MAYO CLINIC

Management of Adult Onset Seizures

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CME Activity

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Learning Objectives: On completion of this article, you should be able to (1) identify the major significant mechanisms of action for antiepileptic medications and which commonly used medications are in each class; (2) review the efficacy of antiepileptic drugs for specific seizure types, and the associated side effects, that guide patient-specific antiepileptic drugs selection; and (3) outline treatments available when patients are refractory to medical therapy, and appraise their indications and efficacy.

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Abstract

Epilepsy is a common yet heterogeneous disease. As a result, management often requires complex decision making. The ultimate goal of seizure management is for the patient to have no seizures and no considerable adverse effects from the treatment. Antiepileptic drugs are the mainstay of therapy, with more than 20 medications currently approved in the United States. Antiepileptic drug selection requires an understanding of the patient's epilepsy, along with consideration of comorbidities and potential for adverse events. After a patient has failed at least 2 appropriate antiepileptic drugs, they are determined to be medically refractory. At this time, additional therapy, including dietary, device, or surgical treatments, need to be considered, typically at a certified epilepsy center. All these treatments require consideration of the potential for seizure freedom, balanced against potential adverse effects, and can have a positive effect on seizure control and quality of life. This review article discussed the treatment options available for adults with epilepsy, including medical, surgical, dietary, and device therapies.

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Epilepsy is one of the most prevalent neurological diseases, affecting an estimated 3 million individuals in the United States and 50 million people world wide.[1] The International League Against Epilepsy defines *epilepsy* as 2 or more seizures occurring greater than 24 hours apart or a single seizure and additional features that are associated with a high risk of recurrent unprovoked seizures.[2] With such a broad definition,

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the reality is that epilepsy is an extremely heterogeneous disease that can affect otherwise healthy adults with 2 or 3 seizures in their lifetime or an individual with a known static encephalopathy and many seizures per day or seizures that begin only after an acute neurologic injury, such as an ischemic stroke or meningitis. The heterogeneity of the disease can require complex considerations for the treatment of seizures.

The guiding principle of epilepsy therapy is to have no seizures and no adverse effects. The execution of this principle can be complicated, requiring decisions tailored for the individual patient. Treatment options include more than 20 approved antiepileptic drugs (AEDs), dietary therapies, multiple neuromodulation devices, and surgery. Choosing the appropriate treatment pathway for a patient requires understanding the patient's epilepsy, indications, adverse effects and efficacy of AEDs, and recognition of additional treatments available for medically refractory epilepsy.

This review article outlines the breadth of epilepsy treatments currently available and under development. The mechanisms of actions, indications, and adverse effects of AEDs are outlined, along with providing guidelines as to how to choose a specific AED for a patient. Nonpharmacological treatments, including dietary and device therapies, are presented. Finally, the role of surgery in treating intractable epilepsy is discussed.

ANTIEPILEPTIC DRUGS

In contrast to the treatment of epilepsy 30 years ago, there are now more than 20 approved AEDs available. This allows better selection of AEDs based on seizure type and adverse effect profile, but can be daunting when it comes to choosing where to start with AED selection. Understanding the seizure type, patient comorbidities, and ease of dosing, along with consideration of the mechanism of action, are all important in guiding AED selection.

The primary aim of AEDs is to inhibit seizure propagation by either increasing neuronal inhibitory signaling or decreasing excitatory signaling. Multiple targets are used to exert this effect (Table 1).

γ-Aminobutyric acid (GABA) is a neurotransmitter with an important role in neuronal inhibition. Increased presence of GABA in the synapse increases inhibition and increases the seizure threshold. Two AEDs were specifically designed to increase GABA: tiagabine, which inhibits the GABA transporter on the presynaptic neuron, inhibiting GABA reuptake; and vigabatrin, which blocks GABA transaminase, preventing breakdown of GABA.[3] Valproic acid also likely exerts its effect partially by increasing availability of GABA.[4]

Increased activation of GABA receptors inhibits postsynaptic signal propagation. Both benzodiazepines and barbiturates exert their action on synaptic $GABA_A$ receptors, causing inhibition of signal transmission when activated. Benzodiazepines bind to a specific site on the $GABA_A$ receptor, causing the channel to open more frequently, increasing the inhibitory signal. Barbiturates activate $GABA_A$ channels when they bind, causing the channel to have a long duration of opening.[4] Neuroactive steroids modulate synaptic and extrasynaptic $GABA_A$ channels, increasing neuronal inhibition and reducing seizure propagation. Multiple neurosteroids are currently in clinical trials for the treatment of epilepsy. Ganaxolone, an analogue of allopregnanolone, has shown benefit for focal epilepsy and infantile spasms in phase 2 trials.[5] It recently received orphan drug status in the treatment of epilepsy-associated syndrome because of sequence variations of the protocadherin 19 (*PCDH19*) gene. An intravenous form of allopregnanolone, SAGE-547, may be of benefit in super-refractory status epilepticus and is now entering phase 3 trials. Allopregnanolone has an advantage over benzodiazepines and barbiturates in refractory status epilepticus, in that it acts on extra synaptic $GABA_A$

TABLE 1. Summary of Mechanisms of Action of Antiepileptic Drugs

Sodium channels	Glutamate receptors	γ-Aminobutyric acid	Other
• Phenytoin	• Topiramate	• Benzodiazepines	• Levetiracetam
• Carbamazepine	• Zonisamide	• Barbiturates	• Ezogabine
• Oxcarbazepine	• Perampanel	• Valproic acid	• Gabapentin
• Lamotrigine	• Felbamate	• Vigabatrin	• Pregabalin
• Lacosamide		• Tiagabine	• Ethosuximide
• Rufinamide		• Neurosteroids[a]	
• Eslicarbazepine			

[a]Neurosteroids are currently in development for the treatment of epilepsy.