, hair loss, weight gain, GI upset, liver damage, alopecia, and sedation. Hepatic failure, pancreatitis, and teratogenic effects such as have been observed. Broad spectrum of antiseizure activity.</td>
</tr>
<tr>
<td>Ethosuximide</td>
<td>Blocks Ca²⁺ channels</td>
<td>Drowsiness, hyperactivity, nausea, sedation, GI upset, weight gain, lethargy, SLE, and rash. Blood dyscrasias can occur; periodic CBCs should be done. Abrupt discontinuation of drug may causes seizures.</td>
</tr>
<tr>
<td>Felbamate</td>
<td>Multiple mechanisms of action</td>
<td>Insomnia, dizziness, headache, ataxia, weight gain, and irritability. Aplastic anemia; hepatic failure. Broad spectrum of antiseizure activity. Requires patient to sign informed consent at dispensing.</td>
</tr>
<tr>
<td>Lamotrigine</td>
<td>Multiple mechanisms of action</td>
<td>Nausea, drowsiness, dizziness, headache, and diplopia. Rash (Stevens-Johnson syndrome—potentially life-threatening). Broad spectrum of antiseizure activity.</td>
</tr>
<tr>
<td>Oxcarbazepine</td>
<td>Blocks Na⁺ channels</td>
<td>Nausea, rash, hyponatremia, headache, sedation, dizziness, vertigo, ataxia, and diplopia.</td>
</tr>
<tr>
<td>Fosphenytoin</td>
<td>Blocks Na⁺ channels</td>
<td>Gingival hyperplasia, confusion, slurred speech, double vision, ataxia, sedation, dizziness, and hirsutism. Stevens-Johnson syndrome—potentially life-threatening. Not recommended for chronic use. Primary treatment for status epilepticus.</td>
</tr>
<tr>
<td>Pregabalin</td>
<td>Multiple mechanisms of action</td>
<td>Weight gain, somnolence, dizziness, headache, weight gain, diplopia, and ataxia. One hundred percent renal elimination.</td>
</tr>
<tr>
<td>Primidone</td>
<td>GABA receptor</td>
<td>Sedation, lethargy, behavioral changes, ataxia, hyperactivity, and nausea. Not recommended for chronic use.</td>
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<tr>
<td>Tiagabine</td>
<td>GABA receptor</td>
<td>Sedation, weight gain, fatigue, headache, tremor, dizziness, and anorexia. Multiple drug interactions.</td>
</tr>
<tr>
<td>Topiramate</td>
<td>Multiple mechanisms of action</td>
<td>Paresthesia, weight loss, nervousness, depression, anorexia, anxiety, tremor, cognitive complaints, headache, and oligohidrosis. Few drug interactions. Broad spectrum of antiseizure activity.</td>
</tr>
<tr>
<td>Zonisamide</td>
<td>Multiple mechanisms of action</td>
<td>Nausea, anorexia, ataxia, confusion, difficulty concentrating, sedation, paresthesia and oligohidrosis. Broad spectrum of antiseizure activity.</td>
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Checklist

*When you complete this chapter, you should be able to:*

List the drugs of choice for partial seizures, generalized tonic-clonic seizures, absence and myoclonic seizures, and status epilepticus.

Identify the mechanisms of antiseizure drug action at the levels of specific ion channels and/or neurotransmitter systems.

Describe the main pharmacokinetic features, and list the adverse effects of carbamazepine, phenytoin, and valproic acid.

Identify the distinctive toxicities of new antiseizure drugs.

Describe the important pharmacokinetic and pharmacodynamic considerations relevant to the long-term use of antiseizure drugs.
A nine-year-old boy is sent for neurologic evaluation because of episodes of confusion. Over the past year, the child has experienced episodes during which he develops a blank look on his face and fails to respond to questions. However, it appears to take several minutes before the boy recovers from the episodes. Which one the following best describes this patient's seizures?

A. Simple partial.
B. Complex partial.
C. Tonic-clonic.
D. Absence.
E. Myoclonic.