Neurology

Melody Ryan, Pharm.D., BCPS
University of Kentucky
Lexington, Kentucky

Learning Objectives:

1. Differentiate between various antiepileptic drugs based on 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 appropriateness of treatment with tissue plasminogen activator for acute stroke treatment.
5. Examine common adverse effects associated with treatment of Parkinson's disease.
6. Differentiate between regimens for acute and prophylactic treatment of migraine, tension, and cluster headaches.

Self-Assessment Questions:
Answers to these questions may 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 following a seizure about 2 months ago. He is currently taking phenytoin 100 mg 3 capsules orally every night. During his clinic visit, he tells you that 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. How would you interpret this concentration?
   A. It is too low.
   B. It is too high.
   C. It is just right.
   D. He should have an albumin determination to interpret this concentration.

2. When T.L. (from question No. 1) returns for his appointment with you, he tells you that his dentist told him 3 months ago that he had gingival hyperplasia. He began an intensive oral hygiene regimen and returned to see the dentist last week. Unfortunately, there has been no improvement and he was told that he will require gum reduction surgery if it does not improve. T.L. wants to discontinue the phenytoin. As you consider drugs to replace the phenytoin, which one of the following is contraindicated for T.L.?
   A. Oxcarbazepine.
   B. Valproic acid.
   C. Zonisamide.
   D. Tiagabine.

3. B.V. is a 28-year-old woman brought to your emergency department for treatment of status epilepticus. She is given lorazepam 4 mg intravenously (IV) with subsequent seizure cessation. Which one of the following medications should be the next treatment step for B.V.?
   A. Topiramate.
   B. Phenobarbital.
   C. Zonisamide.
   D. Diazepam.

4. J.H. is a 42-year-old man with complex partial seizures for which he was prescribed topiramate. He has been increasing the dose of topiramate every other day per instructions from his primary care provider. He comes into the pharmacy where you work, but seems a little confused and has difficulty finding the words to have a conversation with you. Which of the following is the best assessment of J.H.'s condition?
   A. Stop his topiramate; he is having an allergic reaction.
   B. Increase his topiramate dose; he is having partial seizures.
   C. Slow down the rate of topiramate titration; he is having psychomotor slowing.
   D. Get a topiramate serum concentration; he is likely supratherapeutic.

5. R.H. is a 59-year-old man who presents to the emergency department for new-onset left-sided weakness that began 3.5 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 are blood pressure 160/92 mm Hg, pulse 92 beats/minute, respiration rate 14 breathes/minute, and temperature 38°C. The treatment team is assessing this patient for treatment with tissue plasminogen activator and asks your opinion. Which one of the following should be your reply based on this information?
   A. R.H. should be treated with tissue plasminogen activator.
   B. R.H. should not be treated with tissue plasminogen activator because onset of his stroke symptoms was 3.5 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 is taking aspirin.

6. R.H. (from question No. 5) survives his stroke. As part of his discharge treatment plan, you evaluate his risk factors for a second stroke. You recommend beginning which one of the following medications for secondary stroke prevention?
A. Aspirin.
B. Enoxaparin.
C. Heparin.
D. Clopidogrel.

7. C.P. is a 69-year-old man diagnosed with Parkinson's 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 25/100 orally 4 times/day, pergolide 0.25 mg orally 3 times/day, selegiline 5 mg orally 2 times/day, and entacapone 200 mg orally 4 times/day. He has no medication allergies. He also describes a worsening of Parkinson's disease symptoms that fluctuate during the day. He finds that his symptoms return randomly during the day. He has developed a charting system for his symptoms over the course of the day, and there seems to be no relationship with the time he is scheduled to take his doses of carbidopa/levodopa. C.P.'s fluctuating Parkinson's disease symptoms are best described by which of the following conditions?
   A. Wearing off.
   B. On-off.
   C. Dyskinesia.
   D. Dystonia.

8. Which of C.P.'s (from question No. 7) medications has recently been associated with valvular heart disease?
   A. Carbidopa/levodopa.
   B. Pergolide.
   C. Selegiline.
   D. Entacapone.

9. For his symptoms, C.P. (from question No. 7) is given a prescription for apomorphine. Which one of the following is a true statement regarding this medication?
   A. He must be trained on self-injection technique with saline, but he can administer his first dose of apomorphine at home when he needs it.
   B. He should not take apomorphine if he is allergic to penicillin.
   C. If he does not take a dose for more than a week, he should begin with a loading dose with his next injection.
   D. It may cause severe nausea and vomiting.

10. W.S. is a 57-year-old man who is started on rasagiline for treatment of his newly-diagnosed Parkinson's disease. He develops a cough, body aches, and nasal congestion. Which of the following drugs could be safely recommended for W.S.?
   A. Guaifenesin.
   B. Dextromethorphan.
   C. Tramadol.
   D. Pseudoephedrine.

11. R.M. is a 47-year-old woman with long-standing migraine headaches. The headache pain is easily relieved with sumatriptan 100 mg orally as occasion requires. However, with her last dose, she experienced substernal chest pain radiating to her left arm. She reported to her local emergency department and had a complete work-up. Her final diagnosis was coronary artery disease and hypertension. For these conditions, she was placed on hydrochlorothiazide 25 mg orally every morning. R.M.'s family physician asks you which one of the following drugs R.M. should use for her migraine headaches.
   A. Frovatriptan.
   B. Zolmitriptan.
   C. Dihydroergotamine.
   D. Naproxen.

12. If R.M. (from question No. 11) requires a medication for migraine prophylaxis, which one of the following would you recommend?
   A. Propranolol.
   B. Valproic acid.
   C. Amitriptyline.
   D. Gabapentin.

I. Epilepsy

A. Epidemiology
   1. 10% of the population will have a seizure.
   2. About 50 million people worldwide have epilepsy.
   3. About 70% of patients can become seizure-free with appropriate management.

B. Classification of Seizure Types
   Seizures are generally classified according to the International League Against Epilepsy (ILAE) scheme adopted in 1981. There is a proposal currently to alter this scheme somewhat. (A complete discussion of this change can be found in Engle J. A proposed diagnostic scheme for people with epileptic seizures and with epilepsy: report of the ILAE Task Force on Classification and Terminology. Epilepsia 2001;42:796–803. It is available on the Internet at *http://ilae.org/pubs/JUNE2001.pdf*. Accessed December 4, 2006.)
   1. Partial Seizures (proposed name change to Focal Seizures) begin in one hemisphere of the brain.
      a. Simple (proposal to eliminate distinction between simple and complex partial seizures):
         No loss of consciousness throughout seizure. Symptoms may be classified as motor (involving any part of the body), autonomic (e.g., pallor, flushing, vomiting, sweating, vertigo, or tachycardia), or sensory (e.g., visual, auditory, olfactory, or gustatory sensations).
      b. Complex: Loss of consciousness. Complex partial seizures (CPS) may be preceded by a prodrome and begin with an aura. A prodrome is an awareness of an impending seizure before it occurs. The prodrome may consist of headache, insomnia, irritability, or feeling of impending doom. The aura that accompanies a CPS may be a simple partial seizure consisting of sensory or autonomic symptoms. 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, or snapping the fingers. Psychic symptoms include illusions, hallucinations, emotional changes, dysphasia, and cognitive problems. Complex partial seizures usually are short in duration (seconds to minutes).
      c. Secondarily generalized: Begins as a partial seizure, but spreads to involve both hemispheres of the brain.
   2. Generalized Seizures begin in both hemispheres of the brain.
      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 be observed to stare, be motionless, or have a distant expression on his/her face. Electroencephalograms (EEGs) performed during seizure activity usually show three Hz spike-and-wave complexes.
      b. Myoclonic: Consist of brief, lightning-like jerking movements of the whole body or the upper and occasionally lower extremities.
      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 partially open, and the patient may experience upward eye movement, involvement of the extremities, and loss of consciousness. In the extension phase, a patient may be noted to extend his or her back and neck; experience contraction of thoracic and abdominal muscles; be apneic; and have flexation, 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. After the seizure, the patient may be postictal. The length of the entire seizure is usually 1–3 minutes. 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 and/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 where a patient loses tone and falls to the ground.

3. Status epilepticus is a generalized seizure that lasts greater than 20 minutes OR recurrent seizures of sufficient frequency that the patient does not regain consciousness between episodes.
4. Pseudoseizures are paroxysmal nonepileptic episodes resembling epileptic seizures that can be organic or psychogenic in origin.

C. Diagnosis
1. Physical examination should be performed with special attention given to neurological 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, and renal function tests may be required.
3. Electroencephalogram is used to help confirm the diagnosis, classify seizures, locate the site of the seizures, and select the best antiepileptic drug. 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, the EEG 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. Some patients whose seizures are difficult to diagnose and/or control may require prolonged closed-circuit video–EEG monitoring. Keep in mind that a normal inter-ictal (when the patient is not having clinical seizures) EEG may be normal, but does not preclude the diagnosis of epilepsy.
4. Magnetic resonance imaging (MRI) is the neuroimaging technique of choice for epilepsy. Computed tomography (CT) scanning can be useful in finding brain lesions when an MRI cannot be performed in a timely fashion.

D. Treatment
1. Medications (please see Tables 1–4)
   a. Benzodiazepines
      i. Mechanism of action: Augment gamma-aminobutyric acid (GABA)-mediated chloride influx.
      ii. Tolerance may develop: Usually used as adjunctive, short-term therapy.
      iii. Most commonly used drugs: Clorazepate, clonazepam.
   b. Carbamazepine
      i. Mechanism of action: Sodium channel blocker.
      ii. Pharmacokinetics: Enzyme inducer, autoinduction.
      iii. Adverse effects: Rash, syndrome of inappropriate antidiuretic hormone release (SIADH), aplastic anemia, thrombocytopenia, anemia, leucopenia.
      iv. Extended-release tablets (Tegretol XR®)100 mg, 200 mg, 400 mg. Extended-release capsules (Carbatrol®) 200 mg, 300 mg available. Do not crush or chew. Ghost tablets can be seen in the stool with the extended-release tablets (Tegretol XR®).
   c. Ethosuximide
      i. Mechanism of action: T-type calcium current blocker
      ii. Useful only for absence seizures
   d. Felbamate
      i. Mechanism of action: Blocks glycine site on *N*-methyl-D-aspartate (NMDA) 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 medicines and benefit clearly outweighs the potential adverse effects.

Table 1. Medication Selection for Various Seizure Types.

Drug	Simple Partial	Complex Partial	Generalized Tonic–Clonic	Absence	Atypical Absence	Atonic	Myoclonic	Infantile Spasms	Status Epilepticus
Acetazolamide	4	4	4	3	3	–	–	–	–
ACTH	–	–	–	–	–	–	–	1	–
Carbamazepine	1	1	1	–	–	4	4	–	–
Clonazepam	3	3	3	2	2	1	1	2	–
Diazepam	–	–	–	–	4	–	4	4	1
Ethosuximide	–	–	–	1	1	–	4	–	–
Felbamate	5	5	5	5	–	–	5	–	–
Lorazepam	3	–	3	3	3	–	3	–	1
Gabapentin	2	2	4	–	–	–	–	–	–
Lamotrigine	2	2	2	2	4	3	3	–	–
Levetiracetam	4	4	--	4	--	--	--	--	--
Oxcarbazepine	1	1	2	--	--	3	3	--	--
Phenobarbital	1	1	1	1	–	–	3	–	–
Phenytoin	1	1	1	1	–	–	3	–	–
Prednisone	–	--	–	–	–	–	–	–	1
Pregabalin	4	4	--	--	--	--	--	--	--
Primidone	2	2	2	2	–	–	–	–	–
Tiagabine	4	4	--	--	--	4	4	--	--
Topiramate	2	2	2	3	–	–	3	–	–
Valproic Acid	2	2	2	1	1	1	1	1	2
Zonisamide	4	4	--	--	--	--	4	--	--

1 = first-line drug
2 = second-line drug
3 = some therapeutic effect
4 = adjunctive therapy
5 = used only when benefits outweigh risks

e. Fosphenytoin
   i. Mechanism of action: Prodrug for phenytoin; 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 phenytoin = 1.5 mg fosphenytoin = 1 phenytoin equivalent; intramuscular or IV dosing is appropriate.
   v. Adverse effects: Hypotension, perianal itching.
   vi. Advantages over phenytoin
      (a) Intramuscular or IV dosing.
      (b) Phlebitis is minimized.
      (c) Infusion can be faster than 150 phenytoin equivalent/minute.
      (d) Can deliver in normal saline solution or D_5W (5% dextrose [in water] injection).

f. Gabapentin
   i. Mechanism of action: Unknown.
   ii. Pharmacokinetics: not metabolized, eliminated renally; adjustments may be necessary for renal dysfunction and hemodialysis.
   iii. Also has a Food and Drug Administration (FDA) indication for treatment of post-herpetic neuralgia pain.
   iv. Doses frequently exceed product information maximum of 3600 mg/day.

Table 2. Selected Interactions Between Antiepileptic Medications

*AED**	*Added AED*	*Change in Serum Concentration of the Initial AED*	*Mechanism*
Carbamazepine	Ethosuximide	Decreased	Increased carbamazepine metabolism Inhibits epoxide degradation
	Felbamate	Decreased, increased epoxide	Increased carbamazepine metabolism
	Phenytoin	Decreased	Same as above Same as above
	Phenobarbital	Decreased	
	Primidone	Decreased	
Felbamate	Phenytoin	Decreased	Increased metabolism
	Carbamazepine	Decreased	Increased metabolism
Lamotrigine	Phenytoin	Decreased	Increased metabolism
	Carbamazepine	Decreased	Same as above
	Primidone	Decreased	Same as above
	Phenobarbital	Decreased	Same as above
	Valproic acid	Increased	Decreased metabolism
Oxcarbazepine	Carbamazepine	Decreased	Increased metabolism
	Phenobarbital	Decreased	Same as above
	Phenytoin	Decreased	Same as above
Phenobarbital	Oxcarbazepine	Increased	Competition for hepatic metabolism
	Phenytoin	Increased	Same as above
	Valproic acid	Increased	Same as above
Phenytoin	Carbamazepine	Decreased	Increased metabolism
	Oxcarbazepine	Increased/no change	?
	Phenobarbital	Increased/decreased	Decreased/increased metabolism
	Topiramate	Increased	Decreased metabolism
	Valproic acid	Decreased total; increased free	Displacement from binding sites
Primidone	Carbamazepine	Increased phenobarbital conc.	?
	Phenytoin	Increased phenobarbital conc.	?
Topiramate	Carbamazepine	Decreased	Increased metabolism
	Phenytoin	Decreased	Same as above
	Valproic acid	Decreased	Same as above
Valproic acid	Carbamazepine	Decreased	?
	Oxcarbazepine	Decreased	?
	Phenobarbital	Decreased	Increased metabolism
	Phenytoin	Decreased	Same as above
	Primidone	Decreased	Same as above
	Topiramate	Decreased	Same as above
Zonisamide	Carbamazepine	Decreased	Increased metabolism
	Phenobarbital	Decreased	Same as above
	Phenytoin	Decreased	Same as above

*AED = Antiepileptic drug

g. Lamotrigine
   i. Mechanism of action: Decreases glutamate and aspartate release, delays repetitive firing of neurons, blocks sodium channels.
   ii. Rash is a major 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.

Table 3. Selected Interactions of Non-antiepileptic Drugs on Antiepileptic Medications.

*AED**	*Other Drug*	*Effect on the AED*	*Mechanism*
Carbamazepine	Cimetidine	Increased serum conc.	Inhibition of carbamazepine metabolism
	Diltiazem	Same as above	Same as above
	Erythromycin	Same as above	Same as above
	Isoniazid	Same as above	Same as above
	Propoxyphene	Same as above	Same as above
	Theophylline	Decreased serum conc.	Increased theophylline metabolism
	Troleandomycin	Increased serum conc.	Inhibition of carbamazepine metabolism
	Verapamil	Increased serum conc.	Inhibition of carbamazepine 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 within acute ethanol ingestion
Phenytoin	Anticoagulants, oral	May increase phenytoin serum conc.; decreased/increased anticoagulant effects	Complex mechanism (reference 70)
	Antineoplastics (Bleomycin, Cisplatin, Vinblastine, Methotrexate, Carmustine)	Decreased pharmacologic effect	Unknown, possible decreased absorption due to antineoplastic mucosal damage
	Chloramphenicol	Increased phenytoin serum conc.; decreased/ increased chloramphenicol serum conc.	Inhibition of phenytoin metabolism; effect on chloramphenicol unknown
	Cimetidine	Increased serum conc.	Inhibition of phenytoin metabolism
	Diazoxide	Decreased pharmacologic effect; decreased serum conc.	Increased phenytoin metabolism
	Disulfiram	Increased serum conc.	Inhibition of phenytoin metabolism
	Folic acid	Decreased serum conc.	Complex mechanism (reference 70)
	Isoniazid	Increased serum conc.	Inhibition of phenytoin metabolism
	Phenylbutazone	Increased serum conc.	Inhibition of phenytoin metabolism; plasma protein displacement
	Rifampin	Decreased serum conc.	Increased phenytoin metabolism
	Sulfonamides	Increased serum conc.	Inhibition of phenytoin metabolism
	Trimethoprim	Increased serum conc.	Inhibition of phenytoin metabolism
Valproic Acid	Salicylates	Increased pharmacologic effect	Plasma protein displacement; increased free valproic conc.

*AED = Antiepileptic drug; CNS = central nervous system.

h. Levetiracetam
   i. Mechanism of action: May prevent hypersynchronization of epileptiform burst firing and propagation of seizure activity.
   ii. Pharmacokinetics: Not metabolized to great extent, adjust dose in renal dysfunction, no drug interactions with other antiepileptic drugs.
   iii. Parenteral use: Currently only FDA-indicated for replacement of oral dosing.