

# NEUROLOGY

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**Learning Objectives**

1. Differentiate between various seizure medications on the basis of use and adverse effects.
2. Develop a treatment strategy for status epilepticus.
3. Identify appropriate treatment strategies for primary and secondary stroke prevention.
4. Determine the appropriateness of treatment with tissue plasminogen activator for acute stroke.
5. Examine common adverse effects associated with the treatment of Parkinson disease.
6. Differentiate between regimens for acute and prophylactic treatment of migraine, tension, and cluster headaches.
7. Identify common adverse effects of disease-modifying therapies for multiple sclerosis.

**Self-Assessment Questions**

*Answers and explanations to these questions can be found at the end of this chapter.*

1. T.L. is a 35-year-old man with complex partial seizures. He is otherwise healthy. He was placed on phenytoin after a seizure about 2 months ago. He currently takes phenytoin 100 mg 3 capsules orally every night. During his clinic visit, he tells you he has had no seizures, and he has no signs of toxicity. He is allergic to sulfa drugs. His phenytoin serum concentration is 17.7 mcg/mL. Which is the best interpretation of this concentration?
  - A. It is too low.
  - B. It is too high.
  - C. It is just right.
  - D. A serum albumin concentration is necessary to interpret this concentration.
2. B.V. is a 28-year-old woman brought to your emergency department for 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. Phenytoin.
  - C. Zonisamide.
  - D. Diazepam.
3. J.H. is a 42-year-old man with complex partial seizures for which he was prescribed topiramate. He has been increasing the topiramate dose every other day according to instructions from his primary care provider. He comes to the pharmacy where you work but seems a little confused and has difficulty finding the words to have a conversation with you. Which is the best assessment of J.H.'s condition?
  - A. Discontinue topiramate; he is having an allergic reaction.
  - B. Increase the topiramate dose; he is having partial seizures.
  - C. Slow the rate of topiramate titration; he is having psychomotor slowing.
  - D. Get a topiramate serum concentration; he is probably supratherapeutic.

*Questions 4 and 5 pertain to the following case:*

R.H. is a 59-year-old man who presents to the emergency department for new-onset left-sided weakness that began 6 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 325 mg/day orally. His vital signs include blood pressure (BP) 160/92 mm Hg, heart rate 92 beats/minute, respiratory rate 14 breaths/minute, and temperature 38°C. The treatment team assesses this patient for treatment with tissue plasminogen activator and asks for your opinion.

4. Which reply is best, given this information?
  - A. R.H. should be treated with tissue plasminogen activator.
  - B. R.H. should not be treated with tissue plasminogen activator because the onset of his stroke symptoms was 6 hours ago.
  - C. R.H. should not be treated with tissue plasminogen activator because he has hypertension.
  - D. R.H. should not be treated with tissue plasminogen activator because he takes aspirin.

5. R.H. survives his stroke. As part of his discharge treatment plan, you evaluate his risk factors for a second stroke. His aspirin therapy is discontinued. Which medication for secondary stroke prevention is best to initiate at this time?
- Dipyridamole.
  - Enoxaparin.
  - Heparin.
  - Clopidogrel.
8. W.S. is a 57-year-old man initiated on rasagiline for treatment of his newly diagnosed Parkinson disease. He develops a cough, body aches, and nasal congestion. Which medication is best to treat W.S.'s symptoms?
- Guaifenesin.
  - Dextromethorphan.
  - Tramadol.
  - Pseudoephedrine.

*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 masked facial expression. He currently takes carbidopa/levodopa/entacapone 25 mg/100 mg/200 mg orally four times daily, ropinirole 1 mg orally three times daily, and selegiline 5 mg orally twice daily. He has no drug allergies. He also describes a worsening of his Parkinson disease symptoms, which fluctuate randomly during the day. He has developed a charting system for his symptoms during the day, and no relationship seems to exist with the time he is scheduled to take his carbidopa/levodopa/entacapone doses.

6. Which condition best describes C.P.'s fluctuating Parkinson disease symptoms?
- Wearing off.
  - On-off.
  - Dyskinesia.
  - Dystonia.
7. For his symptoms, C.P. is given a prescription for apomorphine. Which statement about this drug is most accurate?
- He must be trained on self-injection techniques with saline, but he can administer his first dose of apomorphine at home when he needs it.
  - He should not take apomorphine if he is allergic to penicillin.
  - If he does not take a dose for more than 1 week, he should begin with a loading dose with his next injection.
  - It may cause severe nausea and vomiting.

*Questions 9 and 10 pertain to the following case:*

R.M. is a 47-year-old woman with long-standing migraine headaches. Her headache pain is easily relieved with sumatriptan 100 mg orally as the occasion requires. However, with her last dose she experienced substernal chest pain radiating to her left arm. She reported to her local emergency department, where she had a complete workup. Her final diagnoses were coronary artery disease and hypertension. For these conditions, she was placed on hydrochlorothiazide 25 mg orally every morning.

9. Which drug is best for R.M. to use for her migraine headaches?
- Frovatriptan.
  - Zolmitriptan.
  - Dihydroergotamine.
  - Naproxen.
10. If R.M. requires a drug for migraine prophylaxis, which agent is best to recommend?
- Propranolol.
  - Valproic acid.
  - Amitriptyline.
  - Gabapentin.

*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 2 years ago. He has been taking glatiramer acetate since then. However, no discernible difference exists in the number of exacerbations he has experienced. He has spasticity in his legs, which has caused several falls during the past month, and he experiences fatigue that worsens as the day progresses.

11. Which drug therapy is best for L.M.'s multiple sclerosis?
- A. Cyclophosphamide.
  - B. Methylprednisolone.
  - C. Azathioprine.
  - D. Fingolimod.
12. Which drug is best to treat L.M.'s spasticity?
- A. Diazepam.
  - B. Baclofen.
  - C. Carisoprodol.
  - D. Metaxalone.
13. Which drug is best to treat L.M.'s fatigue?
- A. Propranolol.
  - B. Lamotrigine.
  - C. Amantadine.
  - D. Ropinirole.

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## I. EPILEPSY

### A. Epidemiology

1. Ten percent of the population will have a seizure.
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.

### B. Classification of Seizures: Seizures are generally classified according to the International League Against Epilepsy (ILAE) scheme, adopted in 1981, with modifications in 2001 and 2010 (Berg AT, Berkovic SF, Brodie MJ, et al. Revised terminology and concepts for organization of seizures and epilepsies: report of the ILAE Commission on Classification and Terminology, 2005-2009. *Epilepsia* 2010;51:676-85).

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 and rapidly engaging bilaterally distributed neural networks.
  - a. 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 the patient may stare, be motionless, or have a distant expression on his or her face. Electroencephalograms (EEGs) performed during seizure activity usually show three Hz spike-and-wave complexes. Absence seizures can be further classified as typical, atypical, myoclonic absence, and eyelid myoclonia.
  - b. Myoclonic: Consist of brief, lightning-like 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. Tonic-clonic: Typically, there are five phases of a primary tonic-clonic seizure: flexion, extension, tremor, clonic, and postictal. During the flexion phase, the patient's mouth may be held partly open, and the patient may experience 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; experience 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 experience rhythmic jerks. The length of the entire seizure is usually 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 experience a prodrome but not an aura.
  - d. Clonic: Only the clonic phase of a tonic-clonic seizure; rhythmic, repetitive, jerking muscle movements
  - e. Tonic: Only the flexion or extension phases of a tonic-clonic seizure
  - f. Atonic: 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. Status epilepticus is any seizure that lasts more than 20 minutes or recurrent seizures of sufficient frequency that the patient does not regain consciousness between episodes. Mortality is up to 20% for status epilepticus.
4. Nonepileptic seizures are paroxysmal nonepileptic episodes resembling epileptic seizures that can be organic or psychogenic.

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5. Other associated symptoms
    - a. Prodrome: Awareness of an impending seizure before it occurs. The prodrome may consist of headache, insomnia, irritability, or 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 experience 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 be performed with special attention 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, 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 to perform an EEG is while the patient is having seizures. If it is not possible to perform the EEG during seizures, it should be performed 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 require prolonged closed-circuit video-EEG monitoring. Keep in mind that an interictal (when the patient is not having clinical seizures) EEG may be normal but that 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 be useful in finding brain lesions when magnetic resonance imaging cannot be performed in a timely fashion.
- D. Treatment
1. Medications (see Tables 1–4)
    - a. Benzodiazepines
      - i. Mechanism of action: Augment  $\gamma$ -aminobutyric acid–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)
    - b. Carbamazepine (Carbatrol, Eptol, 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

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- 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 be seen 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) The prevalence of this allele is 2%–5% in northern European populations and 9.1% of Japanese populations.
    - (b) No recommendations for testing for this allele have been issued.
  - vii. Nonepileptic indication: Trigeminal neuralgia
  - c. Eslicarbazepine acetate (Aptiom)
    - i. Mechanism of action: Fast sodium channel blocker
    - ii. Prodrug for S(+)-licarbazepine, an active metabolite of oxcarbazepine
    - iii. Adjust dose if creatinine clearance (CrCl) is less than 50 mL/minute.
  - d. Ethosuximide (Zarontin)
    - i. Mechanism of action: T-type calcium current blocker
    - ii. Useful only for absence seizures
  - e. Ezogabine (Potiga)
    - i. Mechanism of action: Potassium channel opener
    - ii. Adverse effects: Urinary retention, hallucinations, QT prolongation, pigment changes in retina, or blue discoloration of the lips, nail beds, face, legs, sclera, and conjunctiva
    - iii. Monitoring recommendations: Baseline and periodic eye examinations (every 6 months) with visual acuity testing and dilated fundus photography
    - iv. Ezogabine is a schedule V controlled substance
  - f. 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
  - g. 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 are used; 1 mg of phenytoin = 1.5 mg of fosphenytoin = 1 mg of phenytoin equivalent. Intramuscular or intravenous dosing is appropriate.
    - 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 of phenytoin equivalents per minute.
      - (d) Can deliver in normal saline solution or D<sub>5</sub>W (5% dextrose [in water] injection)
  - h. Gabapentin (Neurontin)
    - i. Mechanism of action: Inhibition of  $\alpha_2\delta$  subunit of voltage-dependent calcium channels
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- 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 neuralgia, 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.
- i. Lacosamide (Vimpat)
  - i. Mechanism of action: Slow sodium channel blocker
  - ii. Maximal dose of 300 mg/day with a CrCl of 30 mL/minute 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 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 a U.S. Food and Drug Administration (FDA) indication only for replacement of oral formulation
- j. 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; 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 bipolar I mood disorder
- k. Levetiracetam (Keppra)
  - i. Mechanism of action: May prevent hypersynchronization of epileptiform burst firing and propagation of seizure activity
  - ii. Pharmacokinetics: Not metabolized largely, adjust dose in renal dysfunction, no drug interactions with other seizure medications
  - iii. Parenteral use: Currently indicated by the FDA 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.
- l. 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).



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- m. Perampanel (Fycompa)
    - i. Mechanism of action: Noncompetitive antagonist of the ionotropic  $\alpha$ -amino-3-hydroxy-5-methyl-4-isoxazole propionic acid (AMPA) glutamate receptor
    - ii. Pharmacokinetics: 95%–96% protein bound to albumin and  $\alpha_1$ -acid glycoprotein; metabolized by cytochrome P450 (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
  - n. Phenobarbital (Luminal)
    - i. Mechanism of action: Increases  $\gamma$ -aminobutyric acid–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
  - o. 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
  - p. Pregabalin (Lyrica)
    - i. Mechanism of action: Inhibition of  $\alpha_2\delta$  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<sup>a</sup>

Drug	Focal	Generalized Tonic-Clonic	Absence	Atypical Absence	Atonic	Myoclonic	Infantile Spasms	Status Epilepticus	Lennox-Gastaut Syndrome
Acetazolamide	4	4	3	3	—	—	—	—	—
Carbamazepine	1	1	—	—	4	4	—	—	—
Clobazam	4	4	3	—	—	3	—	—	1
Clonazepam	3	3	2	2	1	2	2	—	1
Corticotropin	—	—	—	—	—	—	1	—	—
Diazepam	—	—	—	4	—	4	4	1	2
Eslicarbazepine	4	—	—	—	—	—	—	—	—
Ethosuximide	—	—	1	1	—	4	—	—	—
Ezogabine	4	—	—	—	—	—	—	—	—
Felbamate	5	5	5	—	—	5	—	—	5
Gabapentin	1	2	—	—	—	—	—	—	—
Lacosamide	1	—	—	—	—	—	—	3	—
Lamotrigine	1	1	2	4	3	3	—	—	1
Levetiracetam	1	1	4	—	—	3	—	3	—
Lorazepam	3	3	3	3	—	3	—	1	—
Oxcarbazepine	1	1	—	—	3	3	—	—	—
Perampanel	4	—	—	—	—	—	—	—	—
Phenobarbital	2	2	2	—	—	3	—	2	—
Phenytoin	2	2	—	—	—	3	—	1	—
Pregabalin	4	—	—	—	—	—	—	—	—
Primidone	2	2	2	—	—	—	—	—	—
Rufinamide	4	3	3	—	3	—	—	—	1
Tiagabine	4	—	—	—	4	4	—	—	—
Topiramate	1	1	3	—	3	1	—	—	—
Valproic acid	2	1	1	1	1	1	1	2	—
Vigabatrin	5	5	—	—	—	—	5	—	—
Zonisamide	1	3	3	—	—	4	—	—	—

<sup>a</sup>Not all uses are U.S. Food and Drug Administration (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

Antiepileptic Drug	Added Seizure Medication	Change in Serum Concentration of the Initial Seizure Medication	Mechanism
Carbamazepine	Ethosuximide	Decreased	Increased metabolism
	Felbamate	Decreased, increased epoxide (active component of carbamazepine)	Inhibits epoxide degradation
	Phenytoin	Decreased	Increased metabolism
	Phenobarbital	Decreased	Increased metabolism
	Primidone	Decreased	Increased metabolism
	Rufinamide	Decreased	Increased metabolism
Clobazam	Eslicarbazepine	Increased	Decreased metabolism
Eslicarbazepine	Carbamazepine	Decreased	Increased metabolism
	Phenobarbital	Decreased	Increased metabolism
	Phenytoin	Decreased	Increased metabolism
Ezogabine	Carbamazepine	Decreased	Probable increased metabolism
	Phenytoin	Decreased	Probable increased metabolism
Felbamate	Carbamazepine	Decreased	Increased metabolism
	Phenytoin	Decreased	Increased metabolism
Lamotrigine	Carbamazepine	Decreased	Increased metabolism
	Phenobarbital	Decreased	Increased metabolism
	Phenytoin	Decreased	Increased metabolism
	Primidone	Decreased	Increased metabolism
	Rufinamide	Decreased	Increased metabolism
	Valproic acid	Increased	Decreased metabolism
Oxcarbazepine	Carbamazepine	Decreased	Increased metabolism
	Phenobarbital	Decreased	Increased metabolism
	Phenytoin	Decreased	Increased metabolism
	Valproic acid	Decreased	Unknown
Perampanel	Carbamazepine	Decreased	Increased metabolism
	Oxcarbazepine	Decreased	Increased metabolism
	Phenytoin	Decreased	Increased metabolism
Phenobarbital	Oxcarbazepine	Increased	Decreased metabolism
	Phenytoin	Increased	Unknown
	Rufinamide	Increased	Decreased metabolism
	Valproic acid	Increased	Inhibition of metabolism
Phenytoin	Carbamazepine	Decreased	Increased metabolism
	Eslicarbazepine	Increased	Decreased metabolism
	Oxcarbazepine	Increased or no change	Unknown
	Phenobarbital	Increased or decreased	Decreased or increased metabolism
	Rufinamide	Increased	Unknown
	Topiramate	Increased	Decreased metabolism
	Valproic acid	Decreased total; increased free	Displacement from binding sites
	Vigabatrin	Decreased	Increased metabolism

**Table 2.** Selected Interactions Between Seizure Medications (*continued*)

Antiepileptic Drug	Added Seizure Medication	Change in Serum Concentration of the Initial Seizure Medication	Mechanism
Primidone	Carbamazepine	Increased phenobarbital concentration	Unknown
	Phenytoin	Increased phenobarbital concentration	Unknown
Rufinamide	Carbamazepine	Decreased	Increased metabolism
	Phenobarbital	Decreased	Increased metabolism
	Phenytoin	Decreased	Increased metabolism
	Primidone	Decreased	Increased metabolism
	Valproic acid	Increased	Decreased clearance
Topiramate	Carbamazepine	Decreased	Increased metabolism
	Lamotrigine	Decreased	Unknown
	Phenytoin	Decreased	Increased metabolism
	Valproic acid	Decreased	Increased metabolism
Valproic acid	Carbamazepine	Decreased	Increased metabolism
	Felbamate	Increased	Unknown
	Oxcarbazepine	Decreased	Unknown
	Phenobarbital	Decreased	Increased metabolism
	Phenytoin	Decreased	Increased metabolism
	Primidone	Decreased	Increased metabolism
	Topiramate	Decreased	Increased metabolism
Zonisamide	Carbamazepine	Decreased	Increased metabolism
	Phenobarbital	Decreased	Increased metabolism
	Phenytoin	Decreased	Increased metabolism

**Table 3.** Selected Interactions of Non-AEDs on Seizure Medications

Seizure Medication	Other Drug	Effect on the Seizure Medication	Mechanism
Carbamazepine	Cimetidine	Increased serum concentration	Inhibition of carbamazepine metabolism
	Diltiazem	Increased serum concentration	Inhibition of carbamazepine metabolism
	Erythromycin	Increased serum concentration	Inhibition of carbamazepine metabolism
	Isoniazid	Increased serum concentration	Inhibition of carbamazepine metabolism
	Nefazodone	Increased serum concentration	Inhibition of carbamazepine metabolism
	Theophylline	Decreased serum concentration	Increased carbamazepine metabolism
	Troleandomycin	Increased serum concentration	Inhibition of carbamazepine metabolism
	Verapamil	Increased serum concentration	Inhibition of carbamazepine metabolism
Clobazam	Fluconazole	Increased serum concentration	Inhibitor of CYP2C19
	Fluvoxamine	Increased serum concentration	Inhibitor of CYP2C19
	Omeprazole	Increased serum concentration	Inhibitor of CYP2C19
	Ticlopidine	Increased serum concentration	Inhibitor of CYP2C19
Gabapentin	Antacids	Decreased serum concentration	Decreased bioavailability

**Table 3.** Selected Interactions of Non-AEDs on Seizure Medications (*continued*)

Seizure Medication	Other Drug	Effect on the Seizure Medication	Mechanism
Lamotrigine	Estrogen-containing contraceptives	Decreased serum concentration	Possibly induction of glucuronidation of lamotrigine
	Rifampin	Decreased serum concentration	Possibly induction of glucuronidation of lamotrigine
Perampanel	Ethanol and other CNS depressants	CNS additive or supra-additive effects	Additive CNS depression
	Rifampin	Decreased serum concentration	Increased metabolism
	St. John's wort	Decreased serum concentration	Increased metabolism
Phenobarbital; primidone	Ethanol	Acute ethanol ingestion may cause CNS additive effects and respiratory depression; chronic ethanol ingestion may result in variable effects	Additive CNS depression and decreased barbiturate metabolism with acute ethanol ingestion
Phenytoin	Anticoagulants, oral	May increase phenytoin serum concentration; decreased or increased anticoagulant effects	Complex mechanism
	Antineoplastics (bleomycin, cisplatin, vinblastine, methotrexate, carmustine)	Decreased pharmacologic effect	Unknown, possible decreased absorption caused by antineoplastic mucosal damage
	Chloramphenicol	Increased phenytoin serum concentration; decreased or increased chloramphenicol serum concentration	Inhibition of phenytoin metabolism; effect on chloramphenicol unknown
	Cimetidine	Increased serum concentration	Inhibition of phenytoin metabolism
	Diazoxide	Decreased pharmacologic effect; decreased serum concentration	Increased phenytoin metabolism
	Diltiazem	Increased serum concentration	Inhibition of phenytoin metabolism
	Disulfiram	Increased serum concentration	Inhibition of phenytoin metabolism
	Folic acid	Decreased serum concentration	Complex mechanism
	Isoniazid	Increased serum concentration	Inhibition of phenytoin metabolism
	Phenylbutazone	Increased serum concentration	Inhibition of phenytoin metabolism; plasma protein displacement
	Rifampin	Decreased serum concentration	Increased phenytoin metabolism
	Sulfonamides	Increased serum concentration	Inhibition of phenytoin metabolism
	Trimethoprim	Increased serum concentration	Inhibition of phenytoin metabolism
Topiramate	Hydrochlorothiazide	Increased serum concentration	Unknown
Valproic acid	Estrogen-containing oral contraceptives	Decreased serum concentration	Possibly induction of glucuronidation of lamotrigine
	Meropenem	Decreased serum concentration	Increased valproic acid metabolism
	Rifampin	Decreased serum concentration	Increased valproic acid metabolism
	Salicylates	Increased pharmacologic effect	Plasma protein displacement; increased free valproic concentration

AED = antiepileptic drug; CNS = central nervous system; CYP = cytochrome P450.

**Table 4.** Pharmacokinetic Parameters of Seizure Medications When Used as Monotherapy

Drug	Therapeutic Serum Concentration (mcg/mL)	Bioavailability (%)	Plasma Protein Binding (%)	Vd (L/kg)	Eliminated Unchanged (%)	Clinically Active Metabolites	Half-life (hours)
Acetazolamide	10–14	100	>90	0.23	100	None	48–96 10–15 (children)
Carbamazepine	4–12	>70	40–90	0.8–1.9 1.5 (neonates) 1.9 (children)	Little, if any	10,11-epoxide	12–17 8–14 (children)
Clobazam	Not established	100	80–90	100	3	N-desmethyloclobazam	36–2 71–82 (N-desmethyloclobazam)
Clonazepam	20–80 ng/mL	100	47–80	3.2	Low percentage	7-amino, low activity	19–50 22–33 (children)
Eslicarbazepine	Not established	90	<40	0.87	90	R-licarbazepine, oxcarbazepine	13–20
Ethosuximide	40–100	100	0	0.6–0.7	10–20	None	52–60 24–36 (children)
Ezogabine	Not established	60	80	2–3	36	NAMR	7–11
Felbamate	30–60 <sup>a</sup>	>90	22–36	0.74–0.85	40–50	None	11–20 13–23 (children)
Gabapentin	2–20 <sup>a</sup>	Dose-dependent	<3	0.65–1.04	75–80	None	5–7
Lacosamide	Not established	100	<15	0.6	40	None	13
Lamotrigine	1–13	98	55	0.9–1.2	10	None	12–55 24–30 (children)
Levetiracetam	12–46 <sup>a</sup>	100	<10	0.5–0.7	66	None	7 5 (children)
Oxcarbazepine	3–35 <sup>a</sup>	100 <sup>f</sup>	67	0.7	<1	10-monohydroxy	9 <sup>f</sup>
Perampanel	Not established	100	95–96	—	20–36	None	105
Phenobarbital	15–40	80–100	40–60	0.7–1	25	None	80–100 45–173 (neonates) 37–73 (children)
Phenytoin	10–20	85–95	>90	0.6–0.8	<5	None	~20 <sup>b</sup> 10–140 (neonates) <sup>b</sup> 5–18 (children) <sup>b</sup>
Pregabalin	Not established	≥90	0	0.5	90	None	6
Primidone	4–12 (20) <sup>c</sup>	90–100	80	0.6	20–40	Phenobarbital PEMA	10–15; 17 (PEMA) 4.5–18 (children) 10–36 (PEMA; children)
Rufinamide	Not established	85	34	50 <sup>d</sup>	2	None	6–10
Tiagabine	0.02–0.2 <sup>a</sup>	90–95	96	1.2	—	None	3.2–5.7
Topiramate	5–20 <sup>a</sup>	80	13–17	0.6–0.8	70	None	12–21
Valproic acid	40–100 (150) <sup>c</sup>	100	>90 <sup>e</sup>	0.2	<5	Unknown	8–17 4–14 (children)
Vigabatrin	Not established	100	0	1.1	80	None	7.5 5.7 (infants)
Zonisamide	10–40	50	40	1.45	35	None	63

<sup>a</sup>Therapeutic serum concentrations not well established.

<sup>b</sup>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.

<sup>c</sup>Upper end of the serum concentration range is not definitely established.

<sup>d</sup>Depends on dose.

<sup>e</sup>May vary with serum concentration.

<sup>f</sup>Bioavailability decreased in children younger than 8 years and in older adults; clearance is 80% higher in children 2–4 years and 40% higher in children 4–12 years compared with adults.

NAMR = N-acetyl metabolite of ezogabine; PEMA = phenylethylmalonamide; Vd = volume of (drug) distribution.

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- q. Primidone (Mysoline)
    - i. Mechanism of action: Increases  $\gamma$ -aminobutyric–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
  - r. 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
  - s. Tiagabine (Gabitril)
    - i. Mechanism of action: Blocks  $\gamma$ -aminobutyric reuptake in the presynaptic neuron
    - ii. Associated with new-onset seizures and status epilepticus in patients without epilepsy
  - t. Topiramate (Topamax)
    - i. Mechanism of action: Fast sodium channel blocker, enhances  $\gamma$ -aminobutyric 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 formulation (Troken XR)
    - v. Nonepileptic indication: Prophylaxis of migraine headaches
  - u. Valproic acid (Depacon, Depakene, Depakote, Stavzor)
    - i. Mechanism of action: Blocks T-type calcium currents, blocks sodium channels, increases  $\gamma$ -aminobutyric 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 on enzyme inducer, drug is dosed more frequently); 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
  - v. Vigabatrin (Sabril)
    - i. Mechanism of action: Irreversible inhibition of  $\gamma$ -aminobutyric acid 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
- v. Available as oral powder for solution
- w. Zonisamide (Zonegran)
  - i. Mechanism of action: Fast sodium channel blocker, blocks T-type calcium currents, weak carbonic anhydrase inhibitor
  - ii. Nonacrylamine sulfonamide: Avoid in sulfa-sensitive patients; it is sometimes used in patients with nonserious sulfa allergies, particularly when nonacrylamides (i.e., sulfonyleureas) 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 Medicine Doses

Drug	Starting Dose	Usual Maximal Dose
Carbamazepine	200 mg twice daily	1600 mg/day
Clobazam	10 mg/day	40 mg/day
Clonazepam	0.5 mg three times/day	20 mg/day
Eslicarbazepine	400 mg/day	1200 mg/day
Ethosuximide	250 mg twice daily	1.5 g/day
Ezogabine	100 mg three times/day	1200 mg/day
Felbamate	400 mg three times/day	3600 mg/day
Gabapentin	300 mg three times/day	3600 mg/day
Lacosamide	50 mg twice daily	400 mg/day
Lamotrigine	With valproic acid: 25 mg every other day Without carbamazepine, phenytoin, phenobarbital, primidone, or valproic acid: 25 mg/day With carbamazepine, phenytoin, phenobarbital, primidone, and not with valproic acid: 50 mg/day	With valproic acid: 200 mg/day Without carbamazepine, phenytoin, phenobarbital, primidone, or valproic acid: 375 mg/day With carbamazepine, phenytoin, phenobarbital, primidone, and not with valproic acid: 500 mg/day
Levetiracetam	500 mg twice daily	3000 mg/day
Oxcarbazepine	300 mg twice daily	2400 mg/day
Perampanel	With enzyme-inducing seizure medications: 4 mg/day Without enzyme-inducing seizure medications: 2 mg/day	With enzyme-inducing seizure medications: 12 mg/day Without enzyme-inducing seizure medications: 8 mg/day
Phenobarbital	1–3 mg/kg/day	300 mg/day
Phenytoin	100 mg three times/day	600 mg/day
Pregabalin	75 mg twice daily	600 mg/day
Primidone	100 mg at bedtime	2000 mg/day
Rufinamide	200–400 mg twice daily	3200 mg/day



**Table 5.** Starting and Maximal Adult Seizure Medicine Doses (*continued*)

Drug	Starting Dose	Usual Maximal Dose
Tiagabine	With carbamazepine, phenytoin, primidone, phenobarbital: 4 mg/day Without carbamazepine, phenytoin, primidone, phenobarbital: 2 mg/day	With carbamazepine, phenytoin, primidone, phenobarbital: 56 mg/day
Topiramate	25–50 mg/day	1000 mg/day
Valproic acid	10–15 mg/kg/day	60 mg/kg/day
Vigabatrin	500 mg twice daily	3000 mg/day
Zonisamide	100 mg/day	600 mg/day

2. Surgery: Surgery can sometimes drastically reduce the number of seizures; possible surgical procedures include removal of the seizure focus, corpus callosotomy, or vagus nerve stimulators.
3. Status epilepticus
  - a. Treatment principles
    - i. Ascertain ABCs (airway, breathing, and circulation).
    - ii. Laboratory values (fingerstick blood glucose, complete blood cell count, basic metabolic panel, calcium, magnesium, and seizure medicine serum concentrations, if applicable) are sent to determine any reversible causes of status epilepticus.
    - iii. Give an emergent 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 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 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

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- 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, requiring treatment with vasopressors; should have continuous blood pressure (BP) measurement
      - (b) Must be on ventilator
    - ii. Thiopental: Load 2–7 mg/kg up to 50 mg/minute; follow with 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 experience 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.
        - (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 below).
        - (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 (Meador KJ et al. Effects of fetal antiepileptic drug exposure: outcomes at age 4.5 years. *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 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 babies 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 monohydroxylated derivative [MHD]) serum concentrations monitored during pregnancy may be considered.

**Table 6.** Effect of Seizure Medications on Hormonal Contraceptives

<b>Seizure Medication</b>	<b>Oral Contraceptives, Contraceptive Patch, Contraceptive Vaginal Ring, Progestogen Implant</b>	<b>Medroxyprogesterone Acetate Depot Injection, Levonorgestrel-Releasing Intrauterine System</b>
Carbamazepine Clobazam Eslicarbazepine Felbamate Lamotrigine Oxcarbazepine Perampanel Phenobarbital Phenytoin Primidone Rufinamide Topiramate <sup>a</sup>	Decrease effectiveness	No effect
Benzodiazepines Ethosuximide Gabapentin Lacosamide Levetiracetam Pregabalin Tiagabine Valproic acid Vigabatrin Zonisamide	No effect	No effect

<sup>a</sup>Above doses of 200 mg/day.

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## E. Other Issues

1. Driving: All states place driving restrictions on people with epilepsy; some require mandatory physician reporting to the state department of transportation.
2. Medication discontinuation
  - a. The American Academy of Neurology (AAN) has a practice guideline (Practice parameter: a guideline for discontinuing antiepileptic drugs in seizure-free patients—a summary statement. *Neurology* 1996;47:600-2. Available at <http://aan.com/professionals/practice/pdfs/gl0007.pdf>) with the following criteria for withdrawal:
    - 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.
3. 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 to be of benefit:
    - 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 the diagnosis of 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
4. Sexual dysfunction
  - a. Described in 30%–60% of men and women with epilepsy
  - b. Includes hyposexuality, 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.
5. 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

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- 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, 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 detrimental effect 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.
6. Suicidality
- a. Meta-analysis of 199 placebo-controlled clinical trials of 11 drugs (n=43,892 patients older than 5 years) showed 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 (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. An FDA alert was issued on January 31, 2008. Beginning December 16, 2008, the FDA required a warning and a medication guide for all seizure medications.
  - c. A more recent cohort study was performed that showed no increased risk of suicide or suicide attempts with the use of seizure medications in patients with epilepsy compared with patients with epilepsy who were not taking seizure medications.
  - d. An expert consensus statement was released in 2013 making the following points:
    - i. Although some (but not all) antiepileptic drugs can be associated with treatment-emergent psychiatric problems that may lead to suicidal ideation and behavior, the actual suicidal risk is yet to be established; however, it seems to be very low. The risk of discontinuing antiepileptic drugs or refusing to initiate them is significantly worse and can actually 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 starting or switching antiepileptic drugs, 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 new patient in the pharmacy where you work. He presents a prescription for carbamazepine 100 mg 1 orally twice daily with instructions to increase to 200 mg 1 orally three times daily. Currently, he does not take any medications and does not have any drug allergies. During your counseling session, T.M. tells you he must have blood drawn for a test in 3 weeks.

1. Which common potential adverse effect of carbamazepine is best assessed through a blood draw?
  - A. Leukopenia.
  - B. Renal failure.
  - C. Congestive heart failure.
  - D. Hypercalcemia.
  
2. One month later, T.M. returns to your pharmacy with a new prescription for lamotrigine 25 mg with instructions to take 1 tablet daily for 2 weeks, followed by 1 tablet twice daily for 2 weeks, followed by 2 tablets twice daily for 2 weeks, and then 3 tablets twice daily thereafter. He tells you that he is discontinuing carbamazepine because he developed a rash a few days ago. Which response is best?
  - A. The rash is probably caused by carbamazepine because carbamazepine rash often has delayed development.
  - B. The rash is unlikely to be caused by carbamazepine because carbamazepine rash usually presents after the first dose.
  - C. The rash is probably not caused by carbamazepine; it is probably attributable to carbamazepine-induced liver failure.
  - D. The rash is probably not caused by carbamazepine; it is probably attributable to carbamazepine-induced renal failure.
  
3. T.M. wants to know why it is necessary to increase the dose of lamotrigine so slowly. Which reply is best?
  - A. It causes dose-related psychomotor slowing.
  - B. It causes dose-related renal stones.
  - C. It causes dose-related paresthesias.
  - D. It causes dose-related rash.
  
4. J.G. is a 34-year-old patient who has been maintained on carbamazepine extended release 400 mg orally twice daily for the past 2 years. She has had no seizures for the past 4 years. She presents to the emergency department in status epilepticus. Which drug is best to use first?
  - A. Diazepam.
  - B. Lorazepam.
  - C. Phenytoin.
  - D. Phenobarbital.

**Patient Cases** (*continued*)

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 experienced 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 dose to phenytoin 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. 20 mcg/mL.
  
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. Tiagabine.
  - C. Carbamazepine.
  - D. Ethosuximide.
  
7. J.B. is a 25-year-old man with a history of seizure disorder. He has been treated with phenytoin 200 mg orally twice daily for 6 months, and his current phenytoin concentration is 6.3 mcg/mL. His neurologist decides to increase his phenytoin dose to 300 mg twice daily. Which adverse effect is J.B. most likely to experience related to the dose increase?
  - A. Drowsiness.
  - B. Acne.
  - C. Gingival hyperplasia.
  - D. Rash.
  
8. M.G., a 15-year-old boy with a diagnosis of juvenile myoclonic epilepsy, has been prescribed sodium divalproate. On which adverse effect is it best to counsel M.G.?
  - A. Oligohidrosis.
  - B. Renal stones.
  - C. Alopecia.
  - D. Word-finding difficulties.

**Patient Cases** (continued)

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 start 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 beginning drug therapy. Which strategy is best for G.Z.?
  - A. Discontinue her seizure medication immediately.
  - B. Discontinue her seizure medication immediately and give folic acid.
  - 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, based on 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, based on 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.



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- 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 risk of stroke; those with more than 50 mcg of estrogen increase risk 4.5 times; 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 experience 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.
    - a. Recommendations based on Lansberg MG, O'Donnell MJ, Khatri P, et al. Antithrombotic and thrombolytic therapy for ischemic stroke: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed. American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. Chest 2012;141:e601S-36S. Available at <http://journal.publications.chestnet.org/pdfaccess.ashx?ResourceID=6568275&PDFSource=13>. Accessed September 17, 2014; You JJ, Singer DE, Howard PA, et al. Antithrombotic and thrombolytic therapy for atrial fibrillation: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed. American College of Chest Physicians Evidence-Based
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- b. CHA<sub>2</sub>DS<sub>2</sub>-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 TIA or age 75 years or older.
    - iii. Total for the CHA<sub>2</sub>DS<sub>2</sub>-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 gastrointestinal 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.
    - v. Avoid the use of dabigatran and P-glycoprotein (P-gp) inhibitors in patients with a CrCl of 15–30 mL/minute.
    - vi. Avoid use in patients with a CrCl less than 15 mL/minute or advanced liver disease.
    - vii. Avoid use in patients with mechanical heart valves.
    - viii. The capsule should not be opened because it increases bioavailability by 75%.
  - d. Rivaroxaban (Xarelto) is probably as effective as warfarin with similar risk of major bleeding. Higher risk of gastrointestinal 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 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.

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### 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.
  - b. Avoid in hemorrhagic stroke.
2. Streptokinase: Should be avoided because of excess mortality
3. Tissue plasminogen activator (Activase)
  - 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.
  - e. Exclusion criteria
    - i. Minor or rapidly improving stroke signs or symptoms
    - ii. Intracranial or subarachnoid bleeding (or history)
    - iii. Other active internal bleeding
    - iv. Intracranial surgery, head trauma, stroke within 3 months
    - v. Major surgery or serious trauma within 2 weeks
    - vi. Gastrointestinal (GI) or urinary tract hemorrhage within 3 weeks
    - vii. Blood pressure greater than 185/110 mm Hg or aggressive treatment required to lower blood pressure
    - viii. Glucose less than 50 mg/dL or greater than 400 mg/dL
    - ix. Arterial puncture at a noncompressible site or lumbar puncture within 1 week
    - x. Seizure at stroke onset
    - xi. Intracranial neoplasm, arteriovenous malformation, aneurysm
    - xii. Active treatment with warfarin (INR greater than 1.7), heparin (elevated activated partial thromboplastin time), or platelet count less than 100,000 cells/mm<sup>3</sup>
    - xiii. Postmyocardial infarction pericarditis
    - xiv. Pregnancy
    - xv. Additional criteria for the 3- to 4½-hour period
      - (a) Taking any oral anticoagulant
      - (b) Baseline National Institutes of Health Stroke Scale score greater than 25
      - (c) Previous stroke combined with diabetes
      - (d) Age older than 80
4. Initiate aspirin (160- to 325-mg initial dose with 50- to 100-mg maintenance dose) within 48 hours of stroke onset in patients not eligible for tissue plasminogen activator.

### D. Secondary Prevention

1. Reduction in all modifiable risk factors (specific changes below based on Kernan WN, Ovbiagele B, Black HR, et al. Guidelines for the prevention of stroke in patients with stroke and transient ischemic attack: a guideline for healthcare professionals from the American Heart Association/American Stroke Association. *Stroke* 2014;45:2160-236. Available at <http://stroke.ahajournals.org/content/45/7/2160.full.pdf+html?sid=0efbdc13-bba8-4e90-b197-d58dd042f816>. Accessed September 17, 2014.)
  - a. Hypertension: Goal <140/<90 mm Hg. With lacunar stroke, may target <130 mm Hg systolic
  - b. Hyperlipidemia: High-intensity statin therapy should be initiated or continued as first-line therapy in women and men less than 75 years of age 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 might be considered for initiation within 24 hours of a minor ischemic stroke or TIA or in the setting of intercranial atherosclerotic disease and continued for 90 days; however, long-term treatment increases risk of hemorrhage. The American Association of Chest Physicians recommends clopidogrel or aspirin/dipyridamole over aspirin or cilostazol.
    - a. Aspirin
      - i. Dose: Between 75 and 100 mg/day
      - ii. If the patient has an additional stroke while taking aspirin, there is no evidence that 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; there may be interactions 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](http://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: Complete blood cell count with differential every 2 weeks for 3 months, periodically thereafter. Thus, used infrequently
  5. Anticoagulation: Warfarin (Athrombin-K, Coumadin, Jantoven, Panwarfin)
    - a. Prevention of second ischemic event, if patient has atrial fibrillation, rheumatic mitral valve disease, mechanical prosthetic heart valves, bioprosthetic heart valves, or left ventricular mural thrombus formation
    - b. Target INR of 2.5 (3.0 for mechanical prosthetic heart valves)

**Patient Cases**

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

L.R. is a 78-year-old man who presents to the emergency department for symptoms of right-sided paralysis. He states that these symptoms began about 5 hours ago and have not improved since then. He also has hypertension, benign prostatic hypertrophy, diabetes mellitus, erectile dysfunction, and osteoarthritis.

11. Which is the most accurate list of L.R.'s risk factors for stroke?
  - A. Erectile dysfunction, age, osteoarthritis.
  - B. Sex, diabetes mellitus, osteoarthritis.
  - C. Benign prostatic hypertrophy, diabetes mellitus, age, sex.
  - D. Age, diabetes mellitus, sex, hypertension.
  
12. Is L.R. a candidate for tissue plasminogen activator for treatment of stroke?
  - A. Yes.
  - B. No, he is too old.
  - C. No, his stroke symptoms began too long ago.
  - D. No, his diabetes mellitus is a contraindication for tissue plasminogen activator.
  
13. L.R. was previously taking no drugs at home. Which choice is the best secondary stroke prevention therapy for this patient?
  - A. Sildenafil.
  - B. Celecoxib.
  - C. Aspirin.
  - D. Warfarin.
  
14. You are the pharmacist at a community pharmacy and receive a call from M.W., a 60-year-old man recently given a diagnosis of atrial fibrillation. He is concerned about his risk of having a stroke because his friend, who also has atrial fibrillation, asked him which dose of warfarin he is taking. M.W. called you because he is not taking warfarin 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, what should you tell him?
  - A. You need warfarin treatment to prevent a stroke.
  - B. You do not need warfarin, 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 72-year-old woman with a medical history of hypertension, type 2 diabetes mellitus, renal failure, and atrial fibrillation. 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.

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### III. PARKINSON DISEASE

#### A. Epidemiology

1. Prevalence is 160 in 100,000.
2. Onset usually between 40 and 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/Symptoms

1. Cardinal signs
  - a. Akinesia/hypokinesia
  - b. Rigidity
  - c. Tremor
  - d. Posture/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 been unequivocally shown to prevent progression of Parkinson disease; therefore, treatment is based on symptoms.
  - b. In patients who require the initiation of dopaminergic treatment, either levodopa or a dopamine agonist may be used. The 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 individual 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 to treat 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

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- 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 required 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/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/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, and 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 required (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 monitoring of the electrocardiogram 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.
    - iv. Dosing: Always titrate to final dose.

**Table 7.** Usual Dosage Range for Dopamine Agonists

Agent	Usual Dosage Range (mg/day)
Bromocriptine	5–40
Pramipexole	1.5–4.5
Ropinirole	0.75–24
Rotigotine	6–8

- v. Adverse effects: Nausea, vomiting, postural hypotension, hallucinations, hypersexuality, compulsive behaviors, 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/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 nausea and 11% vomiting WITH trimethobenzamide
    - (2) Hypotension
    - (3) Hallucinations
    - (4) Injection site reactions
    - (5) Dyskinesias
  - (e) Dosing
    - (1) Must be titrated in a setting where BP 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 BP 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, reinstate at a 0.2-mL dose.
- f. Anticholinergics
  - i. Drugs: Trihexyphenidyl (Artane), benztropine (Cogentin)
  - ii. Most useful 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



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- 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 C<sub>max</sub> or T<sub>max</sub> 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/vivid dreams
3. Surgery: Several types of surgery are performed 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 frequently performed surgery for Parkinson disease
    - ii. Thought to work by stimulating areas of the basal ganglia to reversibly block the neuronal activity in the area
    - iii. Patient selection focuses on patients with
      - (a) Motor fluctuations and/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 perform the surgery in patients older than 70 years.
    - 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/psychosis may be caused by either Parkinson disease or treatment.
    - i. Discontinue/reduce Parkinson disease medications as tolerated.
    - ii. If an antipsychotic is required, use quetiapine or clozapine as the first choice.
    - iii. Avoid typical antipsychotics, risperidone, and olanzapine because they may worsen Parkinson symptoms.
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- b. Cognitive disorders
  - i. Discontinue/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, and blepharitis can be seen in Parkinson disease; treat as usual.

**Patient Cases**

*Questions 16 and 17 pertain to the following case:*

L.S. is taking 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 he is often confused and experiences constipation; he has trouble talking because of his dry mouth.

16. Which change is best to resolve these symptoms?
- A. Increase carbidopa/levodopa.
  - B. Increase trihexyphenidyl.
  - C. Decrease carbidopa/levodopa.
  - D. Decrease 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. 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 is the most likely cause of 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., a 57-year-old white man who just retired from the New York City Fire Department, has been experiencing tremors in his right hand that have become progressively worse 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. He is given a diagnosis of Parkinson disease. Which is the best treatment for this man?
- A. Trihexyphenidyl.
  - B. Entacapone.
  - C. Apomorphine.
  - 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 experiences 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 patient has a coexisting condition, consider prophylaxis choice (e.g.,  $\beta$ -blockers are contraindicated in patients with asthma but beneficial in hypertension).
  - ii. Medications with established efficacy
    - (a) Frovatriptan (for menstrually associated migraine, short-term prophylaxis only)
    - (b) Metoprolol
    - (c) Petasites (butterbur extract)
    - (d) Propranolol
    - (e) Timolol
    - (f) Topiramate
    - (g) 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 Q10
    - (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
- b. Acute treatment
- i. Triptans (see Table 8)
    - (a) Sumatriptan and zolmitriptan have nonoral administration routes (subcutaneous [sumatriptan] and intranasal [sumatriptan and zolmitriptan]) 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: 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. Isometheptene combination products: Conflicting evidence about efficacy
  - vi. Antiemetics: Prochlorperazine, metoclopramide, and chlorpromazine are most commonly used; there is some suggestion that they have independent antimigraine action; all are available in nonoral routes.
  - 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. Nonsteroidal anti-inflammatory drugs
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

	Dosage Forms	Tmax	Half-life (hours)	Dose	Maximal Dose/ 24 Hours (mg)
<b>Triptans</b>					
Almotriptan (Axert)	Tablets 6.25 mg, 12.5 mg	1–3 hours	2–4	1 tablet, may repeat in 2 hours	25
Eletriptan (Relpax)	Tablets 20 mg, 40 mg	1 hour	4–5	1 tablet, may repeat in 2 hours	80
Frovatriptan (Frova)	Tablets 2.5 mg	2–4 hours	26	1 tablet, may repeat in 2 hours	7.5
Naratriptan (Amerge)	Tablets 1 mg, 2.5 mg	2–3 hours	6	1 tablet, may repeat in 4 hours	5
Rizatriptan (Maxalt)	Tablets 5 mg, 10 mg	1–1.5 hours	1.8	1 tablet, may repeat in 2 hours	30
	Orally disintegrating tablets 5 mg, 10 mg	1.6–2.5 hours	1.8	1 tablet, may repeat in 2 hours	30
Sumatriptan (Imitrex)	SC injection 4 mg, 6 mg	12 minutes	1.9	1 injection, may repeat in 1 hour	12
	Intranasal 5 mg, 20 mg	30 minutes	2	1 spray in one nostril, may repeat in 2 hours	40
	Tablets 25 mg, 50 mg, 100 mg	2 hours	2.5	1 tablet, may repeat in 2 hours	200
Zolmitriptan (Zomig)	Tablets 2.5 mg, 5 mg	1.5 hours	3.75	1 tablet, may repeat in 2 hours	10
	Orally disintegrating tablets 2.5 mg, 5 mg	3 hours	3.75	1 tablet, may repeat in 2 hours	10
	Intranasal 2.5 mg, 5 mg	3 hours	3	1 spray in one nostril, may repeat in 2 hours	10
<b>Triptan/nonsteroidal anti-inflammatory combination</b>					
Sumatriptan/naproxen sodium (Treximet)	Tablets 85 mg/500 mg	1 hour/ 5 hours	2/19	1 tablet, may repeat in 2 hours	170/1000
<b>Ergots</b>					
Ergotamine tartrate (Ergomar)	Sublingual tablets 2 mg	Unknown	2	1 tablet under tongue, may repeat in 1 hour	6
Dihydroergotamine (DHE 45; Migranal)	Intranasal 4-mg ampules	0.9 hour	10	1 spray (0.5 mg) in each nostril, repeat in 15 minutes	3
	IV/IM/SC 1 mg/mL 1-mL vials	SC 15–45 minutes	9	1 mL IV/IM/SC, may repeat in 1 hour	2 mg IV; 3 mg IM/SC

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

**Patient Cases**

21. M.R., a 34-year-old woman, has throbbing right-sided headaches. She experiences nausea, phonophobia, and sonophobia with these headaches but no aura. She usually has headaches twice a month. She is hypertensive and morbidly obese. She takes an ethinyl estradiol/progestin combination oral contraceptive daily and hydrochlorothiazide 25 mg/day orally. She has a diagnosis of migraine headaches. Which medication is best for prophylaxis of her headaches?
- A. Propranolol.
  - B. Valproic acid.
  - C. Amitriptyline.
  - D. Lithium.
22. S.R. is a 54-year-old female homemaker with squeezing, bandlike headaches that occur three or four times weekly. She rates the pain of these headaches as 7/10 and finds acetaminophen, aspirin, ibuprofen, naproxen, ketoprofen, and piroxicam only partly effective. She wants to take a prophylactic drug to prevent these tension headaches. Which drug is best for prophylaxis of her headaches?
- A. Propranolol.
  - B. Valproic acid.
  - 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. Propranolol.
  - B. Valproic acid.
  - C. Amitriptyline.
  - D. Lithium.
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 triptan is best to treat M.K.'s migraine headaches?
- A. Almotriptan.
  - B. Naratriptan.
  - C. Rizatriptan.
  - D. Sumatriptan.

**Patient Cases** (*continued*)

25. One of the neurologists you work with read a meta-analysis of migraine treatments (Oldman AD, Smith LA, McQuay HJ, et al. Pharmacological treatment for acute migraine: quantitative systematic review. *Pain* 2002;91:247-57). He is most interested in the outcome of sustained relief at 24 hours, but he is confused by the number-needed-to-treat (NNT) analyses. He shows you the following table:

Drug	NNT
Ergotamine + caffeine	6.6
Eletriptan 80 mg	2.8
Rizatriptan 10 mg	5.6
Sumatriptan 50 mg	6.0

NNT = number needed to treat.

Which statement provides the best interpretation of these data?

- A. Eletriptan 80 mg is the most effective agent.
- B. Ergotamine plus caffeine is the most effective agent.
- C. Eletriptan has the most adverse effects.
- D. Ergotamine plus caffeine has the most adverse effects.

**V. MULTIPLE SCLEROSIS**

## A. Definitions

1. Autoimmune disorder with areas of CNS demyelination and axonal transection
2. Clinical course
  - a. Clinically isolated syndrome; first clinical presentation for which the criteria of dissemination in time has not been met to diagnose multiple sclerosis (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 usually between 20 and 50 years of age
2. Twice as many women as men develop multiple sclerosis.
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 diseases or migraine; cigarette smoke exposure (women only)

## C. Treatment

1. Acute relapses are treated with corticosteroids.
  - a. Intravenous methylprednisolone: The usual dose is 1 g/day as one dose or divided doses for 3–5 days.
  - b. Oral prednisone: The usual dose is 1250 mg/day given every other day for five doses.
  - c. Intravenous adrenocorticotrophic hormone
  - d. Neurologic recovery is the same with or without an oral prednisone taper.



- 
2. Disease-modifying therapies (Table 9)
    - a. Beta interferons (Avonex, Betaseron, Extavia, Plegridy, Rebif)
      - i. Mechanism of action: Suppress T-cell activity, downregulate 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 beta-1a decreases frequency of injections
      - iii. Injection site reactions: More common in subcutaneously administered products. It may help to bring a drug to room temperature before injection, ice the injection site, and rotate injection sites.
      - iv. Flulike symptoms: Usually dissipate in 2–3 months. It 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 beta interferons
    - b. 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.
    - c. 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.
    - d. Fingolimod (Gilenya)
      - i. Mechanism of action: Binds to the S1P receptor 1 expressed on T cells, prevents activation of T cells
      - ii. 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
      - iii. 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 remonitored.
      - iv. Adverse effects
        - (a) Bradycardia: Electrocardiogram is recommended within 6 months for patients using antiarrhythmics (including  $\beta$ -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 complete blood cell count should be available before therapy starts. 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 begin 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 be seen.
- (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.
- v. Drug interactions
  - (a) Ketoconazole: Increased fingolimod
  - (b) Vaccines: Less effective during and 2 months after fingolimod treatment; avoid live, attenuated vaccines.
- vi. Avoid pregnancy during treatment and for 2 months after treatment.
- e. 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 multiple sclerosis
  - 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 multiple-gated acquisition scans must be performed 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 (complete blood cell count, bilirubin, aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase, and pregnancy test) must be performed before each infusion.
  - viii. Avoid pregnancy during treatment.
- f. Natalizumab (Tysabri)
  - i. Mechanism of action: Block T-cell entry into the CNS
  - ii. Indicated for relapsing forms of multiple sclerosis 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; it 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 duration of natalizumab treatment (especially beyond 2 years), and previous treatment with an immunosuppressant medication (mitoxantrone, azathioprine, methotrexate, cyclophosphamide, mycophenolate mofetil)—are at 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.
- g. Teriflunomide (Aubagio)
- i. Mechanism of action: Prevents activation of lymphocytes
  - ii. Indicated for relapsing forms of multiple sclerosis
  - 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 (TB) infections reported (negative TB 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 experience fatigue, spasticity, urinary incontinence, pain, depression, cognitive impairment, fecal incontinence, constipation, pseudobulbar affect, and sexual dysfunction; treatment should be with standard therapies 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 multiple sclerosis 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

Drug (Brand)	Dose	Route	Frequency	Adverse Effects
Dimethyl fumarate (Tecfidera)	120 mg twice daily x 7 days; then 240 mg twice daily	PO	Twice daily	Skin flushing 38% GI events 41%
Fingolimod (Gilenya)	0.5 mg	PO	Daily	Increased AST/ALT 14% Infections 13% Diarrhea 12% Hypertension 6% Bradycardia 4% Blurred vision 4% Lymphopenia 4% Leukopenia 3%
Glatiramer acetate (Copaxone)	20 mg 40 mg	SC SC	Daily Three times/week	Injection site reaction 90% Systemic reaction 15%
Interferon beta-1a (Avonex)	30 mcg	IM	Weekly	Flulike symptoms 61% Anemia 8%
Interferon beta-1a (Rebif)	22 or 44 mcg	SC	Three times/week	Flulike symptoms 28% Injection site reactions 66% Leukopenia 22% Increased AST/ALT 17%–27%
Interferon beta-1b (Betaseron)	0.25 mg	SC	Every other day	Flulike symptoms 60%–76% Injection site reactions 50%–85% Asthenia 49% Menstrual disorder 17% Leukopenia 10%–16% Increased AST/ALT 4%–19%
Mitoxantrone (Novantrone)	12 mg/m <sup>2</sup> Up to 140 mg/m <sup>2</sup> (lifetime dose)	IV	Every 3 months	Nausea 76% Alopecia 61% Menstrual disorders 61% Urinary tract infection 32% Amenorrhea 25% Leukopenia 19% $\gamma$ -Glutamyl transpeptidase increase of 15%

**Table 9.** Comparison of Disease-Modifying Therapies (*continued*)

Drug (Brand)	Dose	Route	Frequency	Adverse Effects
Natalizumab (Tysabri)	300 mg	IV	Every 4 weeks	Headache 38% Fatigue 27% Arthralgia 19% Urinary tract infection 20% Hypersensitivity reaction <1%
Pegylated interferon beta-1a (Plegridy)	125 mcg	SC	Every 2 weeks	Injection site reactions 62% Flulike symptoms 47% Headache 44% Myalgia 19%
Teriflunomide (Aubagio)	7 mg or 14 mg	PO	Daily	Diarrhea 15%–18% Nausea 9%–14% Alopecia 10%–13% Neutropenia 10%–15% Lymphopenia 7%–10% Elevated ALT 3%–5% Hypertension 4% Peripheral neuropathy 1%–2%

GI, gastrointestinal; IM = intramuscular; IV = intravenous; PO = by mouth; SC = subcutaneous.

### 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 method is best for treating S.F.'s exacerbation?
- Interferon beta-1a.
  - Glatiramer acetate.
  - Mitoxantrone.
  - Methylprednisolone.
27. Which therapy is best for S.F. to prevent further exacerbations?
- Interferon beta-1a.
  - Interferon beta-1b.
  - Glatiramer acetate.
  - Any of the above.

**Patient Cases** (*continued*)

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. Always give the injection at the same time of day.
  - B. Lie down for 2 hours after the injection.
  - C. Rotate injection sites.
  - 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 potential medications to prevent exacerbations. During the discussion, you find that she and her husband are planning to have a baby in the next few years and that she is terrified of needles. Which choice is best for B.B.?
- A. Glatiramer acetate.
  - B. Mitoxantrone.
  - C. Teriflunomide.
  - D. Dimethyl fumarate.

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## ANSWERS AND EXPLANATIONS TO PATIENT CASES

**1. Answer: A**

Leukopenia is a common adverse effect of carbamazepine. Up to 10% of patients experience a transient decrease in their white blood cell count; however, the potential for serious hematologic abnormalities, including agranulocytosis and aplastic anemia, exists. Complete blood cell counts are recommended before initiation and periodically during therapy.

**2. Answer: A**

In general, dermatologic reactions to anticonvulsants occur after a delay of 2–8 weeks rather than immediately after medication initiation.

**3. Answer: D**

The rash that occurs with lamotrigine is often related to the speed of titration. Valproic acid inhibits the metabolism of lamotrigine; therefore, when these drugs are used together, the lamotrigine titration must be slowed even further. Psychomotor slowing, renal stones, and paresthesias are associated with topiramate and zonisamide.

**4. Answer: B**

Lorazepam is the drug of choice for status epilepticus. It is less lipophilic than diazepam; therefore, it does not redistribute from the CNS as quickly. After the seizures are stopped with lorazepam, a long-acting drug (phenytoin, fosphenytoin, or phenobarbital) should be administered to prevent further seizures.

**5. Answer: D**

Phenytoin shows nonlinear pharmacokinetics. A small increase in dose may result in a large increase in serum concentration. Therefore, without performing any calculations, we can surmise that an increase from 300 mg/day to 600 mg/day would more than double the serum concentration.

**6. Answer: D**

Ethosuximide is useful for absence seizures. The other listed medications are not used for absence seizures.

**7. Answer: A**

Drowsiness is a dose-related adverse effect of phenytoin. Acne, gingival hyperplasia, and rash can also be adverse effects, but they are not dose related.

**8. Answer: C**

Valproic acid and its derivatives are associated with alopecia. The hair will grow back if the drug is discontinued and sometimes even if the drug is continued. There are reports of the regrown hair being curly when patients previously had straight hair.

**9. Answer: D**

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

**10. Answer: C**

Alterations to seizure treatment regimens can be made when patients present to the health system before pregnancy. In this case, a different drug may be chosen, or medications may be eliminated if the patient is taking more than one seizure medication. In addition, efforts should be made to maintain the patient on the lowest possible doses that control seizures. However, when the patient presents to the health system already pregnant, the current medications are usually continued to avoid the risk of an increase in seizures during a medication change. Again, the lowest possible doses that control seizures should be used.

**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. Modification of risk factors, if possible, may translate into reduced stroke risk, which should be a focus of all stroke prevention plans.

**12. Answer: C**

Contraindications to administering tissue plasminogen activator for stroke include intracranial or subarachnoid bleeding (or history), other active internal bleeding, recent intercranial surgery, head trauma, BP

greater than 185/110 mm Hg, seizure at stroke onset, intracranial neoplasm, atrioventricular malformation, aneurysm, active treatment with warfarin or heparin, and platelet count less than 100,000. There is no upper limit on age. Until recently, there was a strict 3-hour limit for treating strokes. A recent study suggests this limit can be increased safely to administer tissue plasminogen activator 4½ hours after symptom onset with additional criteria.

**13. Answer: C**

All patients experiencing a stroke should be placed on a drug to prevent future events. Appropriate choices include aspirin, ticlopidine, cilostazol, clopidogrel, dipyridamole/aspirin, and warfarin. However, because of the risk of neutropenia, ticlopidine is usually not used first-line. If the patient has atrial fibrillation, he or she should be treated with warfarin, dabigatran, or rivaroxaban. If the patient does not have atrial fibrillation, warfarin offers no benefit but has considerable risk compared with aspirin. Otherwise, any of these drugs are reasonable choices.

**14. Answer: C**

No therapy is an appropriate choice for this patient (CHA<sub>2</sub>DS<sub>2</sub>-VASc score of 0) because he is younger than 65 years and has no other risk factors such as hypertension or a prosthetic valve.

**15. Answer: C**

The target INR for a patient younger than 75 years with hypertension and diabetes mellitus is 2.5.

**16. Answer: D**

Anticholinergic drugs (benztropine and trihexphenidyl) commonly cause adverse effects such as confusion, dry mouth, urinary retention, and constipation in older patients. Decreasing or eliminating these drugs may resolve the difficulties.

**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, administering the controlled-release formulation of carbidopa/levodopa, or adding a catechol-O-methyl transferase inhibitor. The terms *increase the dosing interval* and *decrease the dosing interval* are often misinterpreted. To increase the dosing interval means to give the doses farther apart.

**18. Answer: C**

Amantadine can cause livedo reticularis, a condition in which the dilation of capillary blood vessels and the stagnation of blood within these vessels cause a mottled, reddish blue discoloration of the skin. This usually occurs on the trunk and extremities; it is more pronounced in cold weather. Although simple venous stasis could occur, livedo reticularis is more likely in this patient.

**19. Answer: D**

Treatment of dyskinesias includes decreasing the levodopa dose, removing selegiline or dopamine agonists from the drug regimen, or adding amantadine.

**20. Answer: D**

Ropinirole, a direct dopamine agonist, is a good choice for initial treatment in a patient with Parkinson disease. Trihexphenidyl would control his tremor but would not improve his difficulty walking, which probably represents bradykinesia. Entacapone is a catechol-O-methyltransferase inhibitor; it should be used only in conjunction with carbidopa/levodopa. Apomorphine is for severe on-off symptoms.

**21. Answer: A**

A β-blocker is a good choice for a patient with the coexisting condition of hypertension. Valproic acid and amitriptyline could both increase weight gain in a morbidly obese patient. Lithium is used for prophylaxis of cluster headaches.

**22. Answer: C**

Amitriptyline is as effective as prophylaxis for tension headaches. β-Blockers and valproic acid are usually used for migraine headache prophylaxis, and lithium is used for prophylaxis of cluster headaches.

**23. Answer: D**

Lithium is a prophylactic agent for cluster headaches. β-Blockers and valproic acid are usually used for migraine headache prophylaxis. Amitriptyline is useful for migraine and tension headaches.

**24. Answer: D**

Sumatriptan is available as an injectable and as a nasal spray and would be more appropriate to use in a patient with severe nausea and vomiting. Zolmitriptan is available as a nasal spray. The other triptans are available only in oral preparations.

**25. Answer: A**

The NNT is a concept used to express the number of patients it would be necessary to treat to have one patient experience benefit (or to experience adverse effects, if looking at harm). It is calculated as  $NNT = 1/[(\% \text{ improved on active therapy}) - (\% \text{ improved on placebo})]$ . The NNT is calculated for each treatment and is therefore treatment-specific. Low NNTs indicate high treatment efficacy. If an NNT of 1 were calculated, it would mean that every patient on active therapy improved and that no patient on placebo improved.

**26. Answer: D**

Methylprednisolone is the only option used for treating acute exacerbations. Other options are high-dose oral prednisone or adrenocorticotropic hormone. Interferon beta-1a, glatiramer acetate, and mitoxantrone are all used as disease-modifying therapies.

**27. Answer: D**

The beta interferons and glatiramer acetate are appropriate initial choices for disease-modifying therapy. Mitoxantrone and natalizumab would not be used as a first-line therapy because of their potential toxicities.

**28. Answer: C**

Rotating the injection sites for the self-injections is a good strategy for preventing injection site reactions. 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, but this is not a strategy for preventing adverse effects.

**29. Answer: D**

Patients unable to give self-injection because of their fear of needles should not be given glatiramer acetate, which is a subcutaneous injection. Mitoxantrone has significant toxicities, and it is infrequently used to treat multiple sclerosis. In addition, this drug is pregnancy category X. Teriflunomide may take up to 2 years for elimination or rapid elimination protocols before pregnancy; thus, it would not be a good choice in this patient. Dimethyl fumarate has no data in human pregnancy right now and is pregnancy category C. However, this patient should carefully plan her conception and can discontinue the medication before pregnancy. Of the available choices, dimethyl fumarate is the best answer.

## ANSWERS AND EXPLANATIONS TO SELF-ASSESSMENT QUESTIONS

**1. Answer: C**

The therapeutic range for phenytoin is 10–20 mcg/mL. Although a serum concentration should never be interpreted without clinical information, this patient is having no seizures, nor is he experiencing toxicity. Because he is otherwise healthy, does not have known kidney dysfunction, and is not elderly, there is no need for an albumin concentration.

**2. Answer: B**

In general, medications to treat status epilepticus should be in parenteral formulation 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. Medications typically used for this purpose include phenytoin, fosphenytoin, phenobarbital, and (sometimes) valproic acid. Another benzodiazepine need not be administered because this patient's seizure activity has ceased.

**3. Answer: C**

Psychomotor slowing is a very troublesome adverse effect for many patients initiated on topiramate. It usually manifests as difficulty concentrating, difficulty thinking, word-finding difficulties, and a feeling of slowness of movement. The usual dosage titration for topiramate calls for increasing the dose every week. This patient has been increasing the topiramate dose every other day. Because psychomotor slowing is related to the speed of titration, this makes slowing the titration rate the most probable answer. Partial seizures could present as confusion; however, they are unlikely to be a continuous condition.

**4. Answer: B**

Patients who can be treated within 3 hours of stroke symptom onset should be considered for tissue plasminogen activator. A recent study showed good outcomes without excess mortality in patients treated within 4½ hours of stroke onset; however, more exclusion criteria must be applied. Uncontrolled hypertension (greater than 185/100 mm Hg) is a contraindication to tissue plasminogen activator treatment. Active use of heparin (with an elevated partial thromboplastin time) or warfarin (with an elevated INR) is a contraindication, but use of aspirin is not. This patient's onset of stroke

symptoms began 6 hours ago, so he is not eligible for tissue plasminogen activator treatment.

**5. Answer: D**

All stroke survivors require secondary stroke prevention drugs. If a patient claims to be adherent to aspirin when his first stroke occurred, a different drug is usually considered. Clopidogrel or dipyridamole/aspirin would be an acceptable choice. Heparin and enoxaparin are not suitable for long-term home use in secondary stroke prevention.

**6. Answer: B**

Wearing-off is the return of symptoms before the next dose. It has a definite pattern, whereas on-off is unpredictable. Dyskinesias and dystonias are long-term adverse effects of carbidopa/levodopa.

**7. Answer: D**

The first dose of apomorphine must be given in a clinic setting. The patient should not take apomorphine if he is allergic to metabisulfite. The dose should be retitrated if he has not taken apomorphine for 1 week. Apomorphine causes severe nausea and vomiting.

**8. Answer: A**

Because of the MAO inhibition induced by rasagiline, patients should not take meperidine, propoxyphene, tramadol, methadone, dextromethorphan, sympathomimetics, fluoxetine, or fluvoxamine. Guaifenesin can be safely taken in this situation.

**9. Answer: D**

The choice of drug for acute treatment of a patient with migraines and cardiac disease presents a difficulty. All triptans and ergotamines are contraindicated in this situation. A nonsteroidal anti-inflammatory drug is a possible choice.

**10. Answer: A**

When possible, a drug for migraine prophylaxis should be selected to confer additional benefit to a patient for a concomitant disease state. In the patient with coronary artery disease and hypertension, propranolol would be an excellent choice for migraine prevention.

**11. Answer: D**

Fingolimod is the only one of the given choices with an FDA indication for the treatment of multiple sclerosis. In addition, it has the best clinical trial evidence of efficacy. Methylprednisolone is used for treating acute multiple sclerosis exacerbations. Cyclophosphamide and azathioprine have been studied in progressive forms of multiple sclerosis, but their data are not as robust as are those for fingolimod.

**12. Answer: B**

Treatment of spasticity in multiple sclerosis requires the use of a centrally acting agent. Of the choices given, only diazepam and baclofen are centrally acting. Because of the significant fatigue and drowsiness occurring with diazepam, baclofen is usually a first-line therapy. Another acceptable choice would be tizanidine.

**13. Answer: C**

Agents used to treat multiple sclerosis-related fatigue include amantadine and methylphenidate. The other choices are not used in multiple sclerosis.