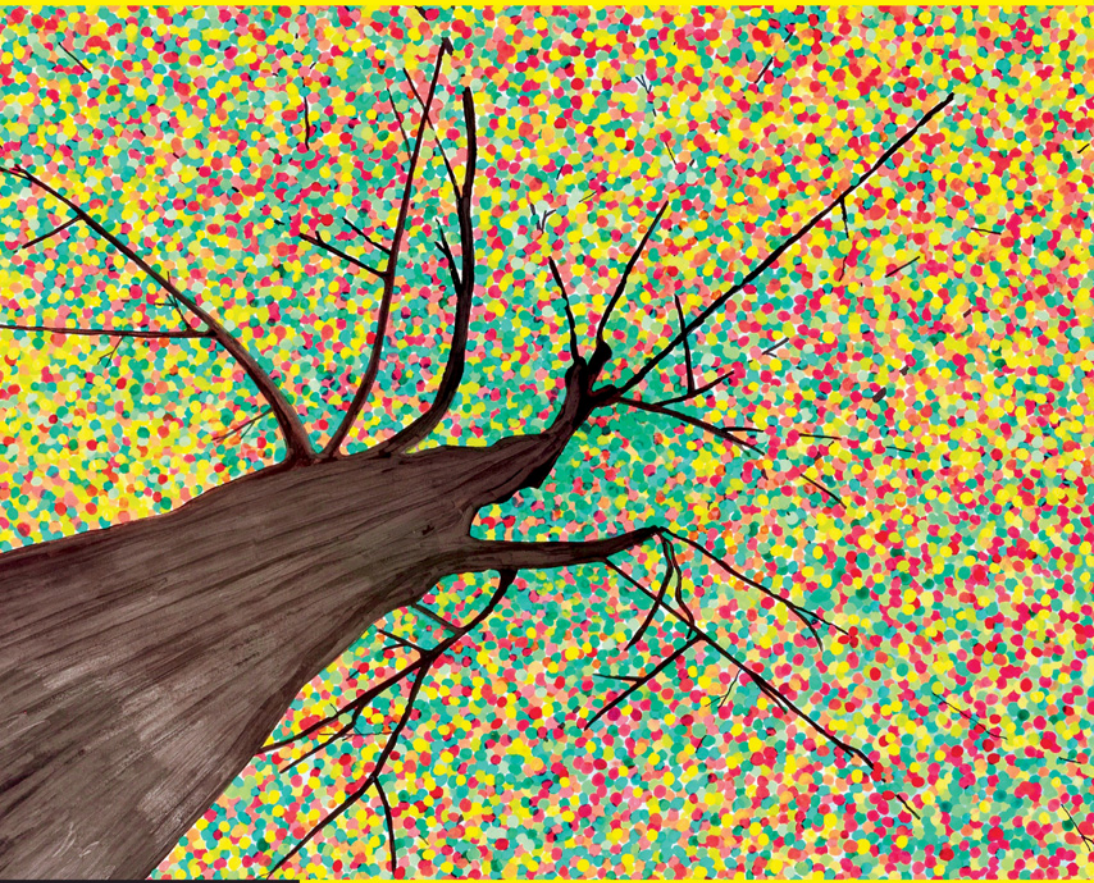
Common Pitfalls in Epilepsy

CASE-BASED LEARNING

DIETER SCHMIDT, WILLIAM TATUM AND STEVEN SCHACHTER



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We dedicate this book to the memories of Théodore Herpin, Norman Geschwind, and Dieter Janz
– three masters of case vignettes.

Contents

Preface

Why did we write a book about pitfalls in the management of epilepsy? The easiest answer is that we encountered these pitfalls the hard way – by falling into these many traps. Doctors learn from mistakes, probably because they become emotionally charged, and the "practice" of medicine implies constant improvement from experience. So we strove to better understand the pitfalls of epilepsy management to help us and others avoid them and to ensure that patients receive the best possible care.

In keeping with the format of the pitfalls series of books, we present case vignettes to illustrate many common pitfalls in epilepsy diagnosis and management, and in doing so we honor the legacies of pioneers who used case vignettes effectively to advance knowledge and teach the following generations. We have dedicated this book to three of the most prominent giants of case studies: Théodore Herpin, who included a series of over 30 vignettes of his patients with treatment-refractory epilepsy which he called rebellious cases (Herpin, 1852); Norman Geschwind, who used case studies to explore the interictal personality of patients with epilepsy (Schachter, 1997); and Dieter Janz, who based a full monograph on the epilepsies on detailed case histories of 250 of his patients (Janz, 1969).

Many of the early observations of patients with seizures continue to remain valid at the present time. As sophistication and refinement in the medical and surgical management of epilepsy grew, academicians sought evidence-based guidance for treatment from randomized controlled trials providing class 1 information. Yet we take care of patients one at a time and the anecdotal evidence from a single patient often shapes our training and later experience as we mature into proficient clinicians. In addition, it is "the one" patient with a rare disease, or the atypical presentation of a common disease such as epilepsy, where we learn about the full spectrum of signs and symptoms. It is the breadth of discovering heterogeneity that accrues over a lifetime to make one a "seizure doctor." While it is certainly true that single patient case histories are unable to provide definitive scientific evidence, they are able to help generate interesting hypotheses that further our understanding of a specific condition. In epilepsy, the number of conditions is legion, and the number of etiologies immense. There are few disorders that compare with the unpredictability of seizures in a seemingly healthy individual. Therefore, with respect to understanding the impact and mechanisms of disease, case reports are critical to shape the role we play in guiding personalized medical care in the treatment of people with recurrent seizures.

When we train during residency and fellowship, the Socratic method of learning often lies at the foundation of our experience. During hospital rounds we encounter individual patients and learn "at the bedside" from our mentors. Questions that arise and information that is discussed are the contents for this book. Additionally, it is hoped that it will aid the clinician's judgment when encountering similar case situations. While there are multiple textbooks, monographs, and journals that offer a scientific fund of knowledge necessary for understanding a medical condition, it is the individual human encounter that transforms our experiences into expertise in a way that is impossible for didactic teaching alone to convey.

When a particular patient's chief complaint or condition evades our understanding, it is important to realize that others may immediately recognize what we do not. Sir Willian Osler, dubbed the "Father of Modern Medicine," was famous for his diagnostic acumen, his broad knowledge, and his prodigious publishing output; yet he would often surprise and impress his students by using his own clinical mistakes as teaching examples (https://profiles.nlm.nih.gov/ps/retrieve/Narrative/GF/p-nid/363).

In "Common Pitfalls in Epilepsy," we attempt to take a fresh approach to case-based learning by providing dialogue about where traps leading to misdiagnosis and mistreatment may occur. Actual case histories have been taken from patients in the United States and Europe and are presented with a series of questions and answers that revolve around important diagnostic and treatment topics. The format is designed as though we are "rounding" on patients with epilepsy within a group of clinicians who seek to specialize in the field of neurology or epileptology. Critical situations may arise that challenge even the most seasoned clinicians. Our goal in this book is to take a problem-based learning approach. We focus on common topics and individual case situations where clinicians are likely to be pulled into a wrong conclusion; a wrong conclusion that could potentially harm the patient–a pitfall to avoid.

As we remember "To Err is Human," it is equally important to recognize that we may have difficulty dissecting the information provided by patients because of the very nature of seizures. Rather than abandon the medical history, though, the insights that can be derived from the patient's history will often outweigh the cumulative value of "tests". The results of tests have their own pitfalls when an accurate history and physical examination is abbreviated or curtailed unnecessarily. From the time of a first seizure to the state of drug-resistant epilepsy, many medical and nonmedical issues arise for the individual patient that require interventions. From antiepileptic drugs, to diets and supplements, to neurostimulation and epilepsy surgery, there are countless areas where crucial information may change the life of a person with epilepsy forever. For neurologists, neurosurgeons, psychiatrists, internists, therapists, and technologists, this book provides a grassroots approach to dealing with common problems that are encountered in people with seizures.

In the forthcoming chapters of this book, we seek to enhance the reader's knowledge by asking questions about seizures and epilepsy that they might ask their mentors or consultants. In the dynamic and often dramatic situations that arise in dealing with patients who have epilepsy, many questions arise. Our hope is to provide information that will be relevant to the patient with epilepsy in different situations by providing an approach that will enhance teachable moments and the resulting treatment outcomes. While the teacher–student relationship is emphasized in the text for the purposes of learning more about the pitfalls in epilepsy, the reverse is also true: we learn from our patients every day.

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Acknowledgments

Why is what we do called medical practice? It is because we learn by doing and by seeing the consequences of our actions and inactions in our quest to help our patients and primum non nocere – first do no harm. Indeed, this book could not have been written if we did not first acknowledge that we had encountered common pitfalls, large and small, in the management of patients with epilepsy and that second these pitfalls can be avoided successfully by sharing experiences. We have come to view these pitfalls as gifts, as long as they are humbly recognized as opportunities to improve patient care. We therefore pass along to the readers of this book the gifts of many generous colleagues and patients who kindly shared their untoward experiences with us. The authors want to thank in particular Professor Christian Erich Elger from the University Epilepsy Clinic, Bonn, Germany, Doctor Greg Cascino from Mayo Clinic, Rochester Minnesota, and Doctor Donald Schomer from Beth Israel Deaconess Medical Center, Boston, Massachusetts, all those who gave us permission to include their work, and our families for their unwavering support.

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Chapter 1

Mistaking Nonepileptic Events for Epilepsy

William O. Tatum

A rose is a rose is a rose.
From the poem "Sacred Emily" (1913; www.lettersofnote.com)

This famous phrase by Gertrude Stein may have had hidden meaning to her, but the word "rose" appears to be used to reflect a variety of different meanings. So, too, the term "seizure" is used differently relative to the perspectives of those who use it. Different interpretations exist when patients with "seizures" are observed by witnesses. Misidentification serves as a pitfall that can lead to mistaking nonepileptic events (NEEs) as seizures or vice-versa. This chapter focuses on the former. The following case illustrates that a rose is a rose but not always the same rose when trying to disentangle the complex history of patients with epilepsy.

Case 1.1 Spells and Seizures

A 23-year-old female presented with recurrent "episodes" and "grand mal seizures" for her initial evaluation. Seizures began at age 13. She was born 6 weeks premature with a left intraventricular hemorrhage and subsequent mild learning disability. There was a history of sexual abuse by a family member in her late childhood through early adolescence though she had kept it as a secret to herself. In addition, her mother reports that she was diagnosed with fibromyalgia, irritable bowel syndrome, insomnia, and chronic depression. Treatment with several antiepileptic drugs (AEDs), including carbamazepine, clonazepam, and lamotrigine, was ineffective and she was currently taking valproate (VPA) for a "seizure disorder" though it too had been ineffective in controlling her recurrent "events." Her family described ongoing daily "episodes" where she would "zone out," close her eyes, appear tearful, and remain unresponsive for 5–10 minutes. She experienced three "grand mal seizures," the last of which occurred at 14 years old when she fell asleep and was witnessed by her mother and brother who heard her cry out. Upon arrival to her bedroom, they found her unresponsive, stiff in all extremities, with bilateral jerking for 1–2 minutes. Afterward, a tongue laceration (Figure 1.1) was evident with confusion and disorientation, which gradually resolved after 1 hour. A high-resolution brain MRI demonstrated subtle left hippocampal hyperintensity (Figure 1.2). A prior EEG from when she was 14 years old was interpreted as "abnormal" due to "spikes everywhere" though repeat EEGs were normal. She is engaged to be married and wants to have a family.

What are the pitfalls involved in this case for the clinician caring for the patient?

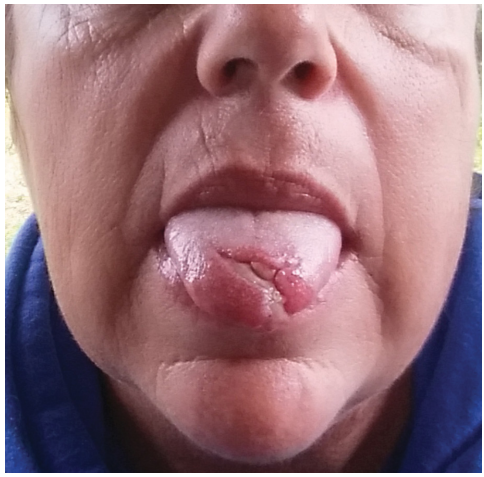

Figure 1.1 Tongue laceration (arrow) sustained during a "grand mal" seizure

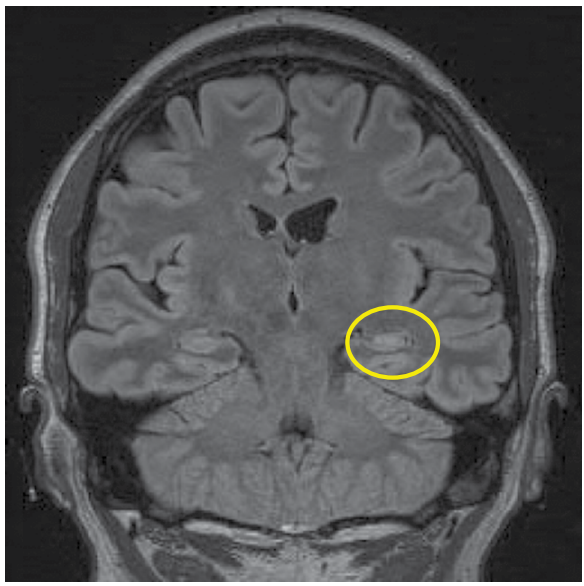

Figure 1.2 High-resolution brain MRI demonstrating left hippocampal hyperintensity on T2/fluid-attenuated inversion recovery sequence

What are the Pitfalls Involved in This Case for the Clinician?

Discussion

In this case, the nocturnal occurrence, lateral tongue laceration, and postictal state are clinical features that are characteristics of epilepsy. Furthermore, onset during adolescence is typical for a genetic generalized epilepsy (GGE) syndrome. However, a history of sexual abuse, subjective diagnoses (e.g., fibromyalgia, chronic pain), depression, prolonged event duration, and resistance of her episodes to all AEDs raises suspicion for NEEs.

In this case, one pitfall is assuming a single diagnosis for two or more event semiologies. The "zone outs" in this case in fact reflect a different semiology than the "grand mal" seizures. By assuming they both reflect epilepsy (e.g., absences and GTC seizures vs. focal seizures and focal seizures evolving to bilateral convulsions), over-treatment may occur by mistaking two separate problems as one, and under-treatment is also possible by inappropriately expecting that AEDs will treat a nonepileptic disorder. In this case, video-EEG monitoring (VEM) was performed with normal interictal EEG. Three "zone outs" with unresponsiveness were captured spontaneously and during activation techniques to confirm the diagnosis of psychogenic nonepileptic attacks (PNEAs).

Another pitfall is assuming that an abnormality on laboratory testing, such as the brain MRI in this case, is relevant to all the patient's presenting signs and symptoms (Labate, 2010). In this case, it was an incidental finding. This is similar to an abnormal EEG that is not interpreted correctly in light of the specific clinical context, leading to the wrong diagnosis of epilepsy (see Chapter 2). In this case, the abnormal EEG with "spikes everywhere" may reflect generalized spike-and-waves associated with a remote diagnosis of genetic generalized epilepsy, but unless the actual tracing is recovered for review, the validity of the result can only be assumed but not confirmed.

After the correct diagnoses for her current events were made, cognitive behavioral therapy was initiated with antidepressants, resulting in resolution of the PNEAs. In addition, a consensus decision was undertaken to pursue a trial of VPA taper which was successfully performed. Currently, she remains free of all events, is married with two healthy children, and works as a security officer.

The diagnosis of epilepsy is a clinical judgment based upon the history obtained from the patient or witnesses of the observed behavior for the patient's event. Seizures in people with epilepsy (PWE) occur as paroxysmal, transient, behavioral events involving experiential, somatosensory, motor, or visual signs or symptoms caused by abnormal excessive neuronal activity (Fisher, 2014). They may be focal seizures, involving brain networks confined to one hemisphere or generalized seizures that involve bilaterally distributed networks beginning synchronously in both hemispheres at onset (Berg, 2010). NEEs are episodes involving similar signs and symptoms though they are distinguished from seizures in PWE by the lack of associated abnormal electrical discharges emanating from the brain, occurring simultaneously with the episodes (Chen, 2016). Identifying witnessed paroxysmal events is the basis and starting point for the diagnosis, classification, and treatment of epilepsy.

Pitfall

Recurrent NEEs are challenging to differentiate from epilepsy by history alone.

Diagnostic errors occur when NEEs are mistaken for epileptic seizures resulting in a misdiagnosis. When the spells are not witnessed, the provider must depend on information given by the patient. Reporting by a witness (such as family members or friends) may be misleading, resulting in diagnostic errors and leading to inappropriate treatment (Benbadis, 2008; Smith, 1999). Additionally, in approximately 40% of PWE, the initial EEG may not reveal epileptiform discharges (Pillai, 2006).

When discussing errors, it is important to address the pitfalls involved with diagnosis and classification of epileptic seizures and epilepsy syndromes. Epilepsy always starts with a first seizure (Chapter 4) and the initial diagnostic assessment is crucial to avoid errors when these first seizures occur (Gavvala, 2016). Routinely, a clinical diagnosis relies on observation derived from the clinical history involving the patient and witnesses with variable recall and ability to describe the event in question, in the context of the clinical course of recurrent events with time. Both are subject to error (Scheeper, 1998). The diagnosis of epilepsy is in stark contrast to NEEs; the former may be characterized by some features that are distinctly different than the features of NEEs (e.g., occurrence directly from sleep, posterior-lateral tongue contusions, postictal disorientation) (Devinsky, 1996). While PNEAs occur in patients of any age, gender, ethnicity, and country of origin, the majority of clinical studies support a disproportionate prevalence among young adult females.

The differential diagnosis of epilepsy therefore involves a careful and deliberate distinction of epilepsy from psychogenic and physiological NEEs. However, the historical report (or lack thereof) of epileptic seizures and NEEs often overlap and blur distinction. Additionally, diagnostic testing (e.g., MRI and EEG) may be unrevealing and results in a tenable diagnosis. Unfortunately, there is no other biomarker with sufficient specificity and sensitivity to make a diagnosis (Engel, 2008). Reasons for a seizure misdiagnosis include the following (Uldall, 2006):

- There is a large differential diagnosis for epilepsy.
- False belief that epilepsy is a single disease.
- Forgetting that the clinical diagnosis of epilepsy is based on history.
- Insufficient knowledge of seizures and spells.
- False perception that delaying diagnosis definitely carries grave risks.
- Barriers to obtaining VEM.
- The EEG is overinterpreted.

The psychosocial consequences of misdiagnosing NEEs as epilepsy include restrictions in driving, implications for employment and insurance, and the psychological impact of the epilepsy label, which together create stigma, isolation, and a significant impact on a patient's quality of life (Lempert, 1990). Additional effects involve unnecessary exposure to AEDs with attendant side effects and risk of idiosyncratic reactions. Further consequences of a missed diagnosis can be devastating and involve morbidity and even mortality if a serious psychiatric or medical condition goes undetected (e.g., suicidal ideation or cardiac arrhythmia).

Distinguishing NEEs from epileptic seizures may be difficult even for the most experienced clinicians. For most patients, the diagnosis is based on a thorough history, often derived from a 2nd or 3rd party in conjunction with neurological examination supplemented by cranial MRI and a routine scalp EEG (Alsaadi, 2004). If needed, VEM is the gold standard for obtaining a definitive diagnosis of NEEs. Mistaking NEEs as seizures associated with epilepsy in the US results in an estimated loss of $110–920 million being spent yearly on diagnostic evaluations, laboratory testing, and inappropriate AED treatment and emergency department visits (Koblar, 1992), with other estimates as high as several billion dollars/year (Martinovic, 1997).

Differential Diagnosis

The differential diagnosis of epilepsy is broad and it is worth repeating that establishing the diagnosis of epilepsy may be challenging even for a seasoned clinician and that many NEEs may mimic epileptic seizures. Historical recall of the seizure semiology or "spell" forms the basis for routine diagnosis and treatment (Van Donselaar, 2006); however, semiology is the foundation for diagnosis (Deacon, 2003; see Chapter 4). In experienced hands, the diagnosis of epilepsy can be made with a high degree of sensitivity and specificity (Alsaadi, 2004; Chen, 2016; Van Donselaar, 2006). However, making the diagnosis of PNEAs or focal seizures for events without impaired consciousness has only modest sensitivity based on history (Deacon, 2003) or video-EEG ($\kappa = 0.57$, 95% confidence interval [CI] 0.39–0.76) (Benbadis, 2009).

Pitfall

Patients with NEEs are frequently misdiagnosed with epilepsy and treated with AEDs.

Some examples of nonepileptic conditions with symptoms that may mimic seizures, potentially leading to the incorrect diagnosis of epilepsy (Benbadis, 2009b), include:

- Psychiatric disorders: anxiety, depression, posttraumatic stress disorder
- Cardiovascular: syncope, anoxic seizures, cardiac arrhythmia/prolonged QT syndrome
- Migraine
- TIA
- Sleep disorders: narcolepsy with cataplexy and parasomnias; somnambulism, night terrors/nightmares, rapid eye movement (REM) behavioral disorder
- Movement disorders: tic, startle, tremor, myoclonus, paroxysmal dyskinesia/dystonia, spasms, intensive care unit (ICU) movements
- Other symptoms: sensory phenomena, vertigo, hallucinations, hypoglycemia, effects of drugs and alcohol
- Medical conditions: acute intermittent porphyria, pheochromocytoma, carcinoid, tetanus

NEEs are categorized as psychogenic or physiological. Psychiatric disorders are the most common reason for NEEs in patients admitted to epilepsy monitoring units (EMUs); in this setting, PNEAs are found in up to 90% of patients who do not have epilepsy (Benbadis, 2009a, 2009b; Chen, 2016; Devinsky, 1996; Scheepers, 1998; Smith, 1999). However, physiological causes for NEEs should always be considered to ensure proper management of a "missed" diagnosis (Benbadis, 2009b; Chen, 2016). Physiological NEEs including syncope, movement disorders, parasomnias, cerebrovascular disease, and delirium are time-limited conditions that may be associated with a paroxysmal change in behavior mimicking seizures in PWE. Similarly, transient conditions that cause disordered brain function such as concussion, metabolic disturbances (e.g., hypoglycemia and sepsis), and medication side-effects may trigger (provoke) seizures, but do not portend epilepsy (Fisher, 2014; Gavvala, 2016; see Chapter 4).

The diagnostic challenge is accentuated when information obtained from a witness is misleading, as occurred in the following case.

Case 1.2

A 66-year-old male is admitted to the hospital for an adrenal mass. His past medical history includes hypertension, hypercholesterolemia, and recently diagnosed diabetes mellitus. He is undergoing phlebotomy before a surgical biopsy when he experiences his first "seizure." The phlebotomist reports witnessing a "grand mal" seizure and emphasizes that she has seen people with seizures before. Her description included pallor prior to whole-body jerking, loss of consciousness, and urinary incontinence. The seizure lasted "for a minute." A neurologist is called and upon arrival the patient's neurological examination is normal. He remembers feeling lightheaded, clammy, and nauseated, with tunnel vision, prior to losing consciousness. He describes being "confused" during recovery with evidence of urinary incontinence.

Discussion

Consultation by a neurologist for "seizure vs. syncope" is common in the hospital-based setting. Intense emotional stimulation (e.g., pain, seeing blood, anxiety) and Valsalva maneuvers (e.g., micturition, lifting) may produce brief loss of consciousness and convulsive movements which may mistakenly be interpreted as a seizure. However, this represents a benign condition termed convulsive syncope. It is understandable why witnesses would readily mistake this physiological NEE for a seizure based on gross appearance. However, the setting of phlebotomy along with the prodromal symptoms, brevity of the jerks, pallor, and quick recovery suggest syncope. The "confusion," if described in more detail, reflected confusion for the situation the patient found himself in after the event, but not true postictal disorientation. Despite widespread opinion to the contrary, incontinence is not specific for an epileptic seizure and may occur with syncope.

Pitfall

Overtreatment of patients with new-onset events diagnosed as symptomatic of epilepsy in the hospital-based setting may occur when the events are actually acute symptomatic seizures (see Chapter 4) or physiological NEEs.

A clinical diagnosis of epilepsy is found to be incorrect in approximately 30% of patients admitted to the hospital for VEM due to paroxysmal neurological events (Leach, 2005; Scheepers, 1998). Syncope is the most frequent physiological NEE and may be mistaken for generalized tonic–clonic (GTC) seizures when syncope is convulsive (Table 1.1) though there are clinical differences (McKeon, 2006).

Syncope may result from a cardiogenic, hypotensive, or neutrally mediated origin, though benign forms such as neutrally mediated syncope (e.g., vasovagal) are most common. Brief body jerks or tonic stiffening postures are frequently observed during syncope in healthy people. When syncope was induced in healthy subjects arising from a squat position with a Valsalva maneuver, 38 of 42 (90%) of the resulting physiological NEEs showed irregular and mild multifocal jerking (Lempert, 1994). Some patients with syncope remain "unexplained" even after thorough investigation (Lempert, 1994; McKeon, 2006). Some have psychogenic pseudosyncope and when risk factors for PNEAs are present, VEM should be considered to facilitate a definitive diagnosis. Differentiating

Table 1.1 The clinical features differentiating convulsive syncope from generalized tonic–clonic seizures

Convulsive syncope	GTC seizure
Triggers are present (i.e., needles)	Triggers are rare
Sweating and nausea common	Déjà vu or ictal fear common
Less than 20 seconds	1–2 minutes
Movements (<15 seconds); multi-focal myoclonus or tonic posturing	Movements sustained; tonic or tonic–clonic
Pallor	Cyanosis
Postictal state absent	Postictal state present
Post-syncope myalgias rare	Postictal myalgias common

syncope and PNEA can be difficult based only on historical information, especially when convulsive movements are witnessed (Heo, 2008; Rugg-Gunn, 2001). The misdiagnosis of epilepsy is further compounded if the true underlying reason for the event is missed.

Injury, morbidity, and mortality may be associated with some causes of syncope. Orthostatic hypotension may result from a rapid drop in systolic blood pressure when the patient arises from a standing or recumbent position, and is particularly problematic in patients with autonomic dysfunction (e.g., diabetes, Parkinson's disease). Malignant reasons for syncope/convulsive syncope require rapid identification and specific treatment. Cardiac arrhythmias; sick sinus syndrome, atrial fibrillation, prolonged QT syndrome, third-degree atrial–ventricular heart block, and states of reduced cardiac output; congestive cardiomyopathy; and cardiac standstill are examples where urgent non-neurological intervention is required. Missing the former conditions could produce death if unrecognized. In contrast to ictal EEG findings, the EEG during a syncopal episode demonstrates an electrographic evolution from diffuse slowing with intermixed theta, background slowing, intermixed high amplitude delta, diffuse amplitude reduction until, finally, there is severe voltage suppression progressing to transient electrocerebral inactivity in survivors (Figure 1.3). When cerebral hypoperfusion is prolonged, reflex anoxic seizures may occur; this is an example of an acute symptomatic seizure (Zaidi, 2000; see Chapter 4).

Physiological NEEs include sleep disorders that manifest as paroxysmal spells (e.g., narcolepsy, parasomnias) (Scammell, 2003). Non-rapid eye movement (NREM) disorders, such as night terrors and somnambulism, and REM sleep disorders, such as REM behavioral disorder and nightmares, are NEEs that produce behaviors during sleep that can mimic epileptic seizures (Derry, 2006). Sleep terrors, somnambulism, and nightmares may be mistaken for frontal lobe seizures (Foldvary-Schaefer, 2009). In contrast to parasomnias, frontal lobe seizures typically arise abruptly and repeatedly directly from sleep, tend to be stereotyped, with sustained, asymmetric dystonic or tonic posturing or hypermotor behavior including thrashing, pedaling, and kicking. Motor movements are typically associated with some but incomplete preservation of awareness, typically last 20–30 seconds, and are followed by a negligible postictal state (Derry, 2006). The scalp EEG may not demonstrate an ictal correlate during frontal lobe seizures (Ryvlin, 2006). Thus, it is important to remember that brief and deep-seated focal seizures with limited spread may elude detection by scalp EEG. Sleep starts commonly occur while

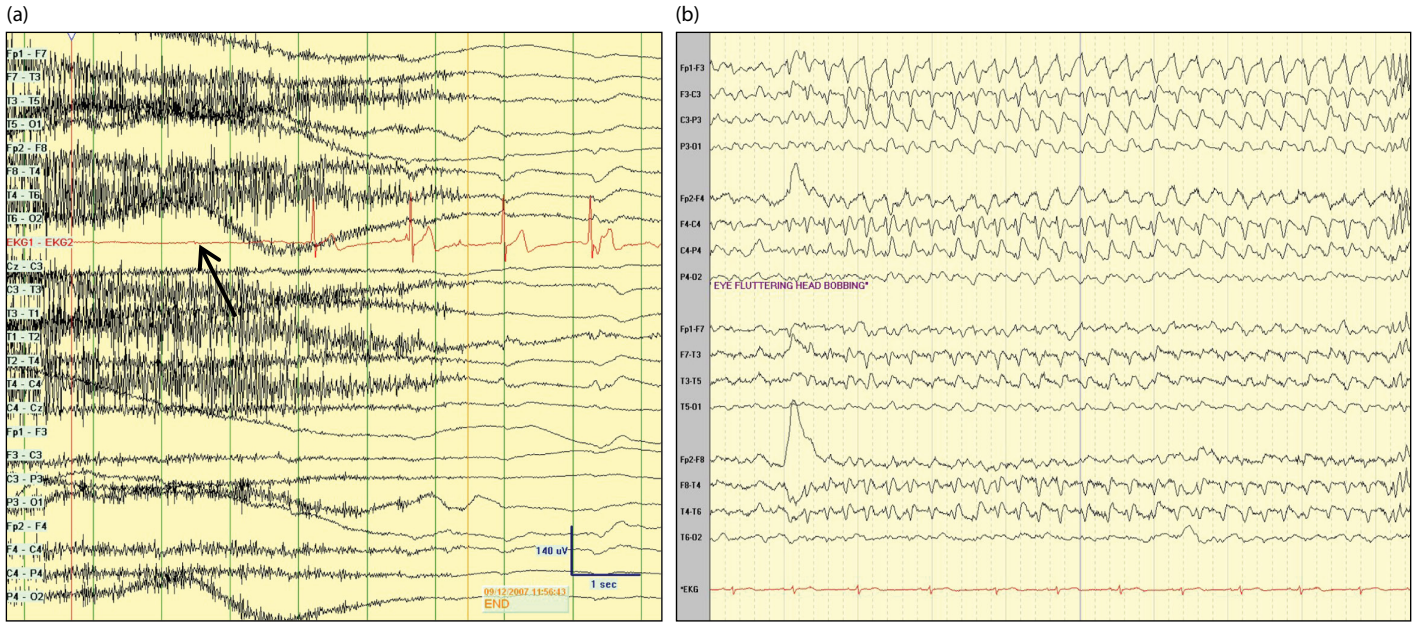

Figure 1.3 (a) EEG of convulsive syncope. Note the increase in myogenic artifact from posturing and the initial absence of EKG artifact (arrow) during asystole. (b) EEG of frontal lobe seizure showing rhythmic ictal delta frequencies

falling asleep and resemble myoclonic seizures; however, they are benign and occur only upon falling asleep. With sleep disorders, VEM will confirm the absence of epileptiform activity during the event in question and identify the associated stage of sleep (NREM vs. REM).

Movement disorders including tic, startle, tremor, myoclonus, paroxysmal dyskinesia, nocturnal dystonia, tonic spasms, and movements in the ICU associated with coma may challenge the clinician. Paroxysmal movement disorders tend to be confused with focal seizures (Bruno, 2004). Acute dystonic episodes and paroxysmal dyskinesia are associated with fully preserved consciousness. Events may be painful and last for long periods of time, as contrasted to the relatively brief period of movements with focal seizures. Episodes may be triggered by dopamine receptor blocking agents such as antipsychotics and antiemetics, usually several days after starting medication. Hemifacial spasm may resemble a focal motor seizure (Benbadis, 2009b). It generally begins with brief, intermittent, irregular, non-evolving, clonic movements of the orbicularis oculi but over years it spreads to involve other facial muscles. The cause of a specific movement disorder may result from a vascular lesion/compression, brain tumor, stroke, and multiple sclerosis, and require neurological intervention. New clinical and molecular genetic observations have begun to further help separate movement disorders from seizures (Berkovic, 2000). Nonepileptic myoclonus can be seen in toxic-metabolic encephalopathies and neurodegenerative disease, and may be confused with epilepsy syndromes that include myoclonus (e.g., juvenile myoclonic epilepsy), especially when convulsions have also occurred.

Neurovascular causes of NEEs include migraines (especially neurologic migraines), transient ischemic attacks (TIAs), and transient global amnesia. Notably, vascular symptoms from TIAs, especially when recurrent or accompanied by "limb shaking" (Figure 1.4), and migraine manifest with "negative" focal deficits (e.g., weakness, numbness, visual loss, language dysfunction) but may nonetheless mimic seizures. By contrast, seizures and migraine auras typically start as "positive" symptoms (e.g., flashing lights, zigzag lines, paresthesia, pain, jerking limb movements) (Nadarajan, 2014). A very important seizure mimic of cerebral ischemia is hemiparesis (Todd's paralysis) resulting from an unwitnessed focal seizure (especially focal motor) (Persoon, 2010). Advanced age and other pertinent history (e.g., hypertension, diabetes, atrial fibrillation) suggest a cerebrovascular cause whereas seizures may be followed by postictal confusion as well as weakness. Nevertheless, it may be difficult to differentiate these two conditions when the onset of the event was not witnessed, complicating the decision whether to administer tissue plasminogen activator (TPA). Migraine auras may mimic focal seizures. Both migraine and seizures are characterized by episodes of neurologic dysfunction. Both may be accompanied by headache and gastrointestinal, autonomic, and cognitive features. Both may have a "march" of symptoms spreading from one area of the body to another, though a seizure usually does so in seconds, and migraine over minutes. The visual aura of migraine is typically gradual and prolonged with black and white, linear or zigzag, central and expanding aspects, commonly associated with fortification spectra and positive visual symptoms in contrast to abrupt, stereotyped, brief, colored, spherical phosphenes that cross the midline associated with focal seizures. It is the clinical history that best clarifies the diagnosis (Haut, 2005).

Systemic medical conditions including hypoglycemia, hypercalcemia, and drug toxicity (including from AEDs) may produce cognitive or motor symptoms that mimic epileptic seizures (Benbadis, 2009b). Metabolic conditions like hypoglycemia can also be

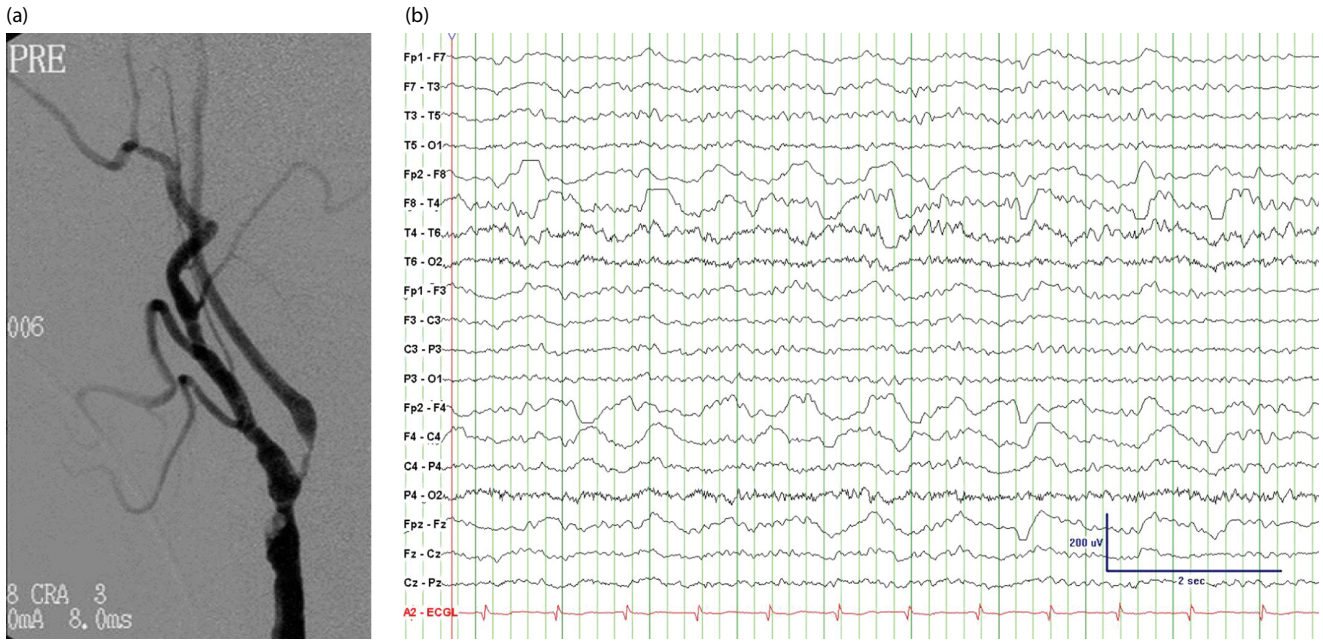

Figure 1.4 (a) Right carotid stenosis on angiography and (b) continuous right hemispheric delta slowing during orthostatic (left-sided) limb-shaking TIAs

mistaken as near-syncope or syncope because they may be heralded by dizziness, confusion, weakness, tremor, and malaise. Psychiatric conditions of panic and anxiety attacks are especially challenging to separate from ictal fear associated with an epileptic seizure arising from mesial temporal structures. Nonspecific symptoms including brain fog, dizziness or vertigo, and paresthesia may be spells that may be mistaken for seizures.

Well-intentioned, but over-vigilant, observers may inadvertently create diagnostic confusion. For example, in the ICU, critically ill patients can have nonspecific abnormal movements such as tremor, shivers, or myoclonus and asterixis that may be misinterpreted by caregivers or ICU staff as seizures, especially when consciousness is already depressed. Another common scenario is when staff at daycare centers for individuals with profound cognitive dysfunction observe a variety of non-seizure movements such as tics but mistake them for seizures.

Pitfall

The boundaries between epileptic seizures and NEEs are often difficult to define and some syndromes or diseases may coexist with the manifestations of one disorder similar to the other.

Children have a wider differential diagnosis for NEEs than adults. More physiological NEEs are present in infants and young children. Breath-holding spells are common in early childhood. They occur in response to over-breathing, usually crying, with the child then becoming apneic with pallid or cyanotic (circumoral) skin color followed by loss of consciousness for a brief period of time (e.g., 15–20 seconds) along with stiffness and a few myoclonic jerks of the extremities. No postictal state is seen and the initial period of crying in response to emotional upset is the clue to breath-holding spells. Sandifer syndrome due to gastroesophageal reflux may occur in infants and manifest as truncal arching with/without extremity involvement and irritability. Self-stimulatory and self-gratifying behaviors are commonly seen in toddlers and young children and may be confused with focal seizures. These behaviors appear to be more common in young girls and may be curtailed with intervention, which confirms they are NEEs. Psychiatric disorders become more common in later childhood and during adolescence. Staring spells due to behavioral inattention ("day-dreaming") or attention deficit disorder are the most common NEEs in healthy children and may be mistaken for absences or focal seizures (Benbadis, 2009b; Uldall, 2006). When these events occur during quiet periods or can be reliably interrupted by external stimuli, benign NEEs is the likely diagnosis. When jerks, myoclonus, incontinence, and upward eye deviation occur, absences should be excluded, especially in school-aged children. Rage attacks, behavioral outbursts, panic/anxiety attacks, and factitious disorder by proxy are psychiatric conditions in children that mimic seizures (Benbadis, 2009b; Uldall, 2006; Van Donselaar, 2006).

- Neonates
  - Jitteriness
  - Benign neonatal myoclonus
  - Neonatal apnea
- Infants
  - Shuddering attacks
  - Benign paroxysmal positional vertigo

  - Sandifer's syndrome
  - Breath-holding spells
  - Self-stimulatory behavior
  - Head banging
- Childhood
  - Attention deficit disorder
  - Daydreaming/attention deficit disorder
  - Episodic abdominal pain
  - Tourette's syndrome/tic/hyperekplexia
  - Stereotyped mannerisms
  - Parasomnias
  - Alternating hemiplegia/migraine

Physiological and psychogenic NEEs are equally frequent in the elderly (Kellinghause, 2004), which is particularly problematic because the clinical manifestations of epileptic seizures in the elderly are more likely to be nonconvulsive and subtle, with a greater likelihood of unawareness, compared to younger PWE (Langston, 2015). Auras and automatisms are more infrequent and postictal confusion may be prolonged (Kellinghause, 2004). Additionally, the causes of epilepsy are different in the elderly compared with younger individuals (Brodie, 2005), and cognitive comorbidities and side effects of medication may camouflage the symptoms of seizures. The true prevalence of a missed diagnosis and misdiagnosis of epilepsy in older people remains uncertain (Brodie, 2005). Many older people live alone, which makes a witnessed event more unlikely. Cognitive impairment may limit important historical information and delay the diagnosis. Epilepsy should be suspected in an elderly person with loss or impairment of consciousness, episodic confusion, transient behavioral change, or episodic unresponsiveness (Ramsay, 2004). Frequent falls with amnesia without head trauma are also a red flag that seizures may be a possible explanation. When unexplained events begin to recur, heightened observation is necessary to define them.

Psychogenic Nonepileptic Attacks

A number of psychiatric syndromes may be mistaken for seizures including fear, anxiety/panic attacks, episodic rage, fugue states, hallucinations, and phobias (Biraben, 2001). However, the most common mimic and reason that most mistakes are made in the diagnosis of epilepsy is PNEA (Benbadis, 2009b; Chen, 2016; Leach, 2005; Reuber, 2003; Scheepers, 1998; Smith, 1999). PNEAs reflect a physical manifestation of psychological distress and may be categorized based on psychological illnesses (e.g., conversion disorder, somatization disorders). Many traps and pitfalls to the diagnosis exist, though minimum diagnostic criteria have been proposed (LaFrance, 2013a), and management recommendations have been made (LaFrance, 2013b). Heightened emotions can serve as a trigger for PNEAs, such as memories of physical, mental, or sexual abuse. The clinical features in Table 1.2 provide a framework to differentiate PNEAs from epileptic seizures.

The prevalence of PNEA is approximately 2–33/100,000 in the US population (Benbadis, 2009b), amounting to approximately 300,000–400,000 persons, which is similar to the US prevalence of demyelinating disease and trigeminal neuralgia. Approximately 5–20% of outpatients seen at comprehensive epilepsy centers are found to

Table 1.2 The clinical features separating psychogenic nonepileptic attacks from epilepsy

Clinical features	PNEA	Epileptic seizure
Age	15–35 years old	All ages (highest <1 year and >60 years)
Gender	Female	Equal number of males and females
Risk factors	Psychiatric diagnosis, chronic pain, sexual abuse, event in office	Febrile seizures, trauma, stroke, CNS infection, craniotomy
Onset of seizures	Gradual	Sudden
Clinical features	Variable; eyes closed	Stereotyped; eyes open
Psychiatric comorbidity	Yes	Often
Occurrence from sleep	Rare between 12 a.m. and 6 a.m. (except pseudo-sleep)	Yes
Duration	Typically prolonged (>2–3 minutes)	Typically 30 seconds to 2 minutes
Postictal state	Little or none	Yes
Injury	Infrequent and minor	Frequent (such as lateral tongue biting and burns)
Incontinence	Rarely	Yes
MRI	Normal	Normal or abnormal
EEG	Normal or nonspecific features	Abnormal epileptiform activity
Neurological examination	Often normal	Maybe abnormal
Suggestable	Often	No

have PNEAS (Chung, 2006), as are approximately one-third of patients referred for surgical treatment of drug-resistant seizures (Benbadis, 2009b; Scheepers, 1998). Co-morbid epilepsy is reported to coexist in approximately 10% of patients with PNEAs (range 1.8–60%) (Benbadis, 2001; Chen, 2016). More women than men are affected and the typical presentation occurs most commonly in the third decade. Most of them have rhythmic tremor (i.e., convulsive), though one-third of patients may present with a limp collapse, and overall up to one-third of patients may present with pseudostatus. Injury may occur though burns or serious injury is rare. Tongue biting may occur – in contrast to the lateral location in epilepsy, in PNEA tongue bites are usually minor and involve the anterior tongue and face (Figure 1.5). The average duration of recurrent PNEAs is from 1 to 7 years before a definitive diagnosis is obtained (Chen, 2016; LaFrance, 2014).

Pitfall

The belief that most patients with PNEA also have epilepsy.

Surrogate biomarkers have been sought to provide additional objective components for the diagnosis of PNEA. Prolactin levels have been used to distinguish seizures from NEE when measured 10–20 minutes after an event. Unfortunately, prolactin levels lack specificity and are neither helpful to differentiate seizures from syncope nor reliably elevated in status epilepticus, acute repetitive seizures, and neonatal seizures. Prolactin levels are also not helpful in identifying the presence of absence seizures, focal seizures without loss of awareness, extratemporal focal seizures, and GTCs in 20% of patients with

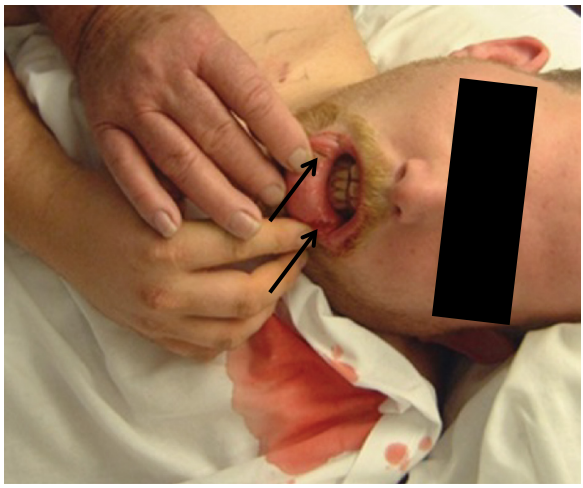

Figure 1.5 Anterior facial trauma incurred during PNEA. Note the furrows on the lower lip (arrows) that were created at the site of incisor contact from biting

GTCs (Chen, 2005). When they are used in the ancillary differential diagnosis of epilepsy, a greater than threefold rise is required (postprandial state and stress may increase the baseline level by up to twofold). Cortisol and creatine phosphokinase (CPK) may be also be elevated in a small number of patients with GTC seizures.

Historical Features

History is the starting point to suspect a diagnosis of PNEAs. The historical clues suggesting that an individual may be at higher risk are:

- History of abuse or traumatic life experiences
- History of medically unexplained symptoms
- Co-morbid psychiatric disorders
- Chronic pain
- Multiple allergies
- In children:
  - History of medically unexplained symptoms
  - History of psychopathology, including anxiety, depression, posttraumatic stress disorder, attention deficit hyperactivity disorder.
  - Family dysfunction and unrealistic parent expectations
  - Psychologically adverse events (e.g., bullying)
  - Undiagnosed learning difficulties
  - Social difficulties

Clinical Features of PNEAs

The semiology of PNEAs forms the cornerstone for suspecting the diagnosis. VEM, the gold-standard diagnostic test, will show characteristic features of a patient's habitual event with an absence of associated epileptiform abnormalities. Classifying PNEAs may

help increase our understanding of subgroups and treatment selection. In one study of 61 patients with 330 spells, PNEAs were identified as rhythmic tremor (46.7%), "auras" of subjective sensations (23.6%), unresponsive without motor manifestations (11.2%), complex combinations (10.0%), mixed types (5.2%), and violent movements (3.3%) (Seneviratne, 2010). The following semiology should suggest PNEAs in a patient that presents for evaluation of spells (Benbadis, 2009b; Biraben, 2001; Chung, 2006; Seneviratne, 2010):

- Eyes are closed
- Never occur from true sleep
- Non-physiological movements
  - Side-to-side shaking/out-of-phase asynchronous activity
  - Back arching
  - Intact awareness despite bilateral motor activity
  - Discontinuous movement ("on-off" or "start-go")
- Ictal weeping/stuttering
- Not stereotypical
- Long duration
- Non-physiological neurological examination

Observation of eye movements and the primary position is important during the event. A blank stare is typical of a focal seizure originating in the mesial temporal lobe; extratemporal lobe onset may manifest as lateral eye deviation; eyes rolling upward into the orbit are suggestive of syncope, while eye closure at the onset is highly suggestive of a PNEA (Elger, 2008). Eye closure during an event has demonstrated a high reliability during VEM, and was both sensitive (98.1%) and specific (96.2%) for patients (50/52) with PNEA and a positive predictive value of 0.987 in one study (Chung, 2006). In contrast, in patients with epilepsy (152/156), the eyes were open during seizures (sensitivity 96.2%, specificity 98.1%, positive predictive value 0.943). The conditions when PNEA should be suspected are listed as follows:

- No response to any AED
- High frequency of seizures (several daily)
- Seizure in the waiting room or doctor's office
- Attacks are reliably precipitated by emotional triggers
- Comorbid psychiatric diagnoses
- Semiology inconsistent with epilepsy
- Low level of concern ("la belle indifference"), over-dramatization, histrionic features
- No amnesia for the attacks
- Lack of serious injury from events

PNEAs are physical symptoms associated with somatoform disorders, factitious disorders, and malingering. Symptoms such as presence of burns during seizures, postictal disorientation, occurrence out of sleep, and significant injury or posterior lateral tongue biting are more specific for seizures in PWE (Figure 1.1). Somatoform disorders involve the unconscious production of physical symptoms due to psychological factors. The two most relevant somatoform disorders for patients with PNEAs are conversion disorder and somatization disorder. Factitious disorder and malingering imply that the patient is purposely deceiving the physician to obtain a secondary gain. In factitious disorder, the

Table 1.3 Clinical features that appear psychogenic though may be seen in patients with epilepsy

Clinical features	Frontal lobe seizures	PNEA
Age of onset	Less than 20 years old	More than 20 years old
Gender	Equal	Females
Etiology	Cortical dysplasia, trauma, mass lesion, unknown cause	Depression, anxiety, posttraumatic stress disorder
Triggers	Sleep	Stressful events
Psychiatric history	Frequent	Frequent
Semiology	Brief, stereotyped, turns prone	Eyes closed, witness intensifies event, non-stereotyped
Seizure duration	Seconds	Minutes
Postictal state	Negligible	Variable
MRI	May be abnormal	Typically normal
EEG	Often normal	Normal
Treatment	AEDs, neuromodulation, surgery	Cognitive behavioral therapy, antidepressant/anxiolytics

motivation is a pathologic need for the patient to occupy the sick role. In malingering, the secondary gain is one of the personal and tangible benefits (e.g., money, insurance reasons, legal benefit). Most patients have PNEAs due to conversion disorder with seizures. A *major pitfall* in delivering the diagnosis is to give the patient the impression that the doctor believes the patient is intentionally "faking" the event to get attention.

Bizarre Seizures

Some focal epileptic seizures appear bizarre and mimic NEEs. Occasionally epileptic seizures may appear so atypical to suggest the events are due to a psychiatric condition ("pseudoseizure") despite a true diagnosis of epilepsy ("pseudo-pseudoseizure"). A significant pitfall in the diagnosis of epilepsy is mistaking seizures for PNEAs (Kanner, 1990). The frontal lobe is the second most common site of focal seizure onset in adults, and the many mimics of frontal lobe seizures include sleep disorders, movement disorders, and psychiatric disorders (Ryvlin, 2006). Seizures of frontal lobe origin are typically brief and stereotyped with abrupt onset hypermotor movements, violent and bizarre automatisms, loud vocalizations, spitting, biting, kicking, pedaling, gesturing, screaming and cursing, which may suggest, incorrectly, PNEAs (Benbadis, 2009b; Devinsky, 1996; Kanner, 1990; Reuber, 2003). Seizures associated with the frontal lobe are stereotypic and sleep-activated, frequently clustering during the N3 stage of sleep (Table 1.3).

Frontal lobe onset seizures are more frequent in adolescents less than 20 years of age, but may occur at any age. Diagnostic testing with interictal scalp EEG and even ictal scalp EEG is usually normal. VEM is the best means to obtain the diagnosis of frontal lobe epilepsy or NEE when frontal interictal discharges (IEDs) or an ictal EEG or stereotyped semiology is unrevealing. Implanted electrodes may be necessary to record characteristic

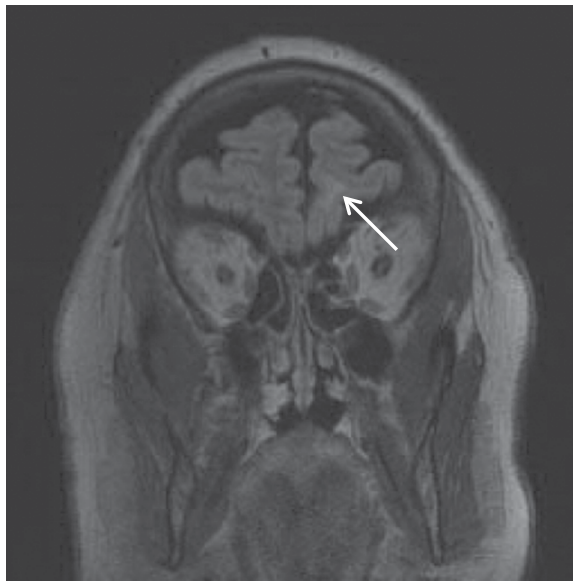

Figure 1.6 Left prefrontal encephalomalacia in a 22-year-old with posttraumatic frontal lobe epilepsy and recurrent bizarre focal seizures

EEG findings, especially if a patient is potentially a candidate for resective surgery. Brain MRI is helpful when a frontal lesion is identified (Figure 1.6) though it is normal in many patients.

EEG

The EEG can be helpful but can also serve as a pitfall in the misdiagnosis of patients with NEEs (Benbadis, 2003). The presence of IEDs on the EEG can support the clinical diagnosis of epilepsy, but an EEG cannot confirm a diagnosis of epilepsy unless an epileptic seizure is recorded during an event and is accompanied by appropriate EEG waveform morphologies. Mistakes made during interpretation of the EEG may lead to misdiagnosis that are easily perpetuated, complicate management, and adversely affect outcome (Benbadis, 2006, 2008; Pillai, 2006). Excessive reliance on the interictal EEG may occur at the expense of recognizing the clinical context for which it was performed. With an EEG, three possible scenarios arise:

- The EEG is normal
- The EEG is abnormal (whether epileptiform or not)
- A normal EEG is misinterpreted as abnormal (whether an epileptiform abnormality or not)

The EEG in most patients with NEEs is either normal or contains nonspecific abnormalities devoid of epileptiform features (Benbadis, 2006). The diagnostic yield of the first EEG in patients after the first unprovoked seizure (Chapter 4) demonstrates IEDs in only one-third of individuals. Additionally there are still about 10–20% of individuals with epilepsy who continue to have nonepileptiform EEGs despite repeat recordings (Gavvala, 2016; Pillai, 2006).

Pitfall

Failing to realize that a normal EEG does not exclude a clinical diagnosis of epilepsy nor does it support a diagnosis of NEE.

Activation is a standard technique used during EEG in patients suspected to have epilepsy to provoke indolent IEDs, a seizure (hyperventilation), or a photo-convulsive response (photic stimulation). Other activating procedures have also been used as an effective provocative technique by many to prove suggestibility in patients with NEE in support of a diagnosis of PNEA (Benbadis, 2004). Activation of a typical behavioral event, such as by placing a tuning fork on the sternum or alcohol pad on the forehead, with no associated ictal changes on EEG has a high degree of specificity for PNEA (Benbadis, 2009b). The ethics of using such provocative techniques have been questioned by some; however, activation has the advantage of augmenting VEM, with potential acceleration of the diagnosis and initiation of appropriate treatment (Benbadis, 2009b). Activation of a typical event with hyperventilation and photic stimulation had a sensitivity of 84% and near-perfect specificity in one study (Benbadis, 2000).

It is important to recognize that EEGs in some patients without epilepsy will demonstrate EDs, including those with the following:

- Congenital blindness
- Cerebral palsy
- Autistic spectrum disorder
- A sibling/family history with epilepsy
- Medications (e.g., lithium, baclofen, antipsychotics)

Because EEG abnormalities are reported to be more common in patients with PNEA than healthy controls (Benbadis, 2006), it is important to appreciate potential pitfalls with the use of EEG in the diagnosis of epilepsy and NEEs (Figure 1.7). Over-reading the EEG is an important contributor to the misdiagnosis of epilepsy (Benbadis, 2003; Tatum, 2013). Distinguishing variations of normal EEG patterns, benign variants that are non-pathologic, and artifacts from true IEDs can be challenging for the interpreter (Tatum, 2013). In addition, the temporal location of some benign variants (e.g., wicket spikes) enhances the potential for mistakes in interpretation due to the frequency of suspected temporal lobe epilepsy as a reason for ordering EEGs (Tatum, 2013; Krauss, 2005). Another pitfall in EEG reading is falsely associating phase reversals with an abnormality and not adhering to strict criteria to define an ED (Benbadis, 2009b; Tatum, 2013). Nonepileptic rhythmic movements can generate artifacts that mimic an electrographic seizure.

Differentiating epileptic seizures from NEEs is a learned skill reflecting training and experience (Ristic, 2015). This can be a hurdle for clinicians today who face ever-increasing time constraints and who may lack sufficient experience in many cases given the limited training during residency and the lack of relevant postgraduate continuing education required for a general neurologist.

Video-EEG Monitoring

VEM is the best available method for diagnosing and characterizing seizures and the gold standard for differentiating epileptic seizures from NEEs. The main reason for pursuing VEM is for diagnosis, but to be successful, the findings need to be interpreted in light of the clinical history so that the semiology of inpatient events can be compared to a

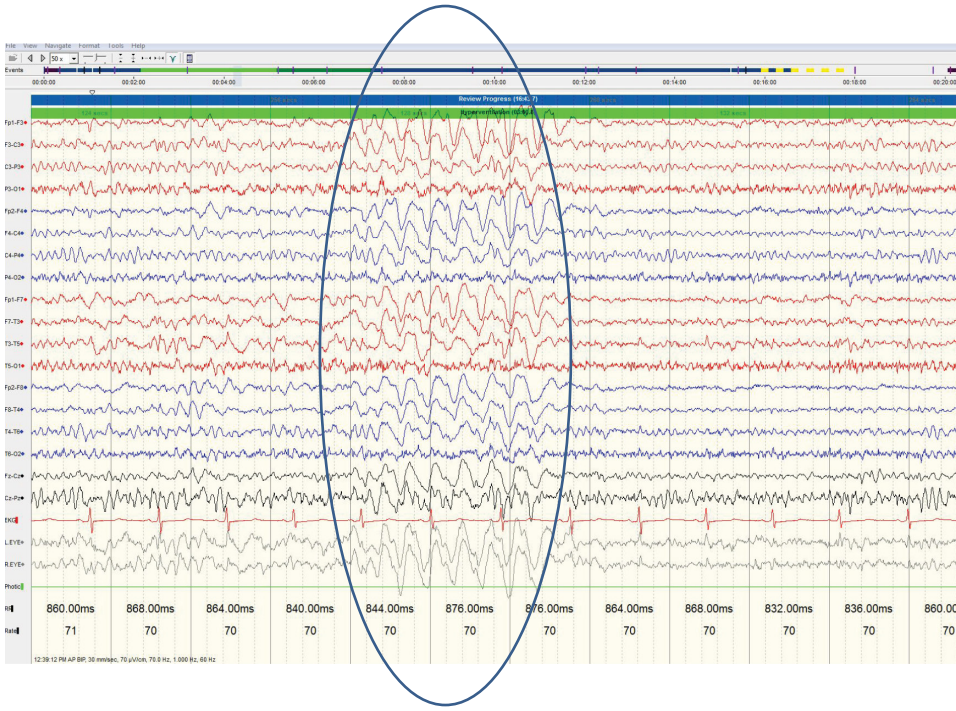

Figure 1.7 A 54-year old with a single seizure. Three Hertz spike-and-waves were misinterpreted on EEG leading to treatment with AEDs.

patient's typical events. Interictal EEG abnormalities alone cannot reliably differentiate between PWE and those with NEE (Friedman, 2009). Some clinical clues may predict a diagnosis of PNEA and prompt monitoring (Davis, 2004).

Rule of Two: 2 Normal EEGs + 2 Seizures/Week + 2 AED Failures = 85% Positive Predictive Value for PNEA

Outside of EMUs, the procedure involved in diagnosing seizures is challenging and the inter-rater reliability is only moderate for PNEA and poor for physiological NEE (Benbadis, 2009a). Inpatient VEM provides the opportunity for behavioral evaluation, ancillary testing, and safe drug withdrawal in an effort to capture a typical event (Sauro, 2014); hence, the yield for diagnosis of undefined events is high, such that in one study, 75% of admissions for spell classification at a tertiary epilepsy center were discharged from the hospital with a definitive diagnosis (Benbadis, 2009b). A habitual spell with prolonged loss of consciousness associated with an uneventful or normal EEG supports a nonepileptic etiology. Provoking a typical event using benign stimuli provides support for suggestibility (commonly psychologically mediated) and therefore PNEA. However, psychophysiological responses may occur (i.e., exaggerated reaction to a physiological event) and serve as a pitfall to diagnosis when symptoms are not carefully analyzed (Seneviratne, 2010). Referral patterns, patient preferences, availability, insurance issues, geographical location, waiting lists, and cost are some of the barriers to inpatient VEM that limit availability and access to a definitive diagnosis.

Home videos and hand-held video-camcorders in the evaluation of seizures are promising adjunctive techniques to history and examination (Chen, 2008). Ambulatory EEG has demonstrated usefulness in the ability to differentiate epilepsy from NEE approximating that of inpatient VEM (Seneviratne, 2013).

Treatment

Treatment of NEEs begins with obtaining the diagnosis and seeking further consultation or evaluation for a diagnosis-specific management plan (e.g., cardiology consultation, sleep evaluation, tilt-table test, treatment for movement disorder). For patients with PNEA, the initial step is to deliver the diagnosis to the patient, which may itself be effective as a treatment in 15% of individuals. Pithiatism (Greek roots meaning "curable by persuasion") involves the art of delivering psychological information to the patient. It is both crucial and an opportunity to effect remission or gain the patient's acceptance of the need for psychological therapy. Delivering information to the patient and families is an essential part of the diagnosis of PNEAs (Hall-Patch, 2010; LaFrance, 2013) in addition to tapering nonessential medication including AEDs, which may produce a negative effect (LaFrance, 2013). All patients with PNEAs should be evaluated by a mental health provider. In this population, cognitive behavioral therapy appears more effective than best medical care alone (LaFrance, 2013, 2014). The following approach has been useful when discussing PNEAs with patients (Hall-Patch, 2010):

- **Diagnosis:** Explain that the symptoms are genuine
  - The attacks are "real" and can be frightening or disabling
  - Give a name for the condition and the alternate names (it is not epilepsy)
  - Cite the common nature of PNEA, the common causes and maintenance factors
  - Identify the predisposing factors (sometimes difficult to find out the precise cause)
  - Identify the precipitating factors (can be related to stress or emotions)
  - Discuss the perpetuating factors (vicious cycle of worry–stress–attacks–worry and provide a model that the patient can understand (e.g., brain overload, computer crash)
- **Treatment:** underscore that the use of AEDs is not effective
  - Discuss the evidence that a psychological treatment is effective and discuss a referral
- **Prognosis:** provide the opportunity for remission and improvement.
  - Discuss restrictions for PNEA vs. epilepsy

Seizures can be associated with serious physical, psychological, and social consequences. So can the incorrect diagnosis of epilepsy. Diagnostic-related errors are frequent and may serve as an important cause of iatrogenic morbidity and mortality. Serious complications may ensue when inappropriate treatment with an AED is prescribed for what are actually recurrent NEEs. Some clinicians consider over-diagnosis to be a recalcitrant problem and no single approach will be able to address the issue (Elmore, 2016). The threat of medical malpractice litigation coupled with financial incentives of performing an EEG in a patient with "spells" (i.e., syncope) when it is not essential are factors that can increase the risk of misdiagnosis. Some other reasons (adapted from Elmore, 2016) contributing to an over-diagnosis are given as follows:

- Physician desire to "do everything" to obtain the best patient outcome
- Fear of missing the diagnosis of epilepsy
- Fear of malpractice litigation if epilepsy goes unrecognized
- Lack of feedback to corroborate the diagnosis
- Financial incentive
- Qualitative interpretation of symptoms
- Lack of continuing education and knowledge of epilepsy (and EEG)
- Low threshold for determination of an "abnormality" on EEG or MRI
- Falsely fearing the patient will die if no treatment is begun

Diagnosis-related harm to the patient may follow a diagnostic error when treatment is undertaken and medication is prescribed (Lazarou, 1998). Patients who are mistakenly diagnosed with epilepsy typically are treated with AEDs and are exposed to higher doses, sustain more adverse effects (even resulting in death), and tend to utilize health care services more often than patients with epilepsy (Reuber, 2004).

Pitfalls are not uncommon in the journey to arrive at a successful diagnosis of epilepsy. Diagnostic variability is found in epilepsy as well as other specialties where clinical judgment is required (Elmore, 1994). The diagnosis of epilepsy has a broad differential diagnosis and is dependent on history obtained from patients and witnesses of an observed event. Pitfalls are significant and occur when a history for epilepsy is in question, limited, vague, or unattainable. Traps for the clinician exist during clinical assessment and ancillary evaluations with neuroimaging and EEG that impede correct diagnoses for both physiological NEEs and PNEAs. PNEAs are the most common seizure mimic resulting in misdiagnosis and over-treatment; both can be reduced by VEM. Physiological NEEs are less frequent but critical to recognize since malignant etiologies may produce "seizure-like" NEEs. Following diagnosis, treatment involves tapering AEDs unless needed for mood stabilization and instituting disease-specific management for the true underlying condition (e.g., cognitive behavioral therapy, antiarrhythmic agents, antiplatelet agents, antimigraine drugs).

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Chapter 2

Mistaking EEG Changes for Epilepsy

William O. Tatum

Electroencephalography (EEG) has traditionally been the most relevant testing modality to identify, classify, quantify, characterize, and monitor seizures, with major implications for selection of treatment. The initial EEG recorded in patients with epilepsy is positive only in 29–55% of patients, though the yield increases to 80–90% with repeated recordings. When abnormal, interictal EEG helps classify whether seizures have a focal or generalized mechanism, again which has treatment implications. It also helps to define a specific epilepsy syndrome (e.g., juvenile myoclonic epilepsy, temporal lobe epilepsy, or Lennox–Gastaut syndrome). One major contributor to the misdiagnosis of epilepsy is the tendency for EEG readers to over-interpret a normal tracing as an abnormal one. When the result is incongruent with the clinical diagnosis, obtaining and reviewing the reportedly abnormal EEG is a form of quality management for patients with epilepsy.

Distinguishing between events attributable to epileptic seizures (ES) and those due to nonepileptic behavioral events can be very difficult (see Chapter 1). This requires a detailed history, thorough neurological evaluation, careful monitoring, and knowledgeable clinicians. Otherwise, errors in diagnosis may occur. The diagnosis may be missed, wrong, or delayed by subsequent definitive testing. These mistakes are particularly likely to occur in patients with psychogenic nonepileptic attacks (PNEAs) and physiological nonepileptic events (both are described in detail in Chapter 1) as well as bizarre epileptic nonconvulsive seizures (see Chapter 4).

The diagnosis of epilepsy is a clinical judgment often solely based on the history supplied by the patient or an observer; both may have difficulty in conveying the information needed by the clinician. In addition, no routine biomarker exists for the diagnosis of epilepsy. Interictal epileptiform discharges (EDs) on routine scalp EEG may support the diagnosis but even their presence is not definitive for a diagnosis. An incorrect diagnosis of epilepsy exposes the patient to a potentially harmful treatment as well as life-limiting psychosocial consequences. Diagnosis-related harm is preventable harm that results from a wrong treatment or delay/failure to treat. In addition, the true underlying diagnosis may go unrecognized and untreated with its own consequences, for example, in the case where a patient has a cardiac arrhythmia that is potentially fatal. Therefore, the consequences of a misdiagnosis are twofold: misdiagnosis and missed diagnosis.

Misdiagnosis can lead to mistreatment with antiepileptic drugs (AEDs) for presumed epilepsy and a missed treatment of the true underlying illness with potentially disastrous results. The misdiagnosis of epilepsy is common as detailed in Chapter 1. One common reason for diagnostic mistakes in epilepsy is that the diagnosis is based on a misinterpreted EEG. Adverse effects from unneeded AEDs may be encountered on an acute, chronic, or idiosyncratic basis and in some cases (e.g., Stevens–Johnson syndrome and

drug reaction with eosinophilia and systemic symptoms) may become life-threatening. Serious reactions to AEDs are infrequent and fortunately the incidence has remained stable for more than 30 years (Lazarou et al., 1998). However, the risk-benefit ratio of AEDs when used for the wrong medical indication is entirely unfavorable for the patient.

Misinterpreted Spells

Case 2.1 EEG Misdiagnosis

A 31-year-old female provides a history of fibromyalgia, low blood pressure, pelvic pain, posttraumatic stress disorder (PTSD), and irritable bowel syndrome. She is accompanied by her significant other who is the primary historian. The patient is being followed by a psychiatrist for PTSD stemming from an early childhood rape and being treated with citalopram and alprazolam for anxiety-depression. She is followed by a gynecologist and the gastrointestinal service who "couldn't find out what was wrong." Her daily episodes are described as gradual buildup of a headache that leads to generalized shaking, back arching, side-to-side head movement, eye fluttering, and unresponsiveness for 5–10 minutes. She is exhausted afterwards and complains of headache. Brain MRI and EEG (awake and asleep) were normal, however, during 24-hour ambulatory EEG monitoring the patient reports she was told that there were "spikes" that prompted treatment with AEDs.

Does She Have Epilepsy?

Discussion

As discussed in Chapter 1, many clues in this patient's history suggest the possibility of PNEAs:

- A history of abuse or traumatic event
- Events do not occur out of sleep
- No amnesia for the episodes
- Events not stereotypic
- A robust *Review of Systems*
- Eyes are closed during events
- Co-morbid psychiatric conditions or chronic pain

Seizures may be so terrifying to a witness that they are unable to provide details to the provider which are sufficient to arrive at a diagnosis. The following clinical signs may help support the diagnosis of PNEA with a reliable witness or video of the event:

- Eye closure
- Side-to-side head or body shaking
- Back arching
- Intact awareness with bilateral motor activity
  - Asynchronous
  - Out-of-phase activity
- Discontinuous movement (start–stop)
- Ictal weeping/stuttering
- Long duration

Case (cont'd)

She tells you that she is taking pregabalin 100 mg three times daily in addition to lamotrigine 200 mg twice daily as treatment for seizures. She had previously taken levetiracetam and carbamazepine after an EEG was interpreted as abnormal. She provides you with a stack of records about 3 inches thick, and in prior reports, you find that a brain MRI was normal the year before, and an ambulatory EEG was reported as abnormal due to "potentially epileptogenic discharges in the temporal region bilaterally with T3 and T4 phase reversals with clinical correlation advised."

Discussion (cont'd)

The clinical impact of EEG on the diagnosis of epilepsy is significant. However, it is easy for EEG interpreters to forget the broad differential diagnosis for patients with seizures and seizure-like episodes. Additionally, many providers falsely think of epilepsy as a singular disorder and, therefore, fail to understand the many epilepsy syndromes and corresponding EEG abnormalities that may sometimes occur. In addition, some clinicians may not have sufficient knowledge of epilepsy and epilepsy mimics. Seizure-like events are commonly encountered in a busy neurological practice, while family practitioners may only encounter several cases yearly, if at all. For those with less experience, there may be a false perception that not making a diagnosis of epilepsy always carries grave risks for injury and death. In fact, while it is important to make an accurate and timely diagnosis of epilepsy, missing the underlying cause of a seizure mimic, such as a cardiogenic source, may be even worse. Furthermore, some clinicians may not have easy access to all diagnostic methods of investigation including video-EEG monitoring (VEM) to arrive at a correct diagnosis.

While these reasons all represent potential traps and pitfalls in an epilepsy diagnosis, over-interpreted EEGs are perhaps one of the worst offenders. The EEG in this case was "abused." It was relied on to confirm a diagnosis of epilepsy rather than to provide support for a clinical diagnosis. Learning the common traps and pitfalls to misinterpretation of the EEG, such as benign variants and common artifacts, is essential to avoid improperly using the EEG in patient management.

Answer

No, this patient is unlikely to have epilepsy on clinical grounds. There are multiple concerns that exist to suggest she is manifesting PNEAs. These include the history of sexual abuse, the presence of chronic pain and fibromyalgia, and the atypical semiology (e.g., eye fluttering, back arching, non-physiological side-to-side head movement, prolonged duration, and absent postictal state).

Misinterpreted EEG

Case 2.2 Clinical-EEG Disconnect

A 17-year-old female had "passing out spells." She was seen by a cardiologist and had a 12-lead ECG, echocardiogram, and event monitor that were normal. Spells increased in frequency and she was forced to home school. She was fine with home schooling because there was a bully at school who always picked on her because she was overweight. The episodes continued and on one occasion she fell to the floor in front of her mother.

She was again seen by cardiology and a tilt table test was "inconclusive." She had some symptoms of light-headedness but did not lose consciousness during head-up tilt. Her episodes always began the same way – she would suddenly develop light-headedness, nausea, and pallor, have a "far away" look, and then collapse with a quick recovery. The episodes occurred on a weekly basis. Her primary care physician diagnosed her with syncope. The cardiologist "found no cardiac disease." She was referred to neurology for the possibility of seizures after she had an episode that resulted in a closed head injury with laceration. Her neurological examination was normal. A brain MRI was normal. Her EEG was interpreted as abnormal due to "potentially epileptogenic sharply contoured bilateral temporal waves."

Does She Have Epilepsy?

Discussion

No, she does not have epilepsy based on her history of the events which are more consistent with syncope (see Chapter 1). The difference between seizures and syncope is summarized and compared in the table below:

Clinical features	Syncope	Seizure
Triggers	Yes	Yes/reflex epilepsy
Onset	Nausea/sweating	Deja vu/ictal fear
Episode	Tonic/clonic	Tonic–clonic
Duration	15 seconds	Minutes
Postictal	No	Yes
Nocturnal	No	Yes
Coloration	Pallor	Cyanosis
Tongue biting	Tip of tongue	Posterior tongue/cheek
Myalgias	No	Yes
Incontinence	Yes/sometimes	Yes/sometimes
EEG (interictal)	Normal	Normal/abnormal
EEG (ictal)	Abnormal/nonepileptiform	Abnormal/ictal rhythm

What about Her Abnormal EEG?

Case (cont'd)

The EEG may be abnormal but based on her symptoms you would not expect it to correlate with her clinical presentation. You try to recover the abnormal EEG realizing that regardless of the number of EEGs that you might perform that are normal, they do not negate the effect from a single abnormal EEG reported by the patient. Two weeks later the disc with the outside EEG arrives. You identify the waveforms in question and they appear to represent a normal feature that is a benign variant (wicket waves). You inform the patient that her EEG was overinterpreted and the result is normal.

Discussion (cont'd)

Some EEGs are challenging to interpret. Still, over-interpretation of normal variations and benign variants, and in addition, failing to recognize artifacts are common reasons leading to misinterpretation of an EEG recording (Box 2.1).

Box 2.1 Common reasons why the EEG is mistaken and falsely leads to the diagnosis of epilepsy

- Normal variants
  - Wicket spikes
  - Benign epileptiform transients of sleep (a.k.a. small sharp spikes)
  - 6-Hz spike-and-waves
  - Rhythmic mid-temporal theta discharges of drowsiness
  - 14- and 6-Hz positive bursts
  - Subclinical rhythmical EEG discharges of adults
- Normal
  - Awake: alpha, mu, beta, lambda, "spike-driving" to photic flash
  - Sleep: vertex-waves, K-complexes, positive occipital sharp transients of sleep (POSTS)
- Artifacts
  - Physiological: Eye movements/flutter, EMG, EKG, pulse
  - Non-physiological: Equipment (electrode, jackbox, wires, etc.)

Neurologists typically read EEGs. Training programs in neurology require 3 years of postgraduate education during residency training after 1 year of Internal Medicine. Yet most training programs offer less than 3 months of clinical neurophysiology. This emphasizes the disparity in education between the experience of a neurologist and the education received to interpret EEG. One trap encountered with EEG is when clinicians base their diagnosis on the EEG rather than using it as a supportive test for their clinical diagnosis. As a general rule, concluding that an EEG is normal when it is actually abnormal will likely not lead to inappropriate treatment or result in a significant delay in essential clinical care. However, an incorrect diagnosis made based on the errant interpretation of an EEG may well lead to mistreatment with AEDs and a lack of treatment for the true underlying etiology.

Diagnosis: Neurocardiogenic Syncope

Specific EEG Changes Mistaken for Epilepsy

The EEG is usually the central component of the diagnostic workup for epilepsy beyond the clinical history and neuroimaging. It allows detection of abnormal cortical excitability that underlies seizures associated with epilepsy. However, discrete boundaries for normal and abnormal are elusive. Criteria for IEDs on the EEG are listed in Box 2.2.

Box 2.2 Criteria for defining epileptiform discharge in EEG

- Every spike is artifact unless 1 or more reasons are present
- Occupy a definable field
- Almost always surface negative in polarity
- Most followed by a slow wave
- Ignore events of simple voltage alteration or superimposition of several components
- Acknowledge physiological spikes and sharp waves

The lack of specificity for nonepileptiform abnormalities is apparent to most EEG interpreters. On the other hand, in contrast to low to moderate sensitivity of an initial EEG, the specificity of EDs is highly associated to people with epilepsy. EDs rarely occur as a false positive in people without epilepsy. These asymptomatic EDs in the interictal EEG are more common in children (1.9–3.5%) than adults (0.2–0.5%). Infrequently, EDs are present in patients without epilepsy (Box 2.3).

Box 2.3 Nonepileptic events that may be associated with epileptiform discharges in the EEG

- Autism, attention deficit disorder, cerebral palsy, neurobehavioral disorders, blindness
- Pre-school/employment screen
- PNEA, syncope, sleep evaluations
- Associated with ECT
- Following head trauma
- Acute encephalopathy/dementia/psychiatric presentations
- Drugs

The estimated prevalence of EDs in the general population is approximately 1–3%. However, some populations have neuropsychological conditions with a higher reported incidence of epileptiform abnormities on EEG. Location may be related to the likelihood of epileptogenicity. When IEDs are encountered, centrotemporal spikes and generalized spike-and-waves are most commonly seen. These criteria include definitions of a spike lasting 20–70 milliseconds and sharp waves as those with durations of 70–200 milliseconds. These definitions of spikes and sharp waves originally developed by the International Federation are "fairly precise but not very helpful" (Maulsby, 1971). The definition of a spike and a sharp wave has existed for more than 50 years, yet our ability to critically differentiate normal and pathological waveforms continues to remain a challenge with the gold standard based on the visual identification by EEG readers. In addition, interpreters are not standardized. Furthermore, some spikes and sharps are normal. Waveforms such as "spiky" vertex in children, vertex "sharp" transients, and "spike-driving" (Figure 2.1) during intermittent photic stimulation are common examples of physiological EDs. Variations in vigilance increase the complexity of EEG interpretation that may lead to mistaking waveforms as abnormal. Sharp transients during light sleep are common yet nonspecific. In overnight recordings, suspicious paroxysmal transients may be identified. Most occur in the temporal or frontal locations.

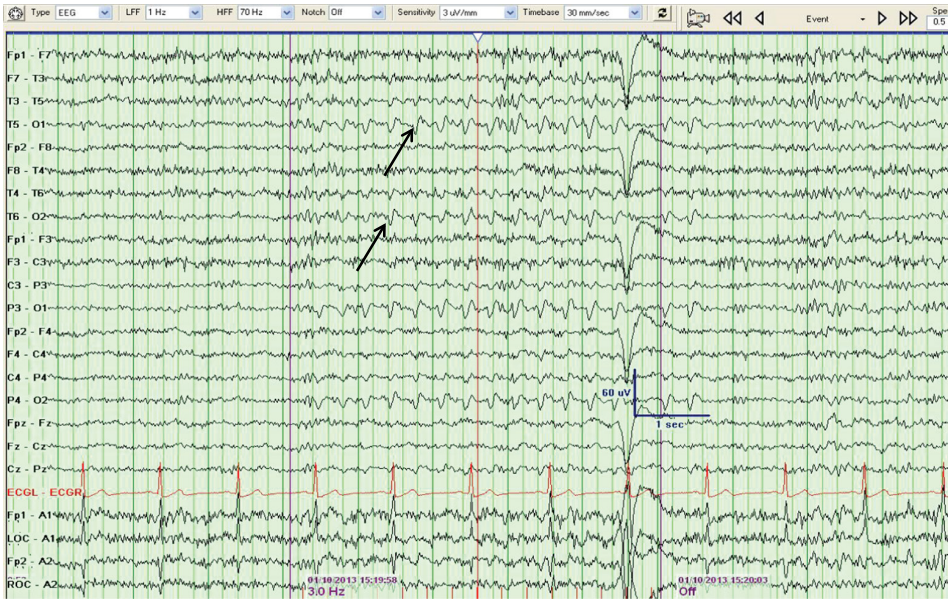

Figure 2.1 Intermittent photic stimulation during EEG resulting in "spike-driving" at low frequencies

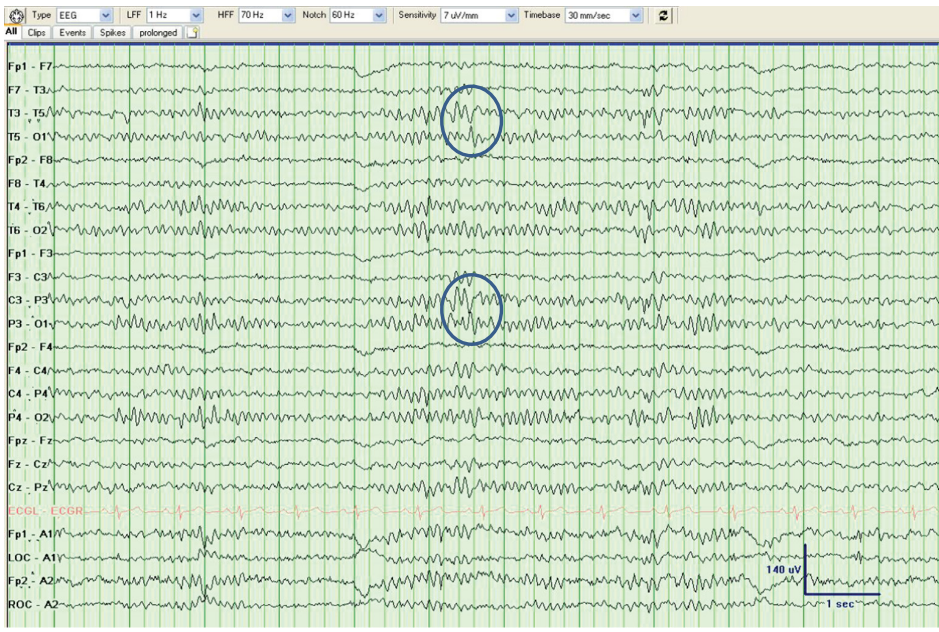

Figure 2.2 Normal sharply contoured alpha mistaken for an epileptiform discharge

Variations of Normal Waveforms

Normal background rhythms and sharply contoured normal waveforms that are variations of normal features in the EEG may together combine to form an apiculate morphology leading to misinterpretation of the EEG. In one series of patients with video-EEG-documented, newly diagnosed PNEAs, 32% had epileptiform abnormalities identified on a previous EEG report, yet upon review by a board-certified electroencephalographer they were found to reflect normal fluctuation of the background in 12/15 EEGs that were available (Benbadis and Tatum, 2003). Even the alpha rhythm may appear sharply contoured or spike-like, leading to misinterpretation of normal waveforms (Figure 2.2).

Case Report

A 36-year-old woman with drug-resistant temporal lobe epilepsy was referred for a presurgical evaluation. Her 3-Tesla, high-resolution brain MRI with an epilepsy protocol demonstrated left mesial temporal sclerosis. VEM demonstrated frequent left anterior temporal IEDs and three focal seizures were captured on EEG demonstrating left regional temporal rhythmic ictal theta onset. She underwent successful left amygdalohippocampectomy and was followed up by her primary neurologist. She was seizure-free for 2 years while on carbamazepine monotherapy, could drive, and was employed. Upon re-referral for complaints of moderate adverse effects from her AED and interest to discontinue AEDs for pregnancy planning, an EEG was performed. The EEG was interpreted as "abnormal due to left temporal sharp waves" (Figure 2.3).

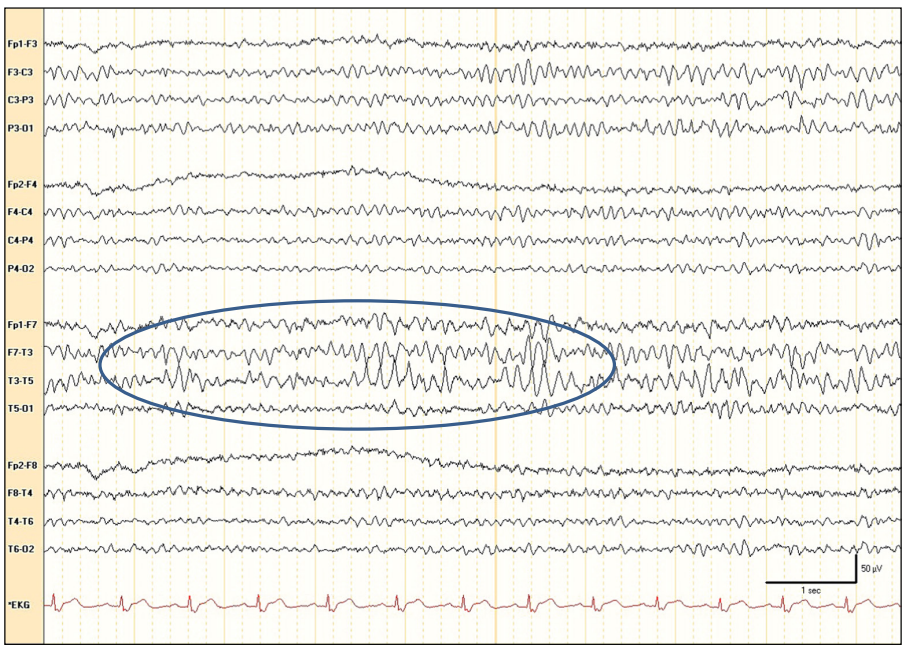

Figure 2.3 Breach rhythm underlying a craniotomy defect (oval). Note the high amplitude sharply contoured background easily mistaken for abnormality

Discussion

Some waveforms are known to have spiky variations that have no pathological significance (e.g., spiky vertex waves). A breach rhythm due to the presence of a skull defect may attain amplitudes that make normal waveforms appear sharp and stand out from the background, thus resulting in interpretation errors. At the site of the breach waveforms in the EEG, higher amplitudes and superimposition of faster frequencies can make the rhythms appear suspiciously epileptiform. With visual analysis, these may be misinterpreted as abnormal IEDs on EEG.

Case (cont'd)

Her AED was continued and a referral was made for a second opinion of continuing medication. Her brain MRI was reviewed, and a 24-hour computer-assisted ambulatory EEG was without IEDs. Eventually, the prior "abnormal" EEG was recovered for review. The EEG was found to have a breach rhythm that was misinterpreted as repetitive sharp waves. Because the EEG was without EDs on reanalysis, she was successfully tapered off AEDs, has remained seizure-free, and had an uneventful pregnancy.

Discussion (cont'd)

The problem with an EEG misinterpreted as demonstrating EDs is that it cannot be circumvented by any number of subsequently normal EEGs. Obtaining the actual tracing that was interpreted as abnormal provides the greatest opportunity to readdress the result as containing epileptiform or benign features including a breach rhythm. Other normal features of the EEG include normal physiological waveforms such as vertex waves, which may impart a spiky appearance to mimic EDs in asymptomatic subjects. In addition, normal physiological waveforms include spiky mu rhythms that may appear epileptiform, especially when they appear in short bursts of central, arciform, 8–10-Hz frequencies. However, these bursts are reactive and may be attenuated by contralateral extremity movement or the thought of movement and can be demonstrated in the EEG laboratory. Lambda waves are sharp waves by definition. However, like posterior occipital sharp transients of sleep, they are located in the occipital head region and are evoked bilaterally when visual scanning takes place. The distinguishing characteristic that separates lambda waves from EDs is polarity. Lambda waves are electropositive as opposed to electronegative with EDs. However, when a series of monomorphic waveforms occurs with a physiological field, such as an apparent evolution of waveforms during arousal, this may mimic ES and subsequently lead to mistakes in EEG interpretation and result in misdirected treatment.

Benign Variants of Uncertain Significance

Some patterns considered to be benign variants of uncertain clinical significance may be epileptiform-appearing discharges that appear as sharp waveforms and even as spikes, though they bear no relationship to epilepsy. The potential pitfall of benign variants of uncertain significance arises because many of these normal waveforms may be mistaken for abnormal EDs. These so-called normal variants become clinically significant when they are overinterpreted and therefore are not benign for patient care if they are identified

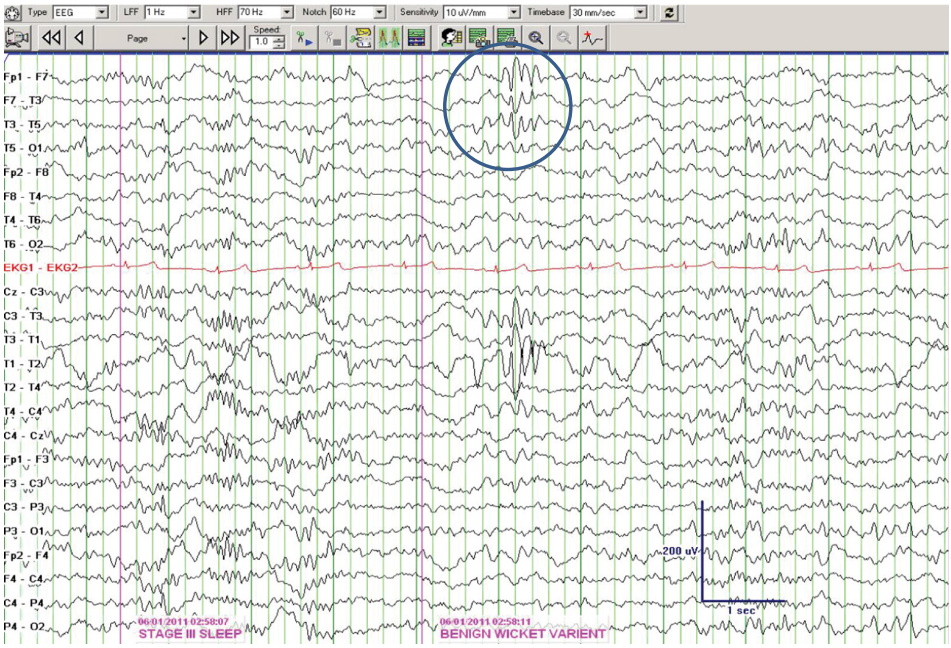

Figure 2.4 Normal variant (wicket waves) in sleep mimics abnormal polysharp-wave discharges

as abnormal. The high prevalence of temporal lobe epilepsy coupled with the predisposition for benign variants to appear in the temporal regions may result in misidentifying benign variants (Box 2.1). Both focal and generalized benign variants exist. Focal patterns are probably more likely to be mistaken than are generalized ones. The most common scenario is temporal transients that are mistaken for IEDs.

Wicket waves (Figure 2.4) are probably the most common benign pattern that are misinterpreted as abnormal. They are bursts or trains of spiky or sharply contoured monophasic arciform waveforms arising from the temporal regions during drowsiness. They appear in the midtemporal derivations on the EEG and are readily identifiable by the presence of a phase reversal in a bipolar montage. However, they are not associated with an after-going slow wave and do not disrupt the background activity. They may fragment from longer discharges. When isolated wicket spikes appear, they represent a particular challenge to separate from an abnormality in the temporal region and may lead to mistakes in interpretation. They are particularly troublesome as a benign variant due to their close similarity to high-amplitude temporal EDs when they are isolated. One study of individuals without epilepsy at an epilepsy center demonstrated wicket waves that were interpreted as abnormal EDs in the EEGs of 25/46 (54%) patients (Krauss et al., 2005). When EEGs were over-interpreted as showing EDs, wicket spikes commonly appeared as a single fragmented discharge as opposed to the normally appearing bursts (Figure 2.4), which are more obvious and less likely to result in misinterpretation.

Normal variants with a generalized pattern may also be mistaken for an abnormality. However, overlap between the morphology of benign variants with abnormal features can occur in some individuals. One example of an EEG with overlap occurs in patients with 6-Hz generalized spike-and-waves (Figure 2.5). In some patients, 5–6-Hz generalized

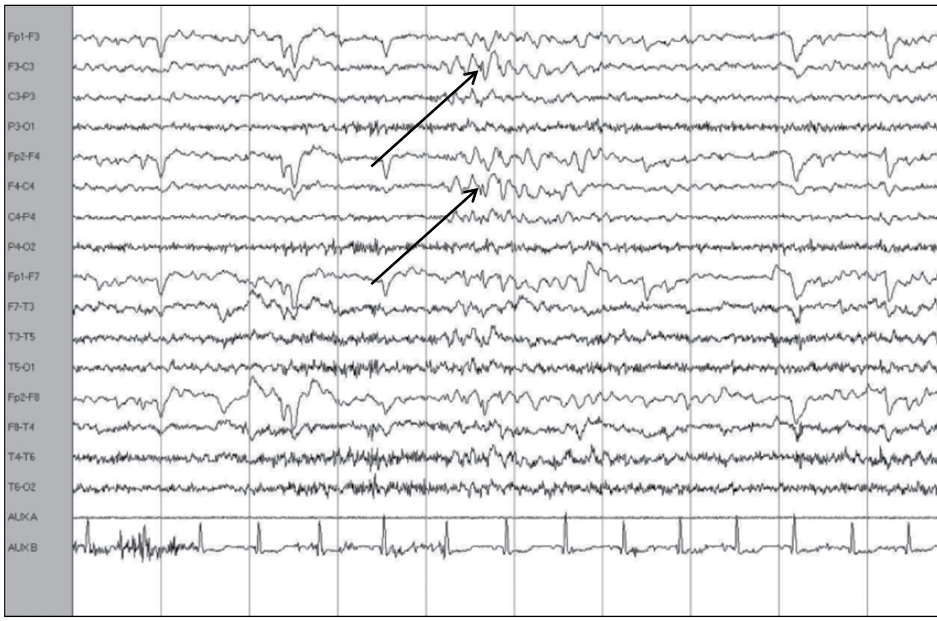

Figure 2.5 EEG during wakefulness with frontally dominant 6-Hz "phantom" spike-and-waves. The arrows denote the low amplitude spike component

spike-and-waves are associated with genetic generalized epilepsy (GGE) such as juvenile myoclonic epilepsy.

Finally, subclinical rhythmic electrographic discharge of adults (SREDA) is one of the rarest benign variants. It is an established finding in EEG interpretation that is unrelated to epilepsy and when present may be mistaken as an ictal rhythm associated with an epileptic seizure.

Artifact

EEG is subject to artifact in virtually every recording. Potentials that do not occupy a physiological field of distribution generated by the brain represent an extracerebral signal otherwise known as *artifact*. While artifact is an essential part of recording EEG to identify levels of arousal, artifact may produce interference and noise to obscure the background activity or mimic a variety of abnormalities derived from both physiological and non-physiological sources. Non-physiological sources of artifact commonly include signals generated by the components of the recording instrument. These include artifact generated by the electrodes, the wires, jackbox, and the machine itself. Electrodes are usually the primary source of artifact in EEG. Most biological tissues possess inherent electrophysiological dipoles that produce electrical fields. Eye movements, muscular contraction, oral and lingual motion, cardiac signals, and patient movement are the most common physiological sources of artifact in the EEG that may lead to misinterpretation. Similar to eye movements, myogenic artifact may be intermittent and result in "spikes" that may mimic abnormal EDs in the EEG and lead to a misdiagnosis of epilepsy. Some basic concepts will help the reader identify artifact (see Box 2.4).

Box 2.4 Concepts to remember during EEG interpretation that suggest the presence of artifact

- Activity present only in a single channel
- Activity appearing at the end of a chain in the montage or in >1 non-contiguous region
- Atypical generalized potentials
- Very slow or fast frequency (<1 Hz or >70 Hz)
- Periodic patterns without variation
- Adjoining double and triple phase reversals

VEM to characterize the electroclinical spectrum of epilepsy during a presurgical evaluation may be limited when artifact obscures the ictal EEG and prevents localization of seizure onset. Additionally, repetitive movements such as tremor inside or outside the EMU may produce artifact that can simulate an electrographic seizure (Figure 2.6). When artifact is episodic, it may be difficult to identify the source and therefore the artifact may be mistaken for an electrographic seizure, especially without simultaneous video recording. For example, tremulousness composed of intermittent rhythmic repetitive movement may be reflected in the EEG as an apparent abnormality with a variable field that suggests propagation and which appears as a pseudo-ictal pattern to challenge the interpreter to differentiate artifact from a seizure. Similarly, despite the use of intracranial electrodes to record EEG during a presurgical evaluation, repetitive motion generating artifact could be misinterpreted and lead to potentially disastrous results if non-physiological waveforms are taken as ictal patterns and result in unnecessary epilepsy surgery.

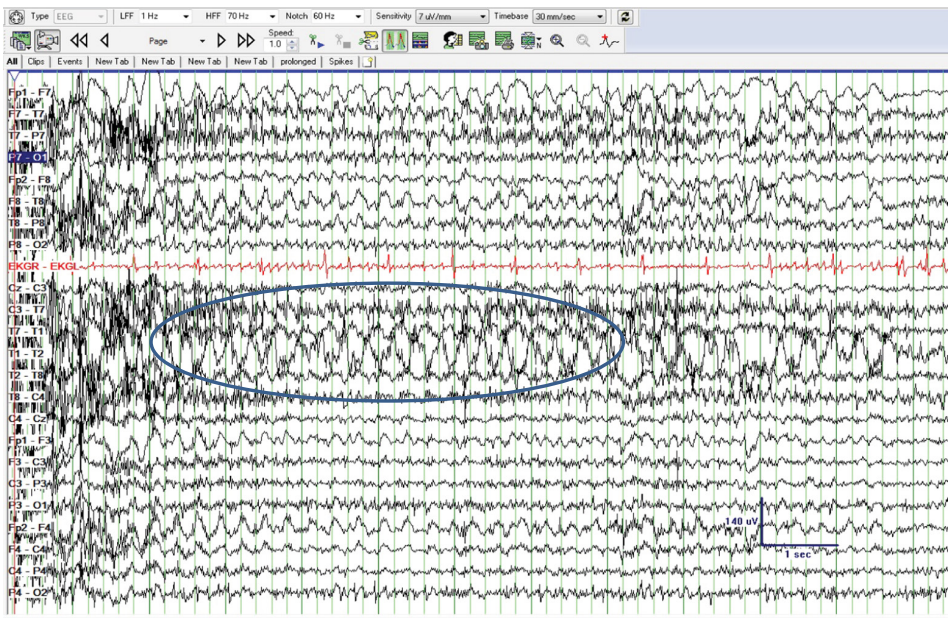

Figure 2.6 Rhythmical artifact (oval) simulating the rhythmicity of a focal seizure

An experienced technologist is crucial to prevent a recording contaminated by artifact. During the EEG, a skilled technologist should be able to prove whether a waveform is artifact or not and identify or eliminate it from the recording. The optimal EEG is represented by cerebral activity alone without significant artifact, thereby reducing the chances for mistakes in interpretation. This is facilitated by a quiet, controlled environment and a qualified EEG technologist.

Traps and Pitfalls in Epilepsy

Case 2.3

MB is a 36-year-old right-handed Caucasian woman with anxiety-depression, chronic daily headaches, sleep disorder, and epilepsy referred for evaluation of uncontrolled seizures. She developed seizures at age 4 and reports an abnormal EEG in the past. She was involved with sexual abuse of a minor and experienced multiple failed relationships. She was taking carbamazepine XR 400 mg twice daily and clonazepam 2 mg three times daily. Her neurological examination was normal. A high-resolution brain MRI was normal. EEG demonstrated frequent left temporal EDs maximal in the mid-temporal derivation with a regional temporal field (Figure 2.7). This pattern was consistent and clearly epileptiform and pathological. However, repeated hospital admissions for VEM resulted in the diagnosis of PNEA each time she was evaluated. Ongoing seizures were all "grand mal," occurring every 1–2 weeks despite multiple AED trials.

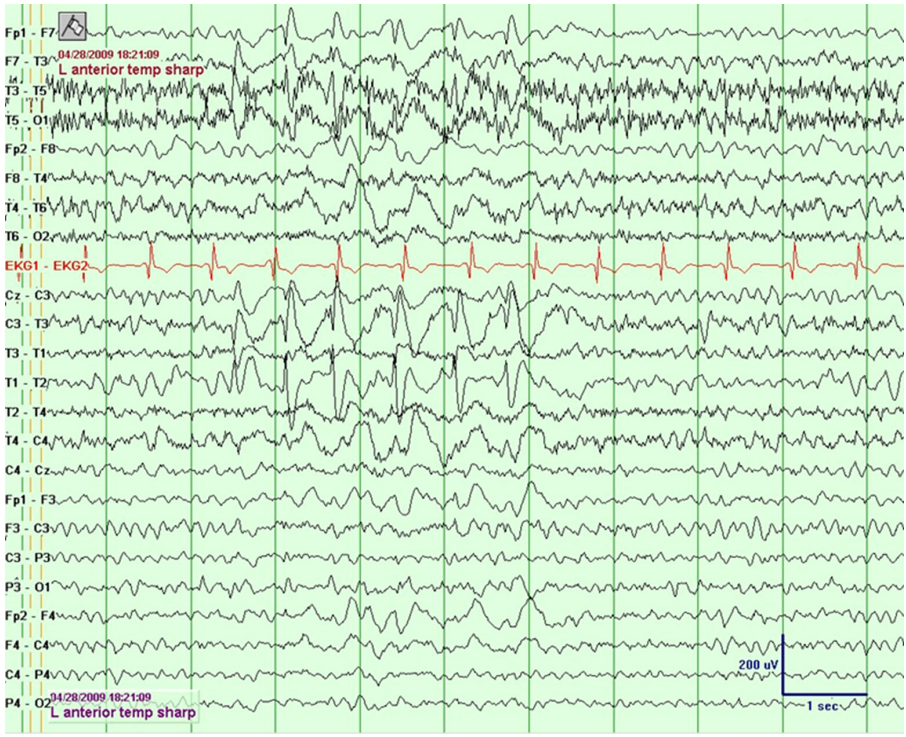

Figure 2.7 Burst of abnormal left mid-temporal spike-and-slow waves with a regional temporal field in drowsiness

Why the Clinical-EEG Disconnect?

Discussion

ES are divided into *focal* and *generalized* seizures and may be classified based on the EEG. However, this patient clinically presented with recurrent PNEAs. Nevertheless, focal epilepsy is suggested by the EEG. Focal epilepsy is characterized by recurrent seizures that arise from networks confined to a single cerebral hemisphere as opposed to generalized epilepsy that originates and rapidly engages a bilaterally distributed cortical and subcortical network. Another trap is identifying fragmented generalized spike-and-wave discharges during light sleep in patients with GGE as focal IEDs. This is not uncommon, and with long-term recordings, fragmented EDs may shift from one hemisphere to the other intermittently. Therefore, the EEG may serve as a pitfall to proper treatment when it is misclassified based on the presence of lateralized EDs in patients with GGE. Occasionally, mixed focal and generalized features may lead to confusion and subsequent mistakes in AED selection (Figure 2.8). In a large cohort of patients with GGE evaluated over 20 years, focal EEG abnormalities were identified in one-third to over half of patients, with most of them localized to the temporal region. This is not the case in this patient – her EEG demonstrated clear focal discharges. What is unclear is whether electroclinical manifestations are controlled and for how long. Abnormal temporal spikes have a high association with clinical seizures and though ES in this patient have not been confirmed, the IEDs raise the suspicion of an active epilepsy.

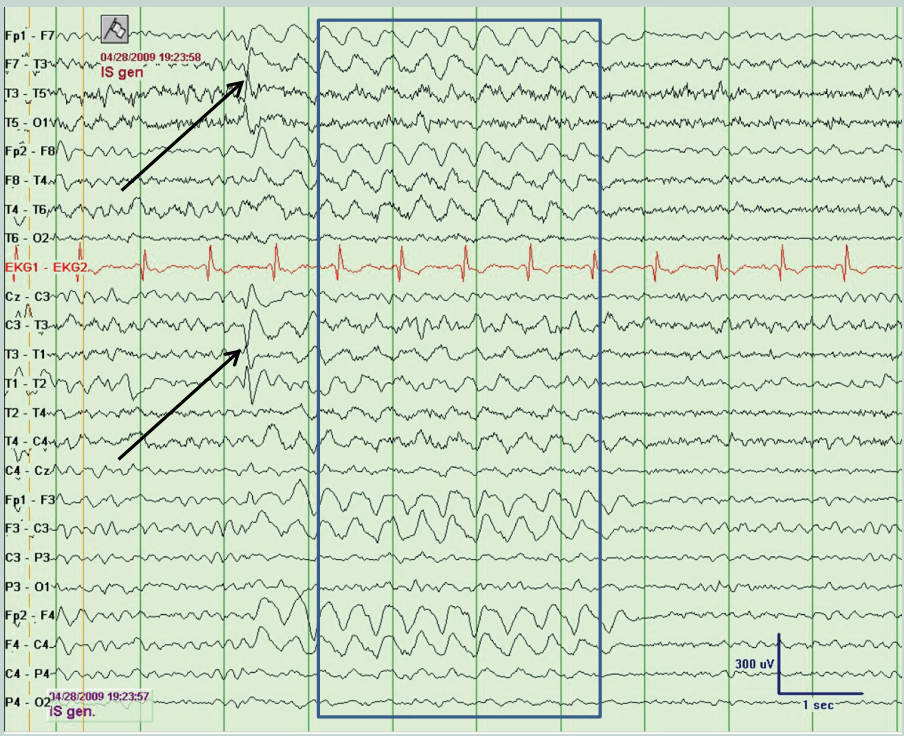

Figure 2.8 Combination of a focal spike (arrow) and intermittent rhythmic delta slowing (rectangle) in the EEG during drowsiness

Case (cont'd)

The patient is admitted once again for VEM, but this time carbamazepine is tapered. Several PNEAs are observed. However, following her last admission, a focal seizure with impaired consciousness occurred that was without self-awareness. Even though the seizure occurred in their presence, it was unrecognized by the family as a seizure and instead mistaken for a nonepileptic behavior. In addition, the patient herself, despite experiencing a focal seizure, had no self-awareness that it had occurred!

Discussion (cont'd)

Seizures without awareness are common with most patients with epilepsy experiencing at least some seizures for which they are unaware. In addition, some seizures are very subtle and validated only by identifying an ictal rhythm during VEM. In this case, both were operational in the same patient but camouflaged by recurrent PNEAs that served as the primary disability.

Pitfall

Assuming there can be only one mechanism for a patient to have recurrent paroxysmal behavioral events.

Diagnosis

1. Focal epilepsy manifested as recurrent focal seizures without awareness
2. Recurrent psychogenic nonepileptic attacks (primary diagnosis)

Gaps in Reporting and Recommendations for Improvement

Any EEG report may be subject to error including routine scalp EEG, ambulatory EEG, or continuous EEG monitoring. A survey was conducted of 47 clinical neurophysiologists during an annual meeting of the American Clinical Neurophysiology Society, of which 60% were board-certified (79% completing more than 1 year of training), with the majority interpreting EEGs on a daily basis. The survey found that 92% of expert readers encountered misread EEGs, and 38% encountered them frequently (Tatum, 2013). Artifact was the most commonly misinterpreted pattern, while over-interpretation of phase-reversals occurred in 90% or more of cases. More worrisome was that 75% of clinical neurophysiologists had encountered encephalopathic features on the EEG interpreted as nonconvulsive status epilepticus. In this cohort, 94% felt that neurology residency training should require formal training in EEG interpretation.

Continuous EEG interpretation has become more prevalent in the ICU. Recognizing non-physiological waveforms is critical to ensure proper treatment of encephalopathic patients because the EEG is the sole means to definitively diagnose nonconvulsive status epilepticus. The addition of video to EEG monitoring may clarify the EEG diagnosis and distinguish artifacts from seizures. Movement of the head, body, and limbs may produce potentials that can be confused with seizures. Synchronized video recording has the advantage of validating the non-physiological origin of a source, eliminating potential errors that could lead to misdiagnosis. Video will often demonstrate simultaneous movement with the identical frequency as noted in the EEG, with the movement appearing ipsilateral to the side of EEG involvement.

The level of education of the EEG reader will always be an error-limiting factor. In a prospective cohort study at a university hospital, a slide presentation assessed pre- and post-test responses to interpreting continuous EEG (Leira et al., 2004). The study was structured by level of education and included 125 neurology and neurosurgery residents, intensive care unit fellows, cardiac care unit/neurology floor nurses, and EEG technologists. Accuracy for identifying EDs initially was 61% compared with a post-test result of 67% ($P = 0.002$). Identification by untrained personnel was unreliable and recommended to be avoided.

Technological standards for performing EEG exist through the American Society of Electroneurodiagnostic Technologists, Inc., and competency is addressed by the American Board of Registration of EEG and Evoked Potential Technologists, Inc. standards for performing EEG. The American Clinical Neurophysiology Society (ACNS) has established guidelines for physicians performing, recording, and reporting EEG in adults and children. The American Board of Clinical Neurophysiology and American Board of Psychiatry and Neurology have set minimal competency examinations for physicians interpreting EEG. Nevertheless, specific classification criteria and guidelines for interpreting EEG have as yet not been established for interpreting EEG (Box 2.5).

Pitfall

Some reports may contain wording that is suspicious for misinterpretation.

Box 2.5 EEG reporting verbiage that is suspicious for a mistaken interpretation

- The report does not fit the clinical diagnosis
- Focus on "phase reversals" to imply abnormality
- Unusual locations for abnormality (e.g., parietal)
- Usual location of an "abnormality" for a normal variant (e.g., temporal lobe)
- Ill-defined waveforms described as "suspicious"
- Vague summary including "borderline" or "equivocal" conclusions
- Clinical correlations in a report with suggestion for clinical correlation

Standardized terminology and an orderly approach to EEG and EEG reporting may limit mistakes and improve communication in clinical care and for research (Hirsch et al., 2013). Additionally, a consistently higher inter-observer agreement occurs if there is a forced choice paradigm that uses a limited set of EEG terms (Beniczky et al., 2013). A consistent reporting system for describing complex waveforms with words will never be perfect. Nevertheless, structured formats are available nationally and internationally. Established guidelines for reporting exist not only to convey clinically relevant information but also to improve interrater reliability that is applicable for clinical and research use (Tatum et al., 2016). With the advent of digital EEG recordings, it is now possible to include samples of abnormal waveforms in final reports. This may be beneficial in clarifying reports to other parties involved in patient care to further improve interpreter reliability when controversial waveforms arise. Other means of improving interpretation include initial blinded review with subsequent re-review maintaining a conservative approach to interpretation. Other low-technology techniques such as independent or second interpretations or over-interpretation by a clinical neurophysiologist specializing

in EEG (similar to cardiologists over-interpreting EKGs) may be more practical than high-technology computer-assisted feature matching at this time. In the future, requiring training programs to provide mandatory EEG education during neurology residency and establishing a core competency level for EEG interpretation will improve the neurologist's skill to prevent mistakes in the use of EEG in the diagnosis of epilepsy.

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Chapter 3

Radiographic Errors in Epilepsy

Dieter Schmidt

Radiographic errors in the evaluation of a patient with epilepsy may have serious consequences. Overlooking a brain lesion that is amenable to epilepsy surgery may deny the patient adequate surgical treatment. This is clinically important because surgery may result in seizure-freedom in the majority of well-selected cases. Seizure-freedom with continued antiepileptic drug (AED) treatment has been reported in 60–80% of patients with unilateral mesial temporal lobe epilepsy or tumors. Among patients with malformations of cortical development or dual pathology, 40–70% become seizure-free. A successful postoperative outcome is less likely in imaging-negative patients with temporal or frontal lobe epilepsy. On the other hand, a false positive magnetic resonance imaging (MRI) finding can expose patients to unnecessary pre-surgical examinations which, albeit rarely, may cause permanent neurological problems, and, possibly, lead to unsuitable surgical interventions.

Another, less common source of radiological errors is the inappropriate use of computer-assisted tomography (CAT) and conventional x-ray in patients with epilepsy. CAT is nowadays obsolete in the evaluation of a patient with chronic epilepsy, except to detect fractures of the cranial skull or hemorrhage in an emergency situation. Head x-ray is also obsolete for the diagnostic evaluation of patients with epilepsy. The only situation where an x-ray is indicated is for evaluation of a patient with acute postictal back pain in whom an x-ray is useful to diagnose a vertebral fracture, usually in the thoracic-lumbar region. Although an extensive discussion of MRI is beyond the scope of this chapter, and the reader is referred to textbooks and monographs, this chapter will briefly review pitfalls and errors in the use of MRI in the diagnostic evaluation of a patient with epilepsy.

MRI

When the seizures are focal or an electroencephalogram (EEG) is focally abnormal, when seizures begin in adulthood, or the history and physical examination reveal focal pathological symptoms or signs, MRI is usually indicated to detect structural lesions caused by, for example, cortical malformation, traumatic brain injury, brain tumor, and cerebrovascular disease, which are the most common causes of symptomatic epilepsy (i.e., epilepsy due to an identifiable cause, in this case a structural lesion). MRI is the radiographic method of choice for identifying structural lesions in patients with chronic focal epilepsy (Box 3.1 and Figure 3.1, also see Berkovic et al., 1995, Li et al., 1995, Lerner et al., 1999, Liu et al., 2003, Jeha et al., 2007, Spencer and Huh, 2008, Levine et al., 2009). In our view, MRI is also useful in generalized epilepsy or generalized seizures to search for dual pathology, for example, an unsuspected brain lesion.

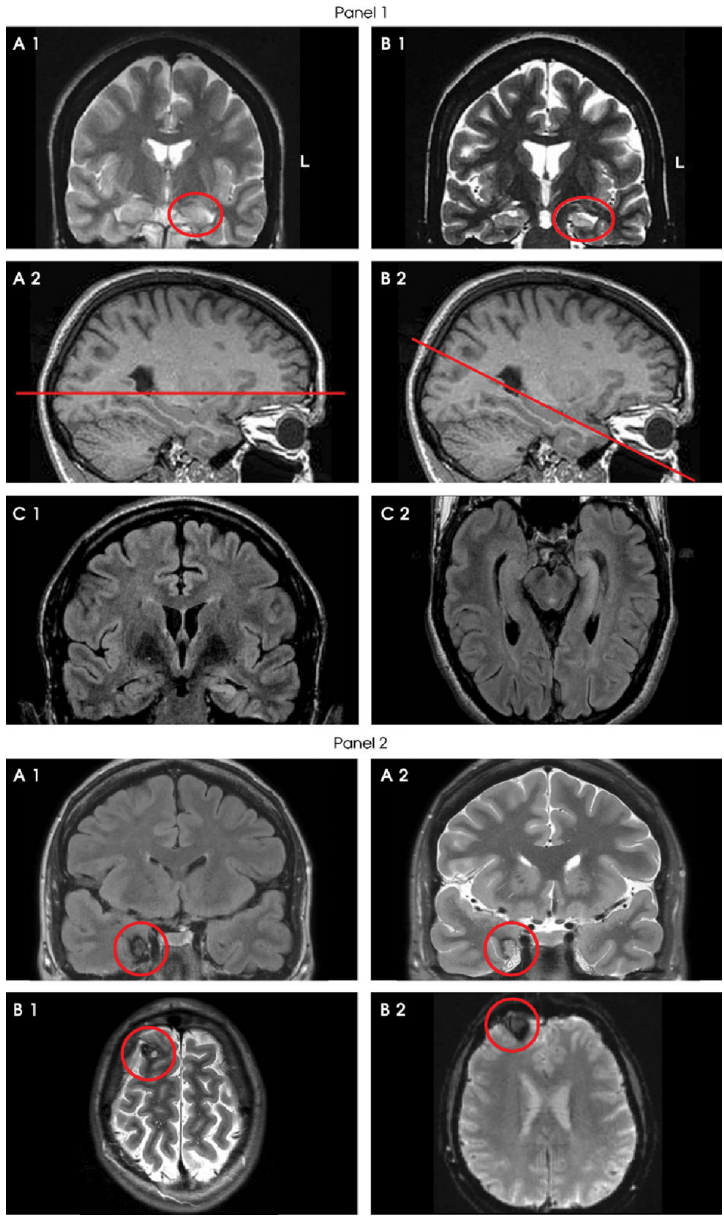

Figure 3.1 Magnetic resonance imaging in epilepsy. Panel 1: A1, Ammons horn sclerosis left, standard coronal angulation; A2, standard coronal angulation; B1, Ammons horn sclerosis (syn.: mesial temporal sclerosis) left, coronal temporal angulation; B2, coronal temporal angulation; C1, flair sequence coronal and axial, temporal angulation. Panel 2: Cavernoma; A1, mesio-temporal right, flair sequence; A2, T2-weighted; B1, frontal right, T2-weighted; B2, T2∗-weighted (pronounced effect of old blood)

(C: courtesy of Department of Radiology, University Bonn, Germany. With permission from Elger and Schmidt, 2008)

Box 3.1 Indications for MRI in adults and children with epilepsy (modified from Woermann and Vollmar, 2009)

- Evidence of focal/multifocal onset of seizures in history or presence of focal interictal EEG abnormalities
- New onset of unclassified or apparently generalized seizures at any age
- Evidence of a focal fixed deficit on neurological or neuropsychological examination or of developmental regression
- Evidence of a neurocutaneous syndrome
- Seizures uncontrolled with first-line antiepileptic drugs (challenging the first-line diagnosis)
- Changes in the pattern of seizures or of neurological deficit (implying a progressive disease)
- Repeat MRI after 6–12 months if previous MRI was negative in any of the indications above

Routine MRI detects an underlying lesion in up to 75% of patients with refractory focal epilepsy seen at tertiary referral centers or in the community. MRI has thus become an obligatory tool for the detection of structural brain abnormalities in epilepsy. The clinical value of MRI critically depends on the expertise of physicians who direct the acquisition of images and those who know how to interpret them. A study from Germany showed the extent of errors in general clinical practice. Standard MRI investigations based on axial images and read by radiologists outside epilepsy centers failed to detect up to 50% of focal epileptogenic lesions, thus leading to false "MRI negativity." The study authors noted dryly, "it seems that the potential for board-certified radiologists to miss obvious MRI features of hippocampal sclerosis (HS) is still high, possibly based on perceptual misses due to poor knowledge about what to expect in temporal lobe epilepsy and how to find it" (von Oertzen et al., 2002).

Mistaken interpretation of radiographic studies (like MRI) can be attributed mainly to poor recognition, but also to poor judgment, incomplete knowledge, or poor technique in obtaining and reviewing radiological images (Woermann and Vollmar, 2009). In plain words, radiologists who have little experience in the evaluation of patients with epilepsy often fail to detect a structural abnormality because they do not know where to look in the brain for a lesion in an individual with a given seizure type or syndrome. To avoid common pitfalls, a standard MRI protocol for investigating patients with epilepsy is mandatory (Box 3.2).

Box 3.2 Suggested standard MRI protocol (modified from Woermann and Vollmar, 2009)

FLAIR for screening, T2-weighted imaging for confirmation, T1-weighted 3D data for anatomical reference and for quantitation

- Sagittal T1-weighted images 5-mm slice thickness (for anatomical reference, especially to allow orientation of the coronal images perpendicular to the long axis of the hippocampus, and for inspection of perisylvian/midline/cerebellar areas)
- Axial FLAIR and T2-weighted images ≤5-mm slice thickness (for screening and confirmation of extratemporal, mainly frontal lobe, pathology)
- Coronal FLAIR ≤5-mm slices (for screening of temporal lobe pathology)

- Coronal double-echo sequence with 5-mm slices (for confirmation and also for T2-relaxometry)
- Axial or coronal T2*-gradient echo images (screening for hemosiderin and calcification)
- Coronal/sagittal T1-weighted three-dimensional volume acquisition with 1–1.5-mm partitions (for three-dimensional reconstruction, quantitation and, at some comprehensive epilepsy centers, to identify focal cortical dysplasia (FCD))
- Pitfall! Note that FLAIR is unhelpful in children less than 18–24 months of age. Before 6 months of age, T2-weighted images are mainly used and, between 6 and 18 months of age, T1- and T2-weighted images are used to visualize the gray–white matter interface during different stages of myelination.

Additional MRI investigations

- With contrast medium to further characterize tumors, vascular malformations, and normal variants (developmental venous anomaly can mimic FCD on FLAIR)
- T2-weighted sequence with a slice thickness <1.5 mm or three-dimensional T2 or FLAIR for subtle FCD
- Some centers use phased array surface coils for detection of subtle FCD
- Quantitation – hippocampal volumetry/T2-relaxometry for bilateral hippocampal sclerosis and texture analysis for detection of FCD
- MR-spectroscopy for grading of malignant tumor or in metabolic disease; some centers use MR-spectroscopy in temporal lobe epilepsy
- Pre-operatively for the localization of the motor strip using fMRI
- Pre-operatively for lateralization of language/memory dominance using fMRI

The following caveats might be useful to avoid common pitfalls in neuroimaging in epilepsy and so that you know where to look for lesions on brain MRI:

- Epileptogenic lesions are often very subtle.
- A temporal angulation is a must.
- Hypothesis-guided analysis based on seizure semiology and EEG helps direct radiographic review.
- Computerized analyses might be useful in special cases, mainly candidates for epilepsy surgery, as might be fMRI, PET, and ictal SPECT.

Although neuroradiological expertise is of significant importance, the diagnostic yield of MRI is additionally influenced by technical developments, though even high-resolution qualitative MRI does not reveal any significant pathology in at least 20% of patients with chronic focal epilepsy. A patient with refractory cryptogenic focal epilepsy in whom as yet no MRI lesion has been found is the target for ongoing imaging research.

In clinical practice, the most common pitfalls for standard MRI investigations include the failure to detect HS in adults with mesial temporal lobe epilepsy; FCD, mainly in children with epilepsy with extratemporal epilepsy; and benign tumors, lesions that are often overlooked on standard MRI (Box 3.1).

In a stepwise approach, a typical epilepsy MRI protocol at 1.5 Tesla first includes axial and coronal fluid-attenuated inversion recovery (FLAIR) imaging, T2- and T2*-weighted images, and a T1-weighted 3D volume acquisition (Box 3.2).

Table 3.1 MRI findings in chronic focal epilepsy and pitfalls

	Hippocampal sclerosis (HS; loss of hippocampal neurons and gliosis)	Focal cortical dysplasia (FCD; with or without balloon cells)	Low grade = benign tumors (distinguished by cellularity; including ganglioglioma and dysembryoplastic neuroepithelial tumor [DNT] and gliomas)
Regions to be inspected	Mesial temporal lobe Hippocampus Parahippocampal gyrus Amygdala	Extratemporal, frontal–parietal > temporal > occipital	Entire brain, but often temporal Intracortical: DNT = ganglioglioma > glioma Subcortical: glioma > ganglioglioma = DNT
Suggested main MRI sequences and orientation	FLAIR, T2 (and T1) Coronal perpendicular to the long axis of the hippocampus Contrast medium not necessary	Age < 6 months: T2 6–18 months: T1 + T2 >18 months: FLAIR + T2 + T1 T2* for calcifications Multiplanar thin-slice MRI (three-dimensional) Serial scanning during ongoing myelination	Multiplanar MRI, including coronal FLAIR T2* for calcification T1 + contrast medium for full pre-operative characterization Serial scanning
MRI features	Main findings: hippocampal atrophy and increased signal intensity on FLAIR and T2 Minor findings: loss of surface and internal structure, atrophy of (extra-)temporal structures (ipsilateral temporal pole, ipsilateral fornix, ipsilateral mamillary body, white matter of the ipsilateral parahippocampal gyrus), decreased signal intensity on T1	Focal and subtle signal change (age < 6 months, T2 hypointense; > 24 months, FLAIR/T2 hyperintense) Thickened cortex Blurred interface between gray and white matter Deepened sulci "Transmantle sign" (signal change in the subcortical white matter that tapers as it extends to the lateral ventricle)	T2-hyperintense Circumscribed, well-demarcated lesion with mass effect Cyst/nodule (single or multiple) Variable contrast enhancement and calcifications
Pitfalls! Do not miss the following pathological MRI findings	Bilateral HS Dual pathology (HS and extrahippocampal or extratemporal abnormalities) In adults with late onset epilepsy and progressive neuropsychological decline or psychiatric disease, consider limbic encephalitis	FCD can be so circumscribed and subtle, it will be overlooked. Tuberous sclerosis (multiple FCD, subependymal nodules, giant cell astrocytoma) Exclude partial volume effect Differential diagnosis tumor: FCD without mass effect, no contrast enhancement, but "transmantle sign" present. Differential diagnosis DVA (developmental venous anomaly): both might produce "blurring of the gray-white-matter-interface" and a transmantle signal change, but DVA enhance regularly	Dual pathology (tumor and HS) If large, a broad differential diagnosis of an acute neurological disorder is needed that includes ischemia, encephalitis, and postictal edema. Serial imaging may be necessary

Source: Modified with permission from Woermann and Vollmar (2009) and Koepp and Woermann (2005).

Advanced MRI techniques (quantification, diffusion-weighted, MR spectroscopy, high-contrast high-resolution imaging at high-field MR scanners ≥3 Tesla) are optional procedures used to increase the method's sensitivity to detect a lesion in an individual patient. False-positive results can be generally avoided by establishing a clinical hypothesis as to where to expect the lesion before the MRI is performed, preferably by seizure semiology and EEG monitoring.

Table 3.1 summarizes the pitfalls and what to expect in MRI investigations in various forms of focal epilepsy.

Recommendation

Every patient with newly diagnosed epilepsy should have an MRI to identify structural causes of epilepsy and an EEG to assist in the diagnosis of the syndrome.

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Chapter 4

The First Seizure: Is It Epilepsy?

William O. Tatum

A single seizure is two to three times more common than epilepsy. There are multiple pitfalls that exist when approaching someone who has experienced a first seizure. The critical first step is to ensure that the event was a seizure as opposed to a non-epileptic event. When treatment is rendered too soon, this is a trap that may result in unnecessary adverse events. Another pitfall is excluding provoked causes that would explain a first seizure and avoid subsequent seizures by elimination of the trigger in contrast to the addition of an antiepileptic drug (AED). In the case of an unprovoked seizure, determining the level of risk for recurrence should be stratified and high-risk patients treated with AEDs (as epilepsy). Brain MRI and EEG provide vital pieces of information that may clarify an unclear history of an event as a seizure and provide evidence for potential recurrent seizures. A structural basis (Figure 4.1) or prior neurological insult to the brain is the most powerful predictor of recurrence following an initial seizure. An abnormal EEG is a significant risk factor when epileptiform discharges (EDs) are present (Figure 4.2) even in the presence of a normal brain MRI. EEG is helpful to not only demonstrate the presence of interictal EDs, but also to help classify seizure type for

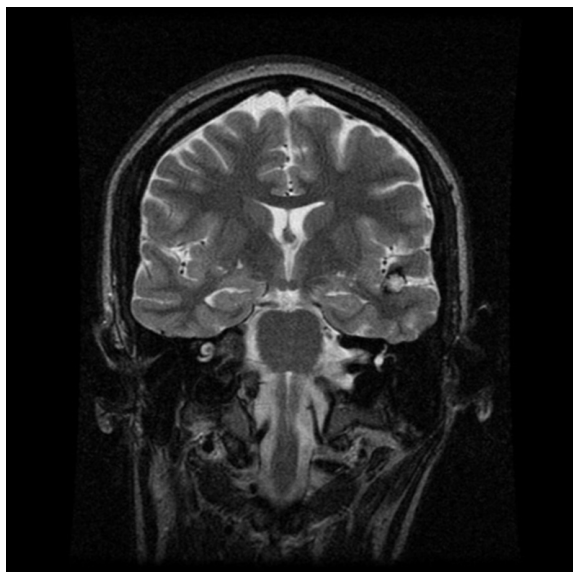

Figure 4.1 Brain MRI demonstrating a left lateral temporal cavernous vascular malformation in a patient following a first seizure

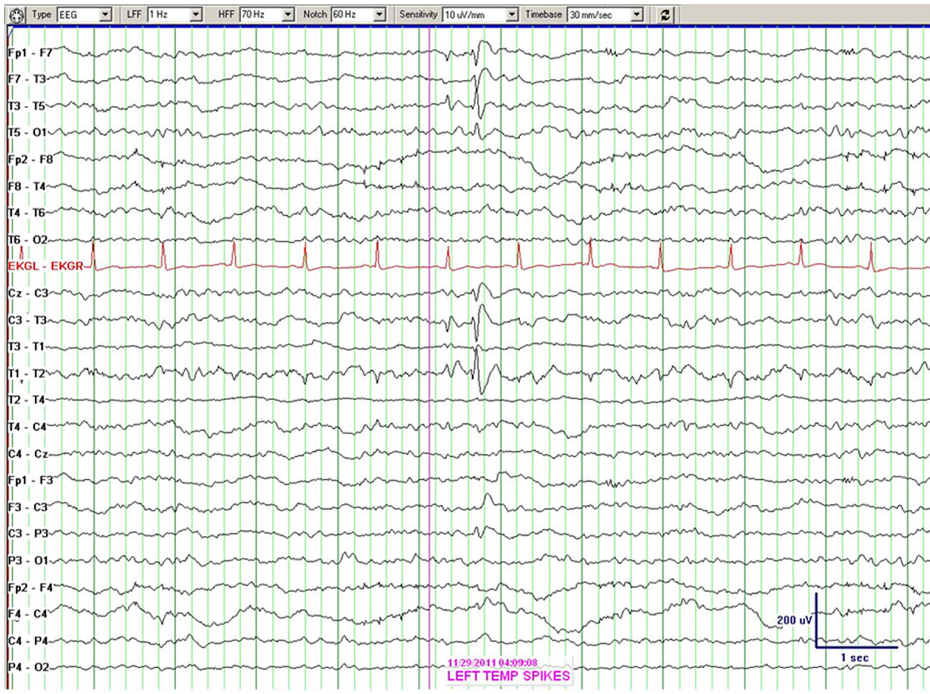

Figure 4.2 Abnormal EEG demonstrating a left mid-temporal spike-and-wave couplet with a regional temporal field during drowsiness in a patient experiencing a first seizure

the purpose of AED selection. Fortunately, a new-onset seizure in most patients will not recur and therefore does not represent epilepsy. For concerned patients, it is important to emphasize that for most, the prognosis after a first seizure is favorable when an enduring cause is not identified. For physicians concerned about sudden unexplained death in epilepsy, and therefore the risk of foregoing AED treatment after a first seizure, it is important to carefully choose who receives AEDs following a first seizure, realizing the potential for treatment-related serious adverse effects and the need to balance that with the risk of recurrence. No untoward evidence exists thus far that foregoing treatment and continuing observation is harmful and in many circumstances this may represent a rational approach to best patient management (Bergey, 2016; Gavvala and Schuele, 2016). When approaching the patient with a first seizure, treatment is predicated on the greatest likelihood that the first seizure is epilepsy.

Seizure Misdiagnosis

Case 4.1 Syncope vs Seizure

BG is a 19-year-old female whose mother, an LPN at your hospital, informs you that she just experienced her first seizure, witnessed by the mother. You agree to see her urgently for evaluation.

Upon arrival to the examination room, the patient is a slender, short, and shy young woman who is accompanied by her mother. Most of the history is obtained from the mother who reports that on the preceding Saturday evening, the patient was preparing to go out with friends. She complained to her mom that she felt dizzy and nauseated. Within 30 seconds, she lost consciousness, had her vision "close in on her" prior to collapsing onto the floor, and a witnessed first time "grand mal" seizure. Mom describes generalized jerking and reinforces that she is a nurse and has seen patients with epilepsy experience similar events. There were no other symptoms to suggest other types of focal or generalized seizures. Upon questioning pertaining to potential provocative factors, mom replies that her daughter is a "straight A" student and does not use drugs or alcohol. A subsequent brain MRI and awake and asleep EEG were normal. A complete blood and metabolic profile are normal. AEDs are recommended and specific agents discussed, in particular lamotrigine and levetiracetam (LEV). Because it is the first seizure you recommend a watch-and-wait approach. The mother notes that her daughter is not sexually active and pushes for AED treatment to "do everything" in an effort to prevent a recurrent event.

What are the Pitfalls Involved in this Case?

Pitfall

Failure to appreciate that epilepsy has a broad differential diagnosis, and adequately differentiate a first seizure from a non-epileptic event.

Discussion

The cornerstone to the accurate diagnostic assessment of a first seizure is obtaining a thorough and adequate historical account of the event after an apparent first seizure or paroxysmal neurological event (Gavvala and Schuele, 2016). Importantly, psychogenic non-epileptic attacks (PNEA) and syncope (or convulsive syncope that occurred in this case) are important seizure mimics that necessitate initial distinction from a seizure due to alternative evaluation and management required. Neuropsychiatric evaluation may provide clues as to the relative risk of a seizure or functional influences. Laboratory studies should include a urine drug screen, HIV, and pregnancy screen where applicable. Neuroimaging with MRI is the best means of identifying structural abnormalities of the brain in patients suspected of focal seizures with 10–30% of patients with new-onset seizures demonstrating structural causation (Ho et al., 2013). Computed tomography (CT) may provide emergency information and detail if bony elements of the skull or skull base are involved, though CT is inferior to MRI in detecting subtle lesions such as low-grade gliomas, cortical malformations, and hippocampal sclerosis (Berg et al., 2010). The EEG is a powerful diagnostic tool in patients with new-onset seizures when used in the proper clinical context. When it demonstrates epileptiform abnormalities, a routine scalp EEG recording can aid in the assessment of both the type of seizure (e.g., focal versus generalized) and risk of recurrence (Pillai and Sperling, 2006). Chemistry screens are usually performed, though typically they play a small role in identifying an underlying etiology in patients with new-onset seizures. The probability of recurrence in this case is low despite mom's insistence of her knowledge of seizures, due to the strong likelihood that the event was non-epileptic, and specifically the possibility of convulsive syncope.

Case (cont'd)

In this case, treatment with an AED was prescribed at the insistence of the mother, who was emotionally invested in treatment without appreciating potential causes or consequences. The patient had a urine drug screen that was positive for cocaine and she later admitted to being sexually active without the use of contraception, which could have resulted in an unwanted pregnancy and exposure to AEDs in the first trimester.

Pitfall

Believing the risk of AED treatment is less than the risk of a subsequent seizure following a single event.

Discussion (cont'd)

The diagnosis of a first seizure and epilepsy is a clinical one that relies upon the clinician's judgment and that can lead to unnecessary treatment. Being cautious in treating females of child-bearing potential is important due to the possibility of an unplanned pregnancy and the teratogenic risk of AEDs. Even after a single generalized tonic–clonic seizure (GTC), a normal brain MRI and EEG reflects lower risk of recurrence, and deferring AED treatment should be considered in otherwise young healthy patients for whom there may be a greater benefit in postponing AED treatment than benefit from AEDs in preventing future seizures. Even in appropriate patients at higher risk for recurrence, it is important to realize that AEDs are capable of producing side-effects including mood disturbances, central nervous system related symptoms, potentially life-threatening cutaneous rashes and solid-organ hypersensitivity syndromes, and overall compromise of the patient's quality of life stemming from adverse effects. To avoid pitfalls in the diagnosis of a first seizure, a standard, orderly approach is recommended (Figure 4.1) (Pohlmann-Eden and Legg, 2013). The diagnosis of a seizure has many important ramifications. Both the patient's ability to describe subjective sensations preceding the event and obtaining the history from a direct observer or indirect historian are crucial for determining the diagnosis of a first seizure and the risk of subsequent seizures.

The differential diagnosis of a seizure is broad, including many paroxysmal "spells" that mimic a seizure that can potentially lead to misdiagnosis (Chapter 1). It is true that the risk of sustaining another seizure could lead to serious physical injury. This requires treatment consideration, but the use of AEDs should take into account an individual's lifestyle and the likelihood of seizure recurrence. Additionally, the risk of serious adverse effects from AEDs needs to be balanced against the risk of a second seizure. If the diagnosis of epilepsy is made, it is important for the individual not to drive a motorized vehicle according to the guidelines set forth by their individual state. It is also important to document this discussion in the case notes. Driving restrictions in many cases impacts their ability to gain or continue employment and form interpersonal relationships, and adversely affects psychosocial well-being and quality of life, which is life-changing. A seizure diagnosis may further impair social relationships and stigmatize the person to others and induce fear and apprehension in the patient who is unable to predict if and when a second event might occur. To date, however, no evidence exists that using current AEDs will induce a long-term remission; rather, they are prescribed to suppress unprovoked seizures in patients with epilepsy.

Final Diagnosis: Convulsive Syncope

Accurate Seizure Diagnosis

Case 4.2 Isolated Seizure vs Epilepsy?

A 20-year-old male comes home from college for Thanksgiving weekend. He visits with his friends and has an uneventful evening. The next morning, he is eating breakfast with his family when he experiences a sudden loss of consciousness, fall to the floor, generalized tonic stiffening, and subsequent rhythmic, clonic jerking bilaterally for 1–2 minutes. He sustains a posterolateral tongue laceration and loses control of his bladder. Afterwards, he was somnolent, confused, and disoriented but redirectable. He is taken to the nearest emergency department (ED) where he is diagnosed with a seizure disorder and admonished to "stop taking drugs." A subsequent neurological evaluation, brain MRI, and EEG (awake and asleep) are normal.

Discussion

It is important to realize that a first seizure is not an uncommon occurrence in otherwise healthy individuals. Prior studies report 8–10% of individuals experience a single seizure at some point over the course of their lives (Hauser and Beghi, 2008). Approximately 400,000 people with new-onset seizures present to the ED each year (Wyman et al., 2017). Worldwide, the incidence of epilepsy is 50.4 per 100,000 per year (Ngugi et al., 2011). In 2014, the International League Against Epilepsy (ILAE) revised the definition of epilepsy to include those patients with a single unprovoked seizure. The new practical clinical definition is based on the following criteria (Fisher et al., 2014):

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
3. Diagnosis of an epilepsy syndrome.

Overall, the average risk of developing a second seizure is dependent upon the type of seizure encountered as the first event. A second seizure occurs in 21–45% of patients in 2 years following a first unprovoked seizure (Krumholz et al., 2015). In one prospective epidemiologic study of adult patients presenting with a first seizure, one-third of patients had a second seizure, and after a second seizure, approximately three-quarters had a third seizure (Hauser et al., 1998). In children, the risk was lower, with a cumulative risk of 42% for a subsequent seizure by the third year (Shinnar et al., 2000). Seizures that begin in childhood have different etiologies than those that begin during adulthood. There is a greater representation of genetic generalized epilepsy (GGE) and epilepsy syndromes during childhood with an abnormal EEG being the greatest predictor of recurrence (Shinnar et al., 2000). While a normal EEG predicts a risk of recurrence of less than 30% after a first seizure, an abnormal non-epileptiform pattern may also carry greater risk, but with EDs on the EEG, the risk goes up to 60% (Shinnar, 2000; Bergey, 2016). Remote symptomatic etiologies, nocturnal seizures, a Todd's phenomenon, and a prior febrile seizure are clinical risk factors for recurrence following a first seizure. Additionally, the

relative risk during activities of daily living are substantially different and the focus on avoiding climbing at heights should be emphasized especially in childhood, whereas in adulthood, driving and certain types of employment are the main safety issues. In children, the risk for a third seizure after the second one was nearly the same as that for an adult, with 72% of patients having a third seizure (Hauser et al., 1998; Shinnar, 1998). Young children or adolescents who have a single convulsive seizure, no risk factors for epilepsy, normal brain MRI and EEG, and presumed genetic or unknown cause had a risk of recurrence of approximately one in five (Gavvala and Schuele, 2016). Identifying a single seizure as epilepsy often requires specialized interpretative skills. Specifically, in assessing recurrence risks, or in diagnosing epilepsy syndromes, consulting neurologists with a particular interest in epilepsy should be considered.

Case (cont'd)

Upon direct questioning during his neurological evaluation, the patient notes that over the past 6 months he experienced recurrent episodes of "deja vu." He then volunteers that he had the same feeling briefly prior to his convulsion.

Discussion (cont'd)

In a patient with a first seizure, it is important to inquire about an aura since it reflects a focal seizure. Subjective symptoms reported with an aura reflect the neuroanatomical region of seizure onset or spread and therefore provide localizing information which has relevance to subsequent neuroimaging and neurophysiological studies. While some auras are nonspecific in their localizing properties, déjà vu and other experiential and psychic auras often reflect seizure onset in the temporal lobe.

In addition, impairment of consciousness and awareness should be identified, and in those circumstances, witness observation will improve overall confidence in a seizure diagnosis. Similarly the presence of a postictal state is characteristic of a seizure as opposed to non-epileptic events. When description is lacking, evidence of injury (e.g., burn, posterolateral tongue laceration) may be taken as characteristic in patients with seizures. It is equally important to identify other seizure types (e.g., absence, myoclonus) in order to determine the presence of epilepsy syndromes.

Seizures are a symptom of disordered brain function. It is therefore essential to assess brain function to determine the etiology leading to its occurrence. Some patients, especially those with an identifiable cause, have a high likelihood of recurrence (i.e., greater than 60%) so that after the first seizure, and particularly following a second seizure, they should be considered as patients with epilepsy and subsequently approached with AED treatment. Factors associated with a high likelihood of recurrence are:

1. A neurological deficit (e.g., hemiparesis, mental retardation)
2. Todd's phenomenon
3. Significant neuroimaging abnormality
4. Epileptiform EEG
5. Remote history of a seizure
6. Family history of seizure in immediate family members (e.g., parents, siblings, children) in patients with an "idiopathic" first seizure.

Stratifying first seizures into low- and high-risk with regard to probability of recurrence is important given the implications for treatment as well as the psychosocial ramifications of a diagnosis of epilepsy. While the cumulative incidence of seizure recurrence following a first unprovoked seizure increases over time, most seizure recurrences occur within the first 2 years with the highest risk within the first year. Treatment with AEDs has been shown to delay a second seizure in a mixed group of children and adult patients after a first unprovoked tonic–clonic seizure by two years when compared to a cohort where treatment was delayed. However, while treatment after a first seizure might prevent a second seizure, it does not prevent the development of epilepsy (FIRS.T. Group, 1993).

Pitfall

Failure to realize most first seizure patients will not experience recurrence, and the inability to accurately stratify patients into high and low risk groups.

Types of First Seizures

Case 4.3 Provoked vs Unprovoked seizure

A 16-year-old healthy adolescent male is on summer break from high school. He drives himself to spend the night over at his friend's house on his day off from his job at a supermarket. Five boys stay up late playing "Call of Duty" during a video-gaming marathon. Each consumes several cans of a high-energy drink and pull an "all-nighter." Another boy shares his Attention Deficit Hyperactivity Disorder medication, a combination of amphetamine and dextroamphetamine, with the patient so that he may stay awake. At approximately 5 a.m. the patient complains of feeling "wired," lets out a scream, loses consciousness, falls over, and has a witnessed convulsion for 1–2 minutes. He is confused and disoriented after the event and lacerates his tongue. The parents properly call the family of our patient and an ambulance that transports the patient to the hospital ED. A CT brain is normal, ECG shows normal sinus rhythm, and laboratory analyses including a urine drug screen are negative. The patient is loaded with phenytoin and prescribed oral phenytoin 100 mg capsules four capsules nightly. He is told not to drive. He is discharged from the ED and seen in follow-up for evaluation and management, complaining of "an inability to think clearly" and feeling depressed.

Pitfall

Failure to recognize seizures that are provoked by a self-limited etiology.

Discussion

Seizures are classified into *unprovoked* seizures and *provoked* seizures, depending on the presence of an underlying cause. An unprovoked seizure occurs in the absence of a triggering event and raises concern for an idiopathic form of epilepsy, a structural lesion involving the brain or a progressive disorder. Provoked seizures in general have an explanation such that seizures are unlikely to reoccur when the cause is eliminated or avoided. Most provoked seizures are generalized convulsive seizures. Seizures do not occur in all patients when they are exposed to the same trigger, raising the concept of a seizure "threshold" that differs from person to person. The qualities of a provoked seizure are similar and portend a lower risk for recurrent unprovoked seizures. Examples of provoked seizures include those commonly precipitated by specific triggers such as metabolic factors (e.g., hypoglycemia, hyponatremia), medication (e.g., tramadol, lithium), and systemic factors (e.g., sepsis) as shown in the table below.

Category of precipitant	Trigger
Prescription medicine	Tramadol, buproprion, lithium, clozapine, theophylline, antibiotics (e.g., cefipime, imipenem)
Illicit drugs	Heroin, cocaine, ecstasy, amphetamines, Phencyclidine (PCP)
Substance withdrawal (acute)	Benzodiazepines (e.g., clonazepam, alprazolam), barbiturates, alcohol
Metabolic	Hypo- and hyperglycemia, hyponatremia, hypo- and hypercalcemia
Toxic-systemic	High fever, sepsis, energy drinks

Rarely, focal seizures may be provoked, though this should raise the possibility of a concomitant structural lesion (e.g., alcohol abuse and prior cerebral contusion), or they may occur atypically if metabolic triggers (e.g., hypoglycemia) are involved and produce focal or lateralized features that results in a diagnosis of focal epilepsy. In general, provoked first seizures that have focal features at the onset should be approached in the same manner as unprovoked seizures (Gavvala and Schuele, 2016).

Pitfall

Provoked seizures do not require AED treatment even when the provocative trigger occurs a second time.

Case 4.4 Acute Symptomatic Seizure

A 71-year-old right-handed man has hypertension, persistent atrial fibrillation, and hypercholesterolemia. Earlier in the day, he was working on a crossword puzzle when he suddenly was unable to come up with the word to answer the question. He attempted to call for his wife and knew what he wanted to say, but was unable to get the words out. At the same time he dropped the puzzle book due to weakness of his right hand. His wife suddenly heard a scream and found her husband on the floor in a "grand mal" seizure. She left to call 911 as he was gradually returning to normal.

Question: Does He Have Epilepsy?

No, he does not have epilepsy at this time. Acute symptomatic seizures are seizures that occur simultaneous or within days of a sudden brain insult like cerebral ischemia, as in this patient. While they are technically "provoked" by acute brain injury, *provoked seizures* indicate a reversible etiology and *acute symptomatic seizures* typically occur in the face of an acute brain insult. Both types of first seizures may not recur though some acute symptomatic seizures are associated with conditions that cause irreversible structural alteration of the cortical anatomy (such as a stroke), resulting in a future risk of late seizure recurrence. Seizures occurring acutely in response to an acute brain injury do so as a symptom in response to the effect of an acute process affecting the brain. Trauma to the brain, central nervous system infection, cerebrovascular diseases such as ischemic and hemorrhagic stroke, transient ischemic attack (TIA), and subarachnoid hemorrhage; and brain surgery are common causes of acute symptomatic seizures and have a recurrence risk for late seizures between 10% and 20% (Krumholtz et al., 2015; Gavvala and Schuele, 2016).

Classifying First Seizures

Case (cont'd)

Five minutes later, the patient's wife hears the same scream and sees him have another "grand mal" seizure for 30–60 seconds. It stopped and almost immediately, a third brief 30-second seizure occurred. He is transported to the nearest ED for evaluation. A head CT is "negative" and the neurological examination is noted to be "non-focal" by the emergency room physician. He is admitted to the hospital where a subsequent MRI brain, EEG, and laboratory studies were normal. Overnight cardiac telemetry demonstrates atrial fibrillation with a variable ventricular response. Echocardiogram and a 12-lead ECG were without significant findings. He is diagnosed and treated for a TIA and given phenytoin intravenously for a seizure disorder.

Discussion (cont'd)

While the occurrence of multiple seizures within a 24-hour period in a patient without previous seizure history instinctively suggests a greater likelihood of seizure recurrence following the initial cluster of seizures, clinical studies have demonstrated that they do not confer a greater risk of recurrent seizures (i.e., epilepsy) when compared to a single first seizure (Krumholtz et al., 2015). This has been shown irrespective of provoked, genetic, or remote symptomatic causes (Kho et al., 2006). Therefore, because most patients with acute symptomatic seizures have less than a 25% likelihood of seizure recurrence, they do not generally require treatment with AEDs. By contrast, when a history of remote symptomatic seizures is encountered (e.g., a prior seizure from head injury, TIA/stroke, meningitis), the "new onset" seizures may actually reflect unprovoked seizures associated with a chronic non-progressive lesion affecting the brain, which should be interpreted as portending a sufficiently high risk of recurrence to warrant AED therapy. High-resolution brain imaging available at epilepsy centers is important in the evaluation of patients with first seizures to detect structural brain abnormalities, whether or not the patient has a history of a prior acute symptomatic seizure, because of the related high risk of recurrence and therefore indication for AED treatment.

Pitfall

Assuming that new-onset multiple seizures within 24 hours represents a higher likelihood of seizure recurrence than an isolated first seizure.

Case (cont'd 1 year later)

The patient returns to see you after 1 year. He is concerned regarding episodes of "speech problems." He notes that while doing his crossword puzzles for 15–30 seconds he is unable to understand the questions in the puzzle. He feels somewhat "off" during these times and afterwards is exhausted and needs to lie down to take a nap. His wife can "see it in his eyes" but notes that during this time he ignores her. The events are getting stronger and his wife prompts the return visit as she is concerned that it may affect his driving. A follow-up EEG demonstrates focal left anterior temporal spike-and-slow waves with a regional temporal field during waking and sleep.

Discussion (cont'd)

The diagnosis of epilepsy is a clinical judgment based upon the history obtained from the patient or witnesses of the observed behavior during the patient's event(s), perhaps supplemented by home videos. However, recurrent focal seizures with or without impaired awareness or a single seizure coupled with an abnormal epileptiform EEG or abnormal brain MRI with a cortical lesion predicts seizure recurrence (epilepsy) and requires AED treatment (Krumholtz et al., 2015; Bergey, 2016).

An aura reflects a time-limited focal seizure without concomitant impaired awareness, so that the patient may remember it unless it immediately proceeds to loss of consciousness. There are many possible symptoms associated with auras, including aphasia as in this case. As mentioned earlier, auras (the initial seizure symptoms) may have localizing value. Relative to the site of seizure onset, the following is a guide to localization for specific seizure symptoms (Noachtar and Peters, 2009):

- **Temporal lobe:**
  - Mesial: aura of déjà vu, or indescribable feeling, blank stare, impaired consciousness, oro-alimentary automatisms, dystonic posturing contralateral to seizure onset with ipsilateral manual automatisms
  - Lateral: language dysfunction (dominant hemisphere) or dysarthria, stare, impaired consciousness, version evolving to a convulsion
- **Frontal lobe:**
  - Dorsolateral: focal clonic jerking contralateral to seizure onset
  - Supplementary motor: bizarre, bilateral complex movements or tonic posture
  - Orbitofrontal: autonomic features, staring, impaired consciousness
  - Frontopolar: rapid evolution to a bilateral convulsion
- **Parietal lobe:**
  - Localized numbness or tingling which may be contralateral (or ipsilateral)
- **Occipital**
  - Visual phosphenes, hallucinations, blindness, and scotomata.

It is important to approach the evaluation and treatment of patients not only based on seizure type, but also by epilepsy syndrome, when possible. For example, the risk of recurrence and need for treatment after a first seizure is different in a patient with focal motor seizures due to trauma from a patient with focal motor seizures associated with Benign Childhood Epilepsy with Centrotemporal Spikes. Though the seizures may appear identical to an observer, they require a very different course of treatment.

Other potential pitfalls exist for patients with seizures that appear to arise from one brain region though actually reflect propagation from another location. An example would be ictal symptoms of mesial temporal lobe involvement due to a seizure originating from another area (e.g., posterior quadrant, orbitofrontal, insula, cingulate gyrus), which then spreads to the mesial temporal lobe via network connections. Therefore, semiology alone is inadequate to determine site of seizure onset. The classification of the seizure phenotypes has evolved (Berg et al., 2010) and this change may be confusing to clinicians who do not see many patients with epilepsy, leading to potential mistakes in assessing seizure semiology relative to potential underlying etiologies (see Chapter 1).

Diagnosis: Focal Epilepsy

Pitfall

Failing to recognize an aura as a focal seizure, in addition to an overlap of symptoms between neurological conditions and seizures that may occur and lead to incorrect treatment.

Case 4.5 Provoked New-onset Epilepsy

An 18-year-old female with a history of migraine headaches experienced her first "grand mal" seizure after partying the night before. She stayed up late with her friends and drank beer around a bonfire on the beach. The next morning, she felt "twitchy," which she had experienced in the past but had ignored. After a cup of coffee, she went into the bathroom to take a shower. Her roommate heard a "blood curdling cry" and went in to find the patient on the floor with blood coming from her mouth and head covered in a pool of blood. In the ED, she was noted to have sustained a large scalp laceration and posterolateral tongue laceration. A CT brain was normal except for scalp edema at the site of contusion. She was admitted for overnight observation. In the ED, she was loaded with IV phenytoin and begun on oral phenytoin 200 mg BID.

Discussion

Seizure symptoms alone may not be specific for a particular seizure type. For example, staring spells in adolescence could either represent focal seizures or absence seizures, and an interictal or ictal EEG is needed to differentiate between the two. Taking a good history is essential in patients who present with an apparent first seizure to ensure that in fact only one seizure has occurred. Generalized seizures cause loss of consciousness and motor function from the onset in their lifetime. A seizure is unclassified when it cannot be categorized as a focal or generalized seizure. The two different seizure types in this case, myoclonic and GTC seizures consistent with GGE, including juvenile myoclonic epilepsy (JME). Many such patients identify convulsive seizures but neglect identifying nonconvulsive seizures, such as the "twitching" in this young lady.

Pearl

When a patient presents with their "first" seizure (often GTC seizure), after a careful history of the presenting event, inquire about other types of events that may have occurred in the past.

In this case, not only was the convulsion not her first-ever seizure, but the presence of myoclonus indicates an epilepsy syndrome that requires the need for long-term therapy.

Another pitfall is assuming the patient's history and estimate of seizure frequency is accurate. Patient reporting may be unreliable, largely because some patients are unaware of their seizures when they occur. The elderly and those with temporal lobe seizures appear most at risk. In addition, postictal confusion and cognitive dysfunction in patients presenting with a first seizure may adversely impact their ability to identify previous seizures. Furthermore, observers who witnessed the current or prior seizures may or may not be available, depending on the social setting of the patient presenting with a first seizure.

Case (cont'd)

During office follow-up after hospital discharge, she reports an increase in her twitching in the form of "jerks" even though she has been compliant with taking her phenytoin. After a normal brain MRI and abnormal EEG showing bursts of generalized polyspikes and slow waves, she was begun on valproate 250 mg twice daily. She was subsequently titrated to extended-release valproate 1,000 mg nightly but complains of dizziness, blurry vision, and unsteady gait a few days later.

Discussion (cont'd)

Myoclonic seizures rarely present as a first seizure, because most patients mistake them for clumsiness or something else other than a seizure. Consequently, it is common for a patient with JME presenting after a GTC seizure, as their "first" seizure, to have a history of myoclonic seizures. Similarly, a generalized seizure associated with a symptomatic/encephalopathic generalized epilepsy syndrome (e.g., Lennox–Gastaut syndrome) typically is not that patient's first seizure.

Focal seizures may rapidly evolve to appear as a generalized convulsion, with the focal onset symptoms not remembered or the focal onset signs not witnessed. Conversely, patients with generalized epilepsy may occasionally manifest lateralizing features that lead to misinterpretation as a focal seizure. Identical semiology does not assume the same risk of recurrence solely because seizures appear the same. Another trap involves failing to consider the overlap between focal and generalized semiologies to differentiate onset from propagation. The resulting pitfall in treatment choice is treating first seizures based solely on a singular seizure semiology. Some AEDs used in focal epilepsy exacerbate generalized seizures. In this case, phenytoin aggravated the patient's myoclonic seizures. The addition of valproate, which has its own issues in a woman of child-bearing potential owing to the risk of teratogenicity, produced a drug–drug interaction leading to displacement of phenytoin from the carrier protein to produce clinical AED toxicity. Substituting a non-enzyme inducing/non-enzyme inhibiting AED like LEV for the valproate–phenytoin combination in this patient could lead to expeditious resolution of side effects and control of myoclonic and GTC seizures.

Diagnosis

Genetic Generalized Epilepsy manifested as first (new-onset) GTC and myoclonic seizures characteristic of generalized epilepsy (JME).

Evaluating a First Seizure

Whether treatment with an AED is rendered after multiple seizures or after a single occurrence is based on the presence of risk factors such as an etiology associated with significant risk for recurrence. The likelihood of having a second seizure can therefore be predicted by certain clinical variables. Yet with few exceptions, the prognosis for seizure recurrence cannot be stated with 100% certainty in a specific patient (yes, seizures will recur vs. no, seizures will never recur). On a population basis, risks vary according to cause. For example, a genetic basis for a first seizure does not carry the same risk for patients compared with a first seizure arising from a structural abnormality. Early studies comparing these etiologies in patients experiencing a first seizure demonstrated

an overall recurrence risk that gradually increased to 34% at year 5 for those with an "idiopathic" basis (e.g., genetic) compared with recurrence risks of 48% for patients with a remote symptomatic seizure (Hauser et al., 1998; Hauser and Beghi, 2008). Age has not been found to be a risk factor independently in multiple studies (Bergey, 2016). The presence of an affected sibling, abnormal EEG demonstrating generalized spike-and-waves, and a previous acute symptomatic seizure in a patient with a first generalized seizure suggests a risk of recurrence after a single seizure of 60% or more (Hauser and Beghi, 1998; Fisher et al., 2014; Krumholtz et al., 2015; Bergey, 2016; Gavvala and Schuele, 2016).

Pitfalls

Failure to diagnosis epilepsy in patients with a high risk for recurrence after an unprovoked seizure and other seizure types, and diagnosing epilepsy in a patient with either a provoked or acute symptomatic seizure and a lower risk for recurrence.

Based on the current pragmatic definition of epilepsy, a first seizure in association with factors listed below suggest a high risk of recurrence following an unprovoked seizure is defined and treated as epilepsy (Fisher et al., 2014).

- Generalized
  - EEG with generalized spike-and-waves/polyspike-and-waves
  - Past family history or sibling with epilepsy
  - History of acute symptomatic seizure
- Focal
  - Particular abnormalities on brain MRI
  - Abnormal neurological examination lateralizing to one of the cerebral hemispheres
  - Nocturnal seizure
  - Todd's phenomenon after the seizure
  - Prior acute symptomatic seizure

Neuroimaging

Overall, a prior brain injury is one of the strongest predictors of seizure recurrence in patients presenting after a first seizure. A significant abnormality on brain neuroimaging suggests the presence of a remote symptomatic etiology and should be evaluated as potentially related to the first seizure. Brain MRI has better resolution for demonstrating a structural lesion than brain CT and is therefore the preferred neuroimaging technique, especially in patients with focal seizures (Bergey, 2016).

Pitfall

Non-specific abnormality on brain MRI is judged to be a significant risk for recurrent seizures in patients following a first seizure.

A significant abnormality in the context of epilepsy is one that is located in the cortex (e.g., cortical dysplasia, congenital brain malformation), immediately subcortical (e.g., brain tumors, cerebral infarct or previous hemorrhage, traumatic brain injury), or one that has been previously associated with epilepsy (e.g., hypothalamic hamartoma, cavernous vascular malformation, hippocampal sclerosis). A structural basis with or without an

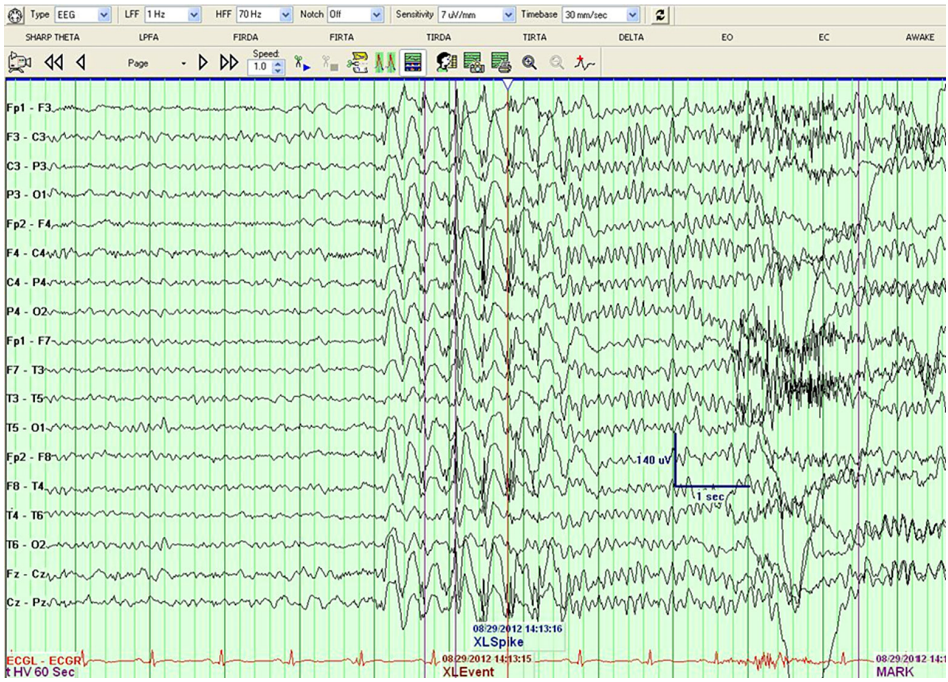

Figure 4.3 EEG with generalized 3.0–3.5-Hz generalized spike-and-wave burst upon awakening in a patient following a first "grand mal" seizure

abnormal examination is a significant risk factor in predicting a high likelihood of seizure recurrence according to the AAN evidence-based guideline (Krumholtz et al., 2015).

EEG

After a first seizure, the EEG may have predictive value in determining the risk of seizure recurrence. In a large multicenter study, an abnormal EEG conferred a higher risk of recurrence (Kim et al., 2006). Having an abnormal EEG has been shown to be a risk in children (Shinnar et al., 2000) and adults (Hauser and Beghi, 2008; Krumholtz et al., 2015). However, according to some studies, focal abnormalities have not been predictive (Hauser et al., 1998). Epileptiform EEG abnormalities have been shown to be associated with a higher risk of seizure recurrence than non-epileptiform abnormalities. In patients with an "idiopathic" (presumed genetic) cause, the presence of EDs in the EEG (Figure 4.3) carries a high risk of recurrence when compared with a normal recording.

Additionally, EEG findings may allow identification of an epilepsy syndrome (e.g., "fast" generalized polyspike-and-waves characteristic of JME).

Pitfall

Not all spikes in the EEG have equal prognostic significance in patients with first seizures.

Benign epileptiform variants of uncertain significance and which are unrelated to epilepsy may occur. Wicket spikes, sharply contoured rhythmic mid-temporal theta bursts of drowsiness, 6-Hz generalized spike-and-waves, 14 and 6 Hz positive spikes, and even subclinical rhythmical EEG discharges of adults may mimic pathological features on the EEG but do not confer an increased risk for seizures. It is also important to remember that some EDs may be present in the EEG for other reasons unrelated to epilepsy as shown below, and therefore do not independently support a need for AED treatment:

- Congenital blindness
- Cerebral palsy
- Autistic spectrum disorder
- A sibling/family history with epilepsy
- Medications (e.g., lithium, baclofen, antipsychotics).

Treatment of a First Unprovoked Seizure

Case 4.6 Unwitnessed Seizure

JM is an 81-year-old attorney practicing law at a high level. He is driving to the office in his usual fashion when he "awakens" on the side of the road realizing that he has been in a car crash with a young pregnant woman who fortunately appears to be all right. He described no warning prior to losing awareness and feels terrible because "he could have hurt someone". He is "confused" regarding the cause of the accident but not disoriented to common knowledge. He does not go an ED and sees a neurologist in follow-up. A brain MRI was normal. An EEG demonstrated left focal temporal slowing but no epileptiform discharges. He complains of a bitten tongue and diffuse body aches since his accident. He is treated with a low dose of LEV and is compliant with restriction of driving privileges. He becomes depressed and requests to be discontinued from the treatment after 6 months.

Discussion

Some patients may experience unwitnessed seizures and themselves be unaware that seizures have occurred, leading to delayed treatment. Others will never have a second seizure even if treatment is foregone after a witnessed event. In both situations, the decisions about whether and when to start AED treatment are challenging. Determining whether a patient is at low risk for recurrence (e.g., normal MRI, EEG, and favorable clinical course) or at high risk (e.g., abnormal neurological examination, cortical abnormality on brain MRI, epileptiform EEG, etc.; see Figure 4.4) factors into these decisions (Leung, 2010). Clinicians should also take into consideration that the likelihood of long-term improvement of quality of life by treating immediately with AEDs may not be different than when treatment is delayed (Fountain et al., 2011). In addition, starting an AED after the second seizure has occurred has the same overall outcome on a population basis as treating after a first seizure (Krumholz et al., 2015; Bergey, 2016; Gavvala and Schuele, 2016). The use of AEDs renders 65–85% of patients seizure-free but produces side-effects in 7–31% of patients, whether or not they would have had a recurrence without AED treatment (Brodie et al., 2012; Krumholtz et al., 2015).

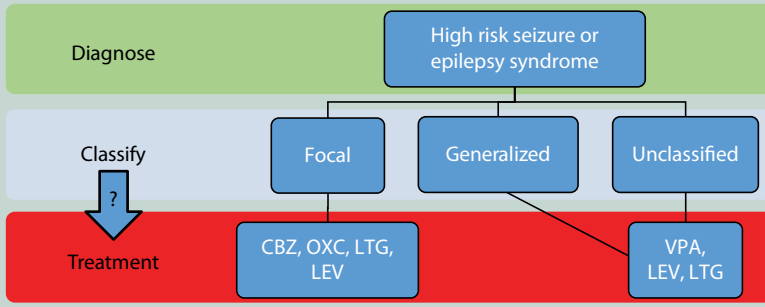

Figure 4.4 Approach to an unprovoked first seizure. CBZ-carbamazepine, OXC-oxcarbazepine, LTG-lamotrigine, LEV-levetiracetam, VAP-valproate

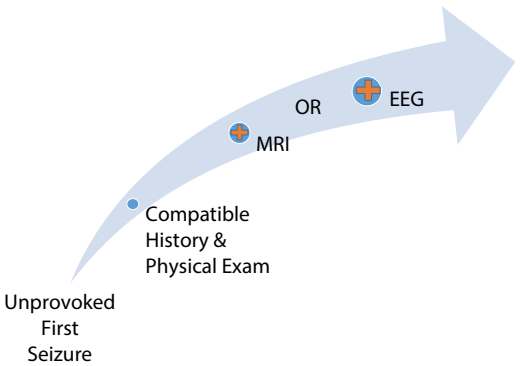

Figure 4.5 Evaluation process following a first seizure that may yield a diagnosis of epilepsy if a significant abnormality exists in the MRI or EEG

Pitfall

Fearing that no treatment after a first seizure or "missing" a seizure diagnosis will result in greater harm than treatment and alternatively not considering AEDs when the risk of a recurrent seizure meets the definition of epilepsy.

Pearl

When AEDs are begun, the goal of treating patients with epilepsy (PWE) is no seizures and no side-effects using the most appropriate AEDs as soon as possible.

Treatment with AEDs requires a personal approach following a first unprovoked seizure (Figure 4.5), as described elsewhere in this book (Perucca and Tomson, 2011).

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Chapter 5

Errors in the Diagnosis of Seizure Types and Epilepsy Syndromes

Dieter Schmidt

The most common diagnostic errors regarding the diagnosis of seizure types and epilepsy syndromes fall into two large groups. The most common error involves mistaking a non-epileptic seizure for epilepsy, or vice versa. The second most common error consists of mistaking an undoubtedly epileptic seizure or an epilepsy syndrome for another type of epilepsy or seizure. Before discussing errors, a brief overview is given about how to diagnose and classify epileptic seizures and epilepsy syndromes. Since epilepsy always starts with a first seizure, this chapter starts with a brief description about how to avoid errors in the diagnostic assessment of the first seizure (see Chapter 4 for more detail).

Diagnostic Assessment of the First Seizure

To avoid pitfalls in the diagnosis of a first epileptic seizure, a straightforward routine examination is recommended (Box 5.1).

Box 5.1 Essential diagnostic steps after a first seizure in adults (modified with permission from Krumholz et al., 2007)

History	Semiology, eye witness
Neurological/psychiatric	Routine clinical examination, blood pressure
Laboratory	Routine clinical chemistry
ECG	Routine
Head CT	Only in case of suspected trauma (bleeding, skull fractures)
Brain MRI	In all cases; using a specialized protocol for epilepsy. Abnormal MRI in an estimated 15% of cases with new-onset epilepsy
EEG	Within 24 hours after the first seizure. If first EEG is normal, consider sleep-deprived EEG within a week. Yield is epileptiform activity in 29% of cases with new-onset epilepsy

Classification of Epileptic Seizures

The clinical classification of the seizure types is constantly evolving, which in itself may be confusing and contribute to misdiagnosis, at least in some cases (Box 5.2). Seizures may be classified by their semiology (behavioral aspects) as focal (syn: partial) or generalized (Box 5.2). A very recent proposal for a pragmatic classification of epileptic seizures was made by the International League Against Epilepsy (ILAE; Fisher et al., 2017) (see below).

The 2010 Classification of Epileptic Seizures

Box 5.2 Older proposal for classification of epileptic seizures (with permission from Berg et al., 2010)

A seizure is called unclassified if it cannot be clearly placed into one of the categories shown below pending further information.

Generalized seizures

- Tonic–clonic (in any combination)
- Absence (Typical, atypical, absence with special features: myoclonic absence, eyelid myoclonia)
- Myoclonic (Myoclonic, myoclonic atonic, myoclonic tonic)
- Clonic
- Tonic
- Atonic

Focal seizures

Unknown

- Epileptic spasms

Focal (partial) seizures. Both simple (meaning that consciousness is not impaired) and complex (consciousness impaired) partial seizures resulting from a localized brain disturbance, also referred to as focal seizures, may evolve into a secondarily generalized tonic–clonic seizure (Commission 1981). The 2010 classification abandoned the above subgroups of focal seizures and recommends instead using a number of descriptors of focal seizures according to the degree of impairment of consciousness or awareness, and whether there are motor, autonomic, or dyscognitive features (Box 5.3). Whatever the classification, the predominant site of focal cerebral dysfunction determines the clinical manifestations of focal (partial) seizures. Examples are chewing movements or smacking of lips (anterior temporal lobe dysfunction), complex automatic behavior (anteromedial temporal lobe), visual hallucinations with formed images (posterior temporal lobe), bilateral tonic posture (supplementary motor cortex, frontal lobe), localized twitching of muscles without impaired consciousness in a Jacksonian seizure (motor cortex, frontal lobe), localized numbness or tingling (sensory cortex, parietal lobe), and visual hallucinations with flashes of light (occipital lobe).

Box 5.3 Unclear terminology can be a source of pitfalls. The 2017 ILAE proposal for classification of epileptic seizures includes 12 very useful rules for classifying seizures which will help to avoid confusion about what is meant by certain terms (Fisher et al., 2017 with permission)

Onset: Decide whether seizure onset is focal or generalized, using an 80% confidence level. Otherwise, onset is unknown.

Awareness: For focal seizures, decide whether to classify by degree of awareness or to omit awareness as a classifier. *Focal aware seizures* correspond to the old *simple partial seizures* and *focal impaired awareness seizures* to the old *complex partial seizures*.

Impaired awareness at any point: A focal seizure is *a focal impaired awareness seizure* if awareness is impaired at any point during the seizure.

Onset predominates: Classify a focal seizure by its first prominent sign or symptom. Do not count transient behavior arrest.

Behavior arrest: A *focal behavior arrest seizure* shows arrest of behavior as the prominent feature of the entire seizure.

Motor/non-motor: A *focal aware or impaired awareness seizure* may be further sub-classified by motor or non-motor characteristics. Alternatively, a focal seizure can be characterized by motor or non-motor characteristics, without specifying level of awareness. Example, a *focal tonic seizure*.

Optional terms: Terms such as motor or non-motor may be omitted when the seizure type is otherwise unambiguous.

Additional descriptors: After classifying seizure type based on initial manifestations, it is encouraged to add descriptions of other signs and symptoms, suggested descriptors or free text. These do not alter the seizure type. Example: *focal emotional seizure* with tonic right arm activity and hyperventilation.

Bilateral versus generalized: Use the term "bilateral" for tonic–clonic seizures that propagate to both hemispheres and "generalized" for seizures that apparently originate simultaneously in both hemispheres.

Atypical absence: Absence is atypical if it has slow onset or offset, marked changes in tone or EEG spike-waves at less than 3 per second.

Clonic versus myoclonic: Clonic refers to sustain rhythmical jerking and myoclonic to a regular unsustained jerk.

Eyelid myoclonia: *Absence with eyelid myoclonia* refers to forced upward jerking of the eyelids during an absence seizure.

Generalized seizures. Generalized seizures cause loss of consciousness (with the exception of myoclonic seizures) and motor manifestations from the onset. Such attacks often have a genetic or metabolic cause. They may be primarily generalized (bilateral cerebral cortical involvement at onset) or secondarily generalized (local cortical onset with subsequent bilateral spread). Common types of generalized seizures include absence, tonic–clonic, and myoclonic seizures (see Box 5.2).

Unclassifiable seizures. Unclassifiable seizures are not clearly focal or generalized based on their clinical or EEG manifestations (e.g., atonic, tonic and tonic–clonic seizures without noticeable focal onset). The term is also used for a seizure with both partial and generalized elements in conjunction with focal and generalized EEG findings. For example, *atonic seizures* are brief, often but not always generalized, seizures in children. They are characterized by complete loss of muscle tone and consciousness. The child falls or pitches to the ground, so that seizures pose the risk of serious trauma, particularly head injury. Atonic seizures, however, may be indistinguishable even for an experienced observer from a tonic seizure with a very rapid focal onset. In the absence of unequivocal evidence from video-EEG–EMG recordings, the categorization of atonic seizures is still a matter of debate, at least for some experts.

The 2017 ILAE Classification of Epileptic Seizures

The ILAE presented a revised operational classification of seizure types. The purpose of such a revision is to recognize that some seizure types can have either a focal or generalized onset, to allow classification when the onset is unobserved, to include some missing seizure types, and to adopt more transparent names. Because current knowledge is insufficient to form a scientifically based classification, the 2017 Classification is

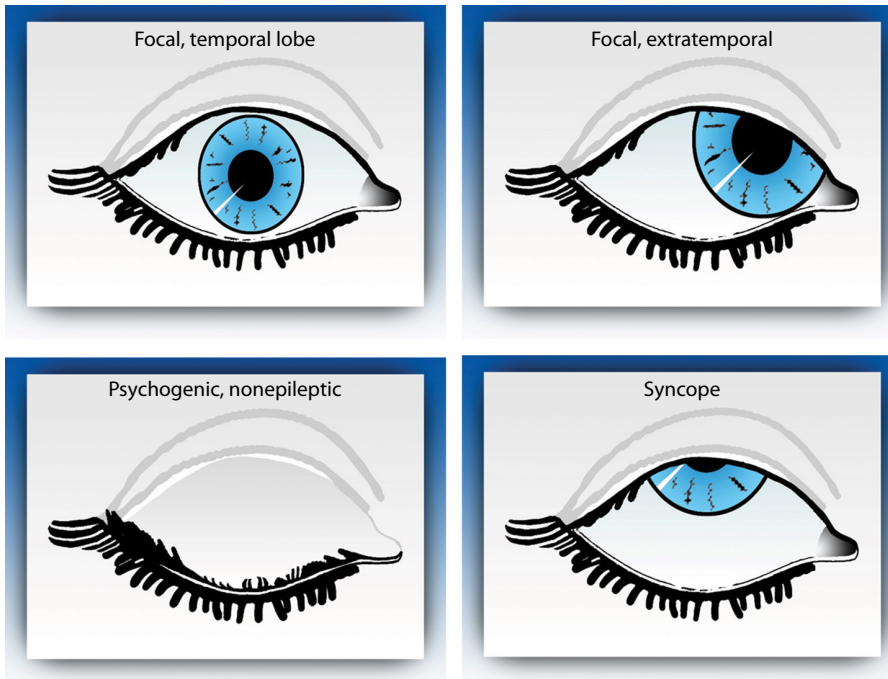

Figure 5.1 The direction of gaze and whether eyes are closed at the onset of a seizure provide valuable clues about the etiology or site of onset of the seizure. A staring gaze is characteristic of a focal seizure of mesial temporal lobe origin, and a lateral gaze is often seen with focal seizures of extra-temporal lobe origin, for example frontal lobe seizures. An upward gaze is often seen at the onset of syncope and closed eyes are typical at the onset of nonepileptic psychogenic seizures (with permission from Elger and Schmidt, 2008)

operational (practical) and based on the 1981 Classification, extended in 2010. Changes include the following: (1) "partial" becomes "focal"; (2) awareness is used as a classifier of focal seizures; (3) the terms dyscognitive, simple partial, complex partial, psychic, and secondarily generalized are eliminated; (4) new focal seizure types include automatisms, behavior arrest, hyperkinetic, autonomic, cognitive, and emotional; (5) atonic, clonic, epileptic spasms, myoclonic, and tonic seizures can be of either focal or generalized onset; (6) focal to bilateral tonic–clonic seizure replaces secondarily generalized seizure; (7) new generalized seizure types are absence with eyelid myoclonia, myoclonic absence, myoclonic–atonic, myoclonic–tonic–clonic; and (8) seizures of unknown onset may have features that can still be classified. As stated by the authors in their summary, the new classification does not represent a fundamental change, but allows greater flexibility and transparency in terminology of seizure types, which is welcome (Fisher et al., 2017a, b).

For differential diagnosis among epileptic seizures, one strategic question is whether the eyes are open or closed at the onset (Figure 5.1). A staring gaze is characteristic of temporal lobe seizures, and a lateral gaze is often seen with extra-temporal lobe seizures, for example frontal lobe seizures. An upward gaze is often seen in patients having a syncopal event and closed eyes are typical for nonepileptic psychogenic seizures, as will be discussed later.

Practical implications. For practical purposes, however, it is sufficient to be able to distinguish between generalized absence (particularly myoclonic seizures) and focal

seizures before starting AED treatment. The main reason is that some AEDs that are useful for treating focal seizures such as carbamazepine, gabapentin, oxcarbazepine, phenytoin, eslicarbazepine, and pregabalin may not work or may even exacerbate absence or myoclonic seizures (see Chapter 7 for further discussion). On the other hand, ethosuximide, which is effective for absence seizures and less often used at present than in the past, is clearly not efficacious against focal seizures. A number of AEDs are useful for both focal and generalized absence or myoclonic seizures as well as for unclassifiable seizures, including valproate, lamotrigine, levetiracetam, topiramate (only for primary GCTS), and zonisamide. Phenobarbital and primidone may be useful for treating myoclonic seizures but may worsen absence seizures. Though efficacious as add-on treatment, the role of levetiracetam and zonisamide for single drug treatment of absence and myoclonic seizures is not fully explored as of now.

Pitfalls in the Diagnostic Assessment of Unequivocally Epileptic Seizures

Clinically relevant pitfalls in the diagnosis of unequivocally epileptic seizures fall into two broad categories. One is mistaking an absence or a myoclonic seizure for a focal seizure or vice versa and the other is confusing a seizure with postictal events.

Pitfall: Underestimating the Difficulty to Accurately Count Seizures in Clinical Practice

Many treatment decisions rely on accurate seizure counts. However, postictal seizure unawareness and general forgetfulness may affect the documentation of seizure occurrence. One study assessed the accuracy of seizure counts entered into seizure diaries by patients versus video-documented seizure counts (Hoppe et al., 2007). A total of 582 focal seizures were recorded by video-electroencephalographic monitoring in 91 adult inpatients with focal epilepsies (Hoppe et al., 2007). Patients did not document 55.5% of all recorded seizures, 73.2% of complex partial seizures, 26.2% of simple partial seizures, 41.7% of secondarily generalized tonic–clonic seizures, 85.8% of all seizures during sleeping, and 32.0% of all seizures while awake. The authors concluded that patient seizure counts do not provide accurate information.

Pitfall: Estimating the Duration of Seizures

Eyewitness accounts of how long a seizure lasted range widely, even if several people observe the same seizure. This is not totally surprising because of the emotional stress that is caused by witnessing a seizure. To study how long seizures last, 579 seizures were recorded in 159 adult patients (Jenssen et al., 2006). Data were collected from a random sample of patients being evaluated with continuous video and scalp EEG. Seizure duration was defined as time from early sign of seizure (clinical or EEG) until the end of seizure on EEG. Seizures were categorized as simple partial (SPS), complex partial (CPS), secondarily generalized tonic–clonic (SGTCS), primary generalized tonic–clonic (PGTCS), and tonic (TS). SGTCS were divided into a complex partial part (SGTCS/CP) and a tonic–clonic part (SGTCS/TC). Median and longest duration of each seizure type in each individual were used. Comparisons of seizure types, first and last seizure, area of onset, and sleep state of onset were performed. The study authors found that seizures

with partial onset spreading to both hemispheres had the longest duration. SGTCS were unlikely to last more than 660 seconds, CPS more than 600 seconds, and SPS more than 240 seconds. PGTCS and TS had shorter durations, though the number of subjects with those two types was small. CPS did not differ in duration according to sleep state at onset nor side of origin (Jenssen et al., 2006).

Pitfall: Mistaking an Absence or a Myoclonic Seizure for a Focal Seizure

Absence seizures lasting 1–2 minutes may be mistaken for CPS, though an interictal EEG usually settles the differential diagnosis, as patients with absence seizures usually have typical spike-wave discharges.

Furthermore, myoclonic seizures may be mistaken for focal seizures, particularly if the myoclonic seizures, for example in patients with juvenile myoclonic epilepsy, are asymmetrical as they sometimes are. In addition, it is worthwhile to note that the EEG may not show bilateral polyspike-wave discharges in some patients with juvenile myoclonic epilepsy.

For differential diagnosis among epileptic seizures, a key question is whether the eyes are open or closed at the onset of the attack (see Figure 5.1). Closed eyes are typical for nonepileptic psychogenic seizures. In contrast, a staring gaze is characteristic of temporal lobe seizures, and a lateral gaze is often seen with extra-temporal lobe seizures, for example frontal lobe seizures. An upward gaze is often seen in patients having a syncopal event.

Pitfall: Ictal (Seizure) or Postictal Symptoms?

Although postictal symptoms can be easily distinguished from ongoing ictal activity in many patients, the distinction of postictal and ictal behavioral phenomena can be difficult even with the use of EEG, since clear-cut definitions of ictal and postictal changes are not available (Shorvon and Trinka, 2010). Clinically relevant scenarios in which the distinction can be particularly difficult include: (1) hallucinatory symptoms recorded during and after a seizure, (2) prolonged postictal confusional states, (3) prolonged postictal psychotic states, (4) epileptic and other encephalopathies, and (5) coma with or without clinical signs of nonconvulsive status epilepticus (Shorvon and Trinka, 2010).

Pitfall: Elementary Ictal Hallucinatory States: Ictal or Postictal or Both?

Affective and cognitive changes, as well as auditory, visual, and perceptual symptoms have been clearly shown to be related to seizure activity electrographically (usually with implanted EEG electrodes) in some patients and can be prolonged and have no correlate on scalp EEG. Ictal and postictal symptoms can merge and the symptomatology of each is not always clearly delineated. Many apparent postictal states are associated with ongoing ictal electrographic activity, especially in limbic structures, with fairly widespread discharges in limbic structures often accompanying complex hallucinatory and affective states.

Pitfall: Prolonged "Postictal" Confusion

Prolonged confusion, bizarre behavior, and amnesia are not uncommon following discrete tonic–clonic epileptic seizures or a cluster of seizures. These symptoms can be accompanied by ictal discharges, in these cases amounting to nonconvulsive status epilepticus (NCSE). A diagnosis of NCSE is straightforward when the EEG shows continuing or repetitive ictal bursts. The confusional state may last 8–36 hours and be associated with various motor signs and psychotic features. Consciousness is usually impaired although only slightly, and there is amnesia for the events. In some patients, however, consciousness is fully preserved and only behavioral changes are noted. The EEG shows a spectrum of epileptic patterns. It is well known that seizures recorded by depth stereo-EEG (SEEG) can occur without associated changes on scalp EEG. Shorvon and Trinka (2010) suggest that it is likely that many more "postictal" confusional states, with unremarkable scalp EEG or with diffuse slow activity, are due to underlying focal status epilepticus, though to what extent is quite unknown.

Pitfall: Recognize "Postictal" Psychosis

Sometimes, ictal activity can be associated with frankly psychotic symptoms and some cases of postictal psychosis are clearly due to ongoing ictal activity as in the following case taken from the literature (Wieser, 1980).

Case 5.1 Ictal anxiety and psychotic behavior?

The patient was anxious and tense and exhibited psychotic behaviors. The scalp EEG was "uncharacteristic" although desynchronization was noted. In contrast, the SEEG showed impressive changes with frequent focal discharges in the right hippocampal region at times replaced by continuous discharges. Spread to the lateral neocortex was associated with a dream-like state and to Heschl's gyrus with musical hallucinations. The diagnosis is electrographic status epilepticus associated with anxiety and psychotic behavior.

There are many reports of complex partial status epilepticus presenting as psychosis and cases of temporal lobe status epilepticus in which the patients exhibited a marked behavioral syndrome with stickiness, aggressivity, dysphoria, and depression. Often this occurs in the aftermath of a single or a cluster of tonic–clonic seizures (see Shorvon and Trinka, 2010 for review).

Pitfall: Ictal versus Postictal Behavior in Childhood Epileptic Encephalopathies and Other Encephalopathies

In a healthy child, the identification of the end of a seizure is usually obvious and can be confirmed by EEG. However, in children with epileptic encephalopathies, in whom cerebral development/integrity is disturbed and the interictal EEG is abnormal, the distinction between the "interictal" and "ictal" state can be difficult. In patients with Lennox–Gastaut syndrome, episodes may last hours or days during which the patient's mentation is slightly slowed, but consciousness is preserved. Additional signs may be obtundation, change in mood or affect, irritability, loss of social interaction, loss of cognitive abilities, alteration of muscle tone, ataxia, delayed motor signs, dystonia, and subtle myoclonic jerks (Shorvon and Trinka, 2010). If these signs are marked, then there

is no doubt that the patient has NCSE, but if these additional signs are mild and occur occasionally, the child might be described by caregivers as having an "off day," and the diagnosis of NCSE may not be made. The EEG in these periods, even if the additional clinical signs are marked, may not be obviously different from the EEG at other times, showing continuous and severe epileptiform changes, such as the presence of long bursts of diffuse slow (1–2.5 Hz) spike-wave activity, widespread in both hemispheres, roughly bilaterally synchronous but often asymmetrical (see Shorvon and Trinka, 2010 for review). The border between normal interictal behavior and unequivocal episodes of NCSE can be difficult to draw. In the view of Shorvon and Trinka (2010), these "off days" are likely to represent NCSE in spite of the fact that the EEG does not show this. However, definition and diagnosis are difficult where symptoms are simply a matter of degree.

In addition, other confusional states due to drug intoxication or metabolic causes may also be difficult to differentiate from ongoing seizure activity, in particular when myoclonus occurs and "epileptiform" discharges are seen in the EEG. A number of drugs have been implicated as triggers of NCSE, including tiagabine, vigabatrin, and antibiotics. Whether these cases of apparent NCSE are truly epileptic or represent some form of toxic encephalopathy is uncertain. Clear-cut epileptic seizures are uncommon, in spite of the epileptiform EEG activity. When the implicated drug is removed, the patient recovers uneventfully (Shorvon and Trinka, 2010).

Pitfall: Coma with or without NCSE. Ictal or Postictal?

The most extreme form of postictal events is represented by postictal coma, which occurs occasionally following tonic–clonic seizures. In generalized convulsive status epilepticus, the postictal coma is followed by another tonic–clonic seizure merging into an epileptic continuum with progressive electro-mechanic dissociation leading to the advanced stages of stuporous status, which has more recently been termed subtle status epilepticus. A clear separation of ictal and postictal events is impossible without EEG monitoring. These patients are usually deeply comatose and show only subtle motor phenomena, especially myoclonic jerks and eye movement abnormalities, which require immediate high-dose AED treatment. The EEG exhibits focal, lateralized or generalized epileptiform discharges (Shorvon and Trinka, 2010). The prognosis largely depends on the etiology of status in these patients and the rapid and rigorous institution of AED treatment. Coma from NCSE versus coma following a tonic–clonic seizure should be differentiated from subtle status because of its relatively benign prognosis and different etiology (Shorvon and Trinka, 2010). In most cases, only EEG monitoring is able to detect ictal epileptiform patterns and distinguish ictal from postictal states.

Take Home Message

The clinical presentation of postictal behavioral symptoms is varied and at times, the clinical differentiation from ongoing ictal activity in the aftermath of a convulsive seizure is very difficult and not always possible. The EEG is supportive of a diagnosis in many patients, but has its well-known limitation of poor spatial resolution. In some patients in deep coma, the EEG shows rhythmic or periodic patterns, resembling status epilepticus. The underlying severe brain insult often leads to death and the differentiation between ictal and postictal changes in these patients is elusive.

Pitfalls: Misdiagnosis of Nonepileptic Seizures as Epilepsy

The wrong diagnosis of epilepsy is surprisingly common. Of patients presenting with a diagnosis of epilepsy at epilepsy centers, 20–30% have been misdiagnosed (Benbadis, 2009). The wrong diagnosis of epilepsy is often perpetuated without being challenged, which may lead to diagnostic delay for several years until the misdiagnosis is corrected, if ever. A misdiagnosis of epilepsy may have serious psychosocial consequences such as loss of driving license or loss of job. In addition, unnecessary treatment with AEDs is started which carries the risk of rare but potentially life-threatening adverse effects such as hypersensitivity reactions or aplastic anemia. Furthermore, the individual is denied adequate treatment of the underlying disease, for example, for cardiac syncope, for psychogenic seizures or for REM-behavioral disorder to name the most common nonepileptic events that are mistaken for epilepsy (Box 5.4). A large group of patients have nonepileptic, non-psychogenic seizures that are not associated with any psychiatric disorder or abnormity while others have psychogenic nonepileptic seizures (PNES). This section reviews the main conditions that can mimic epileptic seizures and be misdiagnosed as epilepsy.

Box 5.4 The most common nonepileptic events mistaken for epilepsy (modified with permission from Benbadis, 2009)

1. Psychogenic nonepileptic seizures (PNES)
2. Syncope
3. Hypoglycemia
4. Panic attacks
5. Paroxysmal movement disorders
6. Sleep disorders
7. Transient ischemic attacks (TIAs)
8. Migraines
9. Transient global amnesia
10. Psychiatric disorders including hypochondria
11. Transient dizziness
12. Limb numbness, head sensations, and various mild and brief involuntary movements

Mistaking Psychogenic Seizures for Epilepsy

A number of psychiatric disorders can mimic epileptic seizures. Misdiagnosis as epilepsy is most common, but not limited to, patients with PNES.

Psychogenic Nonepileptic Seizures

PNES (syn.: psychogenic nonepileptic attacks (PNEA)) are probably the most common reason for the misdiagnosis of epilepsy in patients presenting to referral epilepsy centers and epilepsy monitoring units, with syncope possibly being more common in general neurology and internal medicine settings (see also Chapter 1 for extensive discussion). Despite the ability to make a diagnosis of epilepsy (and its main mimic PNES) with near certainty, it may take several years until the misdiagnosis is corrected. This suggests that

patients and neurologists are often inclined not to question the diagnosis of "seizures" when AEDs do not work. Misdiagnosis of PNES as epilepsy is a major clinical problem. Up to 20% of referrals for surgical treatment of apparently drug-resistant epilepsy have exclusively PNES, as have up to 50% of patients entering intensive care monitoring for presumed drug-resistant status epilepticus (Kapoor et al., 1990). PNES represent a challenge in both diagnosis and management. The cardinal features of PNES are given in Box 5.5.

Box 5.5 Cardinal features of psychogenic nonepileptic seizures (modified from Benbadis, 2009)

History	Vague and contradictory, emotional triggers of attacks, sexual abuse
Patients	Females > males, healthcare professions, familiar with the semiology of epilepsy
Semiology	Eyes closed at onset, hypotonic, wild outbursts, hypermotor, bizarre and expressive, modified by stimulation, waxing, and waning
Response to AEDs	No (not even a mild) reduction in seizure frequency, which is very unusual for epileptic seizures, may have dramatic increase in attacks

Pitfall: How to Avoid Missing Red Flags for PNES

Although most patients with PNES are young women, they also affect men and the elderly. The hallmarks of the diagnosis of PNES are the history and examination. A number of "red flags" should raise awareness for suspecting PNES (Box 5.6).

Box 5.6 When to suspect PNES

- Complete resistance of episodes to AEDs
- High frequency of seizures (several daily)
- Attacks are usually precipitated by triggers that are unusual for epilepsy (e.g., acute stress, getting upset, pain, certain movements, sounds)
- Attacks in the presence of an audience, preferably in the presence of medical personnel or in the waiting room
- Associated psychiatric diagnoses
- Semiology that is inconsistent with epileptic seizures. Eyewitness accounts of medically inexperienced lay persons are more valuable; medical personnel are prone to see the "gestalt" of epilepsy in attacks that are remotely similar to epileptic seizures. EEG-video monitoring is needed if attacks are frequent enough (see below)
- General demeanor, affect, surprisingly low level of concern ("la belle indifference"), overdramatization, and histrionic features such as give-away weakness
- The examination or history taking may induce an attack
- Failure to present with features seen in epileptic seizures including postictal confusion, incontinence, occurrence out of sleep, and significant injury, although injuries may be *reported* by patients with PNEA. In particular, lateral tongue biting is highly specific to generalized tonic–clonic seizures, while median tongue biting is characteristic of PNES (Figure 5.2)

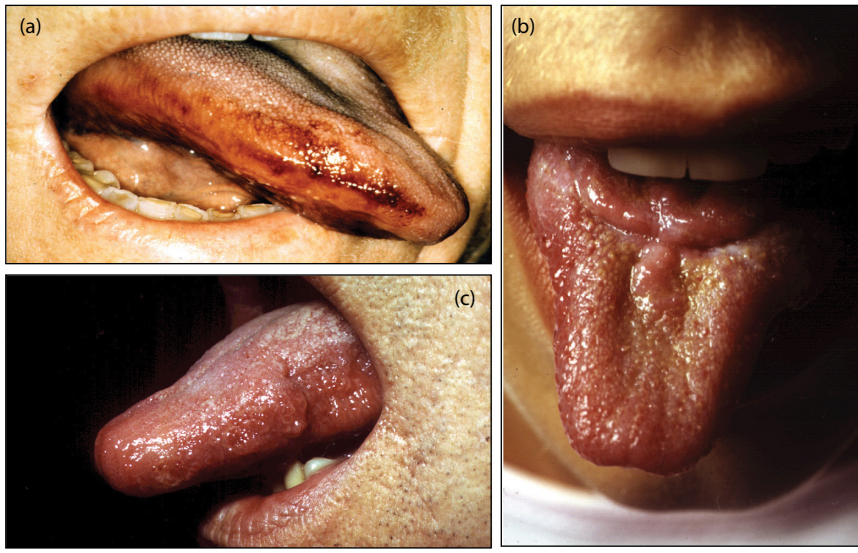

Figure 5.2 The typical tongue bite lesion in epileptic seizures is found in the lateral tongue (a, b). However, medial tongue bite lesions may be seen in patients with PNES (c)

Pitfall: How to Confirm the Diagnosis of PNES

Once PNES is suspected, a number of diagnostic steps are able to confirm the diagnosis. Box 5.7 briefly summarizes how to support the diagnosis of PNES. Although the management of PNES is beyond the scope of this chapter on differential diagnosis, a few comments are made on management of PNES at the end of this section.

Box 5.7 How to support the diagnosis of PNES

- EEG: Because of its low sensitivity, a normal routine EEG is not very helpful in making a diagnosis of PNES. Ambulatory EEG is overvalued, in particular if attacks are too infrequent. A normal ictal EEG supports the diagnosis of PNES. Video-EEG monitoring is needed. Beware of movement artifacts, which can mimic epileptiform activity.
- Prolactin. Not very useful. Determination of prolactin is too cumbersome and may be misleading as frontal lobe seizures do not increase prolactin and breast manipulation during PNES may increase prolactin.
- Video-EEG monitoring is the "gold standard" for diagnosis. With video-EEG monitoring, PNES can be diagnosed with near certainty. This is in contrast to other psychogenic symptoms, which are almost always a diagnosis of exclusion.
- PNES should be suspected in all patients with frequent seizures despite taking medications. The combined electroclinical analysis of the clinical semiology being clearly incompatible with epileptic seizures and the ictal EEG being normal allow a definitive diagnosis in the vast majority of cases. Limitations of video-EEG monitoring include the fact that ictal EEG may be negative in some partial seizures or uninterpretable if movements generate excessive artifact, as discussed below.

- Semiology of PNES include persistent eye closure at the onset of the attack (see Figure 5.1), gradual onset; side-to-side head movements; pelvic thrusting; opisthotonic posturing; stuttering; weeping; pseudosleep; discontinuous (stop and go), irregular, or asynchronous (out of phase) activity; and gradual onset or termination (Benbadis, 2009). Limitations on basing the diagnosis on semiology alone apply (see below).
- Seizure induction (see Benbadis, 2009)
- Psychopathology (see Benbadis, 2009)

Management of PNES

The role of the neurologist or epileptologist is to determine that the attacks are psychogenic, and to discuss the diagnosis of PNES and its consequences with patients and the relatives. The consequences of a firm diagnosis of PNES include the likely loss of driving license, the slow withdrawal of AEDs in patients with PNES only unless needed for mood stabilization, and referring the patient to a psychiatrist or a psychologist with experience in the management of patients with PNES and patients with epilepsy and psychiatric co-morbidity. Psychiatrists who are less experienced in the management of patients with PNES or epilepsy understandably tend to get very nervous if the patient has a seizure of whatever sort in the waiting room. This turns out to be an obstacle in clinical practice, though a psychiatrist should ideally make the exact psychiatric diagnosis and provide the treatment. However, implementing this in practice is plagued by many difficulties. Many psychiatrists are uncomfortable to see patients with PNES, in particular when either patients and relatives or both continue to believe that at least some of the attacks or all of the attacks are in fact epilepsy and insist on treatment with AEDs. The role of the neurologist should not end when the diagnosis of PNES is made. In fact, arguably the most important step in initiating treatment is effectively delivering the diagnosis to patients and families. Patients' reactions can include disbelief, denial, and anger. Another limitation is that some psychiatrists tend to be skeptical about the diagnosis of psychogenic symptoms, even when PNES have been confirmed by video-EEG monitoring (Benbadis, 2009).

Take Home Message

Any seizure with eyes closed at the onset of the attack should raise suspicion for a psychogenic seizure. PNES are identified by the typical eye closure from the beginning and the long duration of the event, typically over 5 minutes, which are both very rare in epileptic seizures or syncope. Although closed eyes are typical for PNES, observing open eyes is not a reliable indicator for epileptic seizures. In fact, an upward gaze is often seen in patients having a syncopal episode.

Mistaking Psychiatric Disorders (Other Than PNES) for Epilepsy

In addition to PNES, a number of paroxsysmal or episodic psychiatric syndromes may be mistaken for epileptic seizures. These include panic attacks, rage attacks, fugues, hallucinations, autism, and phobias (Box 5.8) (Pellock, 1993).

Box 5.8 Behavioral disorders that may be mistaken for epileptic seizures. Paroxysmal movement disorders[a] and transient global amnesia[b] may be mistaken for behavioral disorders

- Head banging
- Night terrors
- Sleepwalking
- Nightmares
- Rage
- Confusion
- Fear
- REM-behavioral disorder[c]
- Non-REM behavioral disorder[d]
- Acute psychotic symptoms
- Fugue
- Phobia
- Panic attacks
- Hallucination
- Autism
- Paroxysmal or episodic psychiatric disorders

Modified from Pellock (1993) with permission.

[a]Kinesiogenic or non-kinesiogenic paroxysmal movement disorder: May start spontaneously or be triggered by movement or exertion, dystonic appearance, no impaired awareness, variable duration, may last for months.

[b]Transient global amnesia (TGA): Attacks of several hours with loss of biographical memory, amnesia for the event, largely adequate behaviour, repetitive questions. Most patients show considerable irritation during the attack.

[c]REM-behavioral disorder: Eyes are closed, second part of the night, often every night, restlessness, periodic movements, complex actions or movement, fluctuating intensity with waxing and waning, recall of dream content immediately after awakening.

[d]Non-REM behavioral disorder: Starts in deep sleep, no recall of dream content after awakening (Elger and Berkenfeld, 2017).

Mistaking Non-psychogenic Attacks for Epilepsy

Although PNES and other psychiatric disorders are probably the most common reasons for nonepileptic seizures in children and adolescents, non-psychogenic, nonepileptic seizures play an important role, particularly in adults. Among these entities, syncope is the most common condition that can be confused with an epileptic seizure. The incidence of syncope is about 10 times higher than that of epilepsy (Kappor, 1990). Among patients presenting at emergency departments with transient loss of consciousness, 51% have had a syncopal event and only 8% have epilepsy (Kapoor et al., 1990).

Syncope Mistaken for Epilepsy

The cardinal features of syncope, which is defined as a transient loss of consciousness and postural tone, are summarized in Table 5.1.

Table 5.1 Cardinal symptoms and signs of syncope (with permission, Lempert et al., 1994)

Presyncope	Syncope
Lightheadedness	Loss of consciousness 10–120 seconds
Dizziness	Flaccidly sinking to the ground (loss of postural tone)
Nausea	Falling like a log (tonic spams, opistothotonus)
Pallor, sweating	Vocalization
Visual and auditory hallucinations	Upward gaze Clonic and myoclonic jerks (in up to 70%) Urinary incontinence (uncommon) Versive movements (in up to 70%)

Diagnosing syncope is a challenge in clinical medicine. Since patients usually do not have symptoms and signs during the medical evaluation, the diagnosis is primarily based on carefully taking the history, if possible also from bystanders (which is particularly important when the patient's recollection is incomplete). The first step is to find out whether or not the patient transiently lost consciousness (i.e., has an amnestic gap), fell or, more often, slumped to the ground (if upright), and whether the eyes were open at the onset of the attack with an upward gaze, and the occurrence of tonic or myoclonic movements. Additional features to look for in the history are predisposing factors (e.g., occurring only in upright position, drugs, sleep deprivation), prodromal sensations (stereotyped or not), oral and limb automatisms, tonic and/or clonic manifestations (bilateral – rhythmical or irregular), phonations (unintelligible sounds or vocalizations), color of the face (normal, pale, or cyanotic), loss of urine (but does not exclude syncope), postictal behavior, and rate of recovery of orientation. A lateral tongue bite must be searched for and is very suggestive of an epileptic seizure, while a median tongue bite is seen with PNES. To distinguish between epileptic seizure and circulatory syncope is often difficult, since the latter frequently shows, contrary to common belief, a stiff backward fall and short tonic and clonic motor manifestations. Conversely, epileptic falls are not always convulsive.

Syncope can be easily confused with PNES and with tonic–clonic seizures for several reasons. While an upward gaze is often seen in patients at the onset of syncope, closed eyes are typically seen at the start of PNES (see Figure 5.1). In contrast, patients with temporal lobe seizures often begin with a straightforward stare, while those with frontal seizures often have a lateral gaze at seizure onset (see Figure 5.1).

Missing the diagnosis of syncope may have serious implications. Diagnostic evaluation of syncope aims to identify patients with cardiac syncope and structural heart disease who may have a high mortality risk. ECG, echocardiography, 24-hour ECG and loop recording may be performed and cardiac pacemaker implantation needs to be considered in suitable cases.

Pitfalls in the Diagnosis of Syncope

Although less common than PNES, syncope is still often misdiagnosed as epilepsy for four main reasons:

- While syncopal episodes are generally thought to be limp motionless events, they in fact may cause tonic stiffening and falling to the ground like a log in a subgroup of patients with syncope (Lempert et al., 1994).

- Brief body jerks are frequently observed during syncope. When syncope was induced in healthy medical students (using hyperventilation, squatting, and Valsalva maneuver), 38 [90%] of 42 episodes were shown to have asymmetric irregular and mild jerking activity (Lempert et al., 1994). The myoclonus persists for a few seconds even after the patient has slumped to the ground during syncope. Motor symptoms associated with syncope are clonic- or myoclonic-like, are irregular, and last only a few seconds, in sharp distinction to the typical generalized tonic–clonic seizure with regular and persisting myoclonus for 30–90 seconds. By contrast, myoclonic epileptic seizures are very short jerks with no detectable loss of consciousness and CPS or absence seizures cause alteration of awareness but no limp slumping to the ground.
- Contrary to conventional teaching, syncope may present with brief tonic movements and oral automatisms in as many as 20% of patients. Some patients may also report scenic hallucinations and other related manifestations during syncope (Lempert et al., 1994). The lesson to be learned is that a number of symptoms that are usually thought to be hallmarks of epileptic seizures may also be seen occasionally and for a very short duration during syncope.
- The third main reason why syncope is misdiagnosed as epilepsy is that eyes are open at the onset of seizures and syncope as well. Open eyes are wrongly seen as the hallmark of epilepsy. Instead, slumping to the ground with eyes closed is the hallmark of PNES masquerading as syncope. In movies, ill-advised actors slump to the ground with eyes closed when they want to portray a syncopal episode.

Management of syncope depends entirely on its cause. The majority of syncopal episodes are benign vasovagal episodes, but the concerning etiologies are cardiac related (Aminoff et al., 1988; Zaidi et al., 2000). Even with extensive evaluations, a high proportion of syncopal episodes remain unexplained. Many patients with "unexplained syncope" (or presyncope) possibly have psychogenic pseudosyncope, and when red flags are present (identical to those for PNES), video-EEG monitoring should be performed as it can easily make the diagnosis.

Non-Psychogenic Attacks Other than Syncope Mistaken for Epilepsy

A host of non-psychogenic, nonepileptic attacks that may be mistaken for epilepsy (see Box 5.9) will be briefly discussed in this section (see Benbadis, 2009).

Hypoglycemia may resemble syncope but is – in contrast to syncope or epileptic seizures – usually preceded by hunger, weakness, tremor, malaise, and abnormal behavior. In addition, hypoglycemia usually occurs in diabetic mellitus, fasting or overuse of insulin and oral antihyperglycemics. Although some patients with epilepsy believe that at least some of their seizures are triggered by hypoglycemia, compelling evidence for the association is elusive (Benbadis, 2009).

Paroxysmal movement episodes such as acute dystonic episodes or oculogyric crisis lasting a few minutes are usually side effects of dopamine receptor blockers such as typical or atypical antipsychotics, antiemetics, and less often other drugs such as carbamazepine, lithium, and trazodone, usually occurring several days after starting the medication. Dystonic reactions can be treated successfully with anticholinergics (trihexyphenidyl, benztropine, diphenhydramine) and levodopa (Benbadis, 2009).

Box 5.9 Misdiagnosis of epilepsy in children (modified from Benbadis, 2009)

Psychiatric disorders: About 50% have psychological disorders (90% being PNES)

- Episodic dyscontrol with rage attacks, behavioral outbursts
- Panic/anxiety disorder
- Factitious disorder by proxy

Non-psychogenic conditions: The other 50% have non-psychogenic conditions, the most common include

- Nonepileptic inattention with staring spells
- Stereotyped mannerisms
- Hypnic jerks, parasomnias, arousals
- Tics
- Gastroesophageal reflux with posturing or laryngospasm
- Shuddering attacks
- Apneas

Hemifacial spasm (HFS) may resemble a facial clonic seizure. While facial motor seizures typically involve the perioral area, the unilateral facial twitching of HFS more often affects the periorbital muscles and may, in the course of the disease, spread ipsilaterally to other parts of the face. *Nonepileptic myoclonus* is defined as myoclonus that is not of cortical origin, i.e., not visible on EEG. Hiccups and hypnic jerks are examples of normal nonepileptic myoclonus, but abnormal nonepileptic myoclonus can be seen in metabolic or toxic encephalopathies and neurodegenerative diseases (Benbadis, 2009).

Parasomnias, in particular, the non-REM parasomnias (night terrors, sleepwalking, and confusional arousals) are mostly seen in children from ages 4 to 12 and can be mistaken for epilepsy since they broadly resemble seizures. Partial responsiveness and amnesia during complex motor behavior are the main symptoms. Night terrors are particularly common. They are often familial and may be worsened by sleep deprivation and intercurrent illnesses. Similarly, rhythmic movement disorder is a parasomnia typically seen at sleep transition or stage 1 sleep, which can also resemble focal seizures. One common example is head banging (jactatio capitis). Among REM sleep parasomnias, nightmares rarely present a diagnostic challenge, but REM behavior disorder may because of violent and injurious behaviors during REM sleep. The diagnosis of REM behavior disorder is usually easy as it affects older men and the description of acting out a dream is quite typical (Benbadis, 2009, see below). Occasionally, video-EEG monitoring may be necessary, provided that the episodes are frequent enough, which will usually confirm the absence of epileptiform activity and often shows that the behavior is occurring only during a certain stage of sleep. When the EEG shows no epileptiform activity, the differentiation between seizure and parasomnia can be difficult (Benbadis, 2009).

Cataplexy is part of the narcolepsy tetrad and consists of an abrupt loss of tone, which can be mistaken for atonic seizures or "drop attacks," but there are several clues leading to the diagnosis of cataplexy. The typical feature of cataplexy is that it is triggered by emotions, most commonly laughter. In addition, patients with narcolepsy usually have daytime sleepiness. Lastly, atonic seizures (if they exist at all in patients with epilepsy, which is controversial) occur typically in association with tonic seizures during sleep in patients with Lennox–Gastaut syndrome.

Hypnic jerks while falling asleep are benign myoclonic jerks that everyone experiences on occasion. They are not a risk factor for epilepsy. They occur at all ages and can lead to evaluations for seizures, especially when the jerks are unusually violent. They are easily identified on video-EEG by the fact that they occur in waking to stage 1 transition and have no EEG correlate associated with the jerks (Benbadis, 2009).

Transient ischemic attacks (TIAs) are rarely confused with epilepsy because TIAs typically involve numbness or weakness over minutes while focal seizures usually do not cause weakness and evolve over seconds. The very rare exception are ictal negative symptoms such as negative myoclonus or aphasia; however, they usually also include positive symptoms. Similarly, limb shaking TIAs exist but are very rare. The differentiation between TIA and seizures may be difficult when the seizure has not been witnessed and the patient presents with a focal deficit (e.g., Todd paralysis or aphasia), especially since both will improve over minutes. Usually, age and associated symptoms will help differentiate the two (Benbadis, 2009).

Complicated migraines and migraine auras may mimic focal (simple partial) seizures or epileptic auras. In addition, both migraine and seizure-related focal symptoms show a "march." However, migraine symptoms tend to evolve in minutes while seizure symptoms evolve in seconds. Associated symptoms (migrainous headache or more obvious seizure symptoms) will make the diagnosis easy. Basilar migraine can also cause loss of consciousness (Benbadis, 2009).

Transient global amnesia consists of dramatic episodes of anterograde amnesia that last several hours and then remits spontaneously. Patients are alert and otherwise cognitively intact but cannot form new memories, and they repeatedly ask questions about their present situation. The cause is unknown, but transient global amnesia is not thought to represent a TIA or a seizure and usually does not recur (Benbadis, 2009).

Impact seizures (Concussive convulsions) are seen in impact sports such as rugby, skiing, soccer or any other sport event in association with massive head trauma (McCrory et al., 1997). Immediately after impact, usually 2 seconds after the trauma, tonic movements and myoclonic jerks are seen which are often asymmetric and may last up to 150 seconds. The individual is quickly reoriented and MRI reveals no structural brain pathology (as seen in posttraumatic epilepsy). In addition, patients with concussive convulsions do not seem to carry an increased risk of subsequently developing epilepsy (McCrory et al., 1997).

Take Home Message

Once syncope and psychogenic or psychiatric disorders are not primary considerations, a host of nonepileptic conditions should be considered.

Misdiagnosis of Epilepsy in Children

Nonepileptic staring spells. Nonepileptic staring spells in children are common. The families report brief episodes of staring and unresponsiveness without any motor manifestations. Several features can help distinguish absence seizures from benign nonepileptic staring spells in otherwise healthy children (Benbadis, 2009). Three features suggest nonepileptic events: (1) the events do not interrupt play; (2) the events were first noticed by a professional such as a school teacher, speech therapist, occupational therapist, or physician (rather than by a parent); and (3) the child, while staring, is responsive to touch or

interruptible by other external stimuli. Other features that have been found to suggest nonepileptic or behavioral cause rather than epileptic staring include lower age and lower frequency (Benbadis, 2009). By contrast, factors that suggest an epileptic etiology include twitches of the extremities, urinary incontinence, and upward eye movement. Benign nonepileptic staring spells are particularly likely to be noticed and reported by overvigilant parents in a child who has or has had unequivocal epileptic seizures.

The differential diagnosis of seizures is broader in children than in adults with many nonepileptic but non-psychogenic conditions to be considered. Physiological events predominate in infants and young children, and psychiatric disorders become more common in later childhood and adolescence (Box 5.9).

Pitfalls: Misdiagnosis of Epilepsy in the Elderly

In most cases, a clear diagnosis of epilepsy can be rapidly made at the first presentation. In some elderly patients, however, making a firm diagnosis can be a challenge because the clinical manifestations of seizures and the differential diagnoses and causes of epilepsy can be different in the elderly compared with younger individuals (Brodie et al., 2009). Further investigations are needed to establish a firm diagnosis of epilepsy or find an alternative cause for the events, most commonly syncope or nonepileptic confusional states. The extent of misdiagnosis is, however, unclear and the true prevalence of epilepsy in older people therefore remains difficult to determine with certainty.

Potential reasons for the false diagnosis of epilepsy in older patients include poor knowledge of features that distinguish epilepsy from other disorders in this age group. In particular, epilepsy is misdiagnosed in patients with syncope and falls of any nature with or without amnesia. Poor awareness that myoclonus, tonic movements, and upward gaze frequently occur in convulsive syncope is another cause for concern (Lempert et al., 1994). Misinterpretation of interictal EEG and failure to consult specialists are also thought to be common causes for misdiagnosis of epilepsy (Brodie et al., 2009).

The challenge of making a diagnosis is further compounded by the fact that older people often live alone, which makes witness accounts more difficult to come by. Another problem is the common coexistence of cognitive impairment, which makes obtaining an accurate history from the patient more difficult and often impossible.

Several clinical clues should prompt consideration of the possibility that an older person might have epilepsy (Ramsay et al., 2004). Epilepsy should be suspected with loss or impairment of consciousness, episodic confusion, transient behavioral change, or unresponsiveness not associated with loss of postural control. Twitching, involuntary movement, or sensory disturbance of one or more limbs or the face without loss of consciousness is another clue for the diagnosis of epilepsy. Frequent falls with amnesia without any head trauma need to alert the clinician to the possibility that the patient has epilepsy. When epilepsy is thought possible after any of these events in an elderly person, obtaining a witness account and referral to a specialist are the key priorities.

Seizures in older people are sometimes atypical. Auras are less commonly reported, and symptoms and signs can be nonspecific. Automatisms can be less frequent, and postictal confusion can be more prolonged, lasting up to days (Kellinghaus et al., 2004).

Several disorders with paroxysmal loss of consciousness or other episodic neurological symptoms that can be confused with epilepsy include transient global amnesia and migraine with visual auras, although new-onset migraine in an elderly person is uncommon.

Misinterpretation of focal neurological symptoms can also lead to misdiagnosis of epilepsy for cerebrovascular events, and vice versa. However, loss of consciousness is rarely, if ever, a feature of a transient ischemic attack.

REM sleep behavior disorders (RBD) are episodes of motor agitation arising during REM sleep due to the absence of muscular atonia and are characterized by more or less purposeful gestures enacting attack or defense reactions, sometimes associated with emotional expressions of joy, laughter, or sorrow. They occur often in elderly men. RBD often herald other signs and symptoms of neurodegenerative disorders like Parkinsonian syndromes. If correctly diagnosed, they can be treated successfully. In contrast to frontal lobe seizures, the patient can be awakened during the attack and typically recalls having been in the middle of a dramatic dream. By contrast, nocturnal frontal lobe epilepsy, which also features violent ictal movements, vocalization, and automatisms, usually begins in childhood, and seizures often cluster in the first 30 minutes of (stage 2) sleep. Periodic leg movements and restless leg syndrome are other parasomnias that are common in old age that need to be considered in the differential diagnosis of nocturnal motor events. A sleep study with concurrent video-EEG monitoring might be required to distinguish epileptic seizures from sleep disorders.

How to Prevent Misdiagnosis of Nonepileptic Events as Epilepsy: No Fast and Hard Rules

Although it is nearly impossible, even for experienced physicians, to completely avoid errors in the misdiagnosis of nonepileptic events or episodes as epilepsy, it may be of interest to briefly discuss major mechanisms of how we can avoid a misdiagnosis (Box 5.10).

Box 5.10 Major pathways leading to a misdiagnosis of epilepsy (modified from Benbadis, 2009)

- Overinterpretation of EEG and MRI
- Overinterpretation of unusual but still normal behavior
- Overinterpretation of individual symptoms of nonepileptic attacks

Overinterpretation of EEG. As discussed extensively in Chapter 2, many patients (about a third) who have been misdiagnosed as having epilepsy have had previous EEGs interpreted as epileptiform that contributed to the misdiagnosis of epilepsy (Benbadis, 2009). In fact, sometimes patients are diagnosed with epilepsy and treated based solely on an EEG, despite the fact that they have no symptoms or that their symptoms are not at all suggestive of seizures. This has led many experts to suggest that EEG can in fact be bad for patients (Benbadis, 2009). There are many well-described normal variants that can be misread as epileptiform, but in reality the vast majority of over-read patterns are simple fluctuations of sharply contoured background rhythms or fragmented alpha activity (Benbadis, 2009). The reasons for the overinterpretation of EEGs are complex (Benbadis, 2009), but the fact that the diagnosis of seizures should be clinical cannot be overemphasized. In children, benign centrotemporal (rolandic) spikes on EEG are a common "red herring" because they occur frequently in asymptomatic children. In summary, most errors in diagnosis are made because the EEG is over-read as abnormal and is interpreted outside of the clinical context.

Overinterpretation of Normal Behavior as Epilepsy. Unexplained symptoms are common in everyday life and include transient dizziness, limb numbness, head sensations, and various mild and brief involuntary movements. The misinterpretation of these symptoms as seizures is more likely to occur in anxious patients (or caregivers) with hypochondriacal tendencies. It is also more common in patients who also have or have had seizures, or who have other organic conditions. Another setting is the intensive care unit, where many patients who are very ill can have nonspecific abnormal movements such as shivers, twitches, or tremors that are of concern to caregivers or intensive care unit personnel, but are neither epileptic nor psychogenic. Video-EEG recordings will usually clarify the situation, but since many of the mild nonspecific symptoms mimic SPS or auras rather than more severe seizures, the mere presence of a normal ictal scalp EEG does not *in itself* exclude seizures. However, the video, i.e., seeing the characteristics of the movements, usually does, as they are nonclonic, nontonic, and not myoclonic (Benbadis, 2009). At times, the distinction can be difficult, and when in doubt it is preferable to be conservative rather than label the episodes as seizures (see Chapter 3) (Benbadis, 2009).

Classification of Epilepsies

Classification of epilepsies is an evolving concept and each generation of academic epileptologists seems eager to generate a new classification of epilepsies which bring incremental improvement in some instances for academic epileptology but may leave some experienced practitioners wondering about the direct clinical benefit as compared to the earlier versions. The 2017 published version has generated comments and a rare position paper by the International League Against Epilepsy (ILAE) (Scheffer et al., 2017).

The 2017 ILAE classification of the epilepsies has been updated to reflect our gains in understanding that have taken place since the last ratified classification in 1989, which was updated in 2010 (Berg et al., 2010). As a critical tool for the practicing clinician, Scheffer et al. (2017) write, in their summary, any epilepsy classification must be relevant and dynamic to reflect changes in thinking, yet robust and translatable to all areas of the globe. The purpose of any classification is for diagnosis of patients, but it is also critical for epilepsy research, development of antiepileptic and surgical therapies, and to simplify communication around the world. The 2017 classification includes three categories, starting with epileptic seizure type, as defined by the new 2017 ILAE Seizure Classification (Fisher et al., 2017a, b). The next step is diagnosis of epilepsy type, including focal epilepsy, generalized epilepsy, combined generalized, and focal epilepsy for patients with generalized and focal seizures and also an unknown epilepsy group (Figure 5.3). The third category is the specific epilepsy syndrome, if possible. The new classification incorporates the need to consider etiology at each step of diagnosis, as it often carries significant treatment implications and pitfalls. Etiology is usually divided into six subgroups, selected because of their potential therapeutic consequences and again is a common source of substantial pitfalls. The six etiologic groups are structural (usually shown with an MRI), genetic, infectious, metabolic, and immune, as well as an unknown group (Figure 5.3).

New terminology is introduced in the 2017 Classification such as developmental and epileptic encephalopathy and the term benign is replaced by the terms self-limited and

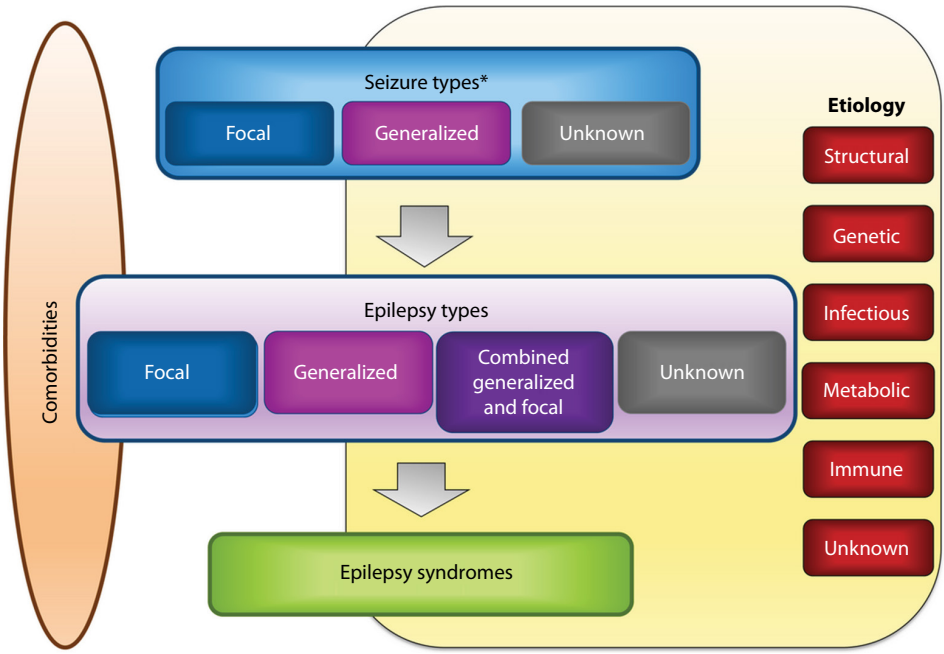

Figure 5.3 Framework for the 2017 classification of the epilepsies. *Denotes onset of seizure (with permission from Scheffer et al., 2017)

pharmacoresponsive (Scheffer et al., 2017). The term "Unknown" is used to denote where it is understood that the patient has epilepsy but the clinician is unable to determine if the epilepsy type is focal or generalized because there is insufficient information available. If the seizure type(s) are unknown, then the epilepsy type may be unknown for similar reasons, although the two may not always be concordant. For example, the patient may have had several symmetrical tonic–clonic seizures without focal features and normal EEG recordings. Thus, the onset of the seizures is unknown and the person has an unknown epilepsy type (Scheffer et al., 2017). Within the generalized epilepsies is the well-recognized and common subgroup of the Idiopathic Generalized Epilepsies (IGEs). The IGEs encompass four well-established epilepsy syndromes: Childhood Absence Epilepsy, Juvenile Absence Epilepsy, Juvenile Myoclonic Epilepsy and Generalized Tonic–Clonic Seizures Alone (formerly known as Generalized Tonic–Clonic Seizures on Awakening but modified in recognition that seizures can occur at any time of day). The intention to remove the term "idiopathic" from the nomenclature of epilepsy classification was suggested in the 2017 Classification, as its definition was "no known or suspected etiology other than possible hereditary predisposition" (Classification, 1989). The Greek term "idios" refers to self, own, and personal, and is thus meant to reflect the genetic etiology without explicitly saying so. Idiopathic may therefore be regarded as an imprecise term given our increasing recognition and discovery of the genes involved in many epilepsies, including those with monogenic (with inherited or de novo pathogenic variants) or complex (polygenic with or without environmental factors) inheritance. In addition, the word "genetic" may sometimes be wrongly interpreted as synonymous

with "inherited" (Scheffer et al., 2017). It is therefore proposed to refer to this group of syndromes as Genetic Generalized Epilepsies (GGEs), where the clinician feels there is sufficient evidence for this classification (Scheffer et al., 2017). Such evidence is drawn from clinical research of the inheritance of these syndromes in twin and family studies and does not imply that specific genetic mutations have been identified. Indeed, it is currently rarely the case that the genetic mutation(s) causing a patient's epilepsy has been determined, perhaps with the exception of the infantile onset developmental and epileptic encephalopathies (Scheffer et al., 2017).

The ILAE Classification Update of 2010

Pragmatically, and this is of major interest for anticipating pitfalls, epilepsies can be classified in at least three different ways according to the 2010 proposal, which is widely used (Box 5.11). Traditionally, epilepsy syndromes are grouped into three broad equivalent categories. The first category is generalized and focal (syn.: partial, localization-related) syndromes according to the predominant seizure type. In generalized epilepsies, the predominant type of seizures begins simultaneously in both cerebral hemispheres. Many forms of generalized epilepsy have a strong genetic component; in most, neurological function is normal. In focal epilepsies, by contrast, seizures originate in one or more defined foci, although they can spread to involve the entire brain. Most focal epilepsies are believed to be the result of one or more central nervous system insults, but in many cases the nature of the insult is never identified. Also, focal epilepsies may show a high variability in seizure types, etiology, natural history, drug response, and co-morbidity. The classification of focal epilepsies in symptomatic, idiopathic, and cryptogenic subgroups suggested in 1989 (Commission, 1989) was revised in 2010 (Berg et al., 2010). The 2010 Classification proposes the following etiological subgroups: genetic = direct effect or genetic effect, structural/metabolic = "distinct structural" or metabolic conditions, and unknown cause at present (Berg et al., 2010).

Box 5.11 Electroclinical syndromes and other epilepsies (Berg et al., 2010, with permission)

Electroclinical syndromes arranged by age at onset

- Neonatal period (Benign familial neonatal epilepsy, BFNE; Early myoclonic encephalopathy, EME; Ohtahara syndrome)
- Infancy (Epilepsy of infancy with migrating focal seizures; West syndrome, Myoclonic epilepsy in infancy, MEI; Benign infantile epilepsy, Benign familial infantile epilepsy, Dravet syndrome, Myoclonic encephalopathy in nonprogressive disorders)
- Childhood (Febrile seizures plus (FS+), which can start in infancy, Panayiotopoulos syndrome, Epilepsy with myoclonic atonic seizures; Benign epilepsy with centrotemporal spikes, BECTS; Autosomal-dominant nocturnal frontal lobe epilepsy, ADNFLE; Late onset childhood occipital epilepsy, Gastaut type; Epilepsy with myoclonic absences, Lennox–Gastaut syndrome; Epileptic encephalopathy with continuous spike-and-wave during sleep, CSWS; Landau–Kleffner syndrome, LKS; Childhood absence epilepsy, CAE)
- Adolescence, adults (Juvenile absence epilepsy, JAE; Juvenile myoclonic epilepsy, JME; Epilepsy with generalized tonic–clonic seizures alone, Progressive myoclonic

epilepsies, PME; Autosomal dominant epilepsy with auditory features, ADEAF; Other familial temporal lobe epilepsies)
- Less specific age relationship (Familial focal epilepsy with variable foci, childhood to adult; Reflex epilepsies)

Distinctive constellations
- Mesial temporal lobe epilepsy with hippocampal sclerosis, MTLE with HS
- Rasmussen syndrome
- Gelastic seizures with hypothalamic hamartoma
- Hemiconvulsion–hemiplegia–epilepsy
- Epilepsies that do not fit into any of these categories can be distinguished first on the basis of the presence or absence of a known structural or metabolic condition, presumed cause; and then on the basis of the primary mode of seizure onset, generalized vs. focal epilepsies attributed to and organized by structural–metabolic causes
- Malformations of cortical development, hemimegaloencephaly, heterotopias, etc.
- Neurocutaneous syndromes (tuberous sclerosis complex, Sturge–Weber, etc.)
- Tumor
- Infection
- Trauma
- Angioma
- Perinatal insults
- Stroke, etc.

Epilepsies of unknown cause

Conditions with epileptic seizures that are traditionally not diagnosed as a form of epilepsy per se: Benign neonatal seizures, BNS; Febrile seizures, FS.

The second category is the age at onset (incidentally, this is not necessarily the age at first presentation). The third category is the proven or presumed cause of the epilepsy syndrome, which may be considered to be unknown, genetic or due to a metabolic-structural cause. To discuss the history and the histrionics of these terms is beyond the scope of this chapter. The interested reader is referred to textbooks and the current ILAE proposal for the classification of epilepsies and epilepsy syndromes (Berg et al., 2010; Scheffer et al., 2017).

Case 5.2 What is your diagnosis?

- 23-year-old woman has a history of occasional waking myoclonus not infrequently followed by generalized tonic–clonic seizures (GTCS) beginning at age 15
- Myoclonus occurs 1–3 times per month, any time while awake
- GTCS occur 1 per 3–6 months, usually after a series of myoclonus
- No risk factors for seizures, family history negative
- Examination is normal

What is your diagnosis?

What would you expect the EEG to show?

Do you need an MRI?

Discussion

The seizure semiology with waking myoclonus and occasional GTCS, normal examination, and the onset during adolescence suggest a diagnosis of juvenile myoclonic epilepsy despite the absence of family history. Contrary to conventional wisdom, the interictal EEG may be normal in a minority of people with juvenile myoclonic epilepsy, as noted in the classical early papers of the late Dieter Janz. In most cases, however, mostly frontal, generalized rapid spike-wave discharges are seen, sometimes even in seizure remission. An MRI is clinically useful if double pathology is suspected or there is uncertainty if it could be a frontal lobe epilepsy syndrome.

Case 5.3 What is your diagnosis? (courtesy of Professor C. E. Elger, University of Bonn)

- A 52-year-old teacher presents after four mesial temporal lobe seizures in the last month. He also noted memory deficits and felt depressed in the last four weeks. What diagnostic measures would you undertake?
- MRI: normal
- EEG: questionable left temporal focal dysrhythmia
- Neuropsychology: significant verbal memory deficit
- CSF: increased cell count (9/3), significantly increased protein
- Diagnosis: Symptomatic MTLE due to limbic encephalitis

Discussion

The pitfall here is to overlook the concurrent massive memory deficit that developed with onset of the epilepsy. This is a red flag that calls for immediate attention, whether it is limbic encephalitis, as in this case, which requires emergency immune therapy, or any neurological deficit. When seizures plus neurological deficit are present at the onset of epilepsy, clinicians should view this combination as an ominous sign indicative of a severe symptomatic epilepsy that carries a high risk of immediate drug refractoriness. An urgent MRI and a lumbar puncture for CSF examination, as done in our case, are the most useful diagnostic measures.

Case 5.4 What is your diagnosis? (courtesy of Professor C. E. Elger, University of Bonn)

21-year-old female presents for evaluation of drug-resistant epilepsy since age 20. She has a normal neurological examination and a normal IQ. The current EEG shows series of generalized bilateral spike-wave discharges. The epilepsy started at age 3 with what had been diagnosed as absence seizures. At age 5 she had her first drop attack. She was seizure-free on and off medication from age 13–18 years. In the last two years, she had several generalized tonic–clonic seizures (without an aura) triggered by loss of sleep and alcohol intake. The current seizures are not controlled by adequate doses of valproate and the patient claims to have taken her medication regularly. What diagnostic steps would you take?

Discussion

The history of her generalized epilepsy is unusual in several aspects. Early onset of absence seizures and drop attacks at age 5 suggest a symptomatic generalized epilepsy. However, it is very unusual to have a normal neurological examination and normal intelligence and that she was seizure-free for several years without medication before the relapse.

The pitfall here is to overlook the history, which does not fit to any of the well-known generalized epilepsy syndromes as noted above. In an unusual case like this, two steps need to be taken. First, explore for lesional epilepsies, often of the occipital lobes; second, if the MRI is normal, ask for specialist help to look for metabolic and genetic abnormalities. In our patient, a malformation of the left occipital lobe was diagnosed. Surgery should be carefully considered in suitable cases, and especially if the patient already has a hemianopia.

Pragmatic Classification to Avoid Major Pitfalls

For pragmatic classification, genetic epilepsy syndromes must be distinguished from epilepsy having a structural-metabolic cause, and focal epilepsy must be distinguished from generalized epilepsy. In clinical practice, as in the 2010 ILAE proposal (Box 5.11), epilepsy syndromes are conveniently divided in those that begin in childhood, adolescence, middle age, and in the elderly. Pragmatically, one should be able to distinguish between epilepsy syndromes that, in general, are often self-limiting and usually are completely controlled with the first or the first few AEDs versus those with mixed outcome where it may take longer to find the right AED and finally versus catastrophic epilepsy syndromes which usually achieve seizure remission in only a few percent of patients, if ever. Furthermore, though this is not considered in any of the current epilepsy classifications, the rate of seizure recurrence after AED discontinuation in seizure-free patients differs considerably among various epilepsy syndromes. For example, the risk is moderate in genetic focal and absence syndromes of childhood-onset, but high in adolescent-onset juvenile myoclonic epilepsy and symptomatic epilepsy, particularly in those with adult onset.

Epilepsy syndromes also differ considerably in their prognosis for cognition, memory, and mortality. Although a detailed discussion is beyond the scope of this book, it may be of interest to briefly consider the risk factor for mortality of childhood-onset epilepsy (Sillanpää and Shinnar, 2010). A remote symptomatic cause of epilepsy (i.e., a major neurological impairment or insult) was associated with an increased risk of death as compared with an idiopathic or cryptogenic cause (37% vs. 12%, $P < 0.001$). Of the 60 deaths, 33 (55%) were related to epilepsy, including sudden, unexplained death in 18 subjects (30%), definite or probable seizure in 9 (15%), and accidental drowning in 6 (10%). The cumulative risk of sudden, unexplained death was 7% at 40 years overall and 12% in an analysis that was limited to subjects who were not in long-term remission and not receiving medication. Among subjects with idiopathic or cryptogenic epilepsy, there were no sudden, unexplained deaths in subjects younger than 14 years of age (Sillanpää and Shinnar, 2010). In summary, childhood-onset epilepsy was associated with a substantial risk of epilepsy-related death, including sudden, unexplained death. The risk was especially high among children who were not in remission (Sillanpää and Shinnar, 2010).

Remote symptomatic (structural-metabolic) epilepsies. The causes of sporadic or recurrent seizures are numerous, and they include acquired structural brain damage, altered metabolic states, and inborn brain malformations. Among focal epilepsies alone, the diversity of demonstrated causes is bewildering, raising the concern that the underlying mechanisms are equally diverse and that no single drug could prevent all forms of partial epilepsy. However, one feature common to the diverse focal epilepsies of humans is a latent period from the time of injury to the first seizure, which may last several months (e.g., after traumatic brain injury) to several years and even one or two decades (e.g., in cases with cortical malformations). By targeting plasticity mechanisms that underlie the enhanced seizure susceptibility that often follows brain insults such as head trauma, status epilepticus or neonatal hypoxia, antiepileptogenic drugs of the future would prevent, or reverse, progressive worsening of the epileptic process. Currently, however, only surgical resection of epileptogenic brain offers a chance to reverse epilepsy that has not fully responded to AED treatment (see below). It would seem that the greatest diagnostic pitfall is to overlook an MRI lesion that is amenable to surgical resection, with temporal lobe epilepsy as the best example.

Temporal lobe epilepsy (TLE) represents the majority of the focal symptomatic/cryptogenic epilepsies. Excellent results of epilepsy surgery in well-selected patients have encouraged a search for localizing and lateralizing signs that could assist in the identification of the best surgical candidates. Seizure types in TLE include (in terms of the 1981 classification of seizures) SPS, CPS, and secondarily generalized seizures (Classification, 1981). In TLE, seizures most often arise in the amygdalo-hippocampal region, the mesial temporal lobe – hence the most common partial epilepsy is called MTLE.

MTLE. More than 90% of patients with mesial TLE report an aura, most commonly an epigastric sensation that often has a rising character. Other autonomic symptoms, psychic symptoms, and certain sensory phenomena such as olfactory aura also occur. CPS of mesial TLE origin often involve motor arrest, oroalimentary automatisms or nonspecific extremity automatisms at onset. Ictal manifestations that have lateralizing value include dystonic posturing (contralateral), early head turning (usually ipsilateral), and aversive head turning in transition to generalization (contralateral). Well-formed ictal language favors right temporal localization. Ictal vomiting, spitting, and drinking tend to be associated with right-sided onset. The duration of CPS in TLE is generally 1–2 minutes and postictal confusion usually occurs. When postictal aphasia is noted, a left-sided lateralization is favored. Men with MTLE with hippocampal sclerosis more often have SGTCS, while women have isolated auras and lateralized EEG seizure pattern more often, suggesting that the seizure spread is more extended or occurs more frequently in men than in women.

Our current knowledge of mesial TLE is extensive, yet still insufficient to draw final conclusions on the optimal approach to its therapy. Mesial TLE has been well characterized and can usually be identified with noninvasive studies including scalp EEG and video-EEG monitoring with ictal recording, magnetic resonance imaging, single-photon-emission computed tomography, positron emission tomography, neuropsychological assessment, and historical and clinical data. Sometimes, invasive EEG is needed to confirm mesial-temporal-lobe seizure onset, which, combined with the underlying pathological abnormality (the substrate) of mesial temporal sclerosis (hippocampal neuronal loss and gliosis), defines MTLE. This disorder is the most common refractory partial epilepsy, and also the one most often treated surgically, because medical treatment fails in

75% of cases, and surgical treatment with continued drug treatment succeeds in a similar percentage.

Although a detailed review of autoimmune epilepsies is beyond the scope of this chapter (see below for further discussion), limbic encephalitis (LE) is increasingly recognized as a precipitating factor of adult onset TLE frequently associated with bilateral hippocampal damage. In a series of patients with adult-onset MTLE with a mean age of 42 years seen in a German tertiary center, the cause of the epilepsy was determined (Soeder et al., 2009). LE was diagnosed in 23 patients (27%), followed by hippocampal sclerosis (HS) in 18 patients (22%); tumors I/II in 12 cases (14%), amygdala lesions (increased volume and T2/FLAIR signal) in 11 cases (13%); and other causes in 20 (24%). MTLE was frequently bilateral in patients with LE (57%) and HS (22%). These groups also showed the poorest memory performance. Patients with amygdala lesions were the oldest (mean age 52 years); their lesions were in part immune-mediated and in part probably dysplastic. With conservative therapy, memory performance remained stable in patients with HS but improved in a proportion of patients with LE. The authors concluded that LE is a common and a previously underestimated cause of MTLE in this age group. Its prognosis is variable. Amygdala lesions, also, are in part encephalitic in nature (Soeder et al., 2009).

Lateral temporal lobe epilepsy. A lateral temporal onset is less common, and is most often suggested by an auditory aura. Somatosensory and visual auras are highly unlikely with lateral TLE, and suggest neocortical extratemporal localization. A cephalic aura is nonspecific, but is more common in frontal lobe epilepsy.

Frontal lobe epilepsy. Seizures are usually brief (30 seconds to 2 minutes), stereotypic, often nocturnal, and frequent, e.g., 3–22/night occurring during slow wave sleep. Clinical features include explosive onset, screaming, agitation, stiffening, kicking or bicycling movements of the legs, and incontinence. Nocturnal frontal lobe epilepsy (NFLE) represents a spectrum of clinical manifestations, ranging from brief, stereotyped, sudden arousals, often recurring several times per night, sometimes with a quasi-periodic pattern, to more complex dystonic–dyskinetic seizures and to prolonged "somnambulic" behavior. Episodes of increasing intensity have been labeled as paroxysmal arousal, nocturnal paroxysmal dystonia, and episodic nocturnal wandering. NFLE affects both sexes with a higher prevalence for men, is frequently cryptogenic, and displays a strong familial trait for parasomnias and epilepsy. Seizures appear more frequently between 14 and 20 years of age, but can occur at any age and tend to increase in frequency during life. Interictal and ictal EEGs are usually normal, though the use of sphenoidal leads may be helpful to elicit an abnormality. Long-term video-EEG monitoring may demonstrate frontal or bifrontal epileptic discharges. Magnetic resonance imaging is normal in many patients. The condition is often misdiagnosed as a sleep disorder or psychiatric problem. Carbamazepine taken at night is often effective at low doses, but seizures in a third of the patients are resistant to AED treatment. Epilepsy surgery is an option. Autosomal-dominant NFLE is a genetic variant of NFLE, in itself both clinically and biologically heterogeneous. NFLE should be suspected in the presence of frequent stereotyped paroxysmal nocturnal motor events arising or persisting into adulthood. Video-EEG–polysomnography is mandatory to confirm the diagnosis.

Idiopathic epilepsies (syn.: epilepsies of unknown cause.). Some people with epilepsy have recurrent unprovoked seizures for no obvious reason and without any remote neurological abnormalities. These are traditionally termed "*idiopathic epilepsies*," generalized or partial, and they are assumed to be mainly genetic in origin and have been classified

as epilepsies of unknown cause in the 2010 update of the classification of the ILAE (Berg et al., 2010). More recently, as discussed above, it has been proposed to rename IGE as genetic generalized epilepsy if adequate evidence exists for a genetic etiology (Scheffer et al., 2017).

So far, little is known about the genes that underlie epileptogenesis in IGEs. In addition to the large group of idiopathic epilepsies, more than 200 single gene disorders are known in which epilepsy is a more or less important part of the phenotype. These include syndromes as diverse as neurodegenerative disorders from the group of progressive myoclonus epilepsies, mental retardation syndromes like fragile X syndrome or Angelman's syndrome, neuronal migration disorders, and mitochondrial encephalomyopathies.

Unclassifiable epilepsies. This category encompasses a number of heterogeneous seizure syndromes which according to the 2010 update cannot be diagnosed as either partial or generalized, partly because of incomplete data (e.g., tonic and atonic or astatic seizures) or failure to clinically observe the onset of seizures (e.g., tonic–clonic seizures during sleep). In addition, a number of syndromes may be unclassifiable because both partial and generalized seizures may occur (e.g., GEFS+, epileptic encephalopathies, progressive myoclonus epilepsies). In addition, epilepsies can be classified according to their time of onset in life, as discussed above.

Epilepsies starting in childhood. The childhood-onset epilepsies have been traditionally (although seen as controversial by some (Berg et al., 2010)) divided into benign, intermediate, and catastrophic based on their impact on childhood development. The clearest benign epilepsy is benign Rolandic epilepsy, which often does not require medication treatment. Although seizures and EEG features usually resolve completely at puberty, neuro-psychological deficits and behavior problems are seen in some children. The definition of benign occipital epilepsy including Panayiotopoulos syndrome is still often vague. In the intermediate category, childhood absence epilepsy often has associated learning disorders and a poor social outcome. About 50% of children with cryptogenic partial seizures have a very benign course, even though their epilepsy syndrome is not well defined. Generalized epilepsy with febrile seizures plus (GEFS+) has a dominant inheritance with a defined defect in cerebral sodium channels, but varies considerably in severity within affected members of the same kindred. The catastrophic epilepsies in childhood all have an inconsistent response to AED treatment and include continuous spike-wave in slow sleep (with variable severity), Landau–Kleffner syndrome (with a confusing overlap with autistic regression), the Lennox–Gastaut syndrome (with broad defining features), and myoclonic-astatic epilepsy (with important overlaps with Lennox–Gastaut syndrome). Although many of the epilepsies that begin in childhood are benign, some interfere seriously with cognitive and social development. Intractable childhood epilepsy may have a negative effect on the mother's mood in many families. Childhood behavior problems are a strong predictor of maternal depressive symptoms.

Epilepsies starting during adolescence. Epilepsy is the commonest serious neurological condition to affect adolescents. Specific epilepsy syndromes begin during adolescence and create a significant neurological burden. Idiopathic generalized epilepsies are the most frequent group with adolescent-onset juvenile myoclonic epilepsy (JME) the most common form. This contrasts with a variety of progressive myoclonic epilepsies that also are first seen in adolescence and have a genetic origin and specific treatments. Finally, although MTLE associated with hippocampal sclerosis may have its origin in childhood,

often the child does not come to surgical evaluation until adolescence or young adulthood. The characteristic clinical history, seizure semiology, and magnetic resonance imaging findings allow the diagnosis. Applying these same criteria to children and adolescents reveals that hippocampal sclerosis is the most common lesion responsible for their intractable temporal lobe epilepsy.

Adolescence is a time of dramatic change in growth, as well as hormonal, psychological, and social aspects. Seizure frequency, teenage pregnancy, driving, and alcohol and drug use often become major issues during the adolescent years. Furthermore, adolescents often have difficulty accepting the chronicity of epilepsy and complying with medications, which can result in physical injury and perceived or real obstacles to employment. There may be an effect of menarche on seizures (see Chapter 12), as well as a relationship of seizures to the menstrual cycle. Epilepsy affects the adolescent's social life, peer interactions, educational and career decisions, driving ability, and reproductive life. Communication with the adolescent regarding the effect epilepsy can have on these issues is crucial for proper management of the patient. Depression in children and adolescents with epilepsy is a common but often unrecognized disorder. Nonepileptic seizures are frequently encountered in adolescents. Adolescents are reluctant to raise personal or sensitive issues or to ask questions that reveal poor adherence. A perceived lack of interest in the wider impacts of having a chronic condition on day-to-day life may be a barrier to adolescents discussing difficulties at school and socio-emotional problems.

Epilepsies starting in the elderly. Longer life expectancy in the general population and a second peak of incidence of epilepsy beyond age 60 is seen exceeding an incidence of 1 per 1,000 at age 70 and above. Focal seizures in the elderly may be associated more frequently with Todd's paresis, and postictal confusion may last longer than 24 hours and be complicated by prolonged aphasia. De-novo absence status may occur, particularly in the elderly with substance abuse. Status epilepticus has a higher mortality in the elderly. The seizure-related risk of injury including fractures is higher in the elderly (Elger and Schmidt, 2008).

Recommendation

Pragmatically, a diagnosis of an epilepsy syndrome is advisable, if possible, because the seizure and mortality prognosis vary for different syndromes. In any case, the diagnosis of an idiopathic generalized epilepsy syndrome should be excluded before starting treatment with an AED that is only useful for partial seizures. If in doubt about the epilepsy syndrome, and treatment is urgent, an AED which works against partial and absence or myoclonic seizures should be considered. Epilepsies that do not fit into any special category can be distinguished first on the basis of the presence or absence of a known structural or metabolic condition presumed as the cause; and then on the basis of the primary mode of seizure onset, generalized vs. focal.

Clinically Relevant Pitfalls in the Diagnosis of Epilepsies

The most clinically relevant pitfalls in the diagnosis of epilepsies fall in two broad categories. One, missing epilepsies that urgently require specific treatment of the underlying cause (e.g., immunological, anti-infectious, vascular or surgical) in addition to AEDs. Two, mistaking other disorders for epilepsy (e.g., stroke, nonepileptic myoclonus), as discussed above. Clues for a possible remote symptomatic etiology with a structural/metabolic cause are listed in Box 5.12. A number of investigations are useful to determine the specific remote etiology (Box 5.13).

Box 5.12 When to suspect remote symptomatic etiology with a structural/metabolic cause (modified from Elger and Schmidt, 2008, with permission)

- Onset at 18 years or older
- Focal seizures
- New-onset neurological, cognitive, or psychiatric complaint or deficit
- Other new-onset complaint or deficit (e.g., fever, skin problem)
- New type of seizures

Box 5.13 How to determine a structural/metabolic cause (modified from Elger and Schmidt, 2008, with permission)

- MRI – obligatory in all cases
- EEG – obligatory for presurgical evaluation, but most useful when used early
- CAT – only for trauma or hemorrhage
- Other – prolactin, vitamin B6

Pitfall: Missing the Diagnosis of Autoimmune Epilepsy

Although a detailed review of autoimmune epilepsies is beyond the scope of this chapter, LE is increasingly recognized as a precipitating factor of adult onset TLE and frequently associated with bilateral hippocampal damage, as discussed above (Soeder et al., 2009). LE is a common and a previously underestimated cause of MTLE in this age group. Its prognosis is variable. Amygdala lesions, also, are in part encephalitic in nature (Soeder et al., 2009). Since its discovery in 2007, the encephalitis associated with antibodies against the *N*-methyl-D-aspartate receptor (NMDAR) has entered the mainstream of neurology and other disciplines (Dalmau et al., 2011). Most patients with anti-NMDAR encephalitis develop a multistage illness that progresses from psychosis, memory deficits, seizures, and language disintegration into a state of unresponsiveness with catatonic features often associated with abnormal movements, and autonomic and breathing instability. The disorder predominantly affects children and young adults, occurs with or without an associated tumor, and responds to treatment, but can relapse. The presence of a tumor (usually an ovarian teratoma) is dependent on age, sex, and ethnicity, being more frequent in women older than 18 years, and slightly more predominant in black women than white women. Patients treated with tumor resection and immunotherapy (corticosteroids, intravenous immunoglobulin, or plasma exchange) respond faster to treatment and less frequently need second-line immunotherapy (cyclophosphamide or rituximab, or both) than do patients without a tumor who receive similar initial immunotherapy. More than 75% of all patients have substantial recovery that occurs in inverse order of symptom development and which is associated with a decline of antibody titers. Patients' antibodies cause a titer-dependent, reversible decrease of synaptic NMDAR (Dalmau et al., 2011).

Recommendation

Rapid recognition of remote symptomatic etiology is important for all patients as it may require specific etiology-dependent treatment in addition to AEDs. A special concern is the early recognition of autoimmune epilepsies and epilepsies that are amenable to epilepsy surgery.

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Chapter 6

When to Start Treatment?

Dieter Schmidt

Epilepsy is one of the most common neurological disorders, and antiepileptic drugs (AEDs), which are mostly antiseizure drugs, are the mainstay of epilepsy treatment. Although there is an abundance of short-term, regulatory, randomized, controlled trials to assess the efficacy and safety of individual investigational AEDs prior to marketing, surprisingly few trials have addressed the management of epilepsy with marketed AEDs in clinical practice. Good management of epilepsy requires knowing when to start AEDs, what AED to choose, how to monitor AED treatment, and when to stop AEDs. This chapter provides a brief critical overview on the strength of the evidence for starting treatment.

The decision to start treatment requires a careful assessment of the risk–benefit for the individual patient sitting in front of the physician (Table 6.1).

Broadly, three scenarios can be envisioned: one, patients who do not need AEDs; two, patients in whom starting AEDs is optional; and, three, patients for whom AEDs are strongly recommended. In this chapter, we will briefly discuss the evidence and the pitfalls for each of these three clinical scenarios. Before making a decision whether a patient needs treatment or not, it may be useful to consider what a physician needs to know about the patient to render an informed opinion about starting AED treatment.

What a Physician Should Know before Deciding to Start Treatment

The decision is based on the individual risk of seizure recurrence and the patient's informed consent. Where possible, the decision as to when to start AED treatment should be informed by the results of randomized controlled trials. The number of past seizures primarily determines the risk of seizure recurrence in the next 6–12 months. In this chapter, the consequences of immediate versus delayed or no AED treatment will be discussed for the following clinical scenarios: first seizure patients and those presenting with two or more seizures.

Table 6.1 The pros and cons of starting AED treatment? Denotes areas of uncertainty

Pro	Cons
– Reduces risk of seizure recurrence	– No drug side-effects
– Reduces stigma?	– No cost for drugs
– Reduces injury risk of injury?	– Early treatment does not affect long-term seizure outcome
– Reduces mortality risk?	

Scenario 1: The Decision Not to Start AEDs

Drug treatment is usually not indicated if the diagnosis of epilepsy is uncertain, when provoked seizures occur which can be prevented without drugs, and last but not least, if the informed patient or caregiver does not want drug treatment (Box 6.1).

Box 6.1 What a physician should know before deciding to start treatment

Single seizure?
Two or three seizures in the last 12 months?
Four or more seizures in the last 12 months?
Neurological disorder or deficit?
Abnormal EEG?
Type of seizure(s)?
Provoked seizure(s) only?
Patient wishes to be treated?

Any discussion whether to start drug treatment is incomplete without including recommendations for non-pharmacological measures. Avoidance of seizure triggers plays an important supporting role for seizure regulation in individually susceptible patients, mostly adolescents with juvenile genetic (idiopathic) generalized epilepsies. Disturbances of their sleep-wake cycle, especially reduction of sleep, may provoke seizures the next morning. Following a regular sleep schedule is helpful; pragmatically, sleep onset should not vary by more than two hours from day to day. Sleep reduction often combined with partying and substance abuse or stress is a common precipitating factor in adolescents and adults with a first epileptic (mostly generalized tonic–clonic (GTC)) seizure. In some of these patients, regular sleep and a less stressful lifestyle may be enough to prevent further seizures. In addition, AEDs may not be able to achieve seizure control if the lifestyle is not changed. In altogether rare reflex epilepsies, specific precipitants of seizures may be the targets for non-pharmacological intervention. For example, most patients with primary reading epilepsy begin to have, with prolonged reading, perioral reflex myoclonias, which enable them to stop reading and thus to avoid a GTC seizure. In photosensitive patients, seizures are often precipitated by television. These can be avoided by viewing the television from a distance and using a remote control, small screens in a well-lit room, and preferably with a 100-Hz line shift. Environmental flicker stimulation often comes unexpectedly, and it is advisable that the patients always wear sunglasses in brightly lit surroundings. Polarized glasses seem to be more protective than plain sunglasses. If the patient has only photically induced seizures, treatment by specific prevention alone may be sufficient, but if spontaneous seizures also occur, drugs are usually needed in addition. Some patients with partial seizures with an extended aura claim that they know how to prevent seizure spread by various nonspecific measures such as relaxation, concentration, or a combination of both. It is often difficult, however, to support such claims.

As AEDs are able to symptomatically block further seizures and reduce the severity of seizures, treatment is generally recommended in all persons with a high risk of seizure recurrence that is considered unacceptable by the patient. High-risk features for seizure recurrence include symptomatic epilepsy with GTC seizures or focal seizures, and idiopathic generalized epilepsies. Any discussion of starting treatment needs to mention the efficacy limitations of current AED treatment.

Pitfall: Failure to Mention the Limitations of Current Treatment

Current AEDs block seizures from occurring, if they work, but are not able to improve the structure or the function of the underlying brain abnormality(ies). This is why as many as 50–70% of patients (in particular adults and those with symptomatic epilepsy) who have become seizure-free on drugs may have seizure recurrences when treatment is stopped (see Chapter 11). This also explains why early treatment, for example after a first GTC, lowers the rate of seizure recurrence by about 50% but has not been shown to improve the long-term prognosis or lower mortality or the risk of injury. Even when AEDs work, only about 50% of patients become seizure-free with their first-ever AED (Kwan and Brodie, 2001). Although there is no doubt that AEDs are beneficial because they are able to substantially reduce the risk of further seizures, unfortunately as many as one in three patients with new-onset epilepsy continues to have seizures despite AED treatment (Kwan and Brodie, 2000; Brodie et al. 2010). The take-home message is therefore not to over-state the efficacy of drug treatment during efforts to convince patients or relatives to start drug treatment.

Pitfall: Failure to Recognize that Not All Patients Need AEDs

In addition, a number of patients with good prognosis (e.g., self-limiting uncomplicated febrile seizures, often benign idiopathic partial epilepsies) may not even need drug treatment (see prognosis). In this context, adverse events of AEDs including CNS toxicity and hypersensitivity reactions have to be balanced against the potential benefit (Schmidt, 2009). Further, AEDs have costs and taking medication is perceived as stigmatizing by some patients. Psychosocial consequences in case of another seizure (e.g., loss of driver's license or seizure in a social setting) may favor drug treatment in some patients. Finally, drug treatment is usually not indicated if provoked seizures occur which can be prevented without drugs, as discussed later (Box 6.2).

Box 6.2 General treatment principles

Treatment aims primarily to control seizures, and a return to health with a minimum of adverse events. Additional goals are social reintegration and preventing or reversing associated psychiatric complications.

The underlying causative disorder, if amenable, and comorbidity need to be treated as well.

A normal life with social activities should be encouraged including challenges that healthy persons face.

A seizure-provoking lifestyle should be avoided; in particular, excessive alcohol intake and sleep deprivation should be minimized. Cocaine and several other illicit drugs can trigger seizures.

In case of fever, continue drug treatment.

Patients should self-monitor drug compliance with a tablet dispenser.

Family members must be taught a commonsense attitude toward the patient. Overprotection should be replaced with sympathetic support that lessens feelings of inferiority and self-consciousness and other emotional handicaps.

Exercise is recommended; even such sports as swimming can be permitted in seizure-free patients with close supervision.

No single drug controls all types of seizures, and different drugs are required for different patients. Patients rarely require several drugs.

If seizures cannot be controlled with the first two drugs, however, surgical options including resection and direct or indirect brain stimulation should be considered. Complacency should be avoided.

Recommendation

Drug treatment is usually not indicated if the diagnosis of epilepsy is uncertain, when provoked seizures occur which can be prevented without drugs, and last but not least, if the informed patient or caregiver does not want drug treatment.

Scenario 2: The Decision to Start AEDs in Patients Presenting with a Single Seizure

The rationale for starting treatment in a patient presenting after a single seizure is to reduce their risk of seizure recurrence and improve their well-being compared to no treatment or deferred treatment. In this section, we discuss the effects of AED treatment versus no treatment on time to recurrence, long-term seizure outcome, and overall quality of life in patients with a single seizure.

The decision to start AED treatment in a patient with confirmed epilepsy or unquestionable epileptic seizures is less straightforward than it may seem. As many, if not most, patients (and relatives or friends) are understandably concerned when they learn that they have experienced their first seizure (see Chapter 4). To alleviate undue concerns about epilepsy, it may be worthwhile to start a discussion on when to start treatment by assuring patients and relatives or caregivers that new-onset epilepsy can be well-treated in the large majority of cases by starting AED treatment, if needed at all.

The first step in any discussion whether to start treatment is to discuss the general principles of AED treatment (Box 6.3). In addition, analyze whether drug treatment is needed at all or whether avoiding seizure precipitants alone is sufficient for seizure-freedom. Any reasonable discussion of starting drug treatment requires a careful risk–benefit assessment of the risk of further seizures and side effects while taking AEDs versus no AEDs for the individual patient.

Box 6.3 Checklist for starting treatment

- Does the patient wish to be treated, after informed consent?
- Do you know the AED you plan to start treatment with? (Test: Do you know the contraindications of the drug you wish to prescribe?)
- Is the risk of seizure recurrence low, medium, or high?
- Can seizures be avoided without drug treatment?
- Have you provided a written schedule for dosing and drug titration?
- Don't promise too much. Discuss the limitations of AED treatment.

Case 6.1 What Would You Do?

A 78-year-old man awoke with left arm > leg weakness. One hour after arrival at the hospital, he had a focal motor seizure starting in the left arm, spreading to the face and leg. The seizure lasted 2 minutes, and the patient had no loss of awareness. Past history included arterial hypertension, hyperlipidemia, and coronary artery disease for which he received medications. There was no history of neurological illness.

Examination showed dysarthria, mild–moderate left sided weakness primarily affecting the arm and face, and mild left-sided sensory impairment. CT scan showed infarction consistent with occlusion of a branch of the right middle cerebral artery. Routine laboratory tests (CBC, electrolytes, liver and kidney function) were normal.

Questions:
Should he be treated with AED therapy?
If so, which agent and for how long?
Which drugs are undesirable?

Discussion

The pitfall here is to overlook the fact that the decision to treat or not to treat relies on the estimate of what will happen in the future. Whether this was a single seizure that will reoccur or whether this was the start of post-stroke epilepsy that needs to be treated cannot be known with confidence. Our ability to predict epilepsy in general is limited although recent ICU data suggest that EEG monitoring may give us clues about the likelihood of developing epilepsy based on EEG findings. Given these uncertainties, many would suggest starting emergency intravenous AED treatment with phenytoin or lacosamide, for example, and continuing oral therapy for a limited time of several weeks. If seizures recur, a longer course of oral treatment may then be the best option.

Case 6.2 What Would You Do?

The mother of a 14-year-old boy wakes up at 7 am because she hears unusual noise coming from her son's room. When she enters the room, she sees his body is shaking and thrashing, and that his eyes are open. His lips are blue. He does not respond when she calls his name. After 2 minutes, the movements gradually end. The mother, who is a nurse, recognizes this event as a GTC seizure. Her son, who never had a seizure before, is examined. His neurological exam is normal as is his brain MRI. The EEG is normal and does not show any epileptiform abnormality.

Discussion: Would You Recommend to Start AED Treatment? Why?

The pitfall here is to overlook that in such a low-risk case, there is no right or wrong answer. The decision to start an AED depends entirely on the preference of the mother and her son. Often, anxiety runs high and an AED is started without a clear medical need as in our case. Treatment is optional in low-risk patients mainly because there is no evidence that delayed treatment in case of a second seizure is detrimental for long-term seizure control.

Are You Aware How Often Seizures Recur after a Single Seizure?

Berg and Shinnar (1994) reviewed 13 observational studies assessing outcome following a first seizure, and found that the overall seizure recurrence risk after a first seizure was 46% [95% confidence interval (CI) 44–49%]. For the subset of 5 prospective studies, the recurrence risk was 40% [95% CI 37–43%]. The 2-year recurrence risk was 42% [95% CI 39–44%] across all studies and 36% [95% CI 32–39%] for the subset of prospective studies. As will be discussed in more detail below, independent risk factors associated with a higher recurrence risk included partial seizures, an abnormal EEG study, and abnormal neurological examination (e.g., learning difficulty, neurological signs).

Among patients with a single seizure, only about 25% will have a recurrence within 2 years in the absence of factors that predict a high probability of recurrence (Berg, 2008). Even in patients with one or more risk factors, the recurrence rate at 2 years is not above 40%. Given that for the majority of patients presenting with a single seizure, the risk of a recurrence within 2 years is less than 50%, and considering the adverse effects of AEDs,

drug treatment is not generally recommended after a single seizure for patients with low risk of recurrence. The exception is of course patients who wish to be treated. These patients may justifiably point out that the lower risk estimate of about 30% (as suggested by the lower CI in the review by Berg and Shinnar (1994)) is unacceptable for them, given the potential social and medical consequences if they have a recurrence. In fact, many patients are concerned that they may not be allowed to drive a car if a second seizure occurs or fear a loss of job or see another seizure as an unacceptable challenge for their public life.

Randomized controlled trials showed that treatment reduces the risk of seizure recurrence on average by about 50% (range: 30–60%) and that those treated earlier have a better short-term seizure outcome versus those with no treatment or deferred treatment (see Berg, 2008). Here, we will only discuss the largest trial (Marson et al., 2005). For patients with a single seizure, the risk of relapse at 2 years of treatment was 32% for immediate treatment and 39% for deferred treatment. However, at 5 years, the risk was similar (42% for immediate and 51% for deferred treatment). The treatment effect between early and deferred treatment for 2-year remission was 12% at 2 years, 2% at 5 years, and 1% at 8 years (Marson et al., 2005). Regression analysis showed that the number of seizures before randomization, an abnormal EEG, and signs of a neurological or cognitive deficit increased the risk of seizure recurrence (Kim et al., 2006). Low-risk patients were those with a single seizure, no neurological deficit, and a normal EEG. Medium risk was seen in those with either 2–3 seizures or neurological signs or an abnormal EEG. All patients who had more seizures or more than one additional factor belonged to the high-risk group.

Case 6.3 What Would You Do? (Case History Courtesy of Professor Christian Elger, University of Bonn, Germany)

At age 50, the patient, a locally well-known businessman, had his first seizure. The tonic–clonic seizure was unprovoked and was preceded by an aura. At the time of the first seizure, neurological examination was normal. An MRI was interpreted as showing no abnormality. The risk of recurrence was considered as low and AED treatment was not started. The patient was instructed that he could not drive a car for three months, in accordance with German law. Three months later, the patient crashed with his car against a house wall during a second tonic–clonic seizure and suffered hip fractures.

Pitfall 1: The initial MRI was misread. A re-reading of the MRI showed left hippocampal abnormalities consistent with a focal cortical dysplasia (see Chapter 3).

Pitfall 2: AED treatment was not started after the first seizure because the MRI was mistakenly read as normal and the risk of seizure recurrence was considered to be low when in fact it was high – given the symptomatic etiology of the first seizure.

The finding that the likelihood of being seizure-free at 3–5 years after a first or second seizure was similar whether treatment was started immediately or was deferred initially and started only if a further seizure occurred (Marson et al., 2005) is clinically important for two reasons: one, it shows for clinical practice that deferring treatment does not worsen prospects for becoming seizure-free, at least for those with low to medium risk for recurrence (Kim et al., 2006); and, two, it provides clues for clinical science that AEDs, even if they are actively blocking seizures, are not able to improve the course of the underlying disease, i.e., epilepsy. This finding is also in agreement with long-term studies of the natural history of treated epilepsy showing that early seizure remission may be followed

Table 6.2 How to establish the individual risk of recurrence

Clinical features	Prognostic index
Single seizure	0
Two or three seizures	1
Four or more seizures	2
Add if present	
Neurological disorder or deficit	1
Abnormal EEG	1
Risk classification group	Final score
Low risk	0
Medium risk	1
High risk	2–4

Based on the results of the Multicentre Study of Early Epilepsy and Single Seizures (MESS) trial, a prognostic assessment of the risk of seizure recurrence has been proposed (Marson, 2008).

by late relapse and thus does not guarantee permanent seizure-freedom (Sillanpää and Schmidt, 2006).

The most reliable method to assess the influence of AEDs upon recurrence rates and other outcomes is the randomized controlled trial. A number of randomized controlled trials have compared AED treatment with delayed treatment in patients presenting with a first seizure (see review by Marson, 2008). The largest trial is the Multicentre Study of Early Epilepsy and Single Seizures (MESS) (Marson et al., 2005), summarized above. Regression modeling showed that the number of seizures before randomization, an abnormal EEG, and the presence of a neurological abnormality (learning disability or neurologic signs) increased the risk of seizure recurrence (Kim et al., 2006). This allowed the creation of a prognosis index to stratify patients into groups with low, medium, or high risk of seizure recurrence as summarized in Table 6.2. The recurrence risks estimated for these groups are given below. Another concern that may have prompted some patients to start treatment early after a first seizure or few seizures is that delayed treatment could be associated with poorer long-term outcome of epilepsy.

Is Failure to Start Early Treatment Associated with Poorer Long-Term Epilepsy Outcome?

Given that 30% of patients with new-onset epilepsy are eventually determined to have drug-refractory epilepsy (Kwan and Brodie, 2000), it is important to find out whether the early use of AEDs might reduce the risk of drug-resistant epilepsy (Marson 2008). In MESS, patients randomized to deferred treatment were allowed to start treatment once the clinician and patient agreed that this was required, primarily following further seizures. Consequently, comparison was possible between immediate treatment and deferred treatment. Results for the entire cohort recruited to the MESS trial show that at 2 years, 64% of the immediate-treatment group and 52% of the deferred-treatment group achieved a 2-year remission in the first 2 years after treatment was commenced; whereas at 5 years, 92% of patients allocated to immediate treatment had achieved a

2-year remission compared with 90% in the deferred-treatment group. The difference between the two groups at 5 years was only 2% [95% CI 1.2–6.1]. The confidence interval around this estimate is narrow and excludes an important effect of treatment. At 8 years, the difference between the two groups was 1% [95% CI 2.5–3.9], which again excludes an important treatment effect. Therefore, in keeping with results from the First Seizure Study Trial Group (FIR.S.T.), MESS confirms that patients starting treatment following a single or few seizures will enter a 2-year remission sooner than those allocated deferred treatment, but treatment has no influence upon the proportion of patients entering a 2-year period of remission after 5 years or longer of follow-up.

Recommendation

For patients presenting with their first seizure, randomized controlled trials have demonstrated that compared to no or delayed treatment, AEDs reduce the risk of a second seizure, but do not alter longer-term seizure (FIR.S.T. Group, 1993) outcomes. A prognostic model has been developed to identify patients at low, medium, and high risk of recurrence to further inform treatment decisions. Opinion remains divided about treating patients who have had only a single seizure, particularly in those with a low to medium risk of recurrence. However, even in those with a low risk who prefer treatment, treatment can be justified as it is for almost all with a much higher risk of recurrence, for example those with two or more seizures within the preceding 6–12 months, and even those with the highest risk of recurrence after the first seizure. We need adequate, comparative double-blind trials for starting treatment with new versus old AEDs.

Scenario 3: The Decision to Start AEDs in Patients Presenting after Two or More Seizures

The rationale for starting treatment in this group is also to have a lower risk of seizure recurrence and better well-being compared to no treatment or deferred treatment. In this section, we discuss the effects of AED treatment versus no treatment on time to recurrence and long-term seizure outcome as well as quality of life in patients with several seizures prior to treatment.

Patients presenting with two or three seizures or even four or more seizures have a higher risk of seizure recurrence, which is further increased in those with neurological signs or an abnormal EEG (Kim et al., 2006). High-risk patients, as defined above (Kim et al., 2006), have a higher 5-year recurrence risk (73% vs. 50%) versus those with early treatment (Table 6.2). However, the risk following a second seizure has not been examined in a prospective population-based study of untreated patients (Marson et al., 2007). The recurrence risk after two or more seizures has not been assessed in randomized controlled trials comparing patients on AEDs with those who preferred not to take AEDs. The explanation for this lack of relevant evidence is self-evident. Prescribing AEDs became accepted practice for patients with epilepsy long before the natural history of untreated epilepsy was known. To deny a control group a treatment that is believed to be effective is unethical. What is then the best available evidence that supports the current practice?

The best available evidence for the risk of seizure recurrence comes from clinical observations by Hauser et al. (1998) who prospectively followed 204 patients, 87% of

whom were treated with AEDs following their second seizure. The risk of a third seizure went up from 57% [95% CI 45–70%] at 1 year to 73% [95% CI 59–87%] at 4 years. The risk was higher in those with symptomatic epilepsy versus those with idiopathic or presumed symptomatic (cryptogenic) epilepsy. Counterintuitively, other factors such as seizure type, EEG abnormality, or neurological abnormality were not significantly associated with the risk of a third seizure. The risk of a fourth seizure following a third was 76% [95% CI 60–90%] at 3 years. Shinnar et al. (2000) reported similar findings in children who were followed long term after their first seizure.

The current recommendations on starting AEDs in patients with two or more seizures, particularly if they occurred within the last 6–12 months, are based on Hauser et al.'s (1998) data. The available evidence indicates that risk of a further seizure following a second or third unprovoked seizure is high, even in patients with prescribed use of AEDs. Given this finding, Hauser et al. (1998) recommend that patients with two or more unprovoked seizures should start AED treatment. A caveat needs to be mentioned – although this study was large, it could not allow an estimate of the magnitude of any effect that AED treatment might have on seizure recurrence rates. The consensus view, therefore, based largely on seizure recurrence rates, is that the majority of patients should be started on AED treatment following two or more seizures, particularly if they have occurred over a relatively short period of time (6–12 months).

However, there are exceptions, such as the syndrome of benign partial seizures of adolescence or seizures that are the result of a clear precipitant that can easily be avoided. Furthermore, there is continued uncertainty regarding the appropriate recommendation for patients with seizures of minor symptomatology (e.g., simple partial seizures), and patients with long periods of time between seizures. Such patients were entered into the MESS study (Marson et al., 2005) when both clinicians and patients were uncertain about the need for AED treatment.

A synopsis of whether to start treatment is provided in Box 6.4.

Box 6.4 Synopsis: When to Start Treatment

Starting AEDs is not recommended

- Single seizure, low recurrence risk, patient wishes no treatment
- Seizure following avoidable provocation, patient wishes no treatment
- Unobtrusive focal seizures, low recurrence risk, patient wishes no treatment
- Unobtrusive absence seizures, patient wishes no treatment

Starting AEDs is optional

- Single seizure, low recurrence risk, patient wishes treatment
- Seizure following avoidable provocation, patient wishes treatment
- Unobtrusive focal seizures, patient does not wish treatment
- Unobtrusive absence seizures, patient does not wish treatment

Starting AEDs is strongly recommended

- High recurrence risk
- Medium recurrence risk, patient wishes treatment
- Multiple obtrusive seizures, symptomatic focal or generalized epilepsy
- Genetic generalized epilepsy with GTC that are not amenable to avoiding seizure precipitants

Case 6.4 What Would You Do?

- An 18-year-old woman has a history of waking myoclonus, and generalized tonic–clonic seizures (GTCS), which are preceded by multiple myoclonus, beginning at age 14. Myoclonus occurs 1–3 times per month, any time of day
- GTCS occur 1 per 3 months
- Family history negative
- Examination is normal
- Would you treat her?

The pitfall here in this patient with juvenile myoclonic epilepsy is to overlook that the likelihood of seizure remission without AED treatment is much less likely once a GTCS has occurred. Starting an appropriate AED is strongly recommended.

Recommendation When to Start Treatment

- Drug treatment of epilepsy is generally advisable if disabling seizures occur or can be reasonably expected to recur sufficiently frequently to adversely affect the individual person more than the adverse effects of AEDs. The decision to start treatment after a single tonic-clonic seizure needs to be individualized because current AEDs prevent seizures in most patients but do not seem to affect the course of epilepsy.
- Following two or more seizures if seizures are of significant symptomatology such that the patient would wish treatment, and occurred over a period of less than 6–12 months. This is a consensus view and the risk–benefit ratio has not been addressed in randomized controlled trials.
- Following a single seizure if the patient is in the medium- or high-recurrence risk group and the patient wishes to start treatment.
- Following two or more seizures of minor symptomatology or following seizures separated by long time periods if the patient is in the medium- or high-recurrence risk group and the patient wishes to start treatment.

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Chapter 7

Which Drug is Best?

Dieter Schmidt

Antiepileptic drugs (AEDs) are the unchallenged mainstay of epilepsy treatment. Currently used AEDs are a diverse group of effective and safe drugs that have provided immeasurable benefits for those afflicted with epilepsy of all kinds. Once the decision to start treatment has been made (see Chapter 6), the first step is to consider the advantages and disadvantages of currently available AEDs for new-onset epilepsy.

Picking the best drug is one of the most important management decisions in epilepsy. Choosing the right AED for the individual patient is the result of a complex decision process that involves a risk-benefit assessment of the drug versus other suitable AEDs for the individual patient. In addition, other factors which may play in the decision to prefer one drug over another include personal preference and ease of use based on past experience, a feeling of comfort, and last but not least, cost. Pragmatically, the choice of the AED among first-line agents needs to be individualized. This chapter discusses common pitfalls of picking the best drug for the individual patient. For detailed discussion of AEDs, see textbooks (e.g., Engel and Pedly, 2007).

Integrative Choice of Antiepileptic Drug

Pragmatically, the choice of the AED among first-line agents is individualized mainly based on the patient profile, including the efficacy for the seizure type or the epilepsy syndrome, tolerability, safety, ease of use, pharmacokinetics, including the current or likely future need for concomitant medication for comorbidity, and cost (Box 7.1). More recently, genetic typing has emerged as a guide for the individual choice of the safest AED in special circumstances (see below).

Box 7.1 General criteria for the choice of AEDs

- With rare exceptions, all AEDs for a given type of seizures are similarly efficacious when measured in percent of patients whose seizures respond. However, for unclear reasons, differences exist for individual response.
- Ideally, the drug should be as efficacious as carbamazepine (CBZ) or valproate (VPA) for the individual patient's seizure type or epilepsy, but be better tolerated and safer (e.g., no increased teratogenicity compared to CBZ, no idiosyncratic reaction), not be metabolized, and have no or less enzyme induction properties compared to CBZ or show no or less enzyme inhibition compared to VPA.
- Choose the AED with the optimal risk-benefit profile for the individual patient. The choice between numerous AEDs will be made after careful consideration of all other individual relevant factors. In particular, suitable new AEDs which are less or not at

all enzyme-inducing should be preferred over classic AEDs in adolescents and adults including women of childbearing age, patients with cognitive deficits or depression, with hormonal or metabolic disturbances, increased risk for osteoporosis, those who are overweight or have concomitant disorders or are on medication, and the elderly. In particular, suitable new AEDs that are not associated with hypersensitivity reactions should be preferred over classic AEDs such as CBZ.

Table 7.1 Recommendations for first-line AEDs for new-onset epilepsy and their commonly used target doses (modified from French et al., 2004a, b)

Recommended modern AEDs	Recommended classic AEDs
Focal epilepsies	Focal epilepsies
Eslicarbazepine 200–1,200 mg/day	Carbamazepine 200–1,200 mg/day
Gabapentin 900–2,400 mg/day	Valproate 600–1,500 mg/day
Lamotrigine 100–300 mg/day	
Levetiracetam 1,000–3,000 mg/day	
Oxcarbazepine 300–1,800 mg/day	
Topiramate 50–200 mg/day	
Genetic (formerly idiopathic) generalized epilepsies	Genetic (formerly idiopathic) generalized epilepsies
Lamotrigine 100–300 mg/day	Valproate 600–1,500 mg/day
Topiramate 50–200 mg/day	Ethosuximide 250–2,000 mg/day

Table 7.2 Modern drug treatment of new-onset epilepsy: what guidelines recommend

Guidelines	Preferred AEDs
NICE	CBZ/VPA
SIGN	CBZ/VPA
AAN	CBZ/VPA
ILAE	CBZ/VPA
DGN	LEV/LTG/VPA

Abbreviations: NICE = National Institute for Clinical Excellence (England and Wales) www.nice.org.uk, SIGN = Scottish Intercollegiate Guidelines (Scotland) www.sign.ac.uk, AAN = American Academy of Neurology (USA) www.aan.com, ILAE = International League Against Epilepsy, www.ILAE.com, DGN = German Society for Neurology www.DGN.org

It is advisable to prescribe only first-line AEDs in new-onset epilepsy. First-line drugs are well-tolerated and safe. AEDs which have proven efficacy for new-onset epilepsy (and for previously treated patients with refractory epilepsy) are shown in Table 7.1.

In addition, several organizations have offered their views on drugs of first choice for new-onset epilepsy (Table 7.2).

The first AED leads to complete seizure control in about 50% of patients with new-onset epilepsy; subsequent regimens with combinations or substitution achieve control in

Table 7.3 Advantages and disadvantages of AEDs preferred for use in new-onset epilepsy

AED	Advantages	Disadvantages
Carbamazepine	Unsurpassed efficacy for focal seizures	Drug interaction, hypersensitivity reactions, sedation, do not use for IGE
Eslicarbazepine	Similar efficacy for focal seizures as carbamazepine	Drug interaction, hypersensitivity reactions, sedation, do not use for IGE
Ethosuximide	Unsurpassed efficacy in absence seizures, low risk of drug interaction, no hypersensitivity reactions	Psychotic episodes, hiccups, do not use in focal epilepsy
Gabapentin	No drug interaction; no hypersensitivity reactions	Less efficacious than carbamazepine, not useful for IGE
Levetiracetam	Low risk of drug interaction; low risk of hypersensitivity reactions	Psychiatric side effects, only add-on use in myoclonic seizures
Lamotrigine	Mood stabilizer, works in focal seizures and absence seizures	Drug interaction; hypersensitivity reactions, slow titration
Oxcarbazepine	Works in focal seizures, possibly better tolerated in children than CBZ	Hyponatremia, does not work in IGE, drug interaction
Topiramate	Works in focal and generalized seizures, low risk of drug interaction at doses below 200 mg/day	Cognitive side effects, kidney stones, anhidrosis in children
Valproate	Unsurpassed efficacy in IGE, works in focal epilepsy	Less efficacious than CBZ for complex partial seizures, high teratogenicity among AEDs, drug interaction, liver failure

a further 10–15%. As a result, one in three patients remains with uncontrolled partial seizures. Realistically, all AEDs for new-onset epilepsy have advantages and disadvantages (Table 7.3). To avoid pitfalls, it is useful to carefully assess the risk-benefit profile of each suitable first-line drug before making a final decision.

The Pitfalls in Finding the Best AED

Finding the best drug for the individual patient is hampered by a number of potential pitfalls. A few general rules to avoid pitfalls in the choice of drugs are shown in Box 7.2.

Box 7.2 A few general rules that often protect from pitfalls in the choice of drugs

1. Use only drugs that you know well.
2. If the drug chosen does not lead to seizure-freedom in the patient with new-onset seizures within 6 months, at most, refer the patient to a specialist who sees at least 100 cases of epilepsy per year.
3. Unless you are conducting a study, do not start a patient on a drug with a documented exposure of less than 3,000 patients.
4. For new-onset epilepsy, use only first-line drugs.
5. Explain clearly and in writing which specific side effects may occur and what the patient should do if they occur (provide your telephone number, provide a note with the date for the return visit).

6. Explain to the patient if the drug may be involved in drug interactions. (By the way, do you know which other drugs and supplements your patient is on at the moment?)
7. Send a note to the patient's other physician(s) with information if the drug you prescribed is involved in drug interaction(s) or may cause hypersensitivity reactions.

The Most Common Sources of Pitfalls

In the following section, the most common pitfalls are briefly discussed.

Although the choice of the best drug for epilepsy may seem straightforward, a number of unresolved issues exist that may present pitfalls in finding the optimal AED for the individual patient (Box 7.3).

Box 7.3 Common pitfalls in the choice of the best drug

- Pitfall: too many drugs to choose from
- Pitfalls in finding out which old or new drugs are best for focal new-onset epilepsy
- Pitfalls in finding out which old or new drugs are best for generalized new-onset epilepsy
- Pitfalls in finding which AEDs are best for refractory epilepsy
- Pitfalls in finding which old or new drugs are best for refractory focal epilepsy
- Pitfalls in finding out which old or new drugs are best for refractory generalized epilepsy
- Pitfalls in using the pharmacokinetic profile as a guide for choice of drug
- Pitfalls in using the adverse effect profile as a guide for choice of drug
- Pitfalls in using the molecular action of AEDs as a guide for choice of drug
- Pitfalls in using gene testing as a guide for choice of drug
- Pitfalls if any, of referring patients to an epilepsy center

Pitfall 1: too many drugs to choose from. At present, over 30 AEDs are on the market for the treatment of epilepsy. Although the large number of AEDs offers a wide variety of choices, the diversity makes it more difficult to find the best drug for the individual patient.

Historically, AEDs can be conveniently classified into three generations (Löscher and Schmidt, 2011). The first generation, entering the market from 1857 to 1958, includes potassium bromide, phenobarbital (PB), and a variety of drugs that were mainly derived by modification of the barbiturate structure, including phenytoin (PHT), primidone (PRM), trimethadione, and ethosuximide (ESM). The second-generation AEDs, including CBZ, VPA, and the benzodiazepines, which were introduced between 1960 and 1975, differed chemically from the barbiturates. The superior tolerability of CBZ and PHT for focal seizures over the more sedative barbiturates, PB and PRM, was shown in a double-blind, benchmark trial comparing all four AEDs as early as 1985 (Mattson et al., 1985). Despite their well-known dose-related CNS side effects, PHT and PB have never been shown to be less efficacious for focal seizures than CBZ (Mattson et al., 1985) and both are still in widespread use in many parts of the world, mainly because of their low cost. However, CBZ, PHT, PB, and PRM (which is metabolized to PB) have two clinically important disadvantages. They are potent enzyme inducers, which lead to clinically important adverse drug interactions, and, in addition, they cause hypersensitivity reactions (Schmidt and Beyenburg 2009).

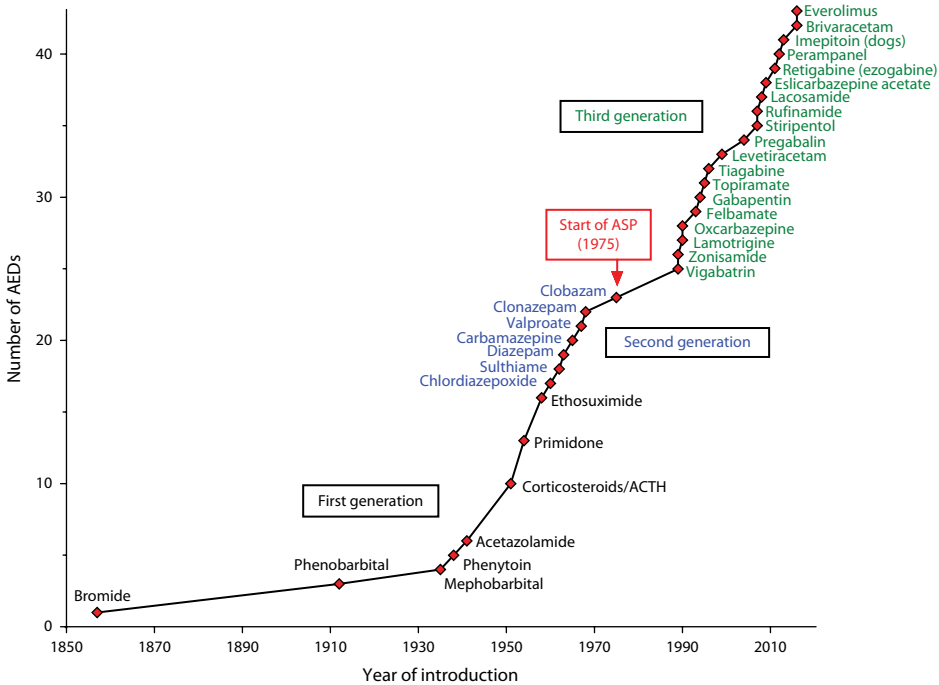

Figure 7.1 Introduction of AEDs to the market from 1853 to 2017 (adapted from Löscher and Schmidt, 2011). Licensing varied from country to country. We have not included all derivatives of listed AEDs or AEDs used solely for treatment of status epilepticus. NINDS Anticonvulsant Screening Program (ASP).

Astute clinical observations by French physicians established VPA as an efficacious drug for genetic or idiopathic generalized and focal epilepsy. However, VPA turned out to be somewhat less effective for complex partial seizures than CBZ (Mattson et al., 1992) and has three other clinically important disadvantages: as an enzyme-inhibitor it is involved in deleterious drug interactions, it causes hepatic failure in predisposed individuals, and it is the most teratogenic among the currently marketed AEDs (Schmidt and Beyenburg. 2009). For a detailed discussion of the current evidence, see Beyenburg et al. (2010).

Following the introduction of VPA in the 1960s, no new AEDs entered the market for almost two decades, except some additional benzodiazepines (see Figure 7.1). Not surprisingly, patients and physicians had great expectations for therapeutic gains over older drugs when the new, third-generation AEDs entered the market, which arbitrarily include all drugs for epilepsy marketed after the introduction of CBZ or VPA in the 1960s (see Figure 7.1). Despite the shortcomings of second-generation AEDs outlined above, the widespread use and the unsurpassed clinical efficacy of CBZ and VPA made them benchmarks for comparison with third-generation AEDs. The era of the third-generation AEDs started in the 1980s with "rational" developments such as progabide, vigabatrin (VGB), and tiagabine (TGB), i.e., drugs that were designed to selectively target a mechanism that was thought to be critical for the occurrence of epileptic seizures (see Löscher and Schmidt, 2011).

Some of the third-generation AEDs have several clinically important advantages. First, all of the new AEDs undoubtedly expanded the therapeutic options, in particular

for those in need for a change in medical regimen. Second, some of the newest AEDs have made the management of epilepsy easier because they are not involved in drug interactions and do not cause hypersensitivity reactions. However, the efficacy of many new AEDs for treatment of new-onset epilepsy seems to be similar to that of older AEDs (Löscher and Schmidt, 2011). Although adjunctive new AEDs have been shown to be more effective than adding placebo, the percentage of patients becoming seizure-free is only in the single digit range (Beyenburg et al., 2010). Yet, as discussed above, some of the new AEDs avoid adverse drug interactions and hypersensitivity reactions seen with earlier drugs such as CBZ (Elger and Schmidt, 2008) and some new AEDs have clinically important utility for disorders other than epilepsy.

Pitfall 2: Are Modern Drugs Generally Preferable over Older Drugs?

Some but not all of the third-generation AEDs seem to have a number of advantages over older drugs. For example, GBP and LEV neither induce nor inhibit hepatic metabolism. This is why, in general, treatment with some of the newer AEDs cause fewer adverse drug interactions. Whether this translates into better tolerability and safety, as one might think, has never been shown convincingly in large randomized studies or population-based studies. However, long-term exposure with some of the newer AEDs can be reasonably expected to be associated with fewer hormonal-metabolic disturbances. Based on current evidence, the major malformation rate associated with the use of LTG is similar to that seen during CBZ treatment or in untreated women with epilepsy and is lower than that observed with VPA treatment. A second very important advantage of some of the newer AEDs is the absence of hypersensitivity reactions, such as for GBP, LEV, or TPM, compared to CBZ. These data suggest – in our view – that a first-line newer AED should be preferred over a first-line classic AED when starting drug treatment in a patient with new-onset epilepsy.

In addition, the choice of an AED is also influenced by the individual patient's characteristics. When first-line AEDs have brought insufficient results, a number of second- and third-line AEDs are available: As these drugs all have quite significant limitations either in evidence of efficacy or, at least in part, safety concerns (see adverse effects), they are recommended only in cases of disabling refractory epilepsy.

What is the Evidence Base for Preferring New over Older Drugs for New-Onset Focal Epilepsy?

One possible pitfall is the concern that we do not have enough evidence to prefer new AEDs to old AEDs for newly diagnosed epilepsy. A series of short-term, randomized, double-blind trials have demonstrated that several of the newer-generation AEDs are equal in effectiveness to the standard old drug, CBZ. This has been shown for LTG (Brodie et al., 1995, 1999), LEV (Brodie et al., 2007), and TPM (Privitera et al., 2003), although the latter is in some dispute (Marson et al., 2007). OXC has also shown similar efficacy compared to CBZ and PHT (Bill et al., 1997; Guerreiro et al., 1997; Marson et al., 2007). The next chapter reviews the evidence from a recent guideline that found clear evidence for the effectiveness of a number of new-generation AEDs in initial monotherapy in adults and children (French et al., 2004a, b).

A recent evidence-based analysis of AED efficacy and effectiveness as initial monotherapy for epileptic seizures and syndromes came to sobering conclusions (Glauser et al., 2006).

The authors concluded that the absence of rigorous comprehensive adverse effects data makes it impossible to develop an evidence-based guideline aimed at identifying the overall optimal recommended initial monotherapy AED, old or new. There is an especially alarming lack of well-designed, properly conducted, randomized controlled trials (RCT) for patients with generalized seizures/epilepsies and for children in general. The majority of relevant existing RCTs have significant methodological problems that limit their applicability to this guideline's clinically relevant main question.

For that study, a 10-member subcommission of the Commission on Therapeutic Strategies of the International League Against Epilepsy (ILAE) evaluated available evidence found through a structured literature review including MEDLINE, Current Contents, and the Cochrane Library for all applicable articles from 1940 until July 2005. The purpose of the review was to assess which AEDs have the best evidence for long-term efficacy or effectiveness as initial monotherapy for patients with newly diagnosed or untreated epilepsy. Articles dealing with different seizure types (for different age groups) and two epilepsy syndromes were assessed for quality of evidence (four classes) based on predefined criteria. Criteria for class I classification were a double-blind, RCT design, ≥48-week treatment duration without forced exit criteria, information on ≥24-week seizure-freedom data (efficacy) or ≥48-week retention data (effectiveness), demonstration of superiority or 80% power to detect a ≤20% relative difference in efficacy/effectiveness versus an adequate comparator, and appropriate statistical analysis. Class II studies met all class I criteria except for having either treatment duration of 24–47 weeks or, for non-inferiority analysis, a power to only exclude a 21–30% relative difference. Class III studies included other randomized double-blind and open-label trials, and class IV included other forms of evidence (e.g., expert opinion, case reports). Quality of clinical trial evidence was used to determine the strength of the level of recommendation. A total of 50 RCTs and seven meta-analyses contributed to the analysis. Only four RCTs had class I evidence, whereas two had class II evidence; the remainder were evaluated as class III evidence. Three seizure types had AEDs with level A or level B efficacy and effectiveness evidence as initial monotherapy: adults with partial-onset seizures (level A, CBZ and PHT; level B, VPA), children with partial-onset seizures (level A, OXC; level B, None), and elderly adults with partial-onset seizures (level A, GBP and LTG; level B, None). One adult seizure type (adults with generalized-onset tonic–clonic [GTC] seizures), two pediatric seizure types (GTC seizures and absence seizures), and two epilepsy syndromes (benign epilepsy with centrotemporal spikes and juvenile myoclonic epilepsy) had no AEDs with level A or level B efficacy and effectiveness evidence as initial monotherapy. As noted above, the ILAE subcommission concluded that the absence of rigorous comprehensive adverse effects data makes it impossible to develop an evidence-based guideline aimed at identifying the overall optimal recommended initial AED, old or new.

Multicenter, multinational efforts are needed to design, conduct, and analyze future clinically relevant RCTs that can answer the many outstanding questions raised by the above studies.

The ultimate choice of an AED for any individual patient with newly diagnosed or untreated epilepsy should include consideration of the strength of the efficacy and effectiveness evidence for each AED along with other variables such as the AED safety and tolerability profile, pharmacokinetic properties, formulations, and expense (Glauser et al., 2006). In a nutshell, the ILAE treatment guidelines for initial monotherapy emphasize the poor quality of information available to inform everyday clinical practice.

When selecting an AED, physicians and patients should consider all relevant variables and not just efficacy and effectiveness. Furthermore, the results of regulatory trials are difficult to translate into clinical practice because they do not typically assess the long-term effects and tolerability of one drug versus another suitable drug at clinically useful dosages. As a consequence, we will limit ourselves in this section to a brief critical review of long-term, randomized trials of comparative risk-benefit outcomes with individual AEDs given at clinically adequate dosages. After reviewing the available evidence, it is apparent that randomized, controlled trials have provided only some of the elements such as efficacy and tolerability needed for the decision to prefer one drug to another. Other important elements that help to form an opinion as to which drug to choose such as patient profile have not been studied. The problem will be discussed in the next section. For a more detailed discussion of the evidence in the literature, the reader is referred to Beyenburg et al. (2010).

A number of AEDs are recommended based on their benefit-to-risk ratio (see Tables 7.1 and 7.3). The newer AEDs for therapy of previously untreated adolescents and adults with focal epilepsy such as (in alphabetical order) GBP, LTG, LEV, OXC, and TPM have a number of advantages compared to classic AEDs such as CBZ, PB/PRM, PHT, and VPA. The new AEDs show similar efficaciousness, with the possible exception of GBP, which seemed to be inferior in efficacy compared to CBZ, and at least similar or perhaps even better tolerability at adequate dosages than classic AEDs for patients with focal epilepsy.

The efficacy and tolerability of some of the newer AEDs versus CBZ or VPA was evaluated in the randomized but unblinded SANAD trials (Marson et al., 2007). Arm A of the SANAD trial was designed as a pragmatic trial to assess whether LTG, GBP, TPM, or OXC should become first-line treatment and thereby replace the existing first-line agent CBZ (Marson et al., 2007). Based on efficacy criteria alone, and only those will be discussed here, none of the new AEDs was superior in efficacy to CBZ. However, LTG and OXC were considered to be non-inferior in efficacy, while CBZ was reported to be more efficacious compared to GBP (Marson et al., 2007). That GBP has been found to be less efficacious indicates that the SANAD trial has assay sensitivity to differentiate efficacious from less efficacious treatment.

LEV, which entered the market later, could not be studied in the SANAD trial. However, a well-controlled non-inferiority trial has shown that, at per-protocol analysis, 73.0% of patients randomized to LEV and 72.8% receiving controlled-release CBZ were seizure-free at the last evaluated dose (adjusted absolute difference 0.2%, 95% CI 7.8–8.2%) for at least 6 months indicating equivalent seizure remission for LEV versus slow-release CBZ (Brodie et al., 2007). One study was inconclusive in establishing non-inferiority of TPM (100 mg/day) versus oral PHT for new-onset focal seizures (Ramsay et al., 2010). A discussion of monotherapy trials in recent-onset epilepsy in those above 65 years is available elsewhere (Schmidt, 2011). Finally, it should be noted that the evidence base of comparative trials or large-scale clinical observations for comparing newer versus older AEDs cannot be considered to be robust. As noted previously, an expert panel of the ILAE commission voiced serious methodological concerns (Glauser et al., 2006). Curiously, the current evidence base for comparing older versus newer AEDs in new-onset epilepsy after the drugs were on the market falls short of the benchmark trials comparing several older AEDs for new-onset epilepsy (Mattson et al., 1985).

In summary, none of the new AEDs was superior in efficacy to old AEDs such as CBZ and VPA in large, well-controlled trials of recent-onset epilepsy (Marson et al., 2007).

However, several new AEDs such as LEV, LTG, and OXC have been shown to be non-inferior in seizure control by a predefined margin to CBZ. Moreover, GBP was shown to be less efficacious versus CBZ in mostly previously untreated focal epilepsy and LTG was less efficacious compared to VPA (Marson et al., 2007).

Should Old or New Drugs Be Preferred for New-Onset Idiopathic Generalized Epilepsy?

AEDs for idiopathic generalized epilepsy (IGE) are recommended based on their benefit-to-risk ratio (Table 7.3). The first common pitfall in treating patients with new-onset IGE is that despite requiring different treatment strategies, absence epilepsy, juvenile myoclonic epilepsy, and related IGE syndromes are often erroneously grouped with focal epilepsies under the broad term "epilepsy." The second source for pitfalls is that AEDs are mainly tested and licensed for focal epilepsies and there may be inappropriate broadening of their use in "epilepsy." Examples are GBP, CBZ, OXC, and PHT, which induce myoclonic seizures, and VGB and TGB, which induce absence seizures; they are contraindicated in IGE, which constitutes more than one-third of patients under the age of 25 with epilepsy. VPA is still the drug of first choice for patients with idiopathic and symptomatic generalized epilepsy despite its disadvantages, particularly weight gain and teratogenicity, because the efficacy of VPA is unsurpassed by any newer suitable AED such as LTG and TPM (Marson et al., 2007). In addition, LTG and TPM, though less teratogenic than VPA, are not free of teratogenic effects.

Although LTG and TPM are used for previously untreated adolescents and adults with generalized or unclassified epilepsies, the efficacy of LTG was inferior to that of VPA, while TPM was not inferior to VPA. Absence seizures are fundamentally different from any other type of seizure, and therefore unique in terms of pharmacological treatment. Typical absence seizures are often easy to diagnose and treat. VPA, ESM, and LTG, alone or in combination, are first-line therapy. VPA controls absences in 75% of patients and also GTCS (70%) and myoclonic jerks (75%); however, it may be undesirable for treatment of women who are in their reproductive years. Similarly, LTG may control absences and GTCS in possibly 50–60% of patients, but may worsen myoclonic jerks; further, skin rashes are common, in particular when LTG is combined with VPA. ESM controls 70% of absences, and may be preferred over VPA (Glauser et al., 2010). One controversy is that ethosuximide has been thought to be unsuitable as monotherapy if other generalized seizures, in particular GTCS, coexist. A recent randomized head-to-head study in new-onset absence epilepsy of childhood found no evidence, however, that those on ESM fared less well than those on VPA and this included patients with GTCS (Glauser et al., 2010). In the same study, LTG was also shown to be less efficacious versus VPA and ESM for previously untreated childhood absence epilepsy (Glauser et al., 2010). This shows convincingly that current postmarketing trial designs for new-onset epilepsy – albeit not designs used for regulatory purposes – are able to detect less efficacious treatment, if it exists.

The efficacy of LTG and TPM versus VPA for treatment of new-onset IGE was studied in a subset of Arm B of the SANAD trial (Marson et al., 2007). SANAD was designed to assess whether LTG or TPM should become first-line treatment and thereby replace VPA as the existing first-line agent (Marson et al., 2007). The result was that VPA was more efficacious than LTG and similar in efficacy to TPM for all

patients and also for the subgroup of patients with IGE (Marson et al., 2007). Although the study showed equal efficacy of TPM and VPA, it should be added that TPM was grossly inferior in terms of effectiveness (which also takes tolerability into account). LTG was also shown to be less efficacious versus VPA for previously untreated juvenile myoclonic epilepsy (Mohanraj and Brodie, 2007). More recently, a multicenter, double-blind, randomized trial compared treatment with ESM, LTG, or VPA in 453 children with new-onset absence epilepsy of childhood (Glauser et al., 2010). After 16 weeks of therapy, the freedom-from-failure rates for ESM and VPA were similar (53% and 58%), but for both the rates were higher than for LTG (29%; $P < 0.001$ for both comparisons).

Are Old or New AEDs Preferred for New-Onset West Syndrome?

Although there seems to be no evidence that any new AEDs are more efficacious than standard AEDs for new-onset epilepsies, VGB received orphan drug status for new-onset West syndrome, though it does not seem to be more efficacious than hormonal treatment over the long term (Darke et al., 2010). However, in earlier small trials, VGB was shown to be superior in efficacy in new-onset West syndrome due to cerebral malformations or tuberous sclerosis, whereas ACTH proved more effective in cases with perinatal hypoxic/ischemic injury. The efficacy of the two drugs was similar in cryptogenic cases (Vigevano and Cilio, 1997). In another study of West syndrome, VGB was more effective than hydrocortisone (Chiron et al., 1997). VGB has caused concentric visual field defects, and so age-appropriate visual field testing is required and discontinuation is recommended in cases where spasm or seizure improvement is not achieved within 12 weeks of initiation (Willmore et al., 2009).

Take home message for treatment of new-onset epilepsy: The choice of the AED among first-line agents needs to be individualized mainly based on the patient profile, including the efficacy for the seizure type(s) or the epilepsy syndrome, tolerability, safety, ease of use, pharmacokinetics, the current or likely future need for concomitant medication for co-morbidity, and finally cost. There is no compelling evidence for better efficacy of new AEDs versus suitable older agents.

The Choice of AEDs When Prior Drugs have Failed

In addition to the first-line AEDs mentioned, efficacious second-line AEDs such as PGB or ZNS are available for combination therapy if the first treatment fails to control seizures.

Pitfall 1: Failure to Recognize the Risk-Benefit Profile of the Drug for Refractory Epilepsy

Realistically, all second-line AEDs for patients in whom first-line AEDs have failed to control seizures have advantages and considerable disadvantages (Table 7.4). To avoid pitfalls, it is useful to carefully assess the risk-benefit profile of each suitable drug before making a decision. A reasonable proposal has been made for the choice of new AEDs for refractory epilepsy and updated by the author of this chapter (Table 7.4).

The pros and cons of AEDs preferred for use in patients in whom prior use of at least two drugs for new-onset epilepsy has failed to control seizures or has caused unacceptable side effects are shown in Table 7.5.

Table 7.4 Choice of AEDs for refractory epilepsy

AED	Focal adjunctive, adult	Monotherapy	Partial, children	Primary generalized, absence (a), myoclonic (m)	Symptomatic generalized Lennox–Gastaut syndrome)
Carbamazepine	Yes	Yes	Yes	No	No
Eslicarbazepine*	Yes	Yes	No	No	No
Gabapentin	Yes	No	Yes	No	No
Lacosamide*	Yes	No	No	No	No
Lamotrigine	Yes	Yes (B)	Yes	No	Yes
Levetiracetam	Yes	No	No	No	No
Oxcarbazepine	Yes	Yes (A)	Yes	No	No
Perampanel	YES	No	Yes	Yes, tonic–clonic	No
Phenobarbital	Yes	Yes	Yes	Yes (m), No (a)	Yes
Phenytoin	Yes	Yes	Yes	No	No
Retigabine*	Yes	No	No	No	No
Tiagabine	Yes	No	No	No	No
Topiramate	Yes	Yes[a] (A)	Yes	Yes[b]	Yes
Valproate	Yes	Yes	Yes	Yes	Yes
Zonisamide	Yes	No	No	No	No

Summary of AAN evidence-based guidelines for treatment of refractory epilepsy with new antiepileptic drugs updated by the author* (DS). Yes = Level A and B recommendations for use, No = insufficient evidence exists to recommend use.
[a]Not FDA approved for this indication.
[b]GTC only (modified from French et al., 2004a, b).

Table 7.5 Pros and cons of AEDs preferred for use in patients in whom prior use of at least two drugs for new-onset epilepsy has failed to control seizures or has caused unacceptable side effects

AED	Advantages	Disadvantages
Clobazam	Works in focal seizures and in IGE, recommended for transient use	Loss of effect, sedation, withdrawal effects
Phenobarbital/Primidone	Works in focal seizures and in myoclonic seizures, iv	Less well tolerated than carbamazepine for focal seizures, drug interaction, hypersensitivity reactions, sedation, do not use for absence seizures
Phenytoin	Works in focal seizures, well tolerated in the elderly, low cost, iv formulation	Drug interaction, hypersensitivity reactions, ataxia, do not use in IGE
Felbamate	Works in refractory Lennox–Gastaut syndrome	Aplastic anemia, liver failure
Eslicarbazepine	Works in focal seizures	Rash, hyponatremia, prolonged PR interval, do not use in IGE
Lacosamide	Works in focal seizures	Do not use in IGE
Perampanel	Works in focal seizures and in tonic–clonic seizures in genetic generalized epilepsies	Only add-on use
Retigabine	Works in focal seizures	Only add-on use, do not use in IGE
Topiramate	Works in focal seizures and in IGE	Cognitive side effects, kidney stones, caveat: can worsen acidosis in ketogenic diet
Tiagabine	Works in focal seizures	Only add-on use, do not use in IGE, may provoke nonconvulsive status epilepticus, depression
Vigabatrin	Works in West syndrome and in focal seizures	Add-on use for focal seizures, visual field defects (testing required)
Zonisamide	Works in focal seizures	Kidney stones, rash, anhidrosis in children

Pitfall 2: No Adequate Guidance of Head-to-Head Comparison from Controlled Trials

Although there is an abundance of short-term, randomized, controlled trials to assess the efficacy and safety of individual investigational AEDs prior to marketing for regulatory purposes, surprisingly few trials have addressed the management of epilepsy with marketed AEDs in clinical practice. One major source for pitfalls is that the evidence base for comparing the efficacy of newer versus older drugs for refractory epilepsy is surprisingly weak. We found only one novel comparative trial, which included placebo as a third arm, showing non-inferiority of PGB versus LTG for refractory focal seizures (Baulac et al., 2010). Although several clinical observations suggested that a change to a new medical regimen, which included third-generation AEDs, has led to seizure-freedom for at least 6–12 months in 14–28% of patients previously considered to have refractory focal seizures (Callaghan et al., 2007; Luciano and Shorvon, 2007),

these reports provide no firm evidence that such AEDs have substantially improved the treatment of epilepsy. The reason is that the publications included no compelling evidence that the patients had received adequate prior treatment with maximum doses of older AEDs. Maximum dose treatment has long been shown to lead to seizure-freedom without a change of drug in up to 31% of patients with prior refractory epilepsy (Schmidt, 1983).

Although the introduction of several new AEDs as orphan drugs such as stiripentol for Dravet syndrome (Chiron et al., 2000), rufinamide for refractory Lennox–Gastaut syndrome (Glauser et al., 2008), and brivaracetam for symptomatic myoclonus (in the United States) can, in general, be considered as a therapeutic gain, none of the orphan drugs has been compared in its efficacy to other drugs.

In clinical drug development, modern adjunctive drugs for refractory epilepsy are usually compared with adding placebo to the existing medication, but not with addition of a standard older drug (see below). Overall, we found no compelling evidence for therapeutic gain in efficacy with new AEDs versus older standard drugs in refractory epilepsy. This raises concern, given the seemingly unimproved proportion of patients with drug-resistant epilepsy, as discussed in the introduction. Finally, another serious concern with the current evidence base is that physicians and cost bearers are not provided evidence if a new AED is superior in any aspect at the time it enters the market and the pricing is determined.

Pitfall 3: Avoid Less-Often-Used Drugs Unless You are Seeing Many Patients with Uncontrolled Seizures

Furthermore, it may be advisable to only use the drugs that a physician feels comfortable with. In fact, many experienced specialists for epilepsy claim anecdotally that they choose the best drug for the individual patients only among a handful of AEDs. A few general rules may help to avoid pitfalls (Table 7.6). Less-often-used drugs include clobazam, phenobarbital, phenytoin, primidone, and tiagabine. Less-often-used agents with either tolerability or safety problems or no Class I evidence for efficacy (acetazolamide, bromide, felbamate, sulthiame, VGB) should be used as a last resort (Table 7.6). Given a similar efficacy for focal seizure control, the choice of the AED among first-line agents needs to be individualized mainly based on the patient profile including the epilepsy syndrome, tolerability, genetic testing for HLA (see below), gender issues, pharmacokinetics, the current or likely future need for concomitant medication for comorbidity, and cost.

Pitfall 4: Delayed Referral to a Comprehensive Epilepsy Center if Two Appropriately Selected and Dosed Drugs have not Achieved Lasting Seizure-Freedom

If two adequate AEDs (alone or in combination treatment) have failed to achieve lasting seizure-freedom, the epilepsy is, by definition, drug-resistant and surgical options should be considered. If the epilepsy is not ideally suited for surgery, the use of further AEDs, including third-line drugs, is a reasonable option (see Tables 7.5 and 7.6). Third-line drugs have considerable disadvantages over first- or second-line drugs, either in tolerability or in lack of evidence for stand-alone efficacy for refractory epilepsy.

Table 7.6 Choice of less-often-used AEDs for refractory epilepsy

AED	Partial adjunctive, adult	Partial monotherapy	Partial children	Primary generalized, absence (a), myoclonic (m)	Symptomatic generalized Lennox–Gastaut syndrome)
Acetazolamide	No	No	No	No	No
ACTH and steroids	No	No	No	No	No
Benzodiazepines	Yes	No	Yes	Yes	No
Bromide	No	No	No	No	No
Ethosuximide	No	No	No	Yes (a,) No (m)	No
Felbamate	Yes	Yes	Yes	No	No
Primidone	Yes	Yes	Yes	Yes (m), No (a)	No
Sulthiam	No	No	Yes	No	No
Tiagabine	Yes	No	No	No	No
Vigabatrin	Yes	No	No	No	No

Yes = Level A and B recommendations for use, No = insufficient evidence exists to recommend use, although evidence class III/IV may exist (modified from French et al., 2004a, b).

Pitfall 5: Refractory Generalized Epilepsy does Exist!

Typical absence seizures are often easy to diagnose and treat in new-onset cases. As discussed above, VPA, ESM, and LTG, alone or in combination, are first-line therapy. It should be noted, however, that VPA cannot control absence seizures in 25% of patients. Among patients with new-onset GTCS and myoclonic jerks, 20–25% continue to have seizures despite treatment with first-line drugs. In addition, valproate may be unsuitable or undesirable because of its high teratogenicity or weight gain for a number of women. Similarly, LTG may control absences and GTCS in possibly 50–60% of patients, but may not control or possibly even worsen myoclonic jerks, at least in some patients, and skin rashes are common. ESM does not achieve seizure-freedom in about 30% of new-onset cases with absence seizures. A combination of any of these three drugs may be needed for patients that have not become seizure-free or who have unacceptable side effects. Anecdotally, low dosages of LTG added to VPA may have a dramatically beneficial effect. The downside of this combination is, however, that the rate of LTG-induced rashes also increases dramatically. Clobazam, particularly for absences with myoclonic components, and acetazolamide may be useful adjunctive drugs.

Pitfall 6: Failure to be Aware of the Best Drug for Lennox–Gastaut and Related Syndromes

Seizures in uncommon syndromes such as Lennox–Gastaut syndrome are often drug-resistant. Table 7.7 shows some of the AEDs that have been shown to be useful.

Pitfalls in the Choice of Drugs for Children

Another source for pitfalls is that controlled studies of new AEDs in pediatric populations are significantly behind those for adults; consequently, such agents are initially licensed for adults only. Pediatricians have to empirically learn by success or failure in daily practice. Although the introduction of several new AEDs as orphan drugs such as stiripentol for Dravet syndrome (Chiron et al., 2000), rufinamide for refractory Lennox–Gastaut syndrome (Glauser et al., 2008), and brivaracetam for symptomatic myoclonus (in the United States) is an advance, none of the orphan drugs has been compared in its efficacy to other drugs. Another pitfall in the treatment of IGE is that pharmacological treatment of generalized myoclonic seizures is different than for absence seizures. PRM and PB, which may be a last resort for treatment of refractory juvenile myoclonic epilepsy, are ineffective and may even worsen absence seizures. The epilepsy syndrome may also play a role. For example, LTG, which is effective in children with typical absence seizures, may worsen myoclonic seizures in infants with severe myoclonic epilepsy.

Pitfall: Is Gene Testing Ready for Prime Time in the Choice of Drugs?

Drug treatment of epilepsy is characterized by unpredictability of efficacy, adverse drug reactions, and optimal doses in individual patients, which, at least in part, is a consequence of genetic variation. Since genetic variability in drug metabolism was reported to affect treatment with PHT more than 25 years ago, numerous studies have explored how variation in genes alters the pharmacokinetics and, more recently, pharmacodynamics of AEDs, suggesting that a wide assortment of genetic variants influence how individuals

Table 7.7 Long-term AED use in various epilepsy syndromes

AED	Lennox–Gastaut syndrome	Progressive myoclonus epilepsies[a]
Clobazam	(b)	(b)
Carbamazepine		
Eslicarbazepine		
Ethosuximide		
Felbamate[b]	(c)	
Gabapentin		
Lacosamide		
Lamotrigine	(b)	(b)
Levetiracetam[b]		(c)
Oxcarbazepine		
Phenobarbital		
Phenytoin		
Pregabalin[b]		
Primidone		
Tiagabine[b]		
Topiramate	(b)	(c)
Vigabatrin		
Valproate	(a)	(a)

Abbreviations: (a) First choice, (b) second choice or adjunctive therapy, (c) third choice or adjunctive therapy, PGTC: primary generalized tonic–clonic seizure, sec. GTC: secondary generalized tonic–clonic seizure.
[a]Consider piracetam 30 g (!) per day.
[b]Adjunctive therapy agent only.

respond to AEDs. Advances in the management of epilepsy include pharmacogenetic studies that predict Stevens–Johnson syndrome and toxic epidermal necrolysis associated with CBZ treatment in Asians and patients of Asian ancestry with the HLA-B*1502 allele (FDA Alert, 2007). Genetic tests for HLA-B*1502 are already used to check for compatibility before tissue transplants. This finding has important implications for clinical practice. Patients with ancestry from areas in which HLA-B*1502 is present should be screened for the HLA-B*1502 allele before starting treatment with CBZ. According to an alert from the FDA (FDA Alert, 2007), CBZ should not be started if the patient tests positive unless the expected benefit clearly outweighs the increased risk of serious skin reactions. Patients who have been taking CBZ for more than a few months without developing skin reactions are at low risk of these events ever developing from CBZ. This is true for patients of any ethnicity or genotype, including patients positive for HLA-B*1502 (FDA Alert, 2007). Patients who test positive for HLA-B*1502 may be at increased risk of SJS/TEN from other AEDs that have been associated with SJS/TEN. Therefore, in HLA-B*1502 positive patients, doctors should consider avoiding use of other AEDs associated with SJS/TEN when alternative therapies are equally acceptable [53]. Tested patients who are found to be negative for HLA-B*1502 have a low risk of SJS/TEN from CBZ, but SJS/TEN

can still rarely occur, so healthcare professionals should still watch for symptoms in these patients. Over 90% of CBZ-treated patients who experience SJS/TEN have this reaction within the first few months of treatment. Pharmacogenetic studies hold the promise of being able to better individualize treatment for each patient, with maximum possibility of benefit and minimum risk of adverse effects.

SCN1A mutations. A large group of infantile- and early-childhood-onset epileptic encephalopathies are associated with mutations of SCN1A, the gene encoding the alpha 1 pore-forming subunit of the sodium channel. Testing for SCN1A has major implications for investigation of such children, genetic counseling, and optimization of therapy. Dravet syndrome and genetic epilepsy with febrile seizures plus (GEFS+) can both arise due to mutations of SCN1A. GEFS+ comprises a range of mild to severe phenotypes varying from classical febrile seizures to Dravet syndrome. Dravet syndrome is a severe infantile-onset epilepsy syndrome with multiple seizure types, developmental slowing, and poor outcome. More than 70% of patients with Dravet syndrome have mutations of SCN1A; these include both truncation and missense mutations. In contrast, only 10% of GEFS+ families have SCN1A mutations and these comprise missense mutations (Scheffer et al., 2009).

Optimization of treatment in Dravet syndrome has the potential to improve developmental outcome. Regression of skills is frequently observed after episodes of status epilepticus, so prevention of status may improve development. For this reason, early diagnosis of Dravet syndrome is important in an effort to achieve complete seizure control. Several AEDs have been reported in observational studies to be efficacious in Dravet syndrome. These include VPA, clobazam, TPM, and LEV (Scheffer et al., 2009). The ketogenic diet can also be effective and deserves consideration (Scheffer et al., 2009). In 2000, Chiron and colleagues reported the striking efficacy of a P450 inhibitor, stiripentol, in a randomized placebo-controlled study in Dravet syndrome (Scheffer et al., 2009). They found a 70% responder rate (50% seizure reduction) in 21 children with Dravet syndrome and nine children were rendered free of convulsive seizures. Stiripentol is used in concert with VPA and a benzodiazepine and is thought to work in part by increasing their levels. Stiripentol is a promising agent for Dravet syndrome but further studies are required (Scheffer et al., 2009). Just as importantly, specific AEDs may exacerbate seizures in Dravet syndrome. CBZ was previously used early in these infants in view of the focal seizures; however, it is now apparent that it aggravated the myoclonic seizures such that myoclonic seizures were more prevalent in the cases described 30 years ago. LTG may also cause myoclonic seizure exacerbation in Dravet syndrome (Scheffer et al., 2009). Thus early diagnosis guides selection of an effective AED and avoidance of AEDs that aggravate seizures in Dravet syndrome.

Pitfall: Relying on the Molecular Action of AEDs as a Guide for the Choice of Drugs

AEDs prevent seizures by acting on diverse molecular targets to selectively modify the excitability of neurons so that seizure-related firing is blocked without disturbing nonepileptic activity. Therefore, the drugs have the remarkable ability to protect against seizures while permitting normal functioning of the nervous system. AEDs protect against seizures by a variety of different mechanisms, as shown in Table 7.8, which also shows each AED's profile in animal models of epilepsy. Unfortunately, the mechanism of therapeutic

Table 7.8 Spectrum of antiepileptic activity of AEDs in animal models and in man as a function of predominant cellular mechanisms of action (from Löscher and Schmidt, 2011)

Drug	Anticonvulsant effect in rodent models			Clinical efficacy (seizure suppression)		
	MES (mice/rats)	s.c. PTZ (mice/rats)	Amygdala-kindling (rats, focal seizures)	Partial seizures	Generalized seizures	
Predominant Na^+ (and $Ca2^+$) channel activity					Convulsive	Nonconvulsive
Phenytoin	+	NE	+	+	+	NE
Carbamazepine	+	NE	+	+	+	NE
Oxcarbazepine	+	NE	+	+	+	NE
Lamotrigine	+	±	+	+	+	+
Zonisamide	+	±	+	+	+	+
Predominant Ca^{2+} channel activity						
Ethosuximide	NE	+	NE	NE	NE	+
GABA systems						
Benzodiazepines	+	+	+	+	+	+
Vigabatrin	NE	+	+	+	+	NE
Tiagabine	NE	+	+	+	+	NE
Mixed						
Valproate	+	+	+	+	+	+
Felbamate	+	+	+	+	+	+
Topiramate	+	NE	+	+	+	+

(*cont.*)

Table 7.8 (*cont.*)

Drug	Anticonvulsant effect in rodent models			Clinical efficacy (seizure suppression)		
	MES (mice/rats)	s.c. PTZ (mice/rats)	Amygdala-kindling (rats, focal seizures)	Partial seizures	Generalized seizures	
Phenobarbital	+	+	+	+	+	±
Novel targets						
Gabapentin	±	±	+	+	+	NE
Pregabalin	+	NE	+	+	+	NE
Levetiracetam	NE	NE	+	+	+	±
Lacosamide	+	NE	+	+		
Retigabine	+	+	+	+		

MES = Maximal electroshock, NE = Not effective, PTZ = Pentylenetetrazole.

action of AEDs, although of great scientific interest and merit, is of little practical help for rational choice of AEDs, unless and until we can pinpoint the mechanism of epilepsy and seizure generation for individual patients.

In the end, AEDs are only a step on the way to the ultimate goal of epilepsy medicine, which is to provide treatments that prevent epilepsy or reverse it. Although AEDs prevent seizures, they are not antiepileptogenic, that is, they are not able to prevent epilepsy or to affect the underlying tendency to generate seizures. Strategies to develop antiepileptogenic therapies are under development using various animal models of chronic epilepsy. By targeting plasticity mechanisms that underlie the enhanced seizure susceptibility that often follows brain insults such as head trauma, status epilepticus, or neonatal hypoxia, antiepileptogenic drugs of the future would ideally prevent or reverse progressive worsening of the epileptic process.

Take Home Message

Unfortunately, the mechanism of therapeutic action of AEDs, although of great scientific interest and merit, is of little practical help at present for the rational choice of AEDs, unless and until we can pinpoint the mechanism of epilepsy and seizure generation for individual patients.

Pitfall: Failure to Adapt the Drug Choice to the Individual Patient Profile

The choice of the AED among first-line agents needs to be individualized mainly based on the patient profile including the efficacy for the seizure or the epilepsy syndrome, tolerability, safety, ease of use, pharmacokinetics, including the current or likely future need for concomitant medication for co-morbidity, and finally cost and physician preference (Boxes 7.4 and 7.5).

Box 7.4 Checklist for assessing individual patient profile

- Efficacy for individual seizure and epilepsy syndrome?
- Tolerability of AED? Any issues?
- Older than 65 years?
- Male hypogonadism?
- Body mass index above 25 kg/m^2
- Depression?
- Cognition?
- Lipid profile?
- Osteoporosis?
- Woman of childbearing potential?
- Comedication, now or probable in 10 years from now?
- History of idiosyncratic reactions?

Box 7.5 List of drugs to consider for specific patient profiles, if possible (class of evidence in parentheses)

- Efficacy for individual seizure and epilepsy syndrome: prefer efficacious first-line agents (I)
- Tolerability of AED? Any issues to be discussed: prefer well-tolerated first-line agents (I)
- Older than 65 years: prefer GBP or LTG to CBZ (I)
- Male hypogonadism: prefer GBP, LEV, LTG over enzyme-inducing agents such as CBZ (III)

- Body mass index above 25 kg/M^2: prefer weight neutral AEDs such as CBZ, LEV, LTG, OXC over VPA, GBP, or pregabalin, or prefer TPM and ZNS if weight loss may be beneficial (III)
- Depression: prefer CBZ, GBP, LTG, VPA, and TPM to PHT, PHB, TGB, and VGB (III)
- Cognition: prefer CBZ, GBP, LTG, and VPA to TPM and high-dose PHB or PRM (III)
- Lipid profile: prefer OXC to CBZ (III)
- Osteoporosis: prefer GBP, LEV, LTG, OXC over enzyme-inducing agents such as CBZ or VPA, which may activate osteoclastic activity
- Woman of childbearing potential: prefer CBZ and LTG to VPA (III)
- Comedication, now or probable in 10 years from now: prefer nonenzyme-inducing agents (III)
- History of idiosyncratic reactions: prefer AEDs which do not cause such reactions such as GBP, LEV (I)
- Avoid TPM and ZNS in patients with a personal or a family history of kidney stones (III)

Pitfall: Is the Pharmacokinetic Profile Ready for Prime Time in the Choice of an AED?

From a clinical perspective, the ideal AED does not require monitoring of plasma concentrations, is metabolically inert and not involved in drug interactions, and can be conveniently given once or twice a day. Unfortunately, a number of currently used classic AEDs induce the CYP P450 system, such as CBZ, PB, and PHT, or inhibit enzymes involved in drug metabolism, such as VPA (Box 7.4). A review of the evidence suggested that the older enzyme-inducing drugs are sometimes involved in deleterious drug–drug interactions and have many detrimental metabolic effects on vitamin D and bone metabolism, gonadal steroids, cholesterol, and other markers of vascular risk (Mintzer and Mattson, 2009). Fortunately, newer AEDs are available that are less enzyme inducing such as OXC or are not metabolized by the oxidative CYP 450 system at all such as GBP, LTG, PGN, or TPM, and therefore are less likely to be involved in drug interactions (Box 7.6).

Box 7.6 Interaction profile of AEDs

Key: (a) No clinically relevant interactions with drugs or endogenous substances, (b) Adding drug causes no interactions, but drug disposition is affected by other drugs (LTG), or few clinically relevant interactions with drugs or endogenous substances (OXC, TPM, VPA), (c) Causes clinically relevant interactions with drugs or endogenous substances.

(a)	CLB, GBP, LEV, LCM, PGN, TGB, VGB
(b)	LTG, OXC, TPM, VPA
(c)	CBZ, PB, PHT, PRM

The absence of drug interactions is a very important advantage for an AED. Most patients with epilepsy are treated for several years, and a majority need AEDs for their lifetime. As a result, the long-term consequences need to be taken into account. For example, a girl might wish to take oral contraceptives in her reproductive years, an adult may become overweight and develop depression, anxiety disorders or migraine or common serious disorders such as cardiovascular disease, diabetes or cancer and may require additional medications. The elderly, who commonly suffer

from multimorbidity, also require AEDs that do not interact with other medications. Finally, one in three patients with new-onset epilepsy will require a combination or a succession of AEDs in their lifetime for optimal seizure control. In addition, AEDs that are involved with drug interactions, e.g., through enzyme induction or enzyme inhibition, will also disadvantageously affect the endogenous sexual and other hormone metabolism, and may contribute to adverse events (see Chapter 12). Consequently, taking enzyme-inducing CBZ, OXC, PB, PHT, or PRM may – in contrast to GBP, LTG, and TPM below 200 mg/day – lead to reduced efficacy of co-medication including oral contraceptives, AEDs, and other medication. Adding an oral contraceptive may lower the plasma concentrations and the efficacy of LTG. VPA is not involved in interactions with oral contraceptives, but it may however inhibit glucuronidation, for example, of LTG. Fewer clinically relevant interactions with drugs or endogenous substances occur when taking OXC, TPM, and VPA instead of classic enzyme-inducing AEDs, which are the least advantageous agents in that respect. Finally, many classic AEDs share the disadvantage of both causing clinically relevant interactions and being affected by other drugs. For all these important reasons, absence of enzyme induction or enzyme inhibition is a plus for any AED (Box 7.6).

Up to one in three patients with new-onset epilepsy will require a combination of different AEDs for seizure control. In uncommon cases, even more than two AEDs may be needed. During combination therapy, a number of drug interactions may arise when classic AEDs are used. Drug interactions may interfere with drug efficacy. A prototypic example is the combination of CBZ and VPA. When VPA is added to CBZ, adequate VPA serum concentrations cannot be achieved in most cases because CBZ lowers the serum concentration of VPA. However, drug interactions may also increase the serum concentrations to toxic levels, for example of LTG in the presence of VPA. Although beneficial for many patients, tremor may develop and the combination of LTG and VPA has been shown to be more teratogenic than LTG alone or LTG in combination with other AEDs. However, newer AEDs such as GBP, LEV, PGN, or TGB are much better suited for combination therapy as they are much less or not involved at all in AED drug interactions (Table 7.9). By starting epilepsy treatment with noninteracting AEDs, such complications can be prevented.

A large number of patients with epilepsy rely on additional medication other than AEDs, e.g., for birth control or management of other disorders. Depression, anxiety disorders, and migraine are common in patients with epilepsy. Patients with epilepsy are not protected from common diseases such as stroke, myocardial infarction, or cancer, which all require medication that may be interfered with by classic enzyme-inducing AEDs. Antibiotic treatment may be needed, which increases serum concentrations of AEDs and may thus cause toxicity (Table 7.9). Again, by starting epilepsy treatment with newer noninteracting AEDs, such complications can be prevented.

Take Home Messages

- Despite the introduction of many new AEDs over the last two decades, the older agents carbamazepine, phenytoin, and phenobarbital, which are potent inducers of the cytochrome P450 (CYP450) system, remain the AEDs most commonly prescribed throughout the world.
- At the same time, there is growing concern regarding the possible adverse consequences of CYP450 induction, such that it is appropriate to pose the question of whether the inducing drugs should still be considered first-line agents for the treatment of focal epilepsy.

Table 7.9 Clinically relevant effect of AEDs on the disposition of other drugs

AED	(▼)	(▲)	Comments
Benzodiazepines (BZP)	No relevant change	No relevant change	Higher sedation when taken with other sedating drugs (e.g., alcohol, PB)
Carbamazepine (CBZ)	Anticoagulants, contraceptives, corticosteroids cyclosporine A, folate, digitalis-glycosides, donepezil, doxycycline, felodipine, mebendazole, methadone, muscle relaxants, nifedipine, nimodipine, quinidine, theophylline, verapamil	Diltiazem	Lithium neurotoxicity may be functionally increased with comedication of AED. MAO inhibitors contraindicated
Eslicarbazepine	Oral contraceptives	Do not use together with oxcarbazepine	
Felbamate (FBM)	No relevant change	No relevant change	
Gabapentin (GBP)	No relevant change	No relevant change	
Lamotrigine (LTG)	No relevant change	No relevant change	
Lacosamide (LCM)	No relevant change		
Levetiracetam (LEV)	No relevant change	No relevant change	
Oxcarbazepine (OXC)	Felodipine, contraceptives, nifedipine, nimodipine	No relevant change	Lithium neurotoxicity may be functionally increased with comedication of AED, MAO inhibitors contraindicated

Phenobarbital (PB)	Anticoagulants, contraceptives, corticosteroids, cyclosporine A, diltiazem, digitalis-glycosides, donepezil, doxycycline, felodipine, folate, griseofulvin, haloperidol, mebendazole, methadone, metoprolol, nifedipine, nimodipine, metronidazole, muscle relaxants, propranolol, quinidine, tacrolimus, tamoxifen, theophylline, verapamil	No relevant change	Methotrexate toxicity may be functionally increased with comedication of AED
Phenytoin (PHT)	Anticoagulants, contraceptives, corticosteroids, cyclosporine A, digitalis-glycosides, donepezil, doxycycline, folate, mebendazole, methadone, muscle relaxants, nifedipine, nimodipine, quinidine, theophylline, verapamil	Diltiazem, disulfiram	Lithium neurotoxicity may be functionally increased with comedication of AED, MAO inhibitors contraindicated
Pregabalin (PGN)	No relevant change	No relevant change	
Primidone (PRM)	See PB	See PB	
Tiagabine (TGB)	No relevant change	No relevant change	
Topiramate (TPM)	Contraceptives (TPM > 200 mg/day)	No relevant change	
Vigabatrin (VGB)	No relevant change	No relevant change	
Valproate (VPA)	Itraconazole	Anticoagulants	VPA may functionally increase anticoagulation

Abbreviations: (▼) efficacy of specified drug may be lower with comedication of specified AED, (▲) toxicity of specified drug may be higher with comedication of specified AED, (◄►) no relevant change in disposition.

- The existing data are sufficiently concerning to suggest that it may be prudent to start treatment for new-onset epilepsy with noninducing AEDs unless there is a clear indication for one of the inducing drugs.
- Avoiding enzyme-inducing or -inhibiting classic AEDs and using beneficial combinations of AEDs, if needed for seizure control, can minimize adverse drug interactions.

An optimal pharmacokinetic profile of an AED, in particular absence or low risk of interaction potential, is a clinically important asset and needs to be taken into account in the selection of the most appropriate drug for the individual patient.

Pitfall: Base Your Choice on the Belief that New AEDs are Better Tolerated or Safer than Older Drugs

The main advantages of some of the newer AEDs include lower risks of hypersensitivity reactions, weight problems, and drug interactions, which can cause toxicity. With some of the newer AEDs, there is no need for routine laboratory monitoring except to monitor adherence and safety is improved with absence of potential life-threatening organ damage. Patients receiving CBZ should have a CBC once a month for the first year of therapy. If the WBC or RBC count decreases significantly, the drug should be discontinued immediately. Patients receiving VPA should have liver function tests every 3 months for 1 year; if serum transaminases or ammonia levels increase significantly (to more than 2 times the upper limit of normal), the drug should be discontinued. An increase in ammonia up to 1.5 times the upper limit of normal can be tolerated safely. When an overdose reaction occurs, the amount of drug is reduced until the reaction subsides. When more serious acute poisoning occurs, the patient is given ipecac syrup or, if obtunded, is lavaged. After emesis or lavage, activated charcoal is administered, followed by a saline cathartic (e.g., magnesium citrate). Hemodialysis may be considered. The suspect drug should be discontinued, and new AEDs started simultaneously. For more detailed discussion of adverse events, see Engel and Pedly (2007).

Although many believe that some newer AEDs are better tolerated than older ones, the authors of the ILAE Treatment Guidelines have suggested that statistically this has been very hard to show, except in a few studies (Glauser et al., 2006). There is concern that many of these studies were designed to support marketing strategies, and some of the methods used in these trials can skew the results in favor of the sponsor's product. For example, choice of inclusion and exclusion criteria, choice of comparator drug and formulation (slow release or not), dosing intervals, titration rates, and end-points can influence outcome (Glauser et al., 2006). There is no doubt, however, that a lower risk of hypersensitivity reactions and detrimental drug interactions have made some newer AEDs, such as LEV or GBP, better tolerated and easier to use than some of the first-generation AEDs such as CBZ or PHT (Schmidt and Beyenburg, 2009). Among third-generation AEDs, LEV has advantages such as ease of use, lower risk of rash and drug interaction, and good utility for adjunctive use in juvenile myoclonic epilepsy that have made it one of the most often used AEDs. The use of LEV is likely to increase even more when it is globally available as a generic medication, as in the United States.Although a detailed discussion of life-threatening adverse effects of AEDs of new versus old AEDs is beyond the scope of this review, the lower risk of hypersensitivity and idiosyncratic

reactions for some third-generation AEDs such as GBP and LEV may offer advantages over classic AEDs such as CBZ, PHT, and PB (Schmidt, 2009). However, serious idiosyncratic adverse effects have also been reported for several newer AEDs such as VGB (concentric visual field defects), felbamate (FBM; aplastic anemia, hepatic failure), and LTG and OXC (Stevens–Johnson syndrome) (Schmidt, 2009). For some of the third-generation AEDs, clinical trials indicated treatment-related depressive symptoms in more than 1% of treated patients (FBM, LEV, TGB, TPM, VGB, zonisamide), whereas frequencies of less than 1% have been noted for GBP, LTG, OXC, and PGB (Mula and Sander, 2007).

It is worthwhile to note that all AEDs currently carry an FDA "class label" indicating that patients taking an AED are at a greater risk for suicide (US Food and Drug Administration, 2008). Nonetheless, epilepsy patients without depression may not be at substantial increased risk of suicidal ideation, behavior or both, when using second- and third-generation AEDs (Arana et al., 2010). Unfortunately, regulatory trials are usually too short and too small to capture rare adverse effects that emerge during post-marketing long-term treatment. In addition, fixed-dose titration, which is used in many regulatory trials, is prone to overstate the side-effect profile seen with prudent flexible dosing in clinical practice or with single drug treatment. Also, surprisingly, there are no comparative trials that have evaluated the general clinical benefits associated with a lower risk of hypersensitivity reactions and drug interactions seen with some of the newer AEDs such as LEV or GBP versus older AEDs such as PHT and CBZ. However, a double-blind comparative trial of LEV versus CBZ-constant release (CR) mimicking clinical practice reported a similar proportion of patients in the LEV (79.6%) and CBZ–CR groups (80.8%) that experienced at least one adverse event during the treatment period (Brodie et al., 2007). Overall, there was no substantial difference in the adverse effects reported between LEV and CBZ and the proportion of patients who discontinued therapy because of adverse events (Brodie et al., 2007). LTG had a lower rate of drug discontinuation because of side effects compared to CBZ in a large randomized but unmasked study of patients with mostly new-onset epilepsy (Marson et al., 2007); however, the same study reported no differences in the proportion of patients with at least one adverse effect during treatment with LTG, GBP, TPM, or OXC compared with CBZ or VPA. Similarly, in other studies, the proportion of patients withdrawing from medication due to adverse effects was similar for the range of newer AEDs when compared to conventional or slow-release CBZ (Brodie et al., 2007; Marson et al., 2007).

Teratogenic effects of AEDs, as discussed in Chapter 12, are an important consideration in women of childbearing potential and could not be assessed in the SANAD study or the study by Brodie et al. (2007). Among old AEDs, VPA is known to be the most teratogenic agent, while CBZ seems to have a lower teratogenic potential than VPA (Tomson and Battino, 2009). Among the often-used newer AEDs, LTG and possibly LEV seem to have a low teratogenic potential, which appears to be similar to that of CBZ and lower than that of VPA (Tomson and Battino, 2009). More recently, the FDA warned that TPM has caused malformations involving the mouth (FDA Safety Alert, 2011). However, as a note of caution, we currently have no large-scale comparative teratogenicity data of new versus old AEDs.

The current review suggests that, in agreement with the literature (Wilby et al., 2005), the available evidence on tolerability and safety does not support a general advantage of all new AEDs over all old AEDs. However, it is clinically important that some of the

newer AEDs such as LEV, GBP, or LTG seem to be safer compared to some other new AEDs, such as VGB and FBM, and to VPA, among the old AEDs. In addition, some of the new AEDs such as LEV, GBP, and LTG seem to be better tolerated than immediate-release CBZ, particularly in the elderly. Compared to slow-release CBZ, however, a head-to-head study in elderly patients found only a nonsignificant trend for better tolerability of LTG (Saetre et al., 2007).

Recommendation

Adverse effects of AED treatment can be minimized by slow dose escalation up to average daily maintenance doses (unless increments are needed for seizure control), by avoiding enzyme-inducing agents and polytherapy, if possible, and by using appropriate well-tolerated newer AEDs both for new-onset cases and refractory epilepsy.

Possible adverse effects of AEDs are listed in Table 7.10.

Pitfall: Are You Aware of the Limitations of Current Treatment?

Lack of epileptogenic action of current AEDs. Current AEDs suppress seizures without influencing the underlying tendency of brain circuits to generate seizures. One major aim of ongoing research is understanding how epilepsy develops so that strategies can be developed and tested to prevent the development of epilepsy (epileptogenesis). Clinically, there is often a "silent interval" between the occurrence of a brain insult and the appearance of recurrent seizures in many acquired forms of epilepsy such as traumatic brain injury. In addition, most genetically determined epilepsy syndromes do not become clinically manifest until well after birth. Both these facts suggest that epileptogenesis is a gradual process that can be specifically targeted. Ideally, we would like to have a drug that prevents the development of epilepsy, rather than one that merely suppresses seizures. Unfortunately, none of the available AEDs appears to have a prophylactic effect in patients who are at risk for the development of epilepsy.

Lack of prophylactic treatment effect prior to the first seizure. Head injuries with skull fractures, intracranial hemorrhages, focal neurological deficits, or amnesia cause posttraumatic epilepsy in 25–75% of cases. Prophylactic treatment with an AED after the head injury reduces the probability of early posttraumatic seizures during the first few weeks after the injury but does not prevent the development of chronic posttraumatic epilepsy months or years later. Likewise, early treatment after a second generalized tonic–clonic seizure irrespective of cause does not improve the long-term outcome of the epilepsy. It is now clear that while the new generation of AEDs is very useful, many patients for whom previous drug regimens were ineffective will likewise not respond to the newer drugs. A challenge for the scientific community is to determine the causes for these drug failures and circumvent obstacles to seizure control by developing novel treatment strategies.

Pitfalls in the Development of New AEDs

Although adjunctive treatment with new AEDs is standard care in refractory epilepsy, as reviewed in the previous section, it is unclear how much of the effect can be directly attributed to the AEDs and how much to the beneficial changes seen with placebo. This prompted a systematic review and meta-analysis of the evidence to determine the placebo-corrected net efficacy of adjunctive treatment with newer AEDs on the market for refractory epilepsy (Beyenburg et al., 2010). A review of 55 publications comprising

Table 7.10 Overview on adverse effect profiles of AEDs

	CBZ	PB	PHT	VPA	ESM	CLB	FBM	GBP	LEV	LTG	OXC	PGN	TGB	TPM	VGB	ZNS	ESL	LCM
CNS																		
Encephalopathy			•	•											•			
Cognition impaired		•												•		•		
Depression/ behavioral problems/ psychotic episodes		•	•		•	•	•		•				•		•	•		
Non-CNS																		
Rash	•	•	•							•	•							
Leucopenia/ anemia/ thrombopenia	•	•	•	•			•											
Pancreatitis				•				•										
Nephrolithiasis														•		•		
Hepatic failure				•			•											
Osteoporosis	•	•	•	•														
Hyponatremia	•										•						•	

(*cont.*)

Table 7.10 (*cont.*)

	CBZ	PB	PHT	VPA	ESM	CLB	FBM	GBP	LEV	LTG	OXC	PGN	TGB	TPM	VGB	ZNS	ESL	LCM
Weight change				•				•				•		•	•			
Drug interaction	•	•	•	•						•	•					•		•
Highest teratogenicity (see text)				•														

There is evidence that most of the listed effects occur with virtually all AEDs, although at much lower rates with some drugs compared with others as indicated by blank boxes. As a note of caution, blank boxes do not indicate that this AED is free of the given adverse effect but only that the rate of the individual adverse effect is less often seen than with other drugs. Filled boxes indicate that the risk is relatively higher compared with other AEDs. In general, although the exposure of some of the newer third-generation AEDs, such as rufinamide and lacosamide (LCM), is still very limited, which makes comparison difficult, a number of third-generation AEDs in longer use, such as LEV, GBP, and LTG, appear to have advantages in their adverse event profile including, in particular, absence or a lower risk of life-threatening complications, hypersensitivity, and drug interactions compared to some of the first- and second-generation AEDs (adapted from Engel and Pedley, 2007). It should be noted, however, that the day-to-day tolerability, which is not covered here, such as dizziness and somnolence, can be reduced for any AED by slow titration and by avoiding overtreatment. For comparison of percentage of patients with at least one adverse event and for the proportion of patients who discontinue treatment because of adverse events, see text. Abbreviations: CBZ, carbamazepine; PB, phenobarbital; PHT, phenytoin; VPA, valproic acid; ESM, ethosuximide; CLB, clobazam; FBM, felbamate; GBP, gabapentin; LEV, levetiracetam; LTG, lamotrigine; OXC, oxcarbazepine; PGN, pregabalin; TGB, tiagabine; TPM, topiramate; VGB, vigabatrin; ZNS, zonisamide; ESL, eslicarbazepine; LCM, lacosamide; • = clinically important part of the adverse effect profile of that AED that is more often seen than with other AEDs.

a total of 11,106 adults and children with refractory epilepsy showed that the overall weighted pooled risk difference in favor of AEDs over placebo for seizure-freedom in the total sample of adults and children was 6% (95% CI 4–8%, $z = 6.47$, $p < 0.001$) and 21% (95% CI 19–24%, $z = 17.13$, $p < 0.001$) for 50% seizure reduction. Although the presence of moderate heterogeneity may reduce the validity of the results and limit generalizations from the findings, the study authors concluded that the placebo-corrected efficacy of adjunctive treatment with newer AEDs is disappointingly small and they suggest that better strategies of finding drugs are needed for refractory epilepsy, which is a major public health problem (Beyenburg et al., 2010).

Therefore, despite the development of various new AEDs since the early 1990s, the available evidence indicates that the efficacy and tolerability of drug treatment of epilepsy has not substantially improved. What are the reasons for this apparent failure of modern AED development to discover drugs with higher efficacy? One reason is certainly the fact that, with few exceptions, the same conventional animal models have been used to screen candidate AEDs, especially the maximal electroshock seizure test (MES) in rodents, which has served as a critical gatekeeper. These tests have led to useful new AEDs, but obviously did not help to develop AEDs with higher efficacy in patients with AED-resistant seizures. This concern is not new but, surprisingly, has largely been unappreciated for several decades. A second – admittedly speculative – reason is that progress in pharmacological treatment of drug-resistant epilepsy will not be made unless and until we develop drugs that specifically target the underlying disease. Although better preclinical approaches will not be able to circumvent regulatory requirements, more efficacious drugs may allow us to abandon clinically questionable trials with intentionally less efficacious controls and non-inferiority designs, and require evidence for comparative effectiveness. The failure of AED development has led to increasing disappointment among clinicians, basic scientists, industry, and patients, and industry may halt their efforts to fund programs to further improve the treatment of epilepsy unless we find ways out of this dilemma. Thus, we need new concepts and fresh thinking about how to radically change and improve AED discovery and development. We will need new ideas that may hopefully lead to more efficacious drug treatment of epilepsy in the future.

Summary of Pitfalls in the Choice of Drugs

The epilepsies are among the most common serious chronic disorders of the brain. The presentations differ widely due to different seizure types, syndromes, causes, comorbidities, and other individual patient factors. Fortunately, up to 70% of patients will have their seizures controlled with drugs, which makes epilepsy one of the most treatable chronic conditions of the brain. However, the remaining patients continue to have seizures and suffer also from their negative effects on quality of life, morbidity, and risk of mortality. Surgical treatment is life changing for a small proportion of properly selected patients. Once the causation of epilepsies becomes better understood, it will lead to better treatment, moving from seizure suppression to prevention of epilepsy. Pharmacogenetic studies hold the promise of being able to better individualize treatment for each patient, with maximum possibility of benefit and minimum risk of adverse effects. We believe that what happens every day in the care of individuals with epilepsy deserves the most attention. People with epilepsy need empathy and sympathetic, holistic care that integrates science with the personal needs of the individual.

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Chapter 8

How to Optimize Treatment and What can Go Wrong?

Dieter Schmidt

The major opportunities to optimize the treatment of epilepsy start with finding the optimal dose of the AED and avoiding under- and overtreatment. Monitoring the treatment is an integral part of the optimization process. Both under- and overtreatment need to be avoided. If necessary, the medical regimen can be modified in the course of treatment. Finally, treatment needs to be adapted to the requirements of specific patient populations and, further, individualized. These steps will be discussed below. Further options for optimization, which are explored in other chapters, include the choice of drug, stopping treatment in seizure-free patients or, alternatively, considering what to do next if drugs don't work.

Finding the Optimal Dose of AEDs for New-Onset Epilepsy

The two clinically most important questions are: one, how many patients with previously untreated epilepsy will become seizure-free at a low dose of the first-ever AED, and two, how many patients will become seizure-free with dose increments if the lowest dose has failed to achieve seizure-freedom. Finding the lowest dose that achieves seizure-freedom in a previously untreated patient is not as straightforward as it seems. Few studies have addressed this important question. Kwan and Brodie (2001) studied the effectiveness of the first AED in a hospital-based observational study of 470 patients with newly diagnosed epilepsy. Outcome was classified as seizure-freedom for at least the last year or failure of initial treatment because of inadequate seizure control, adverse events, or for other reasons. The first important result was that 47% of all patients became seizure-free with the first prescribed AED. In this study, most patients (83%) received carbamazepine (CBZ; $n = 212$), sodium valproate (VPA; $n = 101$), or lamotrigine (LTG; $n = 78$). The most important finding was that the majority of seizure-free patients required only a moderate daily AED dose (93.1% with ≤800 mg CBZ, 91.3% with ≤1,500 mg VPA, 93.8% with ≤300 mg LTG). The most common dose ranges were 400–600 mg for CBZ, 600–1,000 mg for VPA, and 125–200 mg for LTG. Another important outcome was that most withdrawals due to poor tolerability also occurred at or below these dose levels (CBZ: 98%; VPA: 100%; LTG: 75%). Nearly 50% of newly diagnosed patients became seizure-free on their first-ever AED, with >90% doing so at moderate or even modest dosing. Tolerability was as important as efficacy in determining overall effectiveness. Recommended AEDs for new-onset epilepsy and their commonly used target doses are given in Table 8.1.

Table 8.1 Commonly used target doses of AEDs for new-onset epilepsy

Focal epilepsies	Genetic (formerly idiopathic) generalized epilepsies
Newer AEDs Eslicarbazepine 300–1,200 mg Gabapentin 900–2,400 mg/day Lamotrigine 100–300 mg/day Oxcarbazepine 300–1,800 mg/day Topiramate 50–200 mg/day	Newer AEDs Lamotrigine 100–300 mg/day Perampanel 4–12 mg/day Topiramate 50–200 mg/day
Classic AEDs Carbamazepine 200–1,200 mg/day	Classic AEDs Valproate 600–1,500 mg/day Ethosuximide 250–2,000 mg/day

Pitfall: What to Do If the Lowest Dose Does not Achieve Seizure-Freedom

The effectiveness of dose increments in patients who do not become seizure-free at the lowest dose of the first AED was studied in detail by Kwan and Brodie (2001). When monitoring the daily dose of CBZ taken by seizure-free patients, Kwan and Brodie (2001) found that 10% of those becoming seizure-free were only on 200–300 mg/day while at doses of up to 600 mg/day, the vast majority (74%) had achieved seizure-freedom. Only an additional 9% became seizure-free with a dose increment from 600 up to 800 mg/day and a further mere 7% became seizure-free when the dose was doubled from 800 up to 1,600 mg/day. Taken together, increasing the dose from 600 mg/day up to 1,600 mg/day achieved seizure-freedom in 16% of patients. For VPA, similar proportions of patients were seizure-free: 14% at doses up to 500 mg/day, 64% with up to 1,000 mg/day, and only 23% with dose increments above 1,000 mg/day up to 2,500 mg/day. For LTG, 21% were seizure-free at doses of 100 mg/day or below; the percentages of patients becoming seizure-free with dose increments up to 200 mg/day were 63% and 16% for increments above 200 mg/day (Kwan and Brodie, 2001).

Take Home Message

Nearly 50% of newly diagnosed patients become seizure-free on their first-ever AED, with 85% doing so at moderate or even modest dosing of up to 600 mg CBZ, 1,000 mg VPA, and 200 mg LTG. The drug of choice for the particular type of epilepsy is initially maintained at the lowest effective dose. If seizures continue, the daily dose is increased by small increments to the average effective dose. Slow titration up to average maintenance doses is generally advisable, because rapid dose escalation and higher-than-average dosages cause adverse events and improve seizure control in only a further 20–30% of all responders. If the therapeutic benefit is not seen after further dose escalation, returning to the previous dose will avoid unnecessary toxicity.

Pitfall: What to Do If Seizures Persist despite Average Doses of AEDs?

If seizures continue at the lowest effective dose, the daily dose is increased by small increments to the average effective dose (Table 8.2). The usefulness of increasing

Table 8.2 Starting dose and average effective dose plus titration schedule

AED	Starting dose (mg/day)	Average dose (mg/day) up to	Time to reach average dose (weeks)
Brivaracetam	50–100	200	2–4
Bromide	300	2,100	8
Carbamazepine	200	800	2
Clobazam	10	20	1
Eslicarbazepine	300	1,200	2
Ethosuximide	250	1,000	8
Gabapentin	300	2,400	1
Lacosamide	150	400	2
Lamotrigine	25	300	10
Levetiracetam	500	2,000	4
Oxcarbazepine	150	1,200	2
Perampanel	4	12	4
Phenobarbital	50	200	8
Phenytoin	100–200	300	2
Primidone	125	250	8
Tiagabine	5	35	7
Topiramate	25–50	100–200	9
Valproate	500	1,200	2
Vigabatrin	500	3,000	2
Zonisamide	25	300	3

the daily dose of AEDs in patients who were not seizure-free was demonstrated in a study in which single drug therapy with either phenytoin (PHT) or primidone (PRM) resulted in complete seizure control in 11 of 35 patients (31%) referred to an epilepsy clinic for treatment of uncontrolled chronic epilepsy with complex partial seizures (Schmidt, 1983). Complete seizure control was associated with an increase in the mean plasma concentrations from 14 to 23 μg/ml PHT and from 34 to 40 μg/ml phenobarbitone (PB) with no change in the AED. Insufficiently low plasma concentrations of less than 11 μg/ml PHT or PB were measured at the first visit in 14 patients (40%). Noncompliance was admitted by eight patients (23%). The conclusion was that optimum single drug therapy is of considerable clinical value in apparently intractable focal epilepsy (Schmidt, 1983).

However, except in an emergency, there is no need for rapid titration. While the time to reach average daily dosages varies considerably among AEDs, most newer AEDs work within several days to a week after starting treatment. Rapid titration is not only unnecessary but may even be harmful. It increases the risk of hypersensitivity skin reactions, for example with CBZ, LTG, and PHT, and adds avoidable CNS toxicity, particularly during early PRM therapy. As discussed above, the average effective dose achieves seizure control in about 70–80% of those who respond at all. As a consequence, in those whose seizures are not controlled by a well-tolerated average dose, a dose increment is useful although

only for about 20–30%. If seizure control cannot be achieved with a maximum tolerated dose, a dose reduction to the previous average dose is recommended followed by consideration of adjunctive versus replacement therapy. A summary of daily dosages for adults and children is given in Table 8.2.

Pitfall: What to Do in a Patient Who is not Seizure-Free and Reports Intolerable Side Effects

If clinical symptoms or signs suggest unacceptable side effects or high plasma concentrations indicate an increased risk of toxicity developing before seizures are controlled, a second AED is generally added, again guarding against toxicity. Interactions between drugs can interfere with their rate of metabolic degradation (as discussed in Chapter 7). If the patient's seizures did not respond at all to the first AED, once the second AED has been added and titrated, the first AED is withdrawn gradually, if the patient is sufficiently informed and consents. Thus, transfer to a monotherapy with the recently added AED is an option. Many patients will understandably prefer not to change the medical regimen if they have benefited from their first AED (albeit without seizure-freedom) unless forced to do so by intolerable side effects. For this reason, a combination with both drugs is usually maintained unless side effects require a down-titration to lower the total drug load.

Pitfall: How to Avoid Overtreatment

The most common avoidable treatment errors stem from misdiagnosis (see Chapter 5) and inadvertent overtreatment. Common forms of misdiagnosis occur early in the management of a patient who is thought to suffer from epilepsy but in fact has syncope with myoclonia or psychogenic nonepileptic seizures. Subsequent AED use provides no benefit, even at higher doses, which invariably results in adverse events.

Overtreatment may, however, also occur in patients with unequivocal epileptic seizures. Although complete seizure control is the ultimate goal of pharmacological therapy, it should not be sought at any cost, meaning that no patient with epilepsy should suffer more from the side effects of treatment than from the consequences of the underlying disease. Overtreatment is not uncommon in patients taking AEDs, and may occur in many forms and with a variety of mechanisms. Long-term use (or continuation) of AEDs in situations where it is not indicated (e.g., in children with simple febrile seizures) constitutes overtreatment. Other forms of overtreatment include the use of unnecessarily high daily doses, for example, of VPA in women of child-bearing potential. In-utero exposure to VPA was associated with poorer cognitive outcome than exposure to other AEDs (Meador, 2008). This study had another clinically important result: the effect of VPA was dose-dependent. Daily dose below 1,000 mg/day during the first trimester of pregnancy was associated with a risk similar to that of other AEDs while VPA doses of 1,000 mg or more substantially increased the risk of having a child with low IQ (Meador, 2008). In fact, two other studies, one from the United Kingdom and the other from Finland, showed that the smallest IQ decrement was seen in children exposed to 800 mg/day or less compared to those exposed to higher doses of VPA. In addition, the proportion of children with major malformations associated with VPA seems to be dose-dependent. For example, the UK registry (Morrow et al., 2006) showed a lower percentage of major malformations (4.1%) for offspring exposed in utero to doses of 600 mg/day or less compared to higher doses of VPA (6.1% at 600–1,000 mg/day and 9.1% at 1,000 mg/day or more).

Take Home Message

If possible, do not increase the daily dose of VPA above 800 mg/d in women who can become pregnant.

Other forms of overtreatment include the use of unnecessarily fast dose escalation rates, which may expose the patient to potentially serious or severe side effects, or the prescription of unnecessarily high maintenance dosages. The latter occurrence may result from inadequate understanding of dose–response relationships, from misinterpretation of serum drug concentrations (e.g., targeting concentrations within the "range" in patients whose seizures are well controlled at lower concentrations) or, less often, from failure to recognize a paradoxical increase in seizure frequency as a sign of drug toxicity. The most common form of overtreatment, however, involves the unnecessary use of combination therapy (polypharmacy) in patients who could be treated optimally with a single drug. Adverse effects associated with polypharmacy often result from undesirable drug–drug interactions. While pharmacokinetic interactions are somewhat predictable and can be minimized or controlled by monitoring serum drug concentrations and/or dose adjustment, pharmacodynamic interactions leading to enhanced neurotoxicity (as seen, for example, in some patients given a combination of LTG and CBZ) can only be identified by careful clinical observation. There is evidence that not all AED combinations are equally adverse, and that the combined use of specific drugs (e.g., LTG and VPA) may even exhibit an improved therapeutic index in some patients compared with either agent given alone, provided appropriate dose adjustments are made. In women with childbearing potential, however, the same combination is associated more often with fetal malformations than either drug alone. Unless and until we better understand the complexities of drug combinations, single drug therapy will avoid inadvertent overtreatment associated with polypharmacy.

Pitfall: Undertreatment

Unfortunately, treatment of patients with uncontrolled epilepsy with sub-optimal doses may prevent seizure remission. In every patient with uncontrolled epilepsy, a dose increment should be considered unless the patient has symptoms and signs of incipient CNS or other organ drug toxicity. It has been shown that in as many as 1 in 3 patients presenting with uncontrolled seizures, increasing the dose will lead to seizure remission (Schmidt, 1983).

Recommendation

Keep it simple and avoid unnecessary diagnostic or therapeutic interventions with an unfavorable risk-to-benefit ratio. Consider withholding drug treatment until the diagnosis of epilepsy is certain. Avoid combination therapy and enzyme-inducing agents if possible. Both overtreatment and undertreatment with inadequately low doses should be avoided.

Pitfall: Is Add-On Therapy Advisable after Failure to Control Seizures with the First AED?

Once single drug therapy has been shown to be ineffective, adding a second drug or substitution monotherapy are common options. When the initially prescribed AED fails to produce seizure-freedom, transfer to monotherapy with an alternative agent

(substitution) will lead to full seizure control in as many as 15–30% of cases (Kwan and Brodie, 2000; Schmidt and Gram, 1995). The value of adding a second AED in patients with complex partial seizures was studied in a long-term prospective trial in 30 adult patients whose seizures had not responded to maximized treatment with either CBZ, PHT, PB, or PRM as the first drug (Schmidt, 1982). Based on the individual's previous history of one-drug treatment, the most promising AED (CBZ, clobazam, clonazepam, PB, PHT, PRM, VPA) was added and titrated, if necessary, until clinical toxicity occurred. A reduction of seizure frequency by more than 75% was seen in only four patients (13%). The remaining majority of patients (87%) did not benefit from the second drug; in three patients, the seizure frequency increased by more than 100%. Therefore, the common practice of adding another drug in difficult-to-treat cases may not necessarily be more beneficial than one drug in the treatment of intractable epilepsy.

The outcome of two-drug therapy in patients was studied in two subsequent studies. Kwan and Brodie (2000) studied the response to AEDs in 525 hospital-based patients (age, 9–93 years) who were given a new diagnosis of epilepsy, treated, and followed up at a single center between 1984 and 1997. Patients were considered to be seizure-free if they had not had any seizures for at least one year. Among 470 previously untreated patients, 222 (47%) became seizure-free during treatment with their first AED and 67 (14%) became seizure-free during treatment with a second or third drug. In this study, only 12 patients (3%) whose seizures were uncontrolled by the first drug became seizure-free by treatment with two drugs (Kwan and Brodie, 2000). For reasons that are unclear, the second study reported a more favorable outcome if the first AED had failed (Schiller and Najjar, 2008). A cohort of 478 consecutive patients who received AEDs was followed prospectively for 1.5–7.5 years in a single epilepsy clinic. The seizure-free rates decreased from 61.8% for the first AED to 41.7%, 16.6%, and 0% after one, two to five, and six to seven past AEDs proved inefficient. Consequently, although relative drug-resistant epilepsy can be diagnosed after failure of two past AEDs, absolute drug resistance requires failure of six AEDs, as a significant minority of patients (16.6%) is rendered seizure-free by addition of newly administered AEDs even after failure of two to five past antiepileptic drugs (Schiller and Najjar, 2008).

Based on the available evidence, there are no conclusive data in favor of either substitution monotherapy or add-on treatment. Two randomized controlled trials with mostly old, enzyme-inducing AEDs compared substitution with combination therapy and showed a rather similar outcome (Beghi et al., 2003; Hakkarainen, 1980). Except for patients with severe idiosyncratic reactions, where substitution is clearly preferable, a pragmatic choice is to evaluate the combination first and to slowly taper and finally discontinue the first drug. This may prevent the substitution of a partially efficacious drug by a non-efficacious drug. Reduction of the first drug prevents unnecessary drug exposure in case of adverse effects. The choice of the second drug should be based on which first drug has failed. The use of newer-generation AEDs that are not involved in drug interactions may possibly provide a better outcome for add-on treatment, which is more vulnerable to adverse drug interactions than substitution monotherapy. The main advantages of substitution versus combination include simplicity by allowing clear attribution of observed clinical effect, no unnecessary drug load (overtreatment) as in combination therapy, no detrimental AED drug interactions, and, no adverse effects of specific combinations, e.g., increased teratogenicity with a combination of VPA and LTG. Furthermore, transfer to monotherapy has been shown to be useful when combination therapy has

failed to provide sufficient seizure control. A safe and well-communicated transfer schedule is as essential as the choice of the optimal agent for the success of either combination or substitution.

Take Home Message

Except for patients with severe idiosyncratic reactions, where urgent substitution is clearly preferable, a pragmatic choice is to evaluate the combination first and to slowly taper and finally discontinue the first drug if the response to the combination is not impressive. Combining drugs during this process may prevent the substitution of an insufficiently efficacious drug by a non-efficacious drug. Reduction of the first drug prevents unnecessary drug exposure in case of adverse effects. In choosing the next drug, drugs that have failed in the past should be avoided and newer AEDs should be considered, which are better suited for combination because of the lower risk of adverse drug interactions.

Pitfall: Do I Need to Monitor Treatment with AEDs?

The aim of drug treatment for epilepsy is to prevent seizures without causing adverse effects. To achieve this, drug dosages need to be individualized. Measuring AED levels in body fluids (therapeutic drug monitoring) is frequently used to optimize drug dosage for individual patients. Target plasma AED concentrations are available for a number of drugs (see Table 8.3). But what is the evidence for this practice?

Most suggestions for monitoring AED levels routinely are not evidence-based (Tomson et al., 2007) and there is still considerable debate on the clinical usefulness of therapeutic drug monitoring in patients with epilepsy because the impact of therapeutic drug monitoring on clinical outcome has not been evaluated systematically. For example, the authors of a recent Cochrane review (Tomson et al., 2007) found only one randomized controlled trial meeting their inclusion criteria to assess the usefulness of routine AED monitoring in patients with newly diagnosed epilepsy with AED monotherapy. In that open study, 180 patients with newly diagnosed, untreated seizures were randomized to treatment with CBZ, VPA, PHT, PB, or PRM either with or without monitoring of serum AED levels. A 12-month remission from seizures was achieved by 60% of the patients randomized to therapeutic drug monitoring and by 61% in the control group. A total of 56% in the group with AED monitoring and 58% in the control group were seizure-free during the last 12 months of follow-up, and 48% in the intervention group and 47% of the control group patients reported adverse effects. Of those randomized to therapeutic drug monitoring, 62% completed the two-year follow-up compared with 67% of the control group. Thus, there was no clear evidence to support routine AED serum level measurement for the optimization of treatment in these patients in the settings in which they received care (Jannuzzi et al., 2000). In the only other available randomized trial, 127 patients with refractory epilepsy receiving mono- or polytherapy with different AEDs were randomly assigned to treatment with or without measuring AED serum levels. One-hundred and five patients completed the one-year follow-up. Blood sampling for determination of AED levels was done in all patients. However, the treating physician was not informed about the results. As a result, a substantial proportion of the patients in both groups had AED concentrations either below or above the so-called therapeutic range. Moreover, treatment outcome was not different in the two groups (Fröscher et al., 1981). This early study provided no evidence to support routine monitoring of AED serum levels (Fröscher et al., 1981).

Table 8.3 Common doses and ranges of serum concentrations of major AEDs in adults (modified from St. Louis, 2009)

AED	Usual dosages (adults)/day (mg)	Serum levels (µg/ml)
Carbamazepine	400–1,600	4–12
Eslicarbazepine	800–1,200	
Ethosuximide	500–1,500	40–100
Felbamate	1,800–4,800	30–100
Gabapentin	900–3,600	4–20
Lacosamide	200–400	?
Lamotrigine	300–600	1–20
Levetiracetam	1,000–4,000	5–40
Oxcarbazepine	600–3,600	10–40
Phenobarbital	90–180	15–40
Phenytoin	200–400	8–20
Pregabalin	150–450	?
Primidone	500–1,500	5–12
Rufinamide	400–3,200	?
Tiagabine	16–64	100–300 ng/ml
Topiramate	100–600	10–20
Valproate	600–2,500	50–100
Vigabatrin	2,000–3,000	0.8–36
Zonisamide	100–600	10–40

?="therapeutic range" not yet established.

Tomson et al. (2007) found no clear evidence to support routine AED serum concentration measurement to reach predefined target ranges for AED treatment of patients with newly diagnosed epilepsy. However, this does not exclude the possible usefulness of therapeutic drug monitoring of specific AEDs drugs during polytherapy, in special situations (e.g., pregnancy or suspected nonadherence) or in selected patients (e.g., low albumin levels, hepatic dysfunction), although studies to support this approach are unavailable.

Given the lack of evidence, it seems that monitoring plasma AED concentrations should not be a substitute for following the clinical course, though it can provide support for clinical decisions. Some patients have toxic symptoms at low serum concentrations, while others tolerate higher serum concentrations without apparent clinical symptoms. Seizures in some patients respond at very low serum concentrations, while seizures in others do not respond even to very high serum concentrations. If treatment appears to be ineffective, monitoring of AED serum concentrations may unmask irregular drug compliance; conversely, a high serum concentration may indicate that a higher dose is not likely to lead to a better response and in addition involves a higher risk of drug toxicity. In a patient with unexplained CNS toxicity, finding high serum AED concentrations may be useful for diagnosis and management of the intoxication. Except for PHT, for which

monitoring is recommended, particularly at concentrations of above 20 mg/l, because of its nonlinear saturation dose kinetics, routine monitoring of other AED plasma concentrations is optional and should be individualized.

Best practice guidelines for therapeutic drug monitoring were proposed by the ILAE Commission on Therapeutic Strategies (Box 8.1). The group suggested that two separate terms should be used to define drug concentration ranges in relation to their clinical effects. The "reference range" can be defined as a range of drug concentrations, which is quoted by a laboratory and specifies a lower limit below which a therapeutic response is relatively unlikely to occur, and an upper limit above which toxicity is relatively likely to occur. This range represents the balance between antiseizure efficacy and dose-related side effects, and represents a purely statistically based standard of AED serum levels derived from population studies (mostly in patients with drug-resistant seizures). In contrast, the "therapeutic range" can be regarded as the range of drug concentrations that is associated with the best achievable response in a given subject.

Box 8.1 Recommendations for monitoring AED serum concentrations

The primary indications for monitoring AED serum levels have been extensively discussed and may be summarized as follows (from Patsalos et al., 2008):

- Monitoring of AED serum concentrations is helpful after the initiation of treatment or after dose adjustment (to achieve a target concentration in the individual patient and to establish an individual therapeutic range).
- In patients treated with drugs showing dose-dependent pharmacokinetics (e.g., PHT).
- In the case of presumed AED toxicity.
- When seizures persist despite an adequate dosage.
- During treatment of special patient populations (e.g., children and the elderly, women with epilepsy becoming pregnant). The rationale for monitoring in these patients is to elucidate altered pharmacokinetics in association with anticipated physiological alterations due to aging, pregnancy, and co-morbid conditions.
- In patients with presumed drug–drug interactions, to evaluate potential changes in steady state AED concentration.
- When a change in drug formulation is made, including switches involving generic formulations.
- When poor compliance is suspected or whenever there is an unexpected alteration in clinical response.

As discussed above, reference ranges are statistical estimates of the concentration ranges at which the majority of patients can be expected to show an optimal response to AED treatment. Several other limitations should be kept in mind when analyzing the results of serum level measurements. Most of the studies for defining reference ranges have been conducted in patients with medically refractory seizures. For most of the newer AEDs, reference ranges have not yet been clearly defined. Moreover, the limits of the ranges may vary from one patient to another. Thus, dose adjustments should never be made on the basis of serum level concentrations alone, but should always be made on the basis of a careful clinical evaluation of the individual patient ("treat the patient and not the serum concentration").

Take Home Messages

There is no clear evidence to support routine AED serum level measurement for the optimization of treatment in patients treated with AED monotherapy. AED drug monitoring can be clinically useful when altered pharmacokinetics or poor compliance is suspected, in the case of presumed neurotoxicity, and to evaluate drug–drug interactions (e.g., during polytherapy).

- AED monitoring should be only performed when there is a specific clinical question/reason. Except for PHT, where monitoring is useful, particularly at high doses resulting in concentrations of above 20 mg/l, because of the nonlinear saturation dose kinetics, monitoring of other AED plasma concentrations is optional and should be individualized (e.g., poor drug compliance or adverse events).
- Pitfalls in sampling: Blood samples should be taken at steady state (i.e., after a period has elapsed following a dosage change that is greater than four to five times the AED half-life) and immediately before the next oral dose, always (if possible) at a similar time of day.
- Situations that may influence AED serum levels in relation to clinical response should always be considered (e.g., polytherapy with other AEDs or concomitant drugs with possible pharmacodynamic interactions, co-morbidity, conditions or drugs that may alter pharmacokinetics, seizure type and frequency).
- Patient education about limitations and overinterpretation of serum level measurements is important.
- The golden rule to "treat the patient and not the serum concentration" cannot be overemphasized.

Pitfall: Failure to Inform the Referring Physician about Diagnostic or Therapeutic Changes

Failure to inform the referring physician or the patient's other physicians about any change in diagnostic or therapeutic developments is a common error. More specifically, it is clinically important to inform the patient's other physicians if the diagnosis has changed, e.g., if new seizure types have emerged or the syndrome diagnosis has been revised, or if AEDs have been introduced that are involved in clinically relevant drug interactions. One should ask the patient if he or she is on any new drugs or supplements for other indications that may interact with the current AED regimen or may affect the risk for seizures, such as certain antibiotics. Whether the patient has been diagnosed with another disorder, such as cancer, is of importance for the neurologist taking care of the epilepsy. For example, AEDs may interfere with the risk-to-benefit ratio of cancer treatment in two ways: enzyme-inhibiting AEDs such as VPA may cause side effects from the anti-cancer drugs, and, conversely, enzyme-inducers such as CBZ may substantially lower the efficacy of cancer treatment (Relling et al., 2000).

Pitfall: Failure to Address Special Patient Needs

One important step in optimization of AEDs is to adapt the treatment to the special requirements of specific patient populations. Here, we discuss children, adolescents, men, and the elderly; women and those with co-morbidities are discussed in Chapters 11 and 12.

Pitfalls in the Management of Epilepsy in the Elderly

Epilepsy has increasingly been recognized as being very common in the elderly. An increasing trend in the elderly has been reported in many countries (Brodie et al., 2009). Reasons for the rising incidence rate of epilepsy in the elderly are largely unknown but may include increased incidence and better survival of people with underlying medical conditions such as stroke. Stroke and other vascular catastrophes are the most common risk factors for epilepsy in the elderly, particularly in 65- to 74-year-old males. Cerebral tumors and severe brain injury are other major causes of epilepsy in the elderly. The incidence of neurodegenerative diseases, such as Alzheimer's dementia, increases with aging and the prevalence increases with the aging of populations, especially in developed countries. A diagnosis of Alzheimer's disease and other dementias, classified according to the criteria of DSM-III, are associated with at least sixfold risk for epilepsy (Hesdorffer et al., 1996). Increased awareness and, possibly, better identification and ascertainment of epilepsy of Alzheimer's dementia may be an additional factor for the increase.

There are several reasons why it is important to better understand epilepsy in the elderly. Epilepsy is a common condition in the elderly with significant consequences to quality of life. There is a significantly growing number of older adults in the population. Estimates convey that the number of people aged 65 and older will double between 2010 and 2050. A fourfold increase is expected in the number of persons over the age of 85. In combination, an expanding older adult population and an increasing segment with epilepsy both indicate a significant public health issue. Significant medical co-morbidities associated with seizures in the elderly, such as high rates of seizure recurrence, injuries from falls, high unexpected death rates, incidence of status epilepticus, and adverse medication interactions have all been documented. Although patients with childhood-onset epilepsy have an increased mortality, many such patients live to become elderly. Yet, we have limited information if the elderly with long-standing epilepsy are at increased risk for dementia or stroke.

Our understanding of the cognitive consequences of epilepsy has been long appreciated, especially within certain epilepsy syndromes (i.e., temporal lobe epilepsy). However, up until recently, the impact of epilepsy upon cognition in older persons with epilepsy has been disproportionately limited (Hermann et al., 2008). We have very limited understanding of the factors impacting cognition in persons with chronic epilepsy, as well as those experiencing new-onset epilepsy. The course of cognitive change in the older person with epilepsy has also not been well characterized, although recent studies have begun to elucidate these concerns but primarily from the viewpoint of extrapolation from young- and middle-aged populations of adults with epilepsy (Hermann et al., 2008). Although cognitive impact of chronic epilepsy in older adults is acknowledged, such is not the case in new-onset epilepsy in the elderly. It would seem that the presence of cognitive impairment in this patient group is considered a product of the underlying disease state causing the seizures (i.e., stroke). To date, limited data are available that have examined the cognitive outcome and possible progression of new-onset seizures in older adults. Although the majority of new-onset seizures in geriatric populations have a known etiology (i.e., cerebrovascular disease) and cognitive impairment linked to that known etiology, little is known about cumulative effects from the seizures or seizure treatment upon cognition in this group. In addition, up to one-third of cases are considered idiopathic. There exist virtually no data characterizing the cognitive functions or natural history in this patient group.

Pitfall: Diagnostic Errors in Geriatric Epilepsy

In many cases, a clear diagnosis of epilepsy can be rapidly made at the first presentation. In some patients, however, making a firm diagnosis can be a challenge because the clinical manifestations of seizures and the differential diagnoses and causes of epilepsy can be different in the elderly compared with younger individuals (Brodie et al., 2009). Further investigations are needed to establish a firm diagnosis of epilepsy or find an alternative cause for the events, most commonly syncope or nonepileptic confusional states. The extent of misdiagnosis is, however, unclear and the true prevalence of epilepsy in older people therefore remains difficult to determine with certainty. Potential reasons for the false diagnosis of epilepsy in older patients include lack of witness accounts and poor knowledge of features that distinguish epilepsy from other disorders. In particular, epilepsy is misdiagnosed in patients with syncope and falls of any nature with or without amnesia. Poor awareness that myoclonus, tonic movements, and upward gaze frequently occur in convulsive syncope is another cause for concern (Lempert et al 1994). Misinterpretation of interictal EEG and failure to consult specialists are also thought to be common causes for misdiagnosis of epilepsy (Brodie et al., 2009). The extent of misdiagnosis is, however, unclear and the true prevalence of epilepsy in older people therefore remains difficult to determine with certainty (Brodie et al., 2009; see Chapter 6).

Pitfall: Management of Epilepsy in the Elderly

Management of epilepsy in the elderly presents a number of problems (Brodie et al., 2009, Ramsay et al., 2004 and 2008). Age-related changes in pharmacokinetics and the higher sensitivity to adverse events of many AEDs usually require more cautious dosing in the elderly, and overtreatment may occur. In addition, co-morbidities in the elderly often require additional medication. To avoid disturbing drug interactions, AED monotherapy and the use of newer AEDs such as gabapentin (GBP), LTG, or levetiracetam (LEV) are preferable. It has been estimated that 10–12% of all nursing home residents receive AEDs; as a rule the elderly with epilepsy are taken care of by family doctors. Compliance may be more difficult in the elderly with cognitive decline. Multi-morbidity with many co-medications is common. The elderly may have an increased susceptibility for adverse events, especially when treated with CBZ. Ataxia may be more frequent in the elderly, and discontinuation of AEDs because of adverse events is more common in the elderly than in younger adults. Lower glomerular filtration rates in the elderly means that much lower doses of renally excreted AEDs are required. Changes in body fat, albumin, and CYP p 450 also occur in the elderly, and oxcarbazepine (OXC)-related hyponatremia may be more frequent in the elderly. Osteoporosis may be overlooked in the elderly with epilepsy who are on enzyme-inducing AEDs or VPA (Elger and Schmidt, 2008). In general, lower doses of AEDs are often sufficient because treatment response may be better in the elderly.

Pitfall: Failure to Recognize Treatment Options for Epilepsy in the Elderly

As reviewed by Brodie and colleagues (2009), only three randomized, double-blind, comparative clinical trials have been undertaken in older people with newly diagnosed epilepsy. In one study, LTG was as efficacious as and better tolerated than CBZ (Brodie et al.,

1999). However, this difference almost completely disappeared when using a controlled-release formulation instead of the standard formulation of CBZ using an identical study design (Saetre et al., 2007). Both studies had a flexible dosing design with identical low daily maintenance doses of both drugs (CBZ 400 mg vs. LTG 100 mg). The major difference between the studies was the median CBZ concentration, which was 6.9 mg/l with the standard CBZ formulation compared with 5.1 mg/l when a controlled-release formulation was used. The median LTG concentrations were almost identical (2.2 vs. 2.3 mg/l) between the two studies.

In the Veterans Administration study (Rowan et al., 2005), LTG, GBP, and CBZ were compared in a randomized, double-blind design. Seizure control was similar across the treatment groups. However, CBZ was significantly less well tolerated than the other two drugs. In paired-group comparisons, elderly patients randomly assigned to receive monotherapy with CBZ ($n = 197$) were less likely to remain on treatment than were those who were randomly assigned to receive GBP ($n = 194$; $p = 0{\cdot}008$) or LTG ($n = 199$; $p < 0.0001$). The relative maintenance doses of LTG and GBP were lower than that of CBZ, but the use of a standard-release rather than a sustained-release formulation probably accounted for the differences in tolerability among the drugs (Rowan et al., 2005). Discontinuation rates due to adverse events were 12% with LTG, 22% with GBP, and 31% with CBZ. The use of lower dosing schedules explains the retention rates in favor of LTG and GBP, which was the primary endpoint for the study (Rowan et al., 2005).

There are surprisingly few published data reporting the use of other AEDs in elderly patients. Open studies are available in support of LTG, OXC, and LEV in this population (Brodie et al., 2009). A randomized comparison of low-dose (50 mg/day) versus high-dose (200 mg/day) topiramate (TPM) in older people with partial-onset seizures favored the low-dose regimen (Brodie et al., 2009). Although there is a trend away from the use of older AEDs in this population, this pattern does not yet represent a substantial change in clinical practice (Brodie et al., 2009).

Take Home Message

Prefer nonmetabolized, nonenzyme-inducing newer AEDs such as GBP, LTG and possibly lacosamide in the elderly instead of classic enzyme-inducing CBZ. Titrate slowly, expect adverse events, look out for drug–drug interactions, use a simple treatment scheme, and ascertain good drug compliance.

Pitfall: Failure to Address Issues in Treatment for Epilepsy in Adolescents

AED therapy in adolescence is often difficult because there often is noncompliance in this special time of life. Many studies show that the factors that assured good compliance were good motivation, a good therapeutic result, the support of parents, involvement of medical personnel, and a positive attitude to the disease and its treatment. More recent studies have demonstrated the importance of endocrinological function and weight changes in adolescents after AED therapy and especially after long-term therapy with VPA, CBZ, GBP, and TPM. Abnormalities include weight increase (VPA, GBP), weight loss (TPM), possible polycystic ovaries (VPA), and bone disease (osteopenia/osteoporosis, osteomalacia) with CBZ, PHT, phenobarbital (PB), and VPA. Weight remained stable in

adolescents treated with LTG or OXC. Enzyme-inducing AEDs, CBZ, PHT, PB, OXC, TPM < 200 mg/day), may lower the efficacy of oral contraceptives while GBP, LTG, and VPA do not interact with oral contraceptives. Oral contraceptives may, however, lower the efficacy of LTG through pharmacokinetic drug interactions. Folate supplementation (5 mg/day) is recommended in female adolescents if VPA or CBZ is prescribed for epilepsy treatment.

Adolescents often experience constraints from the seizures, limitation of leisure activities, side effects of medication, and feelings of being different. The coping strategies include support and being in control. Paroxysmal nonepileptic events are frequently encountered in adolescents. Resective surgery for drug-resistant mesial temporal lobe epilepsy is as effective in adolescents as in adults.

Pitfall: Failure to Address Issues in Treatment for Male Epilepsy Patients

Up to 57% of men with partial epilepsy, especially temporal lobe epilepsy, have been found to have erectile dysfunction compared with 3–9% in the general population. These findings have been attributed to epilepsy itself, but AEDs also have various effects on male endocrine function. Among 40- to 50-year-old men with partial epilepsy taking enzyme-inducing AEDs, 9/10 had low bioactive testosterone levels as compared with 1/3 taking LTG and 1/3 in healthy controls taking no AED. Sexual function and bioactive testosterone levels are increased with LTG compared with enzyme-inducing AEDs. Similarly, abnormally low bioactive testosterone levels are reached at an earlier age with enzyme-inducing AEDs than with LTG. CBZ appears to decrease the bioactivity of androgens, whereas OXC below 900 mg/day does not.

Men with epilepsy have reduced fertility, and AEDs may affect semen quality. CBZ, OXC, and VPA are associated with sperm abnormalities in men with epilepsy. In addition, VPA-treated men with generalized epilepsy who have abnormal sperm may have reduced testicular volume. Finally, epilepsy itself may negatively affect male endocrine function, and successful mesial temporal lobe epilepsy surgery may lead to a normalization of serum androgen concentrations in men with epilepsy. Long-term AED therapy in young male patients who have seizures causes significant bone loss at the hip in the absence of vitamin D deficiency. Obese VPA-treated men have high serum insulin levels, indicating insulin resistance. Moreover, some of the VPA-treated men have a cluster of cardiovascular risk factors such as obesity, hyperinsulinemia, and elevated serum triglyceride concentrations. CBZ and OXC do not seem to have any significant effects on serum insulin or lipid levels in men with epilepsy.

Take Home Message

If possible, avoid enzyme-inducing AEDs in men with epilepsy, prefer weight-neutral and nonenzyme-inducing AEDs.

Pitfall: Failure to Recognize the Usefulness of Complementary Medicine

The high percentage of patients whose seizures are refractory to AEDs and who are either not candidates for or are reluctant to undergo resective surgery or medical device implantation may perhaps explain why such patients with epilepsy turn to complementary

medicine as a last resort. Complementary and alternative medical therapies include chiropractic, acupuncture, yoga, diet, homeopathy, acupuncture, biofeedback, traditional Chinese medicine, aromatherapy (with or without hypnosis), massage therapy, and herbal remedies, as well as mind-body therapies (such as meditative practices and visualization, Reiki-like healing practices), folk practices, and religious healing. Of these, modalities based on spiritual healing create a number of conundrums for the clinician, including legal, regulatory, and ethical issues. Magnets, electric current, and artificial electromagnetic fields have also been applied in patients with epilepsy. Psychological interventions such as relaxation therapy, cognitive behavior therapy, EEG bio-feedback, and educational interventions have been used alone or in combination in the treatment of epilepsy to reduce seizure frequency and improve the quality of life. Anecdotal accounts suggest that some herbal substances may have an anticonvulsant effect, but randomized double-blind controlled trials are lacking. Alternatively, some herbal substances and dietary supplements may predispose individuals without epilepsy to have seizures and worsen seizure control in those with epilepsy, whether directly or by affecting serum concentrations of AEDs. It remains to be seen whether perceived positive outcomes of complementary medicine could be explained by enhancement of the placebo effect, or a specific action, if any. In view of methodological deficiencies and limited number of individuals studied, there seems to be no reliable evidence to support the use of any of these treatments at this time and randomized, controlled trials are needed.

Take Home Message

Complementary medicine is often sought when and if AEDs have failed to control seizures despite sufficiently high doses to produce toxicity and when surgery is not possible or declined. AED treatment should be continued when complementary medicine is used. The toxicity of unproven complementary medicine is often underestimated.

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Chapter 9

What to Do If Drugs Don't Work?

Dieter Schmidt

After excluding misdiagnosis and poor drug treatment, patients with epilepsy in whom drugs do not work to control seizures have several options for further treatment. The options range from surgery, including resection, radiosurgery, and neurostimulation, to ketogenic diet, avoiding seizure precipitation, investigational medications, and proven complementary medicine. Before the risk-benefit of any of these non-pharmacological treatment options is considered, the patient's past drug response needs to assessed, which in itself is not always straightforward, as pointed out in the following section on drug-resistant epilepsy.

Pitfalls: Drug-Resistant Epilepsy: Elusive Definitions and Unclear Mechanisms

The definition of drug resistance is elusive. A generic definition of drug-resistant epilepsy is offered by Kwan et al. (2010): "epilepsy in which seizures persist and seizure-freedom is very unlikely to be attained with further manipulation of AED therapy." In the broadest sense, all epilepsy is drug-resistant, because drugs are a palliative treatment that prevent the clinical expression of seizures but cannot affect the underlying pathologic state. A recent attempt to define the indefinable proposed the following tentative definition: "failure of adequate trials of two tolerated, appropriately chosen and used antiepileptic drug schedules (whether as monotherapies or in combination) to achieve sustained seizure-freedom" (Kwan et al., 2010). "Sustained" is defined as at least 12-month period of seizure remission and "an adequate period without seizures for a patient to be regarded as seizure-free," is defined as a "seizure-free duration that is at least three times the longest interseizure interval prior to starting a new intervention," which to the authors of the definition constitutes evidence that the intervention has "some therapeutic effect."

The concept of sustained seizure-freedom is relatively new to epileptology. For instance, it would not be surprising for a patient with only one seizure in the previous year to remain seizure-free for the next 6 months after starting a new intervention, even though this patient could be considered to have had a therapeutic success by their doctor. But it would be premature and unwarranted to claim that the therapeutic intervention is responsible for such a patient's freedom from seizures until sufficient time has passed. Hence the "rule of three" that originated from data for calculating confidence intervals for zero events (Hanley and Lippman-Hand, 1983). To be 95% certain that a patient's seizure frequency has at very least decreased (i.e., there has been some therapeutic effect), a seizure-free duration that is at least three times the longest interseizure interval prior

to starting a new intervention would need to be observed, as stated in the above definition. For example, if prior to the intervention the patient had intervals without seizures of up to 6 months, a seizure-free period of 18 months would be required to reasonably conclude that his seizure frequency is lower than that prior to the intervention.

It should be noted that, in theory, patients with even more infrequent seizures would have to be followed up for many years to determine whether their seizures had truly come under control. This is not practical, either in research or clinical settings. For this reason, the authors recommend that three times the longest interseizure interval be used as an indicator of positive treatment response (Kwan et al., 2010).

Given that an initiation or change of intervention regimen is often not indicated for seizures occurring less than once per year, the longest pre-intervention interseizure interval should be determined from seizures occurring within the preceding 12 months. For practical purposes, the interseizure interval should be derived according to days on which one or more seizure has occurred. Obviously, at least two seizures must have been documented to determine the pre-intervention interseizure interval; therefore, this approach cannot be applied to a patient treated after a single seizure. The other main consideration is the need to document a sustained response that is clinically meaningful. Studies including patients treated medically or surgically show that absolute seizure-freedom, usually taken as at least 12 months, is the only relevant outcome consistently associated with meaningful improvement in quality of life.

Elusive Mechanism(s) of Drug-Resistant Epilepsy

The medical, social, and economic consequences of poorly controlled seizures can be enormous (see Chapter 15). Recurrent seizures are associated with significant risks for death, physical injury, cognitive impairment, and psychosocial problems. Frequent seizures not only influence the quality of life, morbidity and mortality in epilepsy, but also significantly increase costs. Therefore, identifying the mechanism(s) underlying drug resistance and developing targeted approaches to reverse these mechanisms are crucially important.

It has been suggested that altered drug permeability across the blood–brain barrier may be involved in pharmacoresistance to AEDs. ATP-dependent multidrug transporters such as P-glycoprotein are found in the luminal membranes of brain capillary endothelial cells and are known to play a role in blood–brain barrier function by limiting drug penetration into the brain. Reduced target sensitivity of use-dependent blockers of voltage-dependent Na+ channels in carbamazepine (CBZ)-resistant patients is another novel mechanism underlying the development of drug-resistant epilepsy. It is now clear that while the new generation of AEDs is very useful, they are not able to reverse drug-resistant epilepsy in the vast majority of patients (Löscher and Schmidt, 2011).

How Many Newly Diagnosed Patients have Drug-Resistant Epilepsy?

In a large observational series, Kwan and Brodie (2000) found that of 470 patients who had never before received an AED, 301 (64%) became seizure-free for at least 12 months during treatment. Of these patients, 113 had discontinued the first drug because of lack of efficacy, 69 because of intolerable side effects, 29 because of idiosyncratic reactions, and 37 for other reasons. Only 79 of these 248 patients (32%) subsequently became seizure-free.

The outcome among these patients was strongly associated with the reason for the failure of treatment with the first drug. Another 12 (11%) patients in whom treatment with the first drug was ineffective subsequently became seizure-free. Seizures in only 4% adequately responded to a third drug. Similarly, seizures in only 3% of patients responded to two drugs.

However, new evidence from several studies has suggested that the results shown by Kwan and Brodie (2000) may have been too pessimistic. Long-term observations indicate that as many as 20–30% of patients with apparently drug-resistant seizures will eventually enter remission after a change of drug regimen (for example, see Luciano and Shorvon, 2007). The good outcome in as many as 1 of 5 patients indicated that there is hope even after many years of having uncontrolled epilepsy.

If one considers epilepsy to be drug-resistant if treatment did not achieve seizure-freedom for 12 months or more, for whatever reason, as many as 36% of newly treated patients are drug-resistant. However, if a definition of frequent and severe seizures despite optimal treatment is used so that alternative therapies including surgery might be indicated, only 5–10% of newly diagnosed patients have been estimated to have drug-resistant seizures (Hauser, 1992).

Pitfall: Are You Aware of the Most Common Reasons for Drug-Resistance?

There are multiple reasons why seizures in patients may be resistant to AED therapy. As discussed in Chapter 5, an incorrect diagnosis may lead to ineffective treatment. For example, use of CBZ in a patient with absence seizures and generalized spike-wave activity could exacerbate seizures (see case below).

Pitfalls in Assessing Drug Response

Although it seems to be straightforward, it is not always easy to assess drug responsiveness, i.e., whether the epilepsy is drug-resistant, drug-responsive, or neither (undefined). One pitfall is that any treatment that does not achieve seizure-freedom is not considered to have a therapeutic effect according to the ILAE criteria, as acknowledged by the authors who proposed the ILAE definition (Kwan et al., 2010). This is in contradiction to clinical reality and to the currently used definition of therapeutic effect in regulatory drug trials where a 50% reduction is considered evidence for (at least some) therapeutic effect.

A traditional definition suggests that epilepsy is drug-resistant if seizures persist and seizure-freedom is very unlikely to be attained with further manipulation of AED therapy, which seems to indicate lack of reversibility once a patient's seizures are determined to be drug-resistant. In contrast, the current ILAE definition allows a patient over the course of their disorder to switch from being drug-resistant to entering remission and, following a relapse, to be drug-resistant again. Switching in and out of drug resistance has been described, for example, by Sillanpää and Schmidt (2006). Epilepsy can be labeled as drug-responsive if the patient receiving the current AED regimen has been seizure-free for a minimum of three times the longest pre-intervention interseizure interval or 12 months, whichever is longer. If drug responsiveness cannot be classified as either drug-responsive or drug-resistant, it remains undefined (Kwan et al., 2010). The following case vignettes, which were first published in the ILAE definition paper (Kwan et al., 2010), illustrate the pitfalls in assessing drug response.

Case 9.1 Define the Drug Response

A 40-year-old man was diagnosed with partial epilepsy 20 years ago. He reported "I was on phenytoin (PHT) initially for a short period, but it didn't work and they took me off." He was then given an adequate trial of CBZ but continued to have monthly seizures. Levetiracetam (LEV) was added 1 year ago with adequate doses and he now has seizures once every 3 months (Kwan et al., 2010).

Comment: Seizures are drug-resistant. The outcome of PHT treatment was undetermined because of lack of sufficient data. Nonetheless, his seizures have not been fully controlled after informative trials with two appropriate AEDs (CBZ and LEV). Treatment with LEV is considered failed because despite the reduction in seizure frequency, the seizure-free duration is < 12 months) (Kwan et al., 2010).

Case 9.2 Define the Drug Response

A patient had one seizure in January 2006 and two seizures in October 2006. After starting treatment in November 2006, he has been seizure-free for 30 months with no adverse effect from his AED.

Comment: Seizures are drug-responsive. The longest pre-treatment interseizure interval was 9 months (January–October 2006). The patient has had no seizures for more than three times the pre-treatment interseizure interval and for more than 12 months (Kwan et al., 2010).

Case 9.3 Define the Drug Response

A patient was newly started on CBZ after two partial seizures over 9 months. He has had no seizures for 12 months.

Comment: Seizure responsiveness is undefined. The pre-treatment interseizure interval was 9 months. Although the patient has had no seizures for 12 months, the duration is less than three times the pre-treatment interseizure interval, hence the outcome of treatment is undetermined and drug responsiveness of this patient's epilepsy is undefined (Kwan et al., 2010).

Case 9.4 Define the Drug Response

A 16-year-old patient was started on valproate (VPA) 2 years ago after experiencing two seizures in 6 months, and has been seizure-free since with mild sedation. He reports a history of an apparently nonfebrile convulsive seizure when he was 6 years of age.

Comment: Seizures are drug-responsive. The longest pre-treatment interseizure interval was 6 months. The patient has had no seizures for more than three times the pre-treatment interseizure interval and for more than 12 months. The seizure that occurred at 6 years of age (more than 12 months prior to starting treatment) is not relevant to determining the responsiveness of his current epilepsy (Kwan et al., 2010).

Case 9.5 Define the Drug Response

A patient is having more than one seizure per day for 3 months despite adequate trials of four appropriate AEDs. Patient is taking one drug currently.

Comment: Seizures are drug-resistant having not been controlled by more than two appropriate AEDs.

After adding another drug, the patient had no seizures for 8 months.

Comment: Four previous drugs with treatment-resistance. One current drug with undetermined outcome. Outcome of treatment with the most recently added drug is undetermined and the epilepsy remains drug-resistant because the patient has not been seizure-free for 12 months.

With further follow-up, the patient has had no seizures for 24 months.

Comment: The patient's seizures are now considered drug-responsive because he has had no seizures for more than three times the pre-treatment interseizure interval and for more than 12 months (Kwan et al., 2010).

Case 9.6 Define the Drug Response

A 16-year-old girl was started on CBZ a week after she had a tonic–clonic seizure in the morning, with a history (not recognized by her doctor at the time) of jerks over the past 3 months. The jerks got worse after 2 months on CBZ 800 mg/day. EEG later showed generalized polyspike and wave discharges. She was diagnosed to have juvenile myoclonic epilepsy and was switched to lamotrigine (LTG), which was stopped after 2 weeks (dosage at the time, 50 mg/day) because of a rash. She is now on VPA 2 g/day for 3 months, but occasional jerks continue.

Comment: One previous inappropriate drug. One previous drug with undetermined outcome. One current drug with treatment failure outcome. Her drug responsiveness is undefined. CBZ is recognized to exacerbate myoclonic seizures and, in this case, is not considered an appropriate treatment for the patient's epilepsy syndrome. TLG and VPAS are appropriate treatments, but outcome in terms of seizure control of LTG is undetermined because it was stopped due to an adverse effect during titration, before a dose range that is regarded as optimal could be reached. Thus, the patient's seizures have not fully responded so far to only one drug (VPA), and therefore the drug responsiveness of her epilepsy remains undefined (Kwan et al., 2010).

Pitfall: Recognize Seizure Aggravation as Cause for Drug Failure

Seizure aggravation is an important limitation of current AEDs. Idiopathic generalized epilepsies (IGEs) are particularly prone to pharmacodynamic aggravation: typical absences are constantly increased by CBZ, vigabatrin, tiagabine (TGB), gabapentin (GBP), while PHT is less aggravating. Juvenile myoclonic epilepsy is often aggravated by CBZ, less constantly by PHT and other AEDs. Generalized tonic–clonic seizures found in IGEs may respond to AEDs that aggravate the other seizure types. Nonconvulsive status epilepticus has been associated with TGB. GBP-associated myoclonus appears to be relatively frequent. It is usually mild and can easily be overlooked. Discontinuation of therapy is not necessary in most cases. In symptomatic generalized epilepsies, patients often have several seizure types that respond differently to AEDs: myoclonias are generally aggravated by the same drugs that aggravated IGEs; tonic seizures in the Lennox–Gastaut syndrome

respond to CBZ, which may, however, aggravate atypical absences. In severe myoclonic epilepsy of infancy, there is a nearly constant aggravating effect of LTG. In some patients with benign rolandic epilepsy, a clear aggravation may be produced by CBZ, with occurrence of negative myoclonias, atypical absences, drop attacks, and at worst, evolution into a state of electrical status epilepticus during sleep. Only a few medications can control IGE without potentially causing seizure aggravation. Broad-spectrum antiepileptic drugs such as VPA, LTG, and topiramate (TPM) are extremely effective at controlling a variety of seizures without causing excessive seizure aggravation. Among these drugs, VPA has the longest clinical experience history and the largest body of published data.

Recommendation

Although the exact mechanism(s) of drug resistance are still elusive, we know that a change of regimen in apparently refractory epilepsy will eventually lead to seizure-freedom in as many as one in five patients. Avoiding resignation on the side of the patient and complacency on the side of the physician is essential for the success of medical treatment. Drug-resistant epilepsy is associated with significant risks for death, physical injury, cognitive impairment, and psychosocial problems. Early referral for exploring surgical treatment is advisable, since seizures in two-thirds of carefully selected patients respond to AEDs after surgery, and one-third will remain seizure-free after AEDs have been withdrawn. If surgery is not an option, a change of medical regimen and indirect or direct brain stimulation modalities are good options.

Pitfall: Recognize Non-Pharmacological Seizure Precipitation as Cause for Why Drugs Fail

Non-pharmacological measures play an important supporting role for seizure regulation in individually susceptible patients, mostly adolescents with juvenile IGEs. Disturbances of their sleep-wake cycle, especially reduction of sleep, may provoke seizures the next morning. Following a regular sleep schedule is helpful; pragmatically, sleep onset should not vary by more than two hours. Sleep reduction, often combined with partying and substance abuse or stress, is a common precipitating factor in adolescents and adults with a first epileptic (mostly generalized tonic–clonic [GTC]) seizure. In some of these patients, regular sleep and a less stressful life style may be enough to prevent further seizures. In addition, AEDs may not be able to achieve seizure control if the lifestyle is not changed. In the rare reflex epilepsies, specific precipitants of seizures may be the targets for non-pharmacological intervention. For example, most patients with primary reading epilepsy begin to have, with prolonged reading, perioral reflex myoclonias, which enable them to stop reading and thus to avoid a GTC seizure. In photosensitive patients, seizures are often precipitated by television. These can be avoided by viewing from a distance and using a remote control, and viewing small screens in a well-lit room, preferably with a 100-Hz line shift. Environmental flicker stimulation often comes unexpectedly, and it is advisable that the patients always wear sunglasses in brightly lit surroundings. Polarized glasses seem to be more protective than plain sunglasses. If the patient has only photically induced seizures, treatment by specific prevention alone may be sufficient, but if spontaneous seizures also occur, drugs are usually needed in addition. Some patients with partial seizures with an extended aura claim that they know how to prevent seizure spread by various nonspecific measures such as relaxation, concentration, or a combination of both. It is often difficult, however, to support such claims.

Pitfall: Failure to Recognize the Clinical Importance of Epilepsy Surgery

Resective surgery of localized seizure-generating tissue is a standard adjunctive procedure for drug-resistant focal epilepsy, mostly for mesial temporal lobe epilepsy (MTLE), where it is an extremely effective treatment (Engel et al., 2003). Palliative adjunctive procedures include vagus nerve stimulation and direct brain responsive neurostimulation, and a number of other non-pharmacological procedures such as deep brain stimulation or radiosurgery are emerging or under study.

Resective Surgery

Adjunctive resective surgery is a standard of care for properly selected patients with drug-resistant partial epilepsy, especially MTLE (Engel et al., 2003). About 10–20% of patients with new-onset epilepsy have severe disabling seizures that are refractory to medical treatment. Most properly chosen patients whose seizures originate from a local area of abnormal brain function improve markedly when the epileptogenic tissue is resected. The surgical approach chosen depends on many considerations mainly including the localization and the extent of the epileptogenic zone, the MRI findings, and the risk-to-benefit ratio of the resective surgery itself and the pre-operative monitoring (Elger and Schmidt, 2008). Any patient with drug-resistant epilepsy, as defined above, should be referred to a specialized epilepsy surgery unit to determine, as early as possible, if surgery is a reasonable treatment option.

Any assessment of a candidate for epilepsy surgery needs to balance the likelihood of becoming seizure-free and the risks of surgery and presurgical monitoring. Presurgical monitoring involves seizure precipitation by withdrawing medical treatment, which may rarely result in seizure-related injury and postictal deficits, and may also involve the implantation of invasive electrodes.

Surgical candidates can be broadly assigned to one of three groups (Figure 9.1). Best-suited surgical candidates are those with a 70% or greater chance to become seizure-free, who require no invasive presurgical assessment, and who have a very small risk of postsurgical deficits. This group mainly includes patients with nondominant MTLE with hippocampal sclerosis and selected cases of focal cortical dysplasias. In these patients, surgery can be recommended after failure of two drugs. In contrast, patients with non-lesional epilepsies or lesional extratemporal lobe epilepsies are, in general, less likely to become seizure-free, with expected rates of approximately 30% or less. They usually require more extensive presurgical evaluation and may have a higher risk of postsurgical deficits. In this group, seizure resistance to more than two properly selected and dosed AEDs should be shown prior to considering surgery. Postponing surgery until better drugs are available or palliative vagus nerve stimulation should be considered. Finally, there are a number of cases that are not amenable to high-benefit, low-risk surgery in whom vagus nerve sitmulation, direct cortical responsive neurostimulation or resective surgery should be considered for palliative effects. This group includes patients with non-lesional, multi-focal epilepsies and posttraumatic epilepsy.

MTLE is the most common surgically remediable refractory partial epilepsy, which accounts for approximately 70% of all patients undergoing epilepsy surgery. MTLE has

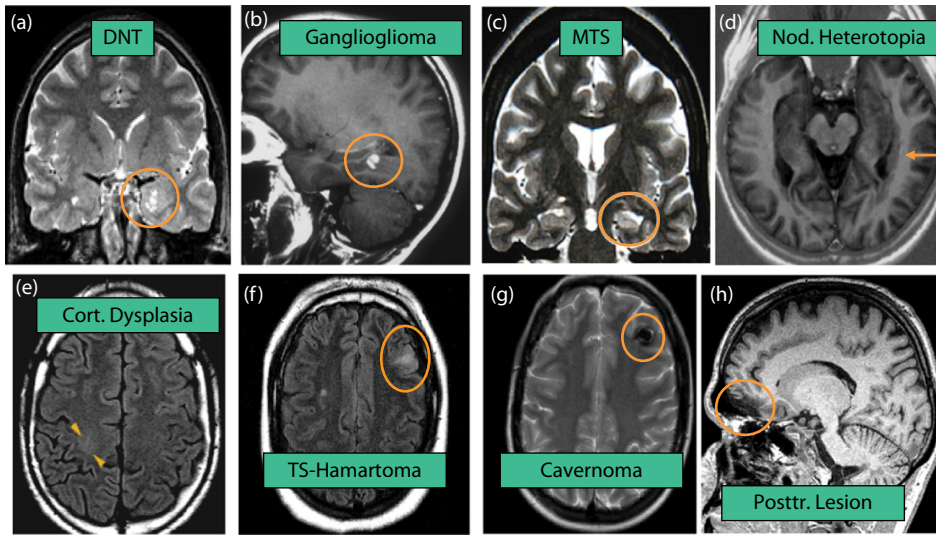

Figure 9.1 Pitfall: recognize drug-resistant symptomatic epilepsies suitable for successful epilepsy surgery (a, Dysembryo-neuroepithelial tumor, DNT; b, Ganglioglioma; c, Hippocampal sclerosis; f, Tuberous sclerosis-related hamartoma; g, Cavernoma) and less suitable candidates (d, Nodular heterotopia; e, cortical dysplasia, h, posttraumatic lesions)
(courtesy of Professor C. E. Elger, Bonn)

been well characterized and can usually be identified with noninvasive studies including scalp EEG and video-EEG monitoring with ictal recording, magnetic resonance imaging, single-photon-emission computed topography, positron emission tomography, neuropsychological assessment, history, and clinical data. Sometimes, invasive EEG is needed to confirm mesial temporal lobe seizure onset, which, combined with the underlying pathological abnormality (the substrate) of mesial temporal sclerosis (hippocampal neuronal loss and gliosis), defines MTLE. It has been estimated that 75% of all patients with MTLE have drug-resistant seizures. With surgical treatment, 25–30% of patients with MTLE are "cured" in the long-run; i.e., they do not need ongoing AEDs for continued seizure-freedom. Another 25–30% become seizure-free or nearly seizure-free with continued drug treatment (Schmidt and Löscher, 2003; Kelley and Theodore, 2005). Because extensive monitoring and skilled medical-surgical teamwork are required, it is recommended that these patients are managed in specialized epilepsy centers.

The Evidence

Compelling short-term evidence exists for the efficacy of resective epilepsy surgery in MTLE from a randomized, controlled trial comparing surgery plus AEDs versus AEDs alone (Wiebe et al., 2001). The patients were randomized prior to presurgical evaluation, so the study allowed intent-to-treat analysis. At 12 months after surgery, 15/40 surgical (including 4 patients who were randomized to surgery but were not operated on) and 1 of 40 medical patients were free of seizures as defined by the authors (Wiebe et al., 2001). The number of patients needed to treat for one patient to become free of

disabling seizures while remaining on AEDs was two, which is superior to most interventions in neurology. A meta-analysis of nonrandomized trials gives almost identical results; about two-thirds of patients become seizure-free with surgery and continuing AED treatment, compared with only 8–24% with medical therapy alone. The results are remarkably similar among studies from different parts of the world. Several supportive studies employing nonrandomized medical controls showed that surgical treatment of drug-refractory MTLE in properly selected patients is superior to that of continued medical treatment. The mechanism(s) by which the resection is able to transform drug-resistant epilepsy into drug-responsive epilepsy (with seizure-freedom on or off AEDs) is(are) unclear.

Quality of life improves early after epilepsy surgery, and the improvements are both statistically and clinically significant. Surgical morbidity with clinically important permanent sequelae is 2%. In addition, successful MTLE surgery appears likely to reduce the risk of seizure-related death. However, it remains largely underused and overly delayed, partly because of the legitimate fears of possible surgical complications, such as verbal memory deficits or failure to control seizures. Reasons for surgical failures are not completely understood, and include bitemporal, pseudotemporal, and temporal-plus epilepsies, as well as insufficient resection of the mesial temporal structures. Although there are similar Class IV results for localized neocortical resections; no Class I or II studies are available (Engel et al., 2003).

Seizure recurrence has been noted during a five-year follow-up in approximately one-third of these seizure-free patients after mesial temporal lobe resection, mostly, but not exclusively, following planned complete discontinuation of AEDs (Schmidt et al., 2004). This leaves one-third of patients without disabling seizures and without AEDs several years after surgery. Despite improvements in seizure frequency or severity, seizures persist in another third of patients undergoing surgery. We need a long-term, randomized, controlled trial on AED discontinuation in seizure-free patients followed by long-term open extension to determine if only one in three adult patients with drug-resistant MTLE is cured by surgical intervention (Schmidt and Löscher, 2003).

In a large observational study of 310 patients with MTLE, mostly due to hippocampal sclerosis, that included many children, who generally have a more favorable surgical outcome compared to adults, 140 patients (45%) had no seizures or auras during the entire post-surgery follow-up period (Rathore et al., 2011). Following attempted AED withdrawal, seizures recurred in 64 patients (25%). Among 64 patients with seizure recurrence, 56 (87.5%) again became seizure-free with AED optimization, while in the remaining 12.5%, seizures remained uncontrolled. Of 26 patients who had a recurrence after complete AED withdrawal, 24 (92.3%) again became seizure-free after restarting AEDs (7.7% did not become seizure-free). Although AED withdrawal was associated with uncontrolled seizures in up to 12.5% of patients, and it is matter of judgment if one considers this outcome safe, it is not known how this compares with outcomes in those who continued treatment.

Compared to lesional MTLE, reported surgical remission rates are lower for non-lesional MTLE or extratemporal epilepsy. In addition, presurgical examination of non-lesional MTLE or extratemporal epilepsy is more complicated and often requires invasive electrode placements. As in any surgical procedure, results vary from center to center, and centers that do the procedure more often are usually those with better outcomes.

Pitfall: Failure to Recognize the Clinical Potential of Epilepsy Surgery for the Elderly

Epilepsy surgery appears to be increasingly considered for some older adults with focal epilepsy, although concerns have been raised (d' Orio et al., 2017). Seizure-free rates can be comparable to younger age groups (d' Orio et al., 2017), but the rate of surgery-related complications may be higher in the elderly compared to younger patients (d' Orio et al., 2017). Much more work needs to be done in this area in order to address concerns such as the heterogeneity of the surgery population under review. Studies in this area often include patients with different seizure types and patients having undergone different types of resections. This seems in part due to the need to obtain sufficient sample size for analysis. Most studies that have examined age as a predictor of surgery outcome typically include patients with ages peaking in the late forties or fifties. It is also not clear whether older patients undergoing epilepsy surgery are at increased risk for long-term cognitive decline as has been noted in long-term postsurgery studies with younger adult samples. Other concerns include a need for appropriate older control groups to compare outcome and practice effects of repeated cognitive testing as well as premorbid characteristics. It would also be important to chart the natural trajectory of cognitive aging in adults with intractable epilepsy and in those who undergo surgery in comparison to healthy older adults as well as demographically matched samples of healthy older adults.

Recommendation

Resective epilepsy surgery is an extremely effective treatment for patients with suitable drug-resistant MTLE, of whom 6 in 10 become seizure-free with continued AED use, while the chance for becoming seizure-free with continued AEDs alone in surgical candidates who did not undergo surgery is usually less than 10%. In one in three operated patients, AEDs can be safely withdrawn. Surgical outcome in focal epilepsy originating from other lobes may be less successful but still worthwhile.

Pitfall: Failure to Recognize the Clinical Importance of Neurostimulation

Deep brain stimulation has been investigated for more than 50 years as a treatment option for patients with medically refractory seizures who cannot be offered epilepsy surgery due to multiple foci or overlap between the epileptogenic zone and eloquent cortical areas. In recent years, stimulation of the subthalamic nucleus, centromedian nucleus of the thalamus, anterior nucleus of the thalamus, hippocampus, and cortex has received most interest. Stimulations were performed in a small number of patients and seizure reduction was noted in some patients (Theodore and Fisher, 2004).

Vagus Nerve Stimulation consists of intermittent electrical stimulation of the left vagus nerve with an implanted pacemaker-like device. On a population basis, vagus nerve stimulation reduces the number of partial seizures by one-third with continued AED therapy. After the device is programmed, patients can activate it with a magnet when they sense a seizure is imminent. Vagus nerve stimulation is used as an adjunct to an AED treatment when resective surgery is not feasible or has been unsuccessful. Adverse effects include voice hoarseness and cough during stimulation, which are less noticed by most patients after several months. Complications are minimal, and use in other than partial epilepsy is not well established.

Following responsive ictal onset zone stimulation in (multi)focal epilepsy patients, a statistically significant reduction in seizure frequency was found (Mean Difference −24.9%; 95% CI −40.1 to −6.0; high-quality evidence). However, there were no statistically or clinically significant changes in the proportion of patients who were seizure-free or experienced a 50% or greater reduction in seizure frequency. Responsive cortical ictal-onset zone stimulation seemed to be well tolerated and had few side effects (Sprengers et al., 2017).

Recommendation

Deep brain stimulation is emerging, while vagus nerve stimulation and, more recently, responsive ictal onset zone stimulation are reasonable palliative alternatives if resective surgery is not possible or has failed. The onset of action of vagus nerve stimulation and responsive intracranial stimulation is delayed for several months and complications are minimal.

Pitfall: Failure to Recognize the Clinical Importance of the Ketogenic Diet

The ketogenic diet (KD) is a very-low-carbohydrate, adequate protein, high-fat diet used to treat refractory epilepsy, especially in children, since the 1920s. For those with difficult-to-control epilepsy on multiple AEDs, the KD is a possible option (Kossoff, 2004). It requires a devoted multidisciplinary approach, which includes physicians, nurses, social workers, dieticians, and parents. The diet mimics the biochemical changes associated with starvation, in particular ketosis. Although less commonly used in later decades because of the increased availability of AEDs, the KD has re-emerged as a therapeutic option if AEDs fail to control seizures and surgery is not an option. The KD should be continued for 1 or 2 years, if effective. Only a decade ago the KD was seen as a last resort. Large observational studies, some prospective, suggest an effect on seizures; these effects need validating in randomized, controlled trials. It has become more commonly used in academic centers throughout the world. A modified version of the Atkins diet is a recently used, less restrictive, therapy that also creates ketosis and may be able to lower the number of seizures. Dietary therapies may become even more valuable in the therapy of epilepsy when the mechanisms underlying their success are better understood. Although the KD has been shown to be useful in the treatment of childhood epilepsy, the long-term effects of the KD on nutritional status and brain development are not clear. Bicarbonate levels should be monitored carefully with TPM and KD co-treatment, and bicarbonate supplements given when children are symptomatic. Excessive bruising is a symptom noted by parents of some children treated with the KD. Patients on the diet undergoing anticoagulation or surgery should be evaluated carefully for symptoms of bleeding tendency. The KD may be associated with nephrolithiasis in some patients.

Recommendation

Ketogenic diet is an option for drug-resistant epilepsy, particularly in children when other established treatments such as resective surgery or vagus nerve stimulation are not possible or acceptable to patients/families.

Pitfalls in the Management of Ketogenic Diets for Epilepsy

As the KD and other similar diets become more frequently utilized as a standard treatment for epilepsy in children and adults, hospital and community neurologists, pediatricians, intensivists, general practitioners, and house officers will readily encounter patients who are receiving these dietary treatments. However, as is true for any other medical therapy, these treatments have known side effects and complications requiring recognition and timely action. The most common pitfalls in the management of epilepsy with dietary treatment are briefly reviewed in this section (Lee and Kossoff, 2011).

Pitfall: Know Who Will Likely Benefit from the KD and Who Will Not

For patients with GLUT-1 transport deficiency or pyruvate dehydrogenase deficiency, the KD is considered a first-line therapy and should be implemented as soon as the patient is diagnosed (Lee and Kossoff, 2011). The KD should also be considered in a child whose seizures have not been controlled by two to three AEDs, regardless of age or gender, and particularly in those with symptomatic generalized epilepsies. Specifically, the KD appears to be a particularly effective treatment for Dravet and Doose syndromes. It is also a particularly good option for the treatment of refractory infantile spasms and seizures associated with mitochondrial disorders and tuberous sclerosis complex.

However, patients with focal epilepsies appear to have a decreased relative chance of seizure-freedom overall, and those who have a readily localized lesion are candidates for epilepsy surgery. In addition, there are conditions in which the KD is contraindicated and these include primary carnitine deficiency, carnitine palmitol transferase I or II deficiency, carnitine translocase deficiency, β-oxidation defects, pyruvate carboxylase deficiency, and porphyria. It is important to screen for these deficiencies in all patients in whom there is a clinical suspicion of an inborn error of metabolism as the initiation of the KD and its reliance on mitochondrial fatty acid metabolism can precipitate a potentially fatal metabolic crisis in the affected individual (Lee and Kossoff, 2011). Finally, it is prudent to consider that the KD diet is a significant intervention requiring rigorous daily adherence; not every family is willing or able to make the necessary commitment to this therapy.

Pitfall: Be Aware of Acute Issues during Initiation of the Ketogenic Diet

Most centers employing the KD feel that inpatient admission is helpful at launch of the diet and important for close monitoring of children and the intense education of their parents. This short (3- to 4-day) admission is needed for patient safety should problems arise during diet initiation and as a means to ensure completion of parental education about the diet. During hospitalizations and as an outpatient, it is critical that all medications the patients take orally be carbohydrate-free. There are no AEDs contraindicated in conjunction with KD, though the usage of concurrent carbonic anhydrase inhibitors may require additional monitoring for metabolic acidosis as discussed above. During initiation of the KD, there are several commonly seen, often anticipated, issues that emerge. Although many centers initiate the diet with 24–48 hours of fasting (clear fluids allowed)

to achieve initial ketosis, fasting may not be obligatory to achieve good long-term seizure control. Following whatever fasting period is chosen, the diet is implemented with increasing caloric content from fat or increasing the ketogenic diet ratio over 3–4 days until the full KD is tolerated and the child is discharged (Lee and Kossoff, 2011).

During fasting and diet initiation, patients require serial serum glucose monitoring for hypoglycemia. Generally, glucose levels >40 mg/dl are tolerated and will resolve during advancement of the KD. Symptomatic hypoglycemia (diaphoresis, excessive fatigue, altered mental status, tachycardia, tachypnea) should always be treated, but usually can be ameliorated with 10–20 cc (2–4 tablespoons) of orange juice or a similar carbohydrate-enriched beverage with a follow-up serum glucose check within 30 minutes. Rarely are intravenous or large oral boluses of glucose necessary to increase serum glucose levels, and when repeated aggressive measures are needed to maintain euglycemia, this should prompt consideration for an unidentified congenital metabolic derangement that may contraindicate dietary therapy (Lee and Kossoff, 2011).

As ketone levels rise in serum, patients may have decreased activity and report gastrointestinal symptoms such as nausea and abdominal pain. These symptoms are often transient and can be monitored without interruption of the diet. If ketone levels rise too precipitously, or if the patient does not tolerate sustained high serum concentrations of ketones, a temporary interruption of the diet with a carbohydrate-laden beverage as described above for symptomatic hypoglycemia is an option. If the issue becomes chronic, then reducing the ketogenic ratio to produce a lower level of sustained ketosis may be warranted (Lee and Kossoff, 2011).

The metabolic acidosis induced by the KD can be exacerbated by carbonic anhydrase-inhibiting AEDs such as acetazolamide, TPM, or zonisamide. There are suggestions the acidosis is greatest at diet initiation, and it is recommended that serum bicarbonate levels be monitored in at-risk patients. Patients with clinically significant signs of acidosis (e.g., altered mental status, emesis) should receive bicarbonate supplementation acutely or on a long-term basis if needed. Vomiting is among the most common occurrences during diet initiation and maintenance phases, with a study reporting vomiting in over 50% of patients, regardless of whether the child is fasted or not (Lee and Kossoff, 2011). Vomiting can be a sign of multiple issues and those should be considered as well as the initiation of the ketogenic diet, including gastroesophageal reflux or a coincidental gastrointestinal viral illness. Intravenous or rectal anti-emetics (e.g., promethazine, metoclopramide) are also short-term options for control of emesis; however, they may reduce the seizure threshold (Lee and Kossoff, 2011). If emesis becomes prolonged (>24 hours) due to the diet, intravenous fluid administration either as a bolus or continuously may be helpful, and care should be taken to ensure the fluids used are carbohydrate-free (e.g., 0.5 normal saline) without dextrose (Lee and Kossoff, 2011).

Generally, it is recommended by Lee and Kossoff (2011) to allow at least three months of compliant treatment in order to fully evaluate the diet's impact on an individual patient's epilepsy before discontinuing it due to inefficacy. However, a significant increase in seizures after diet initiation may require more immediate discontinuation.

Pitfall: Be Aware of Chronic Issues with the Ketogenic Diet

There are other adverse effects that may arise in children on chronic dietary treatment. As a caveat to Occam's razor, it may be worthwhile to note that not all issues occurring while

the patient is on the KD are necessarily caused by the diet. Lee and Kossoff (2011) report an example of a nonverbal patient who suddenly refused to eat while on the KD who was found to have extensive dental abscesses requiring surgical debridement. In another instance, vomiting and abdominal discomfort were identified as acute appendicitis. All children are at risk for viral illnesses, which can lead to emesis, increased seizures, and food refusal as well. These examples demonstrate that attributing any symptom solely to the KD may not be prudent (Lee and Kossof, 2011).

Having said this, the most common reported chronic complications of the KD typically include gastrointestinal issues. Constipation is frequent and can be managed with increasing dietary fiber intake, ensuring adequate carbohydrate-free fluid intake, or, if other measures fail, prescribing carbohydrate-free laxatives such as polyethylene glycol electrolyte solution. These children can present with abdominal distention, and occasionally paradoxical diarrhea. Gastroesophageal reflux can also worsen with the KD and occasionally begin during its use (Lee and Kossoff, 2011). There are no data showing that empiric treatment for reflux with histamine receptor blockers or proton pump inhibitors prevents gastrointestinal complications associated with the KD, but they may be warranted if clinically indicated. Some patients may report increased hunger; increasing intake of sugar-free snacks or decreasing the ketogenic ratio can be effective solutions (Lee and Kossoff, 2011).

However, more serious complications of the KD can present as abdominal pain and need to be assessed. One such complication is the formation of renal calculi. Complaints of flank pain, dysuria, hematuria, or gritty or white sand in the urine should prompt an evaluation for a renal calculus. Administering oral citrate preparations to patients is advised as a preventative measure, but kidney stones may still occur in approximately 1% of children even with their continued use. Conservative treatment with increased fluid intake and monitoring are typically all that is needed; lithotripsy is rarely required. Other reported complications include pancreatitis (likely more common in those treated with VPA), hepatitis, and gallstones (possibly due to the high-cholesterol, low-fiber diet). Unexplained abdominal pain in a child on the KD should be evaluated with amylase, lipase, ALT, AST, and an abdominal and renal ultrasound (Lee and Kossoff, 2011).

Regardless of the type of KD, elevated cholesterol and triglycerides are routine laboratory findings, seen in approximately 60% of patients on the traditional KD. Parents of a child with high cholesterol either at baseline or after 1–3 months on the diet should be screened for dyslipidemia themselves (Lee and Kossoff, 2011). If the patient's lipid values are significantly abnormal (e.g., total cholesterol >300 mg/dl), it is advisable to recheck a fasting specimen 2 weeks later. Should abnormalities persist, the ketogenic ratio could be lowered, MCT oil incorporated, polyunsaturated fats substituted for monounsaturated fats, or carnitine added (Lee and Kossoff, 2011). Lee and Kossoff (2011) noted that they have not started a cholesterol-lowering agent (e.g., statin) on any child at their center as of their report. The role for statin drugs in adults with dyslipidemia on the KD has not been investigated to date. For guidance of how to handle intercurrent disease or surgery, see Lee and Kossoff (2011).

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Chapter 10

How to Avoid Management Errors

Dieter Schmidt

The most common avoidable management errors stem from inadequate patient information, misdiagnosis, undertreatment, and inadvertent overtreatment (Box 10.1).

Box 10.1 Common avoidable management errors

- Inadequate patient communication
- AED use not indicated or off-label
- Dose increment is too much
- Maintenance dose is too high
- Unnecessary two-drug therapy
- Failure to avoid enzyme-inducing AEDs
- Overlooking subtle AED side effects
- Failure to respond to abnormal or suspicious laboratory, EEG or MRI findings

Inadequate Patient Communication

Adequate communication with a patient with epilepsy requires a discussion of the following points shown in Box 10.2.

Box 10.2 What constitutes adequate patient communication?

- Explain the diagnosis
- Inform the patient about risks of planned treatment
- Indicate alternatives to suggested treatment
- Inform patients about risks of not treating the disorder

More specifically, adhering to the following checklist can help prevent the most common errors in patient communication (Boxes 10.3 and 10.4).

Box 10.3 Errors in patient communication (part I)

- Insufficient documentation makes it difficult to support your action or nonaction
- Explain the foreseeable benefit and the risks of diagnostic or therapeutic procedure(s)
- Inform the patient about their medical contraindication to drive a car (document it in your file, duration, and type of vehicle [car, truck, etc.])
- Point out if you prescribe off-label medication and why you recommend it
- Discuss risks and side effects for your specific patient (e.g., VNS-associated hoarseness in a professional singer, teratogenicity in a woman of childbearing age)
- Inform the patient about potential risks when switching from original to generic drug and vice versa or from one generic version to another

Box 10.4 Common errors in patient communication (part II)

- Inform the patient and the referring physician or other treating physicians if you prescribe a medication that is involved in drug interactions
- Discuss the risks of drug interactions (comorbidity, oral contraceptives)
- Discuss the benefit-to-risk ratio of stopping AEDs (relapse, outcome of treating relapse)
- Discuss the risk of drowning, even in very shallow water
- Discuss the risks of presurgical evaluation
- Discuss the risk-to-benefit ratio of epilepsy surgery (memory, visual field loss)

Misdiagnosis: Misdiagnosis may occur early in the management of a patient who is thought to have epilepsy but in fact has syncope with myoclonia or psychogenic nonepileptic seizures (PNES). Subsequent AED use provides no benefit, even at higher doses, which invariably results in adverse events and overtreatment. Chapter 3 reviews pitfalls in the diagnosis of seizure types and epilepsy syndromes.

Recommendation

A patient who does not enter remission with the first appropriately selected and dosed AED may not have epilepsy at all, especially considering that 50% of all patients with new-onset epilepsy will become seizure-free with the first AED.

Common Treatment Errors

A number of common treatment errors can be easily avoided (Box 10.5).

Box 10.5 Common treatment errors

- Non-indicated use of AEDs (e.g., for headache, syncope, PNES, AEDs that aggravate absence or myoclonic seizures)
- Dosing that is above the recommended dose unless a lower dose has failed
- Dosing range or drugs that are involved in harmful drug interactions
- Failure to investigate the reasons for drug resistance (no reevaluation of the diagnosis, no reevaluation of medication, no evaluation for epilepsy surgery)

More specifically, treatment errors fall in two large groups, undertreatment and overtreatment.

Undertreatment: Although approximately 80% of patients with new-onset epilepsy who become seizure-free with a single AED will do so at low to medium doses, dosage increments will achieve seizure-freedom in the remaining 20%. This is why patients with uncontrolled seizures will likely benefit from dose increments or correction of poor compliance. Even in patients with uncontrolled chronic epilepsy, dose increments will achieve seizure-freedom in as many as 15–30% of patients if the current treatment resulted in only low to average serum concentrations.

If the serum concentration is at the higher range, however, dose increments are usually not sufficient to achieve seizure-freedom and adding another AED is preferable. According to several retrospective observations, adding another AED in apparently (but unproven) drug-resistant epilepsy will result in seizure-freedom in as many as 20% of patients. It is advisable not to overstate the benefit of adding another AED in chronic epilepsy. The available evidence is limited to retrospective observations and randomized

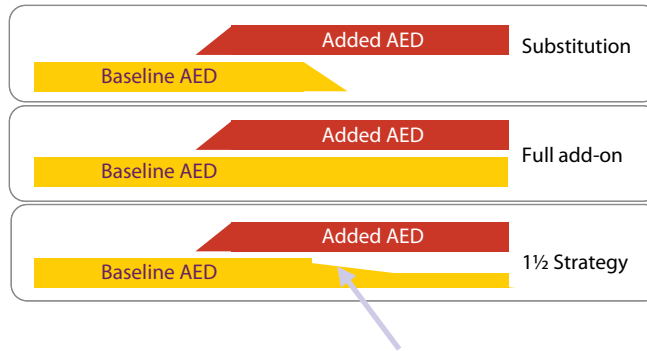

Figure 10.1 Single drug therapy, 1½ therapy, and two-drug therapy (with permission from Elger and Schmidt, 2008)

trials with old AEDs including phenobarbital, and suggests that switching may be as efficacious as adding another drug. While adding another AED (i.e., two-drug therapy) may be beneficial for seizure control, two-drug therapy often results in more side effects simply because of doubled drug load. To avoid unnecessary overtreatment, it is advisable to lower the dose of the first AED, once the second AED has reached an average maintenance dose. This is called 1½ therapy (Figure 10.1).

Three strategies for AED treatment of refractory epilepsy are: switching to single drug therapy with another agent; 1½ therapy; i.e., lowering the dose of the baseline drug by as much as 50%, primarily for individuals developing side effects after adding the new adjunctive agent; and traditional two-drug therapy with full dose of the baseline and the adjunctive agent.

Recommendation

Correcting undertreatment by either adding a dose increment or two-drug therapy will modestly improve the rate of patients becoming seizure-free and will result in a reduction of seizure frequency in many patients. To avoid the unfavorable side-effect profile of two-drug therapy, it is advisable to cautiously lower the dose of the first AED by 50%, resulting in 1½ therapy.

Overtreatment. Overtreatment may occur in patients with nonepileptic seizures as well as in patients with epilepsy. In a patient with syncope or other cause of nonepileptic seizures, AEDs will not work, even after increasing the dose. Switching medication or adding another AED will also have no benefit, even at higher doses, and invariably results in adverse events. Even in patients with epilepsy, overtreatment is an issue. Although complete seizure control is the ultimate goal of pharmacological therapy, it should not be sought at all costs, and no patient with epilepsy should suffer more from the side effects of treatment than from the consequences of the underlying disease. Overtreatment is not uncommon in patients taking AEDs, and it may occur in many forms and with a variety of mechanisms. Long-term use (or continuation) of AED therapy in situations where it is not indicated (e.g., in children with simple febrile seizures) constitutes overt overtreatment. Other forms of overtreatment result from unnecessarily fast dose escalation rates, which may expose the patient to potentially serious or severe side effects, and the prescription of unnecessarily high maintenance dosages. The latter occurrence may result from inadequate

understanding of dose–response relationships, from misinterpretation of serum drug concentrations (e.g., targeting concentrations within the "range" in patients whose seizures are well controlled at lower concentrations, as discussed in Chapter 8) or, less often, from failure to recognize a paradoxical increase in seizure frequency as a sign of AED toxicity.

The most common form of overtreatment, however, involves the unnecessary use of combination therapy (polypharmacy) in patients who could be treated optimally with a single drug. Adverse effects associated with polypharmacy often result from undesirable drug–drug interactions. While pharmacokinetic interactions are somewhat predictable and can be minimized or controlled by monitoring serum drug concentrations and/or dose adjustment, pharmacodynamic interactions leading to enhanced neurotoxicity (as seen, for example, in some patients given a combination of lamotrigine (LTG) and carbamazepine) can only be identified by heightened suspicion and careful clinical observation. There is evidence that not all AED combinations are equally adverse, and that the combined use of specific drugs (e.g., LTG and valproic acid) may even exhibit an improved therapeutic index in some patients compared with either agent given alone, provided appropriate dose adjustments are made. In women with childbearing potential, however, the same combination is associated more often with fetal malformations than either drug alone. Unless and until we better understand the complexities of drug combinations, single drug therapy avoids inadvertent overtreatment associated with polypharmacy.

Recommendation

Keep it simple and avoid unnecessary diagnostic or therapeutic interventions with an unfavorable risk-to-benefit ratio. Try 1½ therapy to avoid side effects. Withholding drug treatment until the diagnosis of epilepsy is certain should be considered. Avoid full two-drug combination therapy and enzyme-inducing agents, if possible.

How to Avoid Medical-Legal Issues

A number of easy-to-follow considerations help to protect against many avoidable medical-legal issues (Box 10.6).

Box 10.6 How to protect against medical-legal issues

- Adequate communication
- Adequate documentation
- Avoid carelessness
- If you act outside of the accepted standards of medical care, you need to be able to justify your action or nonaction

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Chapter 11

When to Stop Treatment?

Dieter Schmidt

The decision to stop antiepileptic drug (AED) treatment is one of the most common management scenarios in epilepsy, simply because AEDs are stopped in two of three patients with new-onset epilepsy who eventually become seizure-free, as do up to 50% of patients with previously refractory epilepsy undergoing successful epilepsy surgery (see Chapter 9). In addition, stopping AEDs in patients with uncontrolled seizures is a common strategy when switching AEDs or reducing overtreatment in refractory epilepsy. As discussed in Chapter 5, patients with a misdiagnosis of epilepsy are often encouraged to stop AEDs, which can be very demanding for patients and physicians. AED discontinuation for patients with a history of epilepsy requires a careful risk-to-benefit assessment in view of the undeniable risks involved. These risks include difficulties to predict individual seizure outcome after discontinuation, frequent seizure recurrence (particularly in high-risk patients), and the potentially grave consequences of seizure recurrence. In addition, successful treatment of seizure recurrence is neither invariably immediate nor assured. Taken together, stopping AEDs is a common and seemingly straightforward step in the management of patients with epilepsy but with a large number of possible pitfalls (Box 11.1) as discussed in this chapter.

Box 11.1 List of possible pitfalls when stopping AEDs

Pitfall: The patient wants to continue treatment despite the physician urging the patient to stop AEDs
Pitfall: Under-communicating the risks of stopping AEDs
Pitfall: Failure to appreciate that estimating the individual outcome of stopping AEDs may not be accurate for specific patients
Pitfall: Failure to relate the seizure-free period to prior seizure frequency
Pitfall: Overstating the benefits of continued treatment
Pitfall: Overstating the benefits of stopping AEDs
Pitfall: Stopping AEDs is not necessarily the end of treatment
Pitfall: Should physicians encourage seizure-free patients to discontinue AEDs?

Pitfall: The Patient Wants to Continue Treatment Despite the Physician's Urge to Stop AEDs

One common scenario is that a physician recommends, in accordance with current guidelines, stopping AEDs in a patient who has been seizure-free for several years. The patient is afraid to stop the medication and afraid to upset the physician by not following the advice.

Case 11.1 Would You Stop Drug Treatment?

A 55-year-old professional musician who has been seizure-free for over 5 years on phenytoin (PHT) and primidone (PRM) presents for a routine visit. Given the long seizure remission, the physician recommends gradual PRM withdrawal over the next 6 months while maintaining PHT treatment. Six months later, the patient reports that he continues to be seizure-free and has stopped taking PRM as recommended. Routine serum monitoring unexpectedly shows PRM and its major metabolite phenobarbital in addition to the expected level of PHT. When shown the results, the patient is embarrassed and admits that he has continued to take PRM out of fear of suffering a seizure against the recommendation of his physician.

Discussion

Some patients will assert their opposition and others will simply continue taking their medication as before without telling the physician that they refuse to stop their AEDs. Whatever the patient does, the physician has violated one major rule, namely that one should not pressure a patient into a change of medication against the patient's wish. If the patient had experienced a seizure relapse after withdrawing PRM, the physician would be blamed, though it is well established that as many as 15% of seizure-free patients experience a seizure relapse despite continued treatment (Sillanpää and Schmidt, 2006a, b).

Pitfall: Under-Communicating the Risks of Stopping AEDs

The risks involved in stopping AEDs are threefold: first and foremost, the risk of seizure relapse; second, the social and psychological consequences of a relapse; and third, the unexpected but common observation that treatment of seizures after relapse does not guarantee an immediate or complete remission in all patients. These risks will be briefly discussed in the following paragraphs.

Pitfall: Failure to Appreciate that the Individual Outcome of Stopping AEDs cannot be Predicted with Certainty

Although approximately 70% of all patients with newly diagnosed epilepsy become seizure-free with AEDs (Kwan and Brodie, 2000), many seizure-free patients (and their physicians) prefer to continue medication, mainly for fear of a seizure recurrence, as discussed above. Another important limitation is that estimating the individual outcome of stopping AEDs is not accurate. The MRC study described below examined factors associated with a higher risk of recurrence.

Pitfall: Failure to Relate the Seizure-Free Period Prior to Stopping with the Seizure Frequency of the Last 12 months

Most commonly, periods of 12 months or more are generally considered necessary before consideration of AED withdrawal, but the longer the seizure-free period, the lower the risk of recurrence (Chadwick, 2006). Studies that include a broad mix of patients and that require 2-year seizure remission before stopping treatment on

average show a risk of relapse of 25% in the first year and 29% after 2 years (Berg and Shinnar, 1994). However, relying on the number of seizure-free years alone, without relating it to the pre-treatment seizure frequency of the patient, is probably the most common pitfall in stopping AEDs. The explanation goes as follows: The general concept is that one should stop AEDs provided the patient does not have a higher risk of relapse after stopping AEDs compared to the risk of having seizures found in the general population. The prediction of relapse based on the number of years being seizure-free is intricately linked to frequency of seizures during treatment. If the maximum seizure frequency was 100 or more seizures per month prior to treatment, a seizure-free period of 2 years on treatment is clearly significant to predict long-term seizure-freedom. If, however, a patient had a much lower seizure frequency of, for example, one seizure per year, being seizure-free on medication is much less predictive for long-term seizure-freedom off drugs. The tentative rule of thumb is that a patient needs to be seizure-free for three times the longest pre-treatment interval between seizures to be considered seizure-free. This definition of seizure-freedom was used by Kwan et al. (2010).

Case 11.2 Would You Stop Drug Treatment?

A patient was newly started on carbamazepine (CBZ) after two focal seizures occurred over 9 months. He has had no seizures for 24 months since.

Discussion

The pre-treatment interseizure interval was 9 months. Although the patient has had no seizures for 24 months, the duration is less than three times the pre-treatment interseizure interval, which is $3 \times 9 = 27$ months; hence, outcome to treatment is undetermined, drug responsiveness of this patient's epilepsy is undefined, and the patient cannot be considered seizure-free. Stopping CBZ is therefore not recommended.

Pitfall: Overstating the Benefits of Remaining on AEDs

When discussing with patients the pros and cons of stopping AEDs, a related pitfall is to overemphasize the benefits of staying on medication. Counterintuitively, there is no evidence that continued treatment with AEDs guarantees permanent seizure-freedom. In a prospective, long-term, population-based study of 144 patients followed on average for 37.0 years, 67% were in terminal remission, with or without treatment (Sillanpää and Schmidt, 2006a, b). However, 28 patients (19%) achieved terminal remission following a relapse after early or late remission, suggesting a remitting–relapsing pattern, and 20 patients (14%) had a relapse after prolonged remission and did not re-enter remission, indicating a worsening course of the disease. The continued use of AEDs in both children and adults may also be associated with adverse effects in a substantial fraction of the exposed population, including behavioral and cognitive side effects, and are shown to improve after drug withdrawal (Lossius et al., 2008). Additional disadvantages of continuing treatment indefinitely include a higher risk of teratogenicity, drug interactions with concurrent medications, and, last but not least, the concern that treatment may be unnecessary.

Pitfall: Overstating the Benefits of Stopping AEDs

Intuitively, one might predict that stopping AEDs will result in having fewer side effects and, as a consequence, a perception of better health, including perceptions of well-being. The reality is more complex. Although some patients have improved neuropsychological outcome, their quality of life is not necessarily better after withdrawal. This finding is in agreement with the MRC study (see below), although Jacoby et al. (1992) found a benefit only in a subgroup of patients with low risk of recurrence.

Pitfall: Rapid versus Slow Withdrawal of AEDs of Patients in Seizure Remission

The ideal objective of treating a person with epilepsy is to completely stop seizures with AEDs and eventually withdraw the AEDs without causing seizure recurrence. Prolonged usage of AEDs may have long-term side effects. Hence, when a person with epilepsy is in remission (free of seizures for an appropriate length of time), it is logical to recommend AED discontinuation and attempt to do so with the patient's approval and adherence. The timing of withdrawal and the mode of withdrawal therefore arise. A review of randomized, controlled trials that evaluate withdrawal of AEDs in a rapid or slow manner after varying periods of seizure control in patients with epilepsy examined the evidence for the rate of withdrawal and its effect on recurrence of seizures (Ranganathan and Ramaratnam, 2006). It also assessed the effect of variables such as age of seizure onset, seizure types, presence of neurological deficits, cognitive dysfunction, etiology of epilepsy, type of AED, EEG findings, and duration of seizure-freedom on the risk of recurrence of seizures with rapid versus slow tapering. One trial with weak methodology involving 149 children was included; patients had a mean age of seizure onset of 4 years and a mean age of 11 years at the time of starting the taper. The rapid taper group (six weeks) recruited 81 participants and the slow taper group (9 months) included 68 participants, of whom 11 and 5, respectively, were lost to follow-up even before the taper began. The number of participants who were seizure-free in the rapid and slow taper groups were 40 and 44, respectively, at the end of 1-year follow-up (OR 0.53, 95% CI 0.27–1.03); 30 and 29, respectively, at the end of 2 years (OR 0.79, 95% CI 0.41–1.53); 24 and 14, respectively, at the end of 3 years (OR 1.62, 95% CI 0.76–3.46); 18 and 8, respectively, at the end of 4 years (OR 2.14, 95% CI 0.87–5.3); and 10 and 6, respectively, at the end of 5 years (OR 1.46, 95% CI 0.5–4.23) (Ranganathan and Ramaratnam, 2006). In view of methodological deficiencies and small sample size, in the solitary study identified, the study authors suggested any reliable conclusions regarding the optimal rate of tapering of AEDs could not be made. Further studies are needed in adults as well as in children to investigate the rate of withdrawal of AEDs and to study the effects of variables such as seizure types, its etiology, mental retardation, EEG abnormalities, presence of neurological deficits, and other co-morbidities on the rate of tapering (Ranganathan and Ramaratnam, 2006).

Pitfall: Early versus Late Antiepileptic Drug Withdrawal for Epilepsy in Remission

In their review, Sirven et al. (2001) quantified seizure relapse risk after early (less than 2 seizure-free years) versus late (more than 2 seizure-free years) AED withdrawal in adults

and children with epilepsy to assess which variables modify the risk of seizure recurrence depending on duration of seizure-freedom. The review assessed randomized, controlled trials that evaluated withdrawal of AEDs after varying periods of seizure remission with or without blinding. Seven eligible controlled trials were included in the analysis, representing 924 randomized pediatric patients. There were no eligible trials evaluating adult seizure-free patients. The pooled relative risk for seizure relapse in children associated with early versus late AED withdrawal was 1.32 (95% confidence interval 1.02–1.70). On the basis of this estimate, the number needed to harm, that is to expose an individual to a higher risk of seizure relapse because of early withdrawal of AED, is 10. Early discontinuation was associated with greater relapse rates in patients with partial seizures (pooled RR = 1.52; 95% confidence interval 0.95–2.41) or an abnormal EEG (pooled RR = 1.67; 95% confidence interval 0.93–3.00). Sirven et al. (2001) concluded that there is evidence to support waiting for at least two or more seizure-free years before discontinuing AEDs in children, particularly if individuals have an abnormal EEG and partial seizures. There is insufficient evidence to establish when to withdraw AEDs in pediatric patients with generalized seizures and there is no evidence to guide the timing of withdrawal of AEDs in adult seizure-free patients. Further blinded, randomized, controlled trials are needed to identify the optimal timing of AED withdrawal and risk factors predictive of relapse (Sirven et al., 2001).

Pitfall: Stopping AEDs is not Necessarily the End of Treatment

Stopping AEDs is unfortunately perceived by some patients, particularly those with juvenile myoclonic epilepsy, as an invitation to return to their seizure-prone lifestyle, for example, partying and going out at night, which may at least in some patients result in seizure relapse after protective drugs have been removed. As a consequence, it is useful to encourage patients to keep their seizure-aversive lifestyle during and after stopping AEDs. It is recommended that the patient see their physician after stopping AEDs in the same way as occurred while the patient was taking medication. Not seeing the patient after stopping AEDs is an unappreciated pitfall that may contribute to a higher relapse rate.

Case 11.3 Seizure recurrence after an all-night party

A 21-year-old female medical student had been diagnosed with juvenile myoclonic epilepsy at age 14. Prior to treatment, she had absence seizures, 2–3 times per week, and series of myoclonic seizures that would evolve into generalized tonic–clonic seizures once a month. Valproate (VPA) was started and the patient had no more seizures for the last 7 years. The patient wanted to stop VPA. Stopping VPA was well tolerated, but she had a series of myoclonic seizures and was afraid of having a tonic–clonic seizure. Going to an all-night party to celebrate the end of drug treatment triggered the myoclonic seizures.

Discussion

Stopping drugs puts the patient at increased risk for seizure recurrence. It is advisable to continue seeing the patient routinely for a year or so after stopping treatment. In addition, the patient should be asked to return for a visit in case of seizure recurrence, which in this patient includes recurrence of any seizure type, such as absence seizures or myoclonic seizures (not just tonic–clonic seizures).

Pitfall: Should Physicians Encourage Seizure-Free Patients to Discontinue AEDs?

AED discontinuation doubled the risk of seizures for up to 2 years after stopping the AED compared to continued treatment (Chadwick et al., 1996) in a prospective multicenter, unblended, randomized study of continued AED versus slow withdrawal conducted in 1,013 patients who had been free of seizures for at least 2 years (MRC study, 1991). By 2 years after randomization, 78% of patients in whom treatment was continued and 59% of those in whom it was withdrawn remained seizure-free, but thereafter the differences between the two groups diminished. This suggests that the long-term seizure outcome is not affected by drug discontinuation. Noncompliance with continued treatment accounted for only a small proportion of the risk to the group continuing with treatment. The most important factors determining outcome were longer seizure-free periods (reducing the risk), more than one AED, and a history of tonic–clonic seizures (increasing the risk). Other factors (e.g., history of neonatal seizures, specific EEG features) seemed to have smaller effects, but even in such a large study the confidence intervals for these observations were wide (MRC study, 1991). The failure to predict the risk of recurrence for the individual patient creates uncertainty and anguish and is a matter of concern.

A physician who indiscriminately proposes AED discontinuation is in a difficult position in case of harmful seizure recurrence. Although continued treatment is no guarantee for remaining seizure-free, patients tend to attribute any harm to the discontinuation of the treatment and may lose confidence and go elsewhere. Given these circumstances, patients at high risk for seizure recurrence should not be encouraged or even advised to discontinue AEDs. Seizure-free patients with juvenile myoclonic epilepsy, and seizure-free adults with symptomatic focal or generalized epilepsy belong to the high-risk group for seizure recurrence in whom discontinuation may in fact be dangerous. It is advisable in these patients, for example, to refrain from encouraging AED discontinuation. The decision process leading to discontinuation should be carefully documented and include the patient's preference.

Pitfall. Failure to appreciate factors influencing risk of relapse have been nicely summarized by Chadwick (2006) (Box 11.2).

Box 11.2 Factors influencing risk of relapse

- Duration of remission
- Electroclinical syndrome
- Age at onset
- Underlying etiology
- The electroencephalogram
- Number of prior AEDs
- Time to remission

Factors found by Berg and Shinnar (1994) to consistently indicate a higher-than-average risk of seizure relapse included adolescent-onset epilepsy, partial seizures, presence of an underlying neurological condition, and abnormal EEG findings (children). Adolescent age at onset of seizures carried a 1.34-fold higher risk of relapse compared to adult age at onset. Remote symptomatic seizures had a 1.55-fold higher risk of relapse.

An abnormal EEG prior to drug discontinuation was associated with a 1.45-fold higher risk of relapse. Factors associated with a lower-than-average risk were childhood epilepsy, idiopathic generalized epilepsy, and – for children – normal EEG. Selected epilepsy syndromes (e.g., benign epilepsy with centrotemporal spikes and juvenile myoclonic epilepsy) may be associated with significantly different outcomes after treatment withdrawal. The MRC AED Withdrawal Study was sufficiently large to develop and test a predictive model for relapse in patients continuing or stopping their medication (MRC study, 1993). The model gives decreasing weight to the following factors: whether or not treatment is withdrawn, period of time seizure-free, taking two or more AEDs, being 16 or older at the time of withdrawal, having myoclonic seizures, and having tonic–clonic seizures of any type. The final factor was an abnormal EEG. Curiously, the model does not include the presence of remote symptomatic epilepsy. However, factors provide surrogate measures for symptomatic epilepsy and capture those aspects of remote symptomatic epilepsy that are most associated with an increased risk.

Individualize AED Withdrawal in Remission

A recent meta-analysis identified 45 studies with 7,082 patients; 10 studies (22%) with 1,769 patients (25%) were analzyed. Median follow-up was 5.3 years (IQR 3.0–10.0, maximum 23 years). Prospective and retrospective studies and randomized controlled trials were included, covering nonselected and selected populations of both children and adults. Relapse occurred in 812 (46%) of 1,769 patients; 136 (9%) of 1,455 for whom data were available had seizures in their last year of follow-up, suggesting enduring seizure control was not regained by this time point. Independent predictors of seizure recurrence were epilepsy duration before remission, seizure-free interval before AED withdrawal, age at onset of epilepsy, history of febrile seizures, number of seizures before remission, absence of a self-limiting epilepsy syndrome, developmental delay, and epileptiform abnormality on electroencephalogram (EEG) before withdrawal. Independent predictors of seizures in the last year of follow-up were epilepsy duration before remission, seizure-free interval before antiepileptic drug withdrawal, number of antiepileptic drugs before withdrawal, female sex, family history of epilepsy, number of seizures before remission, focal seizures, and epileptiform abnormality on EEG before withdrawal. Adjusted concordance statistics were 0.65 (95% CI 0.65–0.66) for predicting seizure recurrence and 0.71 (0.70–0.71) for predicting long-term seizure freedom. Validation was stable across the individual study populations. This study confirmed earlier data and established a framework to individualize the risk of seizures following AED withdrawal in remission (Figure 11.1) (Lamberink et al., 2017).

Pitfall: Failure to Appreciate the Risk of Poor Seizure Control after Relapse

The long-term outcome with respect to seizure relapse after planned discontinuation of AEDs in seizure-free patients is not well known. Relapse and its treatment outcome were evaluated in a longitudinal, population-based study of 148 patients from the onset of the epilepsy to an average follow-up of 37 years (Sillanpää and Schmidt, 2006a, b). During the study, AEDs were completely discontinued by 90 patients while 58 patients remained on medication. Seizure relapse after AED discontinuation was observed in 33 (37%) of 90 patients at an average follow-up of 32 years. Among 8 of the 33 patients who elected

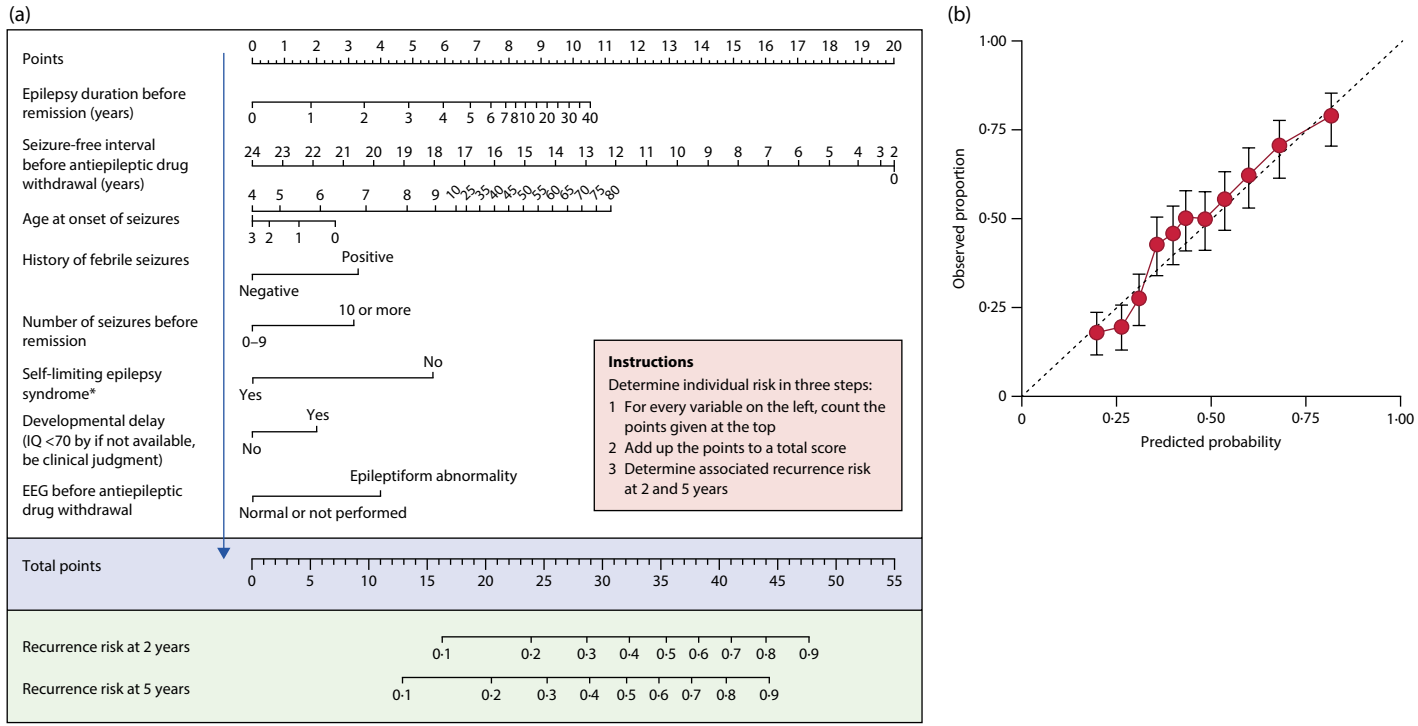

Figure 11.1 Prediction of seizure recurrence after AED withdrawal. (a) Nomogram to predict seizure recurrence after AED withdrawal, validated in the 10 cohorts. For example, a child whose seizures started at the age of 3 years (0 points) who had active epilepsy for 1 year (2) and has been free from seizures for 2 years (20), with no history of febrile seizures (0), less than 10 seizures (0), no self-limiting epilepsy syndrome (5.5), no developmental delay and a normal electroencephalogram (EEG; 0), has a total of 27.5 points, which corresponds to a risk of seizure recurrence of 28% and 36% at 2 and 5 years, respectively. (b) Calibration plot for the prediction of seizure recurrence 5 years after the start of AED withdrawal, as modeled in part (a) and appendix. *For example, absence or Rolandic epilepsy, or Panayiotopoulos syndrome (from Lamberink et al., 2017 with permission)

to restart AEDs, 2 achieved 5-year terminal remission (5YTR), but only 10–19 years after restarting treatment. The other six patients never achieved 5YTR, and two of the six never entered a 5-year remission period during follow-up. Factors associated with failure to reach 5YTR after treatment of relapse were symptomatic etiology and localization-related epilepsy. The authors concluded that drug discontinuation after seizure-freedom results in relapse in one-third of patients and reinstitution of medication that worked for years fails to achieve control in one of four patients. These risks need to be considered, although there is no evidence that discontinuation is responsible for the poor prognosis for treatment of seizure recurrence.

In a systematic review of 13 studies, the seizure recurrence rate after AED discontinuation ranged between 12% and 66% (mean 34%, 95% CI: 27–43) (Schmidt and Löscher, 2005). In these cases, reinstitution of AEDs led to seizure remission in 64–91% (mean of 14 studies, 80%, 95% CI: 75–85%) after a mean follow-up ranging from 1 to 9 years, with no differences between children and adolescents (84%, 95% CI: 75–93) and adults (80%, 95% CI: 74–86). Although seizure control was regained within approximately one year in half of the cases becoming seizure-free, some patients regained seizure control in as many as 5–12 years. In addition, in 19% (95% CI: 15–24%), seizure control was incomplete and chronic drug-resistant epilepsy was seen in up to 23% of patients. Factors associated with poor outcome after treating recurrences were symptomatic etiology, partial epilepsy, and cognitive deficits. Interestingly, treatment of a recurrence was not confirmed to be a predictive factor for better seizure outcome (Matricardi et al., 1995). In the MRC Antiepileptic Drug Withdrawal trial, the risk of recurrence was also similar in patients who relapsed after withdrawal of AEDs and in those who relapsed while remaining on treatment (Chadwick et al., 1996). Although seizure control was regained within approximately one year in half of the cases becoming seizure-free, it took some patients as many as 5–12 years (Schmidt and Löscher, 2005). In 19% (mean of 14 studies, 95% CI: 15–24%), resuming medication did not control the epilepsy as before, and chronic drug-resistant epilepsy with many seizures over as many as 5 years was seen in up to 23% of patients with a recurrence (Schmidt and Löscher, 2005). In a longitudinal, long-term study of childhood-onset epilepsy, it took 24 patients 8 years (mean, median 7.0 years, range: 5–20 years) to re-enter long-term remission after the last recurrence and more than 10 years in 5 of the 24 patients (Sillanpää and Schmidt, 2006a, b). Delayed re-gaining of seizure control, defined as 1-year remission, was noted in an observational study from the Netherlands (Overweg et al., 1987). Among 41 patients, seizure control was regained within 6 months in only 40%. In addition, as will be discussed in detail below, 3 of the 41 patients never became seizure-free again during a follow-up of 5 years and their epilepsy could be considered to be drug-resistant (Overweg et al., 1987).

Pitfall: Underestimate the Risk of Relapse after AED Discontinuation in Patients Seizure-Free after Surgery

Although the literature on stopping AEDs in patients who became seizure-free after surgery is not as extensive and there are no randomized, controlled trials that evaluated stopping AEDs in surgical series, it seems that the relapse rate of surgical patients is similar to that of patients with new-onset epilepsy who became seizure-free on AEDs alone (without surgery). Schmidt et al. (2004) analyzed six retrospective series of patients undergoing planned AED discontinuation under medical supervision. Their review showed an

average relapse rate of 33.8% for all surgeries, most often temporal lobe resections, with recurrence rates increasing with the length of follow-up. Interestingly, among all patients analyzed, only 48% of seizure-free adult patients discontinued AEDs, whereas 71% of seizure-free children did so. Their findings suggested that there was no benefit in waiting to attempt AED tapering (one year in children and two in adults), and that the occurrence of rare seizures or auras did not preclude successful AED discontinuation. In accordance with other studies and observations, more than 90% of adult patients with seizure recurrence regained seizure control after reinstitution of AEDs. This study failed to find a strong association between relapse after AED withdrawal and factors such as age of onset of epilepsy, duration of epilepsy, and preoperative MRI findings.

A study from India (Rathore et al., 2011) reported on AED withdrawal in 258 patients (83.2%) with mesial TLE (mTLE) with radiographic evidence of hippocampal sclerosis (HS) who were seizure-free after anterior temporal lobe surgery (ATL). The authors started AED tapering at 3 months in patients on duotherapy/polytherapy and at 1 year after ATL for those on monotherapy. Sixty-four patients (24.8%) had seizure recurrence while reducing AEDs. Of 26 patients who had seizure recurrence after complete AED withdrawal, 24 (92.3%) again became seizure-free after restarting the AEDs. Absence of HS on pathologic examination and abnormal postoperative EEG predicted seizure recurrence on multivariate analysis. At the end of a follow-up duration of 8.0 ± 2.0 years, 163 patients (52.6%) were AED-free. The authors concluded that AED withdrawal can be safely attempted following successful ATL for mTLE.

Background: Why is Stopping AEDs after Entering Remission Fraught with So Many Pitfalls?

Most patients (up to 70%) diagnosed and treated for new-onset epilepsy will enter long-term remission (Kwan and Brodie, 2000). Most of those who enter remission do so shortly after beginning therapy on low doses of AEDs (see Chapter 8). The problem with the decision to stop AEDs arises firstly from a lack of understanding of the way in which AED treatment may or may not interact with the natural history of epilepsy. Are people with a significant period without seizures cured (i.e., their seizure-freedom is no longer dependent on treatment) of the condition, or is it they simply have symptomatic control of seizures by ongoing treatment? Second, there is little information available to accurately quantify the risk of stopping AEDs for the individual patient. Third, there is concern about unwanted chronic side effects of AEDs. Particular concerns may arise for children with developing brains and women in their childbearing years where reduction in the risk of fetal malformation and other adverse effects may be particularly important. Finally, not stopping treatment does not guarantee continued seizure-freedom.

Given the many areas of uncertainty, it is not surprising that stopping AEDs in patients with prolonged seizure remission is still a matter of debate (Specchio et al., 2002; Specchio and Beghi, 2004; Berg, 2008; Elger and Schmidt, 2008). The main pitfalls stem from issues in assessing the individual risk-to-benefit ratio and factors influencing seizure relapse including the duration of the seizure-free period and the length of the tapering period (Elger and Schmidt, 2008). Although the probability of remaining seizure-free after treatment discontinuation ranges from 70% at best to 25% at worst, the main challenge is to offer specific patients an accurate estimate of their own individual risk. Identifying patients at greater risk for relapse and for poor remission after relapse may be difficult

and drug resistance may even develop in some patients who have been seizure-free on treatment for many years (Schmidt, 2011). As a consequence, the decision to withdraw or withhold treatment must be individualized. In any patient, the decision to discontinue treatment should also take into account social aspects like driving license, job and leisure activities, as well as emotional and personal factors and adverse effects or drug interactions. Patients will ultimately have to decide themselves whether they wish to discontinue drug treatment (Jacoby et al., 2007; Beghi, 2011).

Common Scenarios of Stopping AEDs and Their Pitfalls

As already discussed, AEDs may be stopped for patients who enter several years of remission or those who became seizure-free with surgery. Another common scenario includes patients with uncontrolled seizures in whom one of several AEDs are discontinued to prepare for adding another drug or for complete discontinuation, if it turns out that the prior diagnosis of epilepsy was wrong, for example in patients with psychogenic nonepileptic seizures (PNES) or syncope (see Chapter 5).

Pitfall: Stopping One of Two AEDs in Uncontrolled Epilepsy

The effects of reducing two-drug treatment to single-drug therapy were studied prospectively in 36 patients with intractable complex partial seizures (Schmidt, 1983). In 30 patients (83%), this was possible without an increase in seizure frequency. In six patients (17%), the number of seizures was higher during single-drug therapy. Unwanted withdrawal effects did not complicate the slow transfer. The serum concentration of the single drug was raised if necessary until clinical drug toxicity was observed. An improvement in seizure control was surprisingly noted in 13 patients (36%). In two patients, seizures were completely controlled. In one patient, a seizure reduction of 87% was observed. The number of patients with clinical side effects was similar during two-drug and single-drug therapy. The number of side effects was lower during single-drug therapy. Therefore, reduction of polypharmacy may be beneficial for patients with intractable epilepsy (Schmidt, 1983).

Pitfall: Stopping AEDs Completely in Uncontrolled Epilepsy

A not uncommon scenario for stopping AEDs completely in uncontrolled epilepsy against the advice of the physician is the disappointment of patients and relatives that the AEDs lost their effectiveness as evidenced by an increasing number of seizures. Stopping AEDs is however an unadvisable and risky strategy to deal with loss of efficacy. Status epilepticus can be triggered by AED withdrawal in those with uncontrolled seizures and be sometimes fatal. In a cohort study from the United Kingdom of 6,190 subjects with epilepsy, of whom 8 died in relation to their epilepsy, 2 status epilepticus deaths were associated causally with AED withdrawal (Ackers et al., 2011). Stopping the drug altogether, not introducing any new medication, and thus leaving the patient totally unprotected and exposed to having uncontrolled seizures in this type of situation is a major pitfall.

Pitfalls: Stopping AEDs after Misdiagnosis of Epilepsy

Stopping AEDs in patients with PNES (and not concomitant epilepsy) is not easy. Patients with PNES may be diagnosed with epilepsy and treated with AEDs for many years.

If an epilepsy diagnosis is replaced by a PNES diagnosis, the patient must reconsider the underlying cause for their seizures.

Switch in diagnosis from epilepsy to PNES is demanding and stressful, for patients and the physician, both cognitively and emotionally. The patients may have difficulty in understanding the diagnosis. When epilepsy as the cause of the seizures is suddenly challenged, feelings of hopelessness and helplessness may result. There is a need for re-evaluation of self-understanding. The patients may feel that with the change in diagnosis, responsibility was transferred from the health authorities to themselves. In order to avoid the patients feeling that they have been abandoned with a difficult diagnosis, close cooperation between neurologists and psychiatrists is essential.

Patients, who continue to prefer the diagnosis of epilepsy and reject having a psychiatric disorder may choose another physician who is unaware of the diagnosis of PNES and who continues to prescribe AEDs based on the (ill-advised) impression of epilepsy. An alternative explanation for why the patients are on AEDs again is that the diagnosis of PNES has been rejected by the physician (and the patient) and the diagnosis is reverted to epilepsy or epilepsy plus PNES. The proportion of patients with PNES who stop and restart AEDs is not well known but may not be small. A follow-up questionnaire study of 33 patients with proven (ictal EEG-CCTV) PNES, in whom all AEDs had been withdrawn at the time of diagnosis, found that at follow-up, eight patients (29%) were on AEDs again (all not seizure-free); six were treated by a neurologist and two by a general practitioner. Therefore, the authors suggested the physicians may have reverted to a diagnosis of epilepsy (Jongsma et al., 1999). The study did not, however, provide any information from the physicians or the patients why they restarted AEDs.

Although seizures are not expected to recur in most (70%) individuals, prediction of individual outcome before withdrawal remains uncertain. Patients in whom recurrence occurs still have good chances of achieving renewed seizure-freedom, although this may take several years. It is reassuring that a recurrence itself does not seem to have important consequences: most patients do not suffer complications from a relapse and 80% eventually become seizure-free again. On the other hand, prolonged AED treatment after 2 years without seizures does not guarantee lifelong seizure-freedom in adults and children, with or without AEDs. In this light, discontinuation of drug treatment is not dangerous but exposes patients who were seizure-free for years to an increased risk of seizures for the first 2 years after stopping AEDs. In addition, 20% of patients who were seizure-free for years do not become seizure-free immediately with renewal of AED treatment after relapse. Nevertheless, stopping AEDs is a valuable option in most patients with epilepsy who are seizure-free for 2 years or longer. The decision to withdraw or withhold treatment in these cases must be, however, individualized. The decision is driven by assessing the individual risk of relapse after stopping treatment and by patient preference after informed consent. Although moderate, the risk of provoking uncontrollable epilepsy in some patients undoubtedly exists and must be mentioned when discussing AED discontinuation or taper in seizure-free patients (Schmidt, 2011). In any patient, the individualized decision to discontinue treatment should also take into account social aspects like the need for a valid driving license and job, leisure activities, emotional and personal factors, and adverse effects or drug interactions, and

patients will ultimately have to decide themselves whether they wish to discontinue drug treatment (Beghi, 2011).

Take Home Message

About 4–6 of 10 patients without seizures can eventually discontinue AEDs without relapse, but even with continued drug treatment, relapse occurs in about 3 in 10 patients. With the observed relapse rate (on and off drugs), long-term complete seizure control can be expected in no more than 1 in 3 of patients with new-onset epilepsy. Although AED reinstitution after a recurrence following planned discontinuation in seizure-free patients is successful in about 80% of patients, it is associated with the risk that seizure control will not be regained in about 20%. Also, response to AEDs may occur as late as 12 years after restarting treatment in some patients. These risks must be mentioned when discussing AED discontinuation or taper with seizure-free patients. Higher-than-average relapse rates are seen in patients in whom it took a long time to become seizure-free. Patients with symptomatic partial or generalized epilepsy, those with juvenile myoclonic epilepsy, and those with important social reasons for avoiding seizures should be considered for indefinite treatment.

Pragmatically, definite discontinuation of AED in seizure-free patients should not be encouraged, except for benign epilepsy of childhood and absence epilepsy of childhood.

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Chapter

12 Women with Epilepsy

William O. Tatum

Women with epilepsy (WWE) constitute a group for whom principal care by a neurologist for epilepsy management is indicated (AAN, 1998). In the United States, approximately 1.1 million women of childbearing age have epilepsy and many more exist throughout the world. Care for WWE poses several potential pitfalls. These involve key issues and time periods that are gender-specific occurring over a woman's life cycle; practical considerations of reproductive health and sex steroids, hormone-sensitive seizures, sexuality, contraception, pregnancy and breast feeding, and menopause may complicate treatment with AEDs and adversely affect seizure control. The first step is to ensure an accurate diagnosis of epilepsy before instituting treatment with medication. When the diagnosis is in doubt, or if an atypical history is encountered, video-EEG monitoring may be considered to clarify uncertain paroxysmal neurological events. Over-diagnosis may inadvertently lead to inappropriate use of AEDs that exposes a woman (and fetus) to greater risk of morbidity and mortality, in addition to an unplanned, unwanted pregnancy. Practical considerations are discussed to help avoid errors that may occur during diagnostic and treatment approaches.

AEDs and Fertility

Case 12.1 Teratogenesis

A 28-year-old female was in good health until she developed jerks while taking a shower one morning beginning at 12 years of age. These evaded detection until the first of recurrent generalized tonic–clonic (GTC) seizures began at 14 years of age when she was diagnosed with epilepsy. A brain MRI was normal. EEG demonstrated 3- to 4-Hz generalized frontally dominant spike and polyspike-and-slow waves.

She was diagnosed with juvenile myoclonic epilepsy (JME) and begun on valproate (VPA) 250 mg three times daily. Her seizures were controlled on low doses of VPA (serum level 59 μg/dl), but she experienced a significant weight gain of 15 kg. She was married but unable to have children. Menses were scant and irregular (oligomenorrhea), occurring every 6 weeks. She sought help from a fertility specialist. On clomiphene, she became pregnant, though unfortunately miscarried a set of quadruplets. Her husband had recently been promoted, resulting in relocation, when she sees you for initial evaluation.

Discussion

The reproductive years play an important setting for clinicians caring for WWE (Harden et al., 2009b). It is important to address neurological issues as soon as women become sexually active (Harden et al., 2009a). Hormonal influences may be significant and adversely affect seizure frequency, compromise normal endocrine function, and impair fertility as in this patient (Morrell, 1999). Hormonal influences are important and occur at menarche, during menses, and menopause (Harden et al., 2003). Reproductive steroids possess properties that are capable of modulating the degree of normal neuronal excitability and can influence individual seizure thresholds (Morrell, 1999). In general, estrogen acts as a proconvulsant, while progesterone functions as an anticonvulsant in some WWE. At menarche, estrogen levels gradually increase approximately 2–4 years prior to the first menses (Pennell, 2009). Progesterone production increases after the first ovulation (about 1–2 years after menarche) (Morrell, 1999). Therefore at menarche, there is a relative proconvulsant state for several years where estrogen effects outweigh progesterone. During menarche and puberty, 30% of young women may experience an onset or increase in seizure frequency (Morrell, 1999; Pack and Morrell, 2002; Pennell, 2009).

Pitfall

Failure to recognize the wide range of adverse effects from AEDs on a woman's reproductive health.

Case (cont'd)

On examination, she was overweight, had a mild amount of facial hair (her husband jokingly called her Elvis due to minimal side-burns), with a mild acneiform malar facial rash. Her neurological examination is normal. Testosterone and dehydroepiandrosterone levels were elevated. Pelvic ultrasound demonstrated ovarian cysts bilaterally. She asks if her epilepsy is preventing her from becoming pregnant and is afraid if she does that she will again miscarry.

Discussion (cont'd)

Overall, WWE have a significantly reduced fertility rate compared with the general population of women (Harden et al., 2009a; Gerard and Meador, 2016). In addition to reproductive changes triggering seizures, ongoing seizures may further create reproductive–endocrine dysfunction by involvement of the hypothalamic–pituitary–ovarian axis (Morrell, 1999). Alternatively, because her seizures are controlled, hypothalamic–pituitary–ovarian axis dysfunction likely reflects the effect from her AED. Ongoing seizures may stimulate the axis resulting in alteration of sex hormones including gonadotropin-releasing hormone and prolactin (Morrell, 1999). When enzyme-inducing antiepileptic drugs (EIAEDs) are utilized, they may alter sex-steroid binding globulin and reduce levels of circulating sex steroids (Gerard and Meador, 2016). Epilepsy and AED-induced changes in the hypothalamic–pituitary–gonadal axis hormones have been associated with increased rates of menstrual irregularity, anovulatory cycles, polycystic ovarian syndrome (PCOS), infertility, and catamenial epilepsy (see below) as in our patient (Morrell, 1999; Duncan, 2001; Pack and Morrell, 2002; Mascitelli and Pezzetta, 2005). While polycystic ovaries are often present in PCOS, they are not essential for the diagnosis when androgen levels are elevated (Pennell, 2009). Some of the signs of reproductive dysfunction may be evident to the clinician when the patient manifests several symptoms (Box 12.1).

Box 12.1 Clinical symptoms of reproductive dysfunction

Abnormal menses
<23 to >35 day cycles
Anovulatory cycle
Infertility or pre-term miscarriages
Sexual dysfunction
Weight gain (>20% of ideal body weight)
Hirsutism

Pitfall

Missing clues from the general history and physical examination that reproductive dysfunction is present.

Irregular menses are found in approximately 20–50% of WWE (Morrell, 1999; Pennell, 2009). Cycles less than 23 days or greater than 35 days may occur. Some menstrual irregularities result from an anovulatory cycle and infertility. AEDs may lead to altered body weight (Box 12.2). Weight gain is often associated with oligomenorrhea, PCOS, and VPA (Pack and Morrell, 2002). PCOS is increased in WWE and is comprised of hyperandrogenism and chronic ovulatory dysfunction with or without polycystic ovaries (PCOs; 10 or more follicular cysts 2–8 mm in diameter) on ultrasound (Mascitelli and Pezzetta, 2005). Polycystic ovaries are increased in the general population, too, though fewer women have PCOS than PCOs (Duncan, 2001). Hyperandrogenism may be detected clinically by obesity, hirsuitism, alopecia, and acne, which result from increased circulating testosterone and other androgens (and luteinizing hormone) (Dunan, 2001; Mascitelli and Pezzetta, 2005). These hormonal abnormalities lead to chronic ovulatory dysfunction, oligomenorrhea, and decreased fertility (Mascitelli and Pezzetta, 2005). Hyperinsulinemia is associated with obesity, excess androgens, and potentially oligo-ovulation and anovulatory cycles, diabetes mellitus type 2, hypertension, and dyslipidemia with obesity, representing a significant health risk (Mascitelli and Pezzetta, 2005). Rarely, EIAEDs (e.g., phenytoin) may cause hirsuitism or weight gain that mimics PCOS. A reproductive-endocrine evaluation may be helpful to differentiate the two (Crawford, 2005).

Box 12.2 Effect of AEDs on body weight

Weight gain
Valproate
Carbamazepine
Gabapentin/pregabalin
Weight neutral
Levetiracetam
Lamotrigine
Weight loss
Topiramate
Zonisamide

Diagnosis

1. Reproductive dysfunction due to PCOS associated with VPA
2. Juvenile myoclonic epilepsy

Hormonal Influence on Epilepsy

Case 12.2 Catamenial Seizures

A 32-year-old occupational therapist began having focal seizures at menarche when she was 13 years of age. A brain MRI revealed a right mesial temporal vascular malformation. EEG showed left anterior temporal spike-and-waves with a regional temporal field in drowsiness. More than 75% of her seizures occurred 2–3 days prior to her menstrual period with events at other sporadic times throughout the month. Her seizures always began with an abrupt feeling of anxiety and evolved to a blank stare, impaired responsiveness, and brief lip-smacking automatisms for 30 seconds. She would become depressed after the episode and gradually recover over 30 minutes. Seizures were initially controlled by carbamazepine (CBZ) 400 mg twice daily when she is seen for the first time. The patient asks, "Do hormones affect seizure frequency?"

Discussion

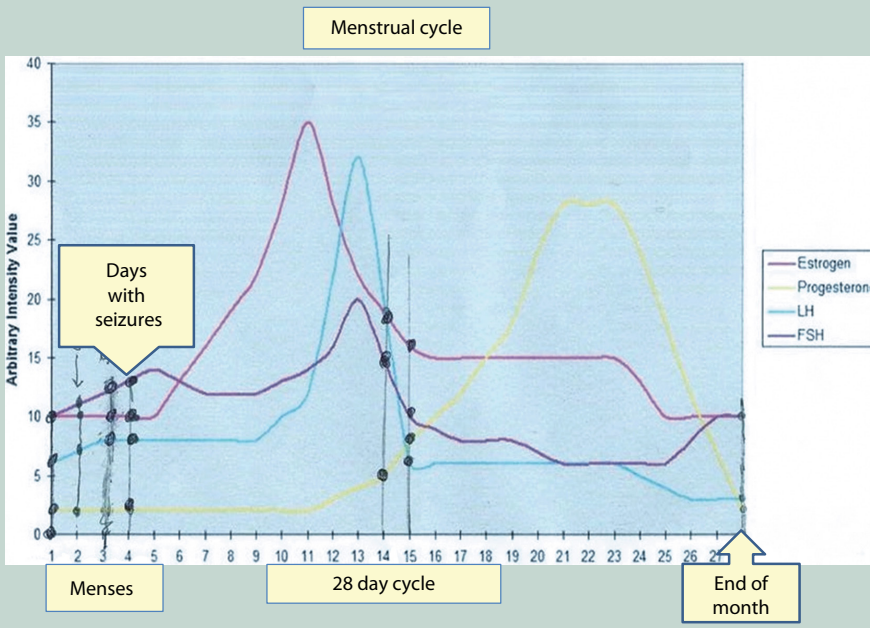

Figure 12.1 Typical diary of a WWE with consistent catamenial seizure exacerbation related to the menstrual cycle and ovulation

It is surprising that some neurologists do not realize that hormones may have a significant impact on seizure frequency. Elevated estrogen or decreased progesterone levels can exacerbate seizure frequency (Morrell, 1999; Pennell, 2009). Estrogen is believed to exacerbate seizures by enhancing the *N*-Methyl-D-aspartic acid receptor (Morrell, 1999; Reddy, 2004). Experimentally, estrogen may increase interictal epileptiform discharges (EDs) on the EEG while progesterone can lead to a reduction (Morrell, 1999; Reddy, 2004). Seizures may occur during puberty at the time of menarche in about one-third of young

WWE (Crawford, 2005). In addition, approximately 30–70% of WWE have exacerbation of their seizures around the time of menses (Crawford, 2005; Herzog, 2015).

The term "catamenial epilepsy" refers to the type of epilepsy where seizure exacerbation occurs as a function of the menstrual cycle (Reddy, 2004). Catamenial epilepsy has had variable definitions though is best regarded as seizure frequency during a particular phase of the menstrual cycle (typically pre-menstrual) that is at least two times greater than baseline frequency (Reddy, 2004; Herzog, 2015). This typically manifests a few days before menses (Figure 12.1). The next most common pattern is associated with seizure increase at the terminal 2–3 days in the second half of the period. The third, the most poorly defined pattern, is periovulatory, occurring near ovulation (days 8–14 of the cycle) (Herzog, 2015). Seizures therefore may be highly hormone-sensitive, an important point to recognize when discussing seizures with WWE (Box 12.3).

Box 12.3 Seizures and their relationship to the menstrual cycle

Seizures increase at menarche.
Seizure increase in relationship to the menses.
Seizures are due to hormonal changes.
Estrogen tends to increase seizure activity.
Progesterone tends to reduce seizure activity.
Seizures may increase during perimenopause and improve during menopause in catamenial epilepsy.
Treatment includes a unique approach (Packand Morrell, 2002). The approach to treating catamenial epilepsy includes various techniques (Box 12.4).

Box 12.4 Treatment approaches for WWE and catamenial seizures

Increased maintenance AED prior to menses
Acetazolamide
Pulse dose benzodiazepines (i.e., clobazam)
Oral contraceptive pills (OCPs)
Medroxyprogesterone
Natural progesterone lozenges

Increasing maintenance AEDs may be used as a reliable means of aborting catamenial seizures. Clinical studies also show possible improvement in seizure frequency in catamenial epilepsy with the use of oral contraceptives. Acetazolamide up to 1 g before and through menses may be helpful. Pulse benzodiazepines around the time of catamenial exacerbation may also prove effective in suppressing hormonally sensitive seizures. Natural progesterone has proven to be effective in WWE such as Prometrium® 100–200 mg lozenges three times daily during days 15–25 to produce progesterone levels >5 ng/ml (Pennell, 2009). While progesterone lozenges are "natural," hormonal side effects may still occur including moodiness, somnolence, abdominal bloating, edema, weight gain, and breast tenderness among others.

Case (cont'd)

Our patient marries. Her seizures worsen and are occurring monthly starting a few days prior to her period. She relays that she and her husband are considering family planning in the future and she asks about hormonal therapy and what her options are to ensure that she limits the dose of her AED as much as possible during pregnancy.

Discussion (cont'd)

Focal epilepsy is most commonly associated with catamenial exacerbation, though all seizure types may show a catamenial pattern in some patients. Inform your patient that she has the most common pattern of catamenial epilepsy (seizure aggravation several days prior to menses) and reiterate the importance of family planning.

Case (cont'd)

The patient opts for increasing her CBZ several days prior to menses in the interest of maintaining single drug therapy. She finds it difficult to predict her menses reliably and develops side-effects when she increases her medication by 200 mg daily (serum level 10 μg/dl). She tells you that she has been compliant with your recommendation to take her AED regularly with folic acid supplements, but privately shares that she has no sexual desire. Her seizures increase in frequency and she requests alternative treatment. She has heard that lamotrigine (LTG) is safe in pregnancy. You discuss the risks of treatment and initiate LTG while maintaining CBZ to pursue seizure control and family planning.

Discussion (cont'd)

Reassure her that the majority of WWE can lead normal sex lives, but also point out that they are at greater risk for impaired sexual desire and arousal, sexual functioning, and fertility (Crawford, 2005; Gerard and Meador, 2016). Higher rates of sexual dysfunction when found involve both men and WWE. A reduction in sexual desire is found in one-fourth to one-third of WWE and one-third report a reduction in sexual arousal (Harden, 2005). Epileptiform activity in brain regions related to sexuality (e.g., temporal and frontal lobes) may disrupt sexual function, probably due to changes in neurotransmitters and altered levels of pituitary and gonadal hormones (Harden, 2005; Pennell, 2009). Seizures may transiently elevate serum prolactin, which has been associated with reduced libido and impotence. Improved seizure control may alleviate some of the dysfunction, though precise mechanisms of restoring function are incompletely understood. Some studies find sexual dysfunction in up to 30–66% of men and 20–30% of women (Harden, 2005). Men experience erectile dysfunction, while women experience dyspareunia, vaginismus, and reduced lubrication (Morrell, 1999). The cause of sexual dysfunction is probably multi-factorial, with effects from seizures, AEDs, and psychosocial pressures. Endocrinology evaluation may include gynecological evaluation with pelvic ultrasound, endocrine assessment, and neuroimaging to search for a reason. Therapy is individualized and switching to a non-EIAED such as LTG or levetiracetam as well as counseling may be beneficial (Hernandez-Dıaz et al., 2012).

Question: What dose of folate is best to recommend?

A higher risk of congenital malformation has been thought to be related to low folic acid levels in pregnant WWE treated with AEDs in their first trimester. Folate supplementation is therefore recommended for all females of childbearing potential and those taking AEDs (Crawford, 2005). Folate is a vitamin that prevents neural tube defects in the general population at doses of 0.4 mg daily. In WWE, supplemental folate appears to reduce the risk of miscarriage, and may possibly have a positive effect on the child's intelligence quotient (IQ) (Harden et al., 2009b). However, it remains unclear whether congenital malformations are reliably reduced by supplemental folate, especially taken during the first trimester, in WWE.

The precise dose of folate to recommend is also unknown, with daily doses between 0.4 and 4 mg generally described in the literature, though 5 mg daily has been suggested by others (Harden et al., 2009a, b). Until the optimal dose of late supplementation is identified, 1 mg of folate and a prenatal vitamin that contains 800 μg of folate (about 2 mg) is a reasonable amount. If doses greater than 5 mg are used, the impact on psychomotor development may be compromised in children born to mothers with epilepsy (Valera-Gran et al., 2014). Therefore like most things, too much or too little is not ideal.

Pitfall: Assuming WWE are 100% Reliable at Planning Pregnancy

Discussion (cont'd)

You review her use of contraception and she informs you that she forgot to take her contraceptive pill one day. Beyond compliance, contraception presents crucial challenges to WWE with regard to family planning. Effective contraception enables WWE to plan pregnancy and help improve outcomes for themselves and their future children. It provides a time before conception that is important to optimize seizure control and general health. Oral contraceptive pills are not usually associated with adverse effects on seizure frequency or severity and are popular among women as in our patient given their ease of use (Herzog et al., 2016). However, they possess complicated drug interactions that can limit their efficacy and reliability. While non-EIAEDs (e.g., LTG and levetiracetam) do not have a clinically relevant interaction with oral hormonal contraceptives (OCPs), EIAEDs such as CBZ often do. Overall, there is a 6% failure rate of OCPs (i.e., unplanned pregnancy) when combined with EIAEDs (Winterbottom et al., 2009). When induced, the P450 hepatic enzyme system, especially CYP 3A4, increases hormone metabolism and alters sex steroid binding, thereby reducing the efficacy of OCPs. This may occur with oral, subdermal, and implanted hormonal contraception (Herzog et al., 2016). The specific AEDs that may adversely affect hormonal contraception are shown in Table 12.1.

For women taking EIAEDs who desire to take the combined oral contraceptive pill:

- Start with an ethinyl estradiol dose in the "pill" of 50 μg daily.
- If breakthrough bleeding occurs, either increase the dose to 75 μg/day or provide continuous dosing for 3 cycles ("tricycling").

Adequate family planning is critically important, since unwanted pregnancies can be life-changing for entire families, and the potential teratogenic effects of AEDs can be reduced by advanced planning (Winterbottom et al., 2009; Tomson et al., 2011). There

Table 12.1 Interactions between AEDs and hormonal contraception

Interaction	No interaction
Phenobarbital	Divalproex
Phenytoin	Ethosuximide
Primidone	Gabapentin
Carbamazepine	Lamotrigine[a]
Topiramate[b]	Levetiracetam
Oxcarbazepine	Zonisamide
Rufinamide	Tigabine
Clobazam	Lacosamide
Eslicarbazepine	Vigabatrin
Perampanel	Ezogabine

[a]HC interaction with LTG reduction.
[b]Potential inactivation at 200 mg/day.

Table 12.2 WWE and the percentage of contraceptive method utilized

Contraceptive method	Percent of WWE
Hormonal	46.6
Barrier	23.2
Intrauterine device	17.0
Withdrawal	4.8
Tubal ligation	4.0
Vasectomy	2.3
None	2.0

Adapted from Herzog et al. (2016).

are many different methods of birth control for WWE to choose from, including barrier methods such as condoms, intrauterine devices (IUDs), birth control pills, surgical sterilizing methods (vasectomy and tubal ligation), in addition to methods without medicine and surgery (rhythm method). WWE utilize a variety of contraceptive methods (Table 12.2) with efficacy and potential for AED interactions often accounting for choices.

Barrier contraceptive techniques are advocated for WWE taking EIAEDs. A progestin-containing IUD is a safe and acceptable long-acting contraceptive for WWE. Similarly, a Mirena coil may be used and there are no contraindications to the use of nonhormonal methods of contraception in general (Herzog, 2015). However, nearly one in three WWE do not appear to use a highly effective form of contraception (Herzog et al., 2016). The frequency of surgical contraception (e.g., tubal ligation, vasectomy) was two to three times less in WWE than the general population (Herzog et al., 2016). Therefore, being proactive to avoid the pitfalls of an unwanted pregnancy requires ensuring an open dialogue with WWE to optimize contraception and the timing of conception.

Box 12.5 General rules to discuss with a WWE planning pregnancy

Advocate for general health measures (e.g., stop smoking, avoid alcohol, healthy diet, etc.)
Optimize seizure control
Use "safe" AEDs in monotherapy at the lowest effective dose
Stress the importance of compliance
Obtain baseline laboratory and serial AED levels
Discuss the importance of folate supplementation
Notify the neurologist immediately of pregnancy

Regardless of the technique used for contraception, pre-pregnancy counseling should be given to all WWE contemplating pregnancy in addition to those of childbearing potential (Winterbottom et al., 2009; Veiby et al., 2013). Overall, WWE have a lower birth rate when compared with the general population. A number of concerns exist for WWE including hereditary aspects of epilepsy, fertility, teratogenicity of AEDs, folate supplementation, labor and delivery, breastfeeding and AEDs, and vitamin K supplementation (Holmes et al., 2004; Ip et al., 2009; Harden et al., 2009a, b; Hernandez-Diaz et al., 2012; Valera-Gran et al., 2014; Meador et al., 2014). The American Academy of Neurology has developed quality measures to reflect the importance of counseling WWE during the reproductive years with recommendations to review pregnancy plans at least on an annual basis (AAN, 1998). A standard approach is shown in Box 12.5.

Case (cont'd)

She calls you to inform you that she is pregnant. She reports an increase of her seizures.

Discussion (cont'd)

Pregnancy is a dynamic state associated with dramatic physiological changes such as vascular proliferation and volume expansion to support adequate fetal growth and development. If AED withdrawal is planned, it should begin 6–12 months before conception. Seizure control during the preceding 9–12 months prior to conception is the best predictor of seizure control during pregnancy. Becoming pregnant can serve as a physiological "stress test" for WWE, altering seizure control (Winterbottom et al., 2009). Overall, seizures in one-fourth of WWE improve, seizures in one-fourth will worsen, and seizures in one-half will remain unchanged relative to baseline seizure frequency (Harden et al., 2009a). The effect of seizures on the fetus is probably cumulative. When seizures impair consciousness of the mother, fetal heart rate may become compromised while the risk of generalized motor seizures is fetal anoxia. Premature contractions, pre-term labor, and small-for-gestational-age babies are associated with pregnancy in WWE (Harden et al., 2009a). Compliance with AEDs may be compromised during pregnancy in a self-directed effort to minimize the consequences of adverse drug reactions on the developing fetus. Death rates are increased in pregnant WWE largely due to sudden unexpected death in epilepsy. Therefore stressing the importance of compliance and obtaining serial AED levels may help improve adherence to optimal management (Harden et al., 2009b).

If seizure exacerbation occurs during pregnancy, re-evaluation with MRI and EEG should be considered. There is general acceptance that an imaging modality during pregnancy that has little or no ionizing radiation such as MRI or ultrasonography should be safe, especially (for MRI) during the second and third trimesters, though it appears also to pose little risk even during the first trimester (Ray et al., 2016). The use of gadolinium should be avoided at any time during pregnancy due to an increased risk of adverse risks including stillbirth and neonatal death.

Assuming that seizure control is optimized during pregnancy, the clinician should:

1. Maintain current AEDs
2. Not switch AEDs
3. Monitor AED levels monthly
4. Ensure OB follow-up for a high-risk pregnancy.

Most WWE remain on AEDs during pregnancy. Proper management of AEDs in WWE requires expertise with their use. Pregnancy databases suggest that VPA is significantly teratogenic compared with other AEDs and should be avoided unless the benefit to treat epilepsy outweighs the risk of birth defects (Hernandez-Diaz et al., 2012). Balancing ongoing seizures and side-effects from AEDs for a specific patient requires frequent evaluation. While no AED is absolutely "safe," some appear to be safer than others in terms of structural fetal malformations and cognitive teratogenic adverse consequences (Harden et al., 2009a).

Major malformations involve significant functional, surgical, or cosmetic consequences and affect between 1% and 3% of pregnancies in the general population (Morrell, 1999; Harden et al., 2009a). Which AED should be used in a woman of childbearing potential should be addressed during pre-pregnancy counseling (Holmes et al., 2004; Winterbottom et al., 2009). Exposure to AEDs during the first trimester is the most crucial time with regard to AED-induced structural congenital malformations (Holmes et al., 2004). The frequency of congenital malformations appears to be different for specific AEDs (Holmes et al., 2004). VPA has been associated in worldwide registries with the highest rate of major congenital malformations, ranging from 4.7% to 13.8%, while phenytoin, phenobarbital, and topiramate carry an intermediate risk (Gerard and Meador, 2016). A distinctive pattern of congenital malformations may occur with specific AEDs. For example, VPA has been associated with neural tube defects, lamotrigine with oral clefting, CBZ and barbiturates with cardiac defects, and hypospadias with topiramate and phenytoin. The risk is independent of the mother's seizure type or the cause for her epilepsy, and is increased by polytherapy (our patient is on CBZ and LTG) and by higher AED serum levels. Cognitive and behavioral development appears most compromised in the offspring of WWE from VPA, with a reduction of 10 IQ points (Gerard and Meader, 2016). For several AEDs including phenobarbital, phenytoin, and VPA, drug-induced apoptosis may be one mechanism impacting cognition in contrast to CBZ, lamotrigine, and levetiracetam which do not cause apoptosis (Holmes et al., 2004, Tomson et al., 2011).

Total serum concentrations of AEDs decrease due to reduced absorption, increased blood volume (>45% by third trimester), and increased drug elimination (maximal in the 2nd–3rd trimester). The magnitude varies across AEDs. For example, serum levels of LTG decrease more so during pregnancy than CBZ (and possibly levetiracetam), which

if not corrected could lead to increased seizure frequency. Free AED drug concentrations increase due to reduced protein binding and reduction in albumin concentration. Therefore, measuring free drug concentrations should be considered for highly protein-bound AEDs (i.e., phenytoin).

Additional pregnancy-related issues include vaginal bleeding, premature birth and miscarriages, and obstetrical complications of delivery, as well an association between non-obstetric operations and postoperative complications (Huang et al., 2016).

Fortunately, the large majority of WWE have normal healthy babies without an increased risk of obstetrical complications. However, it is important to learn whether a WWE would terminate the pregnancy, e.g., if a significant birth defect is found on ultrasound (Winterbottom et al., 2009). Overall, first-trimester terminations were 14 times less likely to result in maternal death compared with childbirth (Harden et al., 2009a). Where appropriate, the emergency contraceptive pill may be used though a higher dose may be required in the setting of EIAEDs (Herzog et al., 2016).

Pitfall

Assuming that WWE are unlikely to have a successful outcome from pregnancy with AED exposure.

Result

1. Healthy term infant
2. Focal epilepsy

Post-Partum Care

Case 12.3 Post-partum Management

A 34-year-old woman is 3-weeks post-partum. She was seen several years ago by your partner but was unable to return due to insurance changes. She has a history of "grand mal" and "petit mal" seizures that started when she was 17 years old. She was prescribed LTG 150 mg twice daily (last serum level 9.4 µg/dl) and took 2 mg of folate daily during her pregnancy. She has been seizure-free for more than 2 years and has just had her first child. During her pregnancy, she required an increase of her LTG due to a "low level" and is now taking 200 mg twice daily. She has several questions.

Question: "How should I balance childcare at night with ensuring I get proper sleep to prevent seizure aggravation?"

Discussion

Following delivery, parenting becomes the focus, and counseling WWE on caring for children requires special emphasis. Safety training in the home is useful to ensure that the particular challenges faced by the mother (e.g., sleep deprivation, breakthrough seizures, holding and bathing the infant) are met. In general, the risk is probably small if time is taken to train mothers and caregivers in safety precautions.

Pitfall: Not recognizing the impact of sleep habits post-partum and potential adverse effects on WWE.

Question: Mom asks "Should I breast-feed?"

Discussion

WWE should be encouraged to breastfeed their babies (Harden et al., 2009b). Breastfeeding confers benefits to the infant. These include reduced infection rates, rates of leukopenia, and sudden infant death syndrome. In addition, the bonding experience between mother and baby reduces the risk of diabetes. For mothers, further benefits include decreased risk of breast and ovarian cancers. In general, higher protein binding of an AED will yield a lower concentration of the drug in breast milk. For WWE, higher IQs and enhanced language development in offspring have been noted in the North American Antiepileptic Drug trial in early childhood sustained at 6 years of age for mothers who breastfed while taking AEDs compared to those who did not (Holmes et al., 2004). Therefore, AEDs including CBZ, phenytoin, VPA, and LTG do not appear to have adverse effects for infants born to WWE who breastfeed (Meador et al., 2014).

The total amount of AED delivered to the infant through breastfeeding is smaller than the mother-baby transplacental concentration due to filtration by the breast (Ip et al., 2009). It is important in the post-partum period to be vigilant during breastfeeding to ensure the child is tolerating feeds as drug elimination mechanisms by infants are undeveloped, which could lead to drug accumulation and toxicity (Veiby et al., 2013).

Pitfall: Believing that continued exposure to AEDs is bad for the infant and that it should be avoided.

Question: Mom has read about bleeding with AEDs and asks about the use of vitamins.

Discussion

Continuing multiple vitamins with folic acid after delivery is advisable. In addition, the pediatrician should be consulted about administering vitamin K to the newborn. Deficiency of vitamin K has been associated with Hemorrhagic Disease of the Newborn (HDN). EIAEDs may compromise the efficacy of vitamin K1 (Harden et al., 2009b). Supplementation of vitamin K in pregnant WWE taking AEDs may prevent vitamin K deficiency and prevent its consequences. Based upon reports of bleeding diathesis in WWE treated with EIAEDs, vitamin K1 10 mg/day was encouraged during the third trimester of pregnancy to prevent intracranial bleeding in the fetus. However, large clinical studies involving vitamin K supplementation have not been able to demonstrate a difference when treatment is used. While the standards in the United States include treatment with vitamin K when EIAEDs are used, there is no evidence for or against its use.

Pitfall: Assuming that "your work is done" after the patient's delivery.

Case (cont'd)

She complains of worsening headache, nausea, dizziness, imbalance, and insomnia since delivery and is afraid she will start to experience recurrent seizures.

Discussion

For the mother, a decline of LTG levels in the latter half of pregnancy may require incremental increases in dose. Following delivery, levels may then substantially increase, causing clinical toxicity. The approach is to reduce the LTG dose back to the last pre-pregnancy effective dose, which should lead to resolution of toxicity. Relative to the infant, the concentrations of AED are proportional to the degree of protein binding.

Pitfall

Failing to assess the need for changes in AED dosage after delivery.

Case 12.4 Menopause and Epilepsy

A 50-year-old female had a prior resection of a ganglioglioma when she was 23 years old. Focal seizures postoperatively have been infrequent, recurring on average once every 2 years, and consisting of a blank stare, impaired awareness, and motion arrest for 20 seconds. No notable postictal state is evident and they do not bother her lifestyle. She does not drive. Her seizures did not improve with several other AEDs and she is currently taking levetiracetam 1,000 mg twice daily in addition to pregabalin for chronic low back pain associated with lumbar spinal stenosis. Her MRI demonstrates a left temporal craniotomy defect which is well-healed. Her EEG demonstrates left mid-temporal sharp waves. She is referred by her gynecologist due to an increase in seizures over the last few months. She reports that she is now entering menopause.

Discussion

Similar to other aspects of the life-span, special considerations are required when managing WWE during menopause. Menopause exists when menstrual periods cease for more than 1 year. Seizure frequency is associated with cessation of reproductive cycling with age. When seizures in WWE are drug-resistant, menopause may occur at an earlier age (Abassi et al., 1999). Seizures may increase during perimenopause, especially in those with a catamenial pattern (Herzog, 2015). This may occur due to transient hyperestrogenism and subsequently subside after menopause. In one study, 41% of WWE report seizure worsening, 33% remained unchanged, and seizures in 27% improved (Abassi et al., 1999). Twenty percent of WWE began having seizures during or after menopause, whereas combined perimenopausal and postmenopausal WWE experienced seizures similar in frequency and severity to other women without epilepsy.

Menopause may also alter the effects of hormone replacement therapy (HRT). In addition, HRT may influence the frequency of seizures. WWE may need to take HRT for symptomatic relief to facilitate adequate sleep when "hot flashes" are disruptive. However, hormonal replacement therapy is more complicated in WWE. Conjugated equine estrogens plus 2.5 mg of medroxyprogesterone acetate may increase the frequency of seizures in some women, especially when catamenial seizures occur (Harden et al., 2003). A combination of single estrogenic compounds such as 17-β-estradiol along with natural progesterone has been considered beneficial and synthetic HRT may be more detrimental (Erel and Guralp, 2011).

Case (cont'd)

She reports taking HRT primarily because she has osteoporosis, which her gynecologist tells her is due to her chronic use of AEDs.

Discussion (cont'd)

Patients with epilepsy have an increased risk of bone disease compared to the general population (Carlson and Anderson, 2016). Osteopenia (T-score of −1 to −2.5 on dual energy x-ray absorptiometry) and osteoporosis (T-score < −2.5) are concerns for WWE not only during menopause but at any time during the life cycle. Treatment with AEDs, especially enzyme-inducers, makes WWE vulnerable to compromised bone health. More than 50% of adults on AEDs have decreased bone mineral density as measured by DEXA scanning.

EIAEDs disrupt normal vitamin D metabolism and thereby adversely affect bone mineral density (Sheth et al., 2008). In addition, they along with VPA have been linked to elevated serum calcium concentrations and reduced levels of vitamin D metabolites, implicating other mechanisms to compromise bone health. The duration of AED therapy correlates with adverse effects on bone health, with treatment over years increasing the risk of bone fractures (Mikati et al., 2006). Elderly WWE are sensitive to fluctuations in AED levels and adverse events may occur at lower blood levels such as dizziness, lethargy, unsteady gait, and visual disturbances that may result in fall-related fractures with associated morbidity and mortality.

Elderly WWE and those with osteoporosis may have their bone health further compromised by reduced physical activity, dietary differences (i.e., "tea and toasters"), and sheltered or assisted environments with limited mobility and sunlight exposure. While behavioral recommendations of adequate nutrition, regular exercise, sunlight exposure, and limiting caffeine, alcohol, and smoking are clear, less clarity is available at this time to recommend high-dose vitamin D or combined calcium and vitamin D supplements. A survey found that less than one-third of neurologists routinely evaluated patients with epilepsy taking AEDs for bone disease, while less than 10% prescribed supplementation with calcium-vitamin D (Pack and Morrell, 2004). Therefore, considering assessment of the bone mineral density after 5 years of AED treatment (and before AED treatment in postmenopausal WWE) is prudent.

Pitfall

Failing to routinely evaluate patients taking AED for bone disease.

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Chapter

13

Management of Psychiatric Issues in Epilepsy

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Psychiatric comorbidity is quite common among patients with epilepsy, but is under-recognized and under-treated. The clinical presentation may be atypical and symptoms may fluctuate, sometimes in a temporal relationship with seizures. The four most significant psychiatric disorders in patients with epilepsy are depression, anxiety, psychosis, and aggression. Of these, depression and anxiety are the most commonly encountered by primary care physicians (PCPs) and general neurologists and are discussed in this chapter.

The biggest two pitfalls in the management of psychiatric issues in patients with epilepsy are failure to diagnose and failure to treat effectively. The latter pitfall – inadequate treatment even when the psychiatric disorder is recognized – is particularly problematic because depression and anxiety negatively affect quality of life and increase the risk for suicide. Therefore, physicians must actively screen for these disorders and initiate therapy or refer patients for proper treatment.

Failure to Diagnose

Case 13.1 Epilepsy-associated Depression

A 32-year-old woman with a 16-year history of drug-resistant focal seizures due to mesial temporal sclerosis presented to her PCP complaining of the recent onset of intermittent neck and shoulder pain without antecedent injury or strain. Her only medication was phenobarbital (PB), 90 mg/day, which she had been taking since diagnosed with epilepsy. Physical examination and X-rays were unrevealing and NSAIDS were prescribed. She returned a few weeks later with continued and more diffuse nonspecific musculoskeletal complaints and also reported an approximate 1-year history of loss of energy, increased daytime sleepiness, and loss of sexual drive. Physical examination and routine laboratory studies were normal. The PCP suspected that the additional symptoms were attributable to the PB and switched her to levetiracetam (LEV) monotherapy over several months.

At follow-up, her seizure frequency had improved but all of her other symptoms continued and were somewhat more pronounced.

Discussion: Clinically significant depression is the most frequently occurring comorbid psychiatric disorder in patients with epilepsy, affecting up to 20% among patients with controlled seizures and up to 60% of those with drug-resistant epilepsy, such as the patient in this case. These rates are significantly higher than in the general population.

Depression greatly affects the patient's quality of life, even more so than seizures in many patients. The presence of depression is associated with more disability, greater

psychosocial difficulties (see Chapter 15), and more side effects from seizure medication. Risk factors for depression that have been identified in patients with epilepsy include frequent seizures (>1 per month) and a known cause for focal seizures, such as mesial temporal sclerosis as in this case. Paradoxically, major depression may also develop when a patient's seizure control significantly improves, a phenomenon called "forced normalization." Hence, physicians must maintain a high degree of suspicion for the possibility of depression irrespective of the extent to which a patient's seizures are controlled.

Why are depression and anxiety underdiagnosed? There are a number of reasons. The symptoms may be nonspecific, the patient may minimize his or her symptoms, the physician may not specifically inquire about psychiatric symptoms or the physician may view depression and anxiety as understandable, "normal" adaptations to the diagnosis and consequences of epilepsy, and hence not targets of specific treatments, as did the first physician in this case. Yet depression and anxiety are serious medical conditions and should not be rationalized as appropriate or understandable reactions to the patient's current situation. There is no question that patients with epilepsy, especially those with drug-resistant seizures, do face enormous challenges in their lives, as discussed in Chapter 15. But depression and anxiety disorders are associated with significant morbidity and mortality that should be treated when indicated to lessen suffering and the possibility of suicide.

Even if the physician is attuned to the typical signs and symptoms of mood disorders, depression and anxiety in the majority of patients with epilepsy may present differently than in nonepileptic patients, which is especially common in children. For example, depression is often categorized as major depressive disorder (MDD), dysthymic disorder, minor depression or depressive disorder not otherwise specified (NOS). The differences between these categories relate to how long the symptoms have lasted, how often they reoccur, and how severe they are. The diagnosis of MDD requires recurring episodes lasting for more than two weeks of four or more symptoms of depression such as low mood, feelings of worthlessness, guilt, loss of energy and interest, insomnia or hypersomnia, changes in appetite, loss of libido, psychomotor retardation or agitation, decreased concentration, thoughts of death, and suicidal ideation.

However, depressed patients with epilepsy may have a chronic waxing and waning pattern to their symptoms, often with varying levels of irritability, frustration, emotionality (euphoria, fear, and anxiousness), low energy, bodily pains, and trouble sleeping. In addition, depressive symptoms may vary in intensity in relation to seizures, such as leading up to the seizure (preictal depression), during the seizure itself (ictal depression), following seizures (postictal depression), or, most commonly, at times unrelated to seizure occurrence (interictal depression).

- Preictal depression consists of a steadily worsening dysphoric mood leading up to a seizure that remits after the seizure is over.
- Ictal depression is uncommon, and consists of brief (<30 seconds), stereotyped episodes of crying and depressive symptoms in association with other seizure manifestations.
- Postictal depression is more common than preictal and ictal depression and causes greater disability, but usually resolves within hours or days after the seizure without treatment. Nonetheless, these depressive symptoms may include suicidal ideation and urgent evaluation.
- Interictal depression is most common and occurs without any apparent temporal relationship to seizures.

Symptoms such as significant weight loss or gain, insomnia or hypersomnia, fatigue or loss of energy, sexual dysfunction, diminished ability to think or concentrate; indecisiveness, irritability, decline in school performance, and social withdrawal, even if elicited by physicians, may be misattributed to other causes, such as the side effects of seizure treatments, as occurred in this case. Pain in particular may be a tipoff for underlying depression, and patients with epilepsy often complain of nonspecific musculoskeletal pains, as did this patient.

Anxiety disorders are usually categorized into generalized anxiety disorder (GAD), panic disorder, obsessive-compulsive disorder, phobias and posttraumatic stress disorder. All can occur in patients with epilepsy, and the most common is GAD, affecting up to 50% of patients in some studies. The usual symptoms are excessive anxiety and worry, restlessness, fatigue, poor concentration, irritability, muscle tension, and trouble sleeping.

Like depression, anxiety negatively impacts quality of life and psychosocial functioning in patients with epilepsy, perhaps even more so than depression and seizures. Further, as with depression, symptoms of anxiety disorders may wax and wane in intensity and may be associated with the preictal, ictal, postictal, or interictal periods in patients with drug-resistant seizures. Preictal anxiety may precede a seizure by hours to days. Patients most often describe ictal anxiety as fear, and if this is the only seizure symptom, it may be mistaken for a panic attack, which typically consists of episodic lightheadedness, tremor, fear of loss of control or death, tingling, shortness of breath, chest pain, palpitations, perspiration, chills, abdominal upset, the sensation of choking, derealization and persistent worry about future attacks. Panic attacks can often be differentiated from ictal anxiety by the gradual onset of symptoms, duration from many minutes to hours, and lack of post-episode confusion.

Postictal anxiety may last up to a day, and is particularly likely to occur in patients with a psychiatric history. Interictal anxiety is the most common form of anxiety in patients with epilepsy and like depression may develop paradoxically as seizures improve or remit with treatment.

The PCP in this case suspected PB was the cause of the patient's mood complaints. In hindsight, this was unlikely since she had been on the same dose for a number of years preceding the onset of depression (though at least her seizure frequency improved with the change to LEV).

Nevertheless, iatrogenic causes of symptoms of depressive and anxiety disorders should be considered and corrected if present. These include:

- recent discontinuation of an antiepileptic drug (AED) with mood-stabilizing properties, such as carbamazepine (CBZ), lamotrigine (LTG), and valproate (VPA);
- withdrawal of anxiolytic medications, such as benzodiazepines, phenobarbital, gabapentin, or pregabalin may also precipitate GAD, particularly in patients with ictal anxiety;
- recent introduction or rapid dosage increase of an AED with potential negative psychotropic properties (e.g., primidone, PB, topiramate (TPM), vigabatrin, tiagabine, felbamate, gabapentin, LEV, zonisamide (ZNS), or perampanel (PMP); and
- addition of an enzyme-inducing AED in a patient already taking an antidepressant that is hepatically metabolized, leading to breakthrough depressive symptoms.

Of particular concern is suicidality associated with the initiation of AEDs. In 2008, the FDA issued an alert regarding suicidality and use of AEDs based upon a meta-analysis of 199 placebo-controlled trials including 11 AEDs. The FDA concluded that the risk of suicidal thoughts or behavior in those taking AEDs was twice that of patients taking placebo (0.43% vs. 0.22%, respectively). The risk of suicidal thoughts or behavior began as early as one week after starting the AED and continued up to 24 weeks, which is when most clinical trials in the meta-analysis ended. The FDA's alert resulted in labeling changes, and physicians should discuss this issue with their patients and closely monitor those receiving AEDs for onset or worsening of depression.

Case (continued)

On further questioning by the PCP, the patient admitted to worrying about her epilepsy and to having problems at work. She was very concerned and increasingly anxious about her job security and personal finances. The PCP concluded that she was understandably upset about her chronic epilepsy and her current situation at work. He reassured her and suggested that she talk to a job counselor. What she didn't tell her doctor was that she was taking St. John's Wort and kava.

A few weeks later, her husband became alarmed when she told him that she and he would both be better off if she were dead. He took her to a local emergency room. She was seen by a psychiatrist who diagnosed major depression and GAD, told her to discontinue the St. John's wort, and started her on a selective serotonin reuptake inhibitor (SSRI).

Discussion: When assessing patients with epilepsy for possible depression, the simplest approach is to ask the patient if he or she is able to experience pleasure. Anhedonia is a reliable marker of depression and not usually due to side effects of medication or other medical problems. In addition, there are easily administered and well-validated self-rating screening instruments that can identify patients whose symptoms of possible mood disorders should warrant further psychiatric evaluation. Perhaps the quickest screening tool for evaluating depression in patients with epilepsy is the Neurological Disorders Depression Inventory for Epilepsy (NDDI-E), which is specifically validated in patients with epilepsy. The scale contains 6 items (everything is a struggle; nothing I do is right; feel guilty; I'd be better off dead; frustrated; and difficulty finding pleasure) that are scored from 1 (never) to 4 (always or often). It takes less than 3 minutes to complete and a score of >15 should be taken as an indication the patient needs urgent evaluation for a major depressive episode. An advantage of this instrument is that the results are not affected by side effects of medication or cognitive problems associated with epilepsy.

For anxiety, available instruments such as the Beck Anxiety Inventory, the State-Trait Anxiety Scale, the Generalized Anxiety Disorder-7 (GAD-7), and the Hamilton Anxiety Rating Scale have not yet been validated in patients with epilepsy. The GAD-7 takes 2–3 minutes to complete, and a score >10 suggests the presence of a GAD.

It is important to note that while screening instruments can identify symptoms of depression and anxiety and therefore suggest the possibility of a current depressive or anxiety disorder, they are not adequate for making a diagnosis, which is best done by referral for a formal psychiatric evaluation. Once the diagnosis of a mood disorder has been established by psychiatric evaluation, the self-rating screening instruments can be given at future visits to measure changes in symptom severity or document symptom remission.

Anxiety often occurs together with depression in the same patient, as happened in this case, and their co-occurrence increases the risk of suicidality, which is already increased in general for patients with epilepsy compared to the general population. For example, the lifetime prevalence of suicidal ideation in patients with epilepsy is double that of the general population at 12%. Suicide attempts occur in up to 30% of patients with epilepsy, more than fourfold higher than controls. For completed suicides, the corresponding figures are 2.32–14% and 0.74–1.4%, respectively. Up to 20% of children with epilepsy have suicidal ideation at some point in their course (Caplan et al., 2005). Patients with seizures originating from their temporal lobes, as the patient in this case, have a 25-fold increased rate of suicide compared to the general population.

The major risk factors for suicide in patients with epilepsy include comorbid anxiety or depression, or a prior history of depression, psychosis, anxiety, personality disorders and bipolar disorder; and ictal and postictal depression, mania, postictal psychosis and command hallucinations. Other risk factors include psychosocial stressors, poor physical health, young age in men (25–49 years), early age of seizure onset (<18 years, particularly during adolescence), presence of brain lesions, inadequate follow-up or treatment of seizures, access to firearms or other methods of self-harm, and cognitive impairment.

Besides directly questioning patients, suicidality can also be assessed by the suicidality modules of the Mini International Neuropsychiatric Interview (MINI), the Beck Depression Inventory-II (BDI-II), and the Children's Depression Inventory (CDI). Importantly:

- patients must be urgently referred for psychiatric evaluation and kept safe, including the removal of firearms from the home, or potential hospitalization until the suicidal ideation resolves and
- physicians need to document the level of risk, interventions, and plans for monitoring, and must consider the patient's access to AEDs and the potential for overdose.

Finally, clinicians should take a history of dietary supplement use, especially in patients with chronic disorders such as epilepsy. This patient had tried St. John's wort and kava, although she did not bring this up to her PCP. Both St. John's wort and kava are often taken by patients with epilepsy, and serve as a clue to the possibility of underlying depression and anxiety, respectively, but more importantly may cause pharmacokinetic interactions with AEDs and psychotropic medications. Other herbal remedies anecdotally reported to improve anxiety or depression include Passionflower extracts, rosenroot, omega-3 fatty acids, *S*-adenosylmethionine (SAMe), and combinations of L-lysine and L-arginine and magnesium-containing dietary supplements.

Patients with epilepsy who try one or more of these natural products should inform their doctor, and doctors should routinely take a history of over-the-counter supplements, since they could affect the blood levels of other medications, including AEDs. This is particularly the case for SAMe and St. John's wort. In addition, supplements may cause side effects that the doctor might otherwise attribute to an AED. St. John's wort, for example, may cause overstimulation, kava can bring on headache and gastrointestinal complaints as well as adversely affect liver function, and SAMe may decrease appetite and produce dry mouth, nervousness and trouble falling asleep (Larzelere et al., 2010).

Diagnosis: MDD and GAD.

Tip: Physicians must have a high index of suspicion for depression and anxiety in patients with epilepsy, especially in those with known risk factors, and take appropriate action to establish the diagnosis and formulate a treatment plan. Failure to diagnose depression and anxiety disorders can result in prolongation and worsening of symptoms and associated disability as well as the possibility of suicide.

Failure to Treat Depression and Anxiety

Case 13.2

A 20-year-old male with a 2-year history of focal seizures treated with LTG went to the infirmary soon after beginning college complaining of difficulty falling and staying asleep. Seizures were completely controlled. In consultation with the patient's PCP, the infirmary physician initiated a switch from LTG to oxcarbazepine (OXC), believing that the LTG was causing insomnia.

The student returned a couple of months later, while preparing for his final examinations. Seizures remained completely controlled, but he was still having trouble falling and staying asleep. He was under considerable stress, felt depressed and anxious, and could not concentrate on his studies. He told the infirmary physician that he had been treated with paroxetine for several prolonged episodes of depression and anxiety in his mid-teenage years, prior to his epilepsy diagnosis, and wondered if he should restart it. The doctor advised against antidepressant treatment because he thought it might trigger seizures or interfere with the patient's OXC.

The patient's depression worsened and he was referred to a psychiatrist who started the patient on paroxetine since it had been effective for him in the past. The OXC dosage was maintained.

Discussion: The primary goal of treating depression, whether the patient has epilepsy or not, is complete freedom from depressive symptoms, which lessens the chance of a future recurrence; conversely, patients with residual symptoms on treatment are more likely to relapse off of treatment. A full response should be evident in 6–12 weeks, and treatment should continue for up to 4–9 months. Patients with three or more episodes of depression, residual symptoms, suicidality, psychosis or an otherwise severe episode should receive long-term prophylaxis. Children tend to have high relapse rates, with continuation of symptoms into adulthood.

Even when the diagnosis is clear to the treating physician, depression and anxiety are often undertreated in patients with epilepsy, as occurred in this case. For example, one study found that depression of one-year duration or longer in two in three patients with epilepsy went untreated for at least 6 months after being diagnosed with depression.

Why are depression and anxiety undertreated even once the disorder is diagnosed? The physician may not appreciate possible iatrogenic causes, which are potentially correctable, or may be concerned that antidepressants could compromise seizure control by lowering the so-called seizure threshold. Another common reason is that physicians consider the mood disorder to be an appropriate reaction to the patient's current situation and therefore not a medical disorder that requires specific treatment. Finally, antidepressants may be avoided or underutilized because of concern that AED effectiveness could be compromised.

Before initiating psychotropic therapy, iatrogenic causes should be excluded, as described earlier. In particular, the physician should be sure that anxiety or depression is not due to one or more AEDs that the patient recently started taking or recently discontinued. The key to evaluating a possible iatrogenic cause is to identify temporal relations between introduction (or increased dose, decreased dose, or cessation) of an AED and the onset of behavioral symptoms, though a temporal relationship does not necessarily establish causation. Nonetheless, if an iatrogenic cause is plausible, this should be addressed as the first step in treatment.

A common misconception is that all antidepressants significantly lower seizure threshold and should be avoided. These fears are largely based upon seizures associated with overdoses, which have little predictive value when serum antidepressant levels are within therapeutic range. The concern that antidepressant drugs cause or exacerbate seizures, including in patients with epilepsy, is a widely cited reason for not treating depression or anxiety or for using inadequately low doses. With a few exceptions, however, the evidence suggests that the opposite is true – antidepressants at usual dosages may have anticonvulsant effects. Data from clinical trials of several SSRIs and the serotonin-norepinephrine reuptake inhibitor (SNRI) venlafaxine show a 19-fold lower incidence of seizures among patients randomized to the antidepressants compared to patients given placebo. Nonetheless, a few antidepressant drugs at toxic doses can cause seizures and four antidepressants are associated with a significant dose-dependent risk of seizures in patients without epilepsy even within approved dosage ranges and should therefore be avoided in patients with epilepsy: maprotyline (incidence: 15.6%), clomipramine (1–12.2%), bupropion (especially the immediate-release preparation; 0.5–4.8%), and amoxapine (36.4%).

Other antidepressants appear to be safe to use, especially the SSRIs. In one study, 100 consecutive patients with drug-resistant epilepsy and depression received sertraline, and worsening of seizures occurred in only one patient.

As mentioned earlier, depression and anxiety are serious medical conditions and should not be rationalized as appropriate or understandable reactions to the patient's current situation. The physician in this case understood this, but was hesitant to prescribe paroxetine because it may have interfered with the patient's OXC. This is a concern, but not a contraindication. Physicians should become familiar with potential pharmacokinetic and pharmacodynamic interactions between antidepressants and AEDs to effectively use both classes of drugs and thereby avoid not prescribing or underutilizing antidepressants when they are clinically indicated. SSRIS such as sertraline, paroxetine, citalopram, and escitalopram as well as the tricyclic antidepressants (TCAs) are metabolized by hepatic cytochrome p450 (CYP) isoenzymes. Therefore, comedication with an AED such as phenytoin, CBZ, phenobarbital and primidone, all of which induce CYP isoenzymes, would be expected to lower serum concentrations of the antidepressant, requiring an increase in antidepressant dosage to achieve and maintain a therapeutic response. OXC and TPM are much less potent inducers of CYP 3A4, and VPA inhibits both CYP 2C9 and UDP-glucuronyltransferase enzymes, which can result in increased serum concentration of TCAs, though there have been no reports of interactions with SSRIs or SNRIs.

Conversely, the SSRIs paroxetine, fluvoxamine and fluoxetine inhibit CYP isoenzymes, which can result in increased serum concentrations of co-administered AEDs such as phenytoin and CBZ that are metabolized by the same CYP isoenzymes, as well as increased serum concentrations of TCAs. The SSRIs and SNRIs citalopram, escitalopram,

venlafaxine, and duloxetine appear to be unlikely to cause significant interactions with older AEDs.

Prior to initiation of therapy, patients should be screened for evidence of bipolar disorder or a family history of bipolar disorder to avoid precipitating a manic or hypomanic episode with antidepressant therapy. It is important to identify whether a patient also has an anxiety disorder, since failure to take this into account when therapy is selected can have a significant impact on treatment response.

Since there have been few controlled trials of antidepressants (or AEDs with psychotropic properties, for that matter) in patients with epilepsy and depression, the evidence base to guide treatment, especially for the large proportion of patients with atypical forms of depression, is limited. In the only controlled trial to date, sertraline was compared to cognitive behavior therapy (CBT) in a single-blind controlled study of 140 patients with epilepsy with a major depressive episode. Symptoms remitted in 60% of patients in both treatment groups. In the absence of controlled trials, the choice of antidepressant should be based upon safety, tolerability, and ease of use (for example, frequency of dosage and likelihood of interactions with the patient's AED(s)). If a particular antidepressant was successful in the past for the patient or family member, another trial of this agent should be considered, as was done in this case.

SSRIs are generally preferred by expert consensus because they are effective in non-epileptic patients, interactions with AEDs are limited (especially citalopram and sertraline), they are generally beneficial for dysthymic disorders (including symptoms of irritability and poor frustration tolerance), and available evidence does not suggest a significant potential for seizure exacerbation. An SNRI should be tried if the initial trial of an SSRI is ineffective. TCAs should be used when SSRIs and SNRIs are found to be ineffective. Monoamine oxidase inhibitors (MAOIs), non-TCAs, clomipramine, and lithium should probably be avoided because of the potential for seizure worsening and toxicity, as well as other ease-of-use factors. Electroconvulsive therapy (ECT) under the supervision of a qualified psychiatrist should be reserved for patients with drug-resistant major depression.

Adding an antidepressant to an AED may potentially worsen one or more side effects associated with either the antidepressant or the AED without necessarily affecting the serum concentration of either one. The magnitude of these pharmacodynamic interactions can vary from patient to patient and therefore require close monitoring and cautious dosage adjustment to achieve a balance of therapeutic effect with good tolerability. Some of the side effects that may be aggravated by combinations of AEDs and antidepressants include weight gain, sexual dysfunction, and bone demineralization.

Sexual dysfunction, such as decreased libido, anorgasmia and sexual impotence, can be relatively common side effects of AEDS such as phenobarbital and primidone, but can also be seen with other enzyme-inducing AEDs, related to increased synthesis of the sex hormone binding globulin, which binds the free fraction of sex hormones, hence limiting their access to the brain. SSRIs and SNRIs are also known to cause sexual adverse events, and additive or synergistic effects with AEDs are possible though not yet established. The seizure disorder can also have a direct effect on sexual functions.

Among the SSRIs, sertraline has been best studied in epilepsy. Compared to sertraline, citalopram and escitalopram may interact less with AEDs. Treatment with an SSRI should begin at a low dose, with gradual increases at 1- to 2-week intervals. Of the SNRIs, venlafaxine is often used in adults with depression and prominent melancholic features.

Dosages as high as 225 mg/day appear to be safe in patients with epilepsy. Lethargy, irritability, and hypertension are the main side effects. Blood pressure elevations are typically seen at doses above 300 mg/day.

In the elderly, SSRIs and venlafaxine may be used, but dosages should begin at one-half the usual starting dose, and treatment should be continued for at least 2 years in those with frequent or severe depressive episodes.

The TCAs (amitriptyline, amoxapine, clomipramine, desipramine, doxepin, imipramine, nortriptyline, protriptyline, trimipramine) have a greater likelihood of side effects and drug–drug interactions than SSRIs or SNRIs. Weight gain and sexual dysfunction are common. A potential for cardiac conduction abnormalities and greater tendency to induce mania are also of concern. The possibility of seizure exacerbation with amoxapine and clomipramine was discussed earlier. Imipramine, amitriptyline, and trimipramine may also cause epileptiform changes on the EEG at high doses, although this is not generally accompanied by clinical seizures. Because drug–drug interactions may be quite complex, at times with increased formation of toxic metabolites but decreased activity of parent compounds, the usual recommendation to start at a low dose and increase the dosage slowly applies.

While MAOIs (rasagiline, selegiline, isocarboxazid, phenelzine, tranylcypromine) are generally safe in patients with epilepsy, they are best avoided because of their side effect profile and propensity for inducing hypertensive crises due to interactions with tyramine-containing foods. Further, combining an MAOI with an SSRI or TCA may produce the potentially fatal serotonin syndrome, characterized by restlessness, myoclonus, diaphoresis, tremor, hyperthermia, and seizures.

The Epilepsy Foundation's Mood Disorders Initiative recommended the following staged treatment for depression in adults with epilepsy:

Stage 1: Monotherapy with an SSRI (citalopram, escitalopram), venlafaxine or mirtazepine, and/or CBT is first-line treatment. If there is an incomplete response, proceed to Stage 2.

Stage 2: Monotherapy with a different agent is recommended (another SSRI, a TCA, venlafaxine or mirtazapine). If there is an incomplete response, proceed to Stage 3.

Stage 3: Monotherapy with an SSRI, a TCA, venlafaxine, mirtazapine or an MAOI is recommended. A medication from a different class than that used in Stage 1 or 2 should be administered. Alternatively, combination therapy may be used (TCA with SSRI, TCA with venlafaxine, TCA with mirtazepine, venlafaxine with mirtazepine). If there is an incomplete response, proceed to Stage 4.

Stage 4: Combination therapy is recommended (TCA with SSRI, TCA with venlafaxine, TCA with mirtazepine, venlafaxine with mirtazepine). If there is an incomplete response, proceed to Stage 5.

Stage 5: Electroconvulsive therapy.

When transitioning between drugs, an overlap and taper strategy should be used to avoid withdrawal symptoms.

Treatment of anxiety in patients with epilepsy currently follows the same approach as in the general population, and no controlled studies in epilepsy have been conducted to date. SSRIs are first-line agents, specifically paroxetine and escitalopram. Venlafaxine can be helpful when SSRIs are ineffective. Benzodiazepines are used for insomnia and acute, severe distress, although continuous use is limited due to addictive properties.

Other infrequently used drugs are imipramine, trazodone, propranolol, and AEDs with anxiolytic effects such as VPA, tiagabine, barbiturates, gabapentin, pregabalin, and oxcarbazepine.

Besides drug therapy, non-pharmacological approaches such as cognitive-behavioral, interpersonal therapy, and exercise therapy may be beneficial, especially for patients with mild to moderate symptoms. Additional benefit may be attained by combining these methods with medication. Physical exercise can improve mood within four weeks, and frequent aerobic exercise (at least three to five times per week) appears to reduce symptoms of depression more than less frequent or lower energetic exercise.

CBT may be as effective as an SSRI in some patients with epilepsy and depression, and CBT has also been shown to be beneficial for primary anxiety disorders by addressing the negative thought patterns that lead to anxiety, followed by desensitization to anxiety-provoking stimuli. Psychotherapy can help patients cope with limitations imposed by epilepsy and may result in significant improvements in rating scales of depression and anxiety, as well as seizure frequency. Psychoeducation, CBT, interpersonal psychotherapy or supportive therapy may also be helpful for children.

For adult patients with epilepsy who are unable to drive or be driven to receive psychiatric therapy, a home-based treatment using a form of CBT called mindfulness-based CBT can be delivered by the internet or telephone. This intervention consists of 8 one-hour sessions with discussions, instruction, and skill building activities addressing depression, epilepsy, and the role of mindfulness and cognitive behavior change. The internet aspect of the intervention facilitates discussions, viewing session materials, and posting between sessions on a secure website.

Diagnosis: Inadequate treatment of depression and anxiety

Tip: Once a depressive or anxiety disorder is diagnosed, appropriate therapy should be started and titrated under close monitoring to appropriate doses until symptoms remit. Physicians should screen patients for these disorders and refer when necessary for appropriate evaluation and treatment, especially when any of the following is present:

- a depressive episode associated with suicidal ideation
- major depressive episode with psychotic features
- major depressive or dysthymic episode that fails to respond to two or more SSRIs or SNRIs at optimal doses
- bipolar disorder.

Further Reading

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Chapter 14

Management of Emergencies in Epilepsy

Dieter Schmidt

This chapter discusses pitfalls in the management of emergencies in epilepsy, which fall in three categories: patients presenting with a first seizure, with a cluster or a series of seizures, and those in status epilepticus (SE). In the broadest definition of SE, seizures follow one another without recovery of consciousness or intervening periods of normal neurological function. However, confusion may be the only manifestation of complex partial or absence status epilepticus, and an EEG may be needed to diagnose seizure activity. Epilepsia partialis continua is a rare form of focal motor seizures, usually in the hand or the face, that recur at intervals of a few seconds or minutes for days to years at a time. In adults, it is usually due to a structural lesion, such as a stroke. In children, it is usually due to a focal cerebral cortical inflammatory process (Rasmussen's encephalitis), possibly caused by a chronic viral infection or autoimmune processes. The diagnosis of status epilepticus should be made only after unequivocal evidence for epilepsy; psychogenic status should be suspected in refractory cases, particularly in persons with the following profile: no clear neurological deficit, a psychiatric history, and, surprisingly, a health professional background.

SE and serial seizures represent neurological emergencies, and mortality rate for both is high, ranging from 3% to 25%, depending on cause and co-morbidity. Because SE and serial seizures become more refractory to treatment the longer they last, rapid, appropriate treatment is extremely important. Generalized tonic–clonic SE, in particular, requires immediate, aggressive, and effective treatment to stop seizure activity, and to prevent neuronal damage, systemic complications and death.

Single Seizure

A single seizure, which usually lasts no longer than 1–2 minutes, requires no emergency antiepileptic drug (AED) treatment. It will stop soon, whether you treat or not. During a seizure, putting a blanket or a pillow under the head or pulling the patient away from traffic, fire, or other dangerous situations should prevent injury. Protecting or straightening the tongue should not be attempted because the patient's teeth and the first responder's fingers may be damaged. As in all emergencies with impairment of consciousness, the patient should be rolled onto his side to prevent aspiration. However, patients with a series of several seizures or SE do require immediate emergency treatment (see below).

In patients with single seizures, chronic AED treatment is usually not started, unless the patient prefers drug treatment or has risk factors for seizure recurrence (see Chapter 6). After a first seizure, one-third of patients have recurrent seizures, signifying chronic epilepsy. As a reminder, anticonvulsants are of little value in preventing alcohol withdrawal seizures.

Case 14.1 Seeing a Tonic–Clonic Seizure for the First Time is a Traumatic Experience

I remember when I first witnessed a seizure, as a young resident. I had just started to do a neurological examination when the patient's whole body became stiff and breathing stopped. The patient turned blue around the mouth. The eyes were open. The body did not move at all. I was fully convinced the patient had just died before my eyes. I felt totally helpless and blamed myself for having been unable to prevent the death of the patient under my care. Only after what appeared to be a very long time, the patient started to jerk in both arms and legs and once that stopped began breathing. With relief, I realized only then that I had seen a tonic–clonic seizure for the first time.

Discussion

Many people observing a tonic–clonic seizure for the first time are convinced that they have just witnessed the death of the patient. Even relatives who have witnessed many seizures are still convinced that the patient may die during a seizure.

Pitfalls in the Management of a Single Seizure

Do's and don'ts for first aid are listed in Box 14.1.

Box 14.1 First aid for an epileptic seizure: do's and don'ts

1. DO NOT be frightened. Keep calm. Despite the appearance, the patient is not suffering and is not in any danger and will start breathing in a short while.
2. DO NOT attempt to stop the seizure, it will stop by itself in 1–2 minutes.
3. DO NOT try to reanimate the patient. Let the seizure runs its course, it is self-limiting.
4. DO NOT slap or pinch the person. It will not stop the seizure and will agitate the patient during the postictal phase.
5. DO NOT try to open the clenched jaws. It will do damage to the teeth and you may hurt yourself if you put your finger between the teeth.
6. DO NOT give the individual anything to drink. The patient may aspirate while being unconscious.
7. DO NOT try to turn the patient to the side during the seizure. After the seizure turn the patient's face to the side to permit release of saliva or gastric contents and make certain that breathing is not obstructed. A coat may be placed under the head.

Medial or Lateral Tongue Bite?

Tongue bites following a tonic–clonic seizure are always found in the lateral parts of the tongue, either on one side only or on both sides. Lateral tongue bites are very rare in patients with syncope. Medial tongue bites are seen in patients with psychogenic nonepileptic seizures and do not occur during epileptic seizures (see Chapter 5).

Lower Back Pain Following a Seizure: Vertebral Fracture?

Fractures of the thoracic and lumbar vertebrae as a direct consequence of muscle contractions occurring during generalized tonic–clonic seizures are the most common nontraumatic type of fracture complicating epileptic seizures. The majority of these fractures

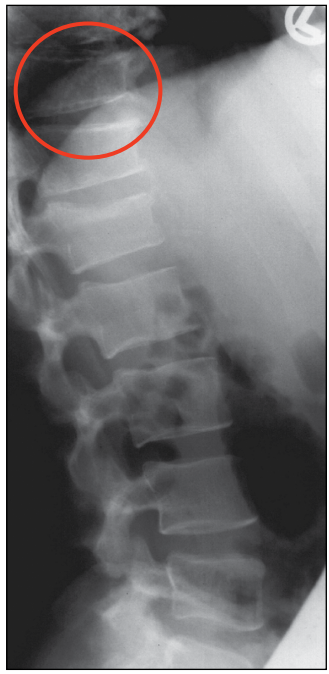

Figure 14.1 Fractures of the thoracic and lumbar vertebrae as a direct consequence of muscle contractions occurring during generalized tonic–clonic convulsions are the most common nontraumatic type of fracture complicating epileptic seizures. The majority of these fractures are vertebral compression fractures that occur with minimal symptoms and virtually no permanent neurological sequelae. Any patient who is reporting lower back pain following a tonic–clonic seizure needs to have an x-ray for diagnosis of a vertebral fracture of the thoracic-lumbar region. In rare cases, however, muscle contractions generated during generalized motor seizures can result in severe axial skeletal trauma and grave neurological complications (with permission from Elger and Schmidt, 2008).

are vertebral compression fractures that occur with minimal symptoms and virtually no permanent neurological sequel. Any patient reporting lower back pain following a tonic–clonic seizure needs to have an x-ray for diagnosis of a vertebral fracture of the thoracic-lumbar region. In rare cases, however, muscle contractions generated during tonic–clonic seizures can result in severe axial skeletal trauma and neurological complications, such as acute cauda equina-conus medullaris syndrome (Figure 14.1) (Roohi and Fox, 2006).

Status Epilepticus

Seizure emergencies with serial seizures or status epilepticus are potentially life-threatening events that are under-recognized. Status epilepticus is associated with considerable rates of morbidity and mortality. Experts currently believe that any episode of seizure activity lasting 5 minutes or longer should be considered status epilepticus. Treatment should be initiated as early as possible; evidence has shown that once seizures persist for 5–10 minutes, they are unlikely to stop on their own in the subsequent few minutes. Prehospital treatment with benzodiazepines has been shown to reduce seizure activity significantly compared with seizures that remain untreated until the patient reaches the emergency department. The consequences of delayed treatment of status epilepticus include a serious risk of subsequent prolonged seizure activity or epileptogenesis, memory deficits, and learning difficulties. The importance of timely intervention in generalized tonic–clonic status epilepticus (GCSE) must be emphasized. Earlier, research found that emergency department personnel fail to recognize the condition in children in 34% of cases (Pellock, 2007).

The Evidence

The Veterans Affairs Cooperative Study

Ideally, pharmacological treatment for GCSE should be easy to administer rapidly, stop seizure activity quickly, and have minimal adverse effects. There have been no prospective clinical trials designed to compare treatment options for GCSE in elderly patients. However, because nearly half of the patients enrolled in a large U.S. Department of Veterans Affairs (VA) cooperative study (Treiman et al., 1998) to compare treatments of GCSE were >65 years of age, it was possible to study the characteristics and treatment responses in this group of 236 elderly patients with GCSE (Treiman, 2007).

Patients presenting with GCSE were classified as having overt or subtle presentations. Overt GCSE was defined as at least two generalized convulsions without full recovery of consciousness between the episodes, or continuous convulsion for more than 30 minutes. Patients were classified as having subtle GCSE if coma and ictal discharge patterns were present on the EEG, with or without the presence of subtle convulsive movements. Within the overt and subtle GCSE groups, patients were randomized into the following four IV treatment groups:

- Phenobarbital (15 mg/kg)
- Lorazepam (0.1 mg/kg)
- Phenytoin alone (18 mg/kg)
- Diazepam (0.15 mg/kg) followed by phenytoin (18 mg/kg).

The study was conducted using a double-blind design. Chi-square techniques were used to analyze rates of treatment success, recurrence, and adverse events. The alpha level was set at 0.05 for analyses of all four treatments. EEG recording began as soon as possible after initiation of the treatment protocol. Seizure activity, blood pressure, heart and respiratory rates, and level of consciousness were recorded every 5 minutes during the first 20 minutes of drug infusion and every 10 minutes for the following 40 minutes. Thereafter, seizure activity and level of consciousness were recorded hourly until the end of the 12-hour study period. Adverse events occurring during the study were documented. The primary outcome measure of the study was success of the first treatment. Treatment success was defined as cessation of all clinical and electrical seizure activity occurring 20–60 minutes after the start of the drug infusion.

Of the 236 elderly patients, GCSE was overt in 167 patients (70.8%) and subtle in 69 patients (29.2%). Mean age was 72.1 years (+SD 6.6 years) in the overt GCSE group and 73.6 years (+SD 5.5 years) in the subtle GCSE group. More than 80% of patients were veterans and more than 85% were male. Remote neurological insult (e.g., past history of stroke, traumatic brain injury) accounted for approximately 70% of the overt GCSE cases, whereas a life-threatening condition (acute stroke, infection, head injury, hypoxia) was the most common etiological factor in the subtle GCSE patients (46.4%).

Patients with overt GCSE were most commonly treated in the emergency department (40.1%) or the intensive care unit (ICU) (32.3%), whereas patients with subtle GCSE were usually treated in the ICU (78.3%) (Treiman and Walker, 2006).

In elderly patients with overt GCSE, first-line treatment with phenobarbital stopped GCSE in 71.4% of cases. First-line treatment with diazepam and phenytoin or phenytoin

alone was not as effective, with success rates of 53.3% and 41.5%, respectively. Lorazepam as first-line therapy was successful in 63.0% of cases. This allowed pair-wise comparison between individual treatment groups. There was no significant difference between the treatment success of phenobarbital and lorazepam. However, in pair-wise treatment comparisons, phenytoin alone was significantly worse than lorazepam or phenobarbital. These results from elderly patients with GCSE differ only slightly from those of the entire original study population.

In the original study, the treatment success rate was highest with lorazepam (64.9%), followed by phenobarbital (58.2%), diazepam and phenytoin (55.8%), and phenytoin alone (43.6%) (Treiman et al., 1998). In the elderly subtle GCSE group, phenobarbital was most effective at stopping seizures (30.8% of cases). Treatment with lorazepam, phenytoin alone, or diazepam and phenytoin was successful in 14.3%, 11.8%, and 5.6% of cases, respectively (Treiman and Walker, 2006). The chi-square analysis showed no significant differences between treatments. These results were similar to those of all subtle GCSE patients in the original study, independent of age: the treatment success rate was highest for phenobarbital (24.2%), followed by lorazepam (17.9%), diazepam and phenytoin (8.3%), and phenytoin alone (7.7%) (Treiman et al., 1998). This similarity in outcome between the entire study population and the elderly cohort is probably a reflection of the high proportion of older patients in the study; in the entire study population, the mean age was 58.6 years (+SD 15.6 years) in the overt GCSE patients and 62.0 years (+SD 15.1 years) in the subtle GCSE patients (Treiman et al., 1998).

In this elderly cohort, the mean duration from onset of GCSE to enrollment in the study was 4.5 hours (+SD 17.9 hours) for patients with overt GCSE, but 17.4 hours (+SD 21.5 hours) for patients with subtle GCSE ($p < 0.001$). Again, these data are similar to those from the entire population of the original study (Treiman et al., 1998) and indicate that the longer SE persists, the more difficult it is to stop.

The results of this analysis suggest that lorazepam, phenobarbital, and possibly diazepam followed by phenytoin are equally likely to be effective at stopping GCSE in elderly patients. Lorazepam has the advantages of ease of use (rapid administration) and of having a shorter duration of sedation than does phenobarbital. Diazepam followed by phenytoin requires a prolonged period for administration, but recovery from sedation is likely to be quicker than with either lorazepam or phenobarbital. Use of diazepam/fosphenytoin rather than diazepam/phenytoin would substantially reduce the time required for administration, so this combination should be considered when avoidance of drug-induced sedation is important in the management of the individual patient. The potential role of valproate or levetiracetam as a second drug following treatment with a benzodiazepine is not yet clear.

The authors of the VA study concluded that GCSE occurs more frequently in elderly individuals than in younger adults and is associated with increased morbidity and mortality. Cerebrovascular disease is the most common cause of GCSE in the elderly. Approximately 75% of elderly patients present with overt GCSE and about 25% with subtle GCSE. Compared with phenytoin, lorazepam and phenobarbital are more effective at stopping overt GCSE when used as first-line treatment in elderly patients. Each drug has advantages and disadvantages, so choice of drug treatment in the elderly should be based on individual patient characteristics (Treiman, 2007).

Pitfalls in the Definition

The current definition of SE includes all types of repeatedly or continuously occurring epileptic seizures, which in total last for longer than 5 minutes (Pellock, 2007), though this time interval is still controversial. Other reports defined GTC status (GCSE) as continuous convulsive activity for 30 or more minutes or ≥2 convulsions with incomplete recovery in the interim (Muayqil et al., 2007). Types of SE are shown in Box 14.2.

Box 14.2 Types of status epilepticus (Elger and Schmidt, 2008)

A. Status of generalized tonic–clonic seizures (GTCSE, convulsive status epilepticus, grand mal status)
B. Nonconvulsive status of complex partial seizures (psychomotor status)
C. Nonconvulsive status of generalized absence (petit mal or absence status) or myoclonic seizures
D. Other epileptic seizure types, e.g., tonic, simple partial (uncommon)
E. Nonepileptic seizures, e.g., psychogenic (not uncommon, Munchausen syndrome, may mimic A–D), myoclonic (postanoxic, intoxication)

Recommendation: until proven otherwise, assume symptomatic etiology of A, B, C in a patient with no history of epilepsy. Perform a neurological examination including MRI, CSF examination, and clinical chemistry including blood glucose, vitamin B6, and substance abuse testing. In case of C, test for substance abuse and alcohol, particularly in the elderly. In a patient with a history of epilepsy, consider poor AED compliance, fever, or unrecognized progressive brain lesion, and a history of status epilepticus.

The approach to SE is outlined in Box 14.3 and pharmacological management is shown in Box 14.4.

Box 14.3 Therapeutic strategy for status epilepticus (Elger and Schmidt, 2008)

1. Make sure you or a reliable witness have seen one indisputable epileptic seizure before you start treatment. If you are in doubt that the seizure was epileptic, do not start or continue medication. Consider observing another seizure.
2. Write down the type of status (A–E, see Box 14.2 for definition) before starting treatment.
3. Write down the medication you give and what the patient has received earlier.
4. If you decide to initiate medical treatment, do it at full dosage, follow your hospital's protocol for treating status epilepticus (several protocols are presented below).
5. Once treatment is started, search for etiology.
6. In case of nonconvulsive absence status, monitor treatment effect by EEG 24 hours later because of the high relapse rate.

Box 14.4 Guideline for emergency treatment of status epilepticus (Elger and Schmidt, 2008)

An example of a protocol for emergency on-site treatment, if possible; if not, in emergency department:

A, B, D (see Box 14.2 for definition): Select one benzodiazepine (diazepam i.v., rectal tube; lorazepam i.v.; clonazepam i.v.) followed by i.v. phenytoin, transfer to immediate inpatient care

C (see Box 14.2 for definition): Select one benzodiazepine (diazepam i.v., rectal tube; lorazepam i.v.; clonazepam i.v.) followed by i.v. valproate, transfer to immediate inpatient care

D (see Box 14.2 for definition): No aggressive parenteral treatment
E (see Box 14.2 for definition): No emergency AED treatment, recommend elective neurological and psychiatric evaluation

Prognosis: Expect seizure control in 60–80%, mortality may be as high as 30%, depends mainly on etiology.

Main pitfalls: Wrong diagnosis, slow AED administration or doses that are too low, overlooking medical complications, e.g., acidosis.

European Federation of Neurological Societies Guideline on the Management of Status Epilepticus

The preferred treatment pathway for GCSE is intravenous administration of 4 mg of lorazepam or 10 mg of diazepam directly followed by 15–18 mg/kg of phenytoin or equivalent fosphenytoin. If seizures continue for more than 10 minutes after first injection, another 4 mg of lorazepam or 10 mg of diazepam is recommended.

Refractory GCSE is treated by anesthetic doses of midazolam, propofol, or barbiturates in intubated patients; anesthetics are titrated up to achieve an EEG burst suppression pattern for at least 24 hours. The initial therapy of nonconvulsive SE depends on the type and the cause.

In most cases of absence SE, a small intravenous dose of lorazepam or diazepam will terminate the SE. Complex partial SE is initially treated such as GCSE; however, if refractory, further non-anesthetizing substances should be given instead of anesthetics. In subtle SE, intravenous anesthesia is required (Meierkord et al., 2006).

Based on the results of the VA study, Treiman (2007) proposed the following recommendation (Box 14.5).

Box 14.5 Treatment protocol for generalized convulsive status epilepticus in the elderly (Treiman, 2007 with permission)

Time (minutes):

0 minute. Establish the diagnosis by observing one additional seizure in a patient with recent seizures or impaired consciousness, or by observing continuous behavioral and/or electrical seizure activity for >10 minutes. Start EEG as soon as possible, but do not delay treatment unless EEG verification of the diagnosis is necessary.

5 minutes. Establish intravenous catheter with normal saline (dextrose solutions may precipitate phenytoin; with fosphenytoin either dextrose or saline is acceptable). Draw blood for serum chemistry, hematological values, and AED concentrations. Test for hypoglycemia by finger stick. Administer 100 mg of thiamine (if indicated) followed by 50 ml of 50% glucose by direct push into the intravenous line.

10 minutes. Administer lorazepam (0.1 mg/kg) by intravenous push (<2 mg/minute)

25 minutes. If status epilepticus continues, start fosphenytoin (20 mg/kg PE) by fast intravenous push (up to 150 mg phenytoin-equivalents (PE)/minute) directly into the intravenous port nearest to patient; if only phenytoin is available, give by slow intravenous push (<50 mg/minute); with either preparation, monitor blood pressure and electrocardiogram during infusion. If status epilepticus continues after 20 mg/kg PE of fosphenytoin (or 20 mg/kg of phenytoin), administer an additional 5 mg/kg PE and, if necessary, another 5 mg/kg PE, to a maximum dose of 30 mg/kg PE.

60 minutes. If status epilepticus persists, give phenobarbital (20 mg/kg) by intravenous push (<100 mg/minute) or start barbiturate coma; support respiration by endotracheal intubation; give pentobarbital (5–15 mg/kg) slowly as an initial intravenous dose to suppress all epileptiform activities and continue 0.5–5 mg/kg/hour to maintain suppression; slow infusion rate periodically to determine cessation of seizure activity; monitor blood pressure, electrocardiogram, and respiratory function. If unable to suppress all epileptiform activity, change to continuous infusion of propofol (1 mg/kg given over 5 minutes, then 2–4 mg/kg/hour; adjust to 1–15 mg/kg/hour) or use midazolam (0.2 mg/kg bolus injection, followed by infusion of 0.05–0.5 mg/kg/hour).

Treatment of Status Epilepticus in Adults: Guidelines of the Italian League against Epilepsy

The guidelines for the management of status epilepticus proposed by the Italian League against Epilepsy also distinguish three different stages of status epilepticus (initial, established, and refractory) based on time elapsed since the onset of the condition and responsiveness to previously administered drugs (Minicucci et al., 2006). Treatment should be started as soon as possible, particularly in GCSE, and should include general support measures, drugs to suppress epileptic activity and, whenever possible, treatments aimed at relieving the underlying (causative) condition. Benzodiazepines are the first-line antiepileptic agents, and intravenous lorazepam is generally preferred because it is associated with a lower risk of early relapses. If benzodiazepines fail to control seizures, intravenous phenytoin is usually indicated, though intravenous phenobarbital or intravenous valproate may also be considered (Minicucci et al., 2006).

Treatment of GCSE in Childhood

GCSE in childhood is a medical emergency and its etiologies and outcomes should be distinguished from adult GCSE. The incidence in developed countries is between 17 and 23/100,000 with a higher incidence in younger children (Neville et al., 2007). Febrile GCSE has a good prognosis in sharp distinction to GCSE related to central nervous system infections, which have a high mortality. The aim of treatment is to intervene after 5 minutes of onset, and studies indicate that intravenous lorazepam may be a better first-line treatment than rectal diazepam and intravenous phenytoin a better second-line treatment than rectal paraldehyde. An epidemiological study strongly supports the role of prehospital treatment, with buccal midazolam becoming a widely used but unlicensed option in the community. More than two doses of benzodiazepines increase the rate of respiratory depression without obvious benefit. The 1-year recurrence rate is 17% and the hospital mortality is about 3% (Neville et al., 2007).

Observational Evidence for the Use of Drugs not Evaluated in the VA Study

This section summarizes the available, mostly observational, evidence on the utility of drugs that were not evaluated in the VA Cooperative Study.

Valproate

Forty-one adult patients (18 males, 23 females) were included in an observational study (Olsen et al., 2007). All had previously been unsuccessfully treated with diazepam. For 19, the main seizure type was generalized tonic–clonic, while 16 had complex partial seizures. Six had seizures that were difficult to classify. The treatment protocol recommended 25 mg/kg of valproate as a loading dose over 30 minutes, followed by continuous infusion of 100 mg/hour for at least 24 hours, then oral administration. If seizures persisted after the loading dose, general anesthesia (barbiturates/propofol/midazolam) was administered. The authors reported no serious side effects. In 76% of the cases (31 of 41), status epilepticus or serial seizures stopped and anesthesia was not required. Of the patients treated within 3 hours, only 5% needed anesthesia, whereas of those treated after 3–24 hours, 38% needed anesthesia. Of those who were not treated for more than 24 hours after SE onset, 60% required anesthesia. Furthermore, 60% of the patients who needed anesthesia were given loading doses below 2,100 mg. The authors concluded that valproate seems to be a safe, effective treatment of SE, but efficacy is dependent on time lapse between onset of symptoms and treatment and administration of a sufficiently high loading dose (Olsen et al., 2007).

Levetiracetam

Preliminary observational reports on the use of intravenous levetiracetam (1000–1840 mg) in patients with refractory complex partial status epilepticus suggest a possible role for intravenous levetiracetam (Wheless and Treiman, 2008). In a series of 16 patients with focal SE (including four cases with GCSE refractory to benzodiazepines), levetiracetam controlled SE (Knake et al., 2009). These reports suggest a possible role for intravenous levetiracetam as initial treatment of SE in view of its good tolerability and ease of use, but randomized, controlled trials are needed for confirmation.

Refractory GCSE

The failure of any of the first-line agents (lorazepam, phenobarbital, diazepam/phenytoin, phenytoin) to terminate SE should define refractory SE (RSE; Bleck, 2007). A number of agents are potentially useful in the treatment of RSE. Some of the more useful ones include midazolam, propofol, ketamine, pentobarbital, topiramate, and isoflurane or other halogenated hydrocarbon anesthetic gases (Bleck, 2007). The adjunctive roles of valproate and levetiracetam remain to be determined (Bleck, 2007). Following termination of SE, other agents may be needed for prevention of its recurrence. In withdrawal from hypno-sedative agents, benzodiazepines may be adequate. In patients with structural lesions, especially infections, phenytoin and phenobarbital remain mainstays of treatment (Bleck, 2007).

Based on the results of the VA study, Treiman (2007) proposed the following recommendation for the management of refractory generalized convulsive status epilepticus in the elderly (Box 14.6).

Box 14.6 Management of refractory generalized convulsive status epilepticus in the elderly (Treiman, 2007 with permission)

- After lorazepam followed by phenytoin, start IV general anesthesia with pentobarbital (5–15 mg/kg load, 0.5–5 mg/kg/hour maintenance); titrate to suppress all epileptiform activity
- Monitor closely for hypotension and infection
- Search for etiology, correct if possible

- Adjust phenytoin concentration to 30 mg/ml, load phenobarbital to 100–150 mg/ml
- Slow infusion periodically (every 24–72 hours) to see if epileptiform activity returns
- Do not give up; patients have recovered consciousness after >2 months of coma

IV = Intravenous.

Refractory Generalized Convulsive Status Epilepticus: A Guide to Treatment from Finland

A Finnish group published recommendations for management of refractory generalized convulsive status epilepticus (Kälviäinen et al., 2005). The authors defined refractory SE as SE that does not respond to first-line benzodiazepines (lorazepam or diazepam) or to second-line AEDs (phenytoin/fosphenytoin, phenobarbital, or valproate). The authors point out that optimal treatment of refractory GCSE has not been defined, but patients should be treated in an ICU; artificial ventilation, invasive hemodynamic monitoring and support, and EEG monitoring are essential (Kälviäinen et al., 2005).

The drug treatment of refractory GCSE involves general anesthesia with continuous intravenous anesthetics given in doses that abolish all clinical and electrographic epileptic activity, often requiring sedation to the point of burst suppression on the EEG. Barbiturate anesthetics, pentobarbital in the United States, and thiopental sodium in Europe and Australia, are the most frequently used agents and are highly effective for refractory GCSE both in children and adults. Indeed, they remain the only way to stop seizure activity with certainty in severely refractory cases. Other options are midazolam for adults and children and propofol for adults only. Regardless of the drug selected, intravenous fluids and vasopressors are usually required to treat hypotension (Kälviäinen et al., 2005).

Once seizures have been controlled for 12–24 hours, continuous intravenous therapy should be gradually tapered off if the drug being administered is midazolam or propofol. Gradual tapering is probably not necessary with pentobarbital or thiopental sodium. Continuous EEG monitoring is required during high-dose treatment and while therapy is gradually withdrawn. During withdrawal of anesthetic therapy, intravenous phenytoin/fosphenytoin or valproate should be continued (these agents having been administered during earlier phases of GCSE) to ensure an adequate baseline of AED so as to prevent the recurrence of status epilepticus. If additional medication is needed, the authors suggest that the most appropriate AEDs are gabapentin for focal seizures and levetiracetam and topiramate for all seizure types, as these drugs can be started at high doses with a low risk of idiosyncratic reactions (Kälviäinen et al., 2005).

Even with current best practices, mortality in patients who experience refractory GCSE is about 50% and only the minority returns to their premorbid functional baseline. Therefore, new treatment options are urgently needed. The ideal new drug for refractory GCSE would be one that has the ability to stop seizures more effectively and safely than current drugs, and that has neuroprotective properties to prevent the brain damage and neurological morbidity caused by GCSE (Kälviäinen et al., 2005).

Treatment of Refractory Status Epilepticus in Adults: Guidelines of the Italian League against Epilepsy

The guidelines for the management of status epilepticus proposed by the Italian League against Epilepsy include RSE, which requires admission to an ICU to allow adequate

monitoring and support of respiratory, metabolic, and hemodynamic functions and cerebral electrical activity (Minicucci et al., 2006). General anesthesia may be required. Propofol and thiopental represent first-line agents in this setting, after careful assessment of potential risks and benefits (Minicucci et al., 2006).

Pitfalls in the Management of Status Epilepticus (Box 14.7)

Pitfall: Failure to Provide Life Support and Adequate Monitoring

Treatment of GCSE should begin with basic life support measures to stabilize the patient (Treiman, 2007). Body temperature, blood pressure, electrocardiogram, and respiratory function should be monitored. Pulse oximetry or arterial blood gas studies should be performed for assessment of oxygenation. Respiratory support should be provided as needed, and intravenous access should be established. Hydration and the use of vasopressors may be necessary if the patient is hypotensive. Cooling may be required if the patient's body temperature exceeds 40°C.

Blood samples should be drawn for determination of hematological and serum chemistry values, as well as serum AED concentrations (Treiman, 2007). If the patient is hypoglycemic, intravenous glucose and thiamine should also be administered, before or with glucose if thiamine deficiency is a concern. Bicarbonate may be administered to treat acidosis, but this is advisable only if the patient's blood pH is life-threateningly low (Treiman, 2007). EEG monitoring of patients in GCSE is also important during treatment because if overt seizures stop, but the patient remains unconscious, he or she may still be experiencing continuing electrographic seizure activity (Treiman, 2007).

Pitfall: Failure to Determine the Etiology

Whenever possible, the underlying cause of the SE should be identified and treated (Elger and Berkenfeld, 2017; Treiman, 2001).

Pitfall: Recognize that Current AEDs Show No Substantial Differences in Efficacy for Initial Treatment

While up to 65% of patients in SE may respond to initial treatment (Treiman et al., 1998), there are no substantial differences in efficacy across first-line treatments. Results in the VA study (Treiman et al., 1998) did not differ significantly by treatment allocation.

Pitfall: Recognize the Need for Transfer to an Intensive Care Unit as Early as Possible

Patients not responding to the first AED will usually require sufficiently aggressive treatment with agents potentially producing respiratory depression or hypotension such that they will need to be admitted to an ICU. Even among those whose SE responds to initial therapy, some will warrant an ICU admission because of the underlying condition that caused SE, and others will need ICU care to manage the complications of SE (Bleck, 2007). The best estimate of the need for ICU admission comes from the San Francisco prehospital study, in which 55% of patients were transferred to the ICU from the emergency department; this did not differ significantly by treatment allocation (Alldredge et al., 2001; Bleck, 2007).

A recent review identified three main reasons for admission to the ICU in patients with SE (Bleck, 2007). These reasons are: one, the need for mechanical ventilation, and its subsequent weaning, following successful therapy for SE in the ED; two, the need to

Box 14.7 Checklist: how to minimize pitfalls in the management of status epilepticus (Elger and Schmidt, 2008, with permission)

Confirm/reassess your diagnostic strategy:

According to observed predominant seizure type, status epilepticus falls in five clinical categories:

A. Status of tonic–clonic seizures (convulsive status epilepticus, grand mal status).
B. Nonconvulsive status of complex partial seizures (psychomotor status)
C. Nonconvulsive status of generalized absence (petit mal or absence status) or myoclonic seizures. Look for paroxysmal, mostly spike wave, activity in the EEG, consider postictal confusion, dehydration, substance abuse for differential diagnosis.
D. Other epileptic seizure types, e.g., tonic, simple partial (uncommon)
E. Nonepileptic seizures, e.g., psychogenic (not uncommon, Munchhausen syndrome, may mimic A–D), myoclonic (postanoxic, intoxication)

Guideline: Until proven otherwise, assume symptomatic etiology of A, B, C in a patient with no history of epilepsy. Perform a neurological examination including MRI, CSF examination, and clinical chemistry including blood glucose, vitamin B6, and substance abuse testing. In case of C, test for substance abuse and alcohol, particularly in the elderly. In a patient with a history of epilepsy, consider poor AED compliance, fever, or unrecognized progressive brain lesion, and a history of status epilepticus.

Confirm/reassess your treatment strategy:

1. Make sure you or a reliable witness have seen one indisputable epileptic seizure before you start treatment. If you are in doubt that the seizure has been epileptic, do not start or continue medication. Consider observing another seizure.
2. Write down the type of status (A–E) before starting treatment.
3. Write down the medication you give and what the patient has received earlier.
4. If you decide to initiate medical treatment, do it at full dosage, follow your house rules for treating status epilepticus.
5. Once status epilepticus has been interrupted, start the search for etiology.
6. In case of nonconvulsive absence status, monitor treatment effect by EEG 24 hours later because of the high relapse rate.

Guideline

Emergency on-site treatment:

A, B, D: Status epilepticus can be terminated by giving diazepam 10–20 mg (for adults) IV or up to 2 doses (if necessary) of lorazepam 4 mg IV. For children, IV diazepam up to 0.3 mg/kg or lorazepam up to 0.1 mg/kg is given. For adults, phenytoin 1.5 g IV may be given to prevent recurrence. Fosphenytoin, a water-soluble product, is an alternative that in equivalent doses reduces the incidence of hypotension and phlebitis

Select one Benzodiazepine (Diazepam i.v., rectal tube, Lorazepam i.v., Expidet, Clonazepam i.v.) followed by i.v. Phenytoin, transfer to immediate inpatient care.

C: Select one Benzodiazepine (Diazepam i.v., rectal tube, Lorazepam i.v., Expidet, Clonazepam i.v.) followed by i.v. Valproate, transfer to immediate inpatient care

E: No emergency AED treatment, recommend elective neurological and psychiatric evaluation

Inpatient treatment:

A, B, C, D: Anesthetic IV doses of phenobarbital, lorazepam, or pentobarbital may be necessary in refractory cases; in such instances, intubation and O_2 therapy are required to prevent hypoxemia (see algorithm)

D: No aggressive parenteral treatment
E: No emergency AED treatment, recommend elective neurological and psychiatric evaluation
Prognosis: Expect seizure control in 80%, mortality may be as high as 30%, depends mainly on etiology.
Main errors: Wrong diagnosis, hesitant administration of too small doses of a number of agents, overlooking of medical complications e.g., acidosis.

treat the underlying condition prompting SE; and three, the need for aggressive therapy to terminate SE.

The most common cause for ICU admission related to SE is the need for mechanical ventilation, and its subsequent weaning, following successful therapy for SE in the emergency department even if this required endotracheal intubation and blood pressure support. These patients generally require only the standard care measures for comatose patients, including elevation of the head of the bed, prophylaxis against gastrointestinal bleeding and deep venous thrombosis, and frequent changes in position while waiting for the respiratory depressant effects of their therapy to wear off. Rarely, these patients will also require hemodynamic support with extra saline or agents such as norepinephrine because of the hypotensive effects of the drugs employed to terminate SE. As with any case of SE, failure to demonstrate a consistently improving mental status is an indication for emergent, continuous EEG monitoring to be sure that SE has been controlled and is not recurring. This monitoring should be available in all ICUs dealing with these patients, or other patients with altered awareness (Bleck, 2007).

The next most common cause for ICU admission was the need to treat the underlying condition prompting SE. While discussion of the management of these diagnoses is beyond the scope of this chapter, attention to intracranial pressure, cerebral perfusion pressure, and the specific treatment of infections are crucial. In the hyperthermic patient, the core temperature should be rapidly corrected to prevent compounding neuronal and systemic damage from the seizures and their etiology (Bleck, 2007).

Where Current Status Epilepticus Treatment Fails: Timing is Everything

A recent review of the medical literature observed deviations from guidelines, and initiatives to improve timely treatment (Hill et al., 2017). The authors found pervasive, substantial gaps between recommended and "real-world" practice with regard to timing, dosing, and sequence of antiepileptic therapy. Applying quality improvement methodology at the institutional level can increase adherence to guidelines and may improve patient outcomes (Hill et al., 2017).

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Chapter 15

Management of Social Issues

Steven C. Schachter

The availability of new pharmacological and non-pharmacological treatments for epilepsy over the past several decades has made it possible for more patients with epilepsy than ever before to live free of seizures. However, whether or not their seizures are controlled, patients with epilepsy continue to face unique challenges in their lives, such as the uncertainty about and fear of the next seizure; limitations on lifestyle, school, driving, insurance, socialization, and employment; cognitive impairment; and treatment-related side effects. When these challenges are not solved, stress levels increase, further complicating the control of seizures, psychiatric comorbidities, and medication-related side effects. In fact, these psychosocial problems associated with epilepsy may have a greater impact on quality of life than seizures for many patients. Conversely, when patients and their families learn to monitor and identify factors that may influence susceptibility to seizures, treatment side effects, and impaired socialization, changes in lifestyle may be instituted that enhance self-confidence and self-management, thereby reducing stress and improving outcomes.

From the physician's perspective, managing patients with epilepsy has become more complex as the goals of therapy have evolved from an exclusive focus on reducing seizures to enabling the patient to live up to their full potential, free from the medical and psychosocial complications of epilepsy. This can only be achieved by optimizing and individualizing management patient by patient. To do so, physicians must be aware of not only the biological aspects of epilepsy, but also the psychological and social factors as well as how they pertain to each of their patients. In addition, physicians must ensure that patients and their families learn how to manage seizures, treatments, and the associated psychosocial problems so that they become partners with their physicians in the overall care plan.

Chapter 13 reviewed comorbid psychiatric disorders, and this chapter presents the pitfalls related to several other important psychosocial issues of epilepsy – driving, quality of life, and employment.

Failure to Discuss Driving

Case 15.1 Talk about Driving!

A 19-year-old college student had his first generalized tonic–clonic seizure after missing sleep for two consecutive nights studying for a final exam. Medical evaluation by a neurologist on referral from the college infirmary revealed he had intermittently experienced jerking movements of his arms in the early morning for years, and the diagnosis of juvenile myoclonic epilepsy was made and supported by an EEG. He was started on valproate and told he should do fine as long as he takes his medication, avoids alcohol, and gets plenty of sleep. He was instructed to see his PCP back home during the next school vacation. There was no discussion of driving.

Discussion

Of all the lifestyle restrictions that are imposed by a diagnosis of epilepsy, perhaps the most impactful for adults is the loss of driving privileges. As a key to employability, independence, and self-reliance, driving can be critically important for self-esteem. Being unable to drive for a prolonged period of time can therefore cause significant psychological distress.

Driving regulations for noncommercial licenses are set by each state in the United States (regulations for commercial driving are beyond the scope of this chapter). In this case, however, the patient was not advised to avoid driving for any length of time. Physicians who fail to advise patients of their responsibilities as drivers or for failing to report patients if required by their state may be liable.

A common misconception is that this responsibility falls to a patient's PCP, while it is actually incumbent on any physician who diagnoses a patient with epilepsy, whether this happens in an emergency room, college infirmary, or doctor's office, to convey the applicable state regulations to the patient and to document this discussion in the patient's medical record, also noting that the risks of having a seizure while driving and the role of the state in granting the legal privilege of driving were conveyed to the patient. Some doctors go so far as to have this information pre-printed and have the patient sign and date the form indicating their understanding of the information. Generally, having this discussion is also a good time to emphasize the importance of taking seizure medication as prescribed and for the patient to be sure to report each seizure they have to their doctor at scheduled visits so that medication can be optimized to achieve seizure-freedom. With regard to the second point, in those states where physicians are required to notify the regulatory authorities, patients may be hesitant to tell their doctors if they have had seizures for fear of losing their driving privileges, but this should be pointed out to patients as counterproductive to their health and long-term goals.

State-by-state guidelines vary from one another and may change over time. Physicians need to stay current in their understanding of the applicable guidelines in their state and can consult their state registry of motor vehicles. Another source of information for the United States is the Epilepsy Foundation (www.epilepsy.com/driving-laws). Some state guidelines specifically mention epileptic seizures, while others pertain to any episodic cause of impaired consciousness or ability to safely operate a motor vehicle, which notably could also cover significant medication-related side effects such as impaired judgment or confusion. Therefore, physicians should advise patients not to drive if their cognitive and neurological function is adversely affected by seizure medication sufficiently to impact driving ability.

The most important aspect of the guidelines is the length of time the patient has to be seizure-free before they may legally drive, assuming they already have a license. The required time periods are set by each state and generally range from 3 to 12 months. A small number of states allow physicians to use their discretion in recommending a particular duration of seizure-freedom on an individualized basis. Other specific situations often arise in clinical practice that are not explicitly covered by state guidelines but for which physicians may wish to provide recommendations to their patients, such as seizures that occur during a physician-initiated modification in seizure medication or seizures that are related to acute illness or metabolic derangement that are viewed as time-limited and not likely to be repeated. A special case is when seizure medication is discontinued because of a prolonged period of seizure-freedom and the determination that recurrent seizures are unlikely. Under these circumstances, physicians may advise their patients not to drive for a particular length of time, perhaps the same duration as specified by their states' regulatory authorities for seizure-freedom needed to drive legally. Given this advice, some patients may wish to stay on their seizure medication and continue driving rather than give up driving for a prolonged period and incur the associated problems.

Case (continued)

The patient made an appointment with his PCP and drove home after his exams. He decided to drive through the night to get home sooner, and the next morning, when he had almost reached his destination, he had an apparent seizure while driving and crashed into a roadside barricade. Fortunately, he was not hurt and did not hit another car. He told the police that he may have had a seizure. When his insurance company discovered he had recently been diagnosed with epilepsy, they refused to cover the costs of repairing his car since they determined he was not driving legally, having had a seizure within the state-mandated period of seizure-freedom.

Discussion

This conclusion to the case raises three issues – the potential for suffering a car accident and its consequences, the ramifications of driving in violation of state guidelines, and not following a doctor's recommendations with regard to avoiding sleep deprivation, which can occur at any age but is particularly common among adolescents and young adults who think they are immune from such vulnerabilities.

Seizures that occur while driving obviously put the driver, any passengers, and others in the vicinity at significant risk for injury and death, in addition to the likely possibility of property damage. These potential consequences are understandably the basis for driving regulations. This patient was fortunate that no one was seriously injured, including himself, but because he was not carrying a valid driver's license, having had a recent seizure and therefore not seizure-free for the period required by his state, his insurance company determined that it was not contractually obligated to cover the costs of his car repairs.

Patients should be told that if they choose to drive before they have been seizure free for the required period of time, they run the risk of losing their insurance coverage in the event of an accident while driving. This can help to reinforce the message that they should adhere to their state guidelines and work with their doctors to achieve seizure-freedom.

Once informed, most patients will refrain from driving in compliance with their state guidelines. However, some do not, even though their physician has clearly told them of the applicable regulations and the potential consequences of noncompliance. A particularly thorny situation arises when a physician is aware that a patient is repeatedly driving when they shouldn't be. Reporting the patient to the regulatory authorities is an option that physicians should consider, but they may wish to discuss this action first with legal counsel; at issue is the duty to protect public safety versus breech of medical confidentiality. Some but not all states provide legal protections for physicians who report patients who are driving when they shouldn't be.

Clinical Scenario: Inappropriate Driving

Tip

Physicians are expected to know their obligations and responsibility for counseling their patients with epilepsy about driving and, in a small number of states, in notifying the regulatory authorities that a patient has epilepsy. Not doing so, or not documenting the discussion with the patient, can make the physician potentially liable for problems that occur from inappropriate driving.

Not Paying Attention to Quality of Life

Case 15.2

A 26-year-old single, unemployed man had a 10-year history of medically refractory focal dyscognitive and secondarily generalized tonic–clonic seizures, resulting in numerous hospital admissions for seizure-related injuries associated with low serum anticonvulsant levels and, at other times, neurotoxic medication-related side effects. He was referred to a new neurologist for outpatient evaluation and it quickly became apparent that the patient did not keep track of his seizures or treatment side effects, and in fact wasn't even aware that the seizure medications only worked if he took them properly. Like his parents, he thought that seizures were a curse, which he took personally, and he felt he wasn't worthy enough to get married and even if he had children, he would pass on the epilepsy to them.

Discussion

While antiepileptic drugs (AEDs) are of particular importance to minimize, if not fully control, seizures, and though the persistence of seizures impacts the quality of life of patients with epilepsy, many other factors do as well, such as mood disorders (see Chapter 13), stigma, seizure worry, low self-esteem, and inadequate knowledge about epilepsy. Irrespective of their level of seizure control from AEDs, patients whose quality of life is sub-optimal may benefit from targeted psychosocial interventions that reduce the negative impact of these factors.

In the past, physicians taking care of patients with epilepsy generally focused their efforts exclusively on reducing or stopping seizures (especially tonic–clonic seizures). The generally held assumption was that the psychosocial impact of epilepsy was entirely determined by seizure frequency and severity, and would therefore resolve with improved seizure control. However, research has challenged this assumption, showing that patients may have impaired quality of life even if they are seizure-free, particularly due to their fears and concerns, experiences with treatment, and schooling or employment status (see next case).

Consequently, optimizing the quality of life for patients requires more than achieving seizure control. Today's overall therapeutic objective is to enable patients to be as free from the medical and psychosocial complications of seizures and epilepsy as possible, which includes but is not limited to minimizing seizure occurrence. Therefore, physicians must be attuned to their patients' perspectives on their health in the physical, mental (including mood disorders, self-esteem, and perceived stigma), and social (activities with others, inter-personal relationships) spheres, which together comprise their quality of life, and to recommend psychosocial interventions when appropriate.

In a busy office practice, it can be challenging to spend enough time with patients to fully assess their quality of life. A variety of surveys, scales, and questionnaires have therefore been developed and validated to specifically assess the quality of life of patients with epilepsy. Perhaps the two most often used in clinical practice are the Quality of Life in Epilepsy Inventory (QOLIE) and the EFA Concerns Index. These epilepsy-specific instruments focus on aspects of physical, mental, and social health that are relevant to people living with epilepsy, such as seizure worry, medication effects, health discouragement, work/driving/social function, language functioning,

attention/concentration, memory, overall quality of life, emotional well-being, emotional and social isolation, social support, energy/fatigue, health perceptions, physical functioning, fear of injury during a seizure, and being treated unfairly by others. These instruments can be completed by patients in the doctor's office while waiting to see their physician and can be used to highlight areas of concern and monitor change over time.

Surveys have shown that fear among patients is the worst part of having epilepsy. This fear can take several different forms – fear of having or dying from a seizure, fear that others will witness a seizure, fear of embarrassment in public, fear of losing employment, and fear of being involved in an automobile accident. Fear related to how others will relate to the person with epilepsy (social anxiety) is particularly problematic for adolescents and is inversely proportional to their knowledge about epilepsy.

The quality of life for children with epilepsy is in large part determined by parental anxiety, which if present can be modified with interventions and support such as respite care, parent support groups, and increased education about seizure risks and psychosocial development.

Stigma affects the quality of life of patients with epilepsy at any age and takes two forms: enacted stigma, which manifests as discrimination in the course of everyday activities, such as attending school, driving, working, and obtaining insurance; and perceived stigma, which is the belief on the part of the person with epilepsy that others view the individual with epilepsy as defective or inferior in some way. The extent of enacted stigma depends on seizure type(s) and frequency, and perceived stigma is inversely associated with self-reported knowledge about epilepsy and self-esteem.

The more that a patient believes that his or her health condition is significantly a matter of chance, and not under their control, the poorer their quality of life. That is, a patient's ability to cope with their epilepsy largely determines how they manage their disorder, and psychosocial interventions that provide social support and teach coping skills increase self-efficacy and quality of life.

Case (continued)

The neurologist referred the patient to an epilepsy nurse specialist who taught the patient the basics about epilepsy, its treatment, and self-management. Over time, the patient became more confident and took greater responsibility for his well-being. He became seizure-free and began dating.

One of the most effective interventions that can improve quality of life is educating patients about epilepsy, as was done in this case. Patients with limited knowledge of epilepsy and the basics of treatment are at increased risk for the complications of seizures, such as fractures, burns, and accidental death, and for medication-related side effects, further reducing quality of life and adding to the economic costs of their medical care. Therefore, patients should be counseled about lifestyle modifications that help to prevent injury to themselves or others, that minimize seizure precipitants, and that enhance their sense of control and independence. Safety precautions include:

- Bathing safety, to prevent accidental drowning and burns.
  - Tubs should be filled no more than 3 in. high for baths
  - Drains must function properly

  - An upper limit to water temperature should be set, or the hot water thermostat should be kept below scalding temperature
  - Family member or carer should be nearby
- Kitchen safety, to prevent burns and injuries
  - Sharp utensils should be kept away
  - A microwave should be used when possible rather than a stove
- Recreation should be encouraged with common sense restrictions
  - Patients should never swim alone
  - Certain activities that would put the patient in imminent danger if a seizure occurred should be avoided, such as scuba diving.

Comprehensive educational programs designed for patients can improve seizure outcomes and tolerance of drug therapy, and reduce seizure worry, with the overall effect of enhancing quality of life for patients with epilepsy. A number of different formal educational programs have been developed, ranging from 2-day sessions to multi-week structured psychoeducational or cognitive-behavioral group treatment experiences. Topics covered by these programs generally include healthy lifestyle behaviors, family and peer relationships, understanding self-image and self-esteem, techniques for reducing stress, and self-management skills. Cognitively oriented programs additionally focus on understanding stress and its relationship to seizures, relaxation training, cognitive restructuring, identification of seizure-provoking situations, systematic desensitization, training in stress management, and communication skills.

Studies have shown the positive impact of these programs on patient satisfaction with therapy, medication management, seizure control, and quality of life. They can lead to increased and sustained epilepsy knowledge, decreased fear of seizures, reduction in hazardous self-management of medications, decreased information misunderstanding, and increased adherence to medication schedules.

Since these programs are not widely available or accessible, telephone- and internet-based educational programs have been developed. These overcome two main barriers to participation in educational programs, transportation and cost. Like the in-person offerings, their objectives are to improve social support, perceived self-efficacy in managing epilepsy, and to set and achieve short-term goals for behavior change in the areas of seizures, safety, information, medications, and lifestyle. WebEase (Epilepsy Awareness Support and Education), an online self-management program, uses motivational interviewing techniques and social cognitive theory, and includes modules on medication, sleep, and stress management. Each interactive module assists the user to assess their readiness for change, establish goals for behavior change, learn information, develop skills, and monitor progress toward goals in their chosen area. Results to date have indicated that participants who complete the relevant modules achieve greater levels of self-efficacy and improvements in medication adherence, improved sleep, and lower levels of stress.

Clinical Scenario: Impaired Quality of Life due to Poor Knowledge about Epilepsy

Tip

Physicians are in a unique position to assess the quality of life of their patients with epilepsy, and to make the necessary referrals for appropriate interventions.

Overlooking the Importance of Employment to Patients

Case 15.3

A 48-year-old accountant was a valued employee of a shoe company, receiving excellent annual reviews and contributing to the company's success. This was all in spite of the fact that he had 2–3 focal dyscognitive seizures a month while at work, sometimes involving removing his clothes and urinary incontinence. His co-workers were supportive and understanding. After an evaluation for epilepsy surgery, he underwent a right temporal lobectomy. While he was recuperating at home, the company management changed. A couple of days after he returned to work, he had a typical seizure in the company lunchroom. The next day, he received a note from the director of human resources stating that since it was the understanding of management that surgery would take care of his seizures, and apparently it hadn't, he was put on permanent disability and told not to return to work.

Discussion

Employment is a major determinant of self-esteem for people in general, including patients with epilepsy. Unfortunately, the rates of unemployment and underemployment in patients with epilepsy who are willing to work and are medically cleared to work are significantly higher than in the general population, bringing economic hardships and psychological distress. There are numerous reasons behind these statistics, including the negative attitudes and misconceptions of employers toward persons with epilepsy, as in this case; negative attitudes of co-workers, which fortunately was not the case here; liability concerns among employers; seizure-related variables such as seizure type(s), frequencies, and associated neuropsychiatric co-morbidities; and transportation barriers.

Physicians may be asked by their patients to become involved in their efforts to find work or to stay employed. In doing so, physicians may be given permission by their patients to talk to employers, company physicians or nurses, job counselors, or therapists at vocational rehabilitation centers. In that role, physicians need to understand the relevant job requirements and the degree to which a particular patient's epilepsy and treatment may or may not preclude them from performing the essential duties of the specific job. The key to this evaluation is a description of the essential duties of the job, and the extent to which the workplace can be modified through reasonable accommodation by the employer to allow the patient to perform those duties. The Americans with Disabilities Act (ADA) and its subsequent Amendment, which apply to employers with 15 or more employees, prohibit discrimination in the workplace against people with disabilities, including epilepsy, and calls on employers to reduce risks to employees related to their particular disability through reasonable accommodations that do not impose an undue hardship with respect to cost and difficulty with implementation for the employer and which allow the employee with a disability to adequately perform their job. Blanket prohibitions of employment of people with epilepsy simply because of the diagnosis, as in this case, are illegal with a few notable exceptions (such as work that requires carrying a loaded firearm).

When interviewing job applicants, employers can inquire whether the interviewee is able to perform the essential job duties with or without reasonable accommodations but cannot ask about medical history that is unrelated to the particular job.

Case (continued)

On return visit to his physician, the patient was still devastated emotionally and overtly depressed. He missed work and the comradery with co-workers. He was complaining more of medication side effects and not sleeping well, though he had not had any further seizures. His physician advised him to contact the Legal Aid Society, which sent a letter to the company stating that a lawsuit for discrimination under the ADA would be brought if the situation was not resolved in the patient's favor. The patient was soon reinstated at work and the director of human resources was terminated.

Discussion

This patient was understandably distraught over the action taken by his company, but fortunately his physician put him in touch with lawyers that were familiar with employment law and who expeditiously resolved the situation in the patient's favor, though the director of human resources wasn't so lucky.

Clinical Scenario: Inappropriate Loss of Employment Resulting in Emotional Distress

Tip

Employment is important in the lives of adult patients with epilepsy and physicians can assist their patients if called upon to help them secure fulfilling jobs.

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