Pharmacological Treatment of Epileptic Seizures

Xuefeng Wang
Liemin Zhou
Editors

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Preface

Epilepsy is a neurological disorder that has impacted humanity for thousands of years, transcending borders, cultures, and social strata. While advances in medicine have dramatically improved the understanding and management of epilepsy, the social consequences of this condition remain profound. People with epilepsy often face significant stigma, discrimination, and psychological challenges that can be as debilitating as the seizures themselves. In this context, effective treatment is not only a medical imperative but also a social one, crucial for improving the quality of life for millions worldwide.

This book, *Pharmacological Treatment of Epileptic Seizures*, is a comprehensive resource compiled by the leading epileptologists in China, whose work has significantly advanced the field of epilepsy treatment, with the contribution of world-famous experts in epilepsy. It aims to equip healthcare professionals with the knowledge and tools necessary to address both the clinical and social dimensions of epilepsy.

This book begins by defining epilepsy and providing a thorough exploration of the Definition and the Classification and diagnosis of epileptic seizures. Understanding the various forms of epilepsy is essential for developing targeted treatment plans that address the specific needs of each patient. Accurate diagnosis is the first step toward effective management, which can significantly reduce the social burden of the disease.

Section 1.3 offers a broader context for understanding how epilepsy treatment has evolved over time. This historical perspective is crucial for appreciating the advances that have brought us to the present day and for anticipating future developments that may further alleviate the social impact of epilepsy.

Section 1.4, addressing "Research on Animal Models of Epilepsy," provides insight into the scientific foundations of epilepsy treatment. This research is vital for developing new therapies that are more effective and have fewer side effects, thus improving the overall well-being of patients and their ability to participate fully in society.

The book also delves into the Antiseizure medication mechanisms of action and reviews currently available medications and those in pipeline. This part of the book

is focused on the pharmacological interventions that are the cornerstone of epilepsy management. By controlling seizures, these medications play a key role in reducing the social stigma and limitations associated with epilepsy, enabling patients to lead more stable and fulfilling lives.

In Chap. 3 the authors review the fundamentals of selection of antiseizure medications and emphasize the importance of individualized treatment plans in individuals across the life span; the treatment options should be based on not only the medical aspects of epilepsy but also the social and psychological needs of patients. Effective treatment can greatly enhance a patient's ability to engage in everyday activities, pursue education, maintain employment, and build relationships—all of which are crucial for social inclusion.

Chapter 4 offers practical guidance for clinicians, helping them to optimize treatment strategies that improve patient outcomes in different clinical conditions, including epilepsy after stroke, brain trauma, tumor-associated epilepsy, and others.

Special attention is given to Chaps. 5 and 6, both of which are critical for managing more severe forms of epilepsy. These chapters highlight the importance of timely and effective treatment in preventing the long-term clinical, social, and psychological consequences of uncontrolled seizures.

An important part of the book, Chap. 7, addresses the "Diagnosis and Treatment of Epilepsy Comorbidities," recognizing that epilepsy often coexists with other conditions such as depression, anxiety, and cognitive impairments. These comorbidities can exacerbate the challenges faced by individuals with epilepsy, making their management an essential component of comprehensive care. Following the same line, Chap. 8 provides highly relevant information for the successful management on the complex issues surrounding epilepsy treatment in individuals with epilepsy.

Throughout this book, the editors, who are the most distinguished epileptologists in China, and eminent authors bring their extensive clinical experience and research expertise to the readers. Their work reflects a deep commitment to improving both the medical and social outcomes for people with epilepsy.

This book will serve as a vital resource for those dedicated to improving the lives of people with epilepsy, helping to create a future where effective treatment leads not only to better health outcomes but also to greater social acceptance and integration.

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Chapter 1
Overview

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1.1 Definition of Epilepsy

The definition of a specific disease is one in which professionals use the simplest language to summarize the characteristics of the disease to facilitate communication among peers and more reasonable treatment of the disease. Because of the different cultures in different countries, it is very difficult to formulate a widely accepted definition. Understanding of diseases varies across time and across countries. Therefore, developing a widely accepted definition of disease has become the most important task of international organizations [1].

Epilepsy is an ancient disease, and there have been descriptions of epilepsy since the beginning of the written human record, but many people still do not know what

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epilepsy is. People can only see epileptic seizures. Therefore, the understanding of epilepsy in humans has progressed from the beginning of epileptic seizures, and epileptic seizures are the basis for people to understand epilepsy [1].

The first human description of epileptic seizures appeared in 1046 BC in the Babylonian treatise on the diagnosis of disease. Since then, people have gradually paid more attention to this episodic disease. Although clinical manifestations vary from individual to individual, they all have a clear beginning and end. The duration is also very short. The clinical manifestation is based on the physiological function of the human body, which supports the strengthening of the physiological function of the human body and does not produce activities outside of those caused by brain function. Each seizure is a temporary disorder of brain function. The symptoms are almost identical in each episode in the same individual, indicating that the dysfunction is spread along specific pathologic pathways [1–4].

Some scholars have summarized the common manifestations of seizures: sudden, transient, stereotypical, and repetitive. The term "paroxysmal" indicates that the patient's seizures occur suddenly and end quickly, and the start and end times are very clear. During the non-seizure period, the patient's brain function is normal. Transient refers to the time of each seizure being very short, from a few seconds to a few minutes, and almost never more than 5 minutes according to the guidelines of the International League against Epilepsy. Stereotypical refers to the fact that although the clinical manifestations of epilepsy are very rich and diverse, every seizure in every patient is similar. However, the scope of the spread of epileptic discharge is different, and its main characteristics must be the same. Repetitive means that the seizures of epilepsy patients not include only one attack but will be repeated. Epilepsy is a prominent manifestation of temporary disorders of normal brain function. Due to the different locations of affected neurons, the range of influence varies, and patients can experience sensory, motor, autonomic nerve, consciousness, and emotional disorders [2–5].

However, an isolated seizure is not epilepsy, and there are many seizures similar to those caused by epilepsy, including those caused by convulsive syncope, hyperventilation syndrome, hypertensive encephalopathy, gestational poisoning in women, hysteria, etc. There are dozens of forms of myoclonus similar to seizures; paroxysmal sleep disorders, such as sleepwalking, night terrors, and periodic tendon movements during sleep, also lead to seizures similar to those of epilepsy, but they are not epilepsy. Nor does it develop in the same way as epilepsy [1, 4].

The greatest difference between epilepsy and epileptic seizures is that people with epilepsy have repeated seizures. Some scholars have shown that 50–60% of patients with similar seizures will not have repeated seizures; therefore, they are not epileptic, and real epilepsy patients have repeated epileptic seizures. Early epidemiological surveys have also shown that epilepsy patients often relapse within 3 years, even if it is an epileptic seizure; before there is a recurrence, the seizure can only be called a pre-seizure, and the presence of epilepsy can only be considered after recurrence [1, 4].

Epileptic seizures are used to understand epilepsy for humans, and epileptic seizures are the basis of the existence of epilepsy. Epilepsy patients also have characteristics of epileptic seizures, that is, sudden, transient, stereotypic and repetitive seizures, and their clinical manifestations should also be classified in the category of brain disorders [1, 4, 5].

In 1870, John Hughlings Jackson proposed a possible mechanism for epileptic seizures by comparing them with nonepileptic seizures. He suggested that epileptic seizures were transient brain disorders caused by sudden seizures and transient, over-synchronous discharge of gray matter neurons. The cause is a sudden release of energy from neurons. Epilepsy is synonymous with this bursting overexcitation of gray matter neurons, in what is known as the Jackson hypothesis [1]. In the following century, many studies investigated the mechanisms of seizures. It has been proposed that epilepsy is a transient disorder of one or several functions of the brain, originates from the highly synchronized discharge of neurons in the cortex, thalamus, and upper brainstem, and is characterized by highly excited lower neurons caused by the reduced inhibitory output of the related upper neuron groups to the lower neuron groups [2–5]. These hypotheses emphasize that electrical and chemical abnormalities in neurons, outside neurons or in the environment are the mechanism of epileptic seizures, greatly enriching the content of the study of epileptic pathogenesis [2–5].

Based on extensive research, the International League against Epilepsy has proposed a definition of epilepsy, epileptic seizures and epileptic syndromes. “Epilepsy is a chronic brain disease characterized by epileptic seizures. The highly synchronized abnormal firing of neurons is the root cause of epileptic seizures. Transient brain dysfunction is the main manifestation of epileptic seizures. Due to the different locations of the affected neurons, the range varies, and due to the differences in the functions of different brain areas, patients can present with sensory, motor, conscious, emotional, language, behavioral, or autonomic dysfunction.” Epilepsy is characterized by specific clinical and EEG manifestations, is supported by a specific etiology, is usually diagnosed as having prognostic and therapeutic significance, is accompanied by age-dependent and specific comorbidities, and is called epileptic syndrome [2–6].

1.2 Classification and Diagnosis of Epileptic Seizures

The classification and diagnosis of epileptic seizures are extremely important for clinicians and care teams, patients, and families, and researchers. For patients, the classification is helpful for clarifying the disease diagnosis and exploring the cause; for clinicians and care teams, the classification helps to facilitate communication and discussion. From a research perspective, accurate classification of epileptic seizures facilitates a comprehensive and orderly investigation of the different types of antiseizure medications and/or surgical treatment modalities, treatment responses, and the typical clinical course of epileptic seizures.

1.2.1 History of Epileptic Seizure Classification

The classification of epileptic seizures can be traced back to 1815, when Esquirol classified epileptic seizures into Grand Mal and Petit Mal according to clinical severity [7]. In 1937, Gibbs and Lennox et al. classified epileptic seizures into Grand Mal, Petit Mal, and psychomotor epileptic seizures based on clinical manifestations and EEG features [8]. In 1954, for the first time, Gastaut, combined with the study of Penfield et al., established a more systematic classification of epileptic seizures.

At present, there are two main types of epileptic seizure classification. One is the electroclinical classification proposed by the International League Against Epilepsy (ILAE). The other is the seizure symptomatology classification, which is mainly based on patient clinical symptoms.

In 1964, Gastaut et al. proposed the first draft of the ILAE classification and diagnosis of epileptic seizures [9], which was first revised in 1970 [10]. After analyzing and summarizing hundreds of video EEG recordings of epileptic seizures [11], the ILAE revised the manuscript in 1981, and BLUME et al. further standardized the terminology of their descriptions of symptoms during epileptic seizures in 2001 [12]. It should be noted that the 1981 ILAE classification of epileptic seizures is the most far-reaching classification in the world, and it is still widely used in clinical practice and scientific research. With the in-depth analysis of the electroclinical features of an increasing number of epilepsy cases, scholars have found that some epileptic seizure types cannot be distinguished by the traditional classification of 1981, and the Classification and Nomology Committee of the ILAE introduced an updated version of the classification in 2010 [13], which enriched the classification framework. In recent years, rapid advances in related disciplines such as neuroimaging, genomic technology, and molecular biology have led to a further increase in the reported types of epileptic seizures, making it difficult for a broad classification to cover new types of epileptic seizures and hindering the understanding of the underlying development of the disease and the complexity of pathological and physiological processes. To adapt to the rapid development and new understanding in the field of epilepsy, the ILAE proposed a new operational classification of epileptic seizures [14] in 2017, which improved the intuitiveness, transparency, and universality of the classification and proposed descriptive reporting of seizure types, allowing for the inclusion of previously unclassifiable epileptic seizures.

The symptomatologic classification of epileptic seizures, also known as the Lüders classification of epileptic seizures, was first established by Lüders et al. in 1993 from the sole perspective of symptomatology [15] and was revised in 1998 [16] and 2019 [17].

1.2.2 Classification of Epileptic Seizures

1.2.2.1 Classification of Seizures by the ILAE, 1981

The 1981 ILAE classification of epileptic seizures [11] was based on clinical manifestations and electroencephalogram (EEG) features (interictal stage and attack period), and epileptic seizures are divided into the following:

1. *Partial seizure*: Initial clinical seizure and EEG features suggest that "a group of neurons in one cerebral hemisphere are first involved." Based on the level of consciousness, partial seizures can be further divided into simple partial seizures (SPSs), complex partial seizures (CPSs) and secondarily generalized tonic–clonic seizures (SGTCs).
2. *Generalized seizure*: Initial clinical manifestations and EEG features suggest "simultaneous involvement of both cerebral hemispheres;"
3. Unclassified seizures.

1.2.2.2 Classification of Seizures by the ILAE(2017)

Seizure Classification

The 2017 ILAE classification of seizure type [18] is an operational classification of seizure types, emphasizing that the specific refinement of the classification (basic version/extended version) can be selected according to clinical needs, and the basic version (Table 1.1) is a reduced form of the extended version (Table 1.2). This classification applies to seizures in adults and children but not to seizures in newborns (neonatal seizures are a separate classification).

It is important to emphasize that the 2017 ILAE classification of seizure types chart is columnar rather than hierarchical, meaning that levels can be skipped, and seizure classification may also be terminated at either level. Classification begins with determining whether the initial manifestations of the seizures are of focal or generalized onset; if the origin is not observed or obscured, then the seizure should be of unknown origin. The next level of classification is based on the initial sign or symptom of a seizure, even if it is not ultimately the most significant sign or symptom (except behavioral arrest of focal nonmotor onset seizure, because transient behavioral termination is difficult to determine, so a diagnosis of behavioral arrest requires behavioral termination to be the primary symptom throughout the seizure).

Focal onset seizures can be classified as "Aware" or "Impaired Awareness," with "retained awareness" meaning "aware of self and environment during the seizure, even if immobile." Awareness impairment at any time during focal onset seizures

Table 1.1 2017 Classification of seizure type, basic version [18]

Focal onset		Generalized onset	Unknown onset
Aware	Impaired awareness	Motor	Motor
Motor onset		Nonmotor (absence)	Nonmotor
Nonmotor onset			Unclassified[a]
Focal to bilateral tonic–clonic			

[a]Due to inadequate information or inability to be placed in other categories

Table 1.2 2017 Classification of seizure type, expanded version [18]

Focal onset		Generalized onset	Unknown onset
Aware	Impaired awareness	Motor	Motor
Motor onset		Tonic–clonic	Tonic–clonic
Automatisms		Clonic	Epileptic spasms
Atonic		Tonic	Nonmotor
Clonic		Myoclonic	Behavioral arrest
Epileptic spasms		Myoclonic–tonic–clonic	Unclassified[a]
Hyperkinetic		Myoclonic -atonic	
Myoclonic		Atonic	
Tonic		Epileptic spasms	
Nonmotor onset		Nonmotor (absence)	
Autonomic		Typical	
Behavior arrest		Atypical	
Cognitive		Myoclonic	
Emotional		Eyelid myoclonia	
Sensory			
Focal to bilateral tonic–clonic			

[a]Due to inadequate information or inability to be placed in other categories

should be classified as focal impaired awareness seizures; if awareness is unknown during a seizure, the classification of this level ("Aware" or "Impaired Awareness") should be ignored when classifying the seizure and go directly to the next level, that is, the classification of "Motor Onset" or "Nonmotor onset." In the classification of motor or nonmotor, motor signals usually dominate unless nonmotor (such as sensory) symptoms and signs are significant. Therefore, some words can be omitted without causing ambiguity, such as "focal onset tonic," rather than "focal motor onset tonic."

When classifying generalized onset seizures, "awareness" can be omitted because awareness impairment is present in most generalized onset seizures.

An episode of "Unknown Onset" is not a truly separate type of seizure but merely a placeholder for those whose origin is unknown. For example, if a wife is awakened in her sleep and observes her husband's first tonic–clonic seizure, the husband's seizure may be classified as "unknown onset tonic–clonic seizure" in the initial diagnosis; however, if a seizure with a clear focal onset is subsequently observed, the husband's seizure type will be reclassified as "focal to bilateral

tonic–clonic." It is recommended that a seizure be classified as having focal or generalized onset only when there is a high degree of confidence (e.g., ≥80%, arbitrarily chosen to parallel the usual allowable beta error) in the accuracy of the determination; otherwise, the seizure should remain unclassified until more information is available. The term "unclassified seizure" means that the nature of the origin of the seizure is not specific, there are no motor or nonmotor characteristics, and the level of awareness is unclear. If any of the above characteristics are known, a certain classification of the seizure can be made.

The major changes and features of the 2017 classification of seizure type compared to those of the 1981 classification include the following:

1. Focusing on the initial symptoms of the seizure and using them as the main basis for detailed classification. With either focal onset or generalized onset, seizures can be roughly divided into motor and nonmotor.
2. The "unknown onset" option was added. Patients with insufficient information about onset can be temporarily classified into this category, and focal or generalized onset can be determined after the information is complete.
3. In terms of the words used to describe the conscious state of focal-onset seizures, the more complex word "consciousness" is replaced by the simple and understandable word "awareness" ["aware of self and environment during the seizure"]. As previously described, "complex partial" can be changed to "focal impaired awareness."
4. New types of focal seizures were identified—myoclonic–atonic, clonic, epileptic spasms, tonic, and myoclonic seizures—which were considered to be either generalized or focal onset seizures. In addition, it also increased the number of types of seizures that are clinically common or may have locational significance, such as automatisms, hyperkinetics, and behavioral arrest.
5. For focal-onset seizures, it is recommended to discard some previously used terms, such as dyscognitive, simple partial, and psychic.
6. New types of generalized seizures—myoclonus-tonic-clonus, myoclonus-atonic, epileptic spasm, and myoclonic and eyelid myoclonia seizures.
7. The previous term "secondarily generalized" was replaced by "focal to bilateral tonic–clonic."

In summary, the 2017 ILAE classification of seizure types does not represent a fundamental change but allows for more flexibility and transparency in the types of names.

Common Seizure Types and Diagnostic Points of the 2017 ILAE Classification of Seizure Types

1. Focal onset seizures.
   (a) Specification of level of awareness (retained awareness means the person is aware of the self and the environment during the seizure, even if immobile, and impaired awareness during any part of the seizure renders it a focal

impaired awareness seizure.) is optional for focal seizures. If awareness is not applicable or is unknown, it can be simply described as a "focal onset seizure."

(b) Automatism refers to the repetitive, aimless, or seemingly purposeful, basically coordinated involuntary movements or behaviors usually made by patients with impaired awareness. The common types of automatism include oropharyngeal automatism, hand automatism, oral automatism and hypermotor automatism.

(c) A hypermotor seizure is a type of focal-onset seizure that mainly involves the trunk and the proximal extremities of the limb, and the range of movement is usually large, fast, and intense. For example, fast flapping movements of the upper limbs or repeated pedaling movements of the lower limbs;

(d) Autonomic seizures refer to focal nonmotor seizures characterized by significant changes in autonomic nervous system function. Changes in the autonomic nervous system may involve cardiopulmonary, papillary, gastrointestinal, perspiratory, vasomotor, and thermoregulatory processes and are often characterized as tachycardia, hyperventilation, elevated gastric gas, flushing, pallor, nausea and vomiting, and erect hair.

(e) Focal behavioral arrest seizures are characterized by the cessation of activity being the dominant feature throughout the seizure and the cessation of activity throughout the entire process;

(f) Cognitive seizures imply impaired language or other cognitive domains or positive features such as déja vu, hallucinations, illusions, or perceptual distortions;

(g) Emotional seizures include anxiety, fear, joy, other emotions, or the appearance of affect without subjective emotions;

(h) Sensory seizures refer to self-perceived and experiential seizures induced by nonexogenous stimuli. Common clinical types include somatosensory, visual, auditory, olfactory, gustatory, temperature, or vestibular seizures.

(i) Focal to bilateral tonic–clonic seizure is a special seizure type, corresponding to the 1981 phrase "partial onset with secondary generalization." Focal to bilateral tonic–clonic seizure reflects a propagation pattern of a seizure rather than a unified seizure type, but it is such a common and important presentation that the separate categorization was continued.

In general, the EEGs of these focal seizures are characterized by epileptic activity with focal initiation and evolution, which may vary according to the initial site of discharge, diffusion rate, and extent.

2. Generalized Onset Seizures

(a) Generalized tonic–clonic seizures (GTCSs) are characterized by loss of consciousness and bilateral symmetrical ankylosis followed by clonic movement and are usually accompanied by autonomic nerve involvement. It is the most obvious form of seizure and used to be called Grand Mal seizure.

(b) Tonic seizures are characterized by continuous contraction and stiffness of the muscles in the central axis of the body, the proximal ends of both limbs,

or the whole body. It usually lasts 2–10 seconds and occasionally lasts for a few minutes. The EEG features during seizures mainly include bilateral spike rhythm [(20 ± 5 Hz)] or low amplitude (10 Hz) rhythmic discharge activity. Tonic seizures are the most important seizure type of Lennox–Gastaut syndrome (LGS).

(c) Clonic seizures are characterized by bilateral limb rhythmic (1–3 Hz) jerks, with awareness or impaired awareness. During the seizure, the EEG is mostly generalized spikes/polyspike complexes or spike and slow wave complexes/polyspikes and slow wave complex synthesis.

(d) Myoclonic seizures are characterized by involuntary, rapid, transient, electric-like muscle seizures that last from 10–50 milliseconds and rarely exceed 100 milliseconds. These can involve the whole body or be limited to certain local muscle or muscle groups. May recur nonrhythmically. The typical EEG manifestations during seizures include burst generalization polyspikes and slow wave complexes. Myoclonic seizures, such as those related to juvenile myoclonic epilepsy (JEM), can be observed in some idiopathic epilepsy patients with a good prognosis. Myoclonic seizures can also be seen in some cases of epileptic encephalopathy with a poor prognosis and diffuse brain damage, such as Dravet syndrome and LGS.

(e) Atonic seizures are characterized by a sudden loss or reduction in muscle tone in the head, trunk, or limbs, with no significant myoclonus or tonic components. The seizure lasts approximately 1–2 seconds or longer. The clinical manifestations vary in severity, with mild cases consisting only of nodding, while severe cases can lead to sudden falls while standing. During seizures, the EEG shows transient generalization of 2–3 Hz spikes and slow wave complexes/polyspikes and slow wave complexes or sudden voltage reductions. Atonic seizures are more common in LGS and Doose syndrome patients.

(f) Myoclonic–tonic–clonic seizures are characterized by single or multiple clonus or myoclonic jerks of both limbs, which then evolve into tonic–clonic seizures. This type of seizure is more common in juvenile myoclonic epilepsy (JME) patients.

(g) Myoclonic–atonic seizures are a type of seizure characterized by a myoclonic twitch of the limb or trunk followed by hypotonia. These seizures during orthosis may cause the patient to fall. These seizures were formerly known as "myoclonic astatic seizures." This type of seizure is commonly observed in Doose syndrome patients.

(h) Absence seizures include typical absence, atypical absence, myoclonic absence, and eyelid myoclonic absence.

Typical Absence Sudden onset and sudden stop of the seizure, manifested by sudden cessation of movement or significant slowing down, with impaired awareness, with or without mild motor symptoms (such as clonus/myoclonus/rigidity/automatism). The seizure usually lasts 5–20 seconds (<30 seconds). EEG reveals a 3 Hz (2.5–4 Hz) spike and slow wave complex burst with bilateral synchronous symme-

try. Hyperventilation can induce a typical absence in approximately 90% of patients. It is mainly observed in children and adolescents, such as children with childhood absence epilepsy (CAE) and juvenile absence epilepsy (JAE), and is rare in adults.

Atypical Absence The onset and end of the seizure are slower than those of a typical absence seizure, with a less severe level of impaired awareness and more complex accompanying motor symptoms (such as automatisms). Muscle tension is usually reduced, and a seizure may last more than 20 seconds. The EEG shows a slow (<2.5 Hz) spike and slow wave complex rhythm during seizures. It is mainly observed in patients with severe neuropsychiatric disorders, such as LGS.

Myoclonic Absence Manifests as absence accompanied by rhythmic 2.5–4.5 Hz myoclonic movements of the limbs, accompanied by tonic components. EEG during the seizure period is similar to that of a typical absence seizure. Mainly seen in myoclonic absence epilepsy.

Eyelid Myoclonic Absence Manifested as a 5–6 Hz myoclonic movement in the muscles of the eyelids and/or forehead simultaneously with the onset of absence. During the seizure period, EEG shows a comprehensive 3–6 Hz polyspike and slow wave complex. This syndrome is commonly observed in Jeavons syndrome patients.

3. Epileptic Spasm

Epileptic spasms were initially clearly classified as a type of seizure in the 2010 ILAE classification report, which can be of focal onset, generalized onset, or unknown onset.

Epileptic spasms are sudden and mainly involve the central axis of the trunk and the proximal muscles of both limbs, with a duration of 0.2–2 seconds and sudden onset cessation. Clinically, spasms can be divided into flexion or extension types, with the former being more common and manifesting as episodic nodding movements, often occurring in clusters after awakening. Interictal EEG signals show hypsarrhythmia, and interictal EEG signals are diverse (such as voltage reduction, high-amplitude biphasic slow waves, or spike and slow wave complexes), often occurring in clusters after awakening. Epileptic spasms, such as those seen in West syndrome, are more common in infants and young children and can also be seen at other ages.

4. Reflex Seizure

Reflex epilepsy is not an independent type of seizure. It can manifest as focal or generalized onset seizures. Its uniqueness lies in the fact that seizures have specific exogenous or endogenous triggering factors; that is, each episode is triggered by a specific sensory stimulus, and there is a close lock-in relationship between seizures and triggering factors. The triggering factors can include nonpathological factors such as vision, thinking, music, reading, eating, and manipulation. These factors can include simple sensory stimuli (such as flashing) or complex intelligence

activities (such as reading and playing chess). Seizures induced by pathological conditions such as fever, alcohol or drug withdrawal are not considered reflexive seizures. It should also be noted that both reflexive seizures and spontaneous seizures can occur simultaneously in patients with epilepsy.

Diagnosis and Classification of Seizures in Neonates

The content of the 2017 ILAE classification mainly targets adults and older children and is not suitable for newborns. Given the differences in clinical and electrophysiological manifestations, etiology, diagnostic methods, and other aspects of neonatal epilepsy, the ILAE released a classification of neonatal seizures in 2021 [19]. The overall framework of this classification is generally consistent with the 2017 ILAE classification and can be considered the revised version of the latter for newborns.

The classification and diagnostic processes for neonatal epilepsy are shown in Fig. 1.1 EEG is the "gold standard" for diagnosing neonatal seizures and can be diagnosed solely based on EEG findings. If there are only clinical events without corresponding EEG seizure patterns, the patient cannot be diagnosed with an epileptic seizure. Neonatal seizures can be divided into electroclinical seizures and electrographic seizures. For the former, the seizure type can be further determined based on specific manifestations: motor seizures, such as automatisms; clonic, epileptic spasms; myoclonic, and tonic; and nonmotor seizures, such as autonomic and behavioral arrest. Moreover, it should be emphasized that newborns have only focal seizures and that there are no generalized seizures.

1.2.2.3 Symptomatologic Classification of Seizures

Although new technologies such as EEG, high-resolution magnetic resonance imaging, and magnetoencephalography have played a significant role in the diagnosis and treatment of epilepsy in recent years, detailed medical history records and detailed observations still have important value. The symptomatologic classification of seizures helps to accurately describe the origin of seizures, especially in preoperative evaluation for epilepsy surgery, which is widely used.

According to the 2019 updated classification of paroxysmal events and the four-dimensional epilepsy classification system [11], paroxysmal events need to be classified across four dimensions: ictal semiology, the epileptogenic zone, etiology, and comorbidities. This classification emphasizes that the descriptions of these four imaging features are independent of one another and can be derived based on different diagnostic methods. For example, a patient may have bilateral tonic–clonic seizures (based on ictal semiology), the epileptogenic area is located in the left temporal lobe (based on EEG), the etiology is a tumor in the left frontotemporal lobe (based on MRI and pathological examination), and the case is also complicated by depression. The independence of different dimensions also allows for a certain correlation

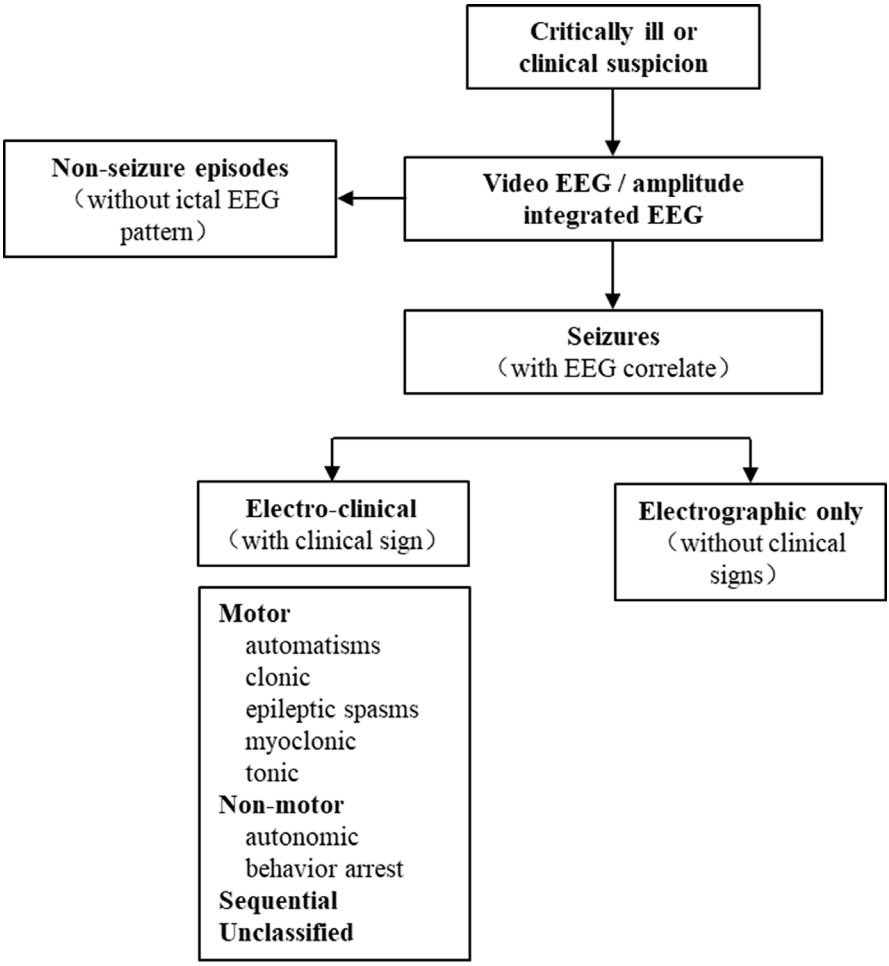

Fig. 1.1 Diagnostic framework of seizures in the neonatal period, including the classification of seizures [13]

between different dimensions (such as the epileptogenic area located in the left temporal lobe or the etiology of a tumor in the left frontal and temporal lobe).

There are six main types of seizures:

1. Auras
   (a) Auditory aura.
   (b) Autonomic aura.
      (i) Abdominal aura/Choking aura.
      (ii) Diaphoretic aura.
      (iii) Disodic aura.
      (iv) Pilomotor aura.

(v) Sialorrheic aura.
(vi) Tachycardic aura.
(vii) Urinary aura.
(viii) Vasomotor aura.

(c) Gustatory aura.
(d) Olfactory aura.
(e) Psychic aura.

(i) Affective aura.

- Pleasure aura (Ecstasy aura/Religious aura/Sexual aura).
- Unpleasant aura (Anger aura/Depression/Sadness aura/Embarrassment aura/Fear/Panic aura/Guilt aura).

(ii) Cognitive aura.
(iii) Experiential aura.
(iv) Familiarity aura.

- Déjà-vu aura.
- Jamais-vu aura.

(v) Illusionary aura.

- Auditory aura.
- Bodily aura.
- Time aura.
- Visual aura.

(f) Somatosensory aura.
(g) Vestibular aura.
(h) Visual aura/Ictal blindness.

2. Autonomic Seizure

(a) Abdominal seizure.
(b) Anisocoric seizure.
(c) Bradycardic seizure.
(d) Emetic seizure.
(e) Fecal incontinence seizure.
(f) Hippus seizure.
(g) Hyperhydrostatic seizure.
(h) Hypertensive seizure.
(i) Lacrimatory seizure.
(j) Pilomotor seizure.
(k) Sexual seizure.
(l) Sialorrheic seizure.
(m) Tachycardic seizure.
(n) Urinary seizure.
(o) Vasomotor seizure.

3. Dyscognitive Seizure
   (a) Amnestic seizure.
   (b) Aphasic seizure.
   (c) Kinetic seizure.
   (d) Dialectic seizure.
4. Motor Seizure
   (a) Simple motor seizure.
      (i) Clonic seizure.
      (ii) Epileptic spasm.
      (iii) Myoclonic seizure.
      (iv) Nystagmoid seizure.
      (v) Tonic seizure.
      (vi) Tonic–clonic seizure.
      (vii) Versive seizure.
      (viii) Vocalization seizure.
   (b) Complex motor seizure.
      (i) Alien limb seizure.
      (ii) Automotor seizure.
      (iii) Dacrystic seizure.
      (iv) Gelastic seizure.
      (v) Hypermotor seizure/Emotional hypermotor seizure.
      (vi) Kissing seizure.
      (vii) Singing seizure.
      (viii) Spitting seizure.
      (ix) Verbalization seizure.
5. Special Seizure
   (a) Astatic seizure.
   (b) Atonic seizure.
   (c) Central apneic seizure.
   (d) Fearful facies seizure.
   (e) Hypnopompic seizure.
   (f) Hypomotor seizure.
   (g) Negative myoclonic seizure.
   (h) Water drinking seizure.
6. Asymptomatic EEG seizure.

2.4 Classification and diagnosis of epileptic syndrome (see Chap. 4).

1.3 History, Present Situation, and Future Perspectives

The first known description of an epileptic seizure is recorded in a 4000-year-old Akkadian tablet from Mesopotamia [19]. At those times, epilepsy was considered to be caused by spirits and gods, and therefore, it was treated with magical rites, including herbal remedies which were not usually ingested, but simply hung around the neck [20]. Herbal remedies as a treatment for epilepsy and seizures have also been used in China for thousands of years, but in traditional Chinese medicine treatments were consumed as part of the diet according to the theory that medicine and food come from the same sources [21]. Plant-derived medicines have been the mainstay of medical therapy for seizures and epilepsy in many other civilizations, and some continue to be used in traditional medicine. Although the evidence base for their efficacy is tenuous [20, 21], and some may even be toxic or interact adversely with modern medicines [22], a number of these treatments deserve to be evaluated through modern methodology [21]. An example of an herbal remedy that withstood the test of scientific scrutiny and was eventually incorporated into the modern pharmacological armamentarium is cannabidiol, which was used as a component of Cannabis to treat epilepsy by Islamic physicians in the twelfth century [23] and is now approved in the United States and Europe for the treatment of seizures associated with Dravet syndrome, Lennox-Gastaut syndrome and tuberous sclerosis complex [24].

Although a myriad of treatments have been applied since the dawn of history as an attempt to control seizures and epilepsy, the modern era of antiseizure medications (ASMs) starts with the introduction of bromide [25, 26]. Accordingly, our description of the history of pharmacological treatments for epilepsy will start from that time.

1.3.1 The Early Period of ASM History: 1857 to 1937

The birth of effective antiseizure treatments has a precise date, May 11, 1857. It was on that date that, at a meeting of the Royal Medical and Chirurgical Society in London, Sir Charles Locock, Queen's Victoria's obstetrician, commented on the excellent efficacy results that he had obtained with potassium bromide in the treatment of young women with 'hysterical epilepsy connected with the menstrual period' [20]. He was probably referring to catamenial epilepsy. Apparently, the rationale for trying bromide in those patients was to exploit its anaphrodysiac properties due to his belief, widely held at that time that epilepsy was caused by masturbation "both in boys and in girls." As we will see later in this chapter, this was not the last time that a wrong hypothesis led to discovery of an effective medications. Within a few years of Charles Locock's presentation, bromides became widely used in the treatment of epileptic seizures. Bromides dominated the therapeutic armamentarium against epilepsy for the last part of the nineteenth century, and continued to do so until the 1920s. When started as initial treatment in newly diagnosed

epilepsy, bromides reportedly resulted in long-term remission in about one quarter of patients, and a significant reduction in seizures in about another quarter [27]. Results, however, were less favorable when bromides were used in patients with chronic epilepsy. After the introduction of phenobarbital and phenytoin, bromides were largely replaced by safer and more effective ASMs, although they are still being used today in exceptional cases, especially in children with drug-refractory seizures [28, 29]. Of note, the introduction of bromides did not immediately result in complete disappearance of older, bizarre and often deleterious "treatments" for epilepsy such as tooth removal, ligatures of the extremities, dry cupping, the abstraction of blood, purgatives, mineral tonics, nitromuriatic acid, decoctions of bark and sulphuric acid, and other similar amenities [20]. In fact, more ineffective and toxic treatments were introduced between 1860 and 1910 [20].

The next milestone in ASM history was the introduction of phenobarbital in 1912. Barbiturates had been used for their sedative and sleep-promoting properties for a number of years. Phenobarbital was synthesized in 1904 and joined other barbiturates in the German market in 1911. The discovery of its antiseizure properties can be ascribed again to serendipity. The prevailing story is that Alfred Hauptmann, then a young physician working at a clinic in Freiburg, Germany, lived in an apartment above a ward that housed patients with epilepsy, and his sleep was disrupted by noisy seizures that the patients were having at night [25]. Guided by the erroneous hypothesis that sedation would reduce susceptibility to seizures, he prescribed phenobarbital to his patients and found that their seizure frequency was greatly improved or even suppressed, both at night and during daytime. His meticulous documentation of phenobarbital's efficacy in controlling seizures was published in a local German language scientific journal which was not readily accessible [20]. Because of this, and because of the communication disruption produced by World Word I (1914–1918), phenobarbital started to be known and used outside Germany only in the 1920s [30]. It became increasingly popular in subsequent years, and it continues to be used even in modern times, particularly in low-income countries, because of its low cost. An intravenous formulation of phenobarbital, which provided a valuable tool for the management of status epilepticus, was introduced in 1926. The establishment of phenobarbital as an effective ASM led to subsequent introduction of other barbiturates for the treatment of seizures, namely phenylmethylbarbituric acid (Rutonal®) in 1925 and methylethylphenylbarbituric acid (mephobarbital, Prominal®, Mebaral®) in 1932, but none of these compounds proved to be as successful as phenobarbital [20].It should be emphasized that none of the treatments discussed thus far had undergone rigorous evaluation through controlled trials. Regulatory oversight of the marketing of medicines was minimal at that time. Prior to the approval of the Food and Drug and Cosmetics Act by the American Congress in 1938, medicines could be marketed in America and other parts of the world without any demonstration of safety being required [31]. Moreover, adequate demonstration of efficacy was not a requirement until 1962 in the US, and until several years later in Europe. This explains why during the same period many toxic and ineffective treatments for

epilepsy continued to be introduced and used, typically with misleading claims concerning their true effectiveness. For example, a 1940 British textbook cited belladonna, borax and nitroglycerine among medications of definite usefulness for the treatment of epilepsy (Kinnear-Wilson, 1940). In an article by William Lennox (1940), epilepsy treatments used in America in the mid-30 s included not only phenobarbital (and phenytoin, for the last two years of that decade), but also borotartrate, brilliant vital red, and antirabies vaccine! The number of people harmed by these treatments is likely to have been substantial, an observation which highlights the danger of relying on uncontrolled clinical reports without proper evaluation of efficacy and safety [31].

1.3.2 From the Discovery of Phenytoin to the Introduction of Valproic Acid: 1938–1967

The introduction of phenytoin in 1938 represents a true landmark because the discovery of this drug was based on a screening program in an animal model (seizures induced by electrical stimulation of brain) and a paradigm that, with a number of additions and modifications, continues to be used today in ASM discovery. Another landmark advance made with the introduction of phenytoin was the demonstration that antiseizure effects can be achieved without inducing sedation [31]. Interestingly, it took only two years from the first experiments in animal models to the introduction of phenytoin in the market [20]. Overall, the clinical development program of phenytoin lasted about one year, and did not include any controlled trial.

The discovery of phenytoin by Merritt and Putnam is a truly fascinating story that has been described masterfully by [20]. Although based on a rational hypothesis (i.e., the hypothesis that electrically induced seizures could provide a model to identify molecules possessing antiseizure activity), Merritt and Putnam's discovery benefited from a great deal of luck. In fact, phenytoin was one of the very first compounds that underwent screening, and clearly showed very promising activity. Thereafter, Merritt and Putnam screened over 700 molecules, but only four of those reached the stage of being tested clinically and none became commercially available. Should phenytoin not have been among the first 50 or 100 compounds tested, one wonders whether Merritt and Putnam would have continued with their testing program!

Merritt and Putnam's experiments were truly a turning point in the history of ASM discovery, because it led to the introduction of animal models of seizures and, at a later time, models of epilepsy as a standard approach to discover and evaluate novel drug candidates prior to their assessment in the clinic [32, 33]. Intense research efforts in the subsequent 30 years led to the marketing many novel drugs for the treatment of seizure disorders, including (in order of year of introduction for use in epilepsy) trimetadione, paramethadione, mephenytoin, phetenylate, phenacemide, metharbital, beclamide, phensuximide, primidone, methsuximide, allomethadione, acetazolamide, pheneturide, ethotoin, aminoglutethimide, sulthiame, diazepam, carbamazepine, and valproate [31]. This list includes highly valuable ASMs which are still in widely used today as well as

compounds that rapidly became obsolete due to poor efficacy or unfavorable tolerability profile. Once more, this reflects the lack of rigorous clinical assessment of these compounds prior to their introduction in the market. Some randomized controlled trials of ASMs were actually conducted during this period, but their application was sparse and trial designs were often suboptimal [31]. This is best summarized by an influential US report on the evidence supporting the efficacy of ASMs introduced prior to the 1970s [20]. Only three of the 110 clinical trials which were closely assessed included an adequate control for bias, and only two had a double-blind design. With respect to modalities of drug discovery, many compounds originated from structural modifications of ASMs, especially phenobarbital and phenytoin, already known to be clinically effective. However, serendipity played again a major role in some instances, the most notable example being valproic acid which was used as a solvent for other drug candidates and discovered by chance when all screening tests done on compounds dissolved in valproic acid turned out to be positive for anticonvulsant activity [34]. In any case, the period between 1938 and 1967 was quite fruitful, because virtually all first-generation ASMs had been introduced by that time. Admittedly, not all of these ASMs became widely available during that period. For example, valproic acid was marketed in France in 1967, but it was approved by the US Food and Drug administration (FDA) in 1978, that is, more than 10 years later.

1.3.3 Establishing the Modern Principles of Epilepsy Treatment and Preparing the Ground for a New Wave of ASMs: 1968–1988

The two decades that followed the introduction of valproic acid were characterized by an improved understanding of the clinical profile of the ASMs existing at the time, as well as the many factors involved in variability in drug response. A number of important developments took place during this period.

First of all, the methodology to evaluate the clinical efficacy and safety of ASMs was greatly improved, with increasing emphasis being placed on high-quality randomized controlled trials. Evaluation of the efficacy of available ASMs was facilitated by the development in the late 1960s of a broadly accepted classification of seizures and epilepsies [35, 36], and reached a high point in the early 1980s with the conduction of a landmark randomized double-blind parallel-group multicenter trial by the US Department of Veterans Affairs (VA) collaborative group [37]. This trial compared the effects of phenytoin, carbamazepine, phenobarbital, and primidone in 622 patients with newly diagnosed (or previously undertreated) focal and/or focal to bilateral tonic–clonic seizures, and demonstrated important differences in the efficacy and tolerability of these drugs. At the same time, smaller-scale studies helped in characterizing the spectrum of efficacy of many ASMs against different seizure types, highlighting the fact that some narrow-spectrum ASMs can paradoxically precipitate or aggravate seizures in patients with certain epilepsy syndromes [38]. Finally, studies conducted in this period led to recognition of the value of monotherapy in the treatment of epilepsy [39], and the appreciation that unnecessary polytherapy can be associated with a major burden of toxicity [40].

A second important advance in this period was the broad recognition that variability in serum drug levels of ASMs contributes to an important extent to differences in clinical response across individuals. Pioneering work on the pharmacokinetics of phenobarbital and phenytoin had been done many years earlier in the USA, and the evaluation of the correlation between serum ASM concentrations and clinical response can be traced back largely to research carried out by Fritz Buchthal and Ole Svensmark in the late 1950s and early 1960s in Copenhagen, Denmark [41]. However, it was only in the 1970s and 1980s that the use of serum ASM concentrations (therapeutic drug monitoring, or TDM) as an aid to dose adjustment became fully established [42–45]. Together with studies on the comparative efficacy and tolerability of existing ASMs, these studies contributed to highlight the importance of tailoring ASM therapy to the characteristics of the individual patient.

Interestingly, not many ASMs were introduced during this period. ASMs marketed between 1968 and 1988 include three benzodiazepine compounds (clonazepam, clobazam and lorazepam), and the GABA-prodrug progabide, which was marketed in France in 1985 but was never widely used because of poor efficacy results and the potential to cause liver toxicity [46–48]. Another investigational drug, cinromide, showed very promising results in Lennox Gastaut syndrome and other seizure disorders, but its development was stopped in 1981 when controlled studies found its efficacy to be similar to that of placebo [20].

In the late 1960s and early 1970s, there was a clear perception that efforts to discover new drugs for epilepsy were relenting, despite an obvious need for safer and more effective treatments. These considerations, coupled with the wisdom and vision of Dr. J. Kiffin Penry at the US National Institute of Neurological Disorders and Stroke, led to the establishment in 1975 of the US Anticonvulsant Screening Program (ASP), with finding from the National Institute of Health (NIH) [20, 49]. The aim of the ASP was to stimulate discovery and development of newer therapies for epilepsy. This program, currently known as the Epilepsy Therapy Screening Program (ETSP), has grown over time into a highly structured testing algorithm that uses a broad range of preclinical models, including models of drug-resistant epilepsy, models of severe genetic epilepsies, and models of epilepsies involving infectious and inflammatory mechanisms [50–52]. Over the years, the ETSP has screened preclinically more than 30,000 drug candidates supplied by the pharmaceutical industry or academia, and has played a role (and often a key role) in the development of many subsequently marketed ASMs, including vigabatrin, lamotrigine, oxcarbazepine, felbamate, gabapentin, topiramate, lacosamide, retigabine, and cannabidiol [20, 49, 53]. In fact, the development of some of these compounds started in the late 1970s or the early 1980s, even though their introduction in the marked occurred at a later time.

1.3.4 The Advent of the New ASMs: 1989–2023

The wave of the so-called "new" ASMs started in 1989 with the introduction in the market of vigabatrin and zonisamide. Since then 21 additional ASMs have been introduced in the European or American market (Table 1.3). These medications differ in mechanism of action, pharmacokinetic profile, drug interaction potential,