

06 - 29.6 Anticonvulsants

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29.6 Anticonvulsants The newer anticonvulsants described in this section were developed for the treatment of epilepsy, but were also found to have beneficial effects in psychiatric disorders. In addition, these agents are used as skeletal muscle relaxants and in neurogenic pain. These drugs have a variety of mechanisms including increasing γ -aminobutyric acid (GABA)ergic function or decreasing glutamatergic function. This chapter includes six of the newer anticonvulsants: gabapentin (Neurontin), levetiracetam (Keppra), pregabalin (Lyrica), tiagabine (Gabitril), topiramate (Topamax), and zonisamide (Zonegran), as well as one of the first used anticonvulsants, phenytoin (Dilantin). Carbamazepine (Tegretol), valproate (Depakene, Depakote), lamotrigine (Lamictal), and oxcarbazepine (Trileptal) are discussed in separate sections. In 2008, the U.S. Food and Drug Administration (FDA) issued a warning that these drugs may increase the risk of suicidal ideation or act in some persons compared with placebo; however, the relative risk for suicidality was higher in patients with epilepsy compared with those with psychiatric disorders. However, some published data contradict the warning by the FDA regarding the use of anticonvulsants and the risk of suicidal thoughts. These studies suggest that anticonvulsants may have a protective effect on suicidal thoughts in bipolar disorder. Considering the inherent increased risk of suicide in persons with bipolar disorder, clinicians should be aware of these warnings.

GABAPENTIN Gabapentin was first introduced as an antiepileptic drug and was found to have sedative effects that were useful in some psychiatric disorders, especially insomnia. It was also found to be beneficial in reducing neuropathic pain, including postherpetic neuralgia. It is used in anxiety disorders (social phobia and panic disorder), but not as a main intervention in mania or treatment-resistant mood disorders.

Pharmacologic Actions

Gabapentin circulates in the blood largely unbound and is not appreciably metabolized in humans. It is eliminated unchanged by renal excretion and can be removed by hemodialysis. Food only moderately affects the rate and extent of absorption. Clearance is decreased in elderly persons,

requiring dosage adjustments. Gabapentin appears to increase cerebral GABA and may inhibit glutamate synthesis as well. It increases human whole blood serotonin concentrations and modulates calcium channels to reduce monoamine release. It has antiseizure as well as antispastic activity and antinociceptive effects in pain. **Therapeutic Indications** In neurology, gabapentin is used for the treatment of both general and partial seizures. It is effective in reducing the pain of postherpetic neuralgia and other pain syndromes associated with diabetic neuropathy, neuropathic cancer pain, fibromyalgia, meralgia paresthetica, amputation, and headache. It has been found to be effective in some cases of chronic pruritus. In psychiatry, gabapentin is used as a hypnotic agent because of its sedating effects. It has anxiolytic properties and benefits patients with social anxiety and panic disorder. It may decrease the craving for alcohol in some patients and improve mood as well; hence, it may have some use in depressed patients. Some bipolar patients have benefited when gabapentin is used adjunctively with mood stabilizers. **Precautions and Adverse Reactions** Adverse effects are mild, with the most common being daytime somnolence, ataxia, and fatigue, which are usually dose related. Overdose (over 45 g) has been associated with diplopia, slurred speech, lethargy, and diarrhea, but all patients recovered. The drug is classified as pregnancy category C and is excreted in breast milk, so it is best to avoid it in pregnant women and nursing mothers. **Drug Interactions** Gabapentin bioavailability may decrease as much as 20% when administered with antacids. In general, there are no drug interactions. Chronic use does not interfere with lithium administration. **Laboratory Interferences** Gabapentin does not interfere with any laboratory tests, although spontaneous reports of false-positive or positive drug toxicology screenings for amphetamines, barbiturates, benzodiazepines, and marijuana have been reported. **Dosages and Clinical Guidelines** Gabapentin is well tolerated, and the dosage can be increased to the maintenance range

within a few days. A general approach is to start with 300 mg on day 1, increase to 600 mg on day 2, 900 mg on day 3, and subsequently increase up to 1,800 mg per day in divided doses as needed to relieve symptoms. Final total daily doses tend to be between 1,200 and 2,400 mg per day but occasionally results may be achieved with dosages as low as 200 to 300 mg per day, especially in elderly persons. Sedation is usually the limiting factor in determining the dosage. Some patients have taken dosages as high as 4,800 mg per day. Gabapentin is available as 100, 300, and 400 mg capsules and as 600 and 800 mg tablets. A 250 mg/5 mL oral solution is also available. Although abrupt discontinuation of gabapentin does not cause withdrawal effects, use of all anticonvulsant drugs should be gradually tapered. **TOPIRAMATE** Topiramate (Topamax) was developed as an anticonvulsant and was found useful in a variety of psychiatric and neurologic conditions, including migraine prevention, treatment of obesity, bulimia, binge eating, and alcohol dependence. **Pharmacologic Actions** Topiramate has GABAergic effects and increases cerebral GABA in humans. It has 80% oral bioavailability and is not significantly altered by food. It is 15% protein bound, and about 70% of the drug is eliminated by renal excretion. With renal insufficiency topiramate clearance decreases about 50%, so the dosage needs to be decreased. It has a half-life of around 24 hours. **Therapeutic Indications** Topiramate is used mainly as an antiepileptic medication and has been found superior to placebo as monotherapy in patients with seizure disorders. It is also used in the prevention of migraine, smoking cessation, pain syndromes (e.g., low back pain), posttraumatic stress disorder (PTSD), and essential tremor. The drug has been associated with weight loss, and that fact has been used to counteract the weight gain caused by many psychotropic drugs. It has also been used in general obesity and in the treatment of bulimia and binge-eating disorder. Self-mutilating behavior may be decreased in borderline personality disorder. It is of little or no benefit

in the treatment of psychotic disorders. In one study, the combination of topiramate with bupropion (Wellbutrin) showed some efficacy in bipolar depression, but double-blind, placebo-controlled trials failed to demonstrate topiramate monotherapy efficacy in acute mania in adults. Precautions and Adverse Reactions The most common adverse effects of topiramate include paresthesias, weight loss, somnolence, anorexia, dizziness, and memory problems. Sometimes disturbances in the sense of taste occur. In many cases, the adverse effects are mild to moderate and can be

attenuated by decreasing the dose. No deaths have been reported during overdose. The drug affects acid-base balance (low serum bicarbonate), which can be associated with cardiac arrhythmias, and the formation of renal calculi in about 1.5% of cases. Patients taking the drug should be encouraged to drink plenty of fluids. It is not known if the drug passes through the placenta or is present in breast milk, and it should be avoided by pregnant women or nursing mothers. Drug Interactions Topiramate has few drug interactions with other anticonvulsant drugs. Topiramate may increase phenytoin concentrations up to 25% and valproic acid 11%; it does not affect the concentration of carbamazepine, phenobarbital (Luminal), or primidone. Topiramate concentrations are decreased by 40% to 48%, with concomitant administration of carbamazepine or phenytoin. Topiramate should not be combined with other carbonic anhydrase inhibitors, such as acetazolamide (Diamox) or dichlorphenamide (Daranide), because this could increase the risk of nephrolithiasis or heat-related problems (oligohidrosis and hyperthermia). Laboratory Interferences Topiramate does not interfere with any laboratory tests. Dosages and Clinical Guidelines Topiramate is available as unscored 25, 100, and 200 mg tablets. To reduce the risk of adverse cognitive and sedative effects, topiramate dosage is titrated gradually over 8 weeks to a maximum of 200 mg twice a day. Off-label topiramate is typically used adjunctively, starting with 25 mg at bedtime and increasing weekly by 25 mg as necessary and tolerated. Final doses in efforts to promote weight loss are often between 75 and 150 mg per day at bedtime. Doses higher than 400 mg are not associated with increased efficacy. All of the dose can be given at bedtime to take advantage of the sedative effects. Persons with renal insufficiency should reduce doses by half. TIAGABINE Tiagabine was introduced as a treatment for epilepsy in 1997 and was found to have efficacy in some psychiatric conditions, including acute mania. However, safety concerns (see later) along with a lack of controlled data have limited the use of tiagabine in disorders other than epilepsy. Pharmacologic Actions Tiagabine is well absorbed with a bioavailability of about 90% and is extensively (96%) bound to plasma proteins. Tiagabine is a cytochrome P450 (CYP)3A substrate and is extensively transformed into inactive 5-oxo-tiagabine and glucuronide metabolites, with

only 2% being excreted unchanged in the urine. The remainder is excreted as metabolites in the feces (65%) and the urine (25%). Tiagabine blocks uptake of the inhibitory amino acid neurotransmitter GABA into neurons and glia, enhancing the inhibitory action of GABA at both GABAA and GABAB receptors, putatively yielding anticonvulsant and antinociceptive effects, respectively. It has mild blocking effects on histamine 1 (H1), serotonin type 1B (5-HT1B), benzodiazepine, and chloride channel receptors. Therapeutic Indications Tiagabine is rarely used for psychiatric disorders, and then it is used only for generalized anxiety disorder and insomnia. Its main indication is in generalized epilepsy. Precautions and Adverse Reactions Tiagabine may cause withdrawal seizures, cognitive or neuropsychiatric problems (impaired concentration, speech or language problems, somnolence, and fatigue), status epilepticus, and sudden unexpected death in epilepsy (SUDEP). Acute oral overdoses of tiagabine have been associated with seizures, status epilepticus, coma, ataxia, confusion, somnolence, drowsiness, impaired speech, agitation, lethargy,

myoclonus, stupor, tremors, disorientation, vomiting, hostility, temporary paralysis, and respiratory depression. Deaths have been reported in polydrug overdoses involving tiagabine. Cases of serious rash may occur, including Stevens-Johnson syndrome. Tiagabine is classified as pregnancy category C because fetal loss and teratogenicity have been demonstrated in animals. It is not known if the drug is excreted in breast milk. Pregnant women and nursing mothers should not be given the drug. Laboratory Tests Tiagabine does not interfere with any laboratory tests. Dosage and Administration Tiagabine should not be rapidly loaded or rapidly initiated because of the risk of serious adverse effects. In adults and adolescents 12 years of age or older with epilepsy who are also taking enzyme inducers, tiagabine should be initiated at 4 mg per day and increased weekly by 4 mg per day during the first month. The dose should then be increased weekly by 4 to 8 mg per day for weeks 5 and 6, yielding 24 to 32 mg per day administered in two to four divided doses by week 6. In adults (but not adolescents), tiagabine doses may be further increased weekly by 4 to 8 mg per day to as high as 56 mg per day. Plasma concentrations in patients with epilepsy commonly range between 20 and 100 ng/mL, but do not appear to be systematically related to antiseizure effects and thus are not routinely monitored.

LEVETIRACETAM Initially developed as a nootropic (memory enhancing) drug, levetiracetam proved to be a potent anticonvulsant and marketed as a treatment for partial seizures. It has been used to treat acute mania and anxiety and to augment antidepressant drug therapy. Pharmacologic Actions The central nervous system (CNS) effects are not well understood, but it appears to indirectly enhance GABA inhibition. It is rapidly and completely absorbed, and peak concentrations are reached in 1 hour. Food delays the rate of absorption and decreases the amount of absorption. Levetiracetam is not significantly plasma protein bound and is not metabolized through the hepatic CYP system. Its metabolism involves hydrolysis of the acetamide group. Serum concentrations are not correlated with therapeutic effects. Therapeutic Indications The major indication is for the treatment of convulsive disorders, including partial onset seizures, myoclonic seizures, and idiopathic generalized epilepsy. In psychiatry, levetiracetam has been used off label to treat acute mania, as an add-on treatment for major depression, and as an anxiolytic agent. Precautions and Adverse Reactions The most common side effects of levetiracetam include drowsiness, dizziness, ataxia, diplopia, memory impairment, apathy, and paresthesias. Some patients develop behavioral disturbances during treatment, and hallucinations may occur. Suicidal patients may become agitated. It should not be used in pregnant or lactating women. Drug Interactions There are few if any interactions with other drugs, including other anticonvulsants. There is no interaction with lithium. Laboratory Interferences No laboratory interferences have been reported. Dosages and Clinical Guidelines The drug is available as 250, 500, 750, and 1,000 mg tablets; 500 mg extended-release tablets; a 100 mg/mL oral solution; and a 100 mg/mL intravenous solution. In epilepsy, the typical adult daily dose is 1,000 mg. In view of its renal clearance, dosages should be reduced in patients with impaired renal function.

ZONISAMIDE Used originally as an anticonvulsant for the treatment of seizure disorders, zonisamide was also found to be useful in bipolar disorder, obesity, and binge-eating disorder. Pharmacologic Actions Zonisamide blocks sodium channels and may weakly potentiate dopamine and serotonin activity. It also inhibits carbonic anhydrase. Some evidence suggests that it may block calcium channels. Zonisamide is metabolized by the hepatic CYP3A system, so enzyme-inducing agents such as carbamazepine, alcohol, and phenobarbital increase the clearance and reduce the availability of the drug. Zonisamide does not affect the metabolism of other drugs.

It has a long half-life of 60 hours, so it is easily dosed once daily, preferably at nighttime.

Therapeutic Indications Its main use is in the treatment of generalized seizure disorders and in refractory partial seizures. In psychiatry, controlled studies found it to be of use in obesity and binge-eating disorder. Uncontrolled trials have found it useful in bipolar disorder, particularly mania; however, further studies are warranted for this indication. **Precautions and Adverse Reactions** Zonisamide is a sulfonamide and thus may cause fatal rash and blood dyscrasias, although these events are rare. About 4% of patients develop kidney stones. The most common side effects are drowsiness, cognitive impairment, insomnia, ataxia, nystagmus, paresthesia, speech abnormalities, constipation, diarrhea, nausea, and dry mouth. Weight loss is also a common side effect, which has been exploited as a therapy for patients who have gained weight during treatment with psychotropics or, as mentioned above, have ongoing difficulty controlling their eating. Zonisamide should not be used in pregnant women or breast-feeding mothers. **Drug Interactions** Zonisamide does not inhibit CYP isoenzymes and does not instigate drug interactions. It is important not to combine carbonic anhydrase inhibitors with zonisamide because of an increased risk of nephrolithiasis related to increased blood levels of urea. **Laboratory Interferences** Zonisamide can elevate hepatic alkaline phosphatase and increase blood urea nitrogen and creatinine. **Dosages and Clinical Guidelines**

Zonisamide is available in 100 and 200 mg capsules. In epilepsy, the dosage range is 100 to 400 mg per day, with side effects becoming more pronounced at doses above 300 mg. Because of its long half-life, zonisamide can be given once a day. **PREGABALIN** Pregabalin is pharmacologically similar to gabapentin. It is believed to work by inhibiting the release of excess excitatory neurotransmitters. It increases neuronal GABA levels, its binding affinity is six times greater than that of gabapentin, and it has a longer half-life. **Pharmacologic Actions** Pregabalin exhibits linear pharmacokinetics. It is rapidly absorbed in proportion to its dose. The time to maximal plasma concentration is about 1 hour and that to steady state is within 24 to 48 hours. Pregabalin demonstrates high bioavailability, and it has a mean elimination half-life of about 6.5 hours. Food does not affect absorption. Pregabalin does not bind to plasma proteins and is excreted virtually unchanged (<2% metabolism) by the kidneys. It is not subject to hepatic metabolism and does not induce or inhibit liver enzymes such as the CYP system. Dose reduction may be necessary in patients with creatinine clearance (CLcr) less than 60 mL per minute. Daily doses should be further reduced by approximately 50 percent for each additional 50 percent decrease in CLcr. Pregabalin is highly cleared by hemodialysis, so additional doses may be needed for patients on chronic hemodialysis treatment after each hemodialysis treatment. **Therapeutic Indications** Pregabalin is approved for the management of diabetic peripheral neuropathy and postherpetic neuralgia, and for adjunctive treatment of partial onset seizures. It has been found to be of benefit to some patients with generalized anxiety disorder. In studies, no consistent dose-response relationship was found, although 300 mg of pregabalin per day was more effective than 150 mg or 450 mg. Some patients with panic disorder or social anxiety disorder may benefit from pregabalin, but little evidence supports its routine use in treating persons with these disorders. It was most recently approved for the treatment of fibromyalgia. **Precautions and Adverse Reactions** The most common adverse events associated with pregabalin use are dizziness, somnolence, blurred vision, peripheral edema, amnesia or loss of memory, and tremors. Pregabalin potentiates sedating effects of alcohol, antihistamines, benzodiazepines, and other CNS depressants. It remains to be seen if pregabalin is associated with benzodiazepine-type withdrawal symptoms. There are scant data about its use in pregnant women or nursing mothers, and it is best avoided in these patients.

Drug Interactions In view of the absence of hepatic metabolism, pregabalin lacks metabolic drug interactions. **Laboratory Interferences** There are no effects on laboratory tests. **Dosage and Clinical Guidelines** The recommended dose for postherpetic neuralgia is 50 or 100 mg orally three times a day. The recommended dose for diabetic peripheral neuropathy is 100 to 200 mg orally three times a day. Patients with fibromyalgia may require up to 450 to 600 mg per day given in divided doses. Pregabalin is available as 25, 50, 75, 100, 150, 200, 225, and 300 mg capsules.

PHENYTOIN Phenytoin sodium (Dilantin) is an antiepileptic drug and is related to the barbiturates in chemical structure. It is indicated for the control of generalized tonic-clonic (grand mal) and complex partial (psychomotor, temporal lobe) seizures and prevention and treatment of seizures occurring during or after neurosurgery. Studies have shown comparable efficacy of phenytoin to other anticonvulsants in bipolar disorder, but clinicians should take into account the danger of gingival hyperplasia, leukopenia, or anemia and the danger of toxicity caused by nonlinear pharmacokinetics. **Pharmacologic Action** Similar to other anticonvulsants, phenytoin causes blockade of voltage-activated sodium channels and hence is efficacious as an antimanic agent. The plasma half-life after oral administration averages 22 hours, with a range of 7 to 42 hours. Steady-state therapeutic levels are achieved at least 7 to 10 days (5 to 7 half-lives) after initiation of therapy, with recommended doses of 300 mg per day. Serum level should be obtained at least 5 to 7 half-lives after treatment initiation. Phenytoin is excreted in the bile, which is then reabsorbed from the intestinal tract and excreted in the urine. Urinary excretion of phenytoin occurs partly with glomerular filtration and by tubular secretion. Small incremental doses of phenytoin may increase the half-life and produce very substantial increases in serum levels. Patients should adhere strictly to the prescribed dosage, and serial monitoring of phenytoin levels is recommended. **Therapeutic Indications** Apart from its indication in generalized tonic-clonic (grand mal) and complex partial (psychomotor, temporal lobe) seizures, phenytoin is also used for the treatment of acute

mania in bipolar disorder. **Precautions and Adverse Reactions** The most common adverse reactions reported with phenytoin therapy are usually dose related and include nystagmus, ataxia, slurred speech, decreased coordination, and mental confusion. Other side effects include dizziness, insomnia, transient nervousness, motor twitching, and headaches. There have been rare reports of phenytoin-induced dyskinesias, similar to those induced by phenothiazine and other neuroleptic drugs. More serious side effects include thrombocytopenia, leukopenia, agranulocytosis, and pancytopenia, with or without bone marrow suppression. A number of reports have suggested the development of lymphadenopathy (local or generalized), including benign lymph node hyperplasia, pseudolymphoma, lymphoma, and Hodgkin's disease. Prenatal exposure to phenytoin may increase the risks for congenital malformations, and a potentially life-threatening bleeding disorder related to decreased levels of vitamin K-dependent clotting factors may occur in newborns exposed to phenytoin in utero. Hyperglycemia has been reported with phenytoin use; in addition, the agent may increase the serum glucose level in patients with diabetes. **Drug Interactions** Acute alcohol intake, amiodarone, chlordiazepoxide, cimetidine, diazepam, disulfiram, estrogens, fluoxetine, H₂-antagonists, isoniazid, methylphenidate, phenothiazines, salicylates, and trazodone may increase phenytoin serum levels. Drugs that may lower phenytoin levels include carbamazepine, chronic alcohol abuse, and reserpine. **Laboratory Interferences** Phenytoin may decrease serum concentrations of thyroxine. It may cause increased serum levels of glucose, alkaline phosphatase, and γ -glutamyl transpeptidase. **Dosage and Clinical Guidelines** Patients may be started on one 100 mg extended oral capsule three times daily, and the dosage then adjusted to suit individual requirements. Patients may then be switched to once-a-day dosing, which is more convenient. In this case, extended-release capsules may be used. Serial monitoring of phenytoin

levels is recommended, and the normal range is usually 10 to 20 µg/mL. REFERENCES Bray GA, Hollander P, Klein S, Kushner R, Levy B. A 6-month randomized, placebo-controlled, dose-ranging trial of topiramate for weight loss in obesity. *Obes Res.* 2003;11(6):722. Crofford LJ, Rowbotham MC, Mease PJ, Russell IJ, Dworkin RH. Pregabalin for the treatment of fibromyalgia syndrome: Results of a randomized, double-blind, placebo-controlled trial. *Arthritis Rheum.* 2005;52(4):1264.

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