At the end of this lecture the students should be able to:

1- Describe the epilepsy symptom, its ethiology, epidemiology and importance in health management.
2- Define seizure and describe the classification of seizure type.
3- Describe the mechanism of action, clinical use and side effects of different antiseizure drugs based on current classification of the symptom.
Introduction

Approximately 1% of the world’s population has epilepsy, the third most common neurologic disorder after dementia and stroke. Epilepsy is a heterogeneous symptom complex—a chronic disorder characterized by recurrent seizures. Seizures are finite episodes of brain dysfunction resulting from abnormal discharge of cerebral neurons. The causes of seizures are many and include the full range of neurologic diseases—from infection to neoplasm and head injury. The term “epilepsy” is not usually applied to such patients unless chronic seizures develop later. Seizures are occasionally caused by an acute underlying toxic or metabolic disorder, in which case appropriate therapy should be directed toward the specific abnormality, eg, hypocalcemia. In most cases of epilepsy, however, the choice of medication depends on the empiric seizure classification.

Drug Development for Epilepsy

Classification of seizure types are shown in Table 24–1. There is some specificity according to seizure type, which is most clearly seen with generalized seizures of the absence type. These seizures respond to ethosuximide and valproate but can be exacerbated by phenytoin and carbamazepine. Drugs acting selectively on absence seizures can be identified by animal screens, using threshold pentylenetetrazol clonic seizures in mice or rats. In contrast, the maximal electroshock (MES) test, identifies drugs such as phenytoin, carbamazepine, and lamotrigine, which are active against generalized tonic-clonic seizures and complex partial seizures. The maximal electroshock test as the major initial screen for new drugs led predominantly to the early identification of drugs with a mechanism of action involving prolonged inactivation of the voltage-gated Na+ channel. New antiseizure drugs are being sought not only by the screening tests noted above but also by more focused approaches. Compounds are sought that act by one of three mechanisms: (1) enhancement of GABAergic (inhibitory) transmission, (2) diminution of excitatory (usually glutamatergic) transmission, or (3) modification of ionic conductances.

<table>
<thead>
<tr>
<th>TABLE 24–1 Classification of seizure types.</th>
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<tr>
<td>Partial (focal) seizures</td>
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<td>Simple partial seizures</td>
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<td>Complex partial seizures</td>
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<tr>
<td>Partial seizures secondarily generalized</td>
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<td>Generalized seizures</td>
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<td>Generalized tonic-clonic (grand mal) seizures</td>
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<td>Absence (petit mal) seizures</td>
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<td>Tonic seizures</td>
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<tr>
<td>Atonic seizures</td>
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<tr>
<td>Clonic and myoclonic seizures</td>
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<tr>
<td>Infantile spasms*</td>
</tr>
</tbody>
</table>

*An epileptic syndrome rather than a specific seizure type; drugs useful in infantile spasms will be reviewed separately.
BASIC PHARMACOLOGY OF ANTISEIZURE DRUGS

Pharmacokinetics
The antiseizure drugs exhibit many similar pharmacokinetic properties, because most have been selected for oral activity and all must enter the central nervous system. Although many of these compounds are only slightly soluble, absorption is usually good, with 80–100% of the dose reaching the circulation. Most antiseizure drugs (other than phenytoin, tiagabine, and valproic acid) are not highly bound to plasma proteins. Antiseizure drugs are cleared chiefly by hepatic mechanisms. Many are converted to active metabolites that are also cleared by the liver. These drugs are predominantly distributed into total body water. Plasma clearance is relatively slow. Some have half-lives longer than 12 hours. Many of the older antiseizure drugs are potent inducers of hepatic microsomal enzyme activity.

DRUGS USED IN PARTIAL SEIZURES & GENERALIZED TONIC-CLONIC SEIZURES
The classic major drugs for partial and generalized tonic-clonic seizures are phenytoin (and congeners), carbamazepine, valproate, and the barbiturates. However, the availability of newer drugs—eslicarbazepine, lamotrigine, levetiracetam, gabapentin, oxcarbazepine, pregabalin, retigabine, topiramate, vigabatrin, lacosamide, and zonisamide—is altering clinical practice in countries where these compounds are available.

PHENYTOIN
Phenytoin is the oldest nonsedative antiseizure drug, introduced in 1938.

Mechanism of Action
The mechanism of phenytoin’s action probably involves a combination of actions at several levels. At therapeutic concentrations, the major action of phenytoin is to block Na+ channels and inhibit the generation of rapidly repetitive action potentials. Presynaptic actions on glutamate and GABA release probably arise from actions other than those on voltage-gated Na+ channels.

Clinical Uses
Phenytoin is effective against partial seizures and generalized tonic-clonic seizures. In the latter, it appears to be effective against attacks that are either primary or secondary to another seizure type.

Pharmacokinetics
Absorption of phenytoin is highly dependent on the formulation of the dosage form. Absorption of phenytoin sodium from the gastrointestinal tract is nearly complete in most patients, although the time to peak may range from 3 to 12 hours. Phenytoin is highly bound to plasma proteins. Drug concentration in cerebrospinal fluid is proportionate to the free plasma level. Phenytoin accumulates in brain, liver, muscle, and fat. Phenytoin is metabolized to inactive metabolites that are excreted in the urine. The elimination of phenytoin is dose-dependent. At very low blood levels, phenytoin metabolism follows first-order kinetics. However, as blood levels rise within the therapeutic range, the maximum capacity of the liver to metabolize phenytoin is approached. Further increases in dosage, though relatively small, may produce very large changes in phenytoin concentrations. The half-life of phenytoin varies from 12 to 36 hours, with an average of 24 hours for most patients in the low to mid therapeutic
range. At low blood levels, it takes 5–7 days to reach steady-state blood levels.

**Drug Interactions & Interference with Laboratory Tests**

Drug interactions involving phenytoin are primarily related to protein binding or to metabolism. Since phenytoin is 90% bound to plasma proteins, other highly bound drugs, such as phenylbutazone and sulfonamides, can displace phenytoin from its binding site. The drug has an affinity for thyroid-binding globulin, which confuses some tests of thyroid function. Phenytoin has been shown to induce microsomal enzymes responsible for the metabolism of a number of drugs.

**Toxicity**

Dose-related adverse effects caused by phenytoin are often similar to those caused by other antiseizure drugs in this group. Nystagmus occurs early. Diplopia and ataxia are the most common dose-related adverse effects requiring dosage adjustment; sedation usually occurs only at considerably higher levels. Gingival hyperplasia and hirsutism occur to some degree in most patients. Long-term use may also result in abnormalities of vitamin D metabolism, leading to osteomalacia. Idiosyncratic reactions to phenytoin are relatively rare. Hematologic complications are exceedingly rare, although agranulocytosis has been reported in combination with fever and rash.

**MEPHENYTOIN, ETHOTOIN, & PHENACEMIDE**

Many congeners of phenytoin have been synthesized, but only three have been marketed in the USA, and one of these (phenacemide) has been withdrawn. The other two congeners, mephenytoin and ethotoin, like phenytoin, appear to be most effective against generalized tonic-clonic seizures and partial seizures.

**CARBAMAZEPINE**

It was initially marketed for the treatment of trigeminal neuralgia but has proved useful for epilepsy as well.

**Mechanism of Action**

Carbamazepine, like phenytoin, blocks Na+ channels at therapeutic concentrations and inhibits high-frequency repetitive firing in neurons in culture. Potentiation of a voltage-gated K+ current has also been described. These effects probably account for the anticonvulsant action of carbamazepine.

**Clinical Uses**

Carbamazepine has long been considered a drug of choice for both partial seizures and generalized tonic-clonic seizures. Carbamazepine is not sedative in its usual therapeutic range. The drug is also very effective in some patients with trigeminal Neuralgia. Carbamazepine is also useful for controlling mania in some patients with bipolar disorder.

**Pharmacokinetics**

The rate of absorption of carbamazepine varies widely among patients, although almost complete absorption apparently occurs in all. Peak levels are usually achieved 6–8 hours after administration. Distribution is slow, and the volume of distribution is roughly 1 L/kg. The drug is approximately 70% bound to plasma proteins; no displacement of other drugs from protein binding sites has been observed. Carbamazepine has a very low systemic clearance at the start of therapy but increased after one month. Typically, the half-life of 36 hours at the start, decreases to as little as 8–12 hours in subjects receiving continuous therapy. Considerable dosage adjustments are thus to be expected during the first weeks of therapy.
**Drug Interactions**
The increased metabolic capacity of the hepatic enzymes may cause a reduction in steady-state carbamazepine concentrations and an increased rate of metabolism of other drugs, eg, primidone, phenytoin, ethosuximide and clonazepam. Other drugs such as valproic acid may inhibit carbamazepine clearance and increase steady-state carbamazepine blood levels.

**Toxicity**
The most common dose-related adverse effects of carbamazepine are diplopia and ataxia. Rearrangement of the divided daily dose can often remedy this complaint. Other dose-related complaints include mild gastrointestinal upsets, unsteadiness, and, at much higher doses, drowsiness. Idiosyncratic blood dyscrasias with carbamazepine, including fatal cases of aplastic anemia and agranulocytosis have been in elderly patients with trigeminal neuralgia, and most have occurred within the first 4 months of treatment. The most common idiosyncratic reaction is an erythematous skin rash.

**OXCARBAZEPINE**
Oxcarbazepine is closely related to carbamazepine and is useful in the same seizure types. Oxcarbazepine has a half-life of only 1–2 hours. Its activity, therefore, resides almost exclusively in its metabolite, eslicarbazepine, to which it is rapidly converted and which has a half-life similar to that of carbamazepine, ie, 8–12 hours. The drug is mostly excreted as the glucuronide of the metabolite. Some studies report fewer hypersensitivity reactions to oxcarbazepine, and crossreactivity with carbamazepine does not always occur. Furthermore, the drug appears to induce hepatic enzymes to a lesser extent than carbamazepine, minimizing drug interactions. Most adverse effects that occur with oxcarbazepine are similar in character to reactions reported with carbamazepine.

**ESLICARBAZEPINE**
Eslicarbazepine acetate (ESL) is a prodrug. ESL is more rapidly converted to S(+) licarbazine (eslicarbazine) than is oxcarbazepine; clearly both prodrugs have the same metabolite as active product. The mechanism of action of carbamazepine, oxcarbazepine, and ESL appears to be the same, ie, blocking of voltage-gated Na+ channels. Clinically, the drug is similar to carbamazepine and oxcarbazepine in its spectrum of action. A possible advantage of ESL is its once-daily dosing regimen. Minimal drug level effects are observed with co-administration of carbamazepine, levetiracetam, lamotrigine, topiramate, and valproate. Oral contraceptives may be less effective with concomitant ESL administration.

**PHENOBARBITAL**
Aside from the bromides, phenobarbital is the oldest of the currently available antiseizure drugs. Because of the sedative effects, many consider the barbiturates the drugs of choice for seizures only in infants.

**Mechanism of Action**
The exact mechanism of action of phenobarbital is unknown, but enhancement of inhibitory processes and diminution of excitatory transmission probably contribute significantly. Phenobarbital binds to an allosteric regulatory site on the GABAA receptor, and it enhances the GABA receptor-mediated current by prolonging the openings of the Cl– channels. Phenobarbital can also decrease excitatory responses. Both the enhancement of GABA-mediated inhibition
and the reduction of glutamate-mediated excitation are seen with therapeutically relevant concentrations of phenobarbital.

**Clinical Uses**
Phenobarbital is useful in the treatment of partial seizures and generalized tonic-clonic seizures, although the drug is often tried for virtually every seizure type, especially when attacks are difficult to control.

**PRIMIDONE**
Primidone, or 2-desoxyphenobarbital, was first marketed in the early 1950s. It was later reported that primidone was metabolized to phenobarbital and phenylethylmalonamide (PEMA). All three compounds are active anticonvulsants.

**Mechanism of Action**
Although primidone is converted to phenobarbital, the mechanism of action of primidone itself may be more like that of phenytoin.

**Clinical Uses**
Primidone, like its metabolites, is effective against partial seizures and generalized tonic-clonic seizures and may be more effective than phenobarbital. Primidone has been shown to be effective in controlling seizures in infants and in older patients beginning treatment with primidone; older patients show seizure control before phenobarbital concentrations reach the therapeutic range. Primidone has an anticonvulsant action independent of its conversion to phenobarbital.

**Pharmacokinetics**
Primidone is completely absorbed, usually reaching peak concentrations about 3 hours after oral administration. Primidone is generally distributed in total body water. It is not highly bound to plasma proteins; approximately 70% circulates as unbound drug. Primidone is metabolized by oxidation to phenobarbital. Both primidone and phenobarbital also undergo subsequent conjugation and excretion. Primidone has a larger clearance than most other antiseizure drugs. Phenobarbital accumulates very slowly but eventually reaches therapeutic concentrations in most patients. During chronic therapy, phenobarbital levels derived from primidone are usually two to three times higher than primidone levels.

**Toxicity**
The dose-related adverse effects of primidone are similar to those of its metabolite, phenobarbital, except that drowsiness occurs early in treatment and may be prominent if the initial dose is too large.

**FELBAMATE**
Although Felbamat is effective in some patients with partial seizures, the drug causes aplastic anemia and severe hepatitis at unexpectedly high rates and has been relegated to the status of a third-line drug for refractory cases. In addition to its usefulness in partial seizures, felbamate has proved effective against the seizures that occur in Lennox-Gastaut syndrome.

**GABAPENTIN & PREGABALIN**
Gabapentin, an analog of GABA, that is effective against partial seizures. Pregabalin is another GABA analog, closely related to gabapentin, and has been approved for both antiseizure activity and for its analgesic properties.

**Mechanism of Action**
In spite of their close structural resemblance to GABA, gabapentin and pregabalin do not act directly on GABA receptors. They may, however, modify the synaptic or nonsynaptic release of GABA. An increase in brain GABA concentration is observed in patients receiving gabapentin. Its main mechanism of action is decreasing Ca2+ entry, with a predominant effect on presynaptic channels. A decrease in the synaptic release of glutamate provides the antiepileptic effect.

**Clinical Uses**
Gabapentin is effective as an adjunct against partial seizures and generalized tonic-clonic seizures Gabapentin has also been promoted for the treatment of neuropathic pain and is now indicated for postherpetic neuralgia in adults. The most common adverse effects are somnolence, dizziness, ataxia, headache, and tremor. Pregabalin is approved for the adjunctive treatment of partial Seizures. Pregabalin is also approved for use in neuropathic pain, including painful diabetic peripheral neuropathy and postherpetic neuralgia.

**Pharmacokinetics**
Gabapentin is not metabolized and does not induce hepatic enzymes. The drug is not bound to plasma proteins. Drug-drug interactions are negligible. Elimination is via renal mechanisms; the drug is excreted unchanged. The half-life is relatively short, ranging from 5 to 8 hours Pregabalin, like gabapentin, is not metabolized and is almost entirely excreted unchanged in the urine. The half-life of pregabalin ranges from about 4.5 hours to 7.0 hours, thus requiring more than once-daily dosing in most patients.

**LACOSAMIDE**
Lacosamide is an amino acid-related compound that has been studied in both pain syndromes and partial seizures. The drug was approved for the treatment of partial seizures.

**Mechanism of Action**
Lacosamide enhances slow inactivation of voltage-gated Na+ channels.

**Clinical Uses**
Lacosamide is approved as adjunctive therapy in the treatment of partial-onset seizures with or without secondary generalization in patients with epilepsy who are age 16–17 years and older. Adverse effects were dizziness, headache, nausea, and diplopia.

**Pharmacokinetics**
Oral lacosamide is rapidly and completely absorbed in adults, with no food effect. ioavailability is nearly 100%. Elimination half-life is 13 hours.

**LAMOTRIGINE**
**Mechanism of Action**
Lamotrigine, like phenytoin, suppresses sustained rapid firing of neurons and produces a voltage- and use-dependent blockade of Na+ channels. Lamotrigine also inhibits voltage-gated Ca2+ channels, which would account for its efficacy in primary generalized seizures in childhood, including absence attacks. Lamotrigine also decreases the synaptic release of glutamate.

**Clinical Uses**
Although most controlled studies have evaluated lamotrigine as add-on therapy, it is generally agreed that the drug is effective as monotherapy for partial seizures, and lamotrigine is now widely prescribed for this indication. The drug is also active against absence and myoclonic seizures in children and is approved for seizure control in the Lennox-Gastaut syndrome. Lamotrigine is also effective for bipolar disorder. Adverse effects include dizziness, headache, diplopia, nausea, somnolence, and skin rash.

**Pharmacokinetics**
Lamotrigine is almost completely absorbed. Protein binding is only about 55%. The drug is metabolized primarily by glucuronidation, which is excreted in the urine. Lamotrigine has a half-life of approximately 24 hours in normal volunteers; this decreases to 13–15 hours in patients taking enzyme-inducing drugs. Valproate causes a twofold increase in the drug’s half-life; in patients receiving valproate.

LEVETIRACETAM

**Mechanism of Action**
Levetiracetam modifies the synaptic release of glutamate and GABA through an action on vesicular function. In addition, levetiracetam inhibits N-type calcium channels and inhibits calcium release from intracellular stores.

**Clinical Uses**
Levetiracetam is marketed for the adjunctive treatment of partial seizures in adults and children for primary generalized tonic-clonic seizures and for the myoclonic seizures of juvenile myoclonic epilepsy. Adverse effects include somnolence, asthenia, ataxia, and dizziness. Less common but more serious are mood and behavioral changes; psychotic reactions are rare.

**Pharmacokinetics**
Oral absorption of levetiracetam is nearly complete. Protein binding is less than 10%. The plasma half-life is 6–8 hours, but may be longer in the elderly. Two thirds of the drug is excreted unchanged in the urine; the drug has no known active metabolites.

PERAMPANEL

Perampanel is an orally active AMPA antagonist approved for the treatment of partial seizures.

**Mechanism of Action**
Perampanel acts selectively at postsynaptic AMPA receptors

**Clinical Uses**
Perampanel is approved for the adjunctive treatment of partial seizures with or without secondary generalization in patients 12 years of age or older. Although the drug was generally well tolerated, more common adverse effects were dizziness, somnolence, and headache. Falls were more common at higher doses. A small number of patients experienced serious or life-threatening behavioral adverse reactions including aggression, hostility, irritability, and anger, with or without a previous history of psychiatric disorders. Perampanel has a long half-life, typically ranging from 70 to 110 Hours. Absorption is rapid and the drug is fully bioavailable. Perampanel is 95% bound to plasma proteins. The drug is extensively metabolized via initial oxidation and subsequent glucuronidation.

**Drug Interactions**
The most significant drug interactions with perampanel are with potent CYP3A inducer antiseizure drugs such as carbamazepine, oxcarbazepine, and phenytoin. When perampanel was administered with carbamazepine, the half-life decreased from 105 hours to 25 hours.

RETIGABINE (EZOGABINE)
Retigabine (ezogabine in the USA) is approved for the adjunctive treatment of partial-onset seizures in adults. It is a potassium channel facilitator and unique in its mechanism of action. Absorption is not affected by food; drug interactions are minimal. Most adverse effects are dose related and include dizziness, somnolence, blurred vision, confusion, and dysarthria. In 2013, reports began to appear of blue pigmentation, primarily on the skin and lips; the problem
is rather common, occurring in about one third of patients on long-term therapy. Decreased visual acuity has been reported. Regulatory agencies have recommended use of retigabine only in cases where other antiseizure drugs are not adequate or not tolerated.

**RUFINAMIDE**

**Mechanism of Action**
Rufinamide decreases sustained high-frequency firing of neurons in vitro and is thought to prolong the inactive state of the Na+ channel.

**Clinical Uses**
Rufinamide is approved in the USA for adjunctive treatment of seizures associated with the Lennox-Gastaut syndrome in patients age 4 years and older. The drug is effective against all seizure types in this syndrome, especially against tonic-ataonic seizures. Recent data also suggest it may be effective against partial seizures. The most common adverse events are somnolence, vomiting, pyrexia, and diarrhea.

**Pharmacokinetics**
Rufinamide is well absorbed, but plasma concentrations peak between 4 and 6 hours. The half-life is 6–10 hours, and minimal plasma protein binding is observed. The drug is extensively metabolized to inactive products. Most of the drug is excreted in the urine; an acid metabolite accounts for about two thirds of the dose.

**STIRIPENTOL**
Stiripentol is used with clobazam and valproate in the adjunctive therapy of refractory generalized tonic-clonic seizures in patients with severe myoclonic epilepsy of infancy (SMEI, Dravet’s syndrome) whose seizures are not adequately controlled with clobazam and valproate. The mechanism of action of stiripentol is not well understood but it has been shown to enhance GABAergic transmission in the brain. It can increase the effect of other AEDs by slowing their inactivation by cytochrome P450. Stiripentol is a potent inhibitor of CYP3A4, CYP1A2, and CYP2C19. Adverse effects of stiripentol itself are few, but the drug can dramatically increase the levels of valproate, clobazam, and the active metabolite of the latter, norclobazam. These drugs must be used cautiously together to avoid adverse effects.

**TIAGABINE**

**Mechanism of Action**
Tiagabine is an inhibitor of GABA uptake in both neurons and glia. It prolongs the inhibitory action of synaptically released GABA, but its most significant effect may be potentiation of tonic inhibition.

**Clinical Uses**
Tiagabine is indicated for the adjunctive treatment of partial seizures. Minor adverse events are dose related and include nervousness, dizziness, tremor, difficulty in concentrating, and depression. Excessive confusion, somnolence, or ataxia may require discontinuation. Rash is an uncommon idiosyncratic adverse effect.

**Pharmacokinetics**
Tiagabine is 90–100% bioavailable, has linear kinetics, and is highly protein bound. The half-life is 5–8 hours and decreases in the presence of enzyme-inducing drugs. The drug is oxidized in the liver by CYP3A. Elimination is primarily in the feces (60–65%) and urine (25%).
TOPIRAMATE
Mechanism of Action
Topiramate mechanism of action, is likely to involve blocking of voltage-gated Na+ channels. It also acts on high-voltage activated (L-type) Ca2+ channels. Topiramate potentiates the inhibitory effect of GABA, acting at a site different from the benzodiazepine or barbiturate sites. Topiramate also depresses the excitatory action of kainate on glutamate receptors.
Clinical Uses
Clinical trials of topiramate as monotherapy demonstrated efficacy against partial and generalized tonic-clonic seizures. The drug is also approved for the Lennox-Gastaut syndrome, and may be effective in infantile spasms and even absence seizures. Topiramate is also approved for the treatment of migraine headaches. Dose-related adverse effects occur most frequently in the first 4 weeks and include somnolence, fatigue, dizziness, cognitive slowing, paresthesias, nervousness, and confusion. Acute myopia and glaucoma may require prompt drug withdrawal. The drug is teratogenic in animal models.
Pharmacokinetics
Topiramate is rapidly absorbed (about 2 hours) and is 80% bioavailable. The drug is primarily excreted unchanged in the urine. The half-life is 20–30 hours. Drug interactions do occur and can be complex, but the major effect is on topiramate levels rather than on the levels of other antiseizure drugs.
VIGABATRIN
Mechanism of Action
Vigabatrin is an irreversible inhibitor of GABA aminotransferase. It may also inhibit the vesicular GABA transporter. A decrease in brain glutamine synthetase activity is probably secondary to the increased GABA concentrations.
Clinical Uses
Vigabatrin is useful in the treatment of partial seizures and infantile spasms. The half-life is approximately 6–8 hours, but considerable evidence suggests that the pharmacodynamic activity of the drug is more prolonged and not well correlated with the plasma half-life. Typical toxicities include drowsiness, dizziness, and weight gain. Less common but more troublesome adverse reactions are agitation, confusion, and psychosis; preexisting mental illness is a relative contraindication. In addition, long-term therapy with vigabatrin has been associated with development of peripheral visual field defects in 30–50% of patients. Vigabatrin is usually reserved for use in patients with infantile spasms or with complex partial seizures refractory to other treatments.
ZONISAMIDE
Zonisamide is a sulfonamide derivative. Its primary site of action appears to be the Na+ channel; it also acts on T-type voltage-gated Ca2+ channels. The drug is effective against partial and generalized tonic-clonic seizures and may also be useful against infantile spasms and certain myoclonias. It has good bioavailability, linear kinetics, low protein-binding, renal excretion, and a half-life of 1–3 days. Adverse effects include drowsiness, cognitive impairment, and potentially serious skin rashes. Zonisamide does not interact with other antiseizure drugs.

DRUGS USED IN GENERALIZED SEIZURES
ETHOSUXIMIDE

Mechanism of Action
Ethosuximide has an important effect on Ca2+ currents, reducing the low-threshold (T-type) current. This effect is seen at therapeutically relevant concentrations in thalamic neurons. Inhibition of this current could therefore account for the specific therapeutic action of ethosuximide. It was introduced as a “pure petit mal” drug.

Clinical Uses
Ethosuximide is particularly effective against absence seizures, but has a very narrow spectrum of clinical activity. Data continue to show that ethosuximide and valproate are the drugs of choice for absence seizures and are more effective than lamotrigine.

Pharmacokinetics
Absorption is complete following administration of the oral dosage forms. Peak levels are observed 3–7 hours after oral administration of the capsules. Ethosuximide is not protein-bound. The drug is completely metabolized, principally by hydroxylation, to inactive metabolites. Ethosuximide has a very low total body clearance (0.25 L/kg/d). This corresponds to a half-life of approximately 40 hours, although values from 18 to 72 hours have been reported.

Drug Interactions & Toxicity
Administration of ethosuximide with valproic acid results in a decrease in ethosuximide clearance and higher steady-state concentrations owing to inhibition of metabolism. The most common dose-related adverse effect of ethosuximide is gastric distress, including pain, nausea, and vomiting. Other dose-related adverse effects are transient lethargy or fatigue and, much less commonly, headache, dizziness, hiccup, and euphoria.

VALPROIC ACID & SODIUM VALPROATE

Valproic acid is one of a series of fatty carboxylic acids that have antiseizure activity. It is fully ionized at body pH, and for that reason the active form of the drug may be assumed to be the valproate ion regardless of whether valproic acid or a salt of the acid is administered.

Mechanism of Action
Valproate is active against both pentylenetetrazol and maximal electroshock seizures. Like phenytoin and carbamazepine, valproate blocks sustained high-frequency repetitive firing of neurons. Its action against partial seizures may be a consequence of this effect on Na+ currents. Blockade of NMDA receptor-mediated excitation may also be important. Several studies have shown increased levels of GABA in the brain after administration of valproate, although the mechanism for this increase remains unclear.

Clinical Uses
Valproate is very effective against absence seizures and is often preferred to ethosuximide when the patient has concomitant generalized tonic-clonic attacks. Valproate is unique in its ability to control certain types of myoclonic seizures; in some cases the effect is very dramatic. The drug is effective in tonic-clonic seizures, especially those that are primarily generalized. Intravenous formulations are occasionally used to treat status epilepticus.

Pharmacokinetics
Valproate is well absorbed after an oral dose, with bioavailability greater than 80%. Peak blood levels are observed within 2 hours. Food may delay absorption, and decreased toxicity may result
if the drug is given after meals. Valproic acid is 90% bound to plasma proteins. Since valproate is both highly ionized and highly protein-bound, its distribution is essentially confined to extracellular water. Clearance for valproate is low and dose dependent; its half-life varies from 9 to 18 hours.

**Drug Interactions**

Valproate displaces phenytoin from plasma proteins. In addition to binding interactions, valproate inhibits the metabolism of several drugs, including phenobarbital, phenytoin, and carbamazepine, leading to higher steady-state concentrations of these agents. Valproate can dramatically decrease the clearance of lamotrigine.

**Toxicity**

The most common dose-related adverse effects of valproate are nausea, vomiting, and other gastrointestinal complaints such as abdominal pain and heartburn. Sedation is uncommon with valproate alone. Other reversible adverse effects, seen in a small number of patients, include weight gain, increased appetite, and hair loss. The idiosyncratic toxicity of valproate is largely limited to hepatotoxicity. The risk is greatest for patients under 2 years of age and for those taking multiple medications. The other observed idiosyncratic response with valproate is thrombocytopenia. There is a substantial increase in the incidence of spina bifida in the offspring of women who took valproate during pregnancy. In addition, an increased incidence of cardiovascular, orofacial, and digital abnormalities has been reported. These observations must be strongly considered in the choice of drugs during pregnancy.

**OXAZOLIDINEDIONES**

Trimethadione is active against pentylenetetrazol-induced seizures. Trimethadione raises the threshold for seizure discharges after repetitive thalamic stimulation. Trimethadione is rapidly absorbed, with peak levels reached within 1 hour after drug administration. Trimethadione is completely metabolized in the liver. The most common and bothersome dose-related adverse effect of the oxazolidinediones is sedation. These drugs should not be used during pregnancy. Use of the oxazolidinediones—trimethadione, paramethadione, and dimethadione—is now very limited; the latter two are not readily available.

**OTHER DRUGS USED IN MANAGEMENT OF EPILEPSY**

Some drugs not classifiable by application to seizure type are discussed in this section.

**BENZODIAZEPINES**

Six benzodiazepines play prominent roles in the therapy of epilepsy. The mechanisms of antiseizure action is the potentiation of GABA action on chloride channel. Diazepam given intravenously or rectally is highly effective for stopping continuous seizure activity, especially generalized tonic clonic status epilepticus. Lorazepam appears in some studies to be more effective and longer acting than diazepam in the treatment of status epilepticus and is preferred by some experts. Clonazepam is a long-acting drug with documented efficacy against absence seizures. It is also effective in some cases of myoclonic seizures and has been tried in infantile spasms. Sedation is prominent, especially on initiation of therapy; starting doses should be small. Nitrazepam is not marketed in the USA but is used in many other countries, especially for infantile spasms and myoclonic seizures. It is less potent than clonazepam, and superiority
to that drug has not been documented. **Clorazepate dipotassium** is approved in the USA as an adjunct to treatment of complex partial seizures in adults. Drowsiness and lethargy are common adverse effects. **Clobazam** is widely used in a variety of seizure types. The drug is approved in the USA for treatment of Lennox-Gastaut syndrome.

**Limitations**
Two prominent aspects of benzodiazepines limit their usefulness. The first is their pronounced sedative effect, which is unfortunate both in the treatment of status epilepticus and in chronic therapy. Children may manifest a paradoxical hyperactivity, as with barbiturates. The second problem is tolerance, in which seizures may respond initially but recur within a few months. The remarkable antiseizure potency of these compounds often cannot be realized because of these limiting factors.

**ACETAZOLAMIDE**
Acetazolamide is a diuretic whose main action is the inhibition of carbonic anhydrase. Mild acidosis in the brain may be the mechanism by which the drug exerts its antiseizure activity. Acetazolamide has been used for all types of seizures but is severely limited by the rapid development of tolerance, with return of seizures usually within a few weeks. The drug may have a special role in epileptic women who experience seizure exacerbations at the time of menses.

Reference: