The Medical Letter®

on Drugs and Therapeutics

Volume 59 July 31, 2017

ISSUE No. 1526

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The Medical Letter®
on Drugs and Therapeutics

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Drugs for Epilepsy

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Treatment of epilepsy should begin with a single antiepileptic drug (AED), increasing its dosage gradually until seizures are controlled or adverse effects become intolerable. If seizures persist, specialists generally recommend trying at least one and sometimes a second alternative drug as monotherapy before considering use of two drugs concurrently. When used for the appropriate seizure type, AEDs are roughly equivalent in efficacy. Drug choice is usually based on factors such as ease of use, adverse effects, drug interactions, presence of comorbidities, and cost.

Newer AEDs are often initially approved by the FDA only as adjunctive therapy for partial seizures, but they are commonly used off-label for treatment of other types of seizures and as monotherapy.

NEW TERMINOLOGY — In the revised International League Against Epilepsy (ILAE) classification of seizure types, "partial" is replaced with "focal" and "primary generalized" with "bilateral tonic-clonic."[1]

BRIVARACETAM — Brivaracetam (*Briviact*), an analog of levetiracetam, is FDA-approved for adjunctive treatment of partial seizures in patients ≥16 years old.[2] Like levetiracetam, it may also prove to be effective for treatment of primary generalized, absence, and myoclonic seizures, but more studies are needed.[3]

Adverse Effects – In clinical trials, the most common adverse effects of brivaracetam were somnolence, dizziness, fatigue, and nausea/vomiting. Psychiatric adverse effects (mainly anxiety and depression) have occurred; whether they occur at a similar rate as with levetiracetam is unclear.

Table 1. Treatment of Epilepsy[1]

Drugs of Choice:	Some Alternatives:
Partial, Including Secondarily Generalized Seizures[2]	
Carbamazepine	Brivaracetam
Lamotrigine	Clobazam
Levetiracetam	Eslicarbazepine
Oxcarbazepine	Gabapentin
	Lacosamide
	Perampanel
	Phenytoin
	Pregabalin
	Topiramate
	Valproate
	Zonisamide
Primary Generalized Tonic-Clonic Seizures[2]	
Lamotrigine	Perampanel
Levetiracetam	Topiramate
Valproate	Zonisamide
Absence Seizures	
Ethosuximide	Clonazepam
Valproate	Lamotrigine
	Levetiracetam
	Zonisamide
Atypical Absence, Myoclonic, Atonic Seizures	
Lamotrigine	Clobazam
Levetiracetam	Clonazepam
Valproate	Felbamate
	Rufinamide
	Topiramate
	Zonisamide

1. Some of the drugs listed here have not been approved by the FDA for such use. Approved indications can be found in the text.
2. In the revised International League Against Epilepsy (ILAE) classification of seizure types, "partial" is replaced with "focal" and "primary generalized" with "bilateral tonic-clonic." Fisher et al. Epilepsia 2017; 58:531.

Drug Interactions – Coadministration of rifampin (*Rifadin*, and generics) decreases serum concentrations of brivaracetam; the dose of brivaracetam may need to be increased by up to 100%. Brivaracetam increases serum concentrations of phenytoin and an active metabolite of carbamazepine; dosage reductions may be needed. Brivaracetam is a substrate of CYP2C19; patients who are CYP2C19 poor metabolizers or are taking CYP2C19 inhibitors may require reductions in the dosage of brivaracetam.[4]

Table 2. Some Oral Antiepileptic Drugs

Drug	Some Oral Formulations	Usual Adult Maintenance Dosage[1]	Usual Pediatric Maintenance Dosage[1]	Cost[2]
Brivaracetam – *Briviact* (UCB)	10, 25, 50, 75, 100 mg tabs; 10 mg/mL, 50 mg/5 mL oral soln	50-200 mg/d in 2 divided doses	Not approved for patients <16 years old	$1000.10
Carbamazepine – generic	200 mg tabs; 100 mg chewable tabs; 100 mg/5 mL susp	800-1600 mg/d in 2 or 3 divided doses[3]	<6 yrs: 20-35 mg/kg/d in 3 or 4 divided doses[3]	100.00
Tegretol (Novartis)				263.20
extended release – generic	100, 200 mg ER caps and tabs; 300 mg ER caps, 400 mg ER tabs	800-1600 mg/d in 2 divided doses[3]	6-12 yrs: 400-1000 mg/d in 3 or 4 divided doses (2 doses if ER)[3]	273.80
Tegretol XR	100, 200, 400 mg ER tabs			281.00
Carbatrol (Shire)	100, 200, 300 mg ER caps			212.70
Equetro (Validus)	100, 200, 300 mg ER caps			435.80
Clobazam – *Onfi* (Lundbeck)	10, 20 mg tabs; 2.5 mg/mL susp	10-60 mg once/d or in 2 divided doses	5-20 mg once/d or in 2 divided doses	949.40
Clonazepam – generic	0.5, 1, 2 mg tabs; 0.125, 0.25, 0.5, 1, 2 mg ODTs	1.5-8 mg/d in 2 or 3 divided doses	<10 yrs or <30 kg: 0.1-0.2 mg/kg/d in 2 or 3 divided doses	3.90
Klonopin (Genentech)	0.5, 1, 2 mg tabs			161.30
Eslicarbazepine – *Aptiom* (Sunovion)	200, 400, 600, 800 mg tabs	800 mg once/d	Not approved for patients <18 years old	834.90
Ethosuximide – generic	250 mg caps; 250 mg/5 mL syrup	750-1250 mg/d in 2 divided doses	20-30 mg/kg/d in 2 or 3 divided doses	118.50
Zarontin (Pfizer)				304.20
Felbamate – generic	400, 600 mg tabs; 600 mg/5 mL susp	2400-3600 mg/d in 3 or 4 divided doses[4]	2-14 yrs: 30-45 mg/kg/d in 3 or 4 divided doses[4,5]	586.50
Felbatol (Meda)				1500.00
Gabapentin – generic	100, 300, 400 mg caps; 600, 800 mg tabs; 250 mg/5 mL soln	1800-3600 mg/d in 3 divided doses	3-4 yrs: 40 mg/kg/d in 3 divided doses 5-11 yrs: 25-35 mg/kg/d in 3 divided doses	47.80
Neurontin (Pfizer)				830.20
Lacosamide – *Vimpat* (UCB)	50, 100, 150, 200 mg tabs; 10 mg/mL soln	200-400 mg/d in 2 divided doses	Not approved for patients <17 years old	830.50
Lamotrigine – generic	25, 100, 150, 200, 250 mg tabs; 2, 5, 25 mg chewable tabs; 25, 50, 100, 200 mg ODTs	100-500 mg/d in 2 divided doses	2-12 yrs: 4.5-7.5 mg/kg/d in 2 divided doses[6]	17.80
Lamictal (GSK)				794.20
extended release – generic	25, 50, 100, 200, 250, 300 mg ER tabs	200-600 mg once/d	Not approved for patients <13 years old	301.80
Lamictal XR				698.50
Levetiracetam – generic	250, 500, 750, 1000 mg tabs; 100 mg/mL soln	500-1500 mg bid	4-<16 yrs: 30 mg/kg bid	22.50
Keppra (UCB)				458.30
Spritam (Aprecia)	250, 500, 750, 1000 mg tabs			463.70
extended release – generic	500, 750 mg ER tabs	1000-3000 mg once/d	Not approved for patients <12 years old	42.50
Keppra XR				415.40
Oxcarbazepine – generic	150, 300, 600 mg tabs; 300 mg/5 mL susp	1200-2400 mg/d in 2 or 3 divided doses	2-<4 yrs: 30-60 mg/kg/d in 2 or 3 divided doses (max 600 mg/d) 4-16 yrs: 20-29 kg: 450 mg bid 30-39 kg: 600 mg bid 40-49 kg: 900 mg bid	72.10
Trileptal (Novartis)				833.00
extended release – *Oxtellar XR* (Supernus)	150, 300, 600 mg ER tabs	1200-2400 mg once/d	≥6 yrs: 20-29 kg: 900 mg once/d 30-39 kg: 1200 mg once/d 40-49 kg: 1800 mg once/d	866.50

ER = extended-release; ODT = orally disintegrating tablet

1. Most antiepileptic drugs (AEDs) are started at a low dose and slowly titrated over a period of weeks. The usual dosage may vary depending on whether the drug is prescribed as monotherapy or adjunctive therapy, or is used concomitantly with one or more interacting drugs. Dosage may also need to be adjusted for renal or hepatic impairment.
2. Approximate WAC for 30 days' treatment at the lowest usual adult maintenance dosage using the smallest whole number of dosage units. WAC = wholesaler acquisition cost or manufacturer's published price to wholesalers; WAC represents a published catalogue or list price and may not represent an actual transactional price. Source: AnalySource® Monthly. July 5, 2017. Reprinted with permission by First Databank, Inc. All rights reserved. ©2017. www.fdbhealth.com/policies/drug-pricing-policy.
3. Measurement of serum concentrations may be useful to guide therapy. Some usual therapeutic serum concentrations are: carbamazepine 4-12 mcg/mL, phenobarbital 10-40 mcg/mL, phenytoin 10-20 mcg/mL, valproate 50-100 mcg/mL. Some patients achieve complete seizure control at lower concentrations, and some may need higher concentrations.
4. When felbamate is added as adjunctive therapy, the doses of other antiepileptic drugs should be reduced by 20%.
5. In children 2-14 years old, only FDA-approved for adjunctive treatment of Lennox-Gastaut syndrome.
6. Maximum 300 mg/d. The recommended dosage for patients taking valproate is 1-5 mg/kg once daily or in 2 divided doses (maximum 200 mg/d; 1-3 mg/kg/d for patients taking lamotrigine and valproate without other antiepileptic drugs). The recommended dosage for patients taking lamotrigine with carbamazepine, phenytoin, phenobarbital, or primidone, but not with valproate, is 5-15 mg/kg/d in 2 divided doses (maximum 400 mg/d).

Table 2. Some Oral Antiepileptic Drugs (continued)

Drug	Some Oral Formulations	Usual Adult Maintenance Dosage[1]	Usual Pediatric Maintenance Dosage[1]	Cost[2]
Perampanel – *Fycompa* (Eisai)	2, 4, 6, 8, 10, 12 mg tabs; 0.5 mg/mL oral susp	4-12 mg once/d	Not approved for patients <12 yrs old	$742.50
Phenobarbital – generic	15, 30, 60, 100 mg tabs; 20 mg/5 mL elixir	90-150 mg/d in 2 or 3 divided doses[3]	3-6 mg/kg/d in 2 or 3 divided doses[3]	23.80
Phenytoin – generic	30, 100, 200, 300 mg caps; 125 mg/5 mL susp; 50 mg chewable tabs	300-400 mg/d in 1-3 divided doses[3,7]	4-8 mg/kg/d in 2 or 3 divided doses (max 300 mg/d)[3]	54.10
Dilantin (Pfizer)	30, 100 mg caps; 125 mg/5 mL susp; 50 mg chewable tabs			101.60
Phenytek (Mylan)	200, 300 mg caps			60.20
Pregabalin – *Lyrica* (Pfizer)	25, 50, 75, 100, 150, 200, 225, 300 mg caps	150-600 mg/d in 2 or 3 divided doses	Not approved for pediatric use	413.20
Primidone – generic	50, 250 mg tabs	750-1250 mg/d in 3 or 4 divided doses	<8 yrs: 125-250 mg tid or 10-25 mg/kg/d in divided doses	40.30
Mysoline (Valeant)				3689.40
Rufinamide – *Banzel* (Eisai)	200, 400 mg tabs; 40 mg/mL susp	3200 mg/d in 2 divided doses	45 mg/kg/d in 2 divided doses (max 3200 mg/d)	4776.00
Topiramate – generic	15, 25 mg caps; 25, 50, 100, 200 mg tabs	100-400 mg/d in 2 divided doses	5-9 mg/kg/d in 2 divided doses	19.80
Topamax (Janssen)	25, 50, 100, 200 mg tabs			625.70
Topamax Sprinkle	15, 25 mg caps			716.90
extended release –				
Trokendi XR (Supernus)	25, 50, 100, 200 mg ER caps	100-400 mg once/d	≥6 yrs: 5-9 mg/kg once/d	634.60
Qudexy XR (Upsher-Smith)	25, 50, 100, 150, 200 mg ER caps			471.90
Valproate				
Valproic acid – generic	250 mg caps; 250 mg/5 mL syrup	1000-3000 mg/d in 2-3 divided doses[3]	≥10 yrs: 20-60 mg/kg/d in 3 divided doses[3]	43.30
Depakene (Abbott)				558.80
Divalproex sodium – generic	125, 250, 500 mg delayed-release tabs; 125 mg caps			29.10
Depakote (Abbott)	125, 250, 500 mg delayed-release tabs			361.10
Depakote Sprinkle	125 mg delayed-release caps			506.80
extended release – generic	250, 500 mg ER tabs	1250-3500 mg once/d[3]	≥10 yrs: 20-60 mg/kg once/d[3]	253.50
Depakote ER				469.80
Vigabatrin – *Sabril* (Lundbeck)	500 mg tabs; 500 mg powder for soln (50 mg/mL)	3 g/d in 2 divided doses	10-16 yrs: 2 g/d in 2 divided doses[8]	21,776.60
Zonisamide – generic	25, 50, 100 mg caps	100-400 mg once/d or in 2 divided doses	Not approved for patients <16 yrs old	20.50
Zonegran (Eisai)	25, 100 mg caps			426.70

ER = extended-release
7. Adjustments in maintenance dosage above 300 mg/day for adults should usually be made in 25- or 30-mg increments.
8. Patients weighing >60 kg should receive the adult dosage.

CARBAMAZEPINE — Carbamazepine (*Tegretol*, and generics) is an older AED with broad indications for use as an anticonvulsant. It is particularly effective for treatment of partial and secondarily generalized tonic-clonic seizures, but it may worsen absence or myoclonic seizures. Carbamazepine induces its own metabolism; serum concentrations often fall after a few weeks of treatment. Storing carbamazepine tablets (both brand and generic) in humid conditions can cause concretion of the tablets, resulting in poor bioavailability and therapeutic failure. Carbamazepine is generally administered as an extended-release formulation (*Tegretol XR*, and generics), which allows for twice-daily dosing. It is also available in an IV formulation *(Carnexiv)*.

Other Uses – Oral carbamazepine is FDA-approved for treatment of pain due to trigeminal neuralgia. *Equetro* is also approved for treatment of acute manic or mixed episodes of bipolar I disorder.

Adverse Effects – Carbamazepine can cause drowsiness, impaired cognition, blurred vision, diplopia, headache, dizziness, ataxia, nausea, and vomiting. Use of an extended-release formulation has been associated with fewer CNS adverse effects.

Mild leukopenia and hyponatremia are fairly common with use of carbamazepine. At high doses, thrombocytopenia can occur, but it is usually reversible with drug discontinuation. Aplastic anemia, agranulocytosis, cardiac toxicity, aseptic meningitis, intractable diarrhea, and hepatitis are rare. Circulating concentrations of

thyroid hormones may be reduced even though thyroid stimulating hormone (TSH) concentrations remain normal. Abnormal color perception can occur rarely.

Carbamazepine can cause rash, particularly with high starting doses or rapid dose escalation. Severe reactions such as Stevens-Johnson syndrome and toxic epidermal necrolysis have occurred rarely; the risk is significantly higher in patients with the human leukocyte antigen (HLA)-B*1502 allele.[5] The FDA recommends that Asian patients, who have a 10-fold higher incidence than non-Asians of carbamazepine-induced Stevens-Johnson syndrome and toxic epidermal necrolysis, be tested for this allele before starting treatment with carbamazepine.

Drug Interactions – Carbamazepine is a strong inducer of multiple hepatic enzymes; it can reduce serum concentrations and possibly the effectiveness of many other drugs, including oral contraceptives and other AEDs. Carbamazepine is metabolized by CYP3A4; drugs that induce or inhibit CYP3A4 could affect its serum concentrations.[4]

CLOBAZAM — The benzodiazepine clobazam *(Onfi)* is FDA-approved only for adjunctive treatment of seizures associated with Lennox-Gastaut syndrome in patients ≥2 years old,[6] but it has been widely used for years in Canada and other countries for treatment of anxiety and many other types of seizures.

Adverse Effects – The most common adverse effects of clobazam are somnolence, pyrexia, lethargy, drooling, and constipation. As with other benzodiazepines, anterograde amnesia, ataxia, withdrawal symptoms, and seizures can occur if the drug is stopped abruptly. Clobazam is classified as a schedule IV controlled substance.

Drug Interactions – Clobazam inhibits CYP2D6; it may be necessary to reduce the dosage of CYP2D6 substrates such as fluoxetine (*Prozac*, and generics) if they are taken concurrently. Clobazam is metabolized primarily by CYP3A4 to its active metabolite, which is further metabolized by CYP2C19. Concurrent use of moderate or strong inhibitors of CYP2C19 such as fluconazole (*Diflucan*, and generics) or omeprazole (*Prilosec*, and generics) can increase serum concentrations of the active metabolite.[4]

CLONAZEPAM — The benzodiazepine clonazepam (*Klonopin*, and generics) is FDA-approved for treatment of Lennox-Gastaut syndrome (petit mal variant) and myoclonic and atonic seizures. It is also used to treat absence seizures resistant to other AEDs, but it is generally less effective than ethosuximide or valproate for this indication, and development of tolerance to its effects is common.

Other Uses – Clonazepam is FDA-approved for treatment of panic disorder and is used to treat other types of anxiety disorders.

Adverse Effects – Clonazepam can cause drowsiness, ataxia, and behavior disorders. As with other benzodiazepines, anterograde amnesia, ataxia, withdrawal symptoms, and seizures can occur if the drug is stopped abruptly. Clonazepam is classified as a schedule IV controlled substance.

Drug Interactions – Clonazepam is partially metabolized by CYP3A4; inducers of CYP3A4 such as carbamazepine and phenytoin may decrease serum concentrations of clonazepam, and strong inhibitors such as clarithromycin (*Biaxin*, and generics) can increase them.[4]

ESLICARBAZEPINE — Eslicarbazepine acetate *(Aptiom)*[7] is FDA-approved as monotherapy and adjunctive therapy for partial-onset seizures in adults.[8] It is rapidly converted to eslicarbazepine, the S-isomer of the active metabolite of oxcarbazepine, which is chemically similar to carbamazepine. The three drugs have similar mechanisms of action, but differ pharmacokinetically and pharmacodynamically.[9]

Adverse Effects – The most common adverse effects of eslicarbazepine are dizziness, somnolence, nausea, headache, diplopia, and tremor. Hyponatremia and serious dermatological reactions including Stevens-Johnson syndrome have been reported; whether these are more or less common than with carbamazepine or oxcarbazepine is unclear.

Drug Interactions – Eslicarbazepine can induce CYP3A4 and inhibit CYP2C19; it can increase serum concentrations of CYP2C19 substrates such as clobazam, and decrease serum concentrations of CYP3A4 substrates such as simvastatin (*Zocor,* and generics) and oral contraceptives. The INR should be closely monitored in patients taking warfarin (*Coumadin,* and others) concomitantly. Enzyme-inducing drugs, such as carbamazepine, can reduce serum levels of eslicarbazepine. Eslicarbazepine should not be administered concomitantly with oxcarbazepine.

ETHOSUXIMIDE — Ethosuximide (*Zarontin*, and generics) is FDA-approved for treatment of absence seizures and is generally well tolerated.[10] It is not effective for treatment of generalized tonic-clonic or partial seizures.

Adverse Effects – Ethosuximide can cause nausea, vomiting, lethargy, hiccups, headache, and behavioral changes. Psychotic behavior can occur. Hematologic abnormalities, erythema multiforme, Stevens-Johnson syndrome, and systemic lupus erythematosus have been reported.

Drug Interactions – Ethosuximide is partially metabolized by CYP3A4; inducers of CYP3A4 such as carbamazepine and phenytoin may decrease serum concentrations of ethosuximide, and strong inhibitors such as clarithromycin can increase them.[4]

GABAPENTIN — Gabapentin (*Neurontin*, and generics) is FDA-approved for adjunctive treatment of partial seizures with and without secondary generalization in patients ≥3 years old. It is also effective as monotherapy for these seizure types. Like carbamazepine, gabapentin can exacerbate myoclonic seizures. The percentage of gabapentin absorbed from the GI tract decreases at higher doses.

Other Uses – Gabapentin is also FDA-approved for treatment of neuropathic pain. A once-daily formulation *(Gralise)* is approved for treatment of postherpetic neuralgia.[11] Gabapentin enacarbil *(Horizant)*, a prodrug, is approved for restless legs syndrome.[12]

Adverse Effects – Gabapentin can cause somnolence, dizziness, ataxia, fatigue, nystagmus, blurred vision, and confusion. Edema, weight gain, and movement disorders have been reported. Behavioral changes have occurred in children, especially those with underlying behavioral or developmental problems.

Drug Interactions – Unlike some other AEDs, gabapentin does not induce or inhibit CYP isozymes, and is not appreciably metabolized.

LACOSAMIDE — Oral lacosamide (*Vimpat*, and generics) is FDA-approved as monotherapy or adjunctive therapy for adults with partial onset seizures.[13] Lacosamide is also available in an IV formulation for short-term use.

Adverse Effects – The most common adverse effects of oral lacosamide have been dizziness, headache, nausea, vomiting, fatigue, ataxia, diplopia, somnolence, and tremor. Lacosamide is classified as a schedule V controlled substance because of reports of euphoria.

Drug Interactions – Lacosamide is a substrate and inhibitor of CYP2C19, but no clinically significant drug interactions have been reported. The drug can cause a small, dose-dependent increase in the PR interval; caution is advised in patients with cardiac conduction abnormalities and in those taking other drugs that may prolong the PR interval, such as beta blockers or calcium channel blockers.

LAMOTRIGINE — Lamotrigine (*Lamictal*, and generics) is FDA-approved for adjunctive treatment of patients ≥2 years old with partial seizures, primary generalized tonic-clonic seizures, or generalized seizures of Lennox-Gastaut syndrome. It is commonly used for secondarily generalized seizures, primary generalized tonic-clonic seizures, and atypical absence, myoclonic, and atonic seizures. In elderly patients with newly diagnosed partial or generalized seizures, lamotrigine has been as effective as carbamazepine and better tolerated.[14] Although generally effective for treatment of myoclonic seizures, some reports suggest that lamotrigine can make myoclonus worse, particularly in severe myoclonic epilepsy of infancy. Lamotrigine may be less effective than ethosuximide or valproate for treatment of absence seizures in children, but some clinicians use it as first-line treatment because of its tolerability.[15]

Adverse Effects – The most common adverse effects of lamotrigine have been dizziness, ataxia, somnolence, headache, diplopia, nausea, vomiting, rash, insomnia, and incoordination. Lamotrigine causes fewer adverse cognitive effects than carbamazepine or topiramate. Acute hepatitis and aseptic meningitis have been reported. Life-threatening rashes including Stevens-Johnson syndrome have occurred rarely, usually during the first two months of use. The risk may be increased by high starting doses, rapid increases in dosage, or coadministration with valproate. The manufacturer recommends discontinuing lamotrigine at the first sign of rash.

Drug Interactions – Lamotrigine does not induce or inhibit CYP isozymes. Enzyme-inducing drugs, such as carbamazepine reduce lamotrigine serum concentrations by about 40%. Valproate increases lamotrigine concentrations more than 2-fold.

LEVETIRACETAM — Oral levetiracetam (*Keppra*, and generics) is FDA-approved as adjunctive therapy for patients ≥1 month old with partial seizures, patients ≥6 years old with primary generalized tonic-clonic seizures, and patients ≥12 years old with myoclonic seizures. It is commonly used, however, as monotherapy for partial and generalized seizures and may also be effective in absence seizures and in Lennox-Gastaut syndrome. A rapidly-disintegrating oral levetiracetam tablet *(Spritam)* is approved for

the same indications, except that in partial seizures it is only approved for use in patients ≥4 years old.[16] Levetiracetam is also available in an IV formulation.

Adverse Effects – Dizziness, somnolence, and weakness occur commonly. Behavioral changes such as agitation, hostility and irritability, hallucinations, and psychosis have also occurred, especially in patients with underlying psychiatric disorders. Coordination difficulties and serious dermatological reactions, including Stevens-Johnson syndrome and toxic epidermal necrolysis, have been reported. Mild decreases in white blood cell count and hematocrit, which do not require discontinuation of the drug, occur rarely. Levetiracetam appears to have a low incidence of adverse cognitive effects.

Drug Interactions – Levetiracetam does not induce or inhibit CYP isozymes, and is not appreciably metabolized. No clinically significant drug interactions have been reported.

OXCARBAZEPINE — Oxcarbazepine (*Trileptal*, and generics) is FDA-approved as monotherapy or adjunctive therapy for partial seizures in patients ≥4 years old, and as adjunctive therapy in children 2-3 years old. The extended-release formulation *(Oxtellar XR)* is approved for adjunctive treatment of partial seizures in patients ≥6 years old. Oxcarbazepine is chemically similar to carbamazepine, but it causes less induction of hepatic enzymes and does not induce its own metabolism. Its clinical effect is mostly due to its 10-monohydroxy (MHD) metabolite, which has a half-life of 8-10 hours. Like carbamazepine, oxcarbazepine is effective for treatment of secondarily generalized seizures, but may worsen myoclonic and absence seizures. Oxcarbazepine has been as effective as carbamazepine for treatment of partial seizures and may be better tolerated.

Other Uses – Oxcarbazepine is used off-label for treatment of bipolar disorder and neuropathic pain.

Adverse Effects – Common adverse effects of oxcarbazepine are somnolence, dizziness, diplopia, ataxia, nausea, and vomiting. Taking the extended-release formulation with food increases peak concentrations of the drug and the likelihood of adverse effects. Stevens-Johnson syndrome and toxic epidermal necrolysis have occurred, and multi-organ hypersensitivity reactions have been reported. Cross-reactivity with carbamazepine hypersensitivity occurs in 20-30% of patients. Hyponatremia is more common with oxcarbazepine than with carbamazepine.

Drug Interactions – Oxcarbazepine induces CYP3A4/5 and inhibits CYP2C19.[4] It can increase phenytoin levels by up to 40%. Levels of its active metabolite are reduced in the presence of enzyme-inducing drugs such as phenobarbital or phenytoin. Oxcarbazepine should not be administered concomitantly with eslicarbazepine.

PERAMPANEL — Perampanel *(Fycompa)* is FDA-approved for adjunctive treatment of partial seizures and primary generalized tonic-clonic seizures in patients ≥12 years old.[17-19]

Adverse Effects – The most common adverse effects of perampanel are dizziness and drowsiness. Weight gain, ataxia, dysarthria, diplopia, vertigo, nausea, and fatigue have also been reported. Serious psychiatric and behavioral reactions, including irritability, aggression, anger, mood changes, and anxiety can occur.

Drug Interactions – Perampanel is partially metabolized by CYP3A; inhibitors of CYP3A such as clarithromycin may increase serum concentrations of perampanel, and CYP3A inducers such as carbamazepine can decrease them.[4]

PHENYTOIN — Phenytoin (*Dilantin*, and generics) is as effective as carbamazepine for treatment of partial and secondarily generalized tonic-clonic seizures, but it is no longer considered a drug of choice because of its complicated pharmacokinetics, adverse effects, and many drug interactions. Different formulations of phenytoin may not be bioequivalent, especially at higher doses. Fosphenytoin (*Cerebyx*, and generics) is a water-soluble prodrug of phenytoin available for IV and IM use.

Adverse Effects – Nystagmus may occur with therapeutic serum concentrations of phenytoin and is usually present at higher concentrations. Drowsiness, ataxia, and diplopia are more likely to occur at serum concentrations >20 mcg/mL, but can also occur at lower levels, particularly in patients with low serum albumin levels and in the elderly. Phenytoin may interfere with cognitive function. Cerebellar atrophy has been reported with long-term use and after acute intoxication.

A morbilliform or scarlatiniform rash may occur, usually in the first four weeks of treatment, sometimes with hepatitis, fever, and lymphadenopathy; rarely, it progresses to exfoliative dermatitis or Stevens-Johnson syndrome. Asian patients who test positive for the HLA-B*1502 allele may have an increased risk of

serious skin reactions with phenytoin or fosphenytoin. Patients who develop hypersensitivity reactions to phenytoin are often susceptible to developing similar reactions with carbamazepine and phenobarbital.

Less common adverse effects include megaloblastic anemia, a lupus-like syndrome, peripheral neuropathy, nephritis, and hepatitis leading rarely to fatal hepatic necrosis. Osteopenia, gingival hyperplasia, coarsening of facial features, and hirsutism can occur with long-term use. Serum folic acid, thyroxine, and vitamin K concentrations may decrease with long-term therapy. Fosphenytoin is less likely to cause soft-tissue injury than older IV formulations, but rapid infusion can cause transient paresthesias and pruritus.

Drug Interactions – Phenytoin is metabolized by CYP2C9 and CYP2C19; inducers and inhibitors of these enzymes may affect its serum concentrations.[4] Like carbamazepine, phenytoin is a strong enzyme inducer; it can reduce serum concentrations and possibly the effectiveness of many other drugs, including oral contraceptives and other AEDs. Phenytoin may initially cause an increase in response to warfarin, followed by a reduction in its anticoagulant effect.

PREGABALIN — Pregabalin *(Lyrica)* is FDA-approved for adjunctive treatment of partial seizures in adults.[20] Its mechanism of action is similar to that of gabapentin, suggesting it will not be useful in the treatment of myoclonic seizures. A randomized trial comparing pregabalin and gabapentin in patients with refractory focal seizures suggested similar efficacy.[21]

Other Uses – Pregabalin is also FDA-approved for treatment of neuropathic pain and fibromyalgia.[22] It has been used off-label for treatment of generalized anxiety disorder; the drug is approved in Europe for this indication.

Adverse Effects – Pregabalin can cause somnolence, dizziness, ataxia, weight gain, dry mouth, blurred vision, peripheral edema, and confusion. Myoclonus has developed in patients with epilepsy taking pregabalin. Pregabalin is classified as a schedule V controlled substance because of reports of euphoria.

Drug Interactions – Like gabapentin, pregabalin does not induce or inhibit CYP isozymes, and is not appreciably metabolized.

RUFINAMIDE — Rufinamide (*Banzel,* and generics) is FDA-approved for adjunctive treatment of Lennox-Gastaut syndrome in patients ≥1 year old.[23] It appears to be particularly effective for treatment of tonic-atonic seizures.[24] There is also evidence that adjunctive treatment with rufinamide reduces the frequency of partial seizures.[25]

Adverse Effects – The most frequent adverse effects of rufinamide have been somnolence and vomiting. Headache, dizziness, fatigue, nausea, diplopia, and tremor have been reported. Rufinamide can shorten the QT interval in some patients; it should not be used in patients with short QT syndrome or in those taking other drugs known to shorten the QT interval, such as digoxin (*Lanoxin*, and others) and magnesium.

Drug Interactions – Rufinamide is a mild inducer of CYP3A4. It has been shown to reduce ethinyl estradiol, norethindrone, and triazolam (*Halcion*, and generics) serum concentrations, and could have a similar effect on other drugs metabolized by CYP3A4.

TOPIRAMATE — Topiramate (*Topamax*, and generics; *Qudexy XR*[26]; *Trokendi XR*) is FDA-approved as monotherapy or adjunctive therapy for partial and primary generalized tonic-clonic seizures in patients ≥2 years old. It is also approved for adjunctive treatment of children ≥2 years old with Lennox-Gastaut syndrome and is effective for treatment of atonic seizures in children.[27] *Trokendi XR* is approved for the same indications in patients ≥6 years old.[28]

Other Uses – Topiramate (*Topamax,* and generics) is also FDA-approved for migraine prophylaxis,[29] and is available in a fixed-dose combination with phentermine *(Qsymia)* for chronic weight management.[30]

Adverse Effects – The most common adverse effects of topiramate are drowsiness, dizziness, headache, and ataxia. Nervousness, confusion, paresthesias, weight loss, and diplopia can occur. Psychomotor slowing, word-finding difficulty, impaired concentration, and interference with memory are common, particularly with rapid dose escalation and higher maintenance doses, and may require dosage reduction or drug discontinuation. Acute myopia associated with secondary angle-closure glaucoma, which is infrequent but severe, typically occurs within one month of starting the drug. Hepatic failure, oligohidrosis, hyperthermia, and heat stroke have been reported. Topiramate is a mild carbonic anhydrase inhibitor and can cause metabolic acidosis, which increases the risk of symptomatic renal stones.

Drug Interactions – Topiramate is a mild inducer of CYP3A and an inhibitor of CYP2C19. It can increase serum lithium levels, particularly at high doses. Carbamazepine and phenytoin decrease topiramate serum concentrations. Coadministration

of valproic acid and topiramate has been associated with hyperammonemia and hypothermia. Use of topiramate with other carbonic anhydrase inhibitors such as zonisamide or acetazolamide could increase the severity of metabolic acidosis.

VALPROATE — Valproic acid (*Depakene*, and generics) and divalproex sodium (*Depakote*, and generics) dissociate to valproate in the GI tract. Valproate products are FDA-approved as monotherapy or adjunctive therapy for complex partial seizures and absence seizures and as adjunctive therapy for multiple seizure types that involve absence. Because valproate is effective and usually well tolerated, it is widely used to treat myoclonic and atonic seizures and is considered a drug of choice for primary generalized tonic-clonic seizures. It is highly effective in treating photosensitive epilepsy and juvenile myoclonic epilepsy. Valproate is less effective than carbamazepine in controlling complex partial seizures, but equally effective in controlling secondarily generalized seizures.

A once-daily extended-release formulation of divalproex sodium (*Depakote ER*, and generics) is as effective as *Depakote*. It is not bioequivalent to other formulations; when switching from valproate capsules or delayed-release tablets to *Depakote ER*, the daily dose should be increased by 8-20%. Valproate is also available in an IV formulation (*Depacon,* and generics).

Other Uses – Valproate is FDA-approved for migraine prophylaxis and divalproex sodium is approved for treatment of manic episodes of bipolar disorder.

Adverse Effects – Drowsiness caused by valproate is usually mild and transient, and adverse cognitive effects are generally minimal. Nausea and vomiting can be minimized by using the enteric-coated formulation (*Depakote*, and generics), by taking the drug with food, and by slow titration to an optimal dose. Weight gain is common. Use of valproate has been associated with polycystic ovary syndrome, hyperinsulinemia, lipid abnormalities, hirsutism, and menstrual disturbances in women, and with increased serum androgen concentrations in men. Dose-related tremor, transient hair thinning and loss, decreased platelet function, and thrombocytopenia can also occur.

Serious adverse effects of valproate are uncommon, but fatal liver failure has occurred, particularly in children <2 years old taking valproate in combination with other AEDs and in patients with developmental delays and/or metabolic disorders; liver failure has also been reported in older children and adults taking valproate alone. Valproate can interfere with conversion of ammonia to urea, causing lethargy associated with hyperammonemia. Fatal hyperammonemic encephalopathy has occurred in patients with genetic defects in urea metabolism; the drug is contraindicated in these patients. Life-threatening pancreatitis, interstitial nephritis, reversible parkinsonism, and edema requiring diuretics have occurred rarely.

Drug Interactions – Valproate interacts with fewer drugs than carbamazepine or phenytoin. Enzyme-inducing AEDs increase valproate clearance. Carbapenem antibiotics such as imipenem may significantly reduce valproate serum concentrations. Valproate is a weak enzyme inhibitor; it can increase serum concentrations of some other AEDs, including carbamazepine, phenytoin, phenobarbital, ethosuximide, lamotrigine, and rufinamide, and of tricyclic antidepressants.

ZONISAMIDE — Zonisamide (*Zonegran*, and others) is FDA-approved for adjunctive treatment of partial seizures in adults. It appears to have a broad spectrum of activity (infantile spasms, myoclonic, generalized, and atypical absence seizures), and there is considerable experience worldwide with its use as monotherapy for various seizure types and in children.

Other Uses – Zonisamide also appears to be effective for migraine prophylaxis and for weight loss in obese patients, but it is not FDA-approved for these indications.[31,32]

Adverse Effects – Adverse effects of zonisamide include somnolence, dizziness, confusion, anorexia, nausea, diarrhea, weight loss, agitation, irritability, and rash. Fatal Stevens-Johnson syndrome and toxic epidermal necrolysis have been reported. Oligohidrosis, hyperthermia, and heat stroke have occurred in children. Psychosis, psychomotor slowing, word-finding difficulty, and impaired concentration can occur. Aplastic anemia and agranulocytosis have been reported. Slow titration and taking the drug with food may decrease the incidence of adverse effects. Zonisamide is a mild carbonic anhydrase inhibitor and can cause metabolic acidosis, which increases the risk of symptomatic renal stones.

Drug Interactions – Zonisamide is metabolized by CYP3A4; drugs that induce or inhibit CYP3A4 could affect its serum concentrations.[4] Zonisamide does not inhibit CYP isozymes. Use of zonisamde with other carbonic anhydrase inhibitors such as topiramate could increase the risk of renal stone formation.

OTHER DRUGS — Felbamate (*Felbatol,* and generics) is FDA-approved as monotherapy and adjunctive therapy

for partial and secondarily generalized seizures, and for adjunctive treatment of seizures associated with Lennox-Gastaut syndrome in patients whose disease has not responded to other drugs. Aplastic anemia and hepatic failure have occurred rarely.

Phenobarbital and **primidone** (*Mysoline*, and generics) are effective for treatment of partial and secondarily generalized tonic-clonic seizures, but they have a higher incidence of sedation than other drugs.

Tiagabine (*Gabitril,* and generics) is FDA-approved for adjunctive treatment of partial seizures. It has GI and CNS adverse effects. Off-label use for treatment of bipolar disorder, anxiety, and neuropathic pain in nonepileptic patients has been associated with development of new-onset seizures and status epilepticus.[33]

Vigabatrin *(Sabril)* is FDA-approved as monotherapy for infantile spasms and as adjunctive treatment for complex partial seizures refractory to several other AEDs.[34] It is only available through a restricted distribution program due to concerns about retinal toxicity and permanent visual field loss.

Diazepam rectal gel *(Diastat AcuDial)* is approved for intermittent treatment of increased seizure activity in patients taking other antiepileptic drugs. When given rectally, diazepam is rapidly and completely absorbed. At-home use of rectal diazepam in children may help terminate seizure activity and reduce emergency room visits.[35]

CANNABIS — Cannabidiol, a major cannabinoid found in cannabis, has been effective in reducing the frequency of drug-related seizures in children with Dravet syndrome.[36] Data are insufficient to recommend use of any cannabinoid for treatment of patients with more common types of epilepsy.

OTHER ISSUES — Suicidality – The results of a large cohort study in the US suggest that patients taking gabapentin, lamotrigine, oxcarbazepine, or tiagabine are at greater risk of suicidal acts than those taking topiramate or carbamazepine.[37] In a cohort study in the UK, use of AEDs in patients with epilepsy was not associated with an increased risk of suicide-related events, but an increased risk was seen in patients with depression taking AEDs.[38]

Bone Density – Prolonged use of AEDs, particularly those that induce hepatic enzymes (phenytoin, carbamazepine, phenobarbital, primidone), may increase the risk of osteoporosis. Valproate has also been associated with decreases in bone mineral density.

AEDs and Oral Contraceptives – Enzyme-inducing AEDs such as carbamazepine, phenytoin, primidone, and phenobarbital and, to a lesser extent, felbamate, topiramate, oxcarbazepine, eslicarbazepine, rufinamide, clobazam, and perampanel, may decrease serum concentrations of estrogens and/or progestins, possibly resulting in contraceptive failure.[39] Hormonal contraceptives may increase seizure frequency in some women with epilepsy.[40]

AEDs and Pregnancy – The risk to offspring from taking AEDs is generally considered to be less than the risk of seizures during pregnancy.[41] Most pregnant women exposed to AEDs deliver infants without birth defects, but fetal exposure to older AEDs, particularly valproate and phenobarbital, can cause congenital anomalies, including oral cleft, cardiac, urinary tract, and neural tube defects.[42] Exposure to valproate *in utero* has also been associated with lower IQ scores and an increased risk of autism.[43,44] Topiramate appears to increase the risk of oral cleft defects[45] and has been associated with hypospadias.

Pregnancy itself tends to induce the metabolism of AEDs, particularly lamotrigine; monitoring lamotrigine serum concentrations may improve seizure control.[46] Use of an enzyme-inducing AED such as phenytoin, carbamazepine, phenobarbital, or primidone may cause neonatal hemorrhage due to vitamin K deficiency; all newborns should receive vitamin K at delivery.[47] Vitamin K supplementation has been recommended for the mother in the final month of pregnancy, but whether it reduces the risk of hemorrhagic complications is unclear.

Generic Substitution – Many AEDs are available generically. Generic drugs must meet FDA standards for bioequivalence to their brand-name counterparts (pharmacokinetic parameters within 80-125%) and are usually less expensive. A meta-analysis of randomized controlled trials comparing use of brand-name and generic formulations of phenytoin, carbamazepine, and valproate found no difference in seizure control.[48] A double-blind, randomized, crossover trial of two generic lamotrigine products confirmed their bioequivalence and found no significant change in seizure frequency or adverse effects.[49] When switching to a different manufacturer, variations in the appearance of pills might concern some patients, but in one study, switching to a different manufacturer was not associated with an increased risk of seizures.[50] ■

Additional Content Available Online

Comparison Table: Some Antiepileptic Drugs
http://medicalletter.org/TML-article-1526b

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Upon completion of this program, the participant will be able to:

1. Explain the current approach to the management of patients with epilepsy.
2. Discuss the pharmacologic agents available for treatment of epilepsy and compare them based on their efficacy, dosage and administration, potential adverse effects, and drug interactions.
3. Determine the most appropriate therapy given the clinical presentation of an individual patient with epilepsy.

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Issue 1526 Questions

(Correspond to questions #21-30 in Comprehensive Exam #77, available January 2018)

1. Which of the following statements regarding treatment of epilepsy is true?
   a. it should begin with a single drug
   b. the dosage of the drug should be increased rapidly
   c. if seizures persist, adding a second drug is preferred to trying an alternative drug
   d. all of the above
2. The drug of choice for treatment of primary generalized tonic-clonic seizures is:
   a. lamotrigine
   b. levetiracetam
   c. valproate
   d. any of the above
3. Carbamazepine is particularly effective for:
   a. partial and secondarily generalized tonic-clonic seizures
   b. absence seizures
   c. myoclonic seizures
   d. all of the above
4. A 12-year-old girl is being treated with levetiracetam for partial seizures. Her mother had similar seizures as a child that were treated successfully with phenytoin, and she asks why her daughter is being treated with something else. You could tell her that:
   a. phenytoin is no longer effective for partial seizures
   b. a large randomized controlled trial found levetiracetam more effective
   c. phenytoin is no longer considered a first-choice drug because of its complicated pharmacokinetics, adverse effects, and frequent drug interactions
   d. all of the above
5. In choosing between lamotrigine and levetiracetam for treatment of partial and generalized seizures, one advantage of levetiracetam is that it:
   a. was shown to be more effective for treatment of partial seizures
   b. was shown to be more effective for treatment of generalized seizures
   c. has not been associated with serious dermatological reactions
   d. has no clinically significant drug interactions
6. Like carbamazepine, gabapentin:
   a. is a strong inducer of hepatic enzymes
   b. can exacerbate myoclonic seizures
   c. can cause Stevens-Johnson syndrome in patients with the HLA-B*1502 allele
   d. all of the above
7. An 8-year-old girl seeing you for the first time has been taking clonazepam for first-line treatment of absence seizures for 12 months. Her seizures were well controlled on the drug initially, but they have recently begun to recur with greater frequency. Her parents ask if she is taking the right medication. You could tell them that:
   a. development of tolerance to the effects of clonazepam is common
   b. abrupt discontinuation of clonazepam can lead to withdrawal symptoms
   c. ethosuximide and valproate are preferred options for treatment of absence seizures
   d. all of the above
8. Enzyme-inducing antiepileptic drugs such as carbamazepine or phenytoin may:
   a. decrease the risk of osteoporosis
   b. increase serum concentrations of hepatically metabolized drugs
   c. reduce the efficacy of oral contraceptives
   d. all of the above
9. Which of the following statements about the use of antiepileptic drugs during pregnancy is true?
   a. valproate appears to be the safest antiepileptic drug to take during pregnancy
   b. pregnancy can inhibit the metabolism of lamotrigine
   c. the risk to the offspring is generally considered to be less than the risk of seizures during pregnancy
   d. all of the above
10. Generic antiepileptic drugs:
    a. are bioequivalent to their brand-name counterparts
    b. are generally less expensive than their brand-name counterparts
    c. may differ in appearance from their brand-name counterparts
    d. all of the above

ACPE UPN: Per Issue Exam: 0379-0000-17-526-H01-P; Release: July 31, 2017, Expire: July 31, 2018
Comprehensive Exam 77: 0379-0000-18-077-H01-P; Release: January 2018, Expire: January 2019

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