Chapter 29
Antiepileptic Agents

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Contents

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A.D. Kaye et al. (eds.), *Essentials of Pharmacology for Anesthesia, Pain Medicine, and Critical Care*, DOI 10.1007/978-1-4614-8948-1_29,

This chapter provides an overview of the currently available antiepileptic drugs. At this time, there are 24 antiepileptic drugs approved by the FDA, several only recently [1]. Some drugs have more than one mechanism of action [2]. Some of these agents have only one particular indication, while others have a broad spectrum of action [3]. A few are approved only for adjunct therapy. A common classification is by generation [2, 4–6]:

First generation: hydantoins, barbiturates, carbamazepine, succinimides, valproic acid, and benzodiazepines [7]

Second generation: lamotrigine, oxcarbazepine, topiramate, gabapentin, levetiracetam, felbamate, pregabalin, tiagabine, and zonisamide [7]

Epilepsy

Epilepsy is a brain disorder causing recurrent seizures. Among possible etiologies for their occurrence are a genetic predisposition, head trauma, stroke, brain tumor, metabolic abnormalities, drug and alcohol withdrawal, and CNS infection [8–10]. Seizures are due to electrical disturbances of cortical neurons leading to a sudden imbalance between excitatory and inhibitory activity resulting in a net excitation [1, 4, 9]. The symptoms depend on the location and function of the epileptic focus. There are several types of seizures [6, 10]:

Partial (*focal*) *seizures* (about 60 % of all seizures), which are divided into *simple*, if consciousness does not get affected, or *complex* if it does (temporal or psychomotor seizures)

Generalized seizures (about 40 % of all seizures) with bilateral symmetric electrical activity resulting in abnormal motor activity and/or loss of consciousness. Inhibitory or nonconvulsive seizures include atonic (petit mal) seizures, with transient lapse in consciousness, and absence seizures that are characterized by a loss of consciousness and staring spells. Excitatory and convulsive seizures include myoclonic (brief involuntary muscle twitches), clonic (series of muscle contractions), and tonic-clonic (grand mal) seizures with tonic-clonic motor activity and loss of consciousness. Partial seizures can progress to secondarily generalized tonic-clonic seizures.

Unclassified Seizures

Seizures also are categorized as epileptic syndrome, including seizure type, etiology, age of onset, etc. There are more than 50 such syndromes.

Mechanism of Action

Antiepileptics change the excitation or inhibition of neurotransmission via an effect on ion channels, receptors, or neurotransmitter metabolism [1–4, 6, 9, 11].

1. Blockade of voltage-gated Na channel
   The sodium channels are responsible for the depolarization phase of the neuronal action potential by allowing sodium influx. This active phase is followed by an inactive refractory period. Some antiepileptics stabilize the inactive state and block the depolarization of the nerve terminal and subsequent release of neurotransmitter and prevent the high-frequency neuronal firing leading to seizures [3, 4, 6, 7].
2. Potentiation of inhibition by GABA
   Gamma-aminobutyric acid is the main inhibitory transmitter in the brain [3]. It binds to GABA-A and GABA-B receptors. GABA-A receptors are coupled to chloride channels [4], where chloride influx decreases the excitability of the postsynaptic membrane [4]. GABA-B receptors are coupled to presynaptic potassium channels which indirectly may inhibit the release of neurotransmitter.
   The inhibition of GABA transaminase increases the amount of released GABA [1, 4, 7].
   Also the reuptake of GABA can be blocked and its effect thereby increased.
3. Blockade of calcium channels
   T-type calcium channels in the thalamic neurons play a role in "spike and wave" discharges typical for absence seizures [2, 3]. Their blockade is effective against absence seizures. Effects on other voltage-gated calcium channels are less studied. Many antiepileptics act on different calcium channels; effect on N-type and P/Q-type seems to contribute to antiepileptic effect and effect on neuropathic pain of drugs, including gabapentin and pregabalin [3, 4, 7].
4. Action on alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA)/kainite/N-methyl-D-aspartate (NMDA)
   They are glutamate receptor sites, which bind glutamate, an excitatory CNS neurotransmitter, activating influx of sodium and calcium ions and outflow of potassium ions leading to excitation. Glutamate antagonists modify these receptors [2, 4, 12–14].
5. Modulation of serotonergic transmission
   Serotonin (5-hydroxytryptamine) is a neurotransmitter modulating mood and behavior. Increased extracellular serotonin levels (i.e., by blockade of reuptake) inhibit seizures. Activation of some serotonin receptor subtypes also inhibits seizures. 5-HT2C depolarizes GABAergic neurons; 5-HT1A hyperpolarizes glutamatergic neurons [3, 4, 7, 15].
6. Effect on potassium current
   The outward potassium current is at least partially responsible for the refractory period after an action potential. Modifying this outward potassium current to flow faster and longer will enhance the refractory period that can slow the repetitive firing of neurons [1, 3, 4, 16].
7. Modulation of SV2A
   SV2A is a synaptic vesicle protein involved in vesicle exocytosis and ejection of stored neurotransmitters. Modulation of the SV2A can lead to decreased action potential-dependent neurotransmission [1, 2, 4, 17].

Drugs

Since 2008, the FDA mandated that all antiepileptic package inserts have to state that they increase the risk of suicidal thoughts/action [1, 5, 7, 18, 19]. Some of these warnings are modest: for example, the risk of suicidal thoughts for gabapentin is 4/10,000 versus 3/10,000 for placebo. Since then studies have cited odds ratios (>1 = increased suicidal risk) for topiramate (OR = 2.53), lamotrigine (OR = 2.08), valproate (OR = 1.4), carbamazepine (OR = 0.65–1.4), gabapentin (OR = 0.9), levetiracetam (OR = 0.7), pregabalin (OR = 0.2), and clonazepam (OR = 2.1) but also questioned if the warning is warranted [20–22]. After initiation of therapy, roughly 50 % of patients experience full control of their seizure activity, and 25 % experience improvement. To decrease toxicity, therapy with one drug is preferred [6]. For some AED drugs, it is recommended to slowly titrate the dose up to avoid or to decrease side effects. First-generation AEDs have been shown to increase the risk of fetal malformations two- to threefold if taken in the first trimester [3, 8]; many induce liver enzymes and increase metabolism of other drugs.

Phenytoin

This agent is a first-line therapy for partial and tonic-clonic seizures, status epilepticus, and prevention of seizures after neurosurgery. It blocks the ion influx and slows the recovery rate of voltage-gated sodium channels. It is 90 % protein bound (more free drug in neonate, hypoalbuminemia, uremia), 95 % of the drug is metabolized in the hepatic endoplasmic reticulum by CYP2C9/10/19, its metabolite is inactive, and its elimination is not linear but varies with its plasma concentration. By inducing liver enzymes (CYPs), phenytoin enhances the metabolism of other drugs (contraceptives, neuromuscular blockers) [2, 5, 6].

Dose

Adult dose is initially 100 mg three times a day, with max 600 mg/day. Loading dose for rapid therapeutic level is 1,000 mg (400, 300,300 mg 2 h apart) or 10–15 mg/kg IV at maximum 50 mg/min or 1–3 mg/kg/min, then 100 mg IV or PO every 6–8 h.

Compatible with normal saline and may precipitate with IV solutions/other drugs.

Therapeutic Level

10–20 mcg/ml; in neonates, 7.5–15 mcg/ml

Onset

1–2 h (IV), 2–24 h (PO)

Half-Life

10–15 h (IV), 22 h (PO)

Fosphenytoin

It is a water-soluble prodrug of phenytoin, and 75 mg of fosphenytoin is equivalent to 50 mg of phenytoin. The level can be checked 2 h after an IV dose.

Dose

15–20 mg/kg IV at max 150 mg/min, then maintenance dose 4–6 mg/kg/day given once daily or divided two times a day; if switching from phenytoin, same daily dose.

Therapeutic Level

10–20 mcg/ml phenytoin

Half-Life

15 min

Side Effects

For fosphenytoin, arrhythmias are less frequent with its IV use; acute overdose shows mostly cerebellar and vestibular signs; very high doses can lead to cerebellar atrophy, GI symptoms, gingival hyperplasia (about 20 %), osteomalacia, megaloblastic anemia, hirsutism, transient increase in liver enzymes (although this by itself is no reason to change therapy), skin reactions like rashes and Steven-Johnson's syndrome, SLE, fatal hepatic necrosis, leukopenia, mild thrombocytopenia, lymphadenopathy and malignant lymphoma due to decreased IGA production, and hemorrhage in newborns of mothers on phenytoin (can be prophylactically dosed with vitamin K); many side effects can be lowered with dose adjustments. Abrupt withdrawal can elicit seizures.

Black Box Warning
Cardiovascular symptoms such as severe hypotension and arrhythmias are possible with rapid infusion. If given IV, patients should be on cardiac monitor [23].

Other Uses

Trigeminal and other neuralgias and cardiac (ventricular) arrhythmias

Barbiturates

Phenobarbital (Luminal) inhibits seizures by binding to specific GABA-A receptor site and prolonging chloride channel opening. It is 40–60 % protein bound, with hepatic metabolism by CYP2C9/19, and 25 % renal excretion. It induces liver enzymes (UGT, CYP2C, 3A). It is used for therapy of secondarily generalized tonic-clonic and partial seizures and status epilepticus [4, 6].

Dose

Adults, 1–4 mg/kg/day up to 200–240 mg/day or divided twice a day [5, 8]

Neonates, 3–5 mg/kg/day IV/PO; infants, 5–6 mg/kg/day; 1–5 years, 6–8 mg/kg/day; 6–12 years, 4–6 mg/kg/day; >12 years, 1–3 mg/kg/day; for status epilepticus in infants and children, 15–20 mg/kg IV once, not faster than 30 mg/min; and in adults, 10–20 mg/kg once at 25–100 mg/min

Therapeutic Level

10–40 mcg/ml

Onset

After IV administration, 5–12 min, with peak levels at 30 min. If given orally, drug reaches steady state after 2–3 weeks.

Half-Life

50–120 h, in infants up to 400 h. Half-life is increased in pregnancy.

Side Effects

Sedation (but tolerance develops with time), rash, hypothrombinemia with hemorrhage in newborns, megaloblastic anemia, osteomalacia, irritability and

hyperactivity in children, agitation and confusion in elderly, ataxia and nystagmus at excessive doses (>60 mcg/ml), respiratory depression with large doses, withdrawal seizures if stopped abruptly; injectable solution is highly alkaline – tissue necrosis can occur with extravasation [5, 6, 8].

Contraindication

Porphyria, severe liver disease, and lactation

Iminostilbenes

Carbamazepine (*Tegretol*, *Carbatrol*) slows recovery of inactivated sodium channels. It is 75 % protein bound, is metabolized in the liver to active 10,11-epoxide which metabolizes to an inactive compound, and is excreted in urine. Carbamazepine induces liver enzymes. It is used for all partial and generalized tonic-clonic seizures [4, 6, 8].

Dose

Initially 200 mg twice daily, suspension 100 mg four times daily, with maximum of 1,200 mg/day, rarely 1,600 mg/day. For ages 12–15 years, 1,000 mg divided into three or four daily doses; for ages under 6 years, 10–20 mg/kg/day in two or three doses [5, 8].

Therapeutic Level

4–12 mcg/ml, autoinduction starts 3–4 weeks after start, decreasing level

Onset

Plasma peak time: regular tab 4.5 h; oral suspension, 1.5 h; 3–12 h extended release tab

Half-Life

25–65 h at first, then decreasing to 12–17 h

Side Effects

Antidiuretic effect (increased antidiuretic hormone), CNS side effects start at 9 mcg/ml, drowsiness, ataxia, diplopia, aplastic anemia (1:200,000), agranulocytosis, eosinophilia, lymphadenopathy, splenomegaly, transient increase of liver enzymes (5–10 %) that resolves in 4 months, mild leukopenia, and thrombocytopenia. Renal and hepatic function need to be monitored.

The black box warning (www.fda.gov) include [24]:

- Concern over occasionally serious dermatologic reactions, which can include mucous membrane ulcers (including Stevens-Johnson syndrome and toxic epidermal necrolysis), painful rash, and elevated temperature (1–6 per 10,000 new users in countries with mainly white populations, but the risk with an almost exclusive Asian allele HLA-B*1502 is much higher, and epidemiological data in some Asian countries estimates risk to be approximately ten times higher).
- Aplastic anemia and agranulocytosis are very rare, but therapy may be halted if there is bone marrow suppression (the risk is 5–8 times greater than in the general population, and the overall risk of these reactions in the untreated general population is minimal, approximately six patients per one million population per year for agranulocytosis and two patients per one million population per year for aplastic anemia).

Contraindication

Sensitivity to tricyclic antidepressives, history of bone marrow depression, and no coadministration with MAO inhibitors (stop MAOI for 14 days) and nefazodone

Other Uses

Trigeminal and glossopharyngeal neuralgia, bipolar disorder, and lightning-type pain with bodily wasting [2, 5, 8, 25–28]

Oxcarbazepine is a prodrug and is a keto-analogue of carbamazepine that becomes converted to active 10-monohydroxy derivative (MHD). It is inactivated by glucuronide conjugation with renal excretion; it is 38 % protein bound and a less potent liver enzyme inducer. It is utilized for mono- or adjunct therapy of partial seizures in adults, monotherapy of partial seizures in children 4–16 years, adjunct therapy in children 2–4 years old, and used also for neuropathies and bipolar disorder.

Dose

Starting dose 300 mg twice daily, recommended 1,200 mg/day, can slowly be increased to up to 2,400 mg/day, but often not tolerated (CNS effects); for children aged 2–4 years, 8–10 mg/kg/day in divided doses up to 600 mg, then slowly increase up to 60 mg/kg/day; if <20 kg, start with 16–20 mg/kg/day; for 4–16 years, 8–10 mg/kg/day in two doses, then titrate over 2 weeks up depending on weight: 20–29 kg, 450 mg twice daily; 29–39 kg, 600 mg twice daily; >39 kg, 900 mg twice daily. Decrease initial dose with renal impairment.

Therapeutic Level

15–35 mcg/ml of active MHD

Onset

Peak drug level after 1–3 h; of active MHD, 4–12 h

Half-Life

1–3 h for oxcarbazepine and 8–10 h for MHD

Side Effects

Antidiuretic action leading to water retention and hyponatremia, especially in elderly patients (7.4 %) and in the first 3 months of therapy, somnolence, dizziness, GI disturbances, alopecia, anaphylaxis, angioedema, epidermal necrolysis, can worsen absence and myoclonic seizures and juvenile idiopathic generalized epilepsy, and diplopia. 25–30 % of those patients that are allergic to carbamazepine will also be allergic to oxcarbazepine.

Contraindications

Hypersensitivity to oxcarbazepine

Succinimides

Ethosuximide (*Zarontin*) is the primary and most selective agent for absence seizures (petit mal). It works by decreasing low-threshold T-type calcium currents in thalamic neurons. It has no significant protein binding; 25 % gets excreted unchanged in urine, and the rest is metabolized by hepatic microsomal enzymes into a major metabolite, hydroxyethyl derivative. Forty percent of drug excreted as glucuronides in urine [4, 5].

Dose

For ages 3–6 years, initial dose 250 mg/day. For 6 years and older, initial 500 mg once, and then optimal dose 20 mg/kg/day in divided doses

Therapeutic Level

40–100 mcg/ml, plasma concentration averages ~2 mcg/ml per 1 mg/kg

Onset

Peak plasma time 4 h

Half-Life

40–60 h, in children 30 h

Side Effects

Most common side effects include nausea and vomiting, anorexia, drowsiness, lethargy, euphoria, headaches, hiccough, occasional Parkinson-like symptoms, photophobia, restlessness, agitation inability to concentrate, lupus, blood dyscrasias, and abnormal renal and hepatic function.

Contraindication

Hypersensitivity

Valproic Acid (Depakote)

Valproic acid is different because it acts against absence as well as complex partial and generalized tonic-clonic seizures and is also used for migraine and bipolar disorder. It acts by increasing the amount of GABA by inhibiting its metabolism, and the drug also acts on sodium channels and on T-type calcium channels. It is metabolized in the liver and exhibits high protein binding and molarity, displacing other drugs from albumin. It inhibits enzyme CYP2C9 and UGT and decreases the metabolism of other drugs [2–5, 8, 13].

Dose

Initially 10–15 mg/kg, increased weekly by 5–10 mg/kg up to max 60 mg/kg, divided doses over 250 mg/day in adults and children. IV dilution is 100 mg/ml, and the IV dose and frequency is the same as PO doses. However, IV doses should be infused over 60 min at <20 mg/min.

Therapeutic Level

30–100 mcg/ml, but poor correlation of concentration and effect

Onset

Peak plasma time, 1–4 h; extended release, 7–14 h

Half-Life

6–16 h; in neonates, 10–67 h

Side Effects

GI symptoms, anorexia in 16 %, sedation, ataxia, occasional tremor, rash, alopecia, increased appetite, 40 % get increase of liver enzymes, asymptomatic, thrombocytopenia, increased bleeding time, weight loss, hyperammonemia, and multiorgan

hypersensitivity reaction; use with clonazepam can trigger absence seizures and, rarely, absence status epilepticus.

Black Box Warning
Hepatotoxicity, hepatic failure especially in children under 2 years and if on multiple drugs or with metabolic disorders, risk decreases for 2–10 year olds and even more for older kids and adults (1:50,000). Serious or fatal hepatotoxicity may be preceded by nonspecific symptoms such as anorexia, facial edema, lethargy, malaise, vomiting, and weakness. Liver damage usually occurs in the first 6 months, and therefore, liver function tests prior to therapy and at frequent intervals are recommended, especially during the first 6 months. A second black box warning is pancreatitis, which can be hemorrhagic and rapidly progressing and may be fatal in both children and in adults. It should be noted that reported cases involve incidence shortly after initial use as well as after several years of use. A third black box warning is teratogenicity. The drug can cause neural tube defects (e.g., spina bifida) with poor cognitive outcome. This risk is greater than with other AEDs [29].

Contraindication

Liver disease, pancreatitis, pregnancy (especially in the first trimester), and urea cycle disorder

Benzodiazepines

Benzodiazepines approved for long-term therapy are *clonazepam* (Klonopin) and *clorazepate* (Tranxene), and those used for status epilepticus are *diazepam* (Valium) and *lorazepam* (Ativan). Benzodiazepines bind to a specific GABA-A receptor subunit and modulate chloride currents by increasing the frequency (but not the duration) of channel openings, increasing the GABA-mediated inhibition of the action potential. At higher doses, they may also act on sodium channels [2–6].

Diazepam is metabolized by hepatic enzymes, and a major metabolite is the partial agonist N-desmethyldiazepam. Both diazepam and its metabolite get hydroxylated into another active metabolite, oxazepam. It is highly lipid soluble and 99 % protein bound. It is used in status epilepticus but can also be used as an anxiolytic, a hypnotic, a muscle relaxant, and a treatment for alcohol withdrawal. Its main disadvantage is its relatively short duration of action [30].

Dose

2–10 mg PO every 6–12 h. For status epilepticus, 5–10 mg IV every 10–15 min up to 30 mg

Therapeutic Level

0.2–0.2 mcg/ml for other uses; for seizures, by effect

Onset

Prompt with rapid redistribution due to high lipid solubility

Half-Life

20–70 h

Side Effects

Sedation, confusion, anterograde amnesia, respiratory depression, ataxia, nausea, vomiting urinary retention, hypotension, increased CNS effects in elderly, dependence and withdrawal symptoms with abrupt cessation, and phlebitis with IV administration

Contraindication

Hypersensitivity, severe hepatic impairment, myasthenia gravis (with exceptions), and acute alcohol intoxication [2, 6]

Clonazepam has a higher affinity for the GABA-A receptor site than diazepam. It is metabolized in the liver to an inactive metabolite, and less than 1 % is excreted unchanged in urine. It is the drug of choice for myoclonic seizures and, to a lesser degree, subcortical myoclonus. It is also effective in status epilepticus. It can also be used for anxiety and panic disorders. Tolerance develops usually after 1–6 months, and once tolerance is developed, the drug has no effect at any dose. It is available in IV and PO form.

Dose

In adults, initially <1.5 mg/day, increase every 3 days by 0.5–1.0 mg/day to max 20 mg/day. In children, 0.01–0.03 mg/kg/day, increase every 3 days by 0.25–0.5 mg/day to max 0.2 mg/kg/day. Side effects are less if given in divided doses.

Therapeutic Level

Tolerance makes plasma concentration of limited value.

Onset

20–60 min, prompt after IV dose

Half-Life

18–60 h; 22–33 h in children

Side Effects

Sedation; anterograde amnesia; drowsiness; lethargy; muscular incoordination; ataxia; hypotonia; dysarthria; behavioral disturbances like aggression, hyperactivity, irritability, and difficulty to concentrate; anorexia or hyperphagia; increased salivation and bronchial secretions; seizure exacerbation; and status epilepticus if stopped abruptly (even after only a few weeks on the drug)

Contraindication

Same as for diazepam, narrow-angle glaucoma

Clorazepate has the same mechanism of action as the previous two benzodiazepines. It is metabolized in liver to desmethyldiazepam and oxazepam, which are excreted in urine. It is used for adjunct therapy of partial seizures, but is not approved for use in children under 9 years of age. It is also used for anxiety and alcohol withdrawal.

Dose

For seizures in children aged 9–12 years, 7.5 mg twice daily, then increase by <7.5 mg every week up to 60 mg/day. For ages 12 years and older, 7.5 mg three times daily, then increase weekly by <7.5 mg up to 90 mg/day. For anxiety and withdrawal, the starting doses are higher – about 30 mg.

Therapeutic Level

Not established

Onset

1–2 h

Half-Life

50–70 h

Side Effects

CNS depression, dry mouth, anterograde amnesia, blurred vision, withdrawal symptoms with abrupt cessation, and respiratory depression

Contraindication

Hypersensitivity and narrow-angle glaucoma

Lorazepam is also metabolized in the liver to inactive metabolites that are excreted in urine. It is 85 % protein bound in plasma. It is used as therapy for status epilepticus, anxiety, sedation, and chemotherapy-induced nausea and vomiting.

Dose

IV for status epilepticus – 4 mg IV, with range of 2–8 mg, repeat every 5–15 min, with maximum dose of 20 mg/h. In children, the dose is 0.05–0.1 mg/kg IV over 2–5 min, up to 4 mg. Repeat every 10–15 min if needed. For anxiety/sedation, 2–3 mg PO every 8–12 h, then 2–6 mg/day in divided doses or 0.02–0.06 mg/kg IV or 0.01–0.1 mg/kg/h; for children, 0.05 mg/kg PO every 4–8 h. With chemotherapy 1–2.5 mg PO or IV half an hour before treatment, then every 4 h if needed; in children, 0.05 mg/kg IV, and repeat every 6 h as needed.

Therapeutic Level

Peak plasma level after 2 mg is 20 ng/ml.

Onset

IV, 1–5 min; IM, 15–30 min

Half-Life

12–18 h

Side Effects

CNS depression, respiratory depression, extrapyramidal symptoms, changes in vision and appetite, increase of liver enzymes, and withdrawal symptoms with abrupt cessation

Contraindication

Hypersensitivity and narrow-angle glaucoma

Clobazam is approved for adjunctive therapy of LGS in patients 2 years and older. It binds also to GABA-A receptor, potentiating GABAergic neurotransmission.

Dose

Adults: Start 10 mg/day and increase up to 40 mg/day over at least 2 weeks. Pediatric: If under 30 kg, start 5 mg/day and then increase up to 20 mg/day. If over 30 kg, dose according to adult dosage [1, 2, 31].

Therapeutic Level

237–285 ng/ml

Onset

30 min to 4 h

Half-Life

36–42 h, but its metabolite, N-desmethylclobazam, has about 70–80 h.

Side Effects

Sedation: avoid other depressants, alcohol, and abrupt discontinuation (withdrawal).

Contraindications

Hypersensitivity: caution with myasthenia gravis.

Gabapentin (Neurontin) and Pregabalin (Lyrica)

Gabapentin is believed to have an effect on calcium channels as it binds to the a2δ subunit of calcium channels. It is highly lipid soluble, but is not metabolized and excreted unchanged in urine. It is not protein bound and does not induce hepatic enzymes. It is used for adjunct therapy of partial seizures with or without secondary generalized seizures. Other uses include migraine, chronic pain, postherpetic neuralgia, bipolar disorder, and other neuropathic pain states [2–6, 8].

Dose

Initially 300 mg PO every 8 h, up to 600 mg every 8 h, with maximum up to 3,600 mg/day. Adjust dose with renal impairment. For partial seizures age 3–12 years, 10–15 mg/kg/day in three doses. Titrate up to maintenance dose for ages 3–4 years old 40 mg/kg/day in three doses, and for 5–12 years, 25–35 mg/kg/day; for ages 12 and older, dosing is the same as adults'. For neuralgia in adults, titrate up to 600 mg three times daily.

Therapeutic Level

Not very helpful, effect at 2–20 mcg/ml, occasionally up to 80 mcg/ml as necessary

Onset

Peak serum level at 2–4 h

Half-Life

5–7 h

Side Effects

Somnolence, ataxia, dizziness, nystagmus, tremor, and diplopia: usually resolves after 2 weeks. Eighty-six percent of patients do not meet target doses because of side effects; a new gastroretentive formulation (Gralise) has similar efficacy with significantly improved side effect profile.

Contraindication

Hypersensitivity

Pregabalin is used for adjunctive therapy of partial seizures and also for neuropathies and fibromyalgia. It works similar to gabapentin, is excreted unchanged in urine, and is not protein bound.

Dose

For adults, start 150 mg/day up to 600 mg/day. Safety in pediatric population is not established.

Therapeutic Level

0.5–16 mcg/ml

Onset

Peak serum level at 1.5 h

Half-Life

6.3 h

Side Effects

Dizziness, peripheral edema, somnolence, ataxia, nystagmus, and tremor

Contraindication

Hypersensitivity

Lamotrigine (Lamictal)

Lamotrigine acts on sodium channels and is metabolized by glucuronidation in the liver. It is used for partial or secondary generalized tonic-clonic seizures, Lennox-Gastaut syndrome, tonic-clonic seizures, and absence seizures in children [2–5, 32].

Dose

If the patient is taking a hepatic enzyme-inducing medication, initial dose is 50 mg/day for 2 weeks, then increase up to 300–500 mg/day over several weeks, divided in two doses. If the patient is taking valproate alone, start with 25 mg/day and increase up to 200 mg/day over several weeks. If on none of those medications, start at 25 mg/day and increase the dose up to 375 mg/day over several weeks.

Therapeutic Level

Has not been established for Lamictal. Dose based on effects.

Onset

Peak serum level at 1.4–4.8 h

Half-Life

24–34 h for monotherapy; 13.5 h if adjunct therapy with enzyme-inducing drugs

Side Effects

Adverse effects include dizziness, ataxia, blurred or double vision, and nausea vomiting.

Black Box Warning
Severe life-threatening skin rashes, including Stevens-Johnson syndrome, and serious toxic epidermal necrolysis can occur, usually after 2–8 weeks. Rashes are more common in children (0.8 %) than in adults (0.3 %). Coadministration with valproic acid requires a reduction in the dose by 50 % to minimize the risk of Stevens-Johnson syndrome and toxic epidermal necrolysis. The incidence has been reported to be approximately 0.8 % (8/1,000) in pediatric patients (2–16 years of age) receiving lamotrigine for epilepsy and 0.3 % (3/1,000) in adults receiving therapy for epilepsy. Benign rashes can occur, and therefore, with any signs of rash, the most reasonable course of action is discontinuation of the agent [33].

Contraindication

Hypersensitivity

Levetiracetam (Keppra)

Levetiracetam is approved for adjunct therapy of myoclonic seizures and partial seizures with or without secondary generalized tonic-clonic seizures and for monotherapy of primary generalized tonic-clonic seizures in adults and children from 4 years and older. It acts on the synaptic vesicle protein SV2 to stop the release of excitatory neurotransmitters. It is not protein bound; about 66 % of the drug is excreted unchanged in the urine. There is no induction of hepatic enzymes.

Dose

For monotherapy in adults, 1,000–3,000 mg/day in both PO and IV forms. (PO and IV doses are interchangeable.) In children under 16, the initial dose is 20 mg/kg/day divided into two doses, up to 60 mg/kg/day. In renal patients, from 500 mg/day up to 1,500 mg/day [2–5, 8, 32, 34].

Therapeutic Level

Not established

Onset

1 h PO, 15 min IV

Half-Life

6–8 h; in renal failure patients, 11 h; in children, 5–6 h

Side Effects

Somnolence, asthenia, dizziness, and nasopharyngitis. Rarely, rashes and even seizures may occur; withdrawal symptoms with abrupt cessation [32].

Contraindications

Hypersensitivity

Tiagabine (Gabitril)

Tiagabine is approved for adjunct therapy of partial seizures in adults. It likely inhibits GABA transporter GAT-1, promoting more GABA binding to neurons. It is metabolized by hepatic CYP3A [4, 5].

Dose

In adults, initially 4 mg/day, and titrate up to 56 mg/day over 8 weeks. Safety not established for children under 12 years of age.

Therapeutic Level

20–100 mcg/l

Onset

45 min

Half-Life

About 8 h, but 2–3 h if taken with enzyme-inducing drugs

Side Effects

Dizziness, somnolence, mild tremor, nervousness, and inability to concentrate. Tiagabine is contraindicated in absence seizures. Most serious adverse effect may be nonconvulsive status epilepticus and withdrawal symptoms with abrupt cessation.

Contraindications

Hypersensitivity and absence seizures (exacerbates spike and wave discharges)

Topiramate (Topamax)

Topiramate is used for monotherapy of partial, primary generalized tonic-clonic seizures and Lennox-Gastaut syndrome. Other uses are for bipolar disorder, eating disorder, addiction disorders, migraine headaches, and chronic pain. It works on sodium and potassium channels and GABA and AMPA/kainate receptors. The drug undergoes little protein binding (10–20 %) and is mainly excreted unchanged in urine [2–5, 35–37].

Dose

For adults, initially 50 mg/day up to 400 mg/day divided into two doses; for children, 10–25 mg/kg/day divided into two doses

Therapeutic Level

10 mcg/ml

Onset

6–8 h

Half-Life

19–23 h

Side Effects

Somnolence, fatigue, weight loss, nervousness, change of taste of carbonated beverages, renal calculi, cognitive impairment, aphasia, metabolic acidosis, and hypohidrosis.

Contraindications

Hypersensitivity, history of kidney stones, and patients on high doses of vitamin C

Felbamate (Felbatol)

Felbamate is approved for adjunct therapy of partial seizures and drop attacks in Lennox-Gastaut syndrome. It works by potentiation of GABA-A receptor currents and blocking of NMDA receptor currents; it inhibits the liver enzyme CYP2C19 [2–5, 14, 38, 39].

Dose

Its recommended dose is 1,200–3,600 mg/day and should be titrated up weekly to achieve the desired dosage. In children, 15 mg/kg/day.

Therapeutic Level

30–60 mcg/ml

Onset

1–4 h

Half-Life

20–23 h

Side Effects

Nausea and vomiting, dizziness, headaches, insomnia, and gastric irritation

Black Box Warning
A black box warning for this agent is aplastic anemia (drug increases the risk 100-fold with a fatality rate of 20–30 %) and hepatic failure (see below). The drug should only be used for severe epilepsy. Risk of death varies with severity and etiology, and due to this drugs reported association with acute hepatic failure, it should not be used with any history of hepatic impairment. Monitor LFTs at baseline, then periodically, and discontinue therapy if LFTs increase or double or clinical signs or symptoms of hepatic failure occur [40].

Contraindication

Hypersensitivity, blood dyscrasias, and hepatic impairment

Zonisamide (Zonegran)

It is approved for adjunct therapy of partial seizures and secondary tonic-clonic seizures in adults. It inhibits T-type calcium currents and also sodium channel currents. 85 % of the drug is excreted unchanged in urine. The rest is metabolized by CYP3A4 and excreted as a glucuronide [2, 4, 5, 8, 9].

Dose

100–400 mg/day and titrated over several weeks. Not used for children under the age of 16. Adjust for renal failure.

Therapeutic Level

10–40 mcg/ml

Onset

2–4 h

Half-Life

63–69 h

Side Effects

Somnolence, ataxia, anorexia, and nervousness. More serious side effects include renal calculi, metabolic acidosis, aphasia, and cognitive impairment.

Contraindication

Hypersensitivity

Lacosamide (Vimpat)

It is approved for adjunct therapy of partial-onset seizures in patients older than 17 years. It acts by enhancing a slow inactivation of voltage-gated sodium channels (as opposed to fast inactivation by other antiepileptics); more than 40 % of the drug is excreted unchanged in urine, the rest as inactive metabolite. It does not induce liver enzymes [1, 2, 5, 9, 41–45].

Dose

200–400 mg/day orally. IV dose is the same as the oral dose.

Therapeutic Level

0.5–50 ng/ml

Onset

1–2 h PO; if IV, at the end of infusion (over 30 min)

Half-Life

13 h

Side Effects

Dizziness, ataxia, diplopia, and possible PR-interval prolongation (EKG prior to therapy)

Contraindications

Hypersensitivity

Rufinamide (Banzel)

It is approved for adjunct therapy of Lennox-Gastaut syndrome, tonic-clonic seizures, and atonic seizures. The exact mechanism of action is unknown, but it is presumed to inhibit high-frequency sodium channel currents. Rufinamide undergoes hepatic metabolism and inhibits CYP2E1. Otherwise, it is a weak inducer of liver enzymes [1, 5, 9, 46].

Dose

Initially 400 mg/day, max up to 3,200 mg/day divided into two doses. In children, 10 mg/kg/day; titrate up to 45 mg/kg/day.

Therapeutic Level

1–50 mcg/ml

Onset

3.4 h

Half-Life

6–10 h

Side Effects

Headaches, dizziness, fatigue, QT-interval shortening, and withdrawal seizures with abrupt cessation

Contraindication

Hypersensitivity and familial short QT syndrome

Vigabatrin (Sabril)

Vigabatrin is approved for adjunct therapy of refractory partial complex seizures in adults and of infantile spasms. It acts by irreversible inhibition of GABA transaminase, increasing the concentration of GABA. It induces some hepatic enzymes, is not protein bound and not metabolized in the liver, and is excreted in urine [1, 3, 47].

Dose

For adults, 1,000 mg/day in two doses; titrate up by 500 mg/d daily up to 3,000 mg/day in two doses. For infantile spasms, 50 mg/kg/day in two doses; titrate up by 25–50 mg/kg/day up to 150 mg/kg/day in two doses.

Therapeutic Level

Not known

Onset

1–2 h

Half-Life

5.3–7.4 h

Side Effects

Fatigue, somnolence, peripheral neuropathy, edema, weight gain, and MRI abnormalities, often transient

Black Box Warning
Progressive and permanent bilateral concentric visual field loss in 30 % of patients. Therefore, the use of vigabatrin is limited for refractory seizures and can only be prescribed through the SHARE program [48].

Contraindication

Hypersensitivity

Ezogabine

Ezogabine is used for adjunct therapy of partial-onset seizures refractory to other therapy. It works by potentiating the potassium channels' M-current. It primarily undergoes hepatic glucuronidation with an active metabolite, does not induce liver enzymes, and is excreted in urine (85 %) and feces (15 %) [1, 2, 16].

Dose

100 mg three times daily up to 1,200 mg/day divided in three doses; it is not approved for use in children.

Therapeutic Level

0.1–2 mcg/ml

Onset

0.5–2 h

Half-Life

8 h

Side Effects

Fatigue, dizziness, urinary retention, neuropsychiatric effects including psychotic symptoms that resolve after cessation of ezogabine, and increased QT interval.

Contraindication

Hypersensitivity

Anesthetic Considerations and Clinical Pearls

- It is important to realize some of the interactions of antiepileptic drugs and anesthetics. When patients are asked to fast prior to surgery, the provider should ask them to continue their antiepileptics to maintain a therapeutic plasma drug level during the perioperative period. If patients are not able to take their medication for a period exceeding the half-life of the antiepileptic medication, the patients' medications should be continued in an intravenous form, if the form is available for the drug [49].
- Some antiepileptic drugs are potent cytochrome P450 isoenzyme inducers, especially phenytoin, carbamazepine, phenobarbital, and primidone, which is metabolized into phenobarbital and the active phenylethylmalonamide. Weaker inducers are oxcarbazepine and topiramide in a dose-dependent fashion. This leads to exaggerated metabolism and lower plasma levels of drugs like oral contraceptives, beta-blockers, calcium channel antagonists, corticosteroids, warfarin, digoxin, other antiepileptic drugs, opioids, propofol, and non-depolarizing muscle relaxants. Valproic acid inhibits the hepatic microsomal enzyme system and leads to a slower clearance of drugs like phenytoin and phenobarbital (up to 50 %). Appropriate dose adjustments may be needed when taking these drugs. Gabapentin, lamotrigine, levetiracetam, tiagabine, and vigabatrin do not affect the enzyme system [2, 6].
- Metabolic changes as well as changes in serum pH and albumin levels during anesthesia can affect the serum drug level and possibly precipitate seizures up to 72 h postoperatively. Hypoxia, hyperventilation and hypocapnia, hypotension, and hyponatremia lower the seizure threshold and should be avoided as well as anesthetics that may provoke seizures [26].

- Among the inhalational anesthetics, halothane, isoflurane, and desflurane are potent anticonvulsants and can safely be used in epileptic patients. Sevoflurane has been reported to provoke seizures, especially in high doses and combined with hypocapnia. Enflurane as well can provoke seizure activity. Both sevoflurane and enflurane should not be used in epileptic patients. Nitrous oxide has not shown to have any effect [50].
- Opioids can increase seizure activity depending on the dose given. Meperidine can have neuroexcitatory effects via its metabolite normeperidine. Whenever it accumulates (i.e., renal disease, prolonged use), seizures may occur. Morphine can safely be used in epileptic patients but has provoked seizures in epileptic patients when given in the epidural space. The phenylpiperidine derivatives fentanyl, alfentanil, remifentanil, and sufentanil have been reported to have epileptogenic properties [50]. They can be useful in localizing epileptic foci. If alfentanil is added to propofol for electroconvulsive therapy, the seizure duration increases. High doses may be avoided in epileptic patients.
- Benzodiazepines are all anticonvulsant. Its antagonist flumazenil, if used to reverse sedation after a short procedure under sedation with a benzodiazepine, can produce seizures and should only be used with extreme caution in epileptic patients [51].
- Methohexital, ketamine, and etomidate can produce excitatory activity and myoclonus and activate an epileptogenic focus and may best not be used in epileptic patients [51].
- Dexmedetomidine has no anti- or proconvulsant effects and can safely be used in epileptic patients [51].
- Local anesthetics cross the blood-brain barrier and decrease cerebral metabolism and electrical activity, which causes sedating and analgesic effects and, at high plasma levels, a convulsant effect. This can happen due to accidental intravascular injection or with use in highly vascular areas (especially pelvic and oral regions) and rapid absorption. Systemic toxicity after regional anesthesia appears in 5/10,000 patients. Seizure threshold seems to be lower in patients who had a recent seizure [51].
- The neuromuscular drugs do not have an epileptogenic effect, but the metabolite of atracurium, laudanosine, causes seizures in animals that are not seen in humans. However, the possibility of seizures from laudanosine may have to be considered in patients with hepatic failure [51].
- Atropine and scopolamine can cause central cholinergic block, which can lead to agitation, seizures, stupor, and coma, which can be treated with physostigmine. Glycopyrrolate does not have that effect, since it does not cross the blood-brain barrier [51].
- In convulsive status epilepticus, the drug of first choice is lorazepam, but if, after 30–60 min, the drug therapy fails, general anesthesia may be required with midazolam, propofol, and thiopental, without the use of opioids. Desflurane and isoflurane may also be used [51].
- In general, Niesen et al. [52]. have found that the more antiseizure medication a person is on, and the longer the person is on the medications, the more likely the patient will have a seizure during the perioperative period. This is due to missed doses and/or decreased doses that lower the threshold for seizures. This fact is

independent on the type of surgery or anesthesia the patient receives. It is imperative that the anesthesiologist be aware of these risks in a patient with seizure disorder and be prepared to treat them during the perioperative period [52].

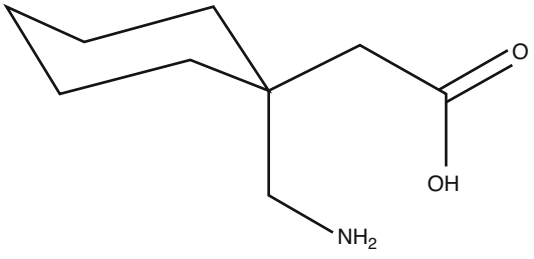
- When patients are anxious before the day of surgery and do not sleep well, the lack of sleep in itself may be a contributing factor to the lowered seizure thresholds [52].
- Seizures caused by anesthetic drugs are most commonly seen during induction and emergence from anesthesia. Careful monitoring of the vital signs may provide the first clues to an imminent seizure for the anesthesiologist.
- Preoperative oral dose (1,200 mg) of gabapentin has shown to decrease the need for narcotics and to decrease the MAC for inhalational anesthetics during surgery [53].
- Among the antiemetic drugs given perioperatively by anesthesiologists, dopamine antagonists may cause extrapyramidal side effects that may be confused for seizures. These drugs, such as prochlorperazine, droperidol, and metoclopramide, should be avoided.

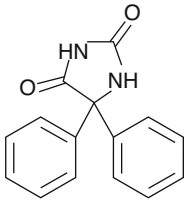
Summary

As many antiepileptic drugs have unpleasant and also serious side effects, the search will go on for more specific and better tolerable therapies. Roughly 2 % of the population have some form of epilepsy, and it will hopefully be possible to treat all effectively someday. For those who have epilepsy refractory to medical therapy, implantation of a vagal nerve stimulator or surgery are options that may provide improvement.

Chemical Structures

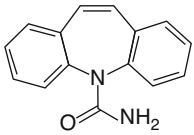
Chemical Structure 29.1 Gabapentin



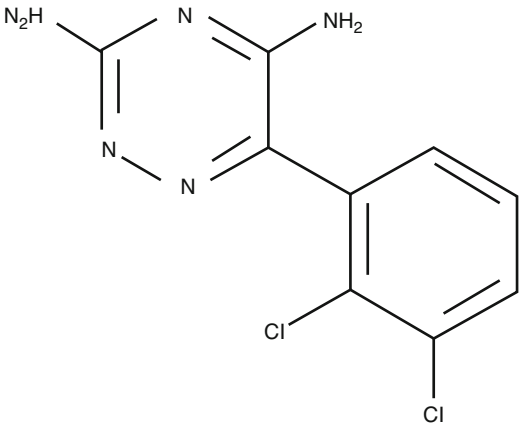


Chemical Structure 29.2 Phenytoin

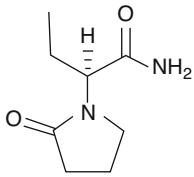
Chemical Structure 29.3 Carbamazepine



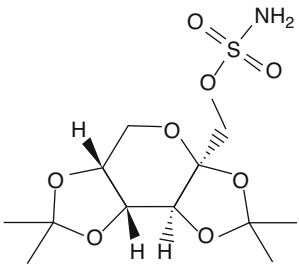
Chemical Structure 29.4 Lamotrigine



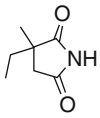
Chemical Structure 29.5 Levetiracetam



Chemical Structure 29.6 Topiramate



Chemical Structure 29.7 Ethosuximide



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