



antiepileptic drugs

A CLINICIAN'S MANUAL

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Second Edition

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Chapter 1

Diagnosis and Evaluation of Patients With Seizures

Approximately 10% of the general population will experience at least one seizure within their lifetimes in most Western countries, and even higher rates are observed in developing countries. However, not all individuals go on to develop epilepsy, which is characterized by recurring epileptic seizures. An *epileptic seizure* is the transient occurrence of signs or symptoms due to abnormal excessive, hypersynchronous firing of neurons in the brain. The new practical clinical definition of epilepsy proposed by the International League Against Epilepsy (ILAE) considers epilepsy to be a disease of the brain defined by any of the following conditions: (1) at least two unprovoked (or reflex) seizures occurring >24 hours apart; (2) one unprovoked (or reflex) seizure and a probability of further seizures similar to the general recurrence risk (at least 60%) after two unprovoked seizures, occurring over the next 10 years; and (3) diagnosis of an epilepsy syndrome (Fisher et al., 2014). Epilepsy may be due to genetic causes (possessing an inherited trait to have seizures), brain tumors, infections (meningitis or encephalitis), brain trauma, stroke, developmental anomalies (eg, cortical dysplasia), malformations (tuberous sclerosis, neurofibromatosis), vascular malformations (arteriovenous malformations), and other causes.

To properly diagnose “epilepsy” a physician must do more than simply establish that recurrent seizures have occurred or are highly likely to occur after the first one. It is important that an attempt be made to diagnose a specific *epilepsy syndrome*. This syndrome forms the basis for the health provider to decide on therapy. The syndrome reflects the constellation of historical features, symptoms, signs, and laboratory test results that define a distinct condition. Hence, the syndromic diagnosis involves more than just the seizure type; frontal lobe seizures, for instance, do not constitute a syndrome. In contrast, benign Rolandic epilepsy of childhood does constitute a distinct syndrome, with its characteristic etiology, natural history, seizure type, developmental history, neurological examination, and electroencephalogram (EEG) abnormality (Box 1.1). An *idiopathic (genetic) epilepsy syndrome* is the direct result of a known or inferred genetic defect(s). Seizures are the core symptom of the disorder. It appears at a specific age (age dependent) with no underlying structural brain lesions or related neurological abnormalities. Examples of idiopathic (genetic) syndromes include benign Rolandic epilepsy of childhood, childhood absence epilepsy, and juvenile myoclonic epilepsy. A *symptomatic (structural-metabolic) epilepsy syndrome* is the result of an identifiable structural or metabolic lesion of the

Box 1.1 Important Epilepsy Syndromes Based on the International League Against Epilepsy (ILAE) Classification

General Classification	Syndrome	Description
Idiopathic (genetic) generalized epilepsies	Childhood and juvenile absence epilepsies	<p>Childhood absence epilepsy (pyknolepsy) occurs in children of school age (peak manifestation age 6 to 7 years), with a strong genetic predisposition in otherwise normal children. It is characterized by very frequent (several to many per day) absences. The EEG reveals bilateral usually 3 Hz, synchronous spike waves or polyspikes and waves, on a normal background activity. During adolescence, generalized tonic-clonic seizures often develop.</p> <p>Juvenile absence epilepsy develops insidiously in physically and mentally healthy adolescents. Age at onset is usually between 10 and 17 years (peak between 10 and 12 years). Because the frequency of the absences is low and the symptoms are relatively trivial, the disorder may go unnoticed until generalized tonic-clonic seizures appear.</p>
	Juvenile myoclonic epilepsy	<p>Juvenile myoclonic epilepsy typically appears in the second decade of life. The age of onset often ranges from 8 to 24 years, with peak onset between 14 and 16 years. It is characterized by myoclonic seizures, associated at times with generalized tonic-clonic seizures or absence seizures.</p>
	Epilepsy with myoclonic-astatic seizures (Doose syndrome)	<p>Prior to the onset of myoclonic-astatic seizures, most affected children show normal development. The seizures usually begin between 2 and 5 years of age. The first seizure is most often a generalized tonic-clonic seizure and rarely a myoclonic, atstatic, myoclonic-astatic, or absence seizure. Drop attacks may result from pure atstatic, myoclonic-astatic, or atypical absence seizures.</p>
Epileptic encephalopathies (in which the epileptiform abnormalities may contribute to progressive dysfunction)	West syndrome	<p>West syndrome is an age-dependent epilepsy syndrome that comprises a triad of epileptic spasms in clusters, mental retardation, and diffuse and profound paroxysmal EEG abnormalities in infancy.</p>

(continued)

Box 1.1 (Continued)		
General Classification	Syndrome	Description
	Severe myoclonic epilepsy in infancy (Dravet syndrome)	Severe myoclonic epilepsy begins during the first year of life. Development is normal prior to the onset of seizures. Affected infants develop either generalized or unilateral clonic seizures without prodromal signs. Myoclonic jerks, absence seizures, and partial seizures usually appear later. The occurrence of status epilepticus is frequent. Psychomotor retardation and other neurological deficits occur in affected children.
	Lennox-Gastaut syndrome	The Lennox-Gastaut syndrome is, with rare exception, a condition of children. It is characterized by the clinical triad of multiple types of seizures, including especially atypical absences and tonic and atonic seizures, diffuse slow spikes-and-waves and/or generalized paroxysmal fast activity on an abnormal background activity in EEG, and mental retardation (mental retardation is not a mandatory element).
	Landau-Kleffner syndrome	Age of onset for Landau-Kleffner syndrome ranges from 3 to 8 years, and boys are more frequently affected than girls. Acquired aphasia (verbal auditory agnosia) is the more prominent feature, because seizures are present in only 70% to 80% of the patients.
Progressive myoclonic epilepsies		Include: ceroid lipofuscinosis, sialidosis, Lafora disease, Unverricht-Lundborg disease, neuroaxonal dystrophy, MERRF, and dentatorubropallidoluysian atrophy.
Idiopathic (genetic) focal epilepsies	BECTS (Rolandic epilepsy)	Benign epilepsy of childhood with centrotemporal spikes (BECTS) has five criteria for the diagnosis: (1) onset between the ages of 2 and 13 years; (2) absence of neurological or intellectual deficit before the onset; (3) partial seizures with motor signs, frequently associated with somatosensory symptoms or precipitated by sleep; (4) a spike focus located in the centrotemporal (rolandic) area with normal background activity on the interictal EEG; and (5) spontaneous remission during adolescence.
	Benign occipital epilepsies	Panayiotopoulos syndrome is best described as early-onset benign childhood seizure susceptibility syndrome with mainly autonomic seizures (e.g., ictus emeticus) and autonomic status epilepticus.

(continued)

Box 1.1 (Continued)

General Classification	Syndrome	Description
		The cardinal features of late-onset childhood occipital epilepsy (Gastaut type) are visual seizures predominantly manifested with elementary visual hallucinations, blindness, or both. They are usually frequent and diurnal, and they usually last from seconds to 1 to 3 minutes.
Symptomatic (or probably symptomatic) focal epilepsies	Limbic epilepsies	Include: mesial temporal lobe epilepsy with hippocampal sclerosis and mesial temporal lobe epilepsy defined by specific etiologies.
	Neocortical epilepsies	Include: Rasmussen syndrome, hemiconvulsion-hemiplegia syndrome, and migrating partial seizures of early infancy.

Note: Febrile seizures (febrile convulsions) are the most common convulsive events in human experience. Febrile seizures can be categorized as either “simple” (generalized tonic-clonic seizure, duration less than 15 minutes and without recurrence within 24 hours) or “complex” (focal seizure, lasting more than 15 minutes or occurring in a cluster of 2 or more convulsions within 24 hours). Febrile seizures are generally benign and only 2% to 3% of children will later develop epilepsy, primarily those who have complex febrile seizures.

From the International League Against Epilepsy website (<http://www.ilae-epilepsy.org/visitors/centre/ctf/>) with minor modifications.

brain, such as cerebral infarction, brain tumor, cortical dysplasia, or ceroid lipo-fuscinosis. A *probable symptomatic (unknown) epilepsy syndrome* is synonymous with cryptogenic epilepsy, and this term defines syndromes that are believed to be symptomatic, but no etiology has been identified (Berg et al., 2010; Blume et al., 2001; Engel, 2006).

The International League Against Epilepsy (ILAE) classifies seizures as either partial (focal) or generalized. Focal epileptic seizures are conceptualized as originating within networks limited to one hemisphere. These may be discretely localized or more widely distributed. Generalized epileptic seizures are conceptualized as originating at some point within, and rapidly engaging, bilaterally distributed networks (Berg et al., 2010).

Definitions for the major seizure types include the following (Blume et al., 2001):

Motor Seizures

- Tonic: A sustained increase in muscle contraction lasting a few seconds to a few minutes.
- Clonic: Myoclonus that is regularly repetitive, involves the same muscle groups, usually at a starting frequency of 2–3 jerks per second, and is prolonged.

- Tonic-clonic: A sequence consisting of a tonic phase followed by a clonic phase. Variants such as clonic-tonic-clonic may be seen.
- Myoclonic: Sudden, brief (<100 milliseconds) involuntary single or multiple contraction(s) of muscles(s) or muscle groups of variable topography (axial, proximal limb, distal limb).
- Atonic: Sudden loss or diminution of muscle tone without apparent preceding myoclonic or tonic event lasting ≥ 1 to 2 seconds, involving head, trunk, jaw, or limb musculature. Synonym: drop attack.
- Astatic: Loss of erect posture that results from an atonic, myoclonic, or tonic mechanism. Synonym: drop attack.
- Epileptic spasm (formerly infantile spasm): A sudden flexion, extension, or mixed extension-flexion of predominantly proximal and truncal muscles that is usually more sustained than a myoclonic movement but not so sustained as a tonic seizure (ie, 1 second). Limited forms may occur: grimacing, head nodding. Epileptic spasms frequently occur in clusters.
- Automatism: The ILAE defines automatism as more or less coordinated, often repetitive, motor activity usually occurring when cognition is impaired and for which the subject is usually amnesic. This often resembles a voluntary movement and may consist of an inappropriate continuation of ongoing preictal motor activity.

Nonmotor Seizures

- Aura: A subjective phenomenon that precedes an observable seizure and for which memory is retained afterward. This may consist of a sensory, psychic, autonomic, or other nonspecific subjective symptoms. Because of retrograde amnesia, some patients may not recall the experience of an aura.
- Sensory seizure: A perceptual experience not produced by stimuli from the external world.
- Dyscognitive seizures: Events in which disturbance of cognition is the prominent or most apparent feature, with alterations in perception, attention, emotion, memory, or execution function.

Seizure types based on the latest proposed ILAE classification scheme include the following (Berg et al., 2010; Blume et al., 2001):

Generalized Seizures

- Tonic-clonic seizures
- Clonic seizures
- Absence seizures
 - Typical
 - Atypical
- Absence with special features
 - Myoclonic-absence
 - Eyelid myoclonia