NEUROLOGY

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Learning Objectives

1. Identify the differences between convulsions, seizures, and status epilepticus.
2. Determine appropriate use of antiepileptic drugs on the basis of their activity, adverse effects, and drug interactions for epilepsy and status epilepticus.
3. Identify appropriate treatment strategies for primary and secondary stroke prevention.
4. Determine the appropriateness of treatment with alteplase for acute stroke.
5. Initiate and monitor pharmacotherapy for Parkinson disease.
6. Differentiate between regimens for acute and prophylactic treatment of migraine, tension, and cluster headaches.
7. Identify appropriate therapies for individuals with multiple sclerosis.
8. Establish appropriate treatment for peripheral neuropathy.

Abbreviations in This Chapter
AED  Antiepileptic drug
CNS  Central nervous system
GABA  γ-Aminobutyric acid
JME  Juvenile myoclonic epilepsy
MAO-B  Monoamine oxidase type B
MS   Multiple sclerosis
NSAID  Nonsteroidal anti-inflammatory drug
TIA  Transient ischemic attack

Self-Assessment Questions
Answers and explanations to these questions may be found at the end of this chapter.

1. T.L. is a 44-year-old man with complex partial seizures who is otherwise healthy. He was initiated on phenytoin after a seizure about 2 months ago. He currently takes phenytoin 100 mg 4 capsules orally every night. During his clinic visit, he continues to have seizures, and he has no signs of toxicity. He is allergic to sulfa drugs. His phenytoin serum concentration is 13.2 mcg/mL. Which is the best new phenytoin dose for this patient?
   A. 400 mg/day.
   B. 450 mg/day.
   C. 430 mg/day.
   D. 500 mg/day.

2. B.V. is a 28-year-old woman brought to your emergency department for the treatment of status epilepticus. She receives lorazepam 4 mg intravenously with subsequent seizure cessation. Which medication is the best next treatment step for B.V.?
   A. Topiramate.
   B. Levetiracetam.
   C. Lamotrigine.
   D. Valproate.

3. J.H. is a 42-year-old man with complex partial seizures for which he was prescribed levetiracetam. He comes to the pharmacy where you work with concerns of agitation. He says his wife is also concerned because he is very irritable and, at times, depressed. Which best assesses J.H.’s condition?
   A. Discontinue levetiracetam; he is having adverse effects.
   B. Increase the levetiracetam dose; he is having focal seizures.
   C. Continue levetiracetam; it is controlling his seizures.
   D. Obtain a levetiracetam serum concentration; he is probably supratherapeutic.

Questions 4 and 5 pertain to the following case.
R.H. is a 62-year-old man who presents to the emergency department for new-onset right-sided weakness and slurred speech that began 2 hours ago. He has a history of hypertension and coronary artery disease. His medication list includes atenolol 50 mg/day orally, hydrochlorothiazide 25 mg/day orally, and aspirin 81 mg/day orally. His vital signs include blood pressure 160/92 mm Hg, heart rate 92 beats/minute, respiratory rate 14 breaths/minute, and temperature 38°C.

4. Which is the best treatment for R.H.?
   A. Alteplase.
   B. Aspirin 81 mg/day immediately.
   C. Clopidogrel 300 mg loading dose; then 75 mg/day with aspirin 81 mg/day for 90 days immediately.
D. Aspirin 25 mg/dipyridamole 200 mg extended release for 30 days.

5. R.H. is treated appropriately and survives his stroke. Three days later, he is discharged to rehabilitation. Which is best to initiate to prevent another stroke?
   A. Aspirin/dipyridamole for 1 month.
   B. Aspirin/clopidogrel for 3 months.
   C. Warfarin for 6 months.
   D. Ticagrelor for 12 months.

Questions 6 and 7 pertain to the following case.
C.P. is a 69-year-old man given a diagnosis of Parkinson disease 7 years ago. He states that he is most bothered by his bradykinesia symptoms. On examination, he also has a pronounced tremor, postural instability, and a masked facial expression. He currently takes carbidopa/levodopa 25 mg/100 mg orally four times daily and selegiline 5 mg orally twice daily. He has no drug allergies. He says that his Parkinson symptoms have increased. During the visit, you notice that he cannot sit still and is constantly moving his facial expressions, arms, torso, and legs.

6. Which best describes C.P.’s symptoms?
   A. Wearing-off.
   B. On-off.
   C. Dyskinesia.
   D. Seizures.

7. Which is the best approach to managing C.P.’s symptoms?
   A. Initiate apomorphine.
   B. Reduce the carbidopa/levodopa dose.
   C. Discontinue selegiline.
   D. Add ropinirole.

Questions 9 and 10 pertain to the following case.
R.M. is a 19-year-old woman with newly diagnosed migraine headaches. She takes an oral contraceptive and has tried nonprescription analgesics, with little relief of her headache. She admits to having trouble sleeping.

9. Which drug is best for R.M. to use for her migraine headaches?
   A. Naproxen.
   B. Sumatriptan.
   C. Dihydroergotamine.
   D. Isometheptene, acetaminophen, dichloralphenazone.

10. If R.M. needs a drug for migraine prophylaxis, which agent is best to recommend?
    A. Amitriptyline.
    B. Valproate.
    C. Topiramate.
    D. Frovatriptan.

Questions 11–13 pertain to the following case.
L.M. is a 43-year-old man who received a diagnosis of progressive-relapsing multiple sclerosis (MS) 2 years ago. He has taken glatiramer acetate since then. However, his exacerbations have not discernibly decreased. He has spasticity in his legs, which has caused several falls in the past month, and fatigue that worsens as the day progresses.

11. Which drug is best for L.M.’s MS?
    A. Cyclophosphamide.
    B. Methylprednisolone.
    C. Azathioprine.
    D. Fingolimod.

12. Which drug is best for L.M.’s spasticity?
    A. Diazepam.
    B. Baclofen.
    C. Carisoprodol.
    D. Metaxalone.
13. Which drug is best for L.M.’s fatigue?
   A. Propranolol.
   B. Lamotrigine.
   C. Amantadine.
   D. Ropinirole.

Questions 14 and 15 pertain to the following case.
B.T. is a 62-year-old man with obesity (weight 122 kg [270 kg]) who comes to the clinic with concerns of burning in the soles of his feet for the past 3 months. These symptoms began about 3 months ago. They are worse at night and keep him from sleeping. On examination, he has decreased sensation in both feet up to the ankles bilaterally and good strength throughout his feet and legs. Ankle reflexes are decreased. He has hypertension treated with lisinopril 10 mg/day. He also has epilepsy that is well controlled with lamotrigine 200 mg twice daily.

14. Which most likely caused B.T.’s pain and decreased sensation?
   A. Diabetic neuropathy.
   B. Chronic inflammatory demyelinating polyneuropathy.
   C. Entrapped nerve.
   D. Genetic neuropathy.

15. Which treatment is best for B.T.’s symptoms?
   A. Phenytoin 200 mg at bedtime.
   B. Lidocaine 5% patch applied to soles of feet at bedtime and removed in the morning.
   C. Acetaminophen 325 mg every 4 hours as needed.
   D. Valproate 250 mg twice daily.
BPS Pharmacotherapy Specialty Examination Content Outline
This chapter covers the following sections of the Pharmacotherapy Specialty Examination Content Outline:
1. Domain 1: Patient-Specific Pharmacotherapy
   a. Tasks 1:1–5, 1:7–8, 1:11–12, 3:2, 4:1–2, 4:5–7
I. EPILEPSY

A. Epidemiology

1. Second to headache, epilepsy is the most common neurologic disorder. Ten percent of the U.S. population will have a seizure. In addition, 1 in 26 individuals in the United States will develop epilepsy at some point in their lives (Epilepsy Across the Spectrum 2012).

2. About 50 million people worldwide have epilepsy.

3. About 50% of patients with a new diagnosis become seizure free on their first treatment, with up to 70% becoming seizure free after treatment adjustment and 30% continuing to have seizures (Neurology 2012;78:1548-54).

B. Classification of Seizures: Seizures are traditionally classified according to the International League Against Epilepsy scheme, adopted in 1981, with modifications in 2001 and 2010. A new classification scheme has been adopted by the International League Against Epilepsy. The classification system for seizures was changed in 2017 (Epilepsia 2017;58:512-21).

1. Focal seizures are conceptualized as originating at some point within networks limited to one hemisphere.
   a. No specific classification within focal seizures is recommended.
   b. The terms simple partial seizure, complex partial seizure, and secondarily generalized seizure have been eliminated from classification; however, they are still used to describe seizures.

2. Generalized seizures are conceptualized as originating at some point within the brain and rapidly engaging bilaterally distributed neural networks.
   a. Nonmotor (absence): Typical absence seizures are brief and abrupt, last 10–30 seconds, and occur in clusters. Absence seizures usually result in a short loss of consciousness, or patients may stare, be motionless, or have a distant expression on their face. Electroencephalograms (EEGs) during seizure activity usually show 3-Hz spike-and-wave complexes. Absence seizures can be further classified as typical, atypical, myoclonic absence, and eyelid myoclonia.
   b. Motor-myoclonic: Consist of brief, rapid jerking movements of the entire body or the upper and occasionally lower extremities. Myoclonic seizures can be further classified as myoclonic, myoclonic atonic, or myoclonic tonic.
   c. Motor-tonic clonic: Typically, a primary tonic-clonic seizure has five phases: flexion, extension, tremor, clonic, and postictal. During the flexion phase, the patient’s mouth may be held partly open, and the patient may have upward eye movement, involvement of the extremities, and loss of consciousness. In the extension phase, the patient may be noted to extend his or her back and neck; have contraction of thoracic and abdominal muscles; be apneic; and have flexion, extension, and adduction of the extremities. The patient may cry out as air is forced from the lungs in this phase. The tremor phase occurs as the patient goes from tonic rigidity to tremors and then to a clonic state. During the clonic phase, the patient will have rhythmic jerks. The entire seizure usually lasts 1–3 minutes. After the seizure, the patient may be postictal. During this time, the patient can be difficult to arouse or very somnolent. Before the seizure, a patient may have a prodrome but not an aura.
   d. Motor-clonic: Only the clonic phase of a tonic-clonic seizure; rhythmic, repetitive, jerking muscle movements
   e. Motor-tonic: Only the flexion or extension phases of a tonic-clonic seizure
   f. Motor-atactic: Characterized by a loss of muscle tone. Atonic seizures are often described as drop attacks, in which a patient loses tone and falls to the ground.

3. Epilepsy is a disease of the brain defined by any of the following conditions:
   a. Two unprovoked (or reflex) seizures occurring more than 24 hours apart;
b. One unprovoked (or reflex) seizure and a probability of subsequent seizures similar to the general recurrence risk (at least 60%) after two unprovoked seizures, occurring over the next 10 years;
c. Diagnosis of an epilepsy syndrome (Epilepsia 2014;55:475-82)

4. Status epilepticus is caused either by the failure of the mechanisms responsible for seizure termination or by the initiation of mechanisms, which lead to abnormally prolonged seizures after 5 minutes. At this point, treatment for status epilepticus should be initiated. After 30 minutes, status epilepticus can have long-term consequences, including neuronal death, neuronal injury, and alteration of neuronal networks (depending on the type and duration of seizures). Mortality is up to 20% for status epilepticus (Epilepsia 2015;56:1515-23).

5. Nonepileptic seizures are paroxysmal nonepileptic episodes (based on EEG) resembling epileptic seizures that can be organic or psychogenic.

6. Other associated symptoms
   a. Prodrome: Awareness of an impending seizure before it occurs. The prodrome may consist of headache, insomnia, irritability, or a feeling of impending doom.
   b. Aura: A focal seizure, without loss of consciousness, consisting of sensory or autonomic symptoms that may precede evolution to a bilateral, convulsive seizure. Patients may have feelings of fear, embarrassment, or déjà vu. Automatic behavior (automatism) and psychic symptoms may occur. Automatisms may include lip smacking, chewing, swallowing, abnormal tongue movements, scratching, thrashing of the arms or legs, fumbling with clothing, and snapping the fingers. Psychic symptoms include illusions, hallucinations, emotional changes, dysphasia, and cognitive problems.

C. Diagnosis
   1. Physical examination should occur, with special attention given to neurologic findings. The neurologic examination may include examination of the head, vision, cranial nerves, motor function, cerebellar function, and sensory function.
   2. Laboratory tests are based on the history and physical examination results; a full diagnostic onslaught is unnecessary in many patients. Because metabolic causes of seizures are common, serum glucose, electrolytes, calcium, complete blood cell counts (CBCs), and renal function tests may be necessary. A toxicology screen may also be prudent.
   3. EEGs are used to help confirm the diagnosis, classify seizures, locate the site of the seizures, and select the best seizure medication. The best time for an EEG is while the patient is having seizures. If doing an EEG is not possible during seizures, the EEG should be done as soon after the seizure as possible. Depending on the clinical situation, an EEG may be obtained under normal conditions, when the patient is sleep deprived, or when the patient is asleep. Patients whose seizures are difficult to diagnose or control may need prolonged closed-circuit video–EEG monitoring. Keep in mind that although an interictal (when the patient is not having clinical seizures) EEG may be normal, this does not preclude the diagnosis of epilepsy.
   4. Magnetic resonance imaging is the neuroimaging technique of choice for epilepsy. Computed tomography (CT) scanning can help find brain lesions when magnetic resonance imaging cannot be done in a timely fashion.

D. Treatment
   1. Medications (see Tables 1–5)
      a. Benzodiazepines
         i. Mechanism of action: Augment γ-aminobutyric acid (GABA)-mediated chloride influx
         ii. Tolerance may develop: Usually used as adjunctive, short-term therapy
         iii. Most commonly used drugs: Chlorazepate (Tranxene), clobazam (Onfi), clonazepam (Klonopin), diazepam (Valium), and lorazepam (Ativan)
iv. All benzodiazepines are controlled substances, scheduled as C-IV.
v. Nonepileptic indications: Chlorazepate (anxiety disorders, anxiety), clonazepam (panic disorder with or without agoraphobia), lorazepam (anxiety disorders, anxiety, alcohol withdrawal)
b. Brivaracetam (Briviact)
i. Mechanism of action: Unknown mechanism, but has high affinity for synaptic vesicle protein 2A
ii. Adverse effects: Somnolence, sedation, dizziness, fatigue
iii. Drug interactions: Carbamazepine, phenobarbital, phenytoin
c. Cannabidiol (Epidiolex)
i. The only U.S. Food and Drug Administration (FDA)-approved cannabis product for epilepsy
ii. Approved for Dravet syndrome and Lennox-Gastaut syndrome
iii. Adverse effects: Sedation, drowsiness, diarrhea, intestinal cramping, increased liver transaminase (11% of patients); 3% of patients discontinued because of increased liver function tests
iv. Metabolized by cytochrome P450 (CYP) 2C19 and 3A4
v. Interaction with clobazam and other antiepileptic drugs (AEDs)
vi. Dose 10–20 mg/kg/day
d. Carbamazepine (Carbatrol, Epitol, Equetro, Tegretol, Teril)
i. Mechanism of action: Fast sodium channel blocker
ii. Pharmacokinetics: Enzyme inducer, autoinduction
iii. Adverse effects: Rash (occurs after a delay of 2–8 weeks), syndrome of inappropriate antidiuretic hormone release, aplastic anemia, thrombocytopenia, anemia, leukopenia
iv. Extended-release tablets (Tegretol XR) 100, 200, and 400 mg; extended-release capsules (Carbatrol) 100, 200, and 300 mg available. Dosing is still twice daily. Do not crush or chew. Extended-release capsules (Carbatrol) can be opened and sprinkled on food. Ghost tablets can occur in the stool with the extended-release tablets (Tegretol XR).
v. Patients with the HLA-B*1502 allele are at a 10-fold elevated risk of Stevens-Johnson syndrome.
   (a) Testing is recommended for Asians (including Indians).
   (b) More than 15% of populations in Hong Kong, Malaysia, the Philippines, and Thailand have this allele.
vi. Patients with the HLA-A*3101 allele are also at a 12-fold elevated risk of hypersensitivity syndrome and a 3-fold elevated risk of maculopapular exanthema.
   (a) Prevalence of this allele is 2%–5% in northern European populations and 9.1% in Japanese populations.
   (b) No recommendations have been issued for testing for this allele.
vii. Nonepileptic indication: Trigeminal neuralgia
e. Eslicarbazepine acetate (Aptiom)
i. Mechanism of action: Fast sodium channel blocker
ii. Prodrug for eslicarbazepine, with active metabolites; R-lcarbazepine 5%, oxcarbazepine 1%
iii. Adjust dose if creatinine clearance (CrCl) is less than 50 mL/minute/1.73 m².
f. Ethosuximide (Zarontin)
i. Mechanism of action: T-type calcium current blocker
ii. Useful only for absence seizures
g. Everolimus (Afinitor)
i. Indicated for seizures caused by tuberous sclerosis
ii. Kinase inhibitor
iii. Titrate dose to achieve a trough whole blood concentration of 5–15 ng/mL. Monitor concentrations every 1–2 weeks during dose titration and dose adjustments. Monitor concentrations every 2 weeks when adding and discontinuing a strong P-glycoprotein (P-gp) or CYP3A4 inducer or inhibitor. Measure concentrations every 3 months on a stable dose with changing body surface area. Measure concentrations every 6–12 months with a stable dose and body surface area.

iv. Reduce dose in severe (Child-Pugh class C) hepatic failure

h. Felbamate (Felbatol)
   i. Mechanism of action: Blocks glycine site on N-methyl-d-aspartate receptor
   ii. Serious adverse effects: Hepatotoxicity, aplastic anemia. Patient or guardian must sign consent form. Used only when seizures are severe and refractory to other medications and when the benefit clearly outweighs the potential adverse effects.

i. Fosphenytoin (Cerebyx)
   i. Mechanism of action: Prodrug for phenytoin; fast sodium channel blocker
   ii. Uses: Parenteral formulation for loading or maintenance dosing in place of phenytoin; status epilepticus
   iii. Pharmacokinetics: Enzyme inducer, nonlinear kinetics
   iv. Dosing: Phenytoin equivalents (PE) are used. Loading dose: 10–20 mg of phenytoin sodium equivalents (PE)/kg intravenous or intramuscular dosing is appropriate. Maintenance dosage: Begin with 4–6 mg PE/kg/day in divided doses after administration of the loading dose.
   v. Adverse effects: Hypotension, perianal itching, other adverse effects of phenytoin
   vi. Advantages over phenytoin
      (a) Intramuscular or intravenous dosing
      (b) Phlebitis is minimized.
      (c) Infusion can be up to 150 mg PE per minute. In status epilepticus, infusion should be at 100–150 mg PE per minute. Maximum infusion rate is not to exceed 150 mg PE per minute.
      (d) Can deliver in normal saline solution or D$_5$W (5% dextrose [in water] injection)

j. Gabapentin (Neurontin)
   i. Mechanism of action: Inhibition of α2δ subunit of voltage-dependent calcium channels
   ii. Pharmacokinetics: Not metabolized, eliminated renally; adjustments may be necessary for renal dysfunction and hemodialysis
   iii. Nonepileptic indication: Postherpetic neuralgia pain
   iv. Doses often exceed product information maximum of 3600 mg/day.
   v. Extended-release tablets (Gralise) 300 and 600 mg are available. Their indication is for postherpetic neuralgta, not epilepsy.
   vi. Gabapentin enacarbil (Horizant) extended-release tablets 300 and 600 mg are available. This agent is a prodrug for gabapentin and is indicated for postherpetic neuralgia and restless legs syndrome, not epilepsy.

k. Lacosamide (Vimpat)
   i. Mechanism of action: Slow sodium channel blocker
   ii. Maximal dose is 300 mg/day with a CrCl of 30 mL/minute/1.73 m$^2$ or less or with mild to moderate hepatic impairment.
   iii. Adverse effects: PR interval prolongation or first-degree atrioventricular block; baseline and steady-state electrocardiogram (ECG) recommended in patients with known cardiac conduction problems, taking medications known to induce PR interval prolongation, or with severe cardiac disease
   iv. Controlled substance schedule V because of euphoric effects
   v. Parenteral formulation: Has an FDA indication only for replacement of oral formulation
l. Lamotrigine (Lamictal)
   i. Mechanism of action: Decreases glutamate and aspartate release, delays repetitive firing of neurons, blocks fast sodium channels
   ii. Rash is a primary concern; lamotrigine must be titrated slowly to avoid a rash.
   iii. Valproic acid decreases lamotrigine metabolism (increases the serum concentration of lamotrigine); this interaction requires even slower titration and lower final doses.
   iv. Estrogen-containing oral contraceptives increase lamotrigine clearance, so twice the amount of lamotrigine may be necessary.
   v. Extended-release tablets (Lamictal XR) are available (25 mg, 50 mg, 100 mg, 200 mg, 250 mg, 300 mg).
   vi. Nonepileptic indications: Maintenance treatment of type I bipolar disorder
m. Levetiracetam (Keppra)
   i. Mechanism of action: May prevent hypersynchronization of epileptiform burst firing and propagation of seizure activity
   ii. Pharmacokinetics: Not metabolized extensively; adjust dose in renal dysfunction; no drug interactions with other seizure medications
   iii. Parenteral use: Currently FDA indicated only for replacement of oral dosing; however, sometimes used for status epilepticus
   iv. Extended-release tablets (500 mg, 750 mg) are available for once-daily dosing.

n. Oxcarbazepine (Trileptal)
   i. Mechanism of action: Fast sodium channel blocker
   ii. Pharmacokinetics: Active metabolite 10-monohydroxy oxcarbazepine; enzyme inducer, no autoinduction
   iii. Adverse effects: Hyponatremia more common than with carbamazepine (increased dose and increased age increase risk of hyponatremia); blood dyscrasias less common than with carbamazepine; 25%–30% of patients with hypersensitivity to carbamazepine will have hypersensitivity to oxcarbazepine; rash
   iv. Extended-release tablets (Oxtellar XR) are available (150 mg, 300 mg, 600 mg).
o. Perampanel (Fycompa)
   i. Mechanism of action: Noncompetitive antagonist of the inotropic α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid (AMPA) glutamate receptor
   ii. Pharmacokinetics: 95%–96% protein bound to albumin and α1-acid glycoprotein; metabolized by CYP 3A4 and 3A5; 105-hour half-life
   iii. Adverse effects: Neuropsychiatric effects (irritability, aggression, anger, anxiety), dizziness, gait disturbance, weight gain
   iv. Perampanel is a schedule III controlled substance.
p. Phenobarbital (Luminal)
   i. Mechanism of action: Increases GABA-mediated chloride influx
   ii. Pharmacokinetics: Enzyme inducer
   iii. Adverse effects: Hyperactivity, cognitive impairment
   iv. Phenobarbital is a schedule IV controlled substance.
v. Nonepileptic use: Anxiety

q. Phenytoin (Dilantin, Phenytek)
   i. Mechanism of action: Fast sodium channel blocker
   ii. Pharmacokinetics: Enzyme inducer, nonlinear kinetics
   iii. Administration considerations
      (a) Intravenous formulation: Very basic product. Phlebitis and extravasation are concerns; hypotension; maximal infusion rate of 50 mg/minute. Can prepare only in normal saline solution
(b) Oral suspension: Must be shaken well; adheres to feeding tubes and is bound by enteral nutrition products

iv. Dose-related adverse effects: Nystagmus, ataxia, drowsiness, cognitive impairment
v. Non-dose-related adverse effects: Gingival hyperplasia, hirsutism, acne, rash, hepatotoxicity, coarsening of facial features

r. Pregabalin (Lyrica)
i. Mechanism of action: Inhibition of α2δ subunit of voltage-dependent calcium channels
ii. Pharmacokinetics: Not metabolized, renally excreted; reduce dose in renal dysfunction
iii. Adverse effects: Drowsiness, blurred vision, weight gain, edema, angioedema, creatine kinase elevations (three reports of rhabdomyolysis), rash
iv. Schedule V controlled substance: Insomnia, nausea, headache, diarrhea reported after abrupt discontinuation
v. Nonepileptic indications: Neuropathic pain associated with diabetic neuropathy, postherpetic neuralgia, and fibromyalgia

Table 1. Medication Selection for Various Seizure Types

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<th>Drug</th>
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<th>Generalized</th>
<th>Absence</th>
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<th>Infantile</th>
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<td>Oxcarbazepine</td>
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<td>3</td>
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</tr>
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</tr>
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<td>Phenytoin</td>
<td>2</td>
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<td>—</td>
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<td>Pregabalin</td>
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<td>Rufinamide</td>
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<td>Topiramate</td>
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<td>Vigabatrin</td>
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<td>Zonisamide</td>
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</tr>
</tbody>
</table>

*Not all uses are FDA-approved indications. 1 = first-line drug; 2 = second-line drug; 3 = some therapeutic effect; 4 = adjunctive therapy; 5 = used only when benefits outweigh risks.
### Table 2. Selected Interactions Between Seizure Medications

<table>
<thead>
<tr>
<th>Antiepileptic Drug</th>
<th>Added Seizure Medication</th>
<th>Change in Serum Concentration of the Initial Seizure Medication</th>
<th>Mechanism</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brivaracetam</td>
<td>Phenobarbital</td>
<td>Decreased</td>
<td>Increased metabolism</td>
</tr>
<tr>
<td></td>
<td>Phenytoin</td>
<td>Decreased</td>
<td>Increased metabolism</td>
</tr>
<tr>
<td></td>
<td>Ethosuximide</td>
<td>Decreased</td>
<td>Increased metabolism</td>
</tr>
<tr>
<td>Carbamazepine</td>
<td>Brivaracetam</td>
<td>Increased epoxide (active component of carbamazepine)</td>
<td>Inhibits epoxide degradation</td>
</tr>
<tr>
<td></td>
<td>Felbamate</td>
<td>Decreased, increased epoxide (active component of carbamazepine)</td>
<td>Inhibits epoxide degradation</td>
</tr>
<tr>
<td></td>
<td>Phenobarbital</td>
<td>Decreased</td>
<td>Increased metabolism</td>
</tr>
<tr>
<td></td>
<td>Phenytoin</td>
<td>Decreased</td>
<td>Increased metabolism</td>
</tr>
<tr>
<td></td>
<td>Primidone</td>
<td>Decreased</td>
<td>Increased metabolism</td>
</tr>
<tr>
<td></td>
<td>Rufinamide</td>
<td>Decreased</td>
<td>Increased metabolism</td>
</tr>
<tr>
<td></td>
<td>Eslicarbazepine</td>
<td>Increased</td>
<td>Decreased metabolism</td>
</tr>
<tr>
<td>Clobazam</td>
<td>Carbamazepine</td>
<td>Decreased</td>
<td>Increased metabolism</td>
</tr>
<tr>
<td>Eslicarbazepine</td>
<td>Phenobarbital</td>
<td>Decreased</td>
<td>Increased metabolism</td>
</tr>
<tr>
<td></td>
<td>Phenytoin</td>
<td>Decreased</td>
<td>Increased metabolism</td>
</tr>
<tr>
<td></td>
<td>Carbamazepine</td>
<td>Decreased</td>
<td>Probable increased metabolism</td>
</tr>
<tr>
<td>Felbamate</td>
<td>Phenytoin</td>
<td>Decreased</td>
<td>Increased metabolism</td>
</tr>
<tr>
<td></td>
<td>Carbamazepine</td>
<td>Decreased</td>
<td>Increased metabolism</td>
</tr>
<tr>
<td>Lamotrigine</td>
<td>Phenobarbital</td>
<td>Decreased</td>
<td>Increased metabolism</td>
</tr>
<tr>
<td></td>
<td>Phenytoin</td>
<td>Decreased</td>
<td>Increased metabolism</td>
</tr>
<tr>
<td></td>
<td>Primidone</td>
<td>Decreased</td>
<td>Increased metabolism</td>
</tr>
<tr>
<td></td>
<td>Rufinamide</td>
<td>Decreased</td>
<td>Increased metabolism</td>
</tr>
<tr>
<td></td>
<td>Valproic acid</td>
<td>Increased</td>
<td>Decreased metabolism</td>
</tr>
<tr>
<td></td>
<td>Carbamazepine</td>
<td>Decreased</td>
<td>Increased metabolism</td>
</tr>
<tr>
<td>OIracarbazepearine</td>
<td>Phenobarbital</td>
<td>Decreased</td>
<td>Increased metabolism</td>
</tr>
<tr>
<td></td>
<td>Phenytoin</td>
<td>Decreased</td>
<td>Increased metabolism</td>
</tr>
<tr>
<td></td>
<td>Valproic acid</td>
<td>Decreased</td>
<td>Unknown</td>
</tr>
<tr>
<td></td>
<td>Carbamazepine</td>
<td>Decreased</td>
<td>Increased metabolism</td>
</tr>
<tr>
<td>Perampanel</td>
<td>Oxcarbazepine</td>
<td>Decreased</td>
<td>Increased metabolism</td>
</tr>
<tr>
<td></td>
<td>Phenytoin</td>
<td>Decreased</td>
<td>Increased metabolism</td>
</tr>
<tr>
<td></td>
<td>Oxcarbazepine</td>
<td>Increased</td>
<td>Decreased metabolism</td>
</tr>
<tr>
<td>Phenobarbital</td>
<td>Phenytoin</td>
<td>Increased</td>
<td>Unknown</td>
</tr>
<tr>
<td></td>
<td>Rufinamide</td>
<td>Increased</td>
<td>Decreased metabolism</td>
</tr>
<tr>
<td></td>
<td>Valproic acid</td>
<td>Increased</td>
<td>Inhibition of metabolism</td>
</tr>
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</table>
### Table 2. Selected Interactions Between Seizure Medications (continued)

<table>
<thead>
<tr>
<th>Antiepileptic Drug</th>
<th>Added Seizure Medication</th>
<th>Change in Serum Concentration of the Initial Seizure Medication</th>
<th>Mechanism</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phenytoin</td>
<td>Brivaracetam</td>
<td>Increased</td>
<td>Unknown, only with brivaracetam doses ≥ 400 mg/day</td>
</tr>
<tr>
<td></td>
<td>Carbamazepine</td>
<td>Decreased</td>
<td>Increased metabolism</td>
</tr>
<tr>
<td></td>
<td>Eslicarbazepine</td>
<td>Increased</td>
<td>Decreased metabolism</td>
</tr>
<tr>
<td></td>
<td>Oxcarbazepine</td>
<td>Increased or no change</td>
<td>Unknown</td>
</tr>
<tr>
<td></td>
<td>Phenobarbital</td>
<td>Increased or decreased</td>
<td>Decreased or increased metabolism</td>
</tr>
<tr>
<td>Rufinamide</td>
<td>Increased</td>
<td><strong>Unknown</strong></td>
<td><strong>Unknown</strong></td>
</tr>
<tr>
<td>Topiramate</td>
<td>Increased</td>
<td><strong>Decreased</strong></td>
<td><strong>Decreased metabolism</strong></td>
</tr>
<tr>
<td>Valproic acid</td>
<td>Decreased; increased free</td>
<td>Displacement from binding sites</td>
<td></td>
</tr>
<tr>
<td>Vigabatrin</td>
<td>Decreased</td>
<td><strong>Increased metabolism</strong></td>
<td></td>
</tr>
<tr>
<td>Primidone</td>
<td>Carbamazepine</td>
<td>Increased phenobarbital concentration</td>
<td>Unknown</td>
</tr>
<tr>
<td></td>
<td>Phenytoin</td>
<td>Increased phenobarbital concentration</td>
<td>Unknown</td>
</tr>
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<td>Rufinamide</td>
<td>Carbamazepine</td>
<td>Decreased</td>
<td>Increased metabolism</td>
</tr>
<tr>
<td></td>
<td>Phenobarbital</td>
<td>Decreased</td>
<td>Increased metabolism</td>
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<td>Phenytoin</td>
<td>Decreased</td>
<td>Increased metabolism</td>
</tr>
<tr>
<td></td>
<td>Primidone</td>
<td>Decreased</td>
<td>Increased metabolism</td>
</tr>
<tr>
<td></td>
<td>Valproic acid</td>
<td>Increased</td>
<td>Decreased metabolism</td>
</tr>
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<td>Topiramate</td>
<td>Carbamazepine</td>
<td>Decreased</td>
<td>Increased metabolism</td>
</tr>
<tr>
<td></td>
<td>Lamotrigine</td>
<td>Decreased</td>
<td>Unknown</td>
</tr>
<tr>
<td></td>
<td>Phenytoin</td>
<td>Decreased</td>
<td>Increased metabolism</td>
</tr>
<tr>
<td></td>
<td>Valproic acid</td>
<td>Decreased</td>
<td>Increased metabolism</td>
</tr>
<tr>
<td>Valproic acid</td>
<td>Carbamazepine</td>
<td>Decreased</td>
<td>Increased metabolism</td>
</tr>
<tr>
<td></td>
<td>Felbamate</td>
<td>Increased</td>
<td>Unknown</td>
</tr>
<tr>
<td></td>
<td>Oxcarbazepine</td>
<td>Decreased</td>
<td>Unknown</td>
</tr>
<tr>
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<td>Phenobarbital</td>
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<td>Increased metabolism</td>
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<td>Increased metabolism</td>
</tr>
<tr>
<td></td>
<td>Primidone</td>
<td>Decreased</td>
<td>Increased metabolism</td>
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<td>Topiramate</td>
<td>Decreased</td>
<td>Increased metabolism</td>
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<td>Zonisamide</td>
<td>Carbamazepine</td>
<td>Decreased</td>
<td>Increased metabolism</td>
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<tr>
<td></td>
<td>Phenobarbital</td>
<td>Decreased</td>
<td>Increased metabolism</td>
</tr>
<tr>
<td></td>
<td>Phenytoin</td>
<td>Decreased</td>
<td>Increased metabolism</td>
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</table>
Table 3. Selected Interactions of Non-AEDs on Seizure Medications

<table>
<thead>
<tr>
<th>Seizure Medication</th>
<th>Other Drug</th>
<th>Effect on the Seizure Medication</th>
<th>Mechanism</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carbamazepine</td>
<td>Cimetidine</td>
<td>Increased serum concentration</td>
<td>Inhibition of carbamazepine metabolism</td>
</tr>
<tr>
<td></td>
<td>Diltiazem</td>
<td>Increased serum concentration</td>
<td>Inhibition of carbamazepine metabolism</td>
</tr>
<tr>
<td></td>
<td>Erythromycin</td>
<td>Increased serum concentration</td>
<td>Inhibition of carbamazepine metabolism</td>
</tr>
<tr>
<td></td>
<td>Isoniazid</td>
<td>Increased serum concentration</td>
<td>Inhibition of carbamazepine metabolism</td>
</tr>
<tr>
<td></td>
<td>Nefazodone</td>
<td>Increased serum concentration</td>
<td>Inhibition of carbamazepine metabolism</td>
</tr>
<tr>
<td></td>
<td>Theophylline</td>
<td>Decreased serum concentration</td>
<td>Increased carbamazepine metabolism</td>
</tr>
<tr>
<td></td>
<td>Troleandomycin</td>
<td>Increased serum concentration</td>
<td>Inhibition of carbamazepine metabolism</td>
</tr>
<tr>
<td></td>
<td>Verapamil</td>
<td>Increased serum concentration</td>
<td>Inhibition of carbamazepine metabolism</td>
</tr>
<tr>
<td></td>
<td>Clobazam</td>
<td>Increased serum concentration</td>
<td>Inhibitor of CYP2C19</td>
</tr>
<tr>
<td></td>
<td>Fluconazole</td>
<td>Increased serum concentration</td>
<td>Inhibitor of CYP2C19</td>
</tr>
<tr>
<td></td>
<td>Fluvoxamine</td>
<td>Increased serum concentration</td>
<td>Inhibitor of CYP2C19</td>
</tr>
<tr>
<td></td>
<td>Omeprazole</td>
<td>Increased serum concentration</td>
<td>Inhibitor of CYP2C19</td>
</tr>
<tr>
<td></td>
<td>Ticloidipine</td>
<td>Increased serum concentration</td>
<td>Inhibitor of CYP2C19</td>
</tr>
<tr>
<td>Gabapentin</td>
<td>Antacids</td>
<td>Decreased serum concentration</td>
<td>Decreased bioavailability</td>
</tr>
<tr>
<td>Lamotrigine</td>
<td>Estrogen-containing contraceptives</td>
<td>Decreased serum concentration</td>
<td>Possibly induction of glucuronidation of lamotrigine</td>
</tr>
<tr>
<td></td>
<td>Rifampin</td>
<td>Decreased serum concentration</td>
<td>Possibly induction of glucuronidation of lamotrigine</td>
</tr>
<tr>
<td>Perampanel</td>
<td>Ethanol and other CNS depressants</td>
<td>CNS additive or supra-additive effects</td>
<td>Additive CNS depression</td>
</tr>
<tr>
<td></td>
<td>Rifampin</td>
<td>Decreased serum concentration</td>
<td>Increased metabolism</td>
</tr>
<tr>
<td></td>
<td>St. John’s wort</td>
<td>Decreased serum concentration</td>
<td>Increased metabolism</td>
</tr>
<tr>
<td>Phenobarbital; primidone</td>
<td>Ethanol</td>
<td>Acute ethanol ingestion may cause CNS additive effects and respiratory depression; chronic ethanol ingestion may result in variable effects</td>
<td>Additive CNS depression and decreased barbiturate metabolism with acute ethanol ingestion</td>
</tr>
</tbody>
</table>
Table 3. Selected Interactions of Non-AEDs on Seizure Medications (continued)

<table>
<thead>
<tr>
<th>Seizure Medication</th>
<th>Other Drug</th>
<th>Effect on the Seizure Medication</th>
<th>Mechanism</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phenytoin</td>
<td>Anticoagulants, oral</td>
<td>May increase phenytoin serum concentration; decreased or increased anticoagulant effects</td>
<td>Complex mechanism</td>
</tr>
<tr>
<td></td>
<td>Antineoplastics (bleomycin, cisplatin, vinblastine, methotrexate, carmustine)</td>
<td>Decreased pharmacologic effect</td>
<td>Unknown, possible decreased absorption caused by antineoplastic mucosal damage</td>
</tr>
<tr>
<td>Chloramphenicol</td>
<td>Increased phenytoin serum concentration; decreased or increased chloramphenicol serum concentration</td>
<td>Inhibition of phenytoin metabolism; effect on chloramphenicol unknown</td>
<td></td>
</tr>
<tr>
<td>Cimetidine</td>
<td>Increased serum concentration</td>
<td>Inhibition of phenytoin metabolism</td>
<td></td>
</tr>
<tr>
<td>Diazoxide</td>
<td>Decreased pharmacologic effect; decreased serum concentration</td>
<td>Increased phenytoin metabolism</td>
<td></td>
</tr>
<tr>
<td>Diltiazem</td>
<td>Increased serum concentration</td>
<td>Inhibition of phenytoin metabolism</td>
<td></td>
</tr>
<tr>
<td>Disulfiram</td>
<td>Increased serum concentration</td>
<td>Inhibition of phenytoin metabolism</td>
<td></td>
</tr>
<tr>
<td>Folic acid</td>
<td>Decreased serum concentration</td>
<td>Complex mechanism</td>
<td></td>
</tr>
<tr>
<td>Isoniazid</td>
<td>Increased serum concentration</td>
<td>Inhibition of phenytoin metabolism</td>
<td></td>
</tr>
<tr>
<td>Phenylbutazone</td>
<td>Increased serum concentration</td>
<td>Inhibition of phenytoin metabolism; plasma protein displacement</td>
<td></td>
</tr>
<tr>
<td>Rifampin</td>
<td>Decreased serum concentration</td>
<td>Increased phenytoin metabolism</td>
<td></td>
</tr>
<tr>
<td>Sulfonamides</td>
<td>Increased serum concentration</td>
<td>Inhibition of phenytoin metabolism</td>
<td></td>
</tr>
<tr>
<td>Trimethoprim</td>
<td>Increased serum concentration</td>
<td>Inhibition of phenytoin metabolism</td>
<td></td>
</tr>
<tr>
<td>Topiramate</td>
<td>Hydrochlorothiazide</td>
<td>Increased serum concentration</td>
<td>Unknown</td>
</tr>
<tr>
<td>Valproic acid</td>
<td>Estrogen-containing oral contraceptives</td>
<td>Decreased serum concentration</td>
<td>Possibly induction of glucuronidation of lamotrigine</td>
</tr>
<tr>
<td></td>
<td>Meropenem</td>
<td>Decreased serum concentration</td>
<td>Increased valproic acid metabolism</td>
</tr>
<tr>
<td></td>
<td>Rifampin</td>
<td>Decreased serum concentration</td>
<td>Increased valproic acid metabolism</td>
</tr>
<tr>
<td></td>
<td>Salicylates</td>
<td>Increased pharmacologic effect</td>
<td>Plasma protein displacement; increased free valproic concentration</td>
</tr>
</tbody>
</table>

AED = antiepileptic drug; CNS = central nervous system.
Table 4. Pharmacokinetic Parameters of Seizure Medications When Used as Monotherapy

<table>
<thead>
<tr>
<th>Drug</th>
<th>Therapeutic Serum Concentration (mcg/mL)</th>
<th>Bioavailability (%)</th>
<th>Plasma Protein Binding (%)</th>
<th>Vd (L/kg)</th>
<th>Eliminated Unchanged (%)</th>
<th>Clinically Active Metabolites</th>
<th>Half-life (hr)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acetazolamide</td>
<td>10–14</td>
<td>100</td>
<td>&gt; 90</td>
<td>0.23</td>
<td>100</td>
<td>None</td>
<td>48–96</td>
</tr>
<tr>
<td>Carbamazepine</td>
<td>4–12</td>
<td>&gt; 70</td>
<td>40–90</td>
<td>0.8–1.9</td>
<td>Little, if any</td>
<td>10,11-epoxide</td>
<td>12–17</td>
</tr>
<tr>
<td>Clonazepam</td>
<td>Not established</td>
<td>100</td>
<td>80–90</td>
<td>100</td>
<td>3</td>
<td>N-desmethylocobazam</td>
<td>36–2</td>
</tr>
<tr>
<td>Eslicarbazepine</td>
<td>Not established</td>
<td>90</td>
<td>&lt; 40</td>
<td>0.87</td>
<td>90</td>
<td>R-licarbazepine, oxcarbazepine</td>
<td>13–20</td>
</tr>
<tr>
<td>Ethosuximide</td>
<td>40–100</td>
<td>100</td>
<td>0</td>
<td>0.6–0.7</td>
<td>10–20</td>
<td>None</td>
<td>52–60</td>
</tr>
<tr>
<td>Felbamate</td>
<td>30–60</td>
<td>&gt; 90</td>
<td>22–36</td>
<td>0.74–0.85</td>
<td>40–50</td>
<td>None</td>
<td>11–20</td>
</tr>
<tr>
<td>Gabapentin</td>
<td>2–20</td>
<td>Dose-dependent</td>
<td>&lt; 3</td>
<td>0.65–1.04</td>
<td>75–80</td>
<td>None</td>
<td>5–7</td>
</tr>
<tr>
<td>Lamotrigine</td>
<td>1–13</td>
<td>98</td>
<td>55</td>
<td>0.9–1.2</td>
<td>10</td>
<td>None</td>
<td>12–55</td>
</tr>
<tr>
<td>Levetiracetam</td>
<td>12–46</td>
<td>100</td>
<td>&lt; 10</td>
<td>0.5–0.7</td>
<td>66</td>
<td>None</td>
<td>7</td>
</tr>
<tr>
<td>Oxcarbazepine</td>
<td>3–35</td>
<td>100</td>
<td>67</td>
<td>0.7</td>
<td>&lt; 1</td>
<td>10-monohydroxy</td>
<td>105</td>
</tr>
<tr>
<td>Perampanel</td>
<td>Not established</td>
<td>100</td>
<td>95–96</td>
<td>20–36</td>
<td>None</td>
<td>80–100 (neonates) 45–173 (children)</td>
<td></td>
</tr>
<tr>
<td>Phenobarbital</td>
<td>15–40</td>
<td>80–100</td>
<td>40–60</td>
<td>0.7–1</td>
<td>25</td>
<td>None</td>
<td>80–100 (neonates) 45–173 (children)</td>
</tr>
<tr>
<td>Phenytoin</td>
<td>10–20</td>
<td>85–95</td>
<td>&gt; 90</td>
<td>0.6–0.8</td>
<td>&lt; 5</td>
<td>None</td>
<td>–20f</td>
</tr>
<tr>
<td>Pregabalin</td>
<td>Not established</td>
<td>≥ 90</td>
<td>0</td>
<td>0.5</td>
<td>90</td>
<td>None</td>
<td>10–140 (neonates) 5–18 (children)</td>
</tr>
<tr>
<td>Primidone</td>
<td>4–12 (20)d</td>
<td>90–100</td>
<td>80</td>
<td>0.6</td>
<td>20–40</td>
<td>Phenobarbital PEMA 10–15; 17 (PEMA) 4.5–18 (children) 10–36 (PEMA; children)</td>
<td></td>
</tr>
<tr>
<td>Rufinamide</td>
<td>Not established</td>
<td>85</td>
<td>34</td>
<td>50f</td>
<td>2</td>
<td>None</td>
<td>6–10</td>
</tr>
<tr>
<td>Tiagabine</td>
<td>0.02–0.2f</td>
<td>90–95</td>
<td>96</td>
<td>1.2</td>
<td>2</td>
<td>None</td>
<td>3.2–5.7</td>
</tr>
<tr>
<td>Topiramate</td>
<td>5–20f</td>
<td>80</td>
<td>13–17</td>
<td>0.6–0.8</td>
<td>70</td>
<td>None</td>
<td>12–21</td>
</tr>
<tr>
<td>Valproic acid</td>
<td>40–100 (150)f</td>
<td>100</td>
<td>&gt; 90f</td>
<td>0.2</td>
<td>&lt; 5</td>
<td>Unknown</td>
<td>8–17</td>
</tr>
<tr>
<td>Vigabatrin</td>
<td>Not established</td>
<td>100</td>
<td>0</td>
<td>1.1</td>
<td>80</td>
<td>None</td>
<td>7.5</td>
</tr>
<tr>
<td>Zonisamide</td>
<td>10–40</td>
<td>50</td>
<td>40</td>
<td>1.45</td>
<td>35</td>
<td>None</td>
<td>63</td>
</tr>
</tbody>
</table>

Notes:
- a) Therapeutic serum concentrations not well established.
- b) Bioavailability decreased in children < 8 yr and in older adults; clearance is 80% higher in children 2–4 yr and 40% higher in children 4–12 yr than in adults.
- c) Michaelis-Menten pharmacokinetics; half-life varies with serum concentration; therefore, it might be better to express phenytoin elimination in the length of time it takes to clear 50% of the drug from the body, for example.
- d) Upper end of the serum concentration range is not definitely established.
- e) Depends on dose.
- f) May vary with serum concentration.

NAMR = N-acetyl metabolite of ezogabine; PEMA = phenylethylmalonamide; Vd = volume of (drug) distribution.
s. Primidone (Mysoline)
   i. Mechanism of action: Increases GABA-mediated chloride influx
   ii. Metabolized to phenobarbital and phenylethylmalonamide
   iii. Primidone, phenobarbital, and phenylethylmalonamide all have antiepileptic action.
   iv. Pharmacokinetics: Enzyme inducer
   v. Also used for essential tremor

t. Rufinamide (Banzel)
   i. Mechanism of action: Fast sodium channel blocker
   ii. Pharmacokinetics: Absorption increased by food (should be administered with food); metabolized by hydrolysis rather than through CYP enzymes
   iii. Decreases concentrations of ethinyl estradiol and norethindrone
   iv. Has an FDA indication only for Lennox-Gastaut syndrome
   v. Slightly shortens the QT interval and therefore should not be used in patients with familial short QT syndrome
   vi. Available as an oral solution

u. Stiripentol (Diacomit)
   i. Indicated for Dravet syndrome in combination with clobazam
   ii. Dose: 50 mg/kg/day in two or three divided doses
   iii. Inhibits CYP 1A2, 2C19, 2D6, and 3A4

v. Tiagabine (Gabitril)
   i. Mechanism of action: Blocks GABA reuptake in the presynaptic neuron
   ii. Associated with new-onset seizures and status epilepticus in patients without epilepsy

w. Topiramate (Topamax)
   i. Mechanism of action: Fast sodium channel blocker, enhances GABA activity and antagonizes AMPA/kainate activity, weak carbonic anhydrase inhibitor
   ii. Pharmacokinetics: Not extensively metabolized, eliminated in urine
   iii. Adverse effects: Drowsiness, paresthesias, psychomotor slowing (titrate slowly), weight loss, renal stones, acute-angle closure glaucoma, metabolic acidosis, and hyperthermia (associated with decreased perspiration, or oligohidrosis)
   iv. Extended-release formulations (Trokendi XR, Qudexy XR)
   v. Nonepileptic indication: Prophylaxis of migraine headaches

x. Valproic acid (Depacon, Depakene, Depakote, Stavzor)
   i. Mechanism of action: Blocks T-type calcium currents, blocks sodium channels, increases GABA production
   ii. Pharmacokinetics: Enzyme inhibitor
   iii. Parenteral use: Has FDA indication only for replacement of oral dosing; however, sometimes used for status epilepticus, especially if absence status epilepticus
   iv. Adverse effects: Hepatotoxicity, nausea and vomiting, weight gain, interference with platelet aggregation, pancreatitis, alopecia, tremor
   v. Available in immediate-release (valproic acid [Depakene]) capsules for three- or four-times-daily dosing; delayed-release (enteric coated) (divalproex sodium [Depakote], valproic acid [Stavzor]) capsules and tablets for twice-daily dosing (if patient taking an enzyme inducer, drug is dosed more often); and extended-release (divalproex sodium [Depakote ER]) tablets for once-daily dosing
   vi. Nonepileptic indications: Manic episodes associated with bipolar disorder, prophylaxis of migraine headaches
y. Vigabatrin (Sabril)
   i. Mechanism of action: Irreversible inhibition of GABA transaminase
   ii. Pharmacokinetics: Induces CYP2C9; renal elimination
   iii. Adverse effects: Fatigue, somnolence, nystagmus, tremor, blurred vision, vision impairment, weight gain, arthralgia, abnormal coordination, and confusional state
   iv. Serious adverse effect: Vision loss; increased risk with higher total dose and duration; periodic vision testing necessary; restricted distribution program; only used for refractory complex partial seizures and infantile spasms
   v. Available as oral powder for solution

z. Zonisamide (Zonegran)
   i. Mechanism of action: Fast sodium channel blocker, blocks T-type calcium currents, weak carbonic anhydrase inhibitor
   ii. Non-arylamine sulfonamide: Avoid in sulfa-sensitive patients; sometimes used in patients with nonserious sulfa allergies, particularly when non-acrylamides (i.e., sulfonylureas) have been used successfully
   iii. Pharmacokinetics: Long half-life
   iv. Adverse effects: Depression, rash, psychomotor slowing, paresthesias, kidney stones, blood dyscrasias, hyperthermia (associated with decreased perspiration, or oligohidrosis)

Table 5. Starting and Maximal Adult Seizure Medication Doses

<table>
<thead>
<tr>
<th>Drug</th>
<th>Starting Dose</th>
<th>Usual Maximal Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brivaracetam</td>
<td>50 mg twice daily</td>
<td>200 mg/day</td>
</tr>
<tr>
<td>Carbamazepine</td>
<td>200 mg twice daily</td>
<td>1600 mg/day</td>
</tr>
<tr>
<td>Clobazam</td>
<td>10 mg/day</td>
<td>40 mg/day</td>
</tr>
<tr>
<td>Clonazepam</td>
<td>0.5 mg three times/day</td>
<td>20 mg/day</td>
</tr>
<tr>
<td>Eslicarbazepine</td>
<td>400 mg/day</td>
<td>1200 mg/day</td>
</tr>
<tr>
<td>Ethosuximide</td>
<td>250 mg twice daily</td>
<td>1.5 g/day</td>
</tr>
<tr>
<td>Felbamate</td>
<td>400 mg three times/day</td>
<td>3600 mg/day</td>
</tr>
<tr>
<td>Gabapentin</td>
<td>300 mg three times/day</td>
<td>3600 mg/day</td>
</tr>
<tr>
<td>Lacosamide</td>
<td>50 mg twice daily</td>
<td>400 mg/day</td>
</tr>
<tr>
<td>Lamotrigine</td>
<td>With valproic acid: 25 mg every other day Without carbamazepine, phenytoin, phenobarbital, primidone, or valproic acid: 25 mg/day With carbamazepine, phenytoin, phenobarbital, or primidone and not with valproic acid: 50 mg/day</td>
<td>With valproic acid: 200 mg/day Without carbamazepine, phenytoin, phenobarbital, primidone, or valproic acid: 375 mg/day With carbamazepine, phenytoin, phenobarbital, or primidone and not with valproic acid: 500 mg/day</td>
</tr>
<tr>
<td>Levetiracetam</td>
<td>500 mg twice daily</td>
<td>3000 mg/day</td>
</tr>
<tr>
<td>Oxcarbazepine</td>
<td>300 mg twice daily</td>
<td>2400 mg/day</td>
</tr>
<tr>
<td>Perampanel</td>
<td>With enzyme-inducing seizure medications: 4 mg/day Without enzyme-inducing seizure medications: 2 mg/day</td>
<td>With enzyme-inducing seizure medications: 12 mg/day Without enzyme-inducing seizure medications: 8 mg/day</td>
</tr>
<tr>
<td>Phenobarbital</td>
<td>1–3 mg/kg/day</td>
<td>300 mg/day</td>
</tr>
<tr>
<td>Phenytoin</td>
<td>100 mg three times/day</td>
<td>600 mg/day</td>
</tr>
</tbody>
</table>
Table 5. Starting and Maximal Adult Seizure Medication Doses (continued)

<table>
<thead>
<tr>
<th>Drug</th>
<th>Starting Dose</th>
<th>Usual Maximal Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pregabalin</td>
<td>75 mg twice daily</td>
<td>600 mg/day</td>
</tr>
<tr>
<td>Primidone</td>
<td>100 mg at bedtime</td>
<td>2000 mg/day</td>
</tr>
<tr>
<td>Rufinamide</td>
<td>200–400 mg twice daily</td>
<td>3200 mg/day</td>
</tr>
<tr>
<td>Tiagabine</td>
<td>With carbamazepine, phenytoin, primidone, phenobarbital: 4 mg/day</td>
<td>With carbamazepine, phenytoin, primidone, phenobarbital: 56 mg/day</td>
</tr>
<tr>
<td></td>
<td>Without carbamazepine, phenytoin, primidone, phenobarbital: 2 mg/day</td>
<td></td>
</tr>
<tr>
<td>Topiramate</td>
<td>25–50 mg/day</td>
<td>1000 mg/day</td>
</tr>
<tr>
<td>Valproic acid</td>
<td>10–15 mg/kg/day</td>
<td>60 mg/kg/day</td>
</tr>
<tr>
<td>Vigabatrin</td>
<td>500 mg twice daily</td>
<td>3000 mg/day</td>
</tr>
<tr>
<td>Zonisamide</td>
<td>100 mg/day</td>
<td>600 mg/day</td>
</tr>
</tbody>
</table>

2. Surgery: Surgery can sometimes drastically reduce the number of seizures; possible surgical procedures include removal of the seizure focus, corpus callosotomy, or implantation of vagus nerve stimulators.

3. Status epilepticus
   a. Treatment principles
      i. Ascertain ABCs (airway, breathing, and circulation).
      ii. Laboratory values (fingerstick blood glucose, CBC, basic metabolic panel, calcium, magnesium, and seizure medication serum concentrations, if applicable) are sent to determine any reversible causes of status epilepticus.
      iii. Give an emergency medication to stop the seizure immediately.
      iv. Follow with an urgent medication to prevent the recurrence of seizures.
      v. In general, all drugs for status epilepticus should be given parenterally.
      vi. Neuromuscular-blocking drugs do not stop seizures; they stop only the muscular response to the brain's electrical activity.

b. Emergency medications
   i. Lorazepam: Drug of choice
      (a) Rapid onset (2–3 minutes)
      (b) Dosage 0.1 mg/kg (up to 4 mg/dose) at rate of up to 2 mg/minute; may repeat every 5–10 minutes
   ii. Diazepam
      (a) Rapid onset, short duration
      (b) Dosage 0.15 mg/kg (up to 10 mg/dose) at rate of up to 5 mg/minute. May repeat every 5 minutes
      (c) Rectal gel formulation can be given in the absence of intravenous access.
   iii. Midazolam: Preferred for intramuscular administration
      (a) Rapid onset, short duration
      (b) Dosage 0.2 mg/kg (up to 10 mg/dose). Can be given intramuscularly, intranasally, or buccally

c. Urgent medications
   i. Phenytoin: Dosage 20 mg/kg; administration rate less than 50 mg/minute
   ii. Fosphenytoin: Administration rate less than 150 mg of phenytoin equivalent per minute
   iii. Phenobarbital: Dosage 20–40 mg/kg at 50–100 mg/minute
   iv. Valproic acid: Dosage 20–40 mg/kg at up to 6 mg/kg/minute; does not have FDA-labeled approval for status epilepticus
v. Levetiracetam: 20–30 mg/kg over 15 minutes; does not have FDA-labeled approval for status epilepticus

vi. Lacosamide: 200- to 400-mg bolus over 15 minutes; does not have FDA-labeled approval for status epilepticus

d. Refractory status epilepticus medications

i. Pentobarbital: Load 5–15 mg/kg up to 50 mg/minute; follow with a 0.5- to 5-mg/kg/hour infusion.
   (a) May have severe hypotension, necessitating treatment with vasopressors; should have continuous blood pressure measurement
   (b) Must be on ventilator

ii. Thiopental: Load 2–7 mg/kg up to 50 mg/minute; follow with a 0.5- to 5-mg/kg/hour infusion.
   (a) May have severe hypotension, respiratory depression, cardiac depression
   (b) Must be on ventilator

iii. Midazolam: Load 0.2-mg/kg infused up to 2 mg/minute; follow with a 0.05- to 2-mg/kg/hour infusion.
   (a) May have hypotension, respiratory depression
   (b) May have tachyphylaxis

iv. Propofol: Load a 1- to 2-mg/kg intravenous bolus for 30–60 seconds; follow with a 20- to 200-mcg/kg/minute infusion.
   (a) Significant source of lipids
   (b) Some reports of seizure exacerbation with propofol
   (c) Must be on ventilator

4. Special populations

a. Older adults: Pharmacokinetic changes in older adults that may affect seizure medications include the following:

   i. Carbamazepine: Decreased clearance
   
   ii. Phenytoin: Decreased protein binding if hypoalbuminemic or in renal failure
   
   iii. Valproic acid: Decreased protein binding
   
   iv. Diazepam: Increased half-life
   
   v. Phenylethylmalonamide (active metabolite of primidone): Decreased clearance if CrCl is decreased

   vi. Lamotrigine: Decreased clearance
   
   vii. Seizure medications with renal elimination must be adjusted according to the CrCl value.

b. Women’s health

   i. During their reproductive years, women with epilepsy should:
      (a) Take the best drug for their seizure type. Women of childbearing age should not be given valproic acid unless other therapies have failed.
      (b) Be treated with monotherapy, if possible
      (c) Discuss the possible decrease in hormonal contraceptive effectiveness if taking enzyme-inducing medications (Table 6)
      (d) Use folic acid supplementation with no less than 0.4 mg/day

   ii. Three practice guidelines exist regarding epilepsy during pregnancy (relevant material excerpted in the text that follows).
      (a) Avoiding valproic acid monotherapy or polytherapy during the first trimester of pregnancy should be considered to decrease the risk of major congenital malformations, particularly neural tube defects, facial clefts, hypospadias, and poor cognitive outcomes. Valproic acid use has now been associated with lower IQ scores at ages 3 and 4½ (Neurology 2012;78:1207-14).
(b) To reduce the risk of major congenital malformations and poor cognitive outcomes, avoiding the use of seizure medication polytherapy during pregnancy, if possible, should be considered.

(c) Limiting the dose of valproic acid (less than 700 mg/day), topiramate, or lamotrigine during the first trimester, if possible, should be considered to lessen the risk of major congenital malformations.

(d) Avoiding the use of phenytoin, carbamazepine, and phenobarbital, if possible, may be considered to reduce the risk of cleft palate (phenytoin), posterior cleft palate (carbamazepine), cardiac malformations (phenobarbital), and poor cognitive outcomes (phenytoin, phenobarbital).

(e) Women with epilepsy taking seizure medications during pregnancy probably have an elevated risk of small-for-gestational-age infants and 1-minute Apgar scores less than 7.

(f) Monitoring of lamotrigine, carbamazepine, and phenytoin serum concentrations during pregnancy should be considered.

(g) Having levetiracetam and oxcarbazepine (as the mono-hydroxylated derivative) serum concentrations monitored during pregnancy may be considered.

Table 6. Effect of Seizure Medications on Hormonal Contraceptives

<table>
<thead>
<tr>
<th>Seizure Medication</th>
<th>Oral Contraceptives, Contraceptive Patch, Contraceptive Vaginal Ring, Progestogen Implant</th>
<th>Medroxyprogesterone Acetate Depot Injection, Levonorgestrel-Releasing Intrauterine System</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carbamazepine</td>
<td>Decrease effectiveness</td>
<td>No effect</td>
</tr>
<tr>
<td>Clobazam</td>
<td>No effect</td>
<td>No effect</td>
</tr>
<tr>
<td>Eslicarbazepine</td>
<td>No effect</td>
<td>No effect</td>
</tr>
<tr>
<td>Felbamate</td>
<td>No effect</td>
<td>No effect</td>
</tr>
<tr>
<td>Lamotrigine</td>
<td>No effect</td>
<td>No effect</td>
</tr>
<tr>
<td>Oxcarbazepine</td>
<td>No effect</td>
<td>No effect</td>
</tr>
<tr>
<td>Perampanel</td>
<td>No effect</td>
<td>No effect</td>
</tr>
<tr>
<td>Phenobarbital</td>
<td>No effect</td>
<td>No effect</td>
</tr>
<tr>
<td>Phenytoin</td>
<td>No effect</td>
<td>No effect</td>
</tr>
<tr>
<td>Primidone</td>
<td>No effect</td>
<td>No effect</td>
</tr>
<tr>
<td>Rufinamide</td>
<td>No effect</td>
<td>No effect</td>
</tr>
</tbody>
</table>
| Topiramate  
* Doses > 200 mg/day. | No effect                                                                                    | No effect                                                                                   |
| Benzodiazepines             | No effect                                                                                    | No effect                                                                                   |
| Ethosuximide                | No effect                                                                                    | No effect                                                                                   |
| Gabapentin                  | No effect                                                                                    | No effect                                                                                   |
| Lacosamide                  | No effect                                                                                    | No effect                                                                                   |
| Levetiracetam               | No effect                                                                                    | No effect                                                                                   |
| Pregabalin                  | No effect                                                                                    | No effect                                                                                   |
| Tiagabine                   | No effect                                                                                    | No effect                                                                                   |
| Valproic acid               | No effect                                                                                    | No effect                                                                                   |
| Vigabatrin                  | No effect                                                                                    | No effect                                                                                   |
| Zonisamide                  | No effect                                                                                    | No effect                                                                                   |

* Doses > 200 mg/day.
E. Other Issues

1. Initiating therapy after a first seizure
   a. Guidance from the American Epilepsy Society and the American Academy of Neurology
   b. Adults with an unprovoked first seizure (e.g., not meningitis, intoxication) will have a 21%–45% chance of having more seizures within the next 2 years. Higher risks are associated with prior brain insults, EEG with epileptiform abnormalities, and nocturnal seizures.
   c. Initiating AED therapy will probably reduce recurrence risk within the first 2 years but may not increase quality of life.
   d. Initiating AED therapy early does not change the long-term risk of seizures.

2. Driving: All states place driving restrictions on people with epilepsy; some require mandatory physician reporting to the state department of transportation.

3. Medication discontinuation
   a. The following criteria can be used to determine the possibility of withdrawal from AED therapy:
      i. Patient should be seizure free for 2–5 years on seizure medication.
      ii. Patient should have a single type of partial or primary generalized tonic-clonic seizures.
      iii. Patient should have a normal neurologic examination and normal IQ.
      iv. Patient’s EEG should have become normalized with seizure medication treatment.
   b. If a drug is discontinued, it is usually tapered for several months; a typical regimen would reduce the dose by one-third for 1 month, reduce it by another one-third for 1 month, and then discontinue it.

4. Monitoring
   a. Number of seizures: The goal number of seizures is always zero.
   b. Signs of toxicity
   c. Laboratory values: Specific for each drug
   d. Blood concentrations: Available for many of the medications; commonly used for carbamazepine, phenobarbital, phenytoin, and valproic acid. The International League Against Epilepsy has a position paper on therapeutic drug monitoring, giving situations in which serum concentrations are most likely beneficial:
      i. When a person has attained the desired clinical outcome, to establish an individual therapeutic concentration that can be used subsequently to assess potential causes for a change in drug response
      ii. As an aid in diagnosing clinical toxicity
      iii. To assess adherence, particularly in patients with uncontrolled seizure or breakthrough seizures
      iv. To guide dosage adjustment in situations associated with increased pharmacokinetic variability (e.g., children, older adults, patients with associated diseases, drug formulation changes)
      v. When a potentially important pharmacokinetic change is anticipated (e.g., in pregnancy, or when an interacting drug is added or removed)
      vi. To guide dose adjustments for seizure medications with dose-dependent pharmacokinetics, particularly phenytoin

5. Sexual dysfunction
   a. Described in 30%–60% of men and women with epilepsy
   b. Includes hypososexuality, orgasmic dysfunction, and erectile dysfunction
   c. Mechanism may be induction of CYP isoenzymes to increase testosterone metabolism, increased hepatic synthesis of sex hormone–binding globulin, or induction of aromatase, which converts free testosterone to estradiol.
   d. Sexual dysfunction has been reported with carbamazepine, phenobarbital, phenytoin, pregabalin, topiramate, and zonisamide.
   e. Improved sexual functioning has been reported with lamotrigine and oxcarbazepine.
6. Bone health
   a. Osteopenia or osteoporosis is found in 38%–60% of patients in tertiary epilepsy clinics.
   b. Increased fractures in patients with epilepsy and with seizure medication use
   c. Risk is increased with increased treatment duration; there is a dose-response relationship; the medications most often associated with poor bone health are carbamazepine, clonazepam, phenobarbital, phenytoin, and valproic acid. However, there is now evidence that all seizure medications may contribute to osteopenia or osteoporosis.
   d. Proposed mechanisms: Hepatic induction of CYP isoenzymes leads to increased vitamin D catabolism, impaired calcium absorption, calcitonin deficiency, vitamin K interference, and direct harmful effects on bone cells.
   e. Proposed treatments: High-dose vitamin D (4000 international units/day for adults and 2000 international units/day for children) improves bone mineral density compared with low doses; estrogen may be helpful for women but may also trigger seizures in some women.

7. Suicidality
   a. Meta-analysis of 199 placebo-controlled clinical trials of 11 drugs (n=43,892 patients older than 5 years) showed that patients who received seizure medications had about twice the risk of suicidal behavior or ideation (0.43%) compared with patients receiving placebo (0.22%), and there were four completed suicides in the treatment group versus zero in the placebo group.
      i. Risk increased at 1 week and continued through week 24.
      ii. Patients with epilepsy (relative risk [RR] 3.6), psychiatric disorders (RR 1.6), or other conditions (RR 2.3) were all at elevated risk of suicidality; no differences between drugs; no differences between age groups
   b. The FDA requires a warning and a medication guide for all seizure medications.
   c. Recent observational studies show mixed results. When specific AEDs are examined, those most associated with depression and suicidality are levetiracetam, perampanel, phenobarbital, primidone, tiagabine, topiramate, and vigabatrin.
   d. A 2013 expert consensus statement made the following points:
      i. Although some (but not all) AEDs can be associated with treatment-emergent psychiatric problems that may lead to suicidal ideation and behavior, the actual suicidal risk has not yet been established; however, it seems to be very low. The risk of discontinuing AEDs or refusing to initiate them is significantly worse and can result in serious harm, including death to the patient.
      ii. Suicidality in epilepsy is multifactorial. Primary operant variables include postictal suicidal ideation; a history of psychiatric disorders, particularly mood and anxiety disorders (and above all, when associated with prior suicidal attempts); and a family history of mood disorder complicated by suicide attempts.
      iii. When initiating or changing AEDs, patients should be advised to report any changes in mood and suicidal ideation.
Patient Cases

Questions 1–3 pertain to the following case.
T.M. is an 18-year-old woman with newly diagnosed juvenile myoclonic epilepsy (JME). She is in good health and takes oral contraceptives.

1. Which is the best medication for T.M.’s seizures?
   A. Valproate.
   B. Phenytoin.
   C. Oxcarbazepine.
   D. Levetiracetam.

2. T.M. is concerned about the impact of levetiracetam on her oral contraceptives. Which response is best?
   A. Levetiracetam does not alter the effectiveness of your oral contraceptives.
   B. You should use alternative forms of birth control because levetiracetam decreases oral contraceptive effectiveness.
   C. You may have breakthrough bleeding, but the effectiveness of the oral contraceptive is not changed.
   D. Oral contraceptives decrease the effectiveness of levetiracetam, so you need another form of birth control.

3. Three months later, T.M.’s seizure are reduced in frequency but continue. Which would be the best alternative?
   A. Lamotrigine.
   B. Carbamazepine.
   C. Cannabidiol.
   D. Valproate.

4. J.G. is a 34-year-old patient who presents to the emergency department in status epilepticus. All of her laboratory values are normal. Which drug is best to use first?
   A. Diazepam.
   B. Lorazepam.
   C. Phenytoin.
   D. Phenobarbital.

5. S.R. is a 37-year-old patient who began taking phenytoin 100 mg 3 capsules orally at bedtime 6 months ago. He has had several seizures since then, the most recent of which occurred 7 days ago. At that time, his phenytoin serum concentration was 8 mcg/mL. The treating physician increased his phenytoin dose to 100 mg 3 capsules orally twice daily. Today, which best represents his expected serum concentration?
   A. 10 mcg/mL.
   B. 14 mcg/mL.
   C. 16 mcg/mL.
   D. 24 mcg/mL.
Patient Cases (continued)

6. S.S. is a 22-year-old woman who has always had episodes of “zoning out.” Recently, one of these episodes occurred after an examination while she was driving home. She had a noninjury accident, but it prompted a visit to a neurologist. She is given a diagnosis of absence seizures. Which drug is best to treat this type of epilepsy?
   A. Phenytoin.
   B. Valproate.
   C. Carbamazepine.
   D. Ethosuximide.

7. J.B. is a 25-year-old man with a history of seizure disorder. He has been treated with carbamazepine for 1 year, and his current carbamazepine concentration is 12 mcg/mL. Which adverse effect is J.B. most likely to have with carbamazepine at this concentration?
   A. Hepatotoxicity.
   B. Acne.
   C. Gingival hyperplasia.
   D. Diplopia.

8. M.G. has been prescribed zonisamide. On which adverse effect is it best to counsel M.G.?
   A. Hepatotoxicity.
   B. Renal stones.
   C. Alopecia.
   D. Word-finding difficulties.

Questions 9 and 10 pertain to the following case.
G.Z., a 26-year-old woman, presents with a 6-month history of “spells.” The spells are all the same, and all begin with a feeling in the abdomen that is difficult for her to describe. This feeling rises toward the head. The patient believes that she will then lose awareness. After a neurologic workup, she is given a diagnosis of focal seizures evolving to a bilateral, convulsive seizure. The neurologist is considering initiating either carbamazepine or oxcarbazepine.

9. Which is the most accurate comparison of carbamazepine and oxcarbazepine?
   A. Oxcarbazepine causes more liver enzyme induction than carbamazepine.
   B. Oxcarbazepine does not cause rash.
   C. Oxcarbazepine does not cause hyponatremia.
   D. Oxcarbazepine does not form an epoxide intermediate in its metabolism.

10. When you see G.Z. 6 months later for a follow-up, she tells you she is about 6 weeks pregnant. She has had no seizures since starting oxcarbazepine. Which strategy is best for G.Z.?
    A. Discontinue her seizure medication immediately.
    B. Change her seizure medication to topiramate.
    C. Continue her seizure medication.
    D. Change her seizure medication to phenobarbital.
II. ISCHEMIC STROKE

A. Epidemiology

1. Updated definitions
   a. Central nervous system (CNS) infarction: Brain, spinal cord, or retinal cell death attributable to ischemia, according to pathologic evidence, imaging, or other objective evidence of cerebral, spinal cord, or retinal focal ischemic injury in a defined vascular distribution, or clinical evidence of cerebral, spinal cord, or retinal focal ischemic injury, given symptoms persisting for 24 hours or more or until death, and other etiologies excluded
   b. Ischemic stroke: An episode of neurologic dysfunction caused by focal cerebral, spinal, or retinal infarction

2. Third or fourth most common cause of death in all developed countries

3. More than 795,000 cases per year in the United States (128,842 deaths)

4. Most common cause of adult disability

5. Risk factors
   a. Nonmodifiable
      i. Age: Stroke risk doubles each decade after 55 years.
      ii. Race: Risk for Native Americans is greater than for African Americans, whose risk is greater than for whites.
      iii. Sex: Risks are greater for men than for women; however, about half of strokes occur in women.
      iv. Low birth weight: Odds of stroke for those with birth weights less than 2500 g are twice as high as the odds for those weighing more than 4000 g.
      v. Family history: Parental history increases risk; some coagulopathies (e.g., protein C and S deficiencies, factor V Leiden mutations) are inherited.
   b. Somewhat modifiable: Diabetes mellitus increases risk 1.8–6 times; risk reduction has not been shown for glycemic control.
   c. Modifiable
      i. Hypertension increases risk 1.4–8 times; 32% risk reduction with control
      ii. Smoking increases risk 1.9 times; 50% risk reduction in 1 year, baseline risk at 5 years with smoking cessation; exposure to environmental cigarette smoke also increases risk
      iii. Oral contraceptives with less than 50 mcg of estrogen double the risk of stroke; those with more than 50 mcg of estrogen have a 4.5 times increased risk; risk increases with age; adding smoking to oral contraceptive use increases risk of stroke 7.2 times; obesity and hypertension also increase the risk with oral contraceptives.
      iv. Postmenopausal hormone therapy increases risk 1.4 times.
      v. Atrial fibrillation increases risk 2.6–4.5 times; 68% risk reduction with warfarin
      vi. Coronary heart disease increases risk 1.55 times (women) to 1.73 times (men).
      vii. Asymptomatic carotid stenosis increases risk 2 times; about a 50% risk reduction with endarterectomy
      viii. Dyslipidemia: High total cholesterol increases risk 1.5 times; low high-density lipoprotein cholesterol (less than 35 mg/dL) increases risk 2 times; 27%–32% risk reduction with statins in patients with coronary heart disease, hypertension, or diabetes. Twenty-five percent risk reduction with high-dose statins compared with low-dose statins
      ix. Obesity (especially abdominal body fat) increases risk 1.75–2.37 times; risk reduction with weight loss is unknown.
      x. Physical inactivity increases risk 2.7 times; risk reduction with increased activity is unknown.
      xi. Sickle cell disease increases risk 200–400 times; 91% risk reduction with transfusion therapy
      xii. Peripheral artery disease increases risk 3 times; impact of risk reduction strategies is unknown.
xiii. Pregnancy increases risk 2.4 times over nonpregnant women; the risk remains elevated for the first 6 weeks postpartum.

xiv. Patent foramen ovale increases the risk of stroke in young patients (younger than 55 years).

xv. Depression increases the risk of stroke 1.35 times compared with nondepressed people.

d. Less well documented: Alcohol abuse (5 or more drinks a day), hyperhomocystinemia, drug abuse (cocaine, amphetamines, and heroin), hypercoagulability, periodontal disease, inflammation and infection, sleep-disordered breathing (sleep apnea and snoring), metabolic syndrome, and migraine with aura

B. Primary Prevention

1. Reduction in risk factors (e.g., control of hypertension, smoking cessation, control of diabetes, cholesterol reduction)

2. Patient education: Patients should be educated about stroke warning signs and instructed to seek emergency care if they have any of them. Warning signs: Sudden numbness or weakness of the face, arm, or leg, especially on one side of the body; sudden confusion; trouble speaking or understanding; sudden trouble seeing in one or both eyes; sudden trouble walking; dizziness, loss of balance or coordination; sudden, severe headache with no known cause

3. Treatment of atrial fibrillation: Up to 70% of cases are inappropriately treated.


b. CHA2DS2-VASc is used for risk stratification.

   i. Assign 1 point each for congestive heart failure, hypertension, age 65–74 years, diabetes, vascular disease, or female sex.

   ii. Assign 2 points for previous stroke or transient ischemic attack (TIA) or age 75 or older.

   iii. Total for the CHA2DS2-VASc score

      (a) If 0, give no therapy.

      (b) If 1, give no therapy, aspirin, or oral anticoagulant.

      (c) If 2 or more, give oral anticoagulant.

c. Dabigatran (Pradaxa)

   i. When oral anticoagulation is recommended, current guidelines suggest dabigatran 150 mg twice daily over warfarin (target international normalized ratio [INR] of 2.5). Dabigatran had similar rates of hemorrhage, but intracranial hemorrhage was less likely with dabigatran, and GI hemorrhage was more likely.

   ii. Mechanism of action: Direct thrombin inhibitor

   iii. Dose: 150 mg twice daily; dose reduction needed in severe renal dysfunction

   iv. Dose reduction to 75 mg twice daily is recommended when administered with dronedarone or systemic ketoconazole in patients with a CrCl of 30–50 mL/minute/1.73 m².

   v. Avoid the use of dabigatran and P-gp inhibitors in patients with a CrCl of 15–30 mL/minute/1.73 m².

   vi. Avoid use in patients with a CrCl less than 15 mL/minute/1.73 m² or advanced liver disease.

   vii. Avoid use in patients with mechanical heart valves.

   viii. Capsule should not be opened because it increases bioavailability by 75%.

   ix. Idarucizumab (Praxbind) is a monoclonal antibody fragment used to reverse dabigatran anticoagulation.

      (a) Specific for dabigatran; can use other anticoagulants to anticoagulate patient, if needed

      (b) Dose is 5 g.

      (c) May reinitiate dabigatran in 24 hours
d. Rivaroxaban (Xarelto) is probably as effective as warfarin with a similar risk of major bleeding. Higher risk of GI bleeding and lower risk of intracranial hemorrhage and fatal bleeding.
   i. Mechanism of action: Direct factor Xa inhibitor
   ii. Dose: 20 mg/day with evening meal; dose reduction needed in renal dysfunction
   iii. Metabolized by CYP3A4/5, CYP2J2, P-gp, and ABCG2; avoid concomitant use with strong inhibitors or inducers

e. Apixaban (Eliquis) is probably more effective than warfarin, with a similar risk of stroke and less risk of bleeding and mortality.
   i. Mechanism of action: Direct, competitive factor Xa inhibitor
   ii. Dose: 5 mg twice daily; dose reduction needed in renal dysfunction
   iii. Metabolized by CYP3A4 and P-gp; reduce dose if given with inhibitors (e.g., ketoconazole, itraconazole, ritonavir, clarithromycin); avoid with strong inducers (e.g., rifampin, carbamazepine, phenytoin, St. John’s wort)

f. Warfarin (Coumadin) is probably more effective than clopidogrel plus aspirin, but intracranial bleeding is more common.
   i. INR range 2–3
   ii. Give warfarin if patient has atrial fibrillation and mitral stenosis or prosthetic heart valve.

C. Treatment of Acute Event

1. Heparin
   a. Good data on outcomes unavailable; generally not recommended for stroke treatment at therapeutic doses; increases risk of hemorrhagic transformation; heparin is often used for deep venous thrombosis prevention at a dose of 10,000–15,000 units/day given subcutaneously
   b. Avoid in hemorrhagic stroke.

2. Streptokinase: Should be avoided because of excess mortality

3. Tissue plasminogen activator (Alteplase)
   a. Within 4½ hours of symptom onset
   b. Three-month outcome significantly improved (decreased disability)
   c. Intracerebral hemorrhage increased but no increase in mortality
   d. Dose 0.9 mg/kg intravenously (maximum is 90 mg), with 10% as a bolus and the remainder over 1 hour. The bolus should be administered within 60 minutes of hospital arrival.
   e. Antiplatelet agents should be held for 24 hours after tissue plasminogen activator administration.
   f. Exclusion criteria
      i. Intracranial bleeding (or history) or subarachnoid bleeding
      ii. Other active internal bleeding
      iii. Intracranial/spinal surgery, head trauma, stroke within 3 months
      iv. Major surgery or serious trauma within 2 weeks, if risk of bleeding outweighs the anticipated benefits of reduced stroke-related neurologic deficits
      v. Gastrointestinal (GI) hemorrhage within 3 weeks or structural GI malignancy
      vi. Blood pressure greater than 185/110 mm Hg. If medications are given to lower blood pressure, blood pressure should be stabilized before beginning treatment and maintained below 180/105 mm Hg for at least the first 24 hours after treatment.
      vii. Glucose less than 50 mg/dL or greater than 400 mg/dL, unless subsequently normalized
      viii. Arterial puncture at a noncompressible site within 1 week
      ix. Intracranial intra-axial neoplasm, arteriovenous malformation, or giant unruptured and unsecured aneurysm
x. INR greater than 1.7, activated partial thromboplastin time greater than 40 seconds, prothrombin time greater than 15 seconds, platelet count less than 100,000 cells/m³, patients who have received a dose of low-molecular-weight heparin within the previous 24 hours, or patients who have taken direct thrombin inhibitors or direct factor Xa inhibitors in the previous 48 hours

xi. Infective endocarditis

xii. Pregnancy, if the anticipated benefits of treating moderate to severe stroke do not outweigh the anticipated risks of uterine bleeding

xiii. Additional criteria for the 3- to 4½-hour period have largely been abandoned. Benefit of treatment with NIH Stroke Scale greater than 25 in this time is uncertain.

4. Initiate aspirin (160- to 325-mg initial dose with a 50- to 100-mg maintenance dose) within 48 hours of stroke onset in patients not eligible for tissue plasminogen activator.

5. A stent retriever within 24 hours may be useful in select patients who have received tissue plasminogen activator.

D. Secondary Prevention

1. Reduction in all modifiable risk factors (specific changes in the text that follows according to Stroke 2014;45:2160-236)

a. Hypertension: Goal less than 140/less than 90 mm Hg. With lacunar stroke, may target less than 130 mm Hg systolic

b. Hyperlipidemia: High-intensity statin therapy should be initiated or continued as first-line therapy in women and men younger than 75 who have had stroke or TIA.

2. Carotid endarterectomy if 70%–99% stenosis. For 50%–69% stenosis, carotid endarterectomy recommendation depends on age, sex, and comorbidities; use aspirin 50–100 mg/day and statin therapy before and after the procedure.

3. Carotid angioplasty and stenting may be an alternative to carotid endarterectomy in some patients, particularly younger patients.

4. Antiplatelet therapy: Each agent has shown efficacy in reducing secondary stroke risk. Guidelines differ slightly on their recommendations. The American Stroke Association suggests that aspirin, aspirin/extended-release dipyridamole, and clopidogrel are all options after a first stroke or TIA, and the combination of aspirin and clopidogrel may be considered for initiation within 24 hours of a minor ischemic stroke or TIA or in the setting of intracranial atherosclerotic disease and continued for 90 days; however, long-term treatment increases the risk of hemorrhage. The American Association of Chest Physicians recommends clopidogrel or aspirin/dipyridamole over aspirin or cilostazol.

a. Aspirin

i. Dose: 75–100 mg/day

ii. If the patient has an additional stroke while taking aspirin, no evidence suggests increasing the aspirin dose will provide additional benefit.

b. Aspirin/dipyridamole (Aggrenox)

i. Capsule contains dipyridamole extended-release pellets (200 mg) and aspirin tablet (25 mg).

ii. Dose: 1 capsule orally twice daily

iii. Most common adverse effects: Headache, nausea, and dyspepsia; can increase liver enzymes

c. Clopidogrel (Plavix)

i. Inhibits adenosine diphosphate–induced platelet aggregation

ii. Dose: 75 mg/day orally

iii. Very low incidence of neutropenia (0.04% severe)

iv. Rarely, thrombotic thrombocytopenic purpura has been reported.
v. Partly metabolized by CYP2C19; interactions may occur with inhibitors of CYP2C19, notably proton pump inhibitors, or with genetic polymorphisms of this enzyme. The FDA has issued an alert on this topic (www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/DrugSafetyInformationforHealthcareProfessionals/ucm190787.htm).

d. Cilostazol (Pletal)
   i. Inhibits cyclic adenosine monophosphate phosphodiesterase type 3–induced platelet aggregation
   ii. Dose: 100 mg orally twice daily on an empty stomach
   iii. Metabolized extensively by CYP3A4 and CYP2C19
   iv. Adverse effects: Headache, palpitation, diarrhea, and dizziness; rarely, thrombocytopenia or agranulocytosis. Contraindicated in patients with congestive heart failure
   v. Monitoring: CBC with differential every 2 weeks for 3 months; periodically thereafter. Thus, used infrequently

5. Anticoagulation: Warfarin (Aethrombin-K, Coumadin, Jantoven, Panwarfin) or new oral anticoagulants (NOACs) (dabigatran, rivaroxaban, apixaban)
   a. Prevention of second ischemic event, if patient has atrial fibrillation (warfarin or NOAC), rheumatic mitral valve disease (warfarin), mechanical prosthetic heart valves (warfarin), bioprosthetic heart valves (warfarin), or left ventricular mural thrombus formation (warfarin)
   b. Target INR: 2.5 with warfarin (3.0 for mechanical prosthetic heart valves)

Patient Cases

*Questions 11–13 pertain to the following case.*

L.R. is a 78-year-old woman who presents to the emergency department for symptoms of right-sided paralysis. She states that these symptoms began about 3 hours ago and have not improved since then. She also has hypertension, breast cancer, diabetes mellitus, minimal cognitive impairment, and osteoarthritis.

11. Which is the most accurate list of L.R.’s risk factors for stroke?
   A. Breast cancer, age, osteoarthritis.
   B. Sex, diabetes mellitus, osteoarthritis.
   C. Minimal cognitive impairment, diabetes mellitus, age, sex.
   D. Age, diabetes mellitus, hypertension.

12. Which best describes whether L.R. is a candidate for tissue plasminogen activator for the treatment of stroke?
   A. Yes.
   B. No, she is too old.
   C. No, her stroke symptoms began too long ago.
   D. No, her breast cancer is a contraindication for tissue plasminogen activator.

13. L.R. previously took no drugs at home. Which choice is the best secondary stroke prevention therapy at this time for her?
   A. Metformin and aspirin.
   B. Celecoxib and clopidogrel.
   C. Aspirin and clopidogrel.
   D. Warfarin.
Patient Cases (continued)

14. As the pharmacist at a community pharmacy, you receive a call from M.W., a 58-year-old man recently given a diagnosis of atrial fibrillation. He is concerned about his risk of a stroke because his friend, who also has atrial fibrillation, asked him which dose of apixaban he is taking. M.W. called you because he is not taking apixaban and wants to know whether he should. He has no other medical conditions and takes atenolol 50 mg/day orally for ventricular rate control. After encouraging M.W. to discuss this with his physician, which best depicts what you should you tell him?

A. You need apixaban treatment to prevent a stroke.
B. You do not need apixaban, but you should take aspirin and clopidogrel.
C. You do not need drug therapy at this time.
D. Because you have atrial fibrillation, nothing can reduce your risk of stroke.

15. L.S. is a 42-year-old woman with a medical history of hypertension, type 2 diabetes, renal failure, and mitral valve replacement. She presents to the anticoagulation clinic for her initial visit. Which best reflects her target INR?

A. 1.5.
B. 2.0.
C. 2.5.
D. 3.0.

III. PARKINSON DISEASE

A. Epidemiology
   1. Prevalence is 160 in 100,000.
   2. Onset is usually at 40–70 years of age, with peak onset in sixth decade.
   3. Slightly more common in men
   4. Observed in all countries, ethnic groups, and socioeconomic classes

B. Signs and Symptoms
   1. Cardinal signs
      a. Akinesia or hypokinesia
      b. Rigidity
      c. Tremor
      d. Posture or gait abnormalities
   2. Secondary signs
      a. Cognitive dysfunction
      b. Autonomic dysfunction
      c. Speech disturbances
      d. Micrographia
      e. Masked facies
C. Treatment

1. General treatment principles

   a. No treatment has unequivocally been shown to prevent the progression of Parkinson disease; therefore, treatment is based on symptoms.

   b. In patients who need the initiation of dopaminergic treatment, either levodopa or a dopamine agonist may be used. Choice depends on the relative impact of improving motor disability (better with levodopa) compared with the lessening of motor complications (better with dopamine agonists) for each patient.

   c. Treatment may be initiated with rasagiline as well, but the effects are not robust.

   d. Treatment with several different classes of medications simultaneously is common.

2. Medications

   a. Monoamine oxidase type B (MAO-B) inhibitors

      i. Selegiline (Eldepryl, Zelapar)

         (a) Loses selectivity for MAO-B at doses greater than 10 mg/day

         (b) Contraindicated with meperidine because of serotonin syndrome risk

         (c) Dose: 5 mg orally twice daily (tablets; usually morning and noon); 1.25–2.5 mg/day (orally disintegrating tablets)

         (d) Adverse effects: Nausea, hallucinations, orthostatic hypotension, insomnia (metabolized to amphetamine)

         (e) Dosage forms: Tablets, orally dissolving tablets, and patches. The patches are FDA indicated for depression; they should not usually be used for Parkinson disease.

      ii. Rasagiline (Azilect)

         (a) Selectivity for MAO-B has not been definitively established.

         (1) Contraindicated with meperidine because of serotonin syndrome risk

         (2) Do not administer with tramadol, methadone, dextromethorphan, sympathomimetics, fluoxetine, or fluvoxamine because of serotonin syndrome risk.

         (3) Ciprofloxacin can double the concentration of rasagiline (through CYP1A2 inhibition).

         (b) Dose: 0.5–1 mg/day orally

      iii. Safinamide (Xadago)

         (a) Highly selective MAO-B inhibitor

         (b) Dose 50–100 mg daily

         (c) Reduce dose in hepatic failure (Child-Pugh class C)

         (d) Adverse effects and drug interactions similar to other MAO-B inhibitors

   b. Levodopa

      i. Improvement in disability and possibly mortality

      ii. Greatest effect on bradykinesia and rigidity; less effect on tremor and postural instability

   c. Carbidopa

      i. Combined in fixed ratios with levodopa

      ii. Prevents some of the peripheral conversion of levodopa to dopamine by inhibiting peripheral dopamine decarboxylase; therefore, levodopa is available to cross the blood-brain barrier

      iii. 75 mg/day is usually needed to inhibit peripheral decarboxylase activity.

   d. Carbidopa/levodopa (Carbilev, Parcopa, Sinemet)

      i. Pharmacokinetic considerations

         (a) High-protein diets decrease absorption.

         (b) Immediate-release half-life 60–90 minutes

         (c) Orally disintegrating tablet available; not absorbed sublingually

         (d) Slow-release considerations: Fewer daily doses; less plasma fluctuations; delay to effect; cannot crush; can divide. No measurable effect on “freezing”
ii. Acute adverse effects: Nausea and vomiting, orthostatic hypotension, cardiac arrhythmias, confusion, agitation, hallucinations

iii. Long-term adverse effects: Wearing-off and on-off phenomena, involuntary movements (dyskinesias)
   (a) Wearing-off phenomenon is the return of Parkinson disease symptoms before the next dose. Treatment of wearing-off includes adding a dopamine agonist, adding a MAO-B inhibitor, adding a catechol-O-methyl transferase inhibitor, or increasing the frequency or dose of levodopa.
   (b) On-off phenomenon is a profound, unpredictable return of Parkinson disease symptoms without respect to the dosing interval. Treatment of on-off includes adding entacapone, rasagiline, pramipexole, ropinirole, apomorphine, or selegiline or redistributing dietary protein.
   (c) Dyskinesias are drug-induced involuntary movements including chorea and dystonia. Treatment of dyskinesias includes decreasing the levodopa dose or adding amantadine as an antidyskinetic drug.

iv. Therapy initiation
   (a) Standard formulation: 25 mg/100 mg 1 tablet orally three times daily; also available as orally disintegrating tablet
   (b) Controlled-release formulation: 1 tablet orally two or three times daily
   (c) Titration always necessary
   (d) A combination of formulations may be needed (e.g., ½ tablet of Sinemet 25 mg/100 mg on awakening and 1 tablet of Sinemet CR 25/100 three times daily).

e. Direct dopamine agonists
   i. Drugs: Apomorphine (Apokyn), bromocriptine (Parlodel), pramipexole (Mirapex), ropinirole (Requip), rotigotine (Neupro)
   ii. Bromocriptine is an ergot-derived product: Very rarely, adverse effects such as retroperitoneal, pleuropulmonary, or cardiac fibrosis have been attributed to it; regular ECG monitoring is recommended.
   iii. Rotigotine is a transdermal system. With the initial formulation, problems occurred with crystallization of the medication. The product was withdrawn from the market and has since been reformulated. Rotigotine is currently available.
   iv. Dosing: Always titrate to final dose (Table 7).

<table>
<thead>
<tr>
<th>Agent</th>
<th>Usual Dosage Range (mg/day)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bromocriptine</td>
<td>5–40</td>
</tr>
<tr>
<td>Pramipexole</td>
<td>1.5–4.5</td>
</tr>
<tr>
<td>Ropinirole</td>
<td>0.75–24</td>
</tr>
<tr>
<td>Rotigotine</td>
<td>6–8</td>
</tr>
</tbody>
</table>

v. Adverse effects: Nausea, vomiting, postural hypotension, hallucinations, impulsive behaviors (e.g., hypersexuality, gambling, shopping, eating), falling asleep during activities of daily living

vi. Pramipexole and ropinirole also have FDA indications for restless legs syndrome.

vii. Ropinirole and pramipexole are available as extended-release formulations.
viii. Apomorphine: Short-acting dopamine receptor agonist
   (a) Indication: Acute, intermittent treatment of “off” episodes associated with advanced Parkinson disease
   (b) Contraindications: Its use with 5-hydroxytryptamine-3 antagonists (ondansetron, granisetron, dolasetron, palonosetron, and alosetron) causes profound hypotension, sulfite sensitivity, or allergy.
   (c) Pharmacokinetics: When given orally, poorly bioavailable and extensive first-pass metabolism; used as subcutaneous injection in a pen self-injector
   (d) Adverse effects
      (1) Severe nausea and vomiting
         (A) Treat with trimethobenzamide 300 mg three times daily for 3 days before initiating treatment and for at least 6 weeks during treatment.
         (B) About 50% of patients can discontinue trimethobenzamide after 2 months.
         (C) Thirty-one percent of patients had nausea and 11% had vomiting with trimethobenzamide.
      (2) Hypotension
      (3) Hallucinations
      (4) Injection site reactions
      (5) Dyskinesias
   (e) Dosing
      (1) Must be titrated in a setting where blood pressure can be monitored
      (2) In the “off” state, the patient should be given a 0.2-mL (2 mg) test dose.
      (3) Supine and standing blood pressure taken before dose; 20, 40, and 60 minutes after dose
      (4) If tolerated, begin with a 0.2-mL dose as needed; increase by 0.1 mL, if necessary.
      (5) Doses greater than 0.6 mL, more than five times daily, or greater than 20 mg/day have limited experience.
      (6) If first dose is ineffective, do not re-dose.
      (7) If patients do not dose for more than 1 week, reinitiate at a 0.2-mL dose.

f. Anticholinergics
   i. Drugs: Trihexyphenidyl (Artane), benztropine (Cogentin)
   ii. Useful only for tremor
   iii. Initial dosing
      (a) Trihexyphenidyl 0.5 mg 1 tablet orally twice daily
      (b) Benztropine 0.5 mg 1 tablet orally twice daily
   iv. Adverse effects: Dry mouth, urinary retention, dry eyes, constipation, confusion

g. Amantadine (Symmetrel)
   i. Has symptomatic benefits and may reduce dyskinesias caused by levodopa or dopamine agonists
   ii. Dosing: 100 mg 1 tablet orally two or three times daily; caution in renal dysfunction
   iii. Adverse effects: Dizziness, insomnia, anxiety, livedo reticularis, nausea, nightmares

h. Catechol-O-methyl transferase inhibitors
   i. Prevent breakdown of dopamine, more levodopa available to cross blood-brain barrier
   ii. Tolcapone (Tasmar): Severely restricted because of hepatotoxicity; must sign consent form
iii. Entacapone (Comtan)
   (a) Increased area under the curve, increased half-life; no change in Cmax or Tmax of levodopa
   (b) Dosing: 1 tablet with each carbidopa/levodopa dose; maximum of eight times daily; one dosage form (Stalevo) includes carbidopa, levodopa, and entacapone 200 mg
   (c) Must use with carbidopa/levodopa
   (d) Adverse effects: Dyskinesias, nausea, diarrhea (may be delayed for up to 2 weeks after initiation or dose increase), urine discoloration (orange), hallucinations or vivid dreams

3. Surgery: Several types of surgery are done for Parkinson disease.
   a. Thalamotomy: Ablation of portions of the thalamus to control tremor
   b. Pallidotomy: Ablation of structures in the globus pallidus for the treatment of Parkinson disease
   c. Fetal transplants: Transplantation of dopaminergic tissue into the striatum; considered experimental
   d. Trophic factors: Glial-derived nerve growth factor and neurturin have been delivered directly to the striatum or substantia nigra; considered experimental
   e. Deep brain stimulation
      i. Most common surgery for Parkinson disease
      ii. Thought to stimulate areas of the basal ganglia to reversibly block the neuronal activity in the area
      iii. Patient selection focuses on patients with
         (a) Motor fluctuations or dyskinesias that are not adequately controlled with optimized medical therapy
         (b) Medication-refractory tremor
         (c) Intolerance of medical therapy
         (d) Some centers will not do the surgery in patients older than 70.
   iv. Two areas are targeted.
      (a) Globus pallidum
         (1) Reduces off-time
         (2) Reduces dyskinesias
         (3) Thought to have fewer cognitive adverse effects than subthalamic nucleus stimulation
      (b) Subthalamic nucleus
         (1) Reduces off-time
         (2) Reduces dyskinesias
         (3) Thought to be more effective than globus pallidum stimulation

4. Special situations
   a. Hallucinations or psychosis may be caused by either Parkinson disease or treatment.
      i. Discontinue or reduce Parkinson disease medications as tolerated.
      ii. If an antipsychotic is needed, use quetiapine or clozapine as the first choice.
      iii. Pimavanserin FDA approved for Parkinson disease psychotic disorder
      iv. Avoid typical antipsychotics, risperidone, and olanzapine because they may worsen Parkinson symptoms.
   b. Cognitive disorders
      i. Discontinue or reduce Parkinson disease medications as tolerated.
      ii. Rivastigmine has an FDA indication for treatment; other cholinesterase inhibitors may have efficacy.
   c. Sleep disorders, depression, agitation, anxiety, constipation, orthostatic hypotension, seborrhea, blepharitis, and restless legs syndrome can occur in Parkinson disease; treat as usual.
Questions 16 and 17 pertain to the following case.
L.S. takes carbidopa/levodopa 25 mg/100 mg orally four times daily and trihexyphenidyl 2 mg orally three times daily for Parkinson disease. L.S.’s wife reports that his movements are very slow and that he is having trouble walking.

16. Given these symptoms, which change seems most reasonable?
   A. Increase carbidopa/levodopa, discontinue trihexyphenidyl.
   B. Continue carbidopa/levodopa, increase trihexyphenidyl.
   C. Decrease carbidopa/levodopa, continue trihexyphenidyl.
   D. Decrease carbidopa/levodopa, increase trihexyphenidyl.

17. Six months later, L.S. returns to the clinic concerned that his carbidopa/levodopa dose is wearing off before his next dose is due, because his tremor and slow movements are worse before the next dose of carbidopa/levodopa. Which recommendation is best?
   A. Increase the carbidopa/levodopa dose.
   B. Decrease the carbidopa/levodopa dose.
   C. Increase the dosing interval.
   D. Decrease the dosing interval.

18. P.J. is a 57-year-old man with an 8-year history of Parkinson disease. His current drugs include carbidopa/levodopa 50 mg/200 mg orally four times daily, entacapone 200 mg orally four times daily, and amantadine 100 mg three times daily. He presents to the clinic with a reddish blue discoloration on his lower arms and legs. Which, if any, of his drugs most likely caused this condition?
   A. Carbidopa/levodopa.
   B. Entacapone.
   C. Amantadine.
   D. None; probably represents venous stasis.

19. L.L. is a 47-year-old man with Parkinson disease. He takes carbidopa/levodopa 50 mg/200 mg orally four times daily. He recently noticed an involuntary twitching movement of his left foot. Which is the best therapy for L.L.’s dyskinesia?
   A. Add ropinirole.
   B. Add selegiline.
   C. Increase the carbidopa/levodopa dose.
   D. Decrease the carbidopa/levodopa dose.
Patient Cases (continued)

20. C.A. is a 70-year-old white man with tremors in his right hand that have progressively worsened for the past 6 months. He has difficulty walking. He also has backaches and no longer plays golf. In addition, he is losing his sense of taste. His wife notes that he is moving more slowly and that his handwriting has deteriorated. He is given a diagnosis of Parkinson disease. Which is the best treatment for this man?
A. Trihexyphenidyl.
B. Entacapone.
C. Carbidopa/levodopa.
D. Ropinirole.

IV. HEADACHE

A. Definitions
1. Classic migraine: At least two attacks with at least three of the following: One or more fully reversible aura symptoms, at least one aura symptom for more than 4 minutes, or two or more symptoms occurring in succession; no single aura symptom lasts more than 60 minutes; headache follows aura within 60 minutes
2. Migraine without aura: At least five attacks of headache lasting 4–72 hours with at least two of the following: Unilateral location, pulsating quality, intensity moderate or severe, aggravation by walking stairs or similar routine physical activity. During headache, at least one of the following: Nausea or vomiting, photophobia, phonophobia
3. Tension: At least 10 previous headaches, each lasting from 30 minutes to 7 days, with at least two of the following: Pressing or tightening (nonpulsating) quality, intensity mild to moderate, bilateral location, no aggravation with physical activity
4. Cluster: Several episodes, short-lived but severe, of unilateral, orbital, supraorbital, or temporal pain. At least one of the following must occur: Conjunctival injection, lacrimation, nasal congestion, rhinorrhea, facial sweating, miosis, ptosis, or eyelid edema.
5. Analgesic rebound headache: If patients use analgesics often (usually defined as more than three times weekly), they may develop analgesic rebound headache. Patients with this condition usually present with a chronic daily headache, for which they take simple or narcotic analgesics. Treatment consists of the withdrawal of all analgesics (but not prophylactic medications).

B. Epidemiology
1. Migraine: 15%–17% of women, 5% of men
2. Tension: 88% of women, 69% of men
3. Cluster: 0.01%–1.5% of population; ratio of men to women is 6:1

C. Treatment
1. Migraine
   a. Prophylaxis should be considered if any of the following criteria are met: Migraines are recurrent and interfere with daily routine, migraines are frequent, patient has inefficacy or inability to use acute therapy, patient prefers prophylaxis as therapy, cost of acute medications is problematic, adverse effects with acute therapies occur, or migraine presentation is uncommon.
i. General principles
   (a) Use lowest effective dose.
   (b) Give adequate trial (2–3 months).
   (c) If the patient has a coexisting condition, consider prophylaxis choice (e.g., β-blockers are contraindicated in patients with asthma but beneficial in patients with hypertension).

ii. Medications with established efficacy
   (a) Frovatriptan (for menstrually associated migraine, short-term prophylaxis only)
   (b) Metoprolol
   (c) Onabotulinum toxin A
   (d) Petasites (butterbur extract)
   (e) Propranolol
   (f) Timolol
   (g) Topiramate
   (h) Valproic acid

iii. Medications with probable efficacy
   (a) Amitriptyline
   (b) Atenolol
   (c) Fenoprofen
   (d) Histamine, subcutaneous
   (e) Ibuprofen
   (f) Ketoprofen
   (g) Magnesium
   (h) MIG-99 (feverfew extract)
   (i) Nadolol
   (j) Naproxen/naproxen sodium
   (k) Naratriptan (for menstrually associated migraine, short-term prophylaxis only)
   (l) Riboflavin
   (m) Venlafaxine
   (n) Zolmitriptan (for menstrually associated migraine, short-term prophylaxis only)

iv. Medications with possible efficacy
   (a) Candesartan
   (b) Carbamazepine
   (c) Clonidine
   (d) Coenzyme O₁₀
   (e) Cyproheptadine
   (f) Estrogen
   (g) Flurbiprofen
   (h) Guanfacine
   (i) Lisinopril
   (j) Mefenamic acid
   (k) Nebivolol
   (l) Pindolol

v. Medications with conflicting or inadequate evidence of efficacy: Acetazolamide, aspirin, bisoprolol, fluoxetine, fluvoxamine, gabapentin, hyperbaric oxygen, indomethacin, nicardipine, nifedipine, nimodipine, omega-3, protriptyline, verapamil

vi. Medications that are possibly ineffective, probably ineffective, or ineffective: Acebutolol, botulinum toxin, clomipramine, clonazepam, lamotrigine, montelukast, nabumetone, oxcarbazepine, telmisartan
vii. Calcitonin gene-related peptide antagonists are highly effective in refractory migraine headache prophylaxis
   (a) Erenumab-aooe (Aimovig): Dose: 70–140 mg subcutaneously monthly
   (b) Fremanezumab-vfrm (Ajovy): Dose: 225 mg subcutaneously monthly or 675 mg subcutaneously quarterly (administered as three separate injections)
   (c) Galcanezumab-gnlm (Emgality): Dose: Two consecutive doses of 120 mg subcutaneously for a total of a 240-mg loading dose, followed by doses of 120 mg subcutaneously monthly

b. Acute treatment
   i. Triptans (Table 8)
      (a) Sumatriptan and zolmitriptan have nonoral administration routes (subcutaneous [sumatriptan], intranasal [sumatriptan and zolmitriptan], transdermal [sumatriptan]) that should be considered for patients with nausea or vomiting.
      (b) Orally disintegrating tablets are available for zolmitriptan and rizatriptan if patients do not have access to water; however, they do not work faster than oral tablets and are not absorbed sublingually.
      (c) All are contraindicated in patients with or at risk of coronary artery disease, stroke, uncontrolled hypertension, peripheral vascular disease, ischemic bowel disease, and pregnancy; they should not be used in patients with hemiplegic or basilar migraines.
      (d) Drug interactions: Contraindicated within 2 weeks of MAO inhibitors; do not use within 24 hours of ergotamines; caution with other serotonin-active medications. Propranolol increases serum concentrations of rizatriptan; thus, a 5-mg dose should be used with propranolol, and the dose should not exceed 15 mg/day.
   ii. Ergots
      (a) Dihydroergotamine has nonoral administration routes (subcutaneous, intravenous, and intranasal) that should be considered for patients with nausea or vomiting.
      (b) All are contraindicated in patients with, or at risk of, coronary artery disease, stroke, uncontrolled hypertension, peripheral vascular disease, ischemic bowel disease, and pregnancy; they should not be used in patients with hemiplegic or basilar migraines.
   iii. Nonsteroidal anti-inflammatory drugs (NSAIDs): Usually effective for only mild to moderate headache pain
   iv. Opioids: Butorphanol has a nonoral administration route (intranasal) that should be considered for patients with nausea or vomiting.
   v. Isomethetene combination products: Conflicting evidence about efficacy
   vi. Antiemetics: Prochlorperazine, metoclopramide, and chlorpromazine are most commonly used; there is suggestion that they have independent antimigraine action; all are available in nonoral forms.
   vii. Status migrainosus: Attack of migraine, with headache phase lasting more than 72 hours despite treatment. Headache-free intervals of less than 4 hours (sleep not included) may occur.
      (a) Corticosteroids: Either intravenous or oral dosing
      (b) Dihydroergotamine: Intravenous dosing
      (c) Sodium valproate: Intravenous loading

2. Tension
   a. Prophylaxis
      i. Tricyclic antidepressants
      ii. Botulinum toxin
   b. Acute treatment
      i. Acetaminophen
      ii. NSAIDs
3. Cluster  
   a. Prophylaxis  
      i. Verapamil  
      ii. Melatonin  
      iii. Suboccipital injection of betamethasone  
      iv. Lithium: May be efficacious at serum concentrations as low as 0.3 mmol/L  
   b. Treatment  
      i. Triptans: Subcutaneous and intranasal sumatriptan and intranasal zolmitriptan are effective. Oral formulations usually do not act quickly enough, but oral zolmitriptan showed efficacy in one trial.  
      ii. Oxygen: 100% oxygen at 6–12 L/minute relieves pain in 50%–85% of patients.  
      iii. Intranasal lidocaine: 20–60 mg as a nasal drop or spray (must be compounded)  
      iv. Octreotide and 10% cocaine have been used with some effect.

Table 8. Selected Agents for Migraine Headache

<table>
<thead>
<tr>
<th>Triptans</th>
<th>Dosage Forms</th>
<th>Tmax</th>
<th>Half-Life (hr)</th>
<th>Dose</th>
<th>Maximal Dose/24 Hr (mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Almotriptan (Axert)</td>
<td>Tablets 6.25 mg, 12.5 mg</td>
<td>1–3 hr</td>
<td>2–4</td>
<td>1 tablet, may repeat in 2 hr</td>
<td>25</td>
</tr>
<tr>
<td>Eletriptan (Relpax)</td>
<td>Tablets 20 mg, 40 mg</td>
<td>1 hr</td>
<td>4–5</td>
<td>1 tablet, may repeat in 2 hr</td>
<td>80</td>
</tr>
<tr>
<td>Frovatriptan (Frova)</td>
<td>Tablets 2.5 mg</td>
<td>2–4 hr</td>
<td>26</td>
<td>1 tablet, may repeat in 2 hr</td>
<td>7.5</td>
</tr>
<tr>
<td>Naratriptan (Amerge)</td>
<td>Tablets 1 mg, 2.5 mg</td>
<td>2–3 hr</td>
<td>6</td>
<td>1 tablet, may repeat in 4 hr</td>
<td>5</td>
</tr>
<tr>
<td>Rizatriptan (Maxalt)</td>
<td>Tablets 5 mg, 10 mg</td>
<td>1–1.5 hr</td>
<td>1.8</td>
<td>1 tablet, may repeat in 2 hr</td>
<td>30</td>
</tr>
<tr>
<td></td>
<td>Orally disintegrating tablets 5 mg, 10 mg</td>
<td>1.6–2.5 hr</td>
<td>1.8</td>
<td>1 tablet, may repeat in 2 hr</td>
<td>30</td>
</tr>
<tr>
<td>Sumatriptan (Alsuma, Imitrex, Sumavel, Zecuity)</td>
<td>SC injection 4 mg, 6 mg</td>
<td>12 min</td>
<td>1.9</td>
<td>1 injection, may repeat in 1 hr</td>
<td>12</td>
</tr>
<tr>
<td></td>
<td>Intranasal 5 mg, 20 mg</td>
<td>30 min</td>
<td>2</td>
<td>1 spray in one nostril, may repeat in 2 hr</td>
<td>40</td>
</tr>
<tr>
<td></td>
<td>Tablets 25 mg, 50 mg, 100 mg</td>
<td>2 hr</td>
<td>2.5</td>
<td>1 tablet, may repeat in 2 hr</td>
<td>200</td>
</tr>
<tr>
<td></td>
<td>Iontophoretic transdermal system 6.5 mg/4 hr</td>
<td>1.1 hr</td>
<td>3.1</td>
<td>1 patch, may repeat in 2 hr</td>
<td>13</td>
</tr>
<tr>
<td>Zolmitriptan (Zomig)</td>
<td>Tablets 2.5 mg, 5 mg</td>
<td>1.5 hr</td>
<td>3.75</td>
<td>1 tablet, may repeat in 2 hr</td>
<td>10</td>
</tr>
<tr>
<td></td>
<td>Orally disintegrating tablets 2.5 mg, 5 mg</td>
<td>3 hr</td>
<td>3.75</td>
<td>1 tablet, may repeat in 2 hr</td>
<td>10</td>
</tr>
<tr>
<td></td>
<td>Intranasal 2.5 mg, 5 mg</td>
<td>3 hr</td>
<td>3</td>
<td>1 spray in one nostril, may repeat in 2 hr</td>
<td>10</td>
</tr>
</tbody>
</table>

IM = intramuscular(ly); IV = intravenous(ly); SC = subcutaneous(ly).
### Table 8. Selected Agents for Migraine Headache (continued)

<table>
<thead>
<tr>
<th>Dosage Forms</th>
<th>Tmax</th>
<th>Half-Life (hr)</th>
<th>Dose</th>
<th>Maximal Dose/24 Hr (mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Triptan/NSAID combination</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sumatriptan/naproxen sodium (Treximet)</td>
<td>Tablets 85 mg/500 mg</td>
<td>1 hr/5 hr</td>
<td>2/19</td>
<td>1 tablet, may repeat in 2 hr</td>
</tr>
<tr>
<td>Ergots</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ergotamine tartrate (Ergomar)</td>
<td>Sublingual tablets 2 mg</td>
<td>Unknown</td>
<td>2</td>
<td>1 tablet under tongue, may repeat in 1 hr</td>
</tr>
<tr>
<td>Dihydroergotamine (DHE 45; Migranal)</td>
<td>Intranasal 4-mg ampules</td>
<td>0.9 hr</td>
<td>10</td>
<td>1 spray (0.5 mg) in each nostril, repeat in 15 min</td>
</tr>
<tr>
<td></td>
<td>IV/IM/SC 1 mg/ mL 1-mL vials</td>
<td>SC 15–45 min</td>
<td>9</td>
<td>1 mL IV/IM/SC, may repeat in 1 hr</td>
</tr>
</tbody>
</table>

IM = intramuscular(ly); IV = intravenous(ly); SC = subcutaneous(ly).

### Patient Cases

21. M.R., a 34-year-old woman, has throbbing right-sided headaches. She has nausea, sonophobia, and photophobia with these headaches but no aura. She usually has headaches twice a month. She has hypertension and morbid obesity. She takes an ethinyl estradiol/progestin combination oral contraceptive daily and hydrochlorothiazide 25 mg/day orally. She has a diagnosis of migraine headaches. Which drug is best for prophylaxis of her headaches?
   A. Propranolol.
   B. Valproate.
   C. Topiramate.
   D. Sumatriptan.

22. S.R. is a 54-year-old businessman with squeezing, band-like headaches that occur three or four times weekly. He rates the pain of these headaches as 7/10 and finds acetaminophen, aspirin, ibuprofen, naproxen, ketoprofen, and piroxicam only partly effective. He wants to take a prophylactic drug to prevent these tension headaches. Which drug is best for prophylaxis of his headaches?
   A. Propranolol.
   B. Valproate.
   C. Amitriptyline.
   D. Lithium.

23. D.S. is a 49-year-old male computer programmer who describes lancinating right-eye pain and tearing several times a day for 2–3 days in a row. He will have no episodes for 2–3 weeks but then will have recurrent episodes. In the office, he receives oxygen by nasal cannula during an episode, and his pain is relieved. He has a diagnosis of cluster headaches. Which drug is best for prophylaxis of his headaches?
   A. Atenolol.
   B. Valproate.
   C. Nortriptyline.
   D. Lithium.
Patient Cases (continued)
24. M.K. is a 44-year-old woman with right-sided headaches of moderate intensity that are accompanied by severe nausea and vomiting. Which drug is best for M.K.’s migraine headaches?
   A. Almotriptan.
   B. Naratriptan.
   C. Promethazine.
   D. Sumatriptan.

25. T.C. is a 30-year-old woman with migraine headaches. She takes sumatriptan 100 mg, which provides immediate relief. However, about 2 hours later, her headache symptoms return. Which would be best for her?
   A. Eletriptan 20 mg.
   B. Frovatriptan 2.5 mg.
   C. Naproxen 250 mg.
   D. Topiramate 25 mg.

V. MULTIPLE SCLEROSIS

A. Definitions
   1. Autoimmune disorder with areas of CNS demyelination and axonal transaction
   2. Clinical course
      a. Clinically isolated syndrome; first clinical presentation for which the criterion of dissemination in time has not been met to diagnose MS
      b. Classified as relapsing or progressive disease; subclassified according to disease activity and progression: Relapsing-remitting: 85% of patients at diagnosis, develops into progressive disease in 50% of patients within 10 years

B. Epidemiology
   1. Diagnosis is usually at 20–50 years of age.
   2. Twice as many women as men develop MS.
   3. Whites and people of northern European heritage are more likely to develop MS.
   4. Risk factors: Family history of MS, autoimmune disease, or migraine; personal history of autoimmune disease or migraine; cigarette smoke exposure (women only)

C. Treatment
   1. Acute relapses are treated with corticosteroids.
      a. Intravenous methylprednisolone: Usual dose is 1 g/day as one dose or as divided doses for 3–5 days.
      b. Oral prednisone: Usual dose is 1250 mg/day given every other day for five doses.
      c. Intravenous adrenocorticotropic hormone
      d. Neurologic recovery is the same with or without an oral prednisone taper.
   2. Disease-modifying therapies (Table 9)
      a. Alemtuzumab (Lemtrada)
         i. Mechanism of action: Binds to CD52, a cell surface antigen on T cells, B cells, natural killer cells, monocytes, and macrophages; causes lysis of T and B cells
ii.  Adverse effects
   (a)  Autoimmunity including thyroid disorders (34%), immune thrombocytopenia, glomerular nephropathies
   (b)  Infusion reactions (e.g., anaphylaxis, angioedema, bronchospasms, nausea, urticaria) occur in up to 92% of patients and necessitate corticosteroids during treatment.
   (c)  Increased infections: Screen for herpes zoster and immunize, if needed; screen for tuberculosis before initiating therapy; prophylaxis for herpes infections is necessary during treatment.
   (d)  May increase risk of thyroid cancer, melanoma, and lymphoma
   (e)  Administered only under a restricted distribution program

iii.  Avoid live virus vaccines during treatment; complete all vaccines 6 weeks before initiating therapy.

b.  β-Interferons (Avonex, Betaseron, Extavia, Plegridy, Rebif)
   i.  Mechanism of action: Suppress T-cell activity, down-regulate antigen presentation by major histocompatibility complex class II molecules, decrease adhesion molecules and matrix metalloproteinase 9, increase anti-inflammatory cytokines, and decrease inflammatory cytokines
   ii.  Adding polyethylene glycol to interferon-β1a decreases the frequency of injections.
   iii.  Injection site reactions: More common in subcutaneously administered products. May help to bring a drug to room temperature before injection, ice the injection site, and rotate injection sites
   iv.  Flu-like symptoms: Usually dissipate in 2–3 months. May help to inject the dose in the evening. Begin at the 0.25- to 0.5-mg dose and slowly increase, and use ibuprofen or acetaminophen.
   v.  Neutralizing antibodies: Develop in some patients 6–18 months after treatment begins; frequency and administration route affect neutralizing antibody development; relapse rates are higher in patients with persistently high antibody titers; antibodies may disappear even during continued treatment; show cross-reactivity with other β-interferons

c.  Dimethyl fumarate (Tecfidera)
   i.  Mechanism of action: Antioxidant and cytoprotective; inhibits proinflammatory cytokines, increases anti-inflammatory cytokines
   ii.  Adverse effects
      (a)  Skin flushing: Occurs in up to 38% of patients, usually within 30–45 minutes of dosing; involves the face, chest, and neck; dissipates after 15–30 minutes; peaks within first month of therapy and decreases thereafter; aspirin may block flushing, taking with food helps prevent
      (b)  GI events: Occur in up to 41% of patients; peak within first month of therapy and decrease thereafter
      (c)  Lymphocytes decrease by 30% in the first year of therapy and then stabilize.

d.  Glatiramer acetate (Copaxone)
   i.  Mechanism of action: Decreases type 1 helper T cells; increases type 2 helper T cells; increases production of nerve growth factors
   ii.  Injection site reactions: Icing the site before and after injection may help.
   iii.  Systemic reactions: May involve flushing, chest tightness, palpitations, anxiety, and shortness of breath; this is noncardiac; recurrence is infrequent

e.  Fingolimod (Gilenya)
   i.  Mechanism of action: Binds to the S1P receptor 1 expressed on T cells, prevents activation of T cells
   ii.  Indicated for patients older than 10 years
iii. Contraindicated in patients with myocardial infarctions, unstable angina, stroke, TIAs, or decompensated heart failure necessitating hospitalization or class III/IV heart failure, history of Mobitz type II second- or third-degree atrioventricular block or sick sinus syndrome unless patient has a pacemaker, baseline QTc interval greater than or equal to 500 milliseconds, or treatment with class Ia or class III antiarrhythmic drugs

iv. Patients must be monitored for bradycardia for 6 hours after the first dose; if therapy is discontinued for more than 2 weeks, patients must be re-monitored.

v. Adverse effects
   (a) Bradycardia: ECG is recommended within 6 months for patients using antiarrhythmics (including β-blockers and calcium channel blockers), those with cardiac risk factors, and those with slow or irregular heartbeat. Heart rate returns to baseline within 1 month of continued dosing.
   (b) Atrioventricular conduction delays: First- and second-degree block
   (c) Decrease in lymphocytes: A recent CBC should be available before therapy begins. Infections may be more common. Discontinue therapy for serious infections; test patients without varicella zoster vaccine or infection history for varicella zoster virus antibodies, and immunize antibody-negative patients (wait 1 month to initiate fingolimod).
   (d) Macular edema: Ophthalmologic evaluation at baseline and 3–4 months after fingolimod initiation; a history of uveitis or diabetes mellitus increases risk
   (e) Respiratory effects: Decreases in forced expiratory volume over 1 second and diffusion lung capacity for carbon monoxide can occur.
   (f) Elevation of liver enzymes
   (g) Hypertension: Monitor during treatment.
   (h) Extended effects of drug for up to 2 months after discontinuation necessitate extended monitoring for many adverse effects.

vi. Drug interactions
   (a) Ketoconazole: Increased fingolimod
   (b) Vaccines: Less effective during and 2 months after fingolimod treatment; avoid live, attenuated vaccines

vii. Avoid pregnancy during treatment and for 2 months after treatment.

f. Mitoxantrone (Novantrone)
   i. Mechanism of action: Decreases monocytes and macrophages, inhibits T and B cells
   ii. Indicated for secondary progressive, progressive-relapsing, and worsening-relapsing-remitting MS; used infrequently because of toxicity
   iii. Because of the potential for toxicity, mitoxantrone is reserved for patients with rapidly advancing disease whose other therapies have failed.
   iv. Patients taking mitoxantrone should not receive live virus vaccines; other vaccines should be held for 4–6 weeks after dose.
   v. Cardiotoxicity: Echocardiograms or multi-gated acquisition scans must be done at baseline and before each infusion. Systolic dysfunction occurs in about 12% of patients; congestive heart failure occurs in about 0.4%. Cardiotoxicity is not dose-, sex-, or age-related. Cyclooxygenase 2 inhibitors should be avoided.
   vi. Therapy-related acute leukemia occurs in about 0.8% of patients.
   vii. Other laboratory tests (CBC, bilirubin, aspartate aminotransferase [AST], alanine aminotransferase [ALT], alkaline phosphatase, and pregnancy test) must be done before each infusion.
g. Natalizumab (Tysabri)
   i. Mechanism of action: Blocks T-cell entry into the CNS
   ii. Indicated for relapsing forms of MS but distributed through restricted distribution program because of progressive multifocal leukoencephalopathy risk (0.24%)
   iii. Adverse effects
       (a) Hypersensitivity reactions: Itching, dizziness, fever, rash, hypotension, dyspnea, chest pain, anaphylaxis, usually within 2 hours of administration
       (b) Progressive multifocal leukoencephalopathy: Rapidly progressive viral CNS infection; usually results in death or permanent disability. Patient selection guidelines are for patients with relapsing-remitting disease whose other treatment (efficacy or intolerability) has failed or who have an aggressive initial course; should not be used in combination with other disease-modifying therapies. On January 20, 2012, an FDA-issued drug safety communication associated positive tests for John Cunningham virus (JCV) antibodies as a risk factor for progressive multifocal leukoencephalopathy. Thus, patients with all three of the following risk factors – presence of anti-JCV antibodies, longer natalizumab treatment duration (especially beyond 2 years), and previous treatment with an immunosuppressant medication (mitoxantrone, azathioprine, methotrexate, cyclophosphamide, mycophenolate mofetil) – have a 1.1% chance of developing progressive multifocal leukoencephalopathy.
       (c) Antibodies to natalizumab, associated with increased relapses and hypersensitivity reactions, develop in 9%–12% of patients.

h. Ocrelizumab (Ocrevus)
   i. Mechanism of action: Thought to bind to CD20 on pre-B and mature B cells
   ii. Indicated for relapsing or primary progressive forms of MS
   iii. Pharmacokinetics: 2-compartment model with central compartment volume 2.78 L. Terminal half-life 26 days
   iv. Adverse effects
       (a) Infectious: Respiratory infections, herpes virus infections
       (b) Psychiatric: Depression
       (c) Infusion reactions
       (d) GI: Diarrhea
   v. Must test for hepatitis B before first dose
   vi. Premedicate with methylprednisolone and an antihistamine before each infusion.

i. Teriflunomide (Aubagio)
   i. Mechanism of action: Prevents activation of lymphocytes
   ii. Indicated for relapsing forms of MS
   iii. Pharmacokinetics: Long half-life (8–19 days); takes about 3 months to reach steady-state concentrations; takes an average of 8 months to eliminate drug (serum concentrations less than 0.02 mcg/mL) and may take up to 2 years
   iv. Adverse effects
       (a) Hepatotoxicity may occur; teriflunomide should not be used in patients with preexisting liver disease or with ALT more than 2 times the upper limit of normal.
       (b) GI effects: Diarrhea, nausea
       (c) Dermatologic effects: Alopecia, rash
       (d) Infection: Neutropenia and lymphopenia may occur; tuberculosis infections reported (negative tuberculosis skin test required at baseline); live virus vaccinations should not be administered
(e) Teratogenic: Pregnancy category X (based on animal studies); negative pregnancy test at baseline; adequate contraception should be ensured; if pregnancy desired for men or women, teriflunomide should be discontinued, accelerated elimination procedures should be undertaken, and two serum concentrations less than 0.02 mcg/mL taken 14 days apart should be confirmed

v. Accelerated elimination procedures
(a) Cholestyramine 8 g every 8 hours for 11 days (if not tolerated, may use 4 g)
(b) Activated charcoal powder 50 g every 12 hours for 11 days

3. Symptomatic therapies

a. Patients may have fatigue, spasticity, urinary incontinence, pain, depression, cognitive impairment, fecal incontinence, constipation, pseudobulbar affect, and sexual dysfunction; standard therapies should be used for these symptoms.

b. Fatigue: Treatment may be nonpharmacologic (rest, assistive devices, cooling strategies, exercise, stress management) or pharmacologic (amantadine, methylphenidate).

c. Spasticity: Therapies must be centrally acting.
   i. First line: Baclofen, tizanidine
   ii. Second line: Dantrolene, diazepam
   iii. Third line: Intrathecal baclofen
   iv. Focal spasticity: Botulinum toxin

d. Walking impairment: Dalfampridine (Ampyra)
   i. Indicated to improve walking in patients with MS by improving walking speed
   ii. Potassium channel blocker, prolongs action potentials in demyelinated neurons
   iii. Dose: 10 mg orally twice daily; extended-release tablets
   iv. Contraindicated in patients with a history of seizures or moderate or severe renal impairment
   v. Adverse effects: Seizures, urinary tract infections, insomnia

e. Pseudobulbar affect: Dextromethorphan/quinidine
   i. Affects 10% of patients
   ii. Episodes of inappropriate laughing or crying
   iii. Dextromethorphan prevents excitatory neurotransmitter release.
   iv. Low-dose quinidine blocks first-pass metabolism of dextromethorphan, thus increasing dextromethorphan serum concentrations.

Table 9. Comparison of Disease-Modifying Therapies

<table>
<thead>
<tr>
<th>Drug (Brand)</th>
<th>Dose</th>
<th>Route</th>
<th>Frequency</th>
<th>Adverse Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alemtuzumab (Lemtrada)</td>
<td>First course: 12 mg/day over 4 hr × 5 days</td>
<td>IV</td>
<td>Daily for 5 days; then daily for 3 days 12 mo later</td>
<td>Infusion reaction 92% Rash 53% Thyroid disorders 34% Headache 52% Infections 13%–19%</td>
</tr>
<tr>
<td></td>
<td>Second course: 12 mg/day over 4 hr × 3 days 12 mo after first course</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dimethyl fumarate (Tecfidera)</td>
<td>120 mg twice daily × 7 days; then 240 mg twice daily</td>
<td>PO</td>
<td>Twice daily</td>
<td>Skin flushing 38% GI events 41%</td>
</tr>
</tbody>
</table>
Table 9. Comparison of Disease-Modifying Therapies (continued)

<table>
<thead>
<tr>
<th>Drug (Brand)</th>
<th>Dose</th>
<th>Route</th>
<th>Frequency</th>
<th>Adverse Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fingolimod (Gilenya)</td>
<td>0.5 mg</td>
<td>PO</td>
<td>Daily</td>
<td>Increased AST/ALT 14%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Infections 13%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Diarrhea 12%</td>
</tr>
<tr>
<td></td>
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<td></td>
<td></td>
<td>Hypertension 6%</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Bradycardia 4%</td>
</tr>
<tr>
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<td></td>
<td></td>
<td></td>
<td>Blurred vision 4%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Lymphopenia 4%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Leukopenia 3%</td>
</tr>
<tr>
<td>Glatiramer acetate (Copaxone)</td>
<td>20 mg</td>
<td>SC</td>
<td>Daily</td>
<td>Injection site reaction 90%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Systemic reaction 15%</td>
</tr>
<tr>
<td></td>
<td>40 mg</td>
<td>SC</td>
<td>Three times/wk</td>
<td></td>
</tr>
<tr>
<td>Interferon-β-1a (Avonex)</td>
<td>30 mcg</td>
<td>IM</td>
<td>Weekly</td>
<td>Flu-like symptoms 61%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Anemia 8%</td>
</tr>
<tr>
<td>Interferon-β-1a (Rebif)</td>
<td>22 mg or 44 mcg</td>
<td>SC</td>
<td>Three times/wk</td>
<td>Flu-like symptoms 28%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Injection site reactions 66%</td>
</tr>
<tr>
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<td></td>
<td></td>
<td></td>
<td>Leukopenia 22%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Increased AST/ALT 17%–27%</td>
</tr>
<tr>
<td>Interferon-β-1b (Betaseron)</td>
<td>0.25 mg</td>
<td>SC</td>
<td>Every other day</td>
<td>Flu-like symptoms 60%–76%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Injection site reactions 50%–85%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Asthenia 49%</td>
</tr>
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<td></td>
<td></td>
<td></td>
<td>Menstrual disorder 17%</td>
</tr>
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<td></td>
<td></td>
<td></td>
<td>Leukopenia 10%–16%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Increased AST/ALT 4%–19%</td>
</tr>
<tr>
<td>Mitoxantrone (Novantrone)</td>
<td>12 mg/m²</td>
<td>IV</td>
<td>Every 3 mo</td>
<td>Nausea 76%</td>
</tr>
<tr>
<td></td>
<td>Up to 140 mg/m² (lifetime dose)</td>
<td></td>
<td></td>
<td>Alopecia 61%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Menstrual disorders 61%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Urinary tract infection 32%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Amenorrhea 25%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Leukopenia 19%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>γ-Glutamyl transpeptidase increase of 15%</td>
</tr>
<tr>
<td>Natalizumab (Tysabri)</td>
<td>300 mg</td>
<td>IV</td>
<td>Every 4 wk</td>
<td>Headache 38%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Fatigue 27%</td>
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<td></td>
<td></td>
<td>Arthralgia 19%</td>
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<td></td>
<td></td>
<td>Urinary tract infection 20%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Hypersensitivity reaction &lt; 1%</td>
</tr>
<tr>
<td>Ocrelizumab (Ocrevus)</td>
<td>300 mg, followed by 300 mg 2 wk later; then 600 mg</td>
<td>IV</td>
<td>Every 6 mo after initial doses</td>
<td>Injection site reactions 34%</td>
</tr>
<tr>
<td>Pegylated interferon-β--1a (Plegridy)</td>
<td>125 mcg</td>
<td>SC</td>
<td>Every 2 wk</td>
<td>Injection site reactions 62%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Flu-like symptoms 47%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Headache 44%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Myalgia 19%</td>
</tr>
<tr>
<td>Teriflunomide (Aubagio)</td>
<td>7 mg or 14 mg</td>
<td>PO</td>
<td>Daily</td>
<td>Diarrhea 15%–18%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Nausea 9%–14%</td>
</tr>
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<td></td>
<td></td>
<td></td>
<td>Alopecia 10%–13%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Neutropenia 10%–15%</td>
</tr>
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<td></td>
<td></td>
<td></td>
<td></td>
<td>Lymphopenia 7%–10%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Elevated ALT 3%–5%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Hypertension 4%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Peripheral neuropathy 1%–2%</td>
</tr>
</tbody>
</table>

PO = oral(ly).
**Patient Cases**

*Questions 26–28 pertain to the following case:*

S.F. is a 33-year-old African American woman of Cuban descent living in the Miami area. This morning, her right leg became progressively weaker over about 3 hours. She was previously healthy except for a broken radius when she was 13 years old and a case of optic neuritis when she was 25 years old.

26. Which treatment is best for treating S.F.’s exacerbation?
   - A. Interferon beta-1a.
   - B. Glatiramer acetate.
   - C. Methylprednisolone.
   - D. Mitoxantrone.

27. Which therapy is best for S.F. to prevent further exacerbations?
   - A. Methylprednisolone.
   - B. Baclofen.
   - C. Glatiramer acetate.
   - D. No treatment.

28. S.F. elects to start interferon beta-1b and wants to know whether she can prevent or minimize some of the adverse effects. Which advice is best?
   - A. Rotate injection sites.
   - B. Lie down for 2 hours after the injection.
   - C. Always give the injection at the same time of day.
   - D. Use a heating pad on the injection sites.

29. B.B. is a 33-year-old woman with a recent diagnosis of multiple sclerosis. Her neurologist wants you to discuss with her the potential medications to prevent exacerbations. During the discussion, you find that she and her husband are planning to have a child in the next few years and that she is terrified of needles. Which is best for B.B.?
   - A. Glatiramer acetate.
   - B. Mitoxantrone.
   - C. Teriflunomide.
   - D. Dimethyl fumarate.

**VI. PERIPHERAL NEUROPATHY**

A. Broad range of diseases that damage nerves outside the brain and spinal cord. Other terms for peripheral neuropathy include *peripheral neuritis*, *polyneuropathy*, and *polyneuritis*.
   1. More than 100 types; each is unique
   2. Can be classified as acute or chronic; also, can be predominantly motor, mixed motor and sensory, or predominantly sensory
B. Epidemiology
   1. 20 million people in the United States have some form of peripheral neuropathy.
   2. The most common form is diabetic neuropathy. Diabetic peripheral neuropathy can occur before an official diagnosis of diabetes and may be the presenting symptom of diabetes.

C. Clinical Course
   1. Patients may initially present with altered sensation, pain, weakness, or autonomic symptoms. Symptoms typically are present distally in the initial stages.
   2. Symptoms may be bilateral or unilateral, symmetrical, or asymmetrical.
   3. Symptoms progress proximally. In advanced stages, distal wasting, weakness, absent deep tendon reflexes, and glove and stocking sensory loss can occur.

D. Diagnosis
   1. Complete medical history, medication history, and neurologic examination
   2. Electromyelogram and nerve conduction studies
   3. Laboratory tests to include serum chemistry, CBC, toxicology screen, vitamin B₁₂ concentration, immune panel

E. Causes

Table 10. Common Causes of Acute Severe Peripheral Neuropathy

<table>
<thead>
<tr>
<th>Cause</th>
<th>Predominantly Motor</th>
<th>Mixed</th>
<th>Predominantly Sensory</th>
</tr>
</thead>
<tbody>
<tr>
<td>Guillain-Barré syndrome</td>
<td>+</td>
<td>+</td>
<td>—</td>
</tr>
<tr>
<td>Vasculitis</td>
<td>—</td>
<td>+</td>
<td>—</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>—</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Drugs¹</td>
<td>—</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Porphyria</td>
<td>+</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Diphtheria</td>
<td>—</td>
<td>+</td>
<td>—</td>
</tr>
<tr>
<td>Paraneoplastic neuropathy</td>
<td>—</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Acute idiopathic sensory neuropathy</td>
<td>—</td>
<td>—</td>
<td>+</td>
</tr>
<tr>
<td>Critical illness</td>
<td>+.</td>
<td>+</td>
<td>—</td>
</tr>
<tr>
<td>Chronic inflammatory demyelinating polyneuropathy</td>
<td>—</td>
<td>+</td>
<td>—</td>
</tr>
</tbody>
</table>

¹Examples include nitrofurantoin, vincristine, cisplatin, and reverse transcriptase inhibitors.

F. Treatments
   1. Most treatments are directed toward symptomatic relief of the sensory component of neuropathies.
   2. Systemic and topical treatments may be combined.
   3. If an immune component is involved, treatment options include immune modulation. Recommendations for specific regimens vary with the disease diagnosis.
      a. Prednisone
      b. Immunoglobulin
      c. Plasmapheresis
      d. Immunosuppressants (e.g., cyclosporine, azathioprine, tacrolimus, sirolimus)
Table 11. Pharmacotherapy for Neuropathic Pain

<table>
<thead>
<tr>
<th>Therapy</th>
<th>Route</th>
<th>Starting Dose</th>
<th>Maintenance Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ORAL</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>First Line</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tricyclic antidepressants</td>
<td>PO</td>
<td>10–25 mg at bedtime</td>
<td>Increase by 10- to 25-mg increments to 100–150 mg at bedtime</td>
</tr>
<tr>
<td>Gabapentin</td>
<td>PO</td>
<td>300 mg thrice daily</td>
<td>Increase by 300- to 400-mg increments to 2400–6000 mg/day in three or four doses</td>
</tr>
<tr>
<td><strong>Second Line</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Carbamazepine</td>
<td>PO</td>
<td>200 mg twice daily</td>
<td>Increase by 200-mg increments to 200–400 mg three or four times daily; follow serum concentrations on doses greater than 600 mg/day</td>
</tr>
<tr>
<td>Tramadol</td>
<td>PO</td>
<td>50 mg two or three times daily</td>
<td>Increase by 50-mg increments to a maximum of 100 mg four times daily</td>
</tr>
<tr>
<td>Duloxetine</td>
<td>PO</td>
<td>30 mg daily</td>
<td>Increase by 30- to 60-mg increments up to 120 mg daily</td>
</tr>
<tr>
<td>Pregabalin</td>
<td>PO</td>
<td>50 mg thrice daily</td>
<td>Increase by 300 mg/day</td>
</tr>
<tr>
<td><strong>Third Line</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Oxcarbazepine</td>
<td>PO</td>
<td>150–300 mg twice daily</td>
<td>Increase by 300-mg increments to 600–1200 mg twice daily</td>
</tr>
<tr>
<td>Lamotrigine</td>
<td>PO</td>
<td>25 mg once daily</td>
<td>Increase by 25-mg increments weekly to 100–200 mg twice daily</td>
</tr>
<tr>
<td>Topiramate</td>
<td>PO</td>
<td>25–50 mg at bedtime</td>
<td>Increase by 50-mg increments weekly to 200 mg twice daily</td>
</tr>
<tr>
<td>Venlafaxine</td>
<td>PO</td>
<td>37.5–75 mg once daily</td>
<td>Increase by 75-mg increments to 150–225 mg/day</td>
</tr>
<tr>
<td>Valproate</td>
<td>PO</td>
<td>250 mg two or three times daily</td>
<td>Increase by 250-mg increments up to 1500 mg/day</td>
</tr>
<tr>
<td><strong>Fourth Line</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bupropion SR</td>
<td>PO</td>
<td>150 mg daily</td>
<td>After 1 wk, increase to 150 mg twice daily</td>
</tr>
<tr>
<td>Tiagabine</td>
<td>PO</td>
<td>4 mg daily</td>
<td>Increase to 4–12 mg twice daily</td>
</tr>
<tr>
<td>Levetiracetam</td>
<td>PO</td>
<td>250 mg at bedtime</td>
<td>Increase by 250– to 500-mg increments to 1500 mg twice daily</td>
</tr>
<tr>
<td>Zonisamide</td>
<td>PO</td>
<td>100 mg at bedtime</td>
<td>Increase by 100-mg increments to 400–600 mg at bedtime</td>
</tr>
<tr>
<td>Mexiletine</td>
<td>PO</td>
<td>200 mg daily</td>
<td>Increase by 200-mg increments to a maximum of 200 mg thrice daily</td>
</tr>
<tr>
<td>Phenytoin</td>
<td>PO</td>
<td>200 mg at bedtime</td>
<td>Increase by 100 mg increments to 300–400 mg daily, follow serum concentrations</td>
</tr>
<tr>
<td><strong>Newer Drugs</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Milnacipran</td>
<td>PO</td>
<td>12.5 mg at bedtime for 1 day</td>
<td>12.5 mg twice daily for 2 days; then 25 mg twice daily for 4 days; then 50 mg twice daily. May increase up to 100 mg twice daily</td>
</tr>
<tr>
<td>Lacosamide</td>
<td>PO</td>
<td>50 mg twice daily</td>
<td>Increase to 100 mg twice daily after 1 wk. May increase up to 200 mg twice daily</td>
</tr>
</tbody>
</table>

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Table 11. Pharmacotherapy for Neuropathic Pain (continued)

<table>
<thead>
<tr>
<th>Therapy Agent</th>
<th>Route</th>
<th>Starting Dose</th>
<th>Maintenance Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>TOPICAL AGENTS</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Over the Counter</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Capsaicin 0.075%</td>
<td>Topical</td>
<td>Apply to affected region three or four times daily</td>
<td>Continue starting dose</td>
</tr>
<tr>
<td>Salicylate 10%–25%</td>
<td>Topical</td>
<td>Apply to affected region three or four times daily</td>
<td>Continue starting dose</td>
</tr>
<tr>
<td>Menthol 16%/camphor 3%</td>
<td>Topical</td>
<td>Apply to affected region three or four times daily</td>
<td>Continue with starting dose</td>
</tr>
<tr>
<td><strong>Prescription</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lidocaine 2.5%/prilocaine 2.5%</td>
<td>Topical</td>
<td>Apply to affected region three or four times daily</td>
<td>Continue with starting dose</td>
</tr>
<tr>
<td>Lidocaine patch 5%</td>
<td>Topical</td>
<td>Apply over adjacent intact skin</td>
<td>Increase up to 3 patches worn for up to 12 hr daily</td>
</tr>
<tr>
<td>Doxepin 5%</td>
<td>Topical</td>
<td>Apply to affected region twice daily</td>
<td>Continue with starting dose</td>
</tr>
<tr>
<td>Diclofenac sodium gel 1%</td>
<td>Topical</td>
<td>Apply to affected region three or four times daily</td>
<td>Continue with starting dose</td>
</tr>
<tr>
<td><strong>Compounded Prescription Products</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ketoprofen 5%/amitriptyline 2%/tetracaine 1%</td>
<td>Topical</td>
<td>Apply to affected area twice daily</td>
<td>Increase up to four times daily</td>
</tr>
<tr>
<td>Ketoprofen 10%/cyclobenzaprine 1%/lidocaine 5%</td>
<td>Topical</td>
<td>Apply to affected region twice daily</td>
<td>Increase up to four times daily</td>
</tr>
<tr>
<td>Ketamine 5%/amitriptyline 4%/gabapentin 4%</td>
<td>Topical</td>
<td>Apply to affected region twice daily</td>
<td>Increase up to thrice daily</td>
</tr>
<tr>
<td>Carbamazepine 5%/lidocaine 5%</td>
<td>Topical</td>
<td>Apply to affected region twice daily</td>
<td>Increase up to four times daily</td>
</tr>
<tr>
<td>Amitriptyline 2%/baclofen 2%</td>
<td>Topical</td>
<td>Apply to affected region three or four times daily</td>
<td>Continue with starting dose</td>
</tr>
</tbody>
</table>
Patient Case

 Questions 30 and 31 pertain to the following case.

S.B. is 55-year-old man referred to a neurologist for numbness, burning, and tingling in his feet that has progressively worsened over the past year. On neurologic examination, he has decreased sensations bilaterally to mid-calf. He takes no medications except for nonprescription analgesics as needed for pain. His current body mass index (BMI) is 32 kg/m².

30. Which test would best determine the cause of S.B.’s neuropathy?
   A. Sodium.
   B. Hemoglobin A1C (A1C).
   C. Serum creatinine.
   D. White blood cell count.

31. Which therapy is best for S.B.?
   A. Naproxen.
   B. Tramadol.
   C. Nortriptyline.
   D. Prednisone.

32. A meta-analysis of treatments for neuropathic pain included data from 26 clinical trials (2007;9:36). The following results of the review included these data.

<table>
<thead>
<tr>
<th>Treatment</th>
<th>No. Needed to Treat</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tricyclic antideprssants</td>
<td>2.1</td>
</tr>
<tr>
<td>SNRIs</td>
<td>5.1</td>
</tr>
<tr>
<td>SSRIs</td>
<td>7</td>
</tr>
</tbody>
</table>

Given these data, which would be most effective for neuropathic pain?
   A. Duloxetine.
   B. Sertraline.
   C. Amitriptyline.
   D. Venlafaxine.
Epilepsy


14. Perucca E, Tomson T. The pharmacological treatment of epilepsy in adults. Lancet Neurol 2011;10:446-56. A solid review of current treatment issues and practices, including when treatment should be initiated, drugs of choice for initial
treatment, treatment of drug-refractory patients, and discontinuation of seizure medications in seizure-free patients.


**Stroke**


**Parkinson Disease**


Headaches


Multiple Sclerosis


Peripheral Neuropathy


ANSWERS AND EXPLANATIONS TO PATIENT CASES

1. **Answer: D**
   Juvenile myoclonic epilepsy is a type of generalized epilepsy that consists of myoclonic and tonic-clonic seizures. Phenytoin (Answer B) and oxcarbazepine (Answer C) can increase myoclonic seizures. Although valproate (Answer A) is effective for JME, it is associated with several teratogenic effects. Because this patient is a woman of childbearing potential, it is advisable to avoid valproate even though she takes oral contraceptives. Levetiracetam (Answer D) is effective for JME and has much less risk of teratogenic effects.

2. **Answer: A**
   Interactions with oral contraceptives are a concern with several AEDs. In these cases, alternative forms of birth control (Answer B) may be necessary. Decreased effectiveness of oral contraceptives may be associated with breakthrough bleeding (Answer C). In addition, oral contraceptives can alter the effectiveness of AEDs (Answer D). However, no evidence supports that levetiracetam alters oral contraceptive effectiveness or that oral contraceptives change the effectiveness of levetiracetam, making Answer A correct.

3. **Answer: A**
   Carbamazepine (Answer B) can increase seizures in JME. Cannabidiol (Answer C) has only been shown effective in Dravet syndrome and Lennox-Gastaut syndrome. Valproate (Answer D) should be avoided in this patient because of its teratogenic adverse effects. Lamotrigine (Answer A) is a reasonable alternative that is effective for JME and is not associated with an increased risk of teratogenic adverse effects.

4. **Answer: B**
   Lorazepam (Answer B) is the drug of choice for status epilepticus. Lorazepam is less lipophilic than diazepam (Answer A); therefore, lorazepam does not redistribute from the CNS as quickly. Phenytoin (Answer C) and phenobarbital (Answer D) should be held in reserve for maintenance therapy or refractory status epilepticus.

5. **Answer: D**
   Phenytoin has nonlinear pharmacokinetics. A small increase in dose may result in a large increase in serum concentration. Therefore, without doing any calculations, we can surmise that an increase from 300 mg/day to 600 mg/day would more than double the serum concentration (Answer D). Lower increases (Answers A–C) would be unlikely with an increase in dose this large.

6. **Answer: D**
   Phenytoin (Answer A) and carbamazepine (Answer C) can increase absence seizure frequency. Valproate (Answer B) is an alternative, but its teratogenic adverse effects makes it less desirable for this patient. Ethosuximide (Answer D) is useful for absence seizures and had fewer adverse effects than valproate in a randomized study.

7. **Answer: D**
   Although hepatotoxicity (Answer A) is a possible adverse effect of carbamazepine, it is most likely to occur within the first few months of starting carbamazepine. Acne (Answer B) and gingival hyperplasia (Answer C) are adverse effects associated with phenytoin. Diplopia (Answer D) is a common adverse effect associated with higher concentrations of carbamazepine.

8. **Answer: B**
   Hepatotoxicity (Answer A) is associated with several AEDs but not with zonisamide. Alopecia (Answer C) is a common adverse effect of valproate. Word-finding difficulties (Answer D) is a common adverse effect of topiramate. Zonisamide is associated with a 1% increase in the risk of renal stones (Answer B).

9. **Answer: D**
   Carbamazepine forms an active epoxide intermediate (carbamazepine-10,11-epoxide), whereas oxcarbazepine does not (Answer D). Carbamazepine induces more liver enzymes than oxcarbazepine (Answer A). However, hyponatremia is more closely associated with oxcarbazepine than with carbamazepine (Answer C). Both drugs can cause allergic rashes (Answer B).

10. **Answer: C**
    Immediate discontinuation of oxcarbazepine (Answer A) would likely increase seizures. Topiramate (Answer B) and phenobarbital (Answer D) are both associated with an increased risk of teratogenic adverse effects.
Continuing the patient’s current medication (Answer C) is the best approach during pregnancy.

11. Answer: D
Nonmodifiable risk factors for stroke include age, race, and male sex. Somewhat modifiable risk factors include hypercholesterolemia and diabetes mellitus. Modifiable stroke risk factors include hypertension, smoking, and atrial fibrillation. Less well-documented risk factors include obesity, physical inactivity, alcohol abuse, hyperhomocystinemia, hypercoagulability, hormone replacement therapy, and oral contraceptives. Breast cancer (Answer C) and osteoarthritis (Answers A and B) are not risk factors for stroke. Answer D is the only response that includes only risk factors for stroke.

12. Answer: C
There are many contraindications to administering tissue plasminogen activator for stroke, mainly focused on bleeding risk. There is no upper limit on age (Answer B). Breast cancer (Answer D) is not a contraindication for tissue plasminogen activator. Her symptoms began within the time interval, less than 4½ hours, making Answer C incorrect and Answer A correct.

13. Answer: C
Warfarin (Answer D) is only indicated for stroke prevention with atrial fibrillation. Other than modifying a partly modifiable risk factor for stroke, metformin (Answer A) has no benefit in preventing stroke. Celecoxib (Answer B) also has no benefit in preventing stroke and, according to some studies, may increase the risk of stroke. Aspirin and clopidogrel (Answer C) should be used together for 90 days after an acute stroke to reduce the risk of another stroke.

14. Answer: C
No therapy (Answer C) is an appropriate choice for this patient (CHA₂DS₂-VASc score of 0) because he is younger than 65 and has no other risk factors such as hypertension or a prosthetic valve. Apixaban (Answer A) would needlessly increase his risk of bleeding. A combination of aspirin and clopidogrel (Answer B) is not indicated to prevent a stroke in atrial fibrillation. The risk of stroke associated with atrial fibrillation can be reduced with the appropriate use of anticoagulants, making Answer D incorrect.

15. Answer: D
With a mitral valve replacement, the target INR is 2.5–3.5, making 3 (Answer D) an optimal target. An INR of 1.5 (Answer A) or 2 (Answer B) is too low for a valve replacement. An INR of 2.5 (Answer C) is at the bottom of the acceptable target range, making it difficult to consistently keep her INR in the range.

16. Answer: A
Anticholinergic drugs like trihexyphenidyl only control tremor, not other symptoms of Parkinson disease. Increasing the trihexyphenidyl dose (Answers B and D) would not improve control of his symptoms and would increase anticholinergic adverse effects. Decreasing the carbidopa/levodopa dose (Answer C) would worsen his Parkinson disease symptoms. Increasing the carbidopa/levodopa dose and discontinuing trihexyphenidyl (Answer A) should improve control of all of his symptoms and reduce any anticholinergic adverse effects.

17. Answer: D
Wearing-off phenomenon is the return of Parkinson disease symptoms before the next dose. This problem can be resolved by giving doses more often (Answer D), administering the controlled-release formulation of carbidopa/levodopa, or adding a catechol-O-methyl transferase inhibitor. Increasing the dosing interval (Answer C) means that doses are given further apart. Increasing the dose (Answer A) would not address wearing-off at the end of a dosing interval and would place the patient at risk of developing dyskinesia. Decreasing the dose (Answer B) would cause the patient’s Parkinson symptoms to worsen.

18. Answer: C
Amantadine can cause livedo reticularis, in which the dilation of capillary blood vessels and the stagnation of blood within these vessels cause a mottled, reddish blue skin discoloration (Answer C). This discoloration usually occurs on the trunk and extremities and is more pronounced in cold weather. Carbidopa/levodopa (Answer A) and entacapone (Answer B) do not cause this adverse effect. Although simple venous stasis could occur (Answer D), livedo reticularis is more likely in this patient.
19. Answer: D
Ropinirole (Answer A) helps with the initial treatment of Parkinson disease, but adding it to his current regimen without adjusting the carbidopa/levodopa dose would worsen his dyskinesia. Selegiline (Answer B) would not address his dyskinesia and could make it worse by decreasing the breakdown of levodopa. Increasing the carbidopa/levodopa dose (Answer C) would make his dyskinesia worse. Decreasing the carbidopa/levodopa dose (Answer D) will improve the dyskinesia.

20. Answer: C
Trihexyphenidyl (Answer A) is only effective for tremors in Parkinson disease and has anticholinergic adverse effects. In this patient, it would not treat the other symptoms of the disease, and anticholinergic adverse effects are not advisable in an older individual. Entacapone (Answer B) decreases the breakdown of dopamine, prolonging the activity of levodopa. Entacapone does not directly treat Parkinson symptoms. Ropinirole (Answer D) is usually preferred for initial treatment in individuals younger than 65 or as add-on therapy to carbidopa/levodopa in older patients. Carbidopa/levodopa (Answer C) is the preferred initial treatment for Parkinson disease in individuals older than 65.

21. Answer: A
A β-blocker (Answer A) is a good choice for a patient with coexisting hypertension. Valproate (Answer B) could increase her weight and has teratogenic adverse effects. Topiramate (Answer C) might decrease her weight, but it has an increased risk of teratogenic adverse effects. Sumatriptan (Answer D) is for the acute treatment of migraine headaches, not for prophylaxis.

22. Answer: C
Amitriptyline (Answer C) is effective as prophylaxis for tension headaches. Propranolol (Answer A) and valproate (Answer B) are usually used for migraine headache prophylaxis. Lithium (Answer D) is used for prophylaxis of cluster headaches.

23. Answer: D
Lithium (Answer D) is a prophylactic agent for cluster headaches. Atenolol (Answer A) and valproate (Answer B) are usually used for migraine headache prophylaxis. Nortriptyline (Answer C) is useful for migraine and tension headaches.

24. Answer: D
Sumatriptan (Answer D) is available as an injectable and as a nasal spray and would be appropriate to use in a patient with severe nausea and vomiting. Almotriptan (Answer A) and naratriptan (Answer B) only come in oral dosage forms and would not be optimal in the face of nausea and vomiting. Promethazine (Answer C) might reduce nausea and vomiting but would not treat the patient’s migraine headache.

25. Answer: B
Topiramate (Answer D) is used as a prophylactic drug and not in the acute treatment of a migraine. Naproxen (Answer C) would be less likely to relieve her headache without being combined with a triptan. The eletriptan dose (Answer A) is the lowest dose of this drug and probably ineffective, given that she is taking the highest dose of sumatriptan. In addition, eletriptan has a short half-life, making it less effective 2 hours later. Frovatriptan (Answer B) has a longer half-life, making it more likely to prevent the headache from returning 2 hours later.

26. Answer: C
Methyprednisolone (Answer C) is the only option used for acute exacerbations. Interferon-β-1a (Answer A), glatiramer acetate (Answer B), and mitoxantrone (Answer D) are all used as disease-modifying therapies.

27. Answer: C
Glatiramer acetate (Answer C) is an appropriate initial choice for disease-modifying therapy. Methyprednisolone (Answer A) is only for exacerbations. Baclofen (Answer B) is only for spasticity and does not have disease-modifying properties. Providing no treatment (Answer D) would be unacceptable because of the patient’s many episodes of exacerbations.

28. Answer: A
Rotating the injection sites for self-injections helps prevent injection site reactions (Answer A). Other strategies that might help prevent these reactions are icing the injection site before injection and bringing the drug to room temperature. The injections should be administered at about the same time of day (Answer C), but this would not prevent adverse effects. Using a heating pad (Answer D) might increase the risk of a site reaction. Lying down after the injection (Answer B) would not alter the risk of injection site reactions.
29. Answer: D
Glatiramer (Answer A) is a category B drug with limited data in pregnancy. It would be best to try an alternative agent, if possible. Mitoxantrone (Answer B) has significant toxicities and is a category X drug. Teriflunomide (Answer C) is also a category X drug. Dimethyl fumarate (Answer D) is a pregnancy category C drug. However, this patient should carefully plan her conception and can discontinue the medication before pregnancy.

30. Answer: B
The most likely cause of peripheral neuropathy in this patient is diabetes mellitus, even if this was not previously diagnosed. Therefore, A1C (Answer B) is the most useful laboratory value for determining the potential cause. Sodium (Answer A), serum creatinine (Answer C), and white blood cell count (Answer D) do not help determine the cause of neuropathy.

31. Answer: C
Naproxen (Answer A) would unlikely be beneficial because the patient has been taking nonprescription analgesics without symptom relief. Although tramadol (Answer B) is a possibility, it is usually considered a second- or third-line option for peripheral neuropathy. Prednisone (Answer D) is not typically used for the initial treatment of neuropathy. Prednisone can be used in very specific immunologic neuropathies, but these are unlikely in this scenario. Nortriptyline (Answer C) is considered a first-line treatment for peripheral neuropathy. Given that the patient has not been previously treated, it is the best initial treatment option.

32. Answer: C
Number needed to treat (NNT) is an estimate of the number of patients who would need to receive treatment for one patient to benefit. Therefore, the lower the NNT, the more likely a treatment is to be effective. Tricyclic antidepressants, including amitriptyline (Answer C), have the lowest NNT value in this comparison, so they are most likely to be effective. Duloxetine (Answer A) and venlafaxine (Answer D) are less likely to effective. Sertraline (Answer B) is the least likely to be effective.
ANSWERS AND EXPLANATIONS TO SELF-ASSESSMENT QUESTIONS

1. **Answer: C**

The therapeutic range for phenytoin is 10–20 mcg/mL. The patient continues to have seizures and does not have dose-related adverse effects. Phenytoin follows zero-order pharmacokinetics, requiring caution in dose adjustments. With a concentration of greater than 12 mg/L, a dose adjustment of 30 mg/day (Answer C) is appropriate. A dose of 400 mg/day (Answer A) is a reduction and is unnecessary, given that the patient does not report adverse effects of phenytoin. Doses of 450 mg/day (Answer B) and 500 mg/day (Answer D) are too large of an increase and would likely result in toxicity of phenytoin.

2. **Answer: B**

In general, medications for status epilepticus should be in parenteral formulations to facilitate rapid administration. Once the seizures of status epilepticus have been stopped, a second, long-acting drug should be initiated to prevent seizure recurrence. Levetiracetam (Answer B) is well tolerated, has good efficacy as monotherapy, and has less risk of teratogenicity than other AEDs. Topiramate (Answer A) and lamotrigine (Answer C) are not available in a parenteral dosage form and have a greater risk of adverse effects. Valproate (Answer D) is available in a parenteral dosage form and could be an option; however, its adverse effects and teratogenic risk make it less than optimal in this patient.

3. **Answer: A**

Agitation and depression are common adverse effects of levetiracetam. Because of the patient’s wife’s concerns for his irritability and depression, it is probably advisable to discontinue levetiracetam (Answer A) and change to a different AED. Increasing the dose (Answer B) could worsen his symptoms, and his symptoms are probably not the result of ongoing seizures. Continuing levetiracetam (Answer C) might be an alternative, but given that he and his spouse have concerns for adverse effects, it is a less-than-optimal approach. No clear correlation has been established between efficacy or toxicity and levetiracetam concentrations (Answer D). Therefore, a concentration would not help guide therapeutic decisions.

4. **Answer: A**

Patients who can be treated within 4½ hours of stroke symptom onset should be considered for tissue plasminogen activator. Because this patient’s stroke symptoms began 2 hours ago and he has no clear contraindication to tissue plasminogen activator, he is a candidate for this treatment (Answer A). Aspirin (Answer B) can be initiated within 24 hours but should not be given immediately because he is a candidate for tissue plasminogen activator. Likewise, aspirin and clopidogrel (Answer C) can be initiated with 24–48 hours after tissue plasminogen activator but should not be given immediately. In addition, a loading dose of clopidogrel is unnecessary. Aspirin and dipyridamole (Answer D) is not recommended for initial stroke prophylaxis after an acute stroke.

5. **Answer: B**

All stroke survivors need secondary stroke prevention drugs. The best data for initial stroke prophylaxis after an acute stroke is a combination of aspirin and clopidogrel for 3 months (Answer B). Aspirin and dipyridamole (Answer A) is not recommended as initial stroke prophylaxis. Warfarin (Answer C) is only indicated for stroke prophylaxis in a patient with atrial fibrillation. Ticagrelor (Answer D) has few data in stroke prophylaxis and is thus not recommended at this point.

6. **Answer: C**

Dyskinesia (Answer C) is a common adverse effect of carbidopa/levodopa. Although dyskinesia is easily misdiagnosed as increased Parkinson symptoms, it has a very different appearance similar to the description in this case. Wearing-off (Answer A) occurs at the end of a dosing interval. On-off (Answer B) occurs randomly but is usually associated with increased bradykinesia and freezing. Seizures (Answer D) are unlikely in this situation.

7. **Answer: B**

The goal of treating dyskinesia is to reduce dopamine activity, which is accomplished by reducing the carbidopa/levodopa dose (Answer B). Apomorphine (Answer A), a dopamine agonist used in treating on-off phenomenon, would potentially worsen his dyskinesia. Likewise, ropinirole (Answer D) is a dopamine agonist.
that would worsen the dyskinesia. Although selegiline (Answer C) mildly inhibits the breakdown of dopamine, discontinuation is unlikely to control dyskinesia.

8. **Answer: D**
Many medications used for nausea, including metoclopramide (Answer B), are dopamine antagonists and potentially worsen nausea and vomiting. Reducing the pramipexole dose (Answer A) would likely result in worsening of his Parkinson symptoms. Changing to carbidopa/levodopa (Answer C) might relieve his symptoms but would not be optimal, given that pramipexole is controlling his Parkinson symptoms. Trimethobenzamide (Answer D) is a medication for nausea that inhibits dopamine activity.

9. **Answer: B**
The first step in treating migraine headache is to use an acute medication. Prophylactic medication is usually reserved until the patient has at least weekly headaches or poor response to several acute treatments. Naproxen (Answer A) would unlikely be beneficial because she has tried nonprescription analgesics for her headache without relief. Dihydroergotamine (Answer C) is usually reserved for status migrainosus because of its adverse effects. The combination product (Answer D) is minimally effective and would likely not be helpful, given her poor response to analgesics. Sumatriptan (Answer B) is the best initial acute treatment for migraine headache.

10. **Answer: A**
Amitriptyline (Answer A) would be reasonable, given the patient’s report of insomnia. Valproate (Answer B) and topiramate (Answer C) have greatly increased the risk of teratogenic adverse effects and are less than optimal in a woman of childbearing potential. Frovatriptan (Answer D) is only indicated for the acute treatment of migraine.

11. **Answer: D**
Fingolimod (Answer D) is the only choice with an FDA indication for the treatment of MS. In addition, fingolimod has the best clinical trial evidence of efficacy. Methylprednisolone (Answer B) is used for acute MS exacerbations. Cyclophosphamide (Answer A) and azathioprine (Answer C) have been studied in progressive forms of MS, but their data are not as robust as those for fingolimod.

12. **Answer: B**
Treatment of spasticity in MS requires a centrally acting agent. Of the choices given, only diazepam (Answer A) and baclofen (Answer B) are centrally acting. Because of the significant fatigue and drowsiness that occur with diazepam, baclofen is usually a first-line therapy. Carisoprodol (Answer C) and metaxalone (Answer D) are indicated for muscle spasms, but not for spasticity.

13. **Answer: C**
Amantadine (Answer C) is used in MS for fatigue. Propranolol (Answer A), lamotrigine (Answer B), and ropinirole (Answer D) are not used in MS.

14. **Answer: A**
Diabetic neuropathy (Answer A) is the most common cause of peripheral neuropathy and may occur even before a patient is given a diagnosis of diabetes. Chronic inflammatory demyelinating polyneuropathy (Answer B) and genetic neuropathy (Answer D) are much less common, and symptoms are not consistent with this presentation. An entrapped nerve (Answer C) would typically be unilateral.

15. **Answer: B**
Phenytoin (Answer A) and valproate (Answer D) are considered third- and fourth-line drugs for diabetic neuropathy pain. Acetaminophen (Answer C) would unlikely relieve symptoms. Lidocaine (Answer B) would be best for initial treatment of the patient’s neuropathic pain.