

# department of veterans affairs epilepsy manual

SECOND EDITION

Editors

**Aatif M. Husain**

**Tung T. Tran**



**VA**  
HEALTH  
CARE

Defining  
**EXCELLENCE**  
in the 21st Century

## ABOUT THE **EPILEPSY CENTERS OF EXCELLENCE** OF THE DEPARTMENT OF VETERANS AFFAIRS

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The mission of the Epilepsy Centers of Excellence (ECoE) is to improve the health and well-being of Veteran patients with epilepsy and other seizure disorders through the integration of clinical care, outreach, research, and education.

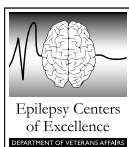
In 2008 under Public Law S. 2162, the Department of Veterans Affairs (VA) set upon its mission to revolutionize services for the Veterans afflicted by epilepsy and other seizure disorders. The VA founded the ECoE, establishing 16 sites that are linked to form 4 regional centers.

The ECoE seeks to provide the best possible epilepsy care to Veterans throughout the United States with state-of-the-art diagnostic and therapeutic services. Our goal is to deliver the highest quality of ongoing medical care to Veterans suffering from epilepsy. We also seek to promote outreach and educational efforts for both patients and their physicians in order to further the understanding of this chronic condition.

The ECoE offers a range of services in both the outpatient and inpatient realms. The ECoE provides outpatient epilepsy clinics with a staff of neurology subspecialists. From these clinics, patients can be directed to the most advanced testing methods for the evaluation of epilepsy, including magnetic resonance imaging (MRI), electroencephalography (EEG), and video monitoring. For those patients that require more intensive testing or attention, the ECoE also provides inpatient units for examining certain seizure types more closely, changing medications in a monitored setting, and presurgical evaluation.

The epilepsy centers are also linked with the Polytrauma Centers to increase the ability to mutually follow Veterans with moderate and severe traumatic brain injury who are at the greatest risk for post-traumatic epilepsy. The sites are developing protocols to identify Veterans with epilepsy and to develop referral networks to enable Veterans to obtain specialized treatment such as epilepsy surgery and advanced electrodiagnosis within the VA healthcare system.

For more information please visit our website at [www.epilepsy.va.gov](http://www.epilepsy.va.gov).



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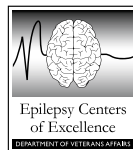
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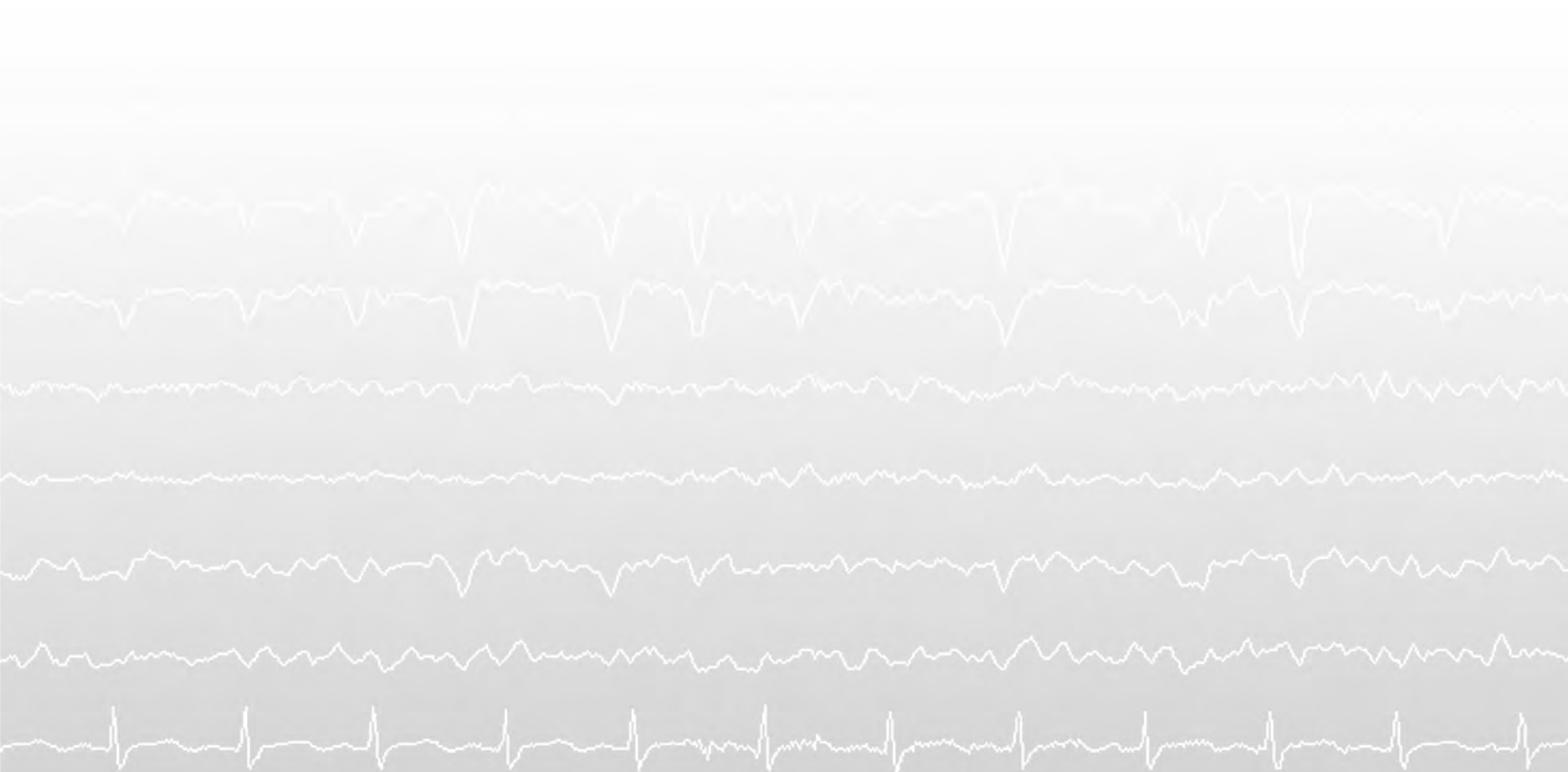
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*This book is dedicated to my brother, Aasim Mairaj Husain, who has always been protective, supportive, and inspirational. I hope someday my sons can do for each other what he has done for me.* AATIF M. HUSAIN

*This book is also dedicated to the memory of my father, So Van Tran, who, as a Veteran and teacher himself, taught his family to strive constantly to serve others.* TUNG T. TRAN





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## PREFACE

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SINCE THE FIRST EDITION OF THE DVA EPILEPSY MANUAL WAS PUBLISHED in 2014, many changes have occurred in our understanding of epilepsy and seizures in Veterans. The Epilepsy Centers of Excellence (ECoE) have also gone through many changes and have evolved into a cohesive, well-managed organization. Because of these and many other changes, we thought the time was right to update this manual and provide contemporary, relevant information for the clinician.

Epilepsy is a very common and complex neurological disorder with not only serious medical but also psychosocial consequences. Veterans are at high risk for developing epilepsy due to the frequency with which they suffer traumatic brain injuries. Moreover, Veterans are at risk of developing other types of nonepileptic seizures because of high incidence of conditions like post-traumatic stress disorder.

Veterans with epilepsy and nonepileptic seizures have many comorbid medical and mental health conditions. Their needs are complex and often different than their civilian counterparts. Health care providers of all specialties may be called upon to care for these patients.

The ECoEs have been providing focused, high level care to Veterans with epilepsy and nonepileptic seizures. Many centers have access to the latest surgical treatments, while others offer cognitive behavioral therapy for psychogenic nonepileptic seizures. Many innovative programs have been established in the VA, such as telemedicine home visits for Veterans who cannot travel, clinical note entry template for data basing, educational case conferences for referring providers, and routine video seminars for patients and interested providers on various topics related to epilepsy. Along with the ECoEs, a Consortium of VA Epilepsy Centers now allows networking of all epilepsy centers within the VA Health System.

The first edition of the DVA Epilepsy Manual was more popular than we could have imagined, being “sold out” very quickly, and soon only electronic copies remained available to be distributed. It is our hope that this second edition will carry on where the first edition left off. This manual provides practical information and tips for not only neurologists, but other types of health care providers caring for these Veterans with epilepsy and other nonepileptic seizures. Information about not only medical issues, but also psychological and social issues (such as disability information) is shared. Essential information is presented to keep the chapters succinct and readable.

All aspects of clinical epilepsy care are addressed in this manual in a practical manner. The manual is divided into four broad categories of chapters: Clinical Aspects, Diagnostic Evaluation, Treatment, and Special Situations. Non VA practitioners, including trainees, will find this manual useful as it condenses what can take up a large textbook to the essential and practical topics. References are provided in case one is interested in more information. Tables, figures and summaries are used to further organize the information.



The authors of the chapters of this manual are all involved in the care of Veterans with seizures. Many of them are at the various ECoE and represent different areas of expertise. We are indebted for their contributions to this manual. Hopefully the DVA Epilepsy Manual will enhance the care of heroes who have given so much of themselves for the sake of their country.

AATIF M. HUSAIN, MD

TUNG T. TRAN, MD

## ACKNOWLEDGEMENTS

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THIS MANUAL WOULD NOT HAVE BEEN POSSIBLE WITHOUT MANY individuals who have supported the Epilepsy Centers of Excellence (ECoE) and encouraged the creation of this manual. Foremost are the authors of the various chapters. They have updated and revised the chapters, and it is their work that makes this book as valuable as it is. Dr. Donald Higgins, National Director for Neurology, must be recognized as a visionary and leader, and it is his support and wisdom that has allowed the ECoE to thrive. Dr. Paul Rutecki, the extremely hard-working and dedicated National Director of the ECoE, must be thanked for his optimism, encouragement and leadership. Dr. Marc Dichter, Chair of the ECoE Advisory Board, has been an advocate for the creation and continuation of the ECoE, and together with the other members of the ECoE Advisory Board has continued to provide invaluable direction. Mr. Andrew David, Administrative Director of the Northeast ECoE, has helped keep the ECoE function in the absence of a National Administrative Director. Finally, we wish to thank Dr. Pamela Kelly, Administrative Director of the Southeast ECoE, who keeps a laser sharp focus on the mission before us and makes sure we are constantly moving to improve the care we provide Veterans. Moreover, without her constant encouragement we would never have been able to meet the publication deadlines required to complete this project.



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## ABBREVIATIONS

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<b>ABG</b>	arterial blood gas	<b>DOD</b>	Department of Defense
<b>AB rating</b>	FDA therapeutic equivalence codes for generic formulations of drugs	<b>DR</b>	delayed-release formulation
<b>ADA</b>	Americans with Disabilities Act of 1990	<b>DRE</b>	drug-resistant epilepsy
<b>ADC</b>	apparent diffusion coefficient	<b>DSM</b>	Diagnostic and Statistical Manual of Mental Disorders
<b>ADH</b>	antidiuretic hormone	<b>DSS</b>	Decision Support System
<b>ADHD</b>	attention deficit hyperactivity disorder	<b>DTI</b>	diffusion tensor imaging
<b>AED</b>	antiepileptic drug	<b>DWI</b>	diffusion-weighted imaging
<b>AEDs</b>	antiepileptic drugs	<b>DXA</b>	dual energy x-ray absorptiometry
<b>AFHSC</b>	Armed Forces Health Surveillance Center	<b>ECD</b>	ethyl cysteinate dimer (imaging contrast agent)
<b>AMPA</b>	a non-NMDA glutamate receptor ligand	<b>ECG (EKG)</b>	electrocardiogram
<b>APOE</b>	apolipoprotein E	<b>ECI</b>	electrocerebral inactivity
<b>ATL</b>	anterior temporal lobectomy	<b>ECoE</b>	Epilepsy Centers of Excellence
<b>AUC</b>	area under the curve	<b>ECT</b>	electroconvulsive therapy
<b>AVM</b>	arteriovenous malformations	<b>EEG</b>	electroencephalogram, electroencephalography
<b>BC</b>	birth control (usually pills)	<b>EMG</b>	electromyogram, electromyography
<b>BDI</b>	Beck Depression Inventory	<b>EMU</b>	epilepsy monitoring unit
<b>BECTS</b>	benign childhood epilepsy with centro-temporal spikes	<b>EPC</b>	epilepsia partialis continua
<b>BETS</b>	benign epileptiform sharp transients of sleep	<b>EPTS</b>	early post-traumatic seizure
<b>BID</b>	twice daily	<b>ER</b>	emergency room
<b>BiPED</b>	bilateral periodic epileptiform discharge	<b>ER</b>	extended-release formulation
<b>BP</b>	blood pressure	<b>ERSET</b>	Early Randomized Surgical Epilepsy Trial
<b>BRFSS</b>	Behavioral Risk Factor Surveillance System	<b>FA</b>	fractional anisotropy
<b>bTBI</b>	blast-related traumatic brain injury	<b>FDA</b>	Food and Drug Administration
<b>C.F.R.</b>	Code of Federal Regulations	<b>FDG</b>	fluorodeoxyglucose, a radiotracer for PET scanning
<b>CAE</b>	childhood absence epilepsy	<b>FIRDA</b>	frontal intermittent rhythmic delta activity
<b>CAM</b>	complementary and alternative medicine	<b>FLAIR</b>	fluid-attenuated inversion recovery
<b>CASES</b>	Canadian Appropriateness Study of Epilepsy Surgery	<b>FLS</b>	frontal lobe seizure
<b>CBC</b>	complete blood count	<b>fMRI</b>	functional MRI
<b>CBF</b>	cerebral blood flow	<b>FT</b>	free testosterone
<b>CBT</b>	cognitive behavioral therapy	<b>FY</b>	fiscal year
<b>CBV</b>	cerebral blood volume	<b>GABA</b>	$\gamma$ -aminobutyric acid
<b>CCM</b>	cerebral cavernous malformations	<b>GAD</b>	glutamic acid decarboxylase
<b>CDW</b>	Corporate Data Warehouse	<b>GAT1</b>	GABA transporter type 1
<b>cEEG</b>	continuous electroencephalogram	<b>GCS</b>	Glasgow Coma Scale
<b>CJD</b>	Creutzfeldt-Jakob disease	<b>GFR</b>	glomerular filtration rate
<b>C<sub>max</sub></b>	maximum (or peak) drug concentration	<b>GI</b>	gastrointestinal
<b>CNS</b>	central nervous system	<b>GMP</b>	good manufacturing process
<b>COPD</b>	chronic obstructive pulmonary disease	<b>GOS</b>	Glasgow Outcome Scale
<b>CPRS</b>	computerized patient record system	<b>GPEDs</b>	generalized periodic epileptiform discharges
<b>CPS</b>	complex partial seizure	<b>GRE</b>	gradient recalled echo
<b>CPSE</b>	complex partial status epilepticus	<b>GTC</b>	generalized tonic-clonic
<b>CSF</b>	cerebrospinal fluid	<b>GTCS</b>	generalized tonic-clonic seizures
<b>CT</b>	computed tomography	<b>HCN</b>	hyperpolarization-activated cation channels
<b>CVSO</b>	County Veteran Service Officer	<b>HIV</b>	human immunodeficiency virus
<b>CYP</b>	cytochrome p450	<b>HMPAO</b>	( <sup>99m</sup> Tc-exametazime) hexamethylpropyleneamine oxime, a radiotracer
<b>DBS</b>	deep brain stimulation	<b>HRT</b>	hormone replacement treatment
<b>DMV</b>	Department of Motor Vehicles	<b>HS</b>	hippocampal sclerosis
		<b>HUD</b>	Housing and Urban Development



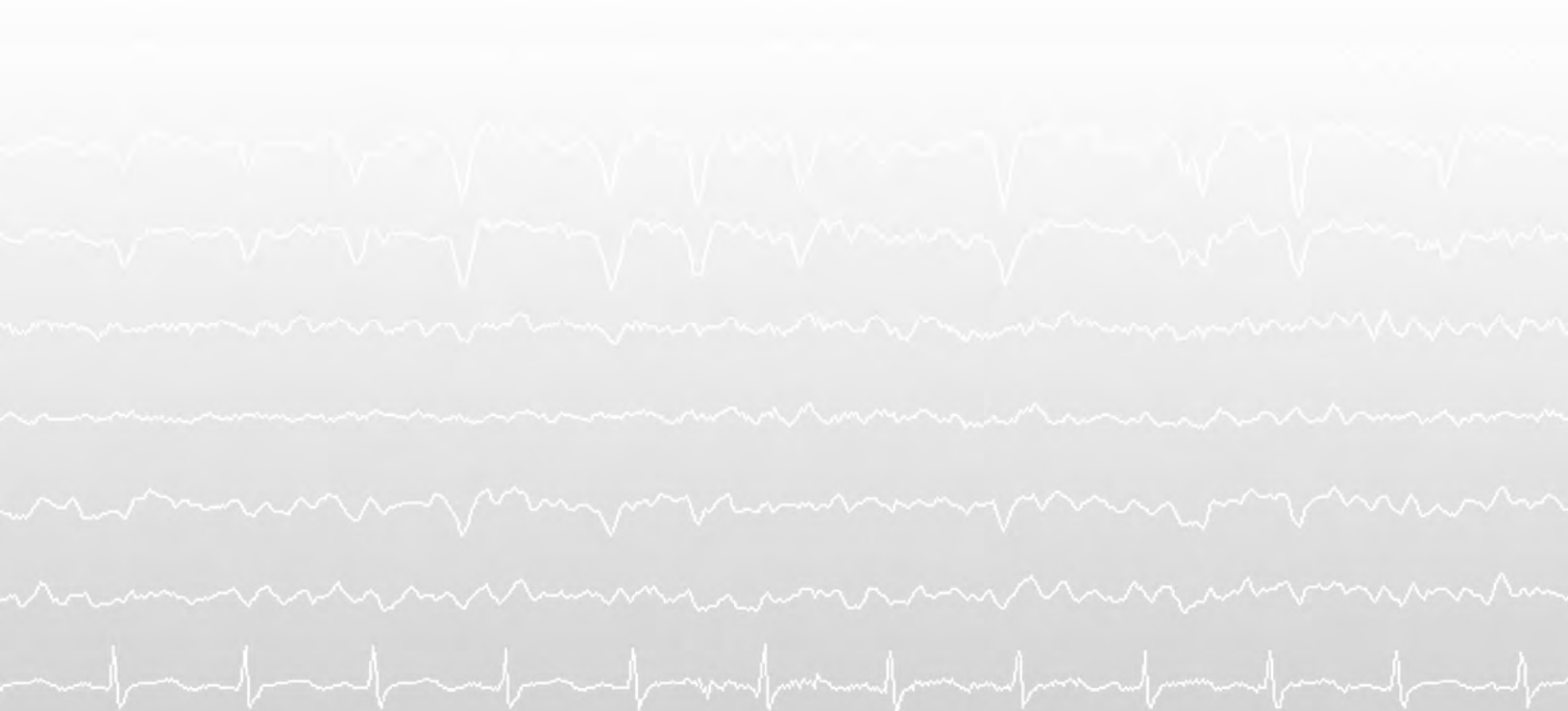
<b>IBE</b>	International Bureau for Epilepsy	<b>PTS</b>	post-traumatic seizure
<b>ICD-9</b>	International Statistical Classification of Diseases	<b>PWE</b>	patients with epilepsy
<b>ICD-9-CM</b>	International Classification of Diseases, Ninth Revision, Clinical Modification	<b>PWWE</b>	pregnant women with epilepsy
<b>ICU</b>	intensive care unit	<b>QOLIE</b>	Quality of Life in Epilepsy
<b>IED</b>	interictal epileptiform discharge	<b>QTc</b>	a cardiac wave interval
<b>Ig</b>	immunoglobulin	<b>REM</b>	rapid eye movement
<b>ILAE</b>	International League Against Epilepsy	<b>RMTD</b>	rhythmic midtemporal theta bursts of drowsiness
<b>IM</b>	intramuscular	<b>RNS</b>	responsive neurostimulation
<b>IOM</b>	Institute of Medicine	<b>RSE</b>	refractory status epilepticus
<b>IPTS</b>	immediate post-traumatic seizure	<b>SE</b>	status epilepticus
<b>IV</b>	intravenous	<b>SGE</b>	symptomatic generalized epilepsy
<b>JME</b>	juvenile myoclonic epilepsy	<b>SGS</b>	partial onset seizure with secondary generalization
<b>LFT</b>	liver function tests	<b>SGTCS</b>	secondarily generalized tonic-clonic seizures
<b>LGS</b>	Lennox-Gastaut syndrome	<b>SHBG</b>	sex hormone-binding globulin
<b>LH</b>	luteinizing hormone	<b>SIADH</b>	syndrome of inappropriate antidiuretic hormone
<b>LOC</b>	loss of consciousness	<b>SJS</b>	Stevens-Johnson syndrome
<b>LPTS</b>	late post-traumatic seizure	<b>SLRE</b>	symptomatic location-related epilepsy
<b>MAO</b>	monoamine oxidase	<b>SMA</b>	supplementary sensorimotor area
<b>MEG</b>	magnetoencephalography	<b>SMR</b>	standardized mortality ratio
<b>MRI</b>	magnetic resonance imaging	<b>SPECT</b>	single-photon emission computed tomography
<b>MSTs</b>	multiple subpial transections	<b>SPS</b>	simple partial seizure
<b>MTLE</b>	mesial temporal lobe epilepsy	<b>SREDA</b>	subclinical rhythmic electrographic discharge of adults
<b>MTS</b>	mesial temporal sclerosis	<b>SSMA</b>	supplementary sensorimotor area
<b>MTT</b>	mean contrast passage time	<b>SSRI</b>	selective serotonin reuptake inhibitor
<b>MVI</b>	multivitamin	<b>SSS</b>	small sharp spike
<b>NAEC</b>	National Association of Epilepsy Centers	<b>STEMI</b>	ST-elevation myocardial infarction
<b>NCSE</b>	nonconvulsive status epilepticus	<b>SUDEP</b>	sudden unexpected (or unexplained) death in epilepsy
<b>NDDI-E</b>	Neurologic Depressive Disorders Inventory for Epilepsy	<b>SV2A</b>	synaptic vesicle protein 2A
<b>NMDA</b>	<i>N</i> -methyl-D-aspartate, a glutamate receptor ligand	<b>SWI</b>	susceptibility-weighted imaging
<b>OC</b>	oral contraceptive	<b>TBI</b>	traumatic brain injury
<b>OCs</b>	oral contraceptives	<b>TCA</b>	tricyclic antidepressant
<b>OEF</b>	Operation Enduring Freedom	<b>TEN</b>	toxic epidermal necrolysis
<b>OIF</b>	Operation Iraqi Freedom	<b>TIRDA</b>	temporal intermittent rhythmic delta activity
<b>OIRDA</b>	occipital intermittent rhythmic delta activity	<b>TLE</b>	temporal lobe epilepsy
<b>OND</b>	Operation New Dawn	<b>TMS</b>	transcranial magnetic stimulation
<b>OR</b>	operating room	<b>TR and TE</b>	T2-weighted images
<b>P/Q</b>	type high-voltage activated calcium channels	<b>TTP</b>	peak attenuation
<b>PBM</b>	pharmacy benefits manager	<b>UGT</b>	UDP glucuronosyltransferase enzymes
<b>PCI</b>	percutaneous coronary intervention	<b>VANF</b>	VA National Formulary
<b>PET</b>	positron emission tomography	<b>VA</b>	Veterans Administration
<b>PICC</b>	peripherally inserted central catheter	<b>VBA</b>	Veterans Benefits Administration
<b>PLEDs</b>	periodic lateralized epileptiform discharges	<b>VEM</b>	video-EEG monitoring
<b>PLEX</b>	plasma exchange	<b>VET</b>	video-electroencephalographic telemetry monitoring
<b>PNEA</b>	psychogenic nonepileptic attacks	<b>VHA</b>	Veterans Health Administration
<b>PNES</b>	psychogenic nonepileptic seizure	<b>VHIS</b>	Vietnam Head Injury Study
<b>POW</b>	prisoner of war	<b>VISN</b>	Veterans Integrated Service Networks
<b>PR</b>	a cardiac wave interval	<b>VNS</b>	vagal nerve stimulator, stimulation
<b>PRIS</b>	propofol infusion syndrome	<b>VSO</b>	Veteran Service Officer
<b>PRL</b>	prolactin serum level	<b>VSSC</b>	VHA Support Service Center
<b>PTBI</b>	penetrating traumatic brain injury	<b>WBC</b>	white blood cell
<b>PTE</b>	post-traumatic epilepsy	<b>WHO</b>	World Health Organization
<b>PTSD</b>	post-traumatic stress disorder	<b>WWE</b>	women with epilepsy

department of veterans affairs  
epilepsy manual



# Classification of Seizures and Epilepsy Syndromes

**ALFRED T. FRONTERA, JR.**



# Introduction

An epileptic seizure is defined as a transient occurrence of signs and/or symptoms that are caused by abnormal excessive or synchronous neuronal activity in the brain.<sup>1</sup> Epilepsy has traditionally been defined as the occurrence of two or more unprovoked epileptic seizures. The term “unprovoked” is meant to emphasize the fact that recurrent seizures in the setting of an acute (and presumably reversible) systemic or neurologic insult do not qualify as epilepsy. “Provoked” could include patients who suffer recurrent seizures in the setting of toxic-metabolic insults such as alcohol withdrawal, cocaine intoxication, or hyponatremia—all acute symptomatic seizures but not of epilepsy. If the respective toxic-metabolic insults are removed, these patients will no longer have seizures.

The ILAE and the IBE have recommended an amended definition of epilepsy as a disorder of the brain “characterized by an enduring predisposition to generate epileptic seizures.”<sup>1</sup> This new definition removes the traditional requirement for recurrent seizures and also the requirement that the seizure be “unprovoked.” It instead requires at least one epileptic seizure and the presence of “an enduring epileptogenic abnormality” that increases the likelihood of future seizures as the two key factors in establishing the diagnosis of epilepsy. By this new definition, a patient who has a single secondarily generalized tonic-clonic seizure and is found to have a brain tumor would qualify for the diagnosis of epilepsy. However, a patient with a single generalized tonic-clonic seizure and normal brain imaging would not. This new definition also emphasizes the key point that epilepsy is not one homogeneous condition but rather a diverse family of disorders that share in common an increased predisposition to epileptic seizures.

Given the heterogeneity of the myriad pathologic conditions that can cause seizures and epilepsy, it is crucial that clinicians have a system by which to classify epileptic seizures, epilepsies, and epileptic syndromes. Being able to classify a given patient’s seizure type and, if possible, the epilepsy syndrome, is often the first step toward making the correct diagnosis and providing an accurate prognosis and effective treatment. This chapter focuses on describing the ILAE classification guidelines for epileptic seizures, epilepsies, and epileptic syndromes that were last revised in 1981 and 1989.<sup>2,3</sup> It also briefly discusses some of the more recent proposed changes to these classification guidelines.<sup>4-6</sup>

## Classification of Epileptic Seizures

The ILAE first published a classification system for epileptic seizures in 1970,<sup>7</sup> and it was subsequently revised and last officially updated in 1981.<sup>2</sup> This classification system, which is based on clinical semiology and interictal/ictal EEG findings (TABLE 1.1), divides seizure into the following three types: partial seizures (also termed “focal” or “local”), generalized seizures (absence, myoclonic, clonic, tonic, tonic-clonic, and atonic), and unclassified epileptic seizures. Under this classification, the fundamental distinction between seizure types is based on what portion of the cerebral cortex is involved at seizure onset.

Partial seizures are known or presumed to start in a specific lobe or hemisphere of the brain while generalized seizures are known or presumed to start simultaneously throughout both hemispheres or at least in widespread areas of both hemispheres. Partial or focal seizures are further subcategorized into simple partial seizures or complex partial seizures based on the presence (complex) or absence (simple) of impaired consciousness.

### Partial (Focal, Local) Seizures

#### *Simple Partial Seizures*

Simple partial seizures are caused by the continuous, abnormally excessive, and hypersynchronous firing of a focal, circumscribed population of neurons. By definition, consciousness is not impaired and the symptoms experienced by the patient vary depending on the area of the brain involved in the seizure. When the seizure involves motor pathways, the clinical manifestations are obvious to observers and may consist of either excitatory phenomena (such as clonus, or tonic or dystonic posturing) or inhibitory phenomena, whereby “negative” motor symptoms such as asterixis (also

termed negative myoclonus) may be seen. When vocal motor areas are involved, the patient can present with rhythmic vocalizations or conversely with speech arrest. One classic form of motor seizures is termed the “Jacksonian march.” This occurs when focal motor seizure activity spreads along the motor strip and is observed as clonic movements that “march” from the hand to the ipsilateral arm, shoulder, face, and then leg. When the seizures consist of focal, continuous, rhythmic clonic movements of the face, eyes, tongue, trunk, arms, or legs, it is termed *epilepsia partialis continua* (EPC).

When motor signs are not present, the manifestations of simple partial seizures can be subtle or imperceptible to the outside observer, who must then rely on the patient’s subjective reports. The range of symptoms produced by simple partial seizures is as varied as the brain regions that can be affected. Some of the more common manifestations include numbness and tingling that may also present with a Jacksonian march (postcentral gyrus involvement); special sensory symptoms such as flashes of light or colors in one hemifield (occipital cortex); ringing or buzzing sounds in the ears (transverse temporal or Heschl’s gyrus); noxious tastes (temporal lobe, insula, or parietal operculum) or noxious odors (mesial temporal region), or more complex visual, auditory, gustatory, or olfactory illusions or hallucinations (temporal-parietal-occipital junction association cortices); autonomic symptoms such as sweating, salivation, pallor, flushing, piloerection, pupillary dilatation, palpitations, tachy- or bradycardia, or hyper- or hypotension (insula); or psychic symptoms such as anger, fear, ecstasy, déjà vu, or jamais vu (amygdala, temporal lobe).

The ictal EEG in simple partial seizures may show any of a range of patterns from focal spikes, polyspikes, spike and waves, suppression, or focal rhythmic discharges of any frequency to a completely normal background without evidence of ictal activity. Because approximately 6 cm<sup>2</sup> of synchronously firing cortex must be involved in order for scalp EEG to detect ictal activity,<sup>8,9</sup> it should not be surprising that many focal seizures will be beyond the resolution of scalp EEG, if the ictal focus is too small, too distant, or unfavorably oriented in relation to the electrodes (eg, originating deep in a sulcus) to be detected by scalp recording. In such instances, functional imaging modalities such as cerebral PET scan or SPECT scan, which measure cerebral glucose metabolism and regional cerebral blood flow respectively, may be helpful in confirming the diagnosis. When such studies are performed during ongoing clinical signs or symptoms, increased local glucose metabolism or regional cerebral blood flow would verify the suspected seizure focus.

## **Complex Partial Seizures**

Complex partial seizures are also caused by abnormal, excessive, synchronous firing of a localized group of neurons. Similar clinical signs and symptoms as those described for simple partial seizures may be present in complex partial seizures and vary depending on the location of the seizure focus. The essential additional feature that defines and distinguishes complex partial seizures is the presence of impaired consciousness. Impaired consciousness is generally defined as the loss of awareness of external stimuli or the inability to respond to it in a purposeful and appropriate manner.

Practically, awareness is assessed by determining whether or not the patient recalls the events that occurred during the ictal period, while responsiveness is assessed by testing the patient’s ability to follow commands and interact in a meaningful way with an outside observer during the ictal event. Of note, care should be taken to distinguish between complex partial seizures and simple partial aphasic seizures, where the patient is aware of events going on around her and can interact appropriately but cannot produce speech. With the impaired consciousness of complex partial seizures, the patient is often unable to report any subjective symptoms caused by the ongoing seizures. Thus, if motor symptoms are not present, the only obvious clinical correlate may be the patient’s altered awareness, which is often subtle and under-recognized. Because a significant amount of cortex (ie, greater than 6 cm<sup>2</sup>)<sup>8,9</sup> is typically involved in order to produce impaired consciousness, complex partial seizures have an ictal correlate on scalp EEG. The ictal footprint is variable and may consist of focal spikes, polyspikes, spike waves, suppression, or focal rhythmic discharges of any frequency.

## **Partial Seizures Evolving to Generalized Tonic-Clonic Convulsions (Secondarily Generalized Tonic-Clonic Seizures [SGTCS])**

When seizure activity starts focally (as seen with either simple or complex partial seizures) but then spreads to involve widespread areas of both hemispheres, this is termed secondary generalization, and such seizures are considered a

TABLE 1.1 1981 ILAE Classification of Epileptic Seizures

1. PARTIAL (FOCAL, LOCAL) SEIZURES	
CLINICAL SEIZURE TYPE	EEG SEIZURE TYPE
<p><b>A. Simple partial seizures (consciousness not impaired)</b></p> <ol style="list-style-type: none"> <li>1. With motor signs               <ol style="list-style-type: none"> <li>a. Focal motor without march</li> <li>b. Focal motor with march (Jacksonian)</li> <li>c. Versive</li> <li>d. Postural</li> <li>e. Phonatory (vocalization or arrest of speech)</li> </ol> </li> <li>2. With somatosensory or special sensory symptoms (simple hallucinations, eg, tingling, light flashes, buzzing)               <ol style="list-style-type: none"> <li>a. Somatosensory</li> <li>b. Visual</li> <li>c. Auditory</li> <li>d. Olfactory</li> <li>e. Gustatory</li> <li>f. Vertiginous</li> </ol> </li> <li>3. With autonomic symptoms or signs (including epigastric sensation, pallor, sweating, flushing, piloerection, and pupillary dilation)</li> <li>4. With psychic symptoms (disturbance of higher cerebral function); these symptoms rarely occur without impairment of consciousness and are much more commonly experienced as complex partial seizures               <ol style="list-style-type: none"> <li>a. Dysphasic</li> <li>b. Dysmnesic (eg, déjà vu)</li> <li>c. Cognitive (eg, dreamy states, distortions of time sense)</li> <li>d. Affective (eg, fear, anger)</li> <li>e. Illusions (eg, macropsia)</li> <li>f. Structured hallucinations (eg, music, scenes)</li> </ol> </li> </ol>	<p>Local contralateral discharge starting over the corresponding area of cortical representation (not always recorded on the scalp)</p>
<p><b>B. Complex partial seizures (with impairment of consciousness; may sometimes begin with simple symptomatology)</b></p> <ol style="list-style-type: none"> <li>1. Simple partial onset followed by impairment of consciousness               <ol style="list-style-type: none"> <li>a. With simple partial features (A1 to A4) followed by impaired consciousness</li> <li>b. With automatisms</li> </ol> </li> <li>2. With impairment of consciousness at onset               <ol style="list-style-type: none"> <li>a. With impairment of consciousness only</li> <li>b. With automatisms</li> </ol> </li> </ol>	<p>Unilateral or, frequently, bilateral discharge, diffuse or focal in temporal or frontotemporal regions</p>
<p><b>C. Partial seizures evolving to secondarily generalized seizures (this may be generalized tonic-clonic, tonic, or clonic)</b></p> <ol style="list-style-type: none"> <li>1. Simple partial seizures (A) evolving to generalized seizure</li> <li>2. Complex partial (B) evolving to generalized seizure</li> <li>3. Simple partial seizures evolving to complex partial seizures evolving to generalized seizure</li> </ol>	<p>Above discharges become secondarily and rapidly generalized</p>

Source: Commission on Classification and Terminology of the International League Against Epilepsy. Proposal for revised clinical and electrographic classification of epileptic seizures. *Epilepsia*. 1981;22:489-501. Reproduced with permission from John Wiley & Sons Publications.

TABLE 1.1 1981 ILAE Classification of Epileptic Seizures (Continued)

2. GENERALIZED SEIZURES (CONVULSIVE OR NONCONVULSIVE)		
CLINICAL SEIZURE TYPE	EEG SEIZURE TYPE	EEG INTERICTAL EXPRESSION
<p><b>A1. Absence seizures</b></p> <ul style="list-style-type: none"> <li>a. Impairment of consciousness only</li> <li>b. With mild clonic components</li> <li>c. With atonic components</li> <li>d. With tonic components</li> <li>e. With automatisms</li> <li>f. With autonomic components</li> </ul> <p><i>(b-f may be used alone or in combination)</i></p>	Usually regular and symmetrical 3 Hz, but may be 2-4 Hz spike-slow-wave complexes and may have polyspike-slow-wave complexes; abnormalities are bilateral	Background activity usually normal, although paroxysmal activity (such as spikes or spike-slow-wave complexes) may occur; this activity is usually regular and symmetrical
<p><b>A2. Atypical absence seizures</b></p> <p>May have:</p> <ul style="list-style-type: none"> <li>a. Changes in tone that are more pronounced than in A1</li> <li>b. Onset and/or cessation that is not abrupt</li> </ul>	EEG more heterogeneous, may include irregular spike-wave complexes, fast activity or other paroxysmal activity; abnormalities are bilateral but often irregular and asymmetrical	Background usually abnormal paroxysmal activity (such as spikes or spike-slow-wave complexes) frequently irregular and asymmetrical
<p><b>B. Myoclonic seizures</b></p> <p>Myoclonic jerks (single or multiple)</p>	Polyspike and wave or sometimes spike and wave or sharp and slow waves	Same as ictal
<p><b>C. Clonic seizures</b></p>	Fast activity (10 cycles/s or more) and slow waves; occasional spike-wave patterns	Spike and wave or polyspike and wave discharges
<p><b>D. Tonic seizures</b></p>	Low-voltage, fast activity or a fast rhythm of 9-10 cycles/s, decreasing in frequency and increasing in amplitude	More or less rhythmic discharges of sharp and slow waves, sometimes asymmetrical; background often abnormal for age
<p><b>E. Tonic-clonic seizures</b></p>	Rhythm at >10 cycles/s decreasing in frequency and increasing in amplitude during tonic phase; interrupted by slow waves during clonic phase	Polyspike and waves or spike and wave or, sometimes, sharp- and slow-wave discharges
<p><b>F. Atonic seizures (astatic)</b></p>	Polyspikes and wave or flattening or low-voltage fast activity	Polyspikes and slow wave
<i>Combinations of the above may occur, eg, B and F, B and D</i>		

Source: Commission on Classification and Terminology of the International League Against Epilepsy. Proposal for revised clinical and electrographic classification of epileptic seizures. *Epilepsia*. 1981;22:489-501. Reproduced with permission from John Wiley & Sons Publications.



subtype of partial seizures. If observed either clinically or electrographically early in its course, localizing or lateralizing signs may be present that verify the focal onset of the seizures. However, if the patient is not observed until after the generalization has already occurred, distinguishing these seizures from generalized tonic-clonic seizures (see typical clinical description below) can be challenging. In such cases, historical features such as history and semiology of past seizures, age of seizure onset, family history of epilepsy, interictal and/or ictal EEG findings, and brain imaging studies often provide critical diagnostic information which helps cinch the diagnosis. The importance of distinguishing secondarily generalized tonic-clonic seizures from generalized onset tonic-clonic seizures cannot be overemphasized; the distinction has important diagnostic, prognostic, and treatment implications.

## Generalized Seizures

### Absence Seizures

The ILAE recognizes six subgroups of absence seizures (TABLE 1.1):

- With impairment of consciousness only
- With mild clonic components
- With atonic components
- With tonic components
- With automatisms
- With autonomic components

In the first type, also termed simple absence seizures, the hallmark manifestation is the abrupt onset and offset of impaired consciousness. Classically, this is noted as staring and behavioral arrest. The seizures characteristically last from 2 to 30 seconds, during which time the patient is unaware of the surrounding environment and unresponsive to it. The patient has neither a warning (aura) that the seizure is about to occur nor postictal confusion or lethargy, and is therefore usually unaware of the seizure. At the cessation of the seizure, the patient will often return to the previous activity as if nothing had happened. The latter five subtypes are often termed complex typical absence seizures.

As their names suggest, these subgroups include all of the features described above with the addition of clonic, tonic, myoclonic, or automatic motor activity, or autonomic symptoms. Usually, the clonic movements are subtle and involve the eyelids, corner of the mouth, or upper extremities, often at a frequency of 3 Hz. Myoclonic jerks may be seen in the axial and appendicular muscles. Atonic activity may manifest as a subtle head drop or slumping forward of the trunk with loss of tone in the arms and hands that causes the patient to drop items they were holding at the start of the seizure. Of note, falls are uncommon with absence seizures with atonic components. Tonic components, if present, can be seen in the facial, neck, and axial muscles and cause neck extension and arching at the trunk (retropulsion). Automatisms are defined as “more or less coordinated, repetitive motor activities usually occurring when consciousness is impaired and for which the subject is usually amnesic afterward. They often resemble voluntary movements and may consist of an inappropriate continuation of ongoing pre-seizure motor activity” (2001 definitions). Automatic features seen with absence seizures include chewing, lip smacking, hand fumbling, picking, or scratching type movements (oromotor or manual automatisms). Autonomic features include tachycardia, pallor, flushing, sweating, piloerection, salivation, mydriasis, or urinary incontinence.

Absence seizures can be precipitated by prolonged hyperventilation (3 to 5 minutes) in about 90% of untreated patients, and photic stimulation may provoke them as well. The classic EEG finding in typical absence seizures is generalized 3 Hz spike-and-wave activity (range 2.5-4 Hz). However, generalized polyspike and wave may also be seen. The intradischarge frequency is classically constant but may vary over the course of the seizure.<sup>10</sup>

### Atypical Absence Seizures

Atypical absence seizures are usually seen in patients with symptomatic generalized or cryptogenic epilepsies such as the Lennox-Gastaut syndrome (LGS), myoclonic-astatic epilepsy (Doose syndrome), and epilepsy with continuous spikes and waves during sleep. These patients usually have some degree of baseline cognitive impairment and suffer

from other seizure types such as myoclonic, tonic, and atonic seizures in addition to the atypical absence seizures. The seizures manifest with some degree of impaired consciousness, which may be difficult to detect due to an already abnormal baseline cognition. In contrast to typical absence seizures, in atypical absences, the onsets and offsets are clinically less abrupt and distinct and the seizures are longer in duration (lasting up to minutes). Additionally, changes in tone are more prominent than in typical absence seizures. The ictal EEG shows slow (<2.5 Hz) generalized spike-and-wave complexes, which may be more irregular and asymmetric than what is classically seen in typical absence seizures.

## **Myoclonic Seizures**

Myoclonic seizures are characterized by brief, shock-like muscle contractions that occur at irregular intervals. Typically the jerks are synchronous and symmetric involving the whole body (face, head, trunk, and extremities) simultaneously. However, they can also be asymmetric and focal, being confined to the head or trunk alone or even individual limbs, muscles, or groups of muscles. They can occur as a single, isolated jerk or as multiple irregularly repetitive jerks and are not associated with an alteration of consciousness. They are typically worse in the late evening or early morning, either prior to going to sleep or soon after awakening. The classic EEG pattern in myoclonic seizures consists of irregular bursts of generalized, bisynchronous polyspikes and polyspike-waves at a frequency of 2 to 5 Hz that precede and are time-locked with the observed myoclonic jerks. Negative myoclonus refers to an apparent jerk that is caused by the brief loss of postural tone when the body part is held against gravity. This is sometimes also termed asterixis.

## **Clonic Seizures**

Clonic seizures are characterized by repetitive, rhythmic, synchronous muscle contractions of the whole body (face, head, trunk, and limbs). They are associated with altered awareness, and it is this feature along with the metronome-like regularity and rhythmicity of the muscle contractions that distinguishes them from myoclonic seizures. Some investigators propose that when clonic seizures occur in isolation, their mechanisms may be different from those of the clonic phase seen in generalized tonic-clonic seizures. In the former, the repetitive clonic movements are thought to be the result of rhythmic excitatory discharges, whereas in the latter, the clonic movements are thought to result from the interruption of tetanic contraction caused by the activation of seizure-suppressing mechanisms.<sup>5</sup> The ictal EEG pattern of clonic seizures typically consists of generalized, synchronous spikes or spike-wave complexes time-locked with the clinical movements.

## **Tonic Seizures**

Tonic seizures are most commonly seen in patients with Lennox-Gastaut syndrome, one of the symptomatic “generalized” epilepsies. Tonic seizures are usually brief, typically lasting 5 to 20 seconds, and range from being so subtle as to go unnoticed by caregivers to dramatic clinical events similar to the tonic phase described below in the section on generalized tonic-clonic seizures. The more subtle forms may involve only upward deviation of the eyes or brief but sustained contractions of the neck, facial, or masticatory musculature (termed axial tonic seizures). Usually these consist of flexion of the head at the neck, opening of the mouth, and grimacing of the facial muscles. When the abdominal and diaphragmatic muscles are involved, the patient may produce an “ictal cry” or may have brief periods of apnea. Global tonic seizures occur when both axial and appendicular musculature are involved, and characteristically consists of the axial features discussed plus abduction of the arms at the shoulders and flexion at the elbows with lower extremities, which are either in flexion at the hip, knees, and ankles or in extension at these joints. Intermediate forms of tonic seizures also exist where, in addition to axial involvement, only the proximal muscles of the upper extremities are affected (axorhizomelic tonic seizures).

Tonic seizures tend to cluster and are more common during non-REM sleep. The electrographic appearance of tonic seizures consists of moderate to high amplitude, frontally predominant, generalized 10-25 Hz spikes, sometimes termed generalized paroxysmal fast activity. A second ictal tonic EEG pattern consists of an abrupt, generalized attenuation or flattening of the background EEG activity (to less than 5 to 10  $\mu$ V) that can be the sole manifestation of the ictal activity or can precede the development of 10 to 25 Hz generalized spikes (generalized paroxysmal fast activity).

## **Tonic-Clonic Seizures**

Tonic-clonic seizures are characterized by loss of consciousness and a repetitive, stereotyped sequence of bilateral stiffening of the face, trunk, and extremities (the tonic phase), alternating with repetitive, symmetric clonic contractions in the face, trunk, and extremities (the clonic phase). Typically, the tonic phase starts with a brief period of flexion where the eyes are open and rotate upward and the neck, trunk, and extremities are in some degree of flexion. Classically, the arms are elevated, adducted, and externally rotated, and the legs are less notably flexed at hips and knees, adducted, and externally rotated. The mouth may be held in a rigid, half-open position. The tonic extension phase follows this and consists of more pronounced neck and back extension with the arms and legs also moving into extension. At this point, forced closure of the mouth may produce oral trauma. The arms may remain flexed to some degree at the elbows or may show complete extension, with some degree of internal rotation at the shoulders and pronation at the elbows. The patient's wrists may be extended with fists clenched, or the wrists may be flexed with fingers extended. Legs are usually extended, adducted, and externally rotated with feet and big toes extended as well. During the tonic phase, the diaphragm also contracts which may produce a characteristic "ictal cry." This is then followed by the clonic phase in which the generalized tonic muscle contraction is replaced by synchronous, rhythmic jerking movements of the face, trunk, and limbs. The tongue may also be bitten during this period, and rhythmic ictal vocalizations may be heard. As the clonic phase progresses, the rhythmic contractions are seen to occur with decreasing force, amplitude, and frequency. Of note, contraction of the urinary sphincter prevents urinary incontinence, which occurs only after the end of the clonic phase. Fecal incontinence and ejaculation are rare phenomena.

Electrographically, the seizures characteristically begin with a flattening of the normal background rhythms, followed by generalized low-voltage fast activity or polyspikes, which increase in amplitude and decrease in frequency until these patterns become obscured by muscle and movement artifact. As the seizure clinically moves into the clonic phase, the EEG characteristically shows a checkerboard type pattern of muscle artifact corresponding to the rhythmic jerking movements observed clinically. During breaks between seizures, the EEG will show diffuse suppression of cerebral activity.

## **Atonic Seizures**

In contrast to tonic seizures—which are characterized by the sudden onset of sustained, increased muscle tone—atonic seizures consist of the sudden loss of muscle tone. This loss of tone is usually very brief, lasting 1 to 2 seconds, and may affect the neck, jaw, trunk, or limb musculature. A brief loss of consciousness occurs corresponding to the loss of motor tone but there is usually minimal postictal confusion. Clinically, the manifestations of these seizures range from subtle head drops to injurious falls. Atonic seizures are very common in patients with Lennox-Gastaut syndrome and are a prominent feature in patients with myoclonic-astatic epilepsy (Doose syndrome). The ictal EEG during atonic seizures typically shows either a generalized polyspike and wave or generalized slow wave followed by diffuse suppression or low-voltage paroxysmal fast activity (rhythmic 10 to 25 Hz activity).

## **Unclassified Epileptic Seizures**

This category was created by the ILAE to include seizure types that cannot be classified due to insufficient data or which do not fit into any of the categories described above. Examples given in the original ILAE document include neonatal seizures such as rhythmic eye movements, chewing, and swimming movements.<sup>2</sup>

# **Classification of Epilepsies and Epileptic Syndromes**

In its 1989 report "Proposal for Revised Classification of Epilepsies and Epileptic Syndromes," the ILAE defines an epileptic syndrome as "an epileptic disorder characterized by a cluster of signs and symptoms customarily occurring

together; these include such items as type of seizure, etiology, anatomy, precipitating factors, age of onset, severity, chronicity, diurnal and circadian cycling and sometimes prognosis.”<sup>3</sup> This report identified over 25 specific epileptic syndromes and classified them along two main axes. The first axis separates epilepsies with generalized seizures (generalized epilepsy) from epilepsies with partial or focal seizures (localization-related, partial, or focal epilepsies). Based on these criteria, this classification identifies four main categories:

- Localization-related (focal, local, or partial) epilepsies and syndromes
- Generalized epilepsies and syndromes
- Epilepsies and syndromes undetermined whether focal or generalized
- Special syndromes

The second axis then subcategorizes the epilepsies in each of these four groups based on etiology or presumed etiology as idiopathic, symptomatic, or cryptogenic (TABLE 1.2).

Idiopathic refers to a group of epilepsies and syndromes that are defined by age-related onset, clinical, and EEG characteristics and a presumed genetic etiology. Classically the idiopathic epilepsies are not associated with structural brain abnormalities or abnormal neurologic signs or symptoms. In contrast, symptomatic epilepsies and syndromes are considered the consequence of a known central nervous system disorder, classically a structural CNS lesion such as an heterotopia, stroke, or tumor.

Cryptogenic is a term that refers to an epilepsy or syndrome that is presumed to be symptomatic, but the presumed lesion cannot be definitively identified or proven. In the age of higher-resolution MRI, many patients whose epilepsies or syndromes were previously classified as cryptogenic can now be reclassified as symptomatic. It is beyond the scope of this article to discuss all of the known or proposed epilepsies and epileptic syndromes in detail, but in the following section the four major subdivisions and some of the more common epilepsies and epileptic syndromes are discussed.

## **Localization-related (Focal, Local, Partial) Epilepsies and Syndromes**

### ***Idiopathic Localization-related Epilepsies and Syndromes***

The idiopathic localization-related epilepsies are childhood-onset disorders characterized by partial (focal) seizures and focal abnormalities on EEG. As with all idiopathic epilepsies, they are presumed to have a genetic basis, and frequently a family history of the epilepsy syndrome is present. The patients typically have normal neurological exams, normal brain imaging studies, and a good prognosis, with most patients experiencing a spontaneous remission of their seizures after childhood.

### **BENIGN CHILDHOOD EPILEPSY WITH CENTRO-TEMPORAL SPIKES (BECTS)**

Previously termed “Rolandic epilepsy” this is the most common idiopathic localization-related epilepsy syndrome. Seizures typically begin between 7 and 10 years of age (range 1 to 14 years) and consist of nocturnal simple partial sensorimotor seizures in which the child complains of numbness or tingling in the face that often progresses to clonic face twitching. The hand and arm can also be involved. Commonly the child may be unable to speak, but comprehension and awareness are not impaired. Secondarily generalized seizures can occur in approximately half the patients with this disorder and is often what brings them to a physician’s attention. These patients are otherwise neurologically normal with normal brain imaging.

EEG often helps cinch the diagnosis and classically shows diphasic spike waves or sharp waves over the central-temporal regions. These spikes or sharps can be unilateral but are more commonly seen independently over the bilateral central-temporal regions. Not all patients require treatment but partial antiepileptic drugs such as carbamazepine are usually started for children with frequent partial seizures or a history of secondarily generalized tonic-clonic seizures. The prognosis for these patients is excellent, the vast majority having complete resolution of their seizures by age 16.

TABLE 1.2 1989 ILAE Classification of Epilepsies and Epileptic Syndromes

<p><b>1. Localization-related (focal, local, partial) epilepsies and syndromes</b></p> <p>1.1 Idiopathic (with age-related onset) At present, the following syndromes are established, but more may be identified in the future:</p> <ul style="list-style-type: none"> <li>▪ Benign childhood epilepsy with central-temporal spike</li> <li>▪ Childhood epilepsy with occipital paroxysms</li> <li>▪ Primary reading epilepsy</li> </ul> <p>1.2 Symptomatic</p> <ul style="list-style-type: none"> <li>▪ Chronic progressive <i>epilepsia partialis continua</i> of childhood (Kojewnikow's syndrome)</li> <li>▪ Syndromes characterized by syndromes with specific modes of precipitation</li> <li>▪ Temporal lobe epilepsies</li> <li>▪ Amygdalohippocampal (mesio basal limbic or rhinencephalic) seizures</li> <li>▪ Lateral temporal seizures             <ul style="list-style-type: none"> <li>▶ Frontal lobe epilepsies</li> <li>▶ Parietal lobe epilepsies</li> <li>▶ Occipital lobe epilepsies</li> </ul> </li> </ul> <p>1.3 Cryptogenic Cryptogenic epilepsies are presumed to be symptomatic and the etiology is unknown. This category thus differs from the previous one by the lack of etiological evidence.</p> <p><b>2. Generalized epilepsies and syndromes:</b></p> <p>2.1 Idiopathic (with age-related onset—listed in order of age)</p> <ul style="list-style-type: none"> <li>▪ Benign neonatal familial convulsions</li> <li>▪ Benign neonatal convulsions</li> <li>▪ Benign myoclonic epilepsy in infancy</li> <li>▪ Childhood absence epilepsy (pyknolepsy)</li> <li>▪ Juvenile absence epilepsy</li> <li>▪ Juvenile myoclonic epilepsy (impulsive petit mal)</li> <li>▪ Epilepsy with grand mal (GTCS) seizures on awakening</li> <li>▪ Other generalized idiopathic epilepsies not defined above</li> <li>▪ Epilepsies with seizures precipitated by specific modes of activation</li> </ul>	<p>2.2 Cryptogenic or symptomatic (in order of age)</p> <ul style="list-style-type: none"> <li>▪ West syndrome (infantile spasms, Blitz-Nick-Salaam Krampfe)</li> <li>▪ Lennox-Gastaut syndrome</li> <li>▪ Epilepsy with myoclonic-astatic seizures</li> <li>▪ Epilepsy with myoclonic absences</li> </ul> <p>2.3 Symptomatic</p> <p>2.3.1 Nonspecific etiology</p> <ul style="list-style-type: none"> <li>▪ Early myoclonic encephalopathy</li> <li>▪ Early infantile epileptic encephalopathy with suppression burst</li> <li>▪ Other symptomatic generalized epilepsies not defined above</li> </ul> <p>2.3.2 Specific syndromes</p> <ul style="list-style-type: none"> <li>▪ Epileptic seizures may complicate many disease states. Under this heading are included diseases in which seizures are a presenting or predominant feature.</li> </ul> <p><b>3. Epilepsies and syndromes undetermined whether focal or generalized</b></p> <p>3.1 With both generalized and focal seizures</p> <ul style="list-style-type: none"> <li>▪ Neonatal seizures</li> <li>▪ Severe myoclonic epilepsy in infancy</li> <li>▪ Epilepsy with continuous spike-waves during slow-wave sleep</li> <li>▪ Acquired epileptic aphasia (Landau-Kleffner syndrome)</li> <li>▪ Other undetermined epilepsies not defined above</li> </ul> <p>3.2 Without unequivocal generalized or focal features. All cases with generalized tonic-clonic seizures in which clinical and EEG findings do not permit classification as clearly generalized or localization related, such as in many cases of sleep grand mal (GTCS) are considered not to have unequivocally generalized or focal features.</p> <p><b>4. Special syndromes</b></p> <p>4.1 Situation-related seizures (Gelegenheitsanfälle)</p> <ul style="list-style-type: none"> <li>▪ Febrile convulsions</li> <li>▪ Isolated seizures or isolated status epilepticus</li> <li>▪ Seizures occurring only when there is an acute metabolic or toxic event due to factors such as alcohol, drugs, eclampsia, nonketotic hyperglycemia.</li> </ul>
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Source: Commission on Classification and Terminology of the International League Against Epilepsy. Proposal for revised classification of epilepsies and epileptic syndromes. *Epilepsia*. 1989;30:389-399. Reproduced with permission from John Wiley & Sons Publications.

## **Symptomatic Localization-related Epilepsies and Syndromes**

The ILAE classification of symptomatic localization-related epilepsies and syndromes is primarily driven by their topographic or anatomic origins. This method of classification does not consider underlying etiology or neuropathology, and this is a criticism of subsequent ILAE work groups on epilepsy and epilepsy syndrome classification that will be discussed later.

### **TEMPORAL LOBE EPILEPSIES**

Temporal lobe epilepsy is the most common type of partial epilepsy, accounting for approximately half of all partial epilepsies and about a third of all epilepsies (partial, generalized, and undetermined combined). Patients with temporal lobe epilepsy syndromes may have simple partial seizures, complex partial seizures, secondarily generalized tonic-clonic seizures, or any combination of these different types. The temporal lobe epilepsies are further anatomically subdivided into “amygdalohippocampal seizures” (hippocampal seizures also called mesial or limbic temporal lobe seizures/epilepsy) and “lateral temporal seizures” (also termed neocortical temporal seizures/epilepsy). This distinction is crucial because these two distinct focal epilepsies respond quite differently to medical and surgical treatment. Amygdalohippocampal seizures are commonly medically refractory but have a high probability for cure with resective surgery while lateral temporal seizures do not respond as well to surgery. Undoubtedly this observation belies fundamentally different and distinct etiologies and pathophysiologies of these two entities, which is not addressed by the current classification system.

#### ► ***Amygdalohippocampal Seizures***

Simple partial seizures originating in the amygdalohippocampal or mesial temporal region can consist of autonomic, affective, psychic, and special sensory symptoms such as epigastric rising, fear, déjà vu or jamais vu, and gustatory (metallic taste) and olfactory (rotting eggs or burning rubber) illusions and hallucinations.

The most common of these symptoms is epigastric rising followed by fear. Epigastric rising is often described by patients as a vague sensation of fluttering or butterflies in their stomach which starts in the lower abdomen and spreads upward.

When the ictal activity spreads beyond the mesial temporal structures, a complex partial seizure can result. The typical semiology of a temporal-onset complex partial seizure consists of behavioral arrest often with oromotor automatisms (chewing or lip smacking; picking or fumbling movements of the hands). Hand automatisms are usually ipsilateral to the side of the seizure onset. If the seizure starts in the dominant hemisphere, paraphasias, dysphasias, or speech arrest can be seen. Postictal confusion is common after a complex partial temporal lobe seizure as is lethargy and fatigue. If the seizure spreads beyond the temporal lobe, secondarily generalized tonic-clonic seizures can result. Usually these are heralded by contralateral head and eye version and contralateral dystonic arm and/or leg posturing, which can be helpful in determining lateralization of the seizure onset.

#### ► ***Lateral Temporal Seizures***

Simple partial seizures originating in the lateral temporal region classically consist of auditory illusions or hallucinations. Most commonly these are simple ringing or buzzing sounds, although more complicated auditory hallucinations such as voices or music can occur. If the seizure starts in or spreads to the posterior temporal-parietal-occipital association cortices, formed visual and auditory hallucinations may be seen, although these are rare. Complex partial seizures that start in the lateral temporal area would be similar to those described above for amygdalohippocampal seizures. Secondary generalized tonic-clonic seizures are thought to be more common with seizures that start in the lateral temporal region as compared with those which originate in the amygdalohippocampal region but would be similar to those described above.

### **FRONTAL LOBE EPILEPSIES**

Frontal lobe epilepsy is the second most common type of partial epilepsy, accounting for approximately 30% of all partial epilepsies. Patients with frontal lobe epilepsy syndromes may have simple partial seizures, complex partial seizures,

secondarily generalized tonic-clonic seizures or any combination of these different types. Frontal lobe seizures have many unique features that help to identify this epilepsy syndrome. They tend to be brief (<30 seconds), occur in clusters, often out of sleep, and are not associated with postictal confusion. They can have a variety of motor manifestations depending on the region of the frontal lobe involved. When the precentral (motor) gyrus is involved, these patients typically present with simple focal motor seizures consisting of clonic jerks on the contralateral side of the body. The face and hand are the most commonly affected areas due to their large cortical representation on the motor homunculus. If the seizure activity spreads along the homunculus, the classic Jacksonian march can be seen as described in the earlier section on simple partial seizures. Contralateral versive eye and head movements may be seen if the frontal eye fields and motor cortex controlling the neck are involved. If the motor speech area is involved (Broca's area), speech arrest may occur. Ipsilateral or bilateral symmetric or asymmetric tonic seizures may also be seen when the supplementary sensorimotor area (SMA) is involved in the seizure. This can manifest as abnormal postures such as the "fencing posture," where the head is turned toward the contralateral arm which is raised and extended above the head while the ipsilateral arm is held flexed at the elbow and adducted against the body. Hypermotor seizures may also occur and are characterized by complex motor automatisms such as jumping out of bed, running around, or making bicycling, thrashing, or kicking movements. These bizarre seizures are often accompanied by complex vocalizations such as yelling and cursing, and often the patient will appear terrified. Hypermotor seizures are one of the rare exceptions where a patient can have bilateral motor involvement from a seizure yet have preserved consciousness (but not awareness). One can readily see how these seizures can often be mistaken for psychogenic nonepileptic attacks. Frontal lobe seizures have a propensity for rapid propagation to bilateral cerebral hemispheres, and hence, secondarily generalized seizures are common with this epilepsy syndrome.

## **PARIETAL LOBE EPILEPSY**

Parietal lobe epilepsy accounts for less than 10% of all partial epilepsies. Patients with parietal lobe epilepsy syndromes can have seizures of any type (simple partial, complex partial, or secondarily generalized) depending on how far and wide the seizure activity spreads outside of the parietal lobe. When the seizures are confined to the parietal lobe, simple partial seizures occur. These often present with contralateral sensory symptoms usually described as tingling or a pins and needles sensation. Again, due to their large cortical representation, the face and hand are most often affected. A Jacksonian march may also be seen with these sensory symptoms. If the nondominant parietal region is involved, neglect syndromes can be seen. Likewise, if the seizure involves association cortices (temporal-parietal-occipital junction), complex and bizarre aural and visual hallucinations may occur.

## **OCCIPITAL LOBE EPILEPSY**

Occipital lobe epilepsy also accounts for less than 10% of all partial epilepsies. Again, patients with occipital lobe epilepsy can have any type of seizure (simple partial, complex partial, or secondarily generalized) depending on the degree of spread of the seizure activity to other regions. When the seizures are confined to the occipital lobes, simple partial seizures occur and usually present with elementary visual hallucinations. These elementary visual hallucinations are often positive phenomena such as sparks, flashes, or phosphenes. Less commonly they present as negative phenomena such as a visual field cut or scotoma.

## ***Cryptogenic Localization-related Epilepsies and Syndromes***

Cryptogenic localization-related epilepsies differ from the symptomatic localization-related epilepsies only in that in the cryptogenic cases the cause of the seizures remains unknown. As an example, if a patient with simple partial sensory seizures that are confirmed by EEG were subsequently discovered to have a parietal glioma on brain MRI, she would be categorized as having a symptomatic localization-related epilepsy. In contrast, a patient who presents with the same symptoms but has a normal brain MRI would be classified as having a cryptogenic localization-related epilepsy.

# Generalized Epilepsies and Syndromes

## ***Idiopathic Generalized Epilepsies and Syndromes***

The idiopathic generalized epilepsies typically present starting in the neonatal period and up through late adolescence, depending on the particular syndrome.

They are characterized by seizures that have generalized ictal EEG patterns from the start of the seizure. Typically their EEG signatures consist of rhythmic, repetitive fast (>3 cycles per second) spikes, polyspikes, spikes and waves, or polyspikes and waves. As with all idiopathic epilepsies, they are presumed to have a genetic basis, and a family history of the epilepsy is common. The patients typically have normal neurological exams and normal brain imaging studies. Prognoses vary depending on the particular syndrome.

### **CHILDHOOD ABSENCE EPILEPSY (CAE OR PYKNOLEPSY)**

Childhood absence seizures typically begin between 4 and 10 years of age and consist of frequent typical absence seizures as described above. Seizures typically last on the order of 4 to 20 seconds and occur tens to hundreds of times per day. These patients are neurologically normal with normal brain imaging but may fall behind in school due to these numerous, repetitive “blank-out spells.” EEG is often diagnostic, showing monomorphic, generalized 3-Hz spike-wave complexes during the seizures, which can often be provoked by prolonged hyperventilation. Patients may also have infrequent tonic-clonic seizures. Most patients respond completely to appropriate medications, and in approximately two thirds of patients the seizures remit by puberty. Ethosuximide is commonly used if the child only has typical absence seizures. Valproic acid or lamotrigine is used if the child has absence and occasional generalized tonic-clonic seizures.

### **JUVENILE MYOCLONIC EPILEPSY (JME)**

JME seizures typically begin after puberty and consist of myoclonic jerks typically affecting the bilateral arms and hands. These myoclonic jerks are more common on awakening and are typically overlooked by the patients, who only note that they are clumsy or tend to drop things in the morning. The vast majority of patients (about 90%) will go on to have a generalized tonic-clonic seizure, and this is what brings them to the physician’s attention. Up to a third of patients with JME also have typical absence seizures, but these are not as frequent as is seen with CAE. These patients are neurologically normal with normal brain imaging. Between seizures the EEG may show bursts of generalized fast (>3 Hz) polyspike and wave activity, and during a seizure repetitive generalized fast (>3Hz) polyspike and wave activity is seen, corresponding to the myoclonic jerks. Most patients respond well to appropriate medications, and valproic acid is still considered the first-line drug of choice. If valproic acid cannot be used due to side effects (such as teratogenicity in women of childbearing age), then other broad-spectrum antiepileptic drugs may be used, such as lamotrigine, levetiracetam, topiramate, or zonisamide. The combination of valproic acid and lamotrigine is considered particularly effective for cases that are difficult to control. Drugs used for partial seizures (such as phenytoin, carbamazepine, oxcarbazepine, gabapentin, and pregabalin) should be avoided as they can potentially exacerbate myoclonic and absence seizures. Although the prognosis for seizure control on medications is very good, the vast majority of patients (80% to 90%) require lifelong treatment.

## ***Cryptogenic or Symptomatic Generalized Epilepsies and Syndromes***

The cryptogenic or symptomatic generalized epilepsies and epilepsy syndromes are characterized by generalized seizures secondary to diffuse or multifocal brain abnormalities or injuries such as hypoxic-ischemic brain injury, inborn errors of metabolism, or abnormalities of cortical migration and development. These patients are not neurologically normal. If an underlying etiology is found they are classified as symptomatic. When an underlying diffuse or multifocal abnormality is suspected but cannot be proven, they are classified as cryptogenic. It is interesting to note that while these epilepsies and syndromes may have a genetic predisposition (as in tuberous sclerosis leading to West syndrome), the seizures are not the primary manifestation of the genetic abnormality but rather a secondary consequence of the primary manifestation of the genetic disorder (ie, the tubers).



## **WEST SYNDROME (INFANTILE SPASMS; BLITZ-NICK-SALAAM KRAMPFE)**

In West syndrome, seizures begin between 3 and 12 months of age and consist of clusters of epileptic spasms (also termed “salaam attacks”). Epileptic spasms consist of brief, bilateral, tonic contractions of the axial and appendicular muscles that are slower than myoclonus but faster than tonic seizures, typically lasting on the order of 0.2 to 2 seconds. Classically, they are characterized by abrupt, symmetric, mixed flexion and extension contractions with flexion seen in the neck, trunk, and arms and extension in the legs. They occur in clusters of tens to hundreds of events with multiple clusters per day. If the patients were not neurologically and developmentally abnormal when the epileptic spasms first begin, they quickly become so.

The interictal EEG shows the classic finding of hypsarrhythmia, which consists of a chaotic, high-amplitude background with multifocal spike waves. The ictal EEG during the epileptic spasms shows either diffuse flattening (electrodecrement) or low-amplitude fast activity. The underlying etiologies are multiple and diverse and include almost any kind of prenatal, perinatal, or postnatal injury, including hypoxic-ischemic injury, trauma, encephalitis, cortical malformations, and inborn errors of metabolism.

Prognosis is generally poor but depends on the underlying etiology. Only a minority of patients have normal neurological development, and approximately half to two thirds will go on to develop other seizure types. Those with normal neurological development before the onset of the spasms, and in whom no clear etiology can be found, tend to have more favorable prognoses. The treatment of the spasms consists of either adrenocorticotrophic hormone or vigabatrin. Vigabatrin has been seen to be particularly effective in cases of epileptic spasms secondary to tuberous sclerosis.

## **LENNOX-GASTAUT SYNDROME (LGS)**

LGS seizures typically start between 1 and 7 years of age, and one of the hallmarks of the syndrome is the fact that patients suffer from multiple seizure types. Tonic seizures are the most frequent, followed by atypical absence and atonic seizures. Atonic seizures are particularly devastating as patients often suffer severe injuries from falls associated with these “drop attack” seizures. Clonic, myoclonic, tonic-clonic, and even partial (focal) seizures can also be seen. Children with this disorder are typically mentally retarded. Interictal EEG findings include generalized slowing, multifocal spike waves, and generalized slow spike-and-wave complexes (<3 Hz).

As with West syndrome, the causative etiologies are multiple and diverse, and include hypoxic-ischemic injury, trauma, encephalitis, cortical malformations, and inborn errors of metabolism. LGS often manifests in children who formerly carried the diagnosis of West syndrome, and likely represents the expression of the same underlying pathology in a slightly more mature brain.

As with West syndrome, the prognosis is generally poor but depends largely on the underlying etiology. The seizures seen with LGS are notoriously refractory to medications. Patients are generally treated with broad-spectrum antiepileptic drugs and commonly are on multiple agents. The ketogenic diet and vagal nerve stimulation are often employed when polypharmacy fails. In patients with frequent potentially injurious atonic seizures, corpus callosotomy is often used to palliate these drop attacks.

# **Revisions to the 1981 ILAE Classification of Seizures and the 1989 Classification of Epilepsies and Epileptic Syndromes**

In recent years, multiple attempts have been made to update the classification schema of seizures, epilepsies, and epileptic syndromes so that they reflect new and current information gleaned from the prolific advances in the basic and clinical neurosciences.<sup>4,5</sup> These efforts culminated in a 2010 report from the ILAE Commission on Classification and Terminology entitled “Revised terminology and concepts for organization of seizures and epilepsies.”<sup>6</sup>

## Classification of Seizures (2010 Revision)

Similar to the older classification of seizures, the updated recommendations emphasize the mode of seizure onset as the fundamental characteristic by which to classify seizures (TABLE 1.3). The concepts of “generalized” and “focal” when used in reference to the region of initiation of seizures were retained, but the authors took pains to replace the older notions that generalized seizures implied involvement of all of the cortex and focal seizures implied involvement of a group of well circumscribed cortical neurons with the more accurate concept of cortical-subcortical epileptic networks. They conceptualize generalized epileptic seizures as “originating at some point within, and rapidly engaging, bilaterally distributed networks. Such bilateral networks can include cortical and subcortical structures but do not necessarily include the entire cortex.”<sup>6</sup> In the same vein, they define focal epileptic seizures as “originating within networks limited to one hemisphere. Such networks may be discretely localized or more widely distributed and may originate in subcortical structures.”<sup>6</sup> However, within the category of focal seizures, the distinction previously made between simple partial (focal) and complex partial (focal) seizures has been abandoned, as was the concept of secondarily generalized seizures. The rationale for these changes was that the concepts of simple, complex, and secondarily generalized were often difficult to define precisely, misused, or misunderstood. The authors contend that there is currently insufficient information to create a “scientific classification” within the category of focal seizures and instead recommend that they be described according to features that are “most useful for a given specific purpose.” For example, if the purpose is to differentiate epileptic from nonepileptic events, then they suggest describing the specific semiologic features of the seizures and their sequence of occurrence. Such descriptors can and should include a statement about the level of cognitive impairment during the seizure if this is relevant to the specific purpose at hand, eg, pragmatic considerations about driving (TABLE 1.4).

Other minor changes proposed to the classification of seizures include:

- Neonatal seizures are no longer regarded as a separate entity but can be classified within the proposed schema.
- The classification of subtypes of absence seizures has been simplified and modified.
- “Myoclonic-astatic” seizures have been renamed “myoclonic-atonic” seizures.
- Epileptic spasms have been included in the classification.

The more general term “epileptic spasms” replaces the previously used “infantile spasms.” However, since there is widespread disagreement over how best to classify spasms, as generalized or focal or both, epileptic spasms were put in their own third category and classified as “unknown” (TABLE 1.3).

## Classification of Epilepsies (2010 Revision)

In a departure from the 1989 classification system, the 2010 report offers no single specific organization for the revised classification of the epilepsies and epileptic syndromes. Instead, the 2010 Commission proposes a more fluid and dynamic system that is “organized according to those dimensions that are most relevant to a specific purpose” (eg, research vs clinical diagnosis). The 2010 Commission does, however, make some recommendations as to what dimensions might be useful to employ when customizing an organizational system. As summarized in previous sections, the 1989 Classification of Epilepsies and Epileptic Syndromes was organized along two main axes. The first axis separated epilepsies with generalized seizures (generalized epilepsy) from epilepsies with partial or focal seizures (localization-related, partial, or focal epilepsies) and the second axis subcategorized the epilepsies based on etiology or presumed etiology as idiopathic, symptomatic or cryptogenic. In the 2010 Revision, the concepts of “generalized” and “focal” as they pertain to the epilepsies and epileptic syndromes are discarded. The reason for this change was that the Commission felt the terms “generalized” and “focal” in reference to epilepsy syndromes do not adequately reflect the processes underlying the epilepsies. That is, the terms emphasize manifestations of the underlying processes but not necessarily the underlying processes or mechanisms themselves. Key examples that illustrate this point are “generalized” spasms arising from a focal lesion, as commonly occurs in West syndrome, and focal seizures arising from a diffuse genetic disorder as occurs in Dravet syndrome.<sup>6</sup> Additionally, while the 2010 Commission retains the concept of underlying

**TABLE 1.3**  
**2010 ILAE Classification of**  
**Epileptic Seizures**

<p><b>I. Generalized Seizures</b></p> <ol style="list-style-type: none"> <li>1. Tonic-Clonic (in any combination)</li> <li>2. Absence             <ol style="list-style-type: none"> <li>i. Typical</li> <li>ii. Atypical</li> <li>iii. Absence with Special Features                 <ol style="list-style-type: none"> <li>a. Myoclonic Absence</li> <li>b. Eyelid Myoclonia</li> </ol> </li> </ol> </li> <li>3. Myoclonic             <ol style="list-style-type: none"> <li>i. Myoclonic</li> <li>ii. Myoclonic Atonic</li> <li>iii. Myoclonic Tonic</li> </ol> </li> <li>4. Clonic</li> <li>5. Tonic</li> <li>6. Atonic</li> </ol> <p><b>II. Focal Seizures</b></p> <p><b>III. Unknown</b></p> <ol style="list-style-type: none"> <li>1. Epileptic Spasms</li> </ol>
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Source: Berg AT, Berkovic SF, Brodie MJ, et al. Revised terminology and concepts for organization of seizures and epilepsies: report of the ILAE commission on classification and terminology, 2005-2009. *Epilepsia*. 2010;51:676-685. Reproduced with permission from John Wiley & Sons Publications.

**TABLE 1.4**  
**2010 ILAE Description of Seizures According**  
**to Degree of Impairment During Seizure**

<p><b>I. Without Impairment of Consciousness or Awareness (corresponds to the older concept of "simple partial seizures")</b></p> <ol style="list-style-type: none"> <li>1. With Observable Motor or Autonomic Components</li> <li>2. Involving Subjective Sensory or Psychic Phenomena Only (corresponds to the older concept of an "aura")</li> </ol> <p><b>II. With Impairment of Consciousness or Awareness (corresponds to the older concept of "complex partial seizures")</b></p> <p><b>III. Evolving to a Bilateral, Convulsive Seizure (corresponds to the older "secondarily generalized seizure")</b></p>
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etiology as a useful dimension by which to organize the various epilepsies, it proposes a revision of the prior terminology such that the terms idiopathic, symptomatic, and cryptogenic are replaced by the terms genetic, structural/metabolic, and unknown cause, respectively. They define the concept of a genetic epilepsy (formerly "idiopathic") as one in which "the epilepsy is, as best understood, the direct result of a known or presumed genetic defect(s) in which seizures are the core symptom of the disorder" (eg, the SCN1A mutation and Dravet syndrome).<sup>6</sup> They described the concept of a "structural/metabolic" epilepsy (formerly "symptomatic") as one where there is "a distinct other structural or metabolic condition or disease that has been demonstrated to be associated with a substantially increased risk of developing epilepsy in appropriately designed studies. Structural lesions of course include acquired disorders such as stroke, trauma, and infection. They may also be of genetic origin (eg, tuberous sclerosis, many malformations of cortical development); however, as we currently understand it, there is a separate disorder interposed between the genetic defect and the epilepsy."<sup>6</sup> Finally, they use "unknown cause" as a neutral designation meant to convey that the underlying cause truly is, as of yet, unknown. This 2010 Commission felt this new terminology was necessary in order to eliminate the misleading use of "cryptogenic" to mean "presumed symptomatic."

The 2010 Commission also proposed the concept of the "electroclinical syndrome" and using the degree of specificity of diagnosis as a means by which to organize or classify the epilepsies. They were critical of the fact that the 1989 report used the terms "syndromes" and "epilepsies" almost interchangeably. "The result of this was that very specific and highly recognizable entities (such as childhood absence epilepsy) and poorly differentiated and not well-described epilepsies (such as cryptogenic parietal lobe epilepsy) tended to be treated as though they represented the

same level of diagnostic precision.”<sup>6</sup> By conflating the concepts of syndromes and epilepsies, one loses vital information regarding treatment, management, and prognosis. To address this shortcoming of the 1989 classification, the 2010 report explicitly defines four categories by which to organize the epilepsies and epilepsy syndromes according to the specificity of the diagnosis. Ordered from most specific to least specific, these categories are:

***Electroclinical Syndromes:*** distinct clinical entities that are reliably identified by a cluster of electroclinical characteristics such as symptoms, signs, age of onset, EEG characteristics, and seizure types, that when taken together permit a specific diagnosis (TABLE 1.5).

***Constellations:*** clinical entities that do not quite meet the criteria of an electroclinical syndrome, yet can and should be recognized based on clinical features. They are diagnostically meaningful forms of epilepsy and may have implications for clinical treatment, particularly surgery. These include mesial temporal lobe epilepsy with hippocampal sclerosis, hypothalamic hamartoma with gelastic seizures, epilepsy with hemiconvulsion and hemiplegia, and Rasmussen “syndrome” (TABLE 1.5).

***Structural/Metabolic Epilepsies:*** nonsyndromic epilepsies known to be caused by underlying structural lesions or metabolic conditions but that do not fit into a specific electroclinical pattern and therefore represent a lower level of specificity of diagnosis. In the 1989 classification these would have been termed “symptomatic focal epilepsies” and distinguished on the basis of localization. The 2010 classification instead organizes these epilepsies according to the underlying structural or metabolic cause, as this is likely to have more importance for understanding the natural history, treatment, and prognosis of these epilepsies than is their localization. As an example, an epilepsy termed “symptomatic temporal lobe epilepsy” under the 1989 classification would instead be termed “epilepsy with focal seizures secondary to cortical dysplasia in the temporal lobe”.

***Epilepsies of Unknown Cause:*** This is the least specific category of this organization system. This term replaces the often misused and misunderstood term of “cryptogenic” from the 1989 classification.

Although the 2010 Commission does not propose any one specific classification for the epilepsies, they do provide a sample of one possible schema organized around the axes of specificity of diagnosis and age of onset when applicable (TABLE 1.5).

The 2010 Commission also introduces additional terms and proposes additional dimensions for organizing the epilepsies. One such dimension is the concept of the natural evolution of the specific epilepsy or epileptic syndrome. Within this dimension they define the terms “epileptic encephalopathy” and “self-limited.” The term “epileptic encephalopathy” may be used to characterize and group syndromes (eg, LGS, West syndrome, Dravet syndrome) or be applied to individuals. The concept reflects the idea that seizures, especially in the developing brain, may themselves be harmful. “Epileptic encephalopathy embodies the notion that the epileptic activity itself may contribute to severe cognitive and behavioral impairments above and beyond what might be expected from the underlying pathology alone (eg, cortical malformation), and that these can worsen over time.”<sup>6</sup> Such cognitive impairments may be global or more selective, they may occur along a spectrum of severity, and they may be seen with any form of epilepsy.

The term “self-limited” refers to those epilepsy syndromes that are known to have a predictable spontaneous remission, usually by a certain age. Examples of such syndromes would be CAE and BECTS. Along the same lines, the 2010 Commission also proposed the term pharmacoresponsive to denote those epilepsies that are known to respond well to medications (eg, JME) and differentiate them from those that don’t (pharmacoresistant epilepsies such as Dravet syndrome and mesial temporal lobe epilepsy with hippocampal sclerosis).

Under the 1989 system, the term “idiopathic” was initially meant to convey the idea that there was no clear underlying cause of the epilepsy other than a possible hereditary or genetic etiology. However, “idiopathic” also came to convey the idea that a particular epilepsy was highly responsive to medications or that it had a self-limited course. Likewise, “symptomatic” epilepsy often carried the connotation of being pharmacoresistant with a poor clinical course. Conflating multiple meanings (cause and prognosis) in one term was not only confusing but also at times flat-out wrong (eg, Dravet syndrome is an “idiopathic” or “genetic” epilepsy but is highly pharmacoresistant). Instead, the new terminology replaces these often misused and misunderstood terms with clear and specific terminology such as “self-limited,” “pharmacoresponsive,” and “pharmacoresistant.”

TABLE 1.5 **2010 ILAE Electroclinical Syndromes and Other Epilepsies**

**I. 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+) (can start in infancy)
- Panayiotopoulos Syndrome
- Epilepsy with Myoclonic Atonic (previously Astatic) Seizures
- Benign Epilepsy with Central-Temporal 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-Adult:

- Juvenile Absence Epilepsy (JAE)
- Juvenile Myoclonic Epilepsy (JME)
- Epilepsy with Generalized Tonic-Clonic Seizures Alone
- Progressive Myoclonus 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

**II. Distinctive Constellations:**

- Mesial Temporal Lobe Epilepsy with Hippocampal Sclerosis (MTLE with HS)
- Rasmussen Syndrome
- Gelastic Seizures with Hypothalamic Hamartoma
- Hemicconvulsion-Hemiplegia-Epilepsy

**III. Epilepsies Attributed to and Organized by Structural-Metabolic Causes:**

- Malformations of Cortical Development (hemimegalencephaly, heterotopias, etc)
- Neurocutaneous Syndromes (Tuberous Sclerosis Complex, Sturge-Weber, etc)
- Tumor
- Infection
- Trauma
- Angioma
- Perinatal Insults
- Strokes

**IV. Epilepsies of Unknown Cause**

**V. Conditions with Epileptic Seizures That Are Traditionally Not Diagnosed as a Form of Epilepsy**

- Benign Neonatal Seizures
- Febrile Seizures

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The 2010 Commission also recommended doing away with the terms “benign” and “catastrophic.” Benign was discarded as it was felt that applying this term to epilepsy ignored the mounting evidence regarding the relationship between epilepsy and cognitive, behavioral, and psychiatric illnesses as well as sudden death and suicide. Catastrophic was discarded due to the strong emotional overtones that made it inappropriate as a diagnostic label or category.

## Conclusion

The 2010 Commission’s goal was to propose changes to the 1981 and 1989 documents that would provide a more flexible and multidimensional classification that could be adaptable to the purpose at hand (eg, drug development, research, or clinical practice). They amended the classification of seizures but they did not recommend a specific classification structure for epilepsies. When taken together, the 1981, 1989, and 2010 ILAE documents provide a framework for how to organize knowledge about seizures and epilepsies. Understanding this framework is crucial to clinical and research endeavors alike and not only aids the diagnosis and treatment of current forms of epilepsy but also facilitates the identification and understanding of new forms in future. ■

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# Epidemiology

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# Introduction

Epilepsy is one of the most common neurological disorders—1 in 26 individuals in the United States will be diagnosed with epilepsy at some point in their lifetime—and the impact of epilepsy goes beyond seizures and issues related to treatment.<sup>1</sup> The profound influence of epilepsy on the patient, family and society led the Institute of Medicine to examine the current status of epilepsy, its treatment and impact on society in the report “Epilepsy Across the Spectrum: Promoting Health and Understanding.”<sup>2</sup> One important finding of the report was that there is no systematic approach to identifying epilepsy cases in the United States, and that surveillance efforts are sporadic, disconnected, and inadequate. The report included a recommendation to continue and expand epilepsy surveillance in an attempt to better understand the magnitude of the problem as one of the foundations of improving care and patient outcomes broadly in the United States.

## Importance of Epidemiology and Surveillance

Epidemiological studies have been key to improvements in healthcare provisions for many disease conditions. Epidemiological data have contributed to new methodology of clinical research, more informed decision making as it relates to new healthcare policies, and evidence-based medicine guidelines for preventive or improved treatment. In the case of epilepsy, it is important to understand the magnitude of the problem largely to determine whether existing resources are adequate to meet the need for care.

Recently published reports indicate a higher prevalence of epilepsy than what was previously assumed in the US population, with the highest incidence of epilepsy in the very young and the elderly.<sup>3</sup> Thus demographic changes in the population and more recent events suggest that epilepsy may also be on the rise in the VA patient population. Baby Boomers, many of whom are Vietnam Veterans, are turning 65 at a rate of approximately 10,000 per day, and this trend will continue for the next 18 years.<sup>4</sup> The aging of the Vietnam Veteran population is likely to have significant impact on VA healthcare resources. Moreover, aging in the new cohort of Veterans from the wars in Afghanistan and Iraq (OEF/OIF/OND) will also require additional resources for generations to come, especially as it relates to provisions of health care.

In addition to aging, traumatic brain injury (TBI)—a common cause of new-onset epilepsy in adults<sup>5</sup>—is more common in the military, and hence, veteran population. Veterans from prior wars including Vietnam were exposed to blast injuries and traumatic brain injuries, similar to Operation Enduring Freedom/Operation Iraqi Freedom/Operation New Dawn (OEF/OIF/OND) Veterans; however, in prior wars those who suffered more severe injuries died. Improvements in body armor and battlefield medicine have resulted in more survivors coping with life-altering injuries. Moreover, the majority of military TBI cases occur in garrison from operational and training activities.<sup>6</sup> Thus, the risk of post-traumatic epilepsy may be greater in the military population than what is found in the general US adult population. Given Lincoln’s motto for the VA to “care for those that bore the battle...” it is imperative that we not only understand the number of Veterans with epilepsy, but also the characteristics of those Veterans to improve the availability of required effective care.

Access to health care data is critical for epidemiological surveillance. Fortunately for the VA, the Veterans Health Administration (VHA) maintains very extensive databases and the electronic medical records. The VHA Support Service Center (VSSC), the VHA Managerial Cost Accounting Program (MCAP, previously known as Decision Support System) and the Corporate Data Warehouse contain information for care received in inpatient and outpatient settings, including ICD diagnostic codes, medications prescribed, lab results, etc. These data are extracted from the electronic medical records and stored in administrative data sets that can be used for operational purposes, surveillance and research. Furthermore, research within the VHA has led to validated algorithms to identify cases of epilepsy within the VA geriatric patient population.<sup>7</sup> The data sets allow the VA to determine the denominator (population who receives VA care each year) and the prevalence (number of Veteran with epilepsy in that population) each year. These data sets not only allow us to estimate the number of newly treated cases (incidence in the VA) per year, these are

also essential to get true incidence of disease. However, the ability to get strong estimates of true incidence are hindered by lack of non-VA data—especially data from the Department of Defense, and private insurance.

As an integrated healthcare system, the VA is also able to use administrative data to examine trends over time in prevalence, risk factors, and treatment patterns. Moreover, the development of a clinical template for epilepsy care is currently being tested in 16 Epilepsy Centers of Excellence sites. With the national implementation of the template we anticipate the access to a specific database will be a giant step for health care improvements in epilepsy. These resources provide the VA with a unique laboratory for epilepsy surveillance, and evaluation of the quality of epilepsy care. Establishment of an epilepsy epidemiology/surveillance system is a key part of the VA Epilepsy Centers of Excellence (ECoE) infrastructure aligned with a number of distinct recommendations proffered by the IOM report, particularly the recommendation to develop an epilepsy surveillance system.

## Epidemiology of Epilepsy

A variety of studies have examined the epidemiology of epilepsy in different settings. Studies that are broadly population-based tend to have lower rates of incidence and prevalence than studies conducted in clinical populations. We first review population-based studies and those conducted in community settings, followed by studies conducted in clinical populations, and then share prevalence and incidence estimates in the VA clinical population.

### Epilepsy Estimates for the General Population

Epilepsy estimates vary due to different study methodologies and definitions of epilepsy. Other factors contributing to variation are access to healthcare, regional environmental exposures, and socioeconomic status. Prevalence or incidence may be underestimated in areas where the condition is greatly stigmatized and cultural beliefs about the causes of epilepsy or negative attitudes toward those with epilepsy lead to the concealing of symptoms of epilepsy, or its diagnosis.<sup>8</sup>

According to World Health Organization (2012),<sup>9</sup> at any given time, it is estimated that 50 million individuals worldwide have a diagnosis of epilepsy. Around 85% of people with epilepsy live in developing countries. Every year two million new cases are diagnosed worldwide. The overall prevalence of epilepsy ranges between 2.7 to 41 per 1,000 population and the incidence of epilepsy is 23-190 per 100,000 individuals. Prevalence and incidence of epilepsy tend to be higher in men but this finding has not attained statistical significance. In industrialized countries the prevalence and incidence of epilepsy tend to peak in elderly people, whereas in developing countries the rates are highest for second decade of life. Causes for disparity may include relatively short life expectancy and under-ascertainment of the disease in older individuals in developing countries.

In the United States about 2.3 million people have epilepsy and 150,000 new cases are diagnosed each year.<sup>10</sup> The incidence of epilepsy is relatively higher in males, and among those  $\geq 60$  years and less than two years of age.<sup>3</sup> About 1.5% of those  $\geq 65$  are affected by epilepsy,<sup>11</sup> and recent studies suggest that the incidence of epilepsy in the elderly nearly doubled between 1935 and 1984.<sup>12</sup> Currently, 25-35% of incident cases of epilepsy are in individuals  $\geq 65$ ,<sup>13</sup> but this will increase to 50% by 2020.<sup>14</sup> This increase in the elderly is attributed to the lower level of mortality in stroke victims and the association of epilepsy with Alzheimer's disease, and other dementias which are the leading known causes of epilepsy in western countries.

Data from Olmstead County, MN suggest that epilepsy is also becoming more common in the broader population. Estimated incidence of epilepsy in Olmstead County using data from 1935 to 1984 was 44 per 100,000 person years. Between 1975 and 1984 the incidence was 48 per 100,000 person years, suggesting higher incidence in more recent years. The prevalence of epilepsy was 6.8 per 1,000 overall, and 14.1/1,000 in adults aged 75 and over.<sup>15</sup>

Using telephone survey approach, a Behavioral Risk Factor Surveillance System (BRFSS) study in 19 states found that 1.65% of non-institutionalized adults had ever been told by a physician that they had epilepsy or a seizure disorder and 0.84% reported having active epilepsy. There were no significant differences by sex or race/ethnicity.<sup>16</sup> Of the few studies that compared prevalence of epilepsy among races, most found a higher prevalence among African

Americans. The largest racially diverse study was from Copiah County, Mississippi, which reported a higher prevalence of epilepsy among African Americans (8.2 per 1,000) compared to Caucasians (5.4 per 1,000); however, it failed to control for socioeconomic status.<sup>17</sup>

## **Epilepsy Estimates for Clinical Populations**

Data from clinical populations is not as commonly available, but the IOM report provided an opportunity to examine the epidemiology of epilepsy within clinical populations.<sup>2</sup> The IOM data gathering experience provided information from four settings: the Henry Ford Health System, the Geisinger Health System, the state of South Carolina, and the Veterans Health Administration.

### **Henry Ford Health System**

The Henry Ford Health System is a managed care organization serving approximately 500,000 patients in the Detroit metropolitan area. As such, individuals may select into the system at any point in their clinical journey. Using health plan administrative data they identified individuals with prevalent epilepsy by identifying those with a diagnosis (ICD-9-CM codes) of epilepsy (345.xx) or seizure (780.39) between 2006 and 2010, and then looked back in their data to determine if those individuals had similar diagnoses in prior data (through 1995). Those without a prior diagnosis were identified as incident epilepsy during the first year in which epilepsy was identified. Incidence rates ranged between 266 and 163 per 100,000 in 2006 and 2010 respectively, and prevalence was relatively stable over time (8 per 1,000). Two thirds of patients were between 19 and 64 years of age. There were no differences by sex or race/ethnicity. Most encounters with a diagnosis of epilepsy or seizure were in a neurology setting, and 74% of individuals with epilepsy received neurology care at some point during the study period.

While these rates of prevalence and incidence are substantially higher than reported in other studies, this study used only ICD-9 codes to identify epilepsy, including the more general 780.39, which likely includes a substantial number of individuals who had a seizure but did not meet the criteria for epilepsy.<sup>18</sup> This hypothesis is supported by their own chart review, which found that, of 100 charts reviewed, 72 cases had confirmed epilepsy. Of those confirmed, all but one received AEDs.

### **Geisinger Health System**

Similarly the Geisinger Health System used administrative data from its electronic medical record to examine epilepsy epidemiology using individuals with a primary care provider in the Geisinger system at least two consecutive years, and who received care January 1, 2004-June 30, 2011 as the denominator. Prevalent cases were defined as individuals with two or more diagnoses indicating epilepsy (ICD-9 345, 780.39, 780.09), or one such code and an outpatient prescription for AED; incident cases were not previously diagnosed with these codes in the medical record. The prevalence estimate for this population was 10.2 per 1,000 with an incidence rate of 20.8 per 100,000 person years. There were no significant differences by age, sex or race/ethnicity. Among incident cases, 33% had a subsequent visit in a neurology setting; 62% of prevalent cases received neurology care.

### **State of South Carolina**

The State of South Carolina had the most comprehensive epilepsy surveillance system (South Carolina Epilepsy Surveillance System) noted in the IOM report with a designated repository of health and human services data in the state which includes billing data and non-institutional claims data extracted from all nonfederal healthcare systems (e.g., emergency departments, hospitals, hospital-based outpatient systems, Medicare data, Medicaid, and state employee health plan). Individuals with a diagnosis of 780.39 with more than one such diagnosis in the past year, who receive seizure medications, have a procedure code for vagus nerve stimulator implantation or epilepsy surgery are identified as having epilepsy. The incidence in South Carolina using this system was 95 per 100,000 person years for 2008. Incidence was highest in those less than 19 years of age (0.19% vs 0.8% age 19-64 and 0.05% 65 and older), and higher

in Blacks (0.16%) than Whites (0.08%), Hispanics (0.09%) and Other (0.07%). There was no significant difference between men and women. Neurology care was received by 23% of those with prevalent epilepsy and by 32% of those with incident epilepsy between 2006 and 2010. The most commonly prescribed AED were phenytoin (55%), valproic acid (19%), carbamazepine (18%), phenobarbital (13%), gabapentin (6%), other AEDs (5%). Data on variation in AED over the period of study was not available.

## **Veterans Health Administration**

The VHA has been examining epilepsy epidemiology since 1999 when inpatient, outpatient and pharmacy data became available on the national level, and the same data was used for the IOM report. The first national study of epilepsy in the VA patient population was published in 2004 and focused on the elderly. This occurred around the same time as VA Cooperative Study 485 examined the effectiveness of three antiepileptic drugs (carbamazepine, gabapentin and lamotrigine) head to head in a sample of older Veterans. That study found that in FY99 approximately 1.2% of older Veterans met criteria for epilepsy (diagnosis of 345.xx or 780.39 with concomitant use of an antiepileptic drug).<sup>18</sup> The vast majority (nearly 70%) of older Veterans received phenytoin and 5% received phenobarbital—drugs that VA epileptologists viewed as suboptimal for older patients. Subsequent studies have found similar prevalence of epilepsy in the geriatric epilepsy population, with increased risk in those with head injury, stroke and dementia; males and African Americans were also at higher risk of epilepsy.<sup>19</sup> Furthermore, we found changes in prescribing with just over 52% receiving phenytoin in 2006, and approximately 20% receiving levetiracetam or lamotrigine.<sup>20</sup> Approximately 40% of those with new-onset epilepsy received neurology care. These data suggest that epilepsy in the geriatric VA population is relatively stable, and that the quality of medication management of this population has improved over time.

Data from the OEF/OIF/OND cohort of Veterans from FY09 indicated that epilepsy is beginning to emerge with a prevalence of 8.1 per 1,000 and incidence of 133 per 100,000 person years.<sup>2</sup> It is important to note that inclusion in this cohort was based on deployment to a war zone. Phenytoin, levetiracetam and valproate were each received by approximately 20% of the cohort, followed by approximately 10% each for lamotrigine, gabapentin and carbamazepine; 10% received other AEDs. Furthermore, 50-60% of those with prevalent and incident epilepsy respectively were not seen in a neurology or epilepsy care setting, suggesting that access to neurology/epilepsy specialty care may be limited.

Closer evaluation of the relationship between TBI severity and epilepsy in OEF/OIF Veterans using a rigorous epidemiological approach used the same approach to identifying epilepsy and the Defense and Veterans Brain Injury Centers definition of TBI severity, controlling for other risk factors for epilepsy (e.g., stroke). TBI and other risk factors were identified prior to the index date (first date of seizure or October 1, 2009 for non-epilepsy controls) for primary analyses. Age-adjusted prevalence in FY10 was 6.1, which was higher than some US estimates and similar to others. Statistically significant associations were found between epilepsy and TBI diagnosis prior to epilepsy diagnosis (penetrating TBI: adjusted odds ratio = 18.77 [95% confidence interval, 9.21-38.23]; other TBI: adjusted odds ratio = 1.64 [1.43-1.89]). The association of epilepsy with mTBI was AOR = 1.28; 95% CI, 1.07-1.53.<sup>21</sup>

After their inception, Epilepsy Centers of Excellence (ECoE) took a lead in the development of algorithms for the identification of epilepsy patients in the VHA. A paper highlighting the efforts, algorithms and results regarding prevalence estimation was published in 2016.<sup>22</sup> Since FY12 ECoE is including epilepsy prevalence estimates in annual reports. Efforts for optimal and accurate estimation of VHA epilepsy patients are summarized below.

**FY11 Prevalence Study** – The first study of seizure epidemiology for VHA general population was conducted in FY11.<sup>23</sup> Patients were identified by implementing a modified version of an established algorithm for managed care organizations.<sup>24</sup> Comorbid TBI and PTSD conditions were also evaluated among seizure patients. VHA inpatient and outpatient data files along with pharmacy data were used to identify FY11 prevalent epilepsy patients. Individuals who received a seizure diagnosis (ICD-9-CM codes 780.39 and/or 345.xx) during FY09-FY11 and at least a 30-day supply of seizure medications in FY11 were considered prevalent epilepsy cases. Three years of data (two years prior to ascertainment of epilepsy status) were used to ensure inclusion of chronic patients in the cohort. The pharmacy (FY10-FY11) and diagnostic data (FY09-FY11) were used to identify new cases of epilepsy in FY11. Among prevalent

cases, individuals with at least one seizure diagnosis in FY11 and who were also prescribed AEDs in FY11 were initially considered for incidence. Those who had no AED prescription in FY10 and no seizure diagnosis two years prior to FY11 were considered incident epilepsy patients. Using look-back period of five years (FY07-FY11), individuals were identified with diagnoses of PTSD (ICD-9-CM diagnosis code 309.81) and TBI. TBI diagnosis codes were adopted from TBI case definition of Armed Forces Health Surveillance Center (AFHSC), consistent with DOD Standard Surveillance case definition of TBI.

Information collected included age, gender, and, OEF/OIF/OND status. During fiscal year 2011, 87,377 Veterans with seizures on AEDs were managed within the VHA. Estimated prevalence was 15.5 per 1,000, and annual incidence was 148.2 per 100,000. The percentages of comorbid TBI and PTSD were 15.8% and 24.1%, respectively. For OEF/OIF/OND Veterans with seizures, these percentages increased to 52.6% (TBI) and 70.4% (PTSD). In addition, among OEF/OIF/OND seizure patients with TBI, approximately 85.4% also had a PTSD diagnosis.

PTSD and TBI are risk factors for both epilepsy and psychogenic non-epileptic seizures.<sup>25-26</sup> Therefore, it is highly likely that the Veterans with seizure diagnoses on an AED identified in FY11 study included not only those with epilepsy, but also other medical conditions like PNES. Furthermore, an unmeasured proportion could consist of patients who were prescribed AEDs for conditions other than epilepsy.

**FY12 through FY15 Prevalence Estimates** – For FY12 epilepsy prevalence estimates another variant of Holden’s algorithm was used, where patients with seizure diagnosis on clinical encounters from EEG and prolonged video EEG monitoring clinics were excluded from three consecutive years’ (FY10-FY12 as done for FY11 study) data of clinical encounters as a criterion for the identification of epilepsy patients. The purpose of excluding patients from diagnostic clinics was to reduce the inclusion of false positives. AEDs considered included carbamazepine, ethosuximide, felbamate, gabapentin, lacosamide, lamotrigine, levetiracetam, oxcarbazepine, phenobarbital, phenytoin, pregabalin, primidone, tiagabine, topiramate, valproate, vigabatrin, and zonisamide. To check the accuracy of modified algorithm a validation study including 500 patients was conducted at four ECoE sites including Durham, NC, Miami, Tampa and Gainesville, FL. A simple random sample of 125 patients identified as having epilepsy by algorithm was drawn at each site and charts were reviewed by epilepsy specialists. Documentation of ICD-09-CM 345.xx on the problem list was considered confirmation of treatment for epilepsy. In the absence of epilepsy codes on the problem list, three years’ clinical notes (FY10-FY12) with list of medications were evaluated for the mention and description of unprovoked seizures. All ambiguous cases were presented in telephone conference calls and decided with consensus. A total of 81,085 patients were identified as having epilepsy in FY12. Out of 500 patients evaluated for validation, epilepsy was confirmed for 410 patients providing an estimated positive predictive value of 82.0% (95% confidence interval: 78.6% to 85.4%). Due to satisfactory results of modified version of excluding diagnostic clinics during FY12 study, same criterion was adopted for FY13-FY15 epilepsy prevalence estimates, and results were published in ECoE annual reports.<sup>27</sup> A summary of FY15 prevalence results is described below.

**FY15 Prevalence Estimates** – In all, 83,362 patients were identified as having epilepsy during FY15. Around 92% of epilepsy patients were males. Three age groups were considered; patients less than 45 years of age, between 45 and 64 years of age and patients 65 and older. Among males 50.1% of patients were identified in older age group, whereas among females 55.0% were middle-aged (between 45 and 64 years of age). The number of epilepsy patients who served in current warfare was 6,188. Hence, around 7% were OEF/OEF/OND Veterans. In contrast with VHA general population with epilepsy, OEF/OIF/OND females comprised approximately 12% of epilepsy cohort. More than 81% OEF/OIF/OND patients were young (less than 45 years of age). The prevalence of epilepsy among general VHA population was 13.8 per 1,000 patients and OEF/OIF/OND cohort prevalence was 8.4 per 1,000 OEF/OIF/OND patients. Age and gender specific percentages for epilepsy and general VHA patients are provided in TABLE 2.1 and epilepsy prevalence estimates are shown in FIGURE 2.1.

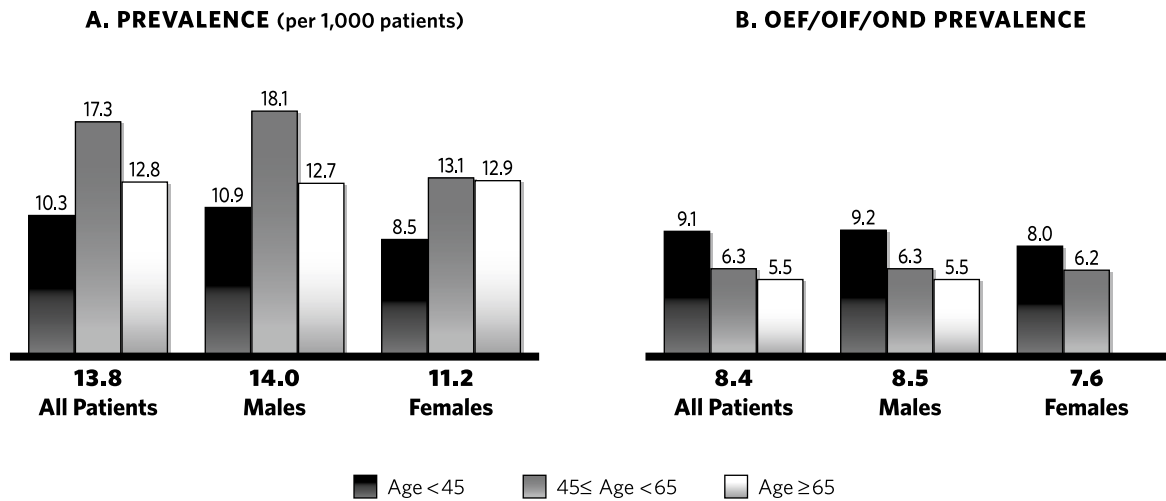
With the implementation of ICD-10 in the VHA during FY16 the more specific codes for epilepsy in ICD-10 system replaced the old ICD-09-CM system. The additional specificity of ICD-10 codes should improve seizure identification for the epidemiological studies using administrative data. However, ICD-09-CM 780.39 (other convulsions) could possibly be replaced by different ICD-10 codes such as G40.89 (other seizures), G40.909 (recurrent seizures not otherwise specified), R40.4 (Transient Alteration of Awareness), R56.1 (Post Traumatic Seizures) and

TABLE 2.1 VHA FY15 Patient Counts

VHA FY15 PATIENT COUNTS				
COHORT	EPILEPSY PATIENTS, %		ALL VA PATIENTS, %	
<b>All Patients</b>	<b>83,362</b>		<b>6,056,301</b>	
Age <45	11,100	13.3%	1,072,632	17.7%
45 ≤ Age <65	32,948	39.5%	1,900,435	31.4%
Age ≥65	39,314	47.2%	3,083,234	50.9%
<b>Males</b>	<b>76,740</b>		<b>5,464,332</b>	
Age <45	8,995	11.7%	825,984	15.1%
45 ≤ Age <65	29,306	38.2%	1,622,936	29.7%
Age ≥65	38,439	50.1%	3,015,412	55.2%
<b>Females</b>	<b>6,622</b>		<b>591,969</b>	
Age <45	2,105	31.8%	246,648	41.7%
45 ≤ Age <65	3,642	55.0%	277,499	46.9%
Age ≥65	875	13.2%	67,822	11.5%
<b>Epilepsy: Males 92.1%, Females 7.9%</b>		<b>All VA: Males 90.2%, Females 9.8%</b>		

OEF/OIF/OND PATIENT COUNTS				
COHORT	EPILEPSY PATIENTS, %		ALL VA PATIENTS, %	
<b>All Patients</b>	<b>6,188</b>		<b>740,703</b>	
Age <45	5,028	81.3%	554,661	74.9%
45 ≤ Age <65	1,124	18.2%	179,516	24.2%
Age ≥65	36	0.6%	6,526	0.9%
<b>Males</b>	<b>5,442</b>		<b>642,409</b>	
Age <45	4,413	81.1%	477,515	74.3%
45 ≤ Age <65	995	18.3%	158,737	24.7%
Age ≥65	34	0.6%	6,157	1.0%
<b>Females</b>	<b>746</b>		<b>98,294</b>	
Age <45	615	82.4%	77,146	78.5%
45 ≤ Age <65	129	17.3%	20,779	21.1%
Age ≥65	2	0.3%	369	0.4%
<b>Epilepsy: Males 87.9%, Females 12.1%</b>		<b>All VA: Males 86.7%, Females 13.3%</b>		

FIGURE 2.1 VHA FY15 Epilepsy Prevalence Estimates



R56.9 (Unspecified Convulsions). Therefore, refinements to current algorithm are necessary by exploring specificities of certain codes. In addition, many AEDs such as gabapentin, pregabalin, carbamazepine, lamotrigine, levetiracetam and valproate are used to treat a range of conditions including headaches, generalized pain and mood disorders. Gabapentin is prescribed widely for different conditions and is becoming controversial for epilepsy treatment. A study conducted for prevalence of epilepsy among OEF/OIF Veterans receiving care at the VHA during FY09-FY10 interrogated the inclusion of gabapentin as a monotherapy for epilepsy and presented prevalence estimates with and without gabapentin.<sup>21</sup> As it is known that gabapentin is likely to be prescribed as a monotherapy for some VHA epilepsy patients. Therefore, one possible improvement to algorithm could be inclusion of mono-gabapentin cohort in the prevalence estimates only if patients had a definitive diagnosis of ICD-09 345.xx before FY16 or G40.xx after FY16.

A study is underway in ECoE for estimation of specificities of ICD-10 seizure codes. This study will be pivotal for modification of current algorithm for FY16 and beyond prevalence estimates.

## Conclusion

Epilepsy is the fourth most common neurological condition that has profound impact on the patient, family, society and healthcare system. Trends suggest an increase in the rates of epilepsy with the aging of America. Recent concerns about TBI have brought additional interest for understanding the epidemiology of epilepsy in the VHA. Evidence from current studies conducted in the VA is emerging that many PNES patients are initially misdiagnosed and treated as having epilepsy.<sup>26</sup> As the demographics of VHA shift towards a younger population of OEF/OIF/OND, future VHA epilepsy patients would comprise of more female and younger patients than served before. As most patients are seen by primary care setting, it is imperative to provide education regarding the accurate diagnosis and treatment options available for young and female patients.

Our assessment of epilepsy in the VHA found that rates of incidence and prevalence were higher than population-based studies and clinical settings. Not only is epilepsy a significant problem for older Veterans, it is a significant problem in middle age, and epilepsy is emerging in the OEF/OIF/OND population which is mostly under the age of 45. Findings suggest that there is significant comorbidity with PTSD in epilepsy population, particularly in OEF/OIF/OND Veterans. This comorbidity leads some to question the possible misdiagnosis of individuals with psychogenic non-epileptic seizures (PNES) as epilepsy, since studies have found significant association of PNES with

comorbid PTSD and mild TBI. There is an opportunity to assess the PTSD-mild TBI-PNES nexus, given the availability of VHA databases and collaboration of VA clinician-researchers who can conduct multi-site evaluations using a standard protocol.

This basic assessment of VHA epilepsy epidemiology is a foundation on which additional studies can build. The VHA current databases and the ECoE clinical templates will facilitate continued epidemiology surveillance as recommended by the IOM report. This epidemiology surveillance will be key to informed decision-making for a fully integrated VHA epilepsy program that leverages technology, expands access to specialty care, and maximizes resources. ■

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# Etiology

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# Overview

The key to the treatment of epilepsy is establishing the diagnosis and, once a diagnosis of epilepsy is established, to identify the cause of the epilepsy. Identification of a cause, the etiology, directs both the treatment and the prognosis.

The underlying causes of epilepsy vary between populations and over time. Etiologies differ between children and adults and between intellectually normal and brain-impaired people. Epilepsy with onset in childhood and adolescence is predominately genetically determined, whereas onset of epilepsy in adults results mainly from acquired structural causes. However, even in patients for whom there is a structural cause, there is clear evidence of genetic influence on their predisposition to epilepsy.

The issue with identifying an etiology is that we only know the etiologies we can measure. An etiological framework depends greatly on scientific progress. Thus etiology is dependent on new technologies and the application of them in epilepsy. The use of EEG, neuroimaging, clinical and molecular biochemistry, molecular genetics, and statistical methodologies in clinical neurology has changed perceptions of etiology. It is also important to note that societal and nonscientific influences have played important roles in theories of epilepsy.<sup>1</sup>

# Classification

Classification of the etiologies is a fundamental tool that affects clinical practice and influences the direction of research. It serves as a means for universal communication. The most widely used system for classification of epilepsies and their etiologies is that proposed by the Commission on Classification and Terminology of the ILAE. In 2010 a major revision was proposed, and despite considerable debate in the professional community it provides a framework of concepts that reflects current understanding.<sup>2</sup> This classification represents a step forward in improving patient management and in understanding the neurobiology of the epilepsies. Epilepsy etiologies are classified into three categories: genetic, structural/metabolic, and unknown. The categories are not meant to be mutually exclusive. There is overlap between categories; one patient's epilepsy may have two or more causes. Etiology in this classification is not equated with prognosis.

TABLE 3.1

ETIOLOGY (underlying cause by type)
<ul style="list-style-type: none"><li>▪ Genetic</li><li>▪ Structural/metabolic</li><li>▪ Unknown cause</li></ul>

Source: Commission on Classification and Terminology of the International League Against Epilepsy, 2010.

The definitions used by the ILAE Classification Commission are:

**Genetic:** The epilepsy is, as best as understood, the direct result of known or presumed genetic defects in which seizures are the core symptom of the disorder. This attribution must be supported by specific forms of evidence.

**Structural/metabolic:** There is a distinct other structural or metabolic condition or disease that has been demonstrated to be associated with a substantially increased risk of developing epilepsy. These disorders may be of acquired or genetic origin. When of genetic origin, there is a separate disorder interposed between the gene defect and the epilepsy.

**Unknown:** The nature of the underlying cause is unknown; it may have a fundamental genetic basis (eg, a previously unrecognized channelopathy) or may be the consequence of an unrecognized structural or metabolic disorder not yet identified.

The discussions that ensued after publication of the etiological classifications have strongly suggested dividing structural and metabolic into their own separate categories, and adding immune and infectious as a category. The classification will continue to evolve as knowledge increases.<sup>3</sup>

## Select Structural and Metabolic Etiologies

### Hippocampal Sclerosis

Hippocampal sclerosis is recognized as one of the most important structural explanations for adult-onset epilepsy. The syndrome involves temporal lobe epilepsy that is usually antiepileptic-drug resistant and MRI imaging showing reduced hippocampal volume, increased signal intensity on T2-weighted imaging, and disturbed internal architecture. Increasingly sophisticated and powerful MRI enables hippocampal sclerosis to be identified—and potentially cured with surgery—in an increasing number of patients worldwide.<sup>4</sup> The excellent response to surgery of these patients makes it important to evaluate for this cause in all Veterans with inadequately controlled seizures. This evaluation must be done at an epilepsy center with an epilepsy monitoring unit and specified protocol for epilepsy brain imaging.

### Cerebral Malformations

Cortical dysplasia and arteriovenous malformations are other structural etiologies that can be found on brain imaging done for an etiological evaluation. Cortical dysplasia is the third most frequent finding in adults undergoing epilepsy neurosurgery. About 60% of patients with cortical dysplasia are seizure free after epilepsy neurosurgery, with the highest rates in complete resections.<sup>5</sup> Cerebral cavernous malformations (CCM) and arteriovenous malformations (AVM) are common; their asymptomatic prevalence on brain MRI is 1 in 625 and 1 in 2,000 respectively. In a population-based study, the 5-year risk of first seizure was 8% for AVM and 4% for CCM.<sup>6</sup>

### Autoimmune and Inflammatory Epilepsies

The role of immunity and inflammation in epilepsy has long been suggested by the anticonvulsant activity of steroids in some infancy and childhood epilepsies. Recently, the detection of autoantibodies in some unexplained epilepsies reinforced the causal place of immunity and inflammation in epilepsies with unknown etiology. Some antibodies are directly pathogenic to the brain, but others might only be markers of the immunopathologic process rather than pathogenic in themselves. These findings have opened up a group of possible causes and investigations in the epilepsies, and have paved the way for new immunosuppressive and immunomodulatory treatments.<sup>7</sup>

### Traumatic Brain Injury and Post-traumatic Epilepsy

In VA populations, TBI may be the most common etiology for epilepsy. This final section looks more in depth at this singular etiology due to its importance in Veterans.

In the general population, TBI accounts for 5% of all epilepsy and 20% of acquired epilepsy.<sup>8</sup> However, in certain military populations, the probability of developing post-traumatic epilepsy (PTE) can exceed 50%. This increased risk has been associated with a higher proportion of severe traumatic brain injuries, particularly those involving dural penetration. Over time and conflicts, the rate of incidence of PTE following missile injuries has remained remarkably consistent. As seen in civilian studies, the rate of developing PTE is highest in the first year following injury. The incidence of epilepsy within 5 years of injury ranges from 22% to 43% and is approximately 50% by 10 years, evidence that a significant number of Veterans develop epilepsy many years after injury.<sup>9</sup>

Much of what is known about TBI and the development of PTE stems from studies of combat Veterans from World War I to present-day conflicts. The Vietnam Head Injury Study (VHIS) has provided some of the most extensive longitudinal data regarding the development of PTE. Of the 421 Vietnam Veterans with penetrating head injury, 53% had PTE 15 years after injury.<sup>10</sup> Moreover, the risk of developing PTE within 1 year of injury was nearly 580 times that of the general age-matched population. Ten to 15 years later, the risk of developing PTE in this population was still 25 times higher than the general population. Phase 3 of the VHIS evaluated 199 of the original VHIS Veterans and demonstrated the prevalence of seizures to be 43.7% 30 to 35 years after injury, similar to the prevalence found in phase 2, 20 years earlier.<sup>11</sup> In addition, 12.6% experienced very late onset of PTE, with their first seizure occurring more than 14 years after injury.

As PTE has become more readily recognized and studied, it has proven extremely difficult to treat both medically and surgically. PTE also is beginning to serve as a model for epileptogenesis in an effort to identify novel biomarkers and target truly antiepileptogenic therapies.

## Conclusion

The clinician evaluating a Veteran with epilepsy must use history, neurological examination findings, EEG, and brain imaging to search for possible etiologies. In the Veteran population structural causes including trauma, stroke, and tumor are the most likely. However, genetic etiologies, such as juvenile myoclonic epilepsy, as well as immune etiologies can also be seen. Despite the increasing knowledge of genetic and immune mechanisms, and clinical laboratory testing to diagnose some of these conditions, this laboratory testing should be reserved for specific patients. It is best done in consultation with an epileptologist, who can appropriately direct evaluation as cost, patient and physician expectations, and ethical considerations may play a role in strategizing appropriateness of further testing.

If an etiology is not apparent after a standard clinical investigation, it may be that the etiology is unknown. However, evaluation at or in conjunction with an epilepsy center will help direct further diagnostic evaluation. ■

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# Differential Diagnosis

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# Introduction

New-onset spells are not uncommon complaints in the outpatient setting, with symptoms ranging from dizziness, light-headedness, and sensory alterations to focal motor symptoms and alterations in consciousness. Because the differential diagnosis is broad, a thorough and systematic approach is needed. The most important initial step in the workup is to get a detailed description of the event from both the patient and whenever possible a witness to the event(s). The importance of a witness cannot be overstated. The additional time it takes to call a first-hand observer (such as a family member, first responder, or bystander) is easily justified—the description they provide is often crucial to determining the correct etiology.

The differential diagnosis of new-onset spells can be broken down into four broad categories (FIGURE 4.1):

- Epileptic seizures
- Physiologic nonepileptic events
- Psychogenic nonepileptic events
- Events of uncertain etiology

While possible new-onset seizures require prompt evaluation, any spell accompanied by concerning symptoms—such as heart palpitations, diaphoresis, chest pain, or focal weakness—should immediately lead to an urgent workup for myocardial infarction, arrhythmias, and stroke, because missing one of these diagnoses can be catastrophic for the patient. Even when obvious symptoms of cardiovascular or cerebrovascular disease are absent, they should remain high on the differential diagnosis until sufficient data is available to rule them out. This is especially true in the older Veteran population, in which risk factors for vascular disease such as hypertension, diabetes mellitus, and hyperlipidemia are common. Furthermore, it has been demonstrated that a number of seizure types have been associated with cardiac arrhythmias, including asystole, and this should be considered as part of the evaluation. In contrast, a diagnosis of psychogenic events should only be entertained once other more serious etiologies have been definitively ruled out.

## Approach to the Evaluation of New-Onset Spells

Key questions that should be asked of both the patient and first-hand observer are outlined in TABLE 4.1. Try to get the patient, and observer if available, to describe in their own words exactly what they experienced or witnessed, from the first moment they became aware that something was wrong. Have them take you through the episode in detail in order to obtain a clear mental image of what they were experiencing throughout the event. When evaluating a patient that may have had many events, it can help if they describe their very first event, even if it was years ago. Then the examiner can question the patient about how subsequent events are similar to or different from the initial event. Once a general description has been obtained, the clinician should use the more directed questions outlined in TABLE 4.1 to fill remaining gaps. It is often necessary to repeat the questioning process over a series of discussions, and with several witnesses, to develop a clear description of the events in question. Supplemental aids, such as video cameras or smartphones, are available to many patients and families, and can be helpful tools.

## Epileptic Seizures

Epileptic seizures (often referred to simply as seizures) are of many different types. Elements of the history can often lead toward the diagnosis of a particular seizure type or epilepsy syndrome.

FIGURE 4.1 **Differential Diagnosis of New-Onset Spells**

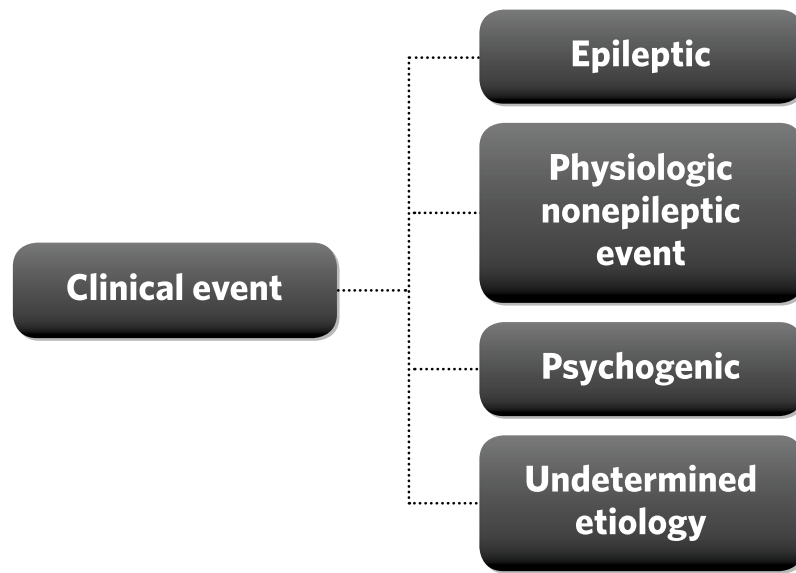


TABLE 4.1

KEY QUESTIONS TO ASK PATIENTS AND WITNESSES AS PART OF A NEW-ONSET SEIZURE WORK-UP
Was there any warning that something was going to happen? If so, what was (were) the warning sign(s)?
How long did the event last?
Was there any post-event confusion?
How long did it take to return to your pre-episode baseline?
How much of the episode do you remember?
Was there loss of bowel or bladder function?
Were there any abnormal movements or shaking? If so, please describe them in detail. <i>(If a witness is available, it can be helpful to get them to demonstrate the motor movements they saw.)</i>
If shaking was present, did it look like tremulousness (low amplitude and more like shivering) or was high-amplitude (clonic) jerking seen?
Did you injure yourself? <i>(Include tongue biting, abrasions, lacerations, and burns)</i>
What time of day do you typically have your spells? Do they occur out of sleep?



## Hallmark Features of Seizures

While seizures may present with a broad range of motor and sensory symptoms, hallmark features include sudden onset and brief duration (typically 1 to 2 minutes or less), with or without alteration in consciousness. Subsequent events tend to have a nearly identical presentation (stereotyped). In older Veterans, seizures may present with symptoms that are relatively nonspecific, such as dizziness, falls, or transient confusion. Making an accurate diagnosis may be especially challenging in the setting of other medical conditions and the use of multiple medications.

## Possible Epileptic Seizure Types

While a full description of the different types of seizures is beyond the scope of this chapter, a basic schema of seizure types is helpful when considering the differential diagnosis (FIGURE 4.2). Seizures are divided into focal or partial, if their onset is localized in the brain, or generalized if they arise from more global abnormal electrical discharges in the brain. Partial or focal seizures are further characterized as “simple,” if there is no alteration in consciousness, or “complex” if they are accompanied by any alteration or loss of consciousness.

Partial seizures can start with focal motor or sensory symptoms without any alteration in consciousness (simple), and progress to altered consciousness (complex) and even to a secondary generalized phase. The secondary generalization may occur so rapidly that an observer sees only the generalized convulsion.

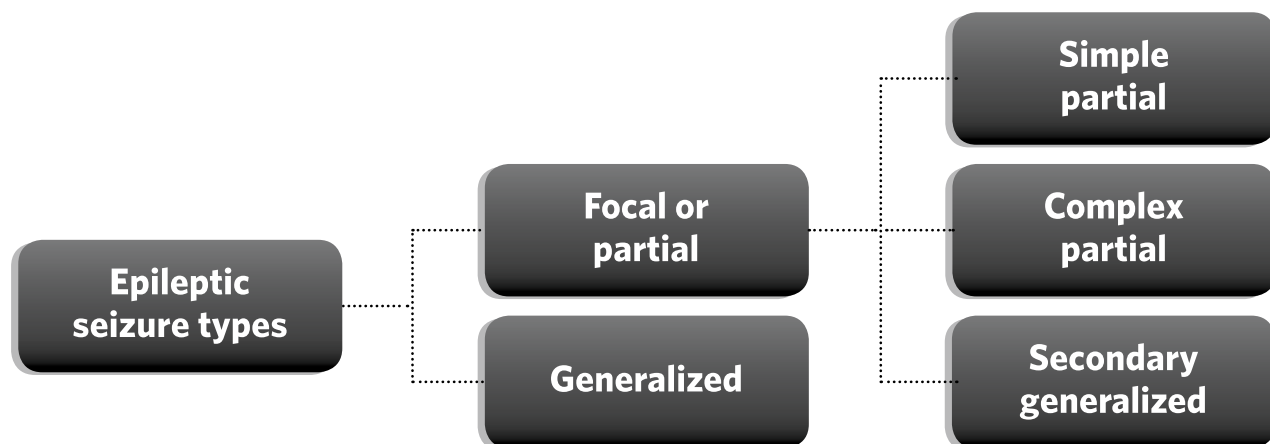
Generalized seizure syndromes are associated with the more global and nonfocal onset of abnormal electrical discharges in the brain. They are much less common than the focal epilepsies, may have a strong heritable component, and are rarely seen in Veterans—they typically have an onset in the first two decades of life. However, the authors have seen a number of cases where generalized epilepsy syndromes have been identified in younger Veterans, who may have had symptoms in their teens that went unrecognized until after they entered military service.

## Physiologic Nonepileptic Events

### Cardiovascular and cerebrovascular events

Heart disease and stroke are common in older Veterans. As previously emphasized, it is essential not to dismiss the possibility of cardiac and cerebrovascular events prematurely when considering a diagnosis of seizures. Cardiac arrhythmias,

FIGURE 4.2 Schema of Seizure Types



which can lead to symptoms ranging from a funny sensation in the chest to sudden loss of consciousness, can be erroneously attributed to partial seizures. They may be described as “drop attacks.” Seizures presenting as “drop attacks” are almost exclusively seen in severe epilepsy syndromes that begin in childhood. Any adult, especially an older individual, presenting with drop attacks should urgently be evaluated for an arrhythmia or other cardiovascular condition.

Similarly, the sudden onset of focal neurological symptoms such as weakness or sensory changes should prompt urgent workup for a stroke. Even if obvious cardiovascular or cerebrovascular symptoms are absent, the clinician should have a low threshold for obtaining an EKG and carotid ultrasound, especially in individuals older than 50 years of age or with increased cardiovascular risk factors.

## **Metabolic and Medication Issues**

Metabolic abnormalities and medication changes may mimic symptoms of seizures, especially in older Veterans or those with chronic conditions such as diabetes mellitus. In debilitated patients, even mild upper respiratory and urinary tract infections or modest medication changes can result in alterations in mental status that, if fluctuating, may mimic the unresponsiveness and brief staring that can be seen with complex partial seizures. Similarly, episodes of hypoglycemia can result in episodes of unresponsiveness or, if severe enough, in actual seizure activity. A history of medication or treatment changes temporally associated with the onset or worsening of spells should prompt further investigation into iatrogenic or medication-induced spells. Examples include spells induced by hypotension or bradycardia with beta blockers and confusion associated with initiation of benzodiazepines, especially in the elderly or debilitated.

## **Other Neurologic Events**

Headaches, sleep, and movement disorders can present with seizure-like symptoms. Headache associated with nausea, vomiting, phonophobia, or photophobia suggests migraine, if typical visual symptoms such as flashing lights or scotoma are seen, especially in the setting of a family history of similar symptoms. However, if the events are of new onset or are not consistent with previous headache symptoms, more serious cardiovascular and cerebrovascular causes should be considered.

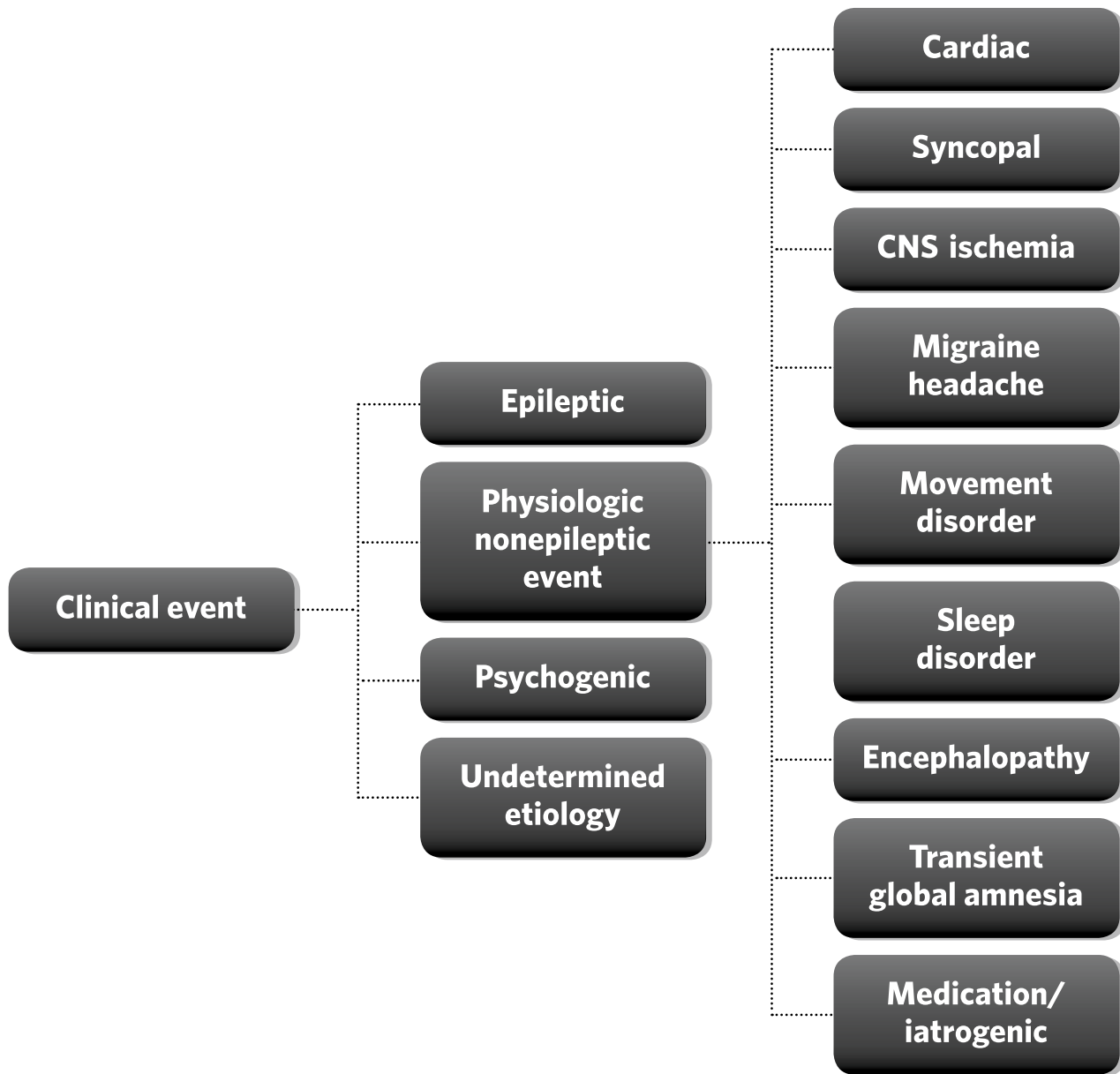
If events occur solely from sleep, a primary sleep disorder may be the problem. Patients with untreated sleep apnea, REM sleep behavior disorder, and periodic limb movements of sleep may thrash around at night and raise concern for seizures. A number of movement disorders such as myoclonus and tremor (especially if intermittent) may at times be confused with seizures. Myoclonus can be cortically generated in some types of generalized seizure disorders, such as juvenile myoclonic epilepsy. In general, the myoclonic epilepsies are associated with other types of seizures, such as absence or generalized tonic-clonic events. They are also notable in that they usually have an onset in the second or third decade of life.

Transient global amnesia and encephalopathy uncommonly mimic seizures but should be considered in the broad differential of new-onset spells. Transient global amnesia may have confusion and memory loss as a prominent feature. It is generally not associated with abnormal movements, and usually presents as a single episode that lasts less than 24 hours. Encephalopathies typically present with altered mental status and may have tremulousness as a component. The mental status changes may wax and wane, raising the possibility of subclinical seizures. In these cases, an EEG may be the only definitive method of ruling out seizures; sometimes continuous monitoring is needed.

## **Psychogenic Nonepileptic Events (Psychogenic Seizures)**

Once epileptic spells and physiological nonepileptic spells have been ruled out, psychogenic causes should be considered. A history of PTSD, anxiety, depression, and physical, psychological, or sexual abuse all increase the risk of psychogenic seizures. Spells that vary greatly from event to event are typical, as are those hallmarked by uncoordinated

FIGURE 4.3 **Differential Diagnosis of Physiologic Nonepileptic Events**



movements that do not fit a physiological pattern (such as contralateral arm and leg shaking or bilateral arm shaking with reported loss of consciousness but no leg involvement). However, making a definitive diagnosis of psychogenic seizures usually requires elective admission to an inpatient EMU and capturing at least 2 to 3 of the patient's typical events and confirming that no electrographic discharges are recorded during the episode. This is important to ensure that atypical epileptic events or other physiologic problems, such as a cardiac cause, are not overlooked. Up to 10% of individuals with epileptic events may also have psychogenic seizures. EMU monitoring can help sort out which episodes require adjustment of antiepileptic medications and which require other interventions such as therapy with a mental healthcare provider.

# Events of Uncertain Etiology

Even when an exhaustive workup has been performed, the exact etiology of spells may remain uncertain. It is important that these patients continue to be followed clinically to ensure that their spells do not progress or to identify new signs or symptoms that emerge. Intermittent reevaluation is often needed in these patients, and all possibilities, including latent cardiac issues, should be considered. When the clinician believes that serious or potentially reversible causes have been ruled out, reassuring the patient, even if a definitive diagnosis has not been made, can bring significant relief. In addition, treatment focused on relieving any accompanying discomfort should be initiated. General education promoting a balanced diet, regular exercise, and stress reduction should be offered and may increase the patient's overall sense of well-being.

## Conclusion

Clinicians seeing patients with new-onset spells should obtain a thorough description of the events, with the goal of determining whether urgent workup for cardiovascular and cerebrovascular disease needs to be undertaken. If these diagnoses seem less likely, and the episodes appear to be stereotyped and short in duration, then the likelihood that they are seizures increases substantially.

If diagnostic uncertainty remains, a broader range of metabolic and psychiatric disorders should be considered. With increasing VA-wide access to EMU, referral to one of these centers should be seriously considered, especially in cases where the spells are substantially interfering with daily function. The earlier a diagnosis can be made, the sooner optimal treatment can be initiated, and the less likely that unnecessary therapies will be undertaken. Furthermore, there is evidence that having poorly controlled spells for extended periods of time, irrespective of their etiology, can result in long-term disability. Early monitoring in the EMU in cases of diagnostic uncertainty is justified, even if the index of suspicion for seizures is low, because it is often possible to rule out seizures, or to identify another potentially reversible etiology.

Even when a thorough history and evaluation have been performed and extensive diagnostic testing has been undertaken, it may not be possible to make a firm diagnosis. In these cases, patients should be seen periodically in clinic until the spells spontaneously remit or until new signs and symptoms emerge, resulting in a specific diagnosis. ■

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# Clinical Evaluation

**AATIF M. HUSAIN**



# Introduction

The clinical evaluation of epilepsy patients, like any other patient, involves a careful review of the history, thorough examination, and directed laboratory and neuroimaging studies. Whereas history from the patient is very important, arguably even more important is observer history from a family member or friend of the epilepsy patient. The observer can provide details of the seizures that the patient cannot provide. The examination provides further clues about whether a brain disorder or lesion is present. Not only is the neurologic examination important, but the general physical and skin examinations also provide important information. Electroencephalography (EEG) and neuroimaging evaluation is also very important, and depending on the clinical situation magnetic resonance imaging (MRI) or computed tomography (CT) may be more appropriate. Laboratory testing helps exclude possible provoking factors for seizures and occasionally, particularly in pediatrics, may lead to a neurologic or metabolic disorder causing seizures. The unique features of the clinical evaluation of an epilepsy patient will be discussed in further detail below, with a focus on the adult patient.

One of the main goals of the clinical evaluation is to classify the seizure type. Recently the International League Against Epilepsy (ILAE) updated seizure classification.<sup>1</sup> A summary of this classification is presented in TABLE 5.1. Once the seizure types are identified, the clinical evaluation can help determine the epilepsy syndrome. Details of these classifications are presented elsewhere in this text.

In this chapter the patient's episodes are referred to as seizures. It is recognized that when initially evaluating a patient, it may not be certain if the episodes are indeed epileptic or nonepileptic seizures. Moreover, there is disagreement as to whether nonepileptic episodes should be called seizures, attacks or spells.<sup>2</sup> There are advantages and disadvantages for each of these terms, but in this chapter the term "seizure" will be used without implication of whether it is epileptic or not, unless otherwise specified.

## History

The history is the most important feature of the clinical evaluation of an epilepsy patient. Whereas the patient can describe many aspects of the history, she/he is necessarily a poor witness of the actual seizure. Since obtaining a description of the actual seizure is important, talking with a family member or friend who has seen the seizures is important. In addition to obtaining the basic demographic information, determining handedness is very important. This helps establish cerebral dominance, which in turn may help with localization of seizure onset.

## Description of Seizures

The examiner must first determine how many different types of seizures the patient has. The nature of each seizure type must be described. Additionally, the age of onset, frequency and evolution over time should be determined.

A detailed description of what happens to the patient during a seizure is very important to obtain. The various features of a seizure that should be noted are presented in TABLE 5.2. The presence of an aura should be determined. Mentation during an aura is not altered, and the patient is aware of their surroundings. An aura can be of various types, including various sensory hallucinations, light-headedness, déjà vu sensation, abnormal taste or sensation or an indescribable sensation. The duration of the aura and the consistency with which the aura precedes the seizure should be noted. Most often the aura is followed quickly by the seizure, but sometimes auras occur in isolation and are only rarely followed by a seizure. By definition, an aura is a restricted, focal epileptic discharge. If the presence of an aura can be confirmed, it becomes very likely that the seizure is focal. The manifestation of the aura represents the site of onset of the ictal discharge.

An aura must be distinguished from a prodrome. The latter is a sense of being unwell or other vague sensation that can precede a seizure by minutes to days. The prodrome may be followed by an aura, which quickly leads into a seizure, or the prodrome may eventually lead to a seizure directly. Whereas an aura is an epileptic phenomenon,

**TABLE 5.1 Classification of Seizures (prior classification presented in italics)**

**FOCAL ONSET (*partial seizures*)**

- ▶ Awareness
  - Aware (awareness preserved) (*simple partial seizures*)
  - Impaired awareness (*complex partial seizures, dyscognitive seizures*)
- ▶ Onset
  - Motor onset
    - Automatism
    - Atonic
    - Clonic
    - Epileptic spasms
    - Hyperkinetic
    - Myoclonic
    - Tonic
  - Nonmotor onset
    - Autonomic
    - Behavior arrest
    - Cognitive
    - Emotional
    - Sensory
- ▶ Focal to bilateral tonic-clonic (*secondarily generalized seizure*)

**GENERALIZED ONSET**

- ▶ Motor
  - Tonic-clonic
  - Clonic
  - Tonic
  - Myoclonic
  - Myoclonic-tonic-clonic
  - Myoclonic-atonic
  - Atonic
  - Epileptic spasms
- ▶ Nonmotor (absence)
  - Typical
  - Atypical
  - Myoclonic
  - Eyelid myoclonia

**UNKNOWN ONSET**

- ▶ Motor
  - Tonic-clonic
  - Epileptic spasms
- ▶ Nonmotor
  - Behavioral arrest
  - Myoclonic
  - Eyelid myoclonia

**UNCLASSIFIED**

Source: Adapted from Fisher RS, Cross JH, French JA, et al. Operational classification of seizure types by the International League Against Epilepsy: Position Paper of the ILAE Commission for Classification and Terminology. *Epilepsia*. 2017;58:522-530.



a prodrome is not. A prodrome can occur with focal or generalized seizures, and does not help establish a site of onset of the ictal discharge.

The degree of mental status impairment during a seizure should be determined. When there is no impairment of consciousness or awareness, the presence of motor, sensory or autonomic features is noted. These are the same as auras. In the previous ILAE classification, these were referred to as simple partial seizures.<sup>3</sup> If the patient is unable to respond to surrounding, the consciousness and awareness is altered, and the seizure is referred to as dyscognitive. Previously these were called complex partial seizures. Various motor, autonomic and other symptoms, such as tongue biting and incontinence, may also be present in seizures with altered consciousness, and their presence is noted. The motor activity may be in the form of automatisms of the hands or mouth, clonic activity, myoclonic jerks, falls, etc. These features help in localizing the site of onset of the seizure.

Various postictal phenomena are frequently noted, and their presence should be determined. These include fatigue, head-aches, confusional state and psychosis. The duration of the seizure and the postictal phase should be determined. Seizures are terrifying events for family, friends and on-lookers, and the duration of the event is frequently overestimated. Most seizures, whether focal or generalized, usually do not last longer than 60-90 seconds.

## Description of First Seizure

Details of the first recognized seizures should be sought from the patient and family members. All features discussed above about individual seizure types should be asked in reference to the first seizure. How this seizure type has evolved

**TABLE 5.2 Features of a Seizure History and Description**

<p><b>Aura</b></p> <ul style="list-style-type: none"> <li>Olfactory hallucinations</li> <li>Visual hallucinations</li> <li>Auditory hallucinations</li> <li>Lightheadedness</li> <li>Déjà vu</li> <li>Abnormal taste</li> <li>Abdominal sensation</li> <li>Indescribable sensation</li> </ul> <p><b>Duration of aura</b></p> <ul style="list-style-type: none"> <li>&lt;30 sec</li> <li>31 to 59 sec</li> <li>1-5 min</li> <li>&gt;5 min</li> </ul> <p><b>Mental status</b></p> <ul style="list-style-type: none"> <li>Loss of awareness</li> <li>Loss of consciousness</li> <li>Aphasia</li> </ul> <p><b>Motor activity</b></p> <ul style="list-style-type: none"> <li>Automatism (facial or manual)</li> <li>Focal motor activity</li> <li>Generalized motor activity</li> <li>Focal to generalized motor activity</li> </ul>	<p><b>Sensory symptoms</b></p> <ul style="list-style-type: none"> <li>Paresthesia</li> <li>Dysesthesia</li> <li>Numbness</li> </ul> <p><b>Autonomic symptoms</b></p> <p><b>Other symptoms</b></p> <ul style="list-style-type: none"> <li>Tongue biting</li> <li>Incontinence</li> </ul> <p><b>Postictal phase</b></p> <ul style="list-style-type: none"> <li>Fatigue</li> <li>Headache</li> <li>Confusional state</li> <li>Psychosis</li> </ul> <p><b>Duration of seizures</b></p> <ul style="list-style-type: none"> <li>&lt;30 sec</li> <li>31-59 sec</li> <li>1-5 min</li> <li>&gt;5 min</li> </ul> <p><b>Duration of postictal state</b></p> <ul style="list-style-type: none"> <li>No postictal period</li> <li>&lt;5 min</li> <li>5-30 min</li> <li>&gt;30 min</li> </ul>
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and whether it is still occurring should be determined. The examiner should appreciate that the first recognized seizure may not have been the first ever seizure. First ever seizure may have been subtle, such as a brief staring spell, and not recognized as a seizure. Some patients only recognize that they have epilepsy after a tonic-clonic seizure.

## General Issues Relevant to Seizures

There are several other details of the patient's overall seizure history that should be determined. A summary of these is presented in TABLE 5.3. Sometimes seizures have specific triggers. Identification of triggers, if present, is very important, as avoiding these triggers, if possible, may have a significant impact on seizure control. Seizures may also have circadian triggers. Sometimes seizures occur during a particular phase of the sleep-wake cycle, such as only upon awakening from sleep or only in sleep. These features, if elicited, help narrow the epilepsy syndromic diagnosis. Whether seizures result in injuries should be noted, as this will help determine what safety advice should be given to patients. Additionally, fitness for driving and operating other machinery may be influenced by prior injuries. Patients should be questioned about a prior history of status epilepticus (SE). This information may help in localization of seizure onset and may affect medical management of these patients.

Many epilepsy patients have a variety of sleep complaints and disorders. Daytime sleepiness is a common complaint and may be due to medications, sleep deprivation or primary sleep disorder such as sleep apnea. Presence of untreated sleep apnea may result in greater difficulty in controlling seizures. Thus asking patients about sleep complaints, in particular symptoms of sleep apnea, is very important and may help in better managing these patients.

TABLE 5.3 Other Seizure Details

<p><b>Triggers</b></p> <ul style="list-style-type: none"> <li>Stress</li> <li>Sleep deprivation</li> <li>Infection/illness</li> <li>Fasting</li> <li>Illicit drugs</li> <li>Alcohol use</li> <li>Menstrual cycle</li> <li>Flashing lights</li> </ul>	<p><b>Seizure occurrence time</b></p> <ul style="list-style-type: none"> <li>Diurnal</li> <li>Nocturnal</li> <li>Upon awakening</li> <li>No pattern</li> </ul> <p><b>Injuries with seizures</b></p> <ul style="list-style-type: none"> <li>Bruise</li> <li>Laceration</li> <li>Burn</li> <li>Fracture</li> </ul> <p><b>History of status epilepticus</b></p>
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TABLE 5.4 Risk Factors for Seizures

<ul style="list-style-type: none"> <li>▪ Maternal illness during pregnancy</li> <li>▪ Prematurity</li> <li>▪ Birth-related injury</li> <li>▪ Congenital malformations</li> <li>▪ Febrile seizures</li> <li>▪ Stroke</li> <li>▪ Tumor</li> </ul>	<ul style="list-style-type: none"> <li>▪ Dementia</li> <li>▪ Meningitis</li> <li>▪ Encephalitis</li> <li>▪ Family history of seizures</li> <li>▪ Trauma</li> <li>▪ Other</li> </ul>
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Mental health problems are common in epilepsy patients. Depression and anxiety should be specifically sought. Antiepileptic drugs (AED) may make these worse (or better in some cases). Untreated, mental health disorders can hinder adequate management of epilepsy patients, both by affecting quality of life and by reducing compliance with AED. Post-traumatic stress disorder (PTSD) is a common disorder in veterans and commonly coexists with psychogenic nonepileptic seizures (PNES).<sup>4</sup>

## Etiology/Risk Factors

When a patient is first diagnosed with epilepsy, one of the foremost questions she/he has is, “Why did I have a seizure?” Every patient must be questioned about risk factors for seizures that may suggest an etiology. The etiology will ultimately be found only in a minority of patients with seizures, but that does not preclude a thorough evaluation. Common historical elements that the patient should be questioned about are presented in TABLE 5.4.

In adult patients questions about childhood are often skipped, but these are very important and should be asked. Birth related history is important to determine: was the delivery premature, were there any congenital malformations, were there any maternal illnesses, and was the delivery Caesarian, vaginal or forceps/suction assisted? Childhood problems such as febrile seizures, educational difficulties, etc. should also be determined. Some conditions that can cause seizures are seen more often in adults, and these include strokes, brain tumors and dementias. Presence of these should be sought. Infections such as encephalitis and meningitis can occur at any age and may be the cause of seizures. Family history of seizures should also be noted to determine if there is any genetic predisposition to seizures. After assessing these risk factors and completing the clinical evaluation, an etiology may be determined. Possible etiologies for seizures are presented in TABLE 5.5.

**TABLE 5.5 Etiology of Seizures**

- Viral, bacterial and parasitic infections
- Traumatic brain injury
- Stroke
- Intraventricular hemorrhage
- Hypoxic-ischemic encephalopathy
- Other metabolic or toxic insults
- Neurocutaneous syndromes; Inborn errors of metabolism
- Genetic and chromosomal development encephalopathies
- Developmental encephalopathy of unknown cause as evidenced by the presence of mental retardation, cerebral palsy, or autism with no evidence of a specific insult of disorder to which cause can be attributed preceding the onset of epilepsy
- Malformations of cortical or other brain development with or without known genetic determinants
- Neoplasia
- Mesial temporal sclerosis
- Dementia
- Other degenerative neurologic diseases
- Genetic or presumed genetic
- Epilepsy of unknown cause, without relevant abnormalities on examination, cognition, history, or imaging
- Other

Source: NINDS. NINDS common data elements: epilepsy [online]. Available at: [http://www.commondataelements.ninds.nih.gov/epilepsy.aspx - tab=Data\\_Standards](http://www.commondataelements.ninds.nih.gov/epilepsy.aspx - tab=Data_Standards). Accessed April 1, 2013.

## Trauma

Traumatic brain injury (TBI) is a common cause of seizure among veterans. Vietnam war era studies showed that TBI was a common cause of epilepsy, and that epilepsy could develop years after the trauma.<sup>5</sup> However, many head injuries in that conflict were of the penetrating type. In more recent wars, blast related TBI has been more common. How likely patients are to develop epilepsy after blast related TBI is unknown. Trauma related questions that the examiner should attempt to get answers to are presented in TABLE 5.6. The most important questions that the patient may be able to answer are the severity and type of trauma. Establishing the approximate time of trauma is important as well.

## Prior Treatment

Questioning the patient about prior treatments is important. Ideally, the drug, dose, plasma concentrations achieved, any side effects and reasons for discontinuation should be determined. This should be determined for each drug the patient has used in the past. Additionally, combination therapies that have been attempted should also be noted. Of course, in many situations patients will not remember all the details of the medications they have tried previously. At a minimum, the name of the AED and why it was discontinued should be determined. If a medication caused a serious allergic reaction, that should be noted.

TABLE 5.6 Traumatic Brain Injury and Epilepsy

<p><b>Cause of traumatic brain injury</b></p> <ul style="list-style-type: none"> <li>Road traffic incident</li> <li>Incidental fall</li> <li>Other non-intentional injury</li> <li>Violence/assault</li> <li>Act of mass violence</li> <li>Suicide attempt</li> <li>Other</li> </ul> <p><b>Severity of trauma</b></p> <ul style="list-style-type: none"> <li>Mild (LOC &lt;30 minutes)</li> <li>Moderate (LOC 30 minutes to 24 hours)</li> <li>Severe (LOC &gt;24 hours)</li> </ul> <p><b>Type of traumatic brain injury</b></p> <ul style="list-style-type: none"> <li>Closed</li> <li>Penetrating</li> <li>Blast</li> <li>Crush</li> <li>Unknown</li> <li>Other</li> </ul>	<p><b>Traumatic brain injury imaging results (if known):</b></p> <ul style="list-style-type: none"> <li>Skull fracture</li> <li>Epidural hematoma</li> <li>Extra-axial hematoma</li> <li>Subdural hematoma</li> <li>Subarachnoid hemorrhage</li> <li>Vascular dissection</li> <li>Traumatic aneurysm</li> <li>Venous sinus injury</li> <li>Midline shift</li> <li>Cisternal compression</li> <li>Fourth ventricle shift/effacement</li> <li>Contusion</li> <li>Intracerebral hemorrhage</li> <li>Intraventricular hemorrhage</li> <li>Diffuse axonal injury</li> <li>Traumatic axonal injury</li> <li>Penetrating injury</li> <li>Cervicomedullary junction/brainstem injury</li> <li>Edema</li> <li>Brain swelling (i.e., hyperemia)</li> <li>Ischemia/infarction/hypoxic ischemic injury</li> <li>Brain atrophy/encephalomalacia</li> <li>Other</li> </ul> <p><b>Surgery needed for TBI?</b></p>
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Source: NINDS. NINDS common data elements: traumatic brain injury [online]. Available at: [http://www.commondataelements.ninds.nih.gov/tbi.aspx?tab=Data\\_Standards](http://www.commondataelements.ninds.nih.gov/tbi.aspx?tab=Data_Standards). Accessed April 1, 2013.

Many AED are available in generic formulation. The interviewer should try to determine if the patient was taking brand name or generic AED, and if there were any problems converting from brand to generic formulation. Having pictures of medication is helpful, as patients may only know their pills by their shape and color and not name.

Patients who have had difficult to control seizures may have had other types of treatments as well. These include vagus nerve stimulator (VNS), dietary therapy (such as the modified Atkins or ketogenic diet) or surgical treatment. Details of these therapies should be obtained from the patient or chart. In particular the VNS should be interrogated and its settings noted.

Many patients use herbal medications and nutritional supplements with the belief that they improve general health and lessen side effects of AED. There is a general belief that these drugs do not cause side effects. In fact, many may interfere with AED and some may be proconvulsants. The examiner should identify which herbal medications and nutritional supplements the patient is using and their interactions with AED.

Many women with epilepsy are advised to take folic acid when they are prescribed an AED. This serves to reduce the risk of fetal malformations should be patient become pregnant while on an AED. Calcium/vitamin D is also prescribed to epilepsy patients, especially those on hepatic enzyme inducing AED. Adequate doses of calcium/vitamin D can prevent bone loss and reduce the risk of pathological fractures. Patients should be questioned about whether they are taking folic acid and calcium/vitamin D and their compliance with these medications.

## Other Medications and Allergies

Medication other than AED that the patient is taking should be determined. This includes both prescription and nonprescription drugs. Many such medications can have important drug-drug interactions with AED. Additionally, AED may affect these other medications. An important example is reduced efficacy of oral contraceptive pills (OCP) and warfarin with some AED like carbamazepine and phenytoin. Additionally, as noted above, herbal medications, nutritional supplements and homeopathic medications that a patient is using should be determined.

Determining allergies to medications is important. AED allergies should be specifically determined, and an attempt should be made to distinguish a true allergy versus an untoward side effect that the patient interpreted as an allergy. Other medicinal allergies should also be prominently noted in the patient's chart.

## Previous Diagnostic Work-up

Investigations that epilepsy patients have often undergone include EEG and MRI. EEG can be of many types, including routine, sleep deprived, ambulatory for 24-96 hours and video EEG monitoring. Results of these tests should be obtained, and ideally the tracing should also be obtained and reviewed by appropriately qualified individuals. "Over interpretation" of EEG, i.e. calling benign variants or variations of normal EEG patterns epileptiform is common and often lead to prolonged, unnecessary treatment with AED.<sup>6</sup> In many cases an "abnormal" EEG turns out to simply show a benign pattern that is not epileptiform. Similarly, MRI results should be obtained. It is now common for patients to present with their MRI scans on media that can be reviewed by the examining clinician. As with EEG, MRI should be reviewed and if there is any doubt about the finding, it should be reviewed with a qualified neuroradiologist.

Several other types of tests may also have been performed, and should be inquired about. These include positron emission tomography (PET), ictal and interictal single photon emission computed tomography (SPECT), neuropsychological testing and magnetoencephalography (MEG). It is unlikely that the patient will be able to provide results of these tests, and these should be obtained from their source. These tests are performed usually when surgical treatment for epilepsy is being contemplated, and consequently only a small percentage of epilepsy patients undergo these procedures.

## Other History

As with any other patient, an epilepsy patient's past medical, social and family history should be determined. Additionally a review of systems should be conducted to elicit other medical issues that did not become evident during history

taking. Positive findings should be explored further as indicated, or the patient should be told to discuss them with her/his primary care provider.

Important features in the social history that should be inquired about include level of education, living arrangements and marital status, current employment and driving. Knowing the level of education a patient has can help the examiner estimate whether substantial cognitive impairment is present, either due to the epilepsy, mental health problems or medications. Living arrangements and marital status will dictate the degree of services a patient might require. Employment (or student) status and driving will provide an insight into the degree of independence and social integration with the community. A patient in school will be able to avail support services (financial and social) through the community as well as the VA system. Most counties and schools have vocational rehabilitation counselors who can assist students with obtaining financial support from the state to attend school. This may be in the form of assistance with tuition, books and supplies and room and board. Additionally, they can assist patients with finding employment after completion of school. The patient's nicotine, caffeine, alcohol and recreational drug use history should be noted. Many of these, especially caffeine and alcohol, can affect seizure control when used in excess.

Family history about epilepsy should be determined. This may already have been asked earlier when discussing risk factors for seizures. It is not enough to know that there is a family history of seizures, but which relatives were/are affected and the type of seizures they have is important to establish. Not all patients will be able to provide these details. Family history of other significant medical conditions should also be determined.

## Examination

In addition to a general physical examination, a detailed neurological examination must also be conducted. The physical examination should focus on determining presence and severity of concomitant medical problems. Additionally, examination of the skin, nails, eyes and other organ systems can provide clues to underlying epilepsy etiology. Often neurocutaneous syndromes will have obvious findings that lead to a diagnosis even before neuroimaging. Dysmorphic facial and body features may also provide clues to the presence of brain malformations.

The purpose of a detailed neurological examination is to determine if a focal brain lesion is present. Such a focal lesion could serve as the focus of epileptic discharges. Focal findings on examination should be followed by appropriate neuroimaging studies to confirm the presence and cause of the lesion. Presence of focal findings on examination makes it more likely that AED will need to be used, as discussed below.

## Epilepsy Related Health Screening

Screening for medical conditions commonly coexisting with epilepsy is useful. The examiner may be alerted to potential problems that she/he may not have suspected, and because of the screening may be able to implement therapies that reduce future morbidity. Common conditions that are typically screened for in patients with epilepsy include depression (and suicidal ideation), quality of life and bone health.

### Depression and Suicidal Ideation

Screening for depression can be done simply by asking relevant questions during history. Various brief questionnaires are also available that can be used by the examiner or given to the patient to complete. The VA has a 2 question depression screening tool in its computerized patient record system (CPRS) that can be used whenever necessary (TABLE 5.7). If the score is greater than 5, a more comprehensive depression questionnaire opens automatically and needs to be completed. A score of 20 or greater on this evaluation is considered "positive" and further mental health evaluation and treatment should be considered. The Beck Depression Inventory (BDI) is another easy to use screen that can be given to patients to complete. The BDI score can be tallied to determine the presence and severity of depression. Patients

TABLE 5.7 VA Depression Screen

Over the past two weeks, how often have you been bothered by the following problems?

1. Little interest or pleasure in doing things

1. Not at all
2. Several days
3. More than half the days
4. Nearly every day

2. Feeling down, depressed, or hopeless

1. Not at all
2. Several days
3. More than half the days
4. Nearly every day

Scoring: A score of greater than 5 automatically leads to a more comprehensive depression screen. See text for details.

should also be specifically questioned about suicidal ideation. This is also addressed in the BDI, as a question specifically addresses this. Asking about and documenting suicidality is important as all AED have this listed as a potential complication. Of course, if suicidality is elicited, appropriate treatment and referrals should ensue.

## Quality of Life

The limitations imposed by epilepsy, in particular restrictions surrounding driving and compromised independence, can adversely impact quality of life. This can have a wide ranging impact, including on mood, medication compliance and seizure control. The Quality of Life in Epilepsy (QOLIE) questionnaire was developed to assess this issue. The QOLIE-89, QOLIE-31 and QOLIE-10 are validated measures having 89, 31 and 10 questions, respectively.<sup>7</sup> Whichever inventory is chosen can be completed by the patient before her/his appointment. The latest version of the QOLIE-10 (called the QOLIE-10-P) is available in CPRS and can be completed during a clinical evaluation by the physician or at any other time by any health care provider. Higher QOLIE-10-P scores represent better functioning, and if these are completed at regular intervals, changes in quality of life can be longitudinally evaluated.

## Bone Health

Bone health is a major public health concern. Reduced bone density can occur due to life style, increasing age, hormonal changes, lack of exercise, medications and many other reasons. This is common in older women, but epilepsy patients of all ages are particularly susceptible. Many AED, particularly enzyme inducing AED, can increase bone loss, leading to osteopenia and in severe cases osteoporosis. Bone density is best evaluated by a dual energy x-ray absorptiometry (DEXA) scan. How frequently a DEXA scan should be performed in epilepsy patients varies depending on age and AED, but generally it should be considered every 2-5 years. Measurement of serum vitamin D can be helpful when evaluating bone health. A low serum 25-hydroxy vitamin D level indicates a vitamin D deficiency. Supplementation should be recommended in these cases.

# Investigations

The most important investigations that are typically performed on patients with epilepsy are EEG and MRI. There are several types of EEG that can be done, and various neuroimaging tests other than MRI can also be performed to diagnose epilepsy and localize site of seizure onset. Additionally, serological tests, in particular AED serum concentration determinations, are important adjuncts to the clinical evaluation of epilepsy.

## EEG

An EEG is one of the most important tests that can be performed on a patient with epilepsy. Epileptiform activity can be detected on EEG, which greatly increases the likelihood that the patient has epileptic seizures. However, sometimes several EEG need to be obtained before a convincing epileptiform activity is detected.

Many different types of EEG can be performed. A routine EEG is a 20-30 minute recording, while a sleep deprived EEG is done after a full night or 24 hours of staying awake. This increases the probability of capturing epileptiform activity. Ambulatory EEG is a tracing in which electrodes are applied to the scalp in the EEG laboratory and then the patient is sent home. After 24-96 hours, the patient returns to the laboratory to return the machine and have their data downloaded. With ambulatory EEG the odds of capturing epileptiform activity increases as the amount of data recorded is much greater than a routine EEG. Video EEG monitoring encompasses admission to the hospital and recording video and EEG until the patient has a typical event. This latter type of testing can help characterize whether the event is an epileptic seizure or not, and if it is a seizure, its site of origin. The value of EEG is discussed elsewhere in this text.

## Neuroimaging

An imaging study of the brain is indicated in patients suspected of having seizures. MRI is the preferred technique for brain imaging, and several MRI protocols have been developed to evaluate specifically for seizures. These protocols include special cuts and sequences that better evaluate parts of the brain that are most likely to be the sites of seizure onset, such as the temporal lobes. A CT scan may be used to evaluate the brain when there is a contraindication to performing a MRI. When a patient presents emergently, a CT scan may be appropriate if there is an abnormal neurological exam, history of head injury or a focal seizure onset.<sup>8</sup> Other types of neuroimaging studies, such as PET, SPECT, MEG and functional MRI (fMRI) are various other tests that are used when evaluating a patient for epilepsy surgery. Details about MRI and other neuroimaging studies are discussed elsewhere in this text.

## Other Laboratory Tests

Other types of laboratory tests, such as serological, urine or cerebrospinal fluid (CSF), should be performed as dictated by the his-tory. Abnormalities in serum chemistries, particularly sodium and glucose, may cause seizures. Cell counts may suggest an infection. Urine and serum toxicology screen should be considered if there is a suggestion that recreational drugs could have caused the seizure. A CSF evaluation will not be needed in many patients, and clinical circumstances, such as an unexplained infection, will dictate if this is obtained.<sup>9</sup> A serum prolactin level can help distinguish an epileptic from a nonepileptic seizure. An elevated serum prolactin level obtained within 20 minutes of a generalized tonic-clonic seizure has a high sensitivity for the episode being epileptic.<sup>10</sup> A 25-hydroxy vitamin D level should be considered if bone health issues are present, as discussed above.

Serological tests are also used to monitor AED use. Serum concentrations for many AED can be measured. Care must be exercised to not try to dose AED so that plasma concentrations are within the “normal range”. AED dose should be adjusted to seizure control without side effects, whatever the plasma concentration may be. Checking plasma concentrations also aids in determining compliance of a patient with prescribed AED therapy. Liver function tests, serum chemistries and cell counts are also obtained to monitor potential adverse consequences of AED.



Specialized tests such as neuropsychological testing and sodium amytal (Wada) test are typically performed when surgical treatment is being considered. Neuropsychological testing may sometimes also be obtained to evaluate memory or mood related issues in epilepsy patients.

## Diagnosis Codes

After a complete evaluation, a diagnosis must be determined. If possible, seizures should be classified according the most recent ILAE classification. Additionally, the epilepsy syndrome should be determined. If the spells are nonepileptic, they should be noted as such. Also, whether the spell is psychogenic nonepileptic or some other type of nonepileptic spell (such as a sleep disorder or a syncopal event) should be specified. Many clinicians will also have to select an International Statistical Classification of Diseases and Related Health Problems – ICD-10 code for billing or workload credit purposes. TABLE 5.8 lists the various ICD-10 codes used in adult patients with epilepsy. Also included are codes for other types of spells (nonepileptic) that may be seen by neurologists and epileptologists. The most precise diagnosis code should be selected.

## Evaluation of First Seizure

Many patients are brought to the emergency department after their first seizure; some are seen by their primary care providers. A thorough evaluation is needed regardless of the setting in which the patient is seen. A thorough history must be obtained and examination conducted. Many of the history and examination items discussed above should be obtained, and ideally an observer should be questioned about what happened during the spell. Any provoking factors, such as sleep deprivation, trauma, infections, alcohol and recreational drugs should be sought. If no provoking factors are identified, the seizure is considered the “first unprovoked seizure”. Serological tests, including cell counts, serum chemistries and toxicology screens should be considered. Neuroimaging should be obtained. Urgently often only a CT scan of the brain is available. Acute neurological events, such as hemorrhage and trauma, can be evaluated well with a CT scan. The patient should be referred for an MRI scan as soon as possible, however. A routine EEG should also be obtained as soon as possible. Many patients will benefit from neurological consultation. Guidelines for evaluation of first unprovoked seizures have been published.<sup>9</sup>

Whether AED are started after the first unprovoked seizure depends on the clinical circumstances. In most instances, treatment is withheld unless the neurological examination is abnormal, there is a history of chronic static encephalopathy, the EEG shows clear epileptiform abnormalities or the MRI demonstrates a lesion that could generate seizures. If the decision is made to start an AED, the clinician has many choices, and the drug is picked based on the patient characteristics.

Regardless of whether an AED is started after the first unprovoked seizure or not, the patient will require counseling about safety issues and driving. Driving restrictions and whether patients need to be reported to the driving authorities depends on the state.

## Follow-up Evaluations

When an epilepsy patient returns for follow-up, certain features of the history are important to obtain. How many seizures occurred since last visit is important to know. If seizures have occurred, the circumstances in which they happen should be elicited. Particularly important is whether AED noncompliance, fevers and infections or illicit drug use contributed to the seizures. If several seizures have occurred, the seizure frequency should be determined. The type of seizures should be documented again, and if they are different than reported previously, the new seizure type should be carefully documented.

**TABLE 5.8 ICD-9 Epilepsy and Spells Diagnostic Codes**

<b>ICD 10 CODE</b>	<b>CONDITION</b>
G40A01	Absence epileptic syndrome, not intractable, with status epilepticus
G40A09	Absence epileptic syndrome, not intractable, without status epilepticus
G40A11	Absence epileptic syndrome, intractable, with status epilepticus
G40A19	Absence epileptic syndrome, intractable, without status epilepticus
G40309	Generalized idiopathic epilepsy and epileptic syndromes, not intractable, without status epilepticus
G40311	Generalized idiopathic epilepsy and epileptic syndromes, intractable, with status epilepticus
G40319	Generalized idiopathic epilepsy and epileptic syndromes, intractable, without status epilepticus
G40409	Other generalized epilepsy and epileptic syndromes, not intractable, without status epilepticus
G40411	Other generalized epilepsy and epileptic syndromes, intractable, with status epilepticus
G40419	Other generalized epilepsy and epileptic syndromes, intractable, without status epilepticus
G40209	Localization-related (focal) (partial) symptomatic epilepsy and epileptic syndromes with complex partial seizures, not intractable, without status epilepticus
G40211	Localization-related (focal) (partial) symptomatic epilepsy and epileptic syndromes with complex partial seizures, intractable, with status epilepticus
G40219	Localization-related (focal) (partial) symptomatic epilepsy and epileptic syndromes with complex partial seizures, intractable, without status epilepticus
G40109	Localization-related (focal) (partial) symptomatic epilepsy and epileptic syndromes with simple partial seizures, not intractable, without status epilepticus
G40111	Localization-related (focal) (partial) symptomatic epilepsy and epileptic syndromes with simple partial seizures, intractable, with status epilepticus
G40119	Localization-related (focal) (partial) symptomatic epilepsy and epileptic syndromes with simple partial seizures, intractable, without status epilepticus
G40B09	Juvenile myoclonic epilepsy, not intractable, without status epilepticus
G40B11	Juvenile myoclonic epilepsy, intractable, with status epilepticus
G40B19	Juvenile myoclonic epilepsy, intractable, without status epilepticus
G40509	Epileptic seizures related to external causes, not intractable, without status epilepticus
G40909	Epilepsy, unspecified, not intractable, without status epilepticus
G40911	Epilepsy, unspecified, intractable, with status epilepticus
G40919	Epilepsy, unspecified, intractable, without status epilepticus
G9381	Mesial temporal sclerosis
F445	Conversion disorder with seizures or convulsions
R404	Transient alteration of awareness
R401	Stupor
R400	Somnolence
R569	Unspecified convulsions
R561	Post traumatic seizures

It is best to encourage patients and family members to keep a diary to note their seizure. These diaries can be simple sheets of paper or electronic, cloud based versions. Various electronic diaries are available for patients to log on to and note their seizures. One such electronic resource is [epilepsy.com](http://epilepsy.com).

The AED the patient is taking should be reconciled with what she/he been prescribed. Any changes to preparation (brand vs generic) should be determined. Other medications should also be reviewed and any changes noted. The use of over-the-counter drugs, nutritional supplements and herbal medications should be reviewed. In particular, use of calcium/vitamin D and folic acid should be noted and encouraged. Every patient should be asked about side effects of AED.

The follow-up examination of an epilepsy patient is usually focused on eliciting signs of medication toxicity. These will typically include mood disturbances, rash, nystagmus, ataxia and gait disturbance. Some medication may have idiosyncratic side effects that must be evaluated, such as visual fields for patients taking vigabatrin. Other aspects of the neurological exam should be conducted as dictated by the clinical circumstances.

Epilepsy related health screening is important to consider at each visit. An assessment of the patient's mood is important, and the presence of depression should be evaluated. This can be a result of AED, epilepsy itself or an unrelated comorbid condition. Depression screening questionnaires discussed above should be considered. Of course, if significant depression is identified, its relationship to AED should be determined. Referral to a mental health provider should also be considered. Quality of life questionnaires should also be administered if possible. The QOLIE-10-P discussed above provides a reasonable assessment of how the patient's quality of life is changing with their disease and treatment. The need for a DEXA scan to evaluate bone health should be evaluated. The frequency with which a DEXA scan is performed varies with the clinical situation, but it should be considered every 2-5 years. Along with a DEXA scan, a 25-hydroxy vitamin D level may be obtained.

Appropriate laboratory tests should be ordered. These may include serum AED concentrations or cell counts and chemistries to evaluate for medication toxicity. There are many other specialized tests that may be needed depending on the clinical scenario. Similarly, EEG and neuroimaging tests should be ordered as indicated.

The most appropriate diagnosis should be listed and ICD-9 diagnosis code selected (TABLE 5.8). If this is different than the diagnosis in previous visits, that should be noted and discussed. Appropriate referrals should be made.

## Patient Education

Educating patients about epilepsy and its consequences is one of the clinician's most important roles. Certainly patients with new onset seizures but also those with established epilepsy have many questions about why they have seizures, whether they lose "brain cell" with each seizures, psychosocial consequences, risk of passing on the epilepsy to their children, etc. In addition to answering these questions, the clinician should consider educating the patient on several other issues that are important to many patients with epilepsy. A list of these is presented in TABLE 5.9. All of these cannot be covered in a single visit, and follow-up visits should be used to continue to educate patients about their disorder.

## Driving

One of the most frequently asked questions is about driving. Generally, patients whose seizures are not controlled are restricted from driving. However, in the US, each state has different laws about how long a patient must be seizure free before they can start driving. The practitioner should be aware what the regulations are in the state in which they practice. Several website maintain up-to-date lists of these requirements sorted by state. One such example is the Epilepsy Foundation, whose website (<http://www.epilepsyfoundation.org/resources/drivingandtravel.cfm>) has this information. In addition to whether a patient should be driving, the clinician must be aware of the reporting rules of the state. Some states mandate that the treating clinician report any patient with seizures, whereas others allow reporting only if there is a significant public safety concern.

TABLE 5.9 **Epilepsy Patient Education**

- Driving
- Antiepileptic drug side effects
- Treatment compliance
- Pregnancy
- Contraception
- Bone health
- Safety issues
- Mental health
- Suicidal ideation
- Sudden unexpected death in epilepsy (SUDEP)
- Epilepsy education resources

## **Antiepileptic Drug Adverse Effects**

Before any AED is prescribed, patients should be told of the typical side effects that they might experience. The frequency with which these side effects are seen should be mentioned as well. Some drugs have useful side effects, such as weight loss with topiramate, and these should be mentioned as well. Additionally any unusual and unusually severe side effects that could occur should be discussed with the patient. All AED have a warning about suicidality, and depression and suicidality should be discussed with the patient. If anything can be done to mitigate the side effects of AED that should be discussed as well. Potential interaction of AED with other medications the patient may be taken should be noted.

## **Treatment Compliance**

Treatment compliance should be stressed. The commonest cause of breakthrough seizures is medication noncompliance. Patients should be encouraged to get devices like pill boxes to help them remember to take their medications. Additionally services are available that will text page patients when it is time to take their medication.

## **Pregnancy and Contraception**

With women of childbearing potential, pregnancy and contraception issues must be discussed prior to initiating AED treatment. Some AED are more teratogenic than others, and the affect the selected AED can have on the fetus should be discussed with the patient. Why the particular drug was chosen should be shared with the patient as well. Folic acid use should be encouraged to minimize the risk of teratogenicity. Some AED interact with hormonal contraception and reduce their contraceptive efficacy. For women using hormonal contraception, whenever possible AED that do not affect this should be used. If that is not possible, the patient should be clearly informed of the consequence and encouraged to seek alternate forms of contraception. Some AED, such as lamotrigine, do not reduce the efficacy of hormonal contraception, however OCP increase its metabolism and result in lower plasma concentrations. In these cases lamotrigine dose may need to be increased.

## **Bone Health**

All patients should be counseled about bone health. Many factors can lead to reduced bone density, including epilepsy and AED. The risk of developing osteopenia and osteoporosis depends on the AED, with enzyme inducing AED, such as carbamazepine and phenytoin, carrying a higher risk. Ways to mitigate bone loss, such as with calcium/vitamin D supplementation should be discussed and patients started on supplements if indicated. The need for a DEXA scan and 25-hydroxy vitamin D level should be discussed.

## Safety Issues

There are many safety issues that potentially can be discussed with epilepsy patients. Which ones are discussed will depend on the patient's circumstances. Among the most important safety concern is driving. Employment related safety should also be reviewed. If the patient works in an environment in which she/he may be dangerous to self or others, that should be addressed. The patient should be removed from such an environment. Climbing on ladders and swimming unattended should be disallowed. Whereas safety issues are important to remind patients of, it should be recognized that safety concerns should not prevent epilepsy patients from leading full and productive lives.

## Mental Health and Suicidal Ideation

As noted previously, epilepsy and AED can adversely affect mental health. Depression and anxiety disorder are common in epilepsy patients. Moreover, many psychiatric disorders such as PTSD may be linked to development of PNES. Treatment of the underlying disorder is imperative for recovery. Sometimes the severity of the mental health condition is such that the patient is suicidal. It should be recognized that all AED carry a heightened risk of suicidality. If this is thought to be because of AED, that AED should be discontinued. Many patients will require referral to mental health experts for further evaluation and treatment.

## Sudden Unexpected Death in Epilepsy (SUDEP)

The vast majority of epilepsy patients enjoy full and long lives. However, the risk of death is higher in epilepsy patients than healthy peers. Death can occur due to an epilepsy related accident, a severe medication related adverse effect or due to the underlying condition. However, sudden unexpected death in epilepsy (SUDEP) is one of the most common causes of premature death in epilepsy patients. It is more common in patients with generalized tonic-clonic seizures, refractory seizures and in those with cognitive impairment. When SUDEP is discussed with patients and families depends on both the comfort of the practitioner in discussing this issue and the patient in hearing about it. There is general agreement that it should be addressed at some point during treatment.

## Epilepsy Education Resources

There are many resources available for epilepsy patients. These include websites that provide education and other services (such as seizure calendars) and others that provide an avenue for advocacy and research. A brief list of such websites is presented in TABLE 5.10. Patients can be referred to these resources to learn about epilepsy, participate in advocacy, contribute to or participate in research and connect with other patients with epilepsy.

Governmental resources may be available for epilepsy patients as well. Vocational rehabilitation services are available in many universities and states and provide education and vocational assistance. Other resources through the VA and other agencies may also be available. Resources for patients are discussed elsewhere in this text as well.

## Epilepsy Quality Measures

The American Academy of Neurology (AAN) has developed quality measures for epilepsy.<sup>11</sup> These measures were derived by reviewing literature for guidelines, recommendations and expert statements on what constitutes high quality care for epilepsy patients. Eight quality measures have been identified, and their implementation will likely improve the quality of care delivered to patients with epilepsy. These measures are presented in TABLE 5.11.

These quality measures summarize what is most important to assess in the clinical evaluation of patients with epilepsy. Seizure type and frequency must be determined. An attempt must be made to determine the etiology of seizures and identify the epilepsy syndrome if possible. An EEG and MRI or other neuroimaging study should be obtained or reviewed if previously performed. Patients should be queried about AED side effects. In those patients whose seizures are not controlled with medications, surgical therapy should be considered. Confirmatory video EEG

TABLE 5.10 **Websites with Epilepsy Resources\***

RESOURCE	WEB ADDRESS	SERVICE PROVIDED
<b>Epilepsy Foundation**</b>	<a href="http://www.epilepsyfoundation.org">www.epilepsyfoundation.org</a>	Education, information, research, advocacy, support
<b>Epilepsy.com**</b>	<a href="http://www.epilepsy.com">www.epilepsy.com</a>	Education, information, research, advocacy, support
<b>American Epilepsy Society</b>	<a href="http://www.aesnet.org/patients">www.aesnet.org/patients</a>	Information
<b>Centers for Disease Control (CDC)</b>	<a href="http://www.cdc.gov/epilepsy">www.cdc.gov/epilepsy</a>	Education, information
<b>Citizens United for Research in Epilepsy (CURE)</b>	<a href="http://www.cureepilepsy.org">www.cureepilepsy.org</a>	Research, awareness, advocacy
<b>Epilepsy Advocate</b>	<a href="http://www.epilepsyadvocate.com">www.epilepsyadvocate.com</a>	Education, information, scholarships
<b>International League Against Epilepsy (ILAE)</b>	<a href="http://www.ilae.org/Visitors/Centre/Index.cfm">www.ilae.org/Visitors/Centre/Index.cfm</a>	Information
<b>Patientslikeme</b>	<a href="http://www.patientslikeme.com/conditions/3-epilepsy">www.patientslikeme.com/conditions/3-epilepsy</a>	Social media, education, information
<b>National Institute of Neurological Disorders and Stroke (NINDS)</b>	<a href="http://www.ninds.nih.gov/disorders/epilepsy/epilepsy.htm">www.ninds.nih.gov/disorders/epilepsy/epilepsy.htm</a>	Education, information, research
<b>Veterans Affairs Epilepsy Centers of Excellence</b>	<a href="http://www.epilepsy.va.gov">www.epilepsy.va.gov</a>	Education, information

(\*) This is an incomplete list. There are many more organizations and websites that provide education, information and other services to patients with epilepsy.

(\*\*) Most useful websites for patients with epilepsy.

TABLE 5.11 **AAN Epilepsy Quality Measures<sup>11</sup>**

1. Seizure type and current seizure frequency
2. Documentation of etiology of epilepsy and epilepsy syndrome
3. EEG results reviewed, requested or test ordered
4. MRI/CT scan reviewed, requested or scan ordered
5. Querying and counseling about antiepileptic drug side effects
6. Surgical therapy referral consideration for intractable epilepsy
7. Counseling about epilepsy specific safety issues
8. Counseling for women of childbearing potential with epilepsy

monitoring should also be considered to differentiate between epileptic and nonepileptic seizures. Counseling patients about safety, in particular driving, is very important. Additionally, appropriate counseling for women of childbearing potential is essential.

## Conclusion

An orderly approach to the clinical evaluation of a patient with seizures is necessary to arrive at the correct diagnosis. A complete and thorough history and examination complemented by EEG and neuroimaging are most likely to provide the correct diagnosis. At every visit the patient provides additional information that supplements their history and may further refine the assessment. Educating the patient about epilepsy, its consequences and AED is an essential part of every clinical evaluation. The availability of quality measures provides a guide for practitioners regarding what is most important to assess in the clinical evaluation of epilepsy patients. ■

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6

# Seizure Semiology

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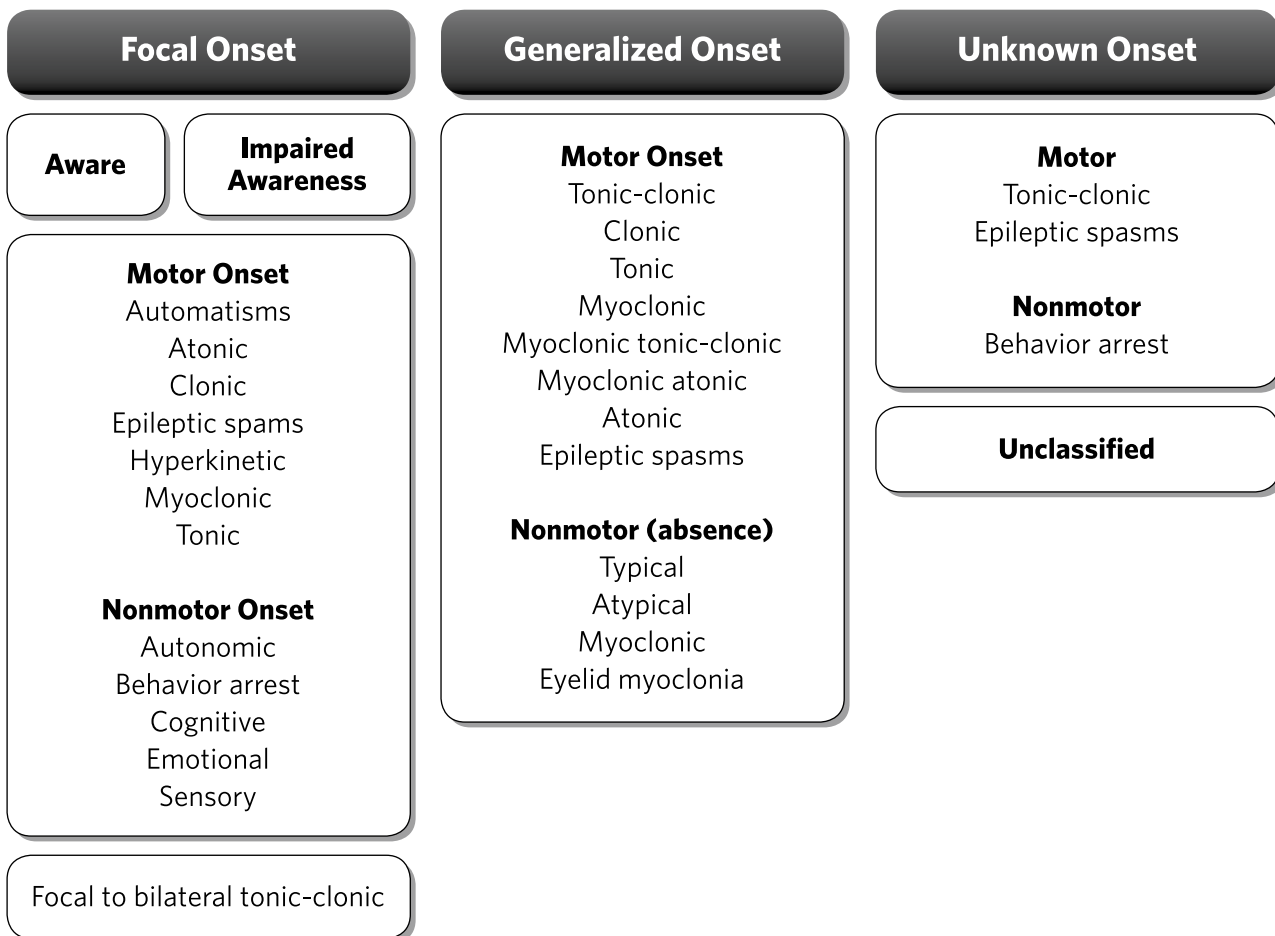
# Introduction

Epileptic seizures are events caused by abnormal hypersynchronous electrical activity of the cortex and may have myriad manifestations and features, including but not limited to motor, sensory, cognitive, autonomic, psychic, and visual phenomena. Semiology is the art of using the observed seizure manifestations in order to localize the site of cerebral onset. In addition, semiology provides information that may be useful in distinguishing epileptic seizures from seizure mimics such as psychogenic non-epileptic seizures (PNES). This chapter will provide localizing features of seizures in order to classify and guide appropriate treatments.

## Overview of Classification of Seizures

Broadly, seizures can be divided into two categories: generalized and focal (see FIGURE 6.1). Focal seizures may arise from cortical or subcortical structures, but remain limited to activation of networks in one hemisphere, whereas generalized seizures involve bilaterally distributed networks.<sup>1</sup> In addition, focal seizures may spread and become generalized, which is termed a focal to bilateral tonic-clonic seizure (previously secondarily generalized).<sup>2</sup> This is more than an academic point, as different medication choices and treatment strategies—such as epilepsy surgery, vagus nerve stimulator (VNS)—may be employed depending on the determined classification.

FIGURE 6.1 ILAE 2017 Classification of Seizure Types - Expanded Version



Adapted from Fisher et al.<sup>2</sup>

Focal seizures have myriad manifestations and have previously been known as terms such as complex partial seizures, simple partial seizures, auras, psychomotor seizures and petit-mal seizures. Generalized seizures have previously been known as grand-mal in the case of convulsions, petit mal in the case of absence seizures and drop attacks referring to tonic or atonic seizures. Generalized seizures types include tonic, clonic, atonic, myoclonic, and absence. As one can imagine, these variety of terms can cause difficulties when trying to communicate information about a patient between providers. Presently, as suggested by the International League Against Epilepsy (ILAE), the preferred terminology with regards to focal seizures is based on level of awareness and primary manifestation at onset.<sup>2</sup> A focal seizure may be described as with or without impaired awareness, depending on whether there is an alteration of consciousness associated with the event. Thus focal aware seizure replaces the term simple partial seizure (SPS) and focal impaired awareness seizures replaces the term complex partial seizures (CPS).<sup>2</sup> Focal seizures may be further classified by whether motor or non-motor manifestations are predominant at onset, ideally providing as much description as possible.<sup>2</sup> Focal seizures provide information as to the potential epileptogenic zone, which is a very important concept in determining whether a patient is a surgical candidate.

Generalized seizures types include tonic, clonic, atonic, myoclonic and absence as well as other seizure types and may be classified into motor or non-motor as suggested in FIGURE 6.1<sup>2</sup>

## Motor Manifestations

Motor manifestations are often the most striking component of a seizure. Motor activity can be simple, complex, unilateral, bilateral, tonic, dystonic, clonic, myoclonic, or hypermotor and may be a feature of focal or generalized seizures. Isolated motor seizures are often associated with frontal lobe seizures and epilepsy.

**CLONUS** is characterized by repetitive short contractions of agonist and antagonist muscles, occurring regularly at a rate of 0.2-5 Hz. Unilateral clonic motor activity may be seen with activation of the contralateral motor cortex, premotor cortex or supplementary sensorimotor area (SSMA).<sup>3</sup> Bilateral synchronous clonus is also seen often in generalized tonic-clonic seizures.

**MYOCLONUS** is characterized by sudden brief (<400 ms) irregular muscle jerks. They can be unilateral, bilateral and may affect any part of the body, but most commonly affect the arms and shoulders. Unilateral myoclonus or negative myoclonus can arise from the contralateral primary motor cortex or premotor/primary somatosensory cortex.<sup>3</sup> However, this seizure type can also be found in generalized epilepsy syndromes, such as Juvenile Myoclonus Epilepsy (JME) and progressive myoclonus epilepsies. In addition, nonepileptic myoclonus can arise sub-cortically (as evidenced in Lance Adams syndrome) or from the spine. An EEG may be helpful in determining the localization of the myoclonus.

**TONIC** seizures are characterized by sustained contraction of >3 seconds of one or more muscle groups. Unilateral tonic activity arises from the contralateral motor and supplementary motor region.<sup>3</sup> Like myoclonus, tonic seizures may be seen in generalized epilepsy syndromes like Lennox-Gastaut syndrome or in the setting of generalized tonic-clonic seizures. So while unilateral tonic activity may be a localizing sign in partial epilepsy, bilateral tonic activity is not.

**ATONIC** seizures are another type of generalized seizure characterized by a complete loss of tone, often resulting in falls. Like tonic seizures they may be seen in Lennox-Gastaut syndrome. This seizure type is usually witnessed in patients with cognitive impairment.

**VERSIVE** seizures are characterized by sustained forced turning of the trunk, eyes or head, in either a tonic or clonic manner. Forced head version is frequently caused by activation of the contralateral dorsolateral frontal cortex.<sup>4</sup> It may be seen in the setting of focal seizures or secondary generalization of focal seizures. Non-versive (or non-forced) head

turning is a more natural appearing head turn and has been described in both frontal and temporal lobe epilepsies and often localizes to the ipsilateral hemisphere, although this is a less sensitive sign than versive head turning.<sup>3</sup>

## Ocular Findings

Eye version can be either forced or passive. Forced conjugate eye movements are typically described as sustained and extreme, there are frequently two components: a smooth tonic component and superimposed saccades, which progressively move the eye more laterally, although saccades are not always noted.<sup>4</sup> When preceding secondary generalization, forced eye version localizes to the contralateral frontal eye fields. In the absence of secondary generalization, it may lateralize to either the contralateral frontal eye field or the ipsilateral occipital eye fields.<sup>3</sup>

Unilateral blinking is frequently contralateral in origin, arising from either the amygdala or mesial temporal structures.<sup>3</sup> Nystagmus is an uncommon epileptic phenomenon suggesting a parieto-occipital epilepsy.<sup>3</sup>

Dystonic limb posturing suggests activation of the contralateral basal ganglia. Whereas, tonic limb posturing may arise from the supplementary motor cortex, basal ganglia, cingulum or primary motor cortex. Both of these may be seen in either temporal or frontal lobe epilepsy, depending on the path of propagation.<sup>3</sup>

TABLE 6.1 Localization of Motor Features

FEATURE	LOCALIZATION/LATERALIZATION
<b>Head Turn</b>	
Non-forced/early	Ipsilateral temporal
Early versive	Contralateral frontal
Late versive	Contralateral temporal with spread
<b>Eye Deviation</b>	
Forced	Contralateral frontal eye field or extrastriate (area 19)
Passive	Ipsilateral occipital eye fields or contralateral frontal eye fields <i>May also indicate neglect of hemifield contralateral to seizure focus</i>
<b>Focal Clonic</b>	Contralateral motor cortex
<b>Dystonic Limb Posturing</b>	Contralateral temporal > frontal
<b>Unilateral Tonic Posturing</b>	Contralateral frontal > temporal
<b>Fencing Posture</b>	Contralateral frontal > temporal (CL to the extended arm)
<b>Figure-4 Sign</b>	Contralateral
<b>Unilateral Automatism</b>	Ipsilateral > contralateral hemisphere
<b>Bipedal Automatisms</b>	Frontal > temporal
<b>Hypermotor</b>	Supplementary sensorimotor area
<b>Gelastic</b>	Hypothalamic, mesial temporal
<b>Postictal Nose Wiping</b>	Ipsilateral temporal > frontal (IL to wiping hand)

CL: contralateral; IL: ipsilateral.

## Complex Motor Seizures

More complex motor activities may also be observed, which are more difficult to lateralize and/localize. These seizures manifest with relatively complex movements simulating natural movements, but they are contextually inappropriate. These include hypermotor seizures, automotor seizures, and gelastic seizures as well as specific other findings, such as fencers posture and the figure-4 sign.<sup>4</sup>

**HYPERKINETIC** seizures are characterized by rapid, repetitive complex movements that involve predominantly proximal limbs and trunk, and may simulate natural activities, a classic example of which is bicycling of the legs.<sup>4</sup> Other examples include clapping, waving, thrashing, and kicking. Laughing and vocalization are frequently noted.<sup>3</sup> Of note, there may be preserved consciousness with these events, especially if they arise from the frontal cortex.

These seizures most frequently arise from the frontal lobe (ventromedial more frequently than dorsolateral), but may also arise from the temporal lobe, insula or posterior cortex. One can also see rhythmic writhing or thrusting movements predominantly involving the pelvis or extremities, also arising from the frontal lobes.<sup>3</sup>

**AUTOMOTOR** seizures (also known as automatisms) are defined as complex motor seizures in which the main manifestation consist of automatisms involving the distal extremities or the mouth and tongue. These are typically associated with alteration of consciousness, but this does not always occur, particularly if arising from the non-dominant hemisphere.<sup>4</sup>

Oral automatisms include lip smacking, whistling, chewing and kissing, while extremity automatisms include actions such as picking, fumbling and gesticulating.<sup>3,4</sup> These may arise from either the frontal or temporal lobe. Temporal lobe automatisms tend to be complex, perseverative and involve the distal portion of the upper extremities. Frontal lobe automatisms tend to affect the proximal upper limb and to be more hyperkinetic and irregular.<sup>3</sup> Typically, unilateral automatisms localize ipsilateral to the seizure focus, however in a significant portion of patients they may localize contralaterally, with one study showing this phenomenon in up to 1/3 of patients.<sup>5</sup>

**GELASTIC** seizures are seizures in which the prominent motor manifestation is laughter. It may be the only manifestation, but may be preceded and followed by any other type of seizure, depending on the pattern of spread.<sup>4</sup> They are common in patients with hypothalamic hamartomas but may also be seen to arise from the frontal or temporal regions.

Other helpful localizing signs include the figure-4 sign and the fencing position. The figure-4 sign is characterized by rigid flexion of one elbow over the chest with extension of the contralateral arm resembling the numeral 4; localization is contralateral to the extended arm and it is typically seen in temporal lobe seizures with secondary generalization.<sup>4</sup> The fencer's posture (also known as the M2e sign) is characterized by forced head turn to one side and lateral abduction and external rotation of the upper limb on that side, with or without flexion at the elbow.<sup>6</sup> This localizes to the supplementary motor area (SMA) contralateral to the flexed extremity and is seen more frequently in frontal than temporal lobe seizures.

## Sensory Seizures

### Somatosensory Seizures

These include various sensations including numbness (often tingling), shock like sensations, feelings of hot and/or cold and pain. They may arise from the primary somatosensory cortex, in which case they are often discrete in location and arise contralateral to the seizure focus.<sup>3</sup> If the sensation arises from secondary sensory areas, they may be bilateral or ipsilateral to the focus.<sup>3</sup>

Somatosensory illusions such as swelling, shrinking and movement have been described arising from the non-dominant inferior parietal lobe or the temporo-parieto-occipital junction.<sup>3</sup>

## Special Senses

**OLFACTORY SEIZURES** are typically unpleasant in nature and associated with gustatory sensations. These can arise from the amygdala, insula, olfactory bulb, and posterior orbitofrontal region. Gustatory seizures can arise from the parietal operculum and mesiobasal temporal lobe.<sup>3</sup>

**VISUAL SEIZURES** may be simple or complex in nature. Seizures arising from the primary visual cortex and neighboring association cortices are often more simple, manifesting in static, flashing, or moving lights in various colors and shapes.<sup>3</sup> As can be expected from anatomy, visual phenomena restricted to one hemifield suggests onset in the contralateral visual cortex, while phenomena restricted to an inferior or superior quadrant suggests involvement of the contralateral supra- or infracalcarine cortices.<sup>3</sup>

Complex or formed visual phenomena, involving people, objects, etc. are consistent with seizures arising from the temporo-occipital junction or basal temporal cortex. Blurred vision or visual motion can arise from the precuneus, posterior cingulum or mesial parieto-occipital region.<sup>3</sup>

**VERTIGINOUS SEIZURES** are usually associated with auditory and visual phenomenon. These can arise from a wide region in the lateral temporo-parieto-occipital junction as well as the middle and posterior portions of the middle and superior temporal gyri.<sup>3</sup>

## Autonomic Seizures

There are many manifestations of autonomic seizures, which include but are not limited to abdominal sensations, palpitations, tachycardia, dyspnea, vomiting, sweating, piloerection, pupil dilatation, pallor, flushing, borborygmi, genital sensations, urinary urgency and incontinence.<sup>3,7</sup> These seizures arise from activation of the insula, anterior cingulate gyrus, SSMA, or amygdala.<sup>3</sup>

The most frequent autonomic seizures involve abdominal auras. They may take many forms including nausea, pain, or an indescribable sensation. They may remain localized or may be described as a ‘rising sensation’ moving to the chest and throat. Isolated abdominal auras have a high (74%) correlation with temporal lobe epilepsy, which increases to 98% if the patient then progresses to having automatisms.<sup>3,8</sup> If abdominal symptoms are associated with vomiting, this suggests involvement of the contralateral temporal lobe.<sup>3,9</sup> Furthermore, an abdominal sensation at onset may localize further, as it is more suggestive of a mesial temporal rather than lateral neocortical temporal onset.<sup>7</sup>

Other sensations, such as orgasm and genital pain, have been reported. Orgasmic seizures are more common in women and appear to arise from the right temporal lobe.<sup>3</sup> Painful genital sensations are often associated with fear and can arise from the parasagittal region.<sup>3</sup>

## Cognitive and Emotional Seizures

Patients with epilepsy may describe various psychic sensations that arise out of context. These include a myriad of pleasant and unpleasant sensations. Patients may experience a sense of déjà vu or jamais vu. Typically these are seen with temporal lobe epilepsy and arise from the uncus, entorhinal cortex or temporal neocortex, there is no lateralizing feature to this semiology.<sup>3</sup> Fear is another non-lateralizing sensation that is often reported; it localizes to the amygdala, hippocampus and mesial frontal lobe.<sup>3</sup>

# Impaired Consciousness

Starting with impaired consciousness is a non-specific finding that may be seen in many seizure types. It may be seen in absence seizures, a type of generalized seizure, which are typically brief, lasting less than 20 seconds and can at times be provoked by hyperventilation. If they are longer, lasting a few minutes, this is more suggestive of focal seizures, which are often temporal in origin and may be associated with automatisms. If they last more than 2-3 minutes, one must consider nonepileptic events.

**TABLE 6.2 Features of Different Seizure Types**

FEATURE	FRONTAL LOBE EPILEPSY	TEMPORAL LOBE EPILEPSY	PNES
Onset and Offset	Sudden	Gradual	Gradual
Duration	Brief (<1 minute)	Longer (1 to 2 min)	Variable, often longer than 2 min
Occurrence	Often sleep related	Usually awake	Awake
Aura	Olfactory, gustatory, cephalic	Epigastric, psychic, auditory	Variable
Time to Motor Component	Early, prominent	Later in ictal sequence	Variable
Automatisms	Uncommon	Common	Uncommon
Autonomic Signs	Uncommon	Common	Rare, may coincide with exertion
Unilateral Clonic Activity	Common	Uncommon	Uncommon
Vocalization	Common	Uncommon	Throughout event
Dystonic Arm Posturing	Uncommon	Common	Rare
Asymmetric Tonic Posturing	Common	Uncommon	Rare
Version of Head or Eyes	Common	Uncommon	Rare
Hypermotor or Violent Motor	Common	Uncommon	Common
Secondary Generalization	Uncommon	Common	—
Todd's Paralysis	Common	Uncommon	Rare
Postictal Confusion	Uncommon	Common	Variable
Awareness	Typically aware	Impaired if dominant hemisphere	Variable
Clustering	Common	Uncommon	Variable

PNES: psychogenic nonepileptic seizures.

# Psychogenic Nonepileptic Seizures

Psychogenic Nonepileptic Seizures (PNES) are a phenomenon frequently encountered, especially in medically refractory patients referred for epilepsy monitoring unit admissions. As opposed to epileptic seizures which are caused by abnormal cerebral electrical activity, psychogenic seizures are typically due to psychiatric disturbances.

Psychogenic seizures (or psychogenic events) are commonly encountered in epilepsy centers. In fact, up to 40% of patients referred to tertiary care centers for refractory epilepsy are found to have PNES.<sup>10</sup> Studies in the veteran population have shown that this holds true in patients admitted to VA monitoring units, where a recent study showed 25% of Veterans admitted to VA EMU had nonepileptic events.<sup>11</sup>

Although it may be impossible to distinguish between PNES and epileptic seizures by history alone, there are some key features that should raise suspicion for nonepileptic events. Beginning with the seizure history, the following features should raise red flags:

- Seizures that are frequent from onset and difficult to control medically.
- The presence of multiple semiologies, especially if this is the case from onset.
- Prolonged seizures, lasting more than 2 minutes (often up to 30 minutes or more), or that vary in duration.
- Onset coincident with a significant psychological trauma or minor physical trauma.

In addition, these events commonly have a clear precipitant, occur in the presence of a significant other, and are less likely to be associated with serious self-injury than epileptic seizures.<sup>10</sup>

Whereas epileptic seizures tend to be stereotyped in nature, nonepileptic events are not always so. Motor manifestations can wax and wane in intensity, be asynchronous between contralateral extremities and there can be movements in multiple directions at the same joint. Traditionally, pelvic thrusting is described as being suggestive of PNES, however this motion may also be seen with equal or greater frequency in frontal lobe seizures or generalized tonic-clonic seizures, although there is some suggestion that forward pelvic thrusting is seen more frequently in nonepileptic events and backwards thrusting is seen in epileptic events.<sup>10</sup> Opisthotonus, however, may be more suggestive of a nonepileptic etiology.<sup>10</sup>

Ictal eye closure is not common in epileptic seizures, however it is seen rather frequently in PNES, with one study showing this finding in 2/3 of patients.<sup>12</sup> Often eye closure is described as forceful, with resistance to opening.<sup>10</sup>

Prolonged atonia or limpness with unresponsiveness and no other motor signs lasting 10-15 minutes, has been seen in 7%-76% of all PNES manifestations.<sup>10</sup> As opposed to true atonic seizures, which tend to be brief and variably associated with a change in mental status.

Tongue biting is less common than in epileptic seizures and frequently occurs on the tip of the tongue, whereas in generalized tonic-clonic seizures tongue biting tends to occur on the side of the tongue.<sup>10</sup> Incontinence is also less common, and fecal incontinence almost unheard of in psychogenic seizures.<sup>10</sup>

## Conclusion

Determination of seizure semiology depends on observation of the events in question. Traditionally, this has been based on verbal description by the patient or reliable witness. Recently, the increased availability of prolonged video EEG at home or in epilepsy monitoring units has allowed epileptologists to concomitantly view the semiology and electrographic correlate. These data allows the clinician to feel more comfortable in the determination of diagnosis and classification, permitting more targeted treatment. In the absence of video-EEG monitoring, another helpful tool may be to video-record the events on a phone or digital camera, as in the authors' experience reviewing these videos may aid in classification, using the observed features described earlier. This information can be crucial to the practitioner in determining whether he/she is treating a focal seizure, generalized seizure, or nonepileptic seizure and tailoring treatment appropriately. Finally, the information gleaned from an epilepsy monitoring unit admission can be especially helpful in patients that are medically refractory and are potential surgical candidates. ■

TABLE 6.3 Features of Nonepileptic and Epileptic Seizures

FEATURE	PNES	EPILEPTIC SEIZURE
<b>Onset</b>	Gradual, from waking or pseudosleep	Abrupt
<b>Duration</b>	Varies, often longer than 2 minutes	Usually less than 2 minutes
<b>Response to Verbal Stimulus</b>	Frequent	Rare, never during GTC
<b>Asynchronous Movements</b>	Occasional/common	Rare in GTC, may see in FLS
<b>Waxing-Waning or Pausing/ Resumption of Symptoms</b>	Occasional/common	Rare in GTC
<b>Eye Closure</b>	Common	Rare
<b>Pelvic Thrusting</b>	Occasional/common (typically forward, often in women)	Occasional in FLS Rare in GTC (typically backwards)
<b>Opisthotonic Posturing</b>	Common/very common	Rare
<b>Tongue Biting</b>	Rare (at the tip)	Occasional/common in GTC (on the side)
<b>Incontinence</b>	Very rare	Common in GTC
<b>Prolonged Unresponsiveness with No Prominent Motor Signs</b>	Occasional	Very rare
<b>Postictal Memory</b>	Common	Very rare with GTC, may see with FLS
<b>Postictal Confusion</b>	Occasional	Common/very common

GTC: generalized tonic-clonic (seizure); FLS: frontal lobe seizure.

Adapted from Mostacci et al.<sup>10</sup>

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7

# Electroencephalography

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# Introduction

This chapter aims to briefly discuss common indications for electroencephalography (EEG) studies, as well as some of the more relevant epileptiform and non-epileptiform EEG patterns that neurophysiologists and clinicians frequently encounter. Also, indications for other specialized EEG methods, including continuous bedside video-EEG, epilepsy unit monitoring, and ambulatory EEG studies are briefly discussed.

## Indications for Ordering EEGs

### Primary Indications

One of the most common indications for a routine EEG study is to evaluate the patient with a suspected diagnosis of seizures for the presence of interictal epileptiform discharges (e.g., “focal spikes or generalized spike-waves”). However, the presence of epileptiform abnormality in itself is not necessarily diagnostic of epilepsy, as epileptiform discharges can be transiently present in some reversible conditions that can provoke seizures (e.g., nonketotic hyperglycemia). Fundamentally, epilepsy is a clinical diagnosis based on the presence of two or more unprovoked seizures, and is supported by (but does not require) the documentation of EEG epileptiform discharges.

When combined with the appropriate clinical presentation, the electrographic characteristics of epileptiform discharges can help distinguish epileptic seizure types, such as focal vs generalized seizures. This distinction can portend etiologic, therapeutic, and prognostic significance. In some cases, specific syndromic classification of the patient’s epilepsy may be possible.

Another common indication for EEG, particularly in the inpatient setting, is to rule out the occurrence of sub-clinical electrographic seizures. Clinical situations for which suspicion of subclinical seizures should be raised include<sup>1</sup>:

1. After apparent successful treatment of overt seizures or status epilepticus (SE), the patient’s mental status fails to recover as would be typically expected over time (taking into account the effects of sedative medications). This concern is especially relevant for the patient whose treatment for SE has required pharmacologic paralysis during intubation, which can abolish the clinical, but not cerebro-electrical, manifestations of seizures. Such a scenario represents a well-accepted indication for a stat EEG study, if available. Conversely, in a scenario where the visible convulsion has stopped and the patient’s mental status is improving (albeit in small increments) over serial examinations, then EEG study can be ordered on a non-stat basis.
2. Situations in which the patient’s altered mental state remains unexplained or is out of proportion to what can be expected from the results of conventional work-ups (i.e., imaging, metabolic/infectious investigations). The suspicion for subclinical seizures is further raised by the presence of abnormal ocular movements (e.g., nystagmus, eye deviation, or hippus), remote seizure risk factors, or severely depressed mental status (very low GCS scores)<sup>2</sup> in which case the EEG study can be ordered on a stat basis, if available. Conversely, if the patient’s altered mental status can be readily explained by well defined etiologies, then the EEG study can be ordered on a non-stat basis.

When contemplating withdrawal of an anti-epileptic regimen, EEG characteristics can help to a limited extent in assessing seizure recurrence risk. For example, for patients with localization-related epilepsy (LRE), it is less certain whether the persistence of occasional focal epileptiform discharges significantly affect seizure recurrence risk. Less controversially, should copious amounts of epileptiform discharges be demonstrated (either focal or generalized discharges), such active EEG findings would indicate persistence of significant cortical irritability, supporting very high seizure recurrence risk.

### Secondary Indications

In encephalopathic patients, the EEG can help assess the underlying extent of the encephalopathy. Encephalopathies are expressed on the EEG as diffusely slow background activity, and the extent of this slow activity combined with

other background characteristics can reflect a mild, moderate, or severe degree of encephalopathy. By contrast, certain dementias (up to moderate severity) have been known to demonstrate essentially normal background frequency distributions on the EEG. Similarly, patients with a functional contribution to behavioral changes (e.g., catatonia from schizophrenia, or psychomotor retardation from depressive disorders) are expected to demonstrate generally unremarkable EEG findings, unless confounded by significant medication effects. Therefore, the EEG can help distinguish delirium from dementia/functional processes in some situations where such distinction may be enigmatic.

The demonstration of electrocerebral inactivity (ECI) on EEG can support the diagnosis of brain death. Under proper EEG recording conditions (with symmetrically placed electrode pairs >10 cm apart, inter-electrode resistance between 100 and 10,000 ohms, and exclusion of drug, hypothermia, and recent hypotension), the absence of cerebral activity over 2  $\mu$ V despite at least 30 minutes of recording is consistent with ECI.<sup>3</sup> A notable caveat is that the demonstration of ECI on EEG is supportive, but not in itself diagnostic of brain death. Brain death requires a rigorous clinical diagnosis and is confirmed by the apnea test.

## Interictal Patterns

### Epileptiform Patterns

According to the International Federation of Societies for Clinical Neurophysiology, epileptiform discharges represent “distinctive waves or complexes, distinguished from background activity, and resembling those in a proportion of human subjects suffering from epileptic disorders.”<sup>4</sup> The somewhat circumferential nature of this definition underscores the importance of proper clinical correlation, as epilepsy cannot be diagnosed based on EEG alone.

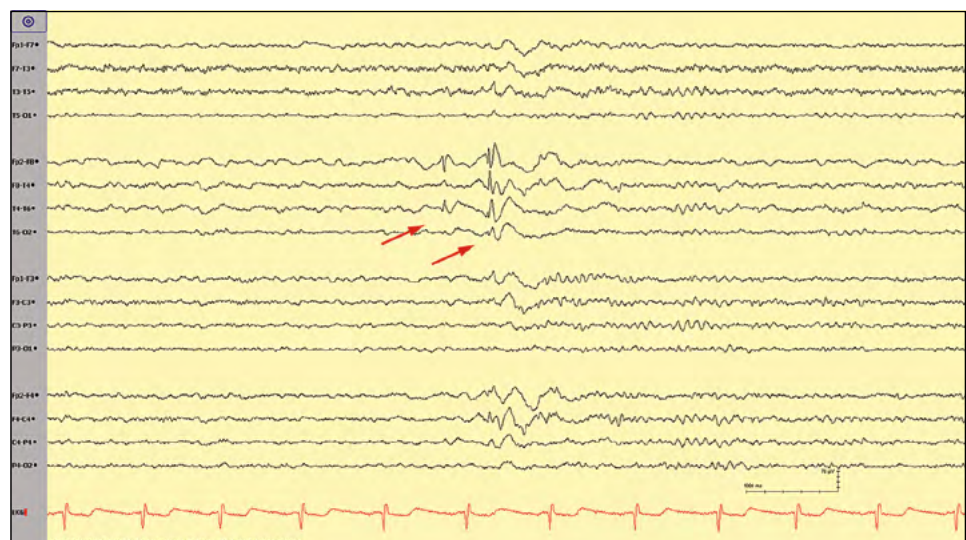
### Focal Discharges

Several features distinguish focal epileptiform patterns from non-epileptiform sharp transients.<sup>5</sup> Epileptiform discharges tend to show relatively higher voltage compared to the background activity, asymmetrical shape, a logical field of distribution, typically more than one phase, and an after-going slow wave that disrupts the ongoing background activity (FIGURE 7.1). Furthermore, epileptiform discharges frequently emerge from regions of pre-existing EEG background abnormality (e.g., focal slowing).

Focally distributed sharp wave, spike, or polyspike discharges all fall within this category. Though morphologically distinct, these discharges generally represent the same clinical significance—the presence of an underlying focal, potentially epileptogenic process. The location of a focal interictal epileptiform discharge (IED) can, but does

**FIGURE 7.1**  
**Focal Spike Discharges**

Two focal spike discharges occur sequentially within 1 second of each other. Both discharges demonstrate asymmetrical shape, logical field of distribution through the left temporo-frontal region, multiple phases, and after-going slow wave that disrupts the background. Also notable is the pre-existing left temporal focal slowing within EEG background.



not necessarily, reflect the localization of the actual epileptogenic focus. For instance, while patients with temporal lobe epilepsies frequently show temporal spike discharges in their EEGs, there are some patients with occipital or parietal lobe epilepsies in whom the interictal spike discharges are projected more anteriorly into the temporal regions on the EEG. Such temporal spike discharges appear similar to those seen in temporal lobe epilepsy patients.

The presence of two or more independent, focal IEDs continue to indicate the potential for underlying focal epileptogenic processes in most cases. Under such a situation, many patients may still have focal seizures that start from a single focus, despite having multiple independent IEDs. Other patients, however, may truly have independent seizure onsets from multiple foci.

## **Generalized Discharges**

Compared to focal IEDs, generalized IEDs are more commonly expressed as brief bursts of repetitive or rhythmic epileptiform complexes.<sup>6</sup> Each complex typically consists of an initial sharply contoured waveform (a spike or a sharp wave) followed by a slow wave of higher amplitude, thus its name of “spike-wave” complex. These discharges usually show a preferential expression over the frontal, central, and parietal regions (FIGURE 7.2).

Generalized IEDs indicate the presence of an underlying generalized, potentially epileptogenic process. Such generalized discharges may occur in a variety of settings, including: (1) inherited or genetic conditions (e.g., primary generalized epilepsies, associated with 3 Hz or faster spike-wave discharges); (2) acquired widespread and lasting cerebral insults (e.g., symptomatic generalized epilepsies, associated with slower 1.5-2.5 Hz spike-wave discharges); or, (3) acquired transient but severe cerebral disturbances (e.g., toxic-metabolic, vascular, inflammatory processes) involving large and significant areas of the brain.

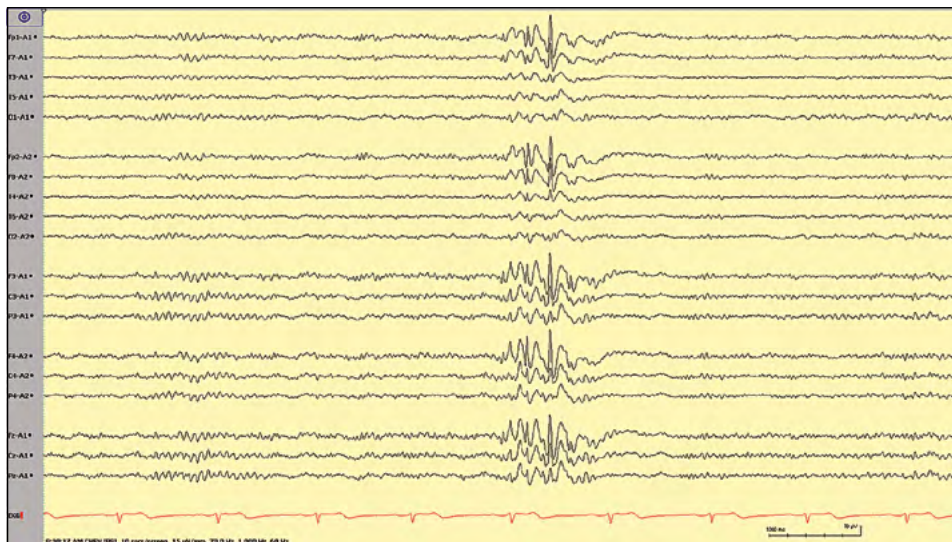
Sometimes, what appears to be generalized IEDs may in actuality represent extremely rapid bilateral spread of epileptiform activity from a focal epileptogenic focus (secondary bilateral synchrony).

## **Non-epileptiform Patterns**

### ***Rhythmic Synchronous Slow Activity***

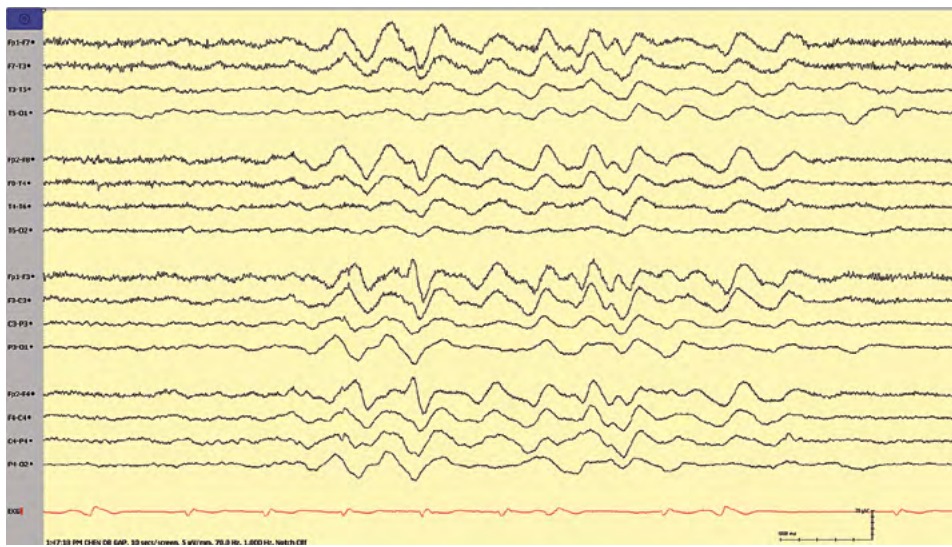
The slow activity in this pattern is time-locked and morphologically similar when comparing corresponding regions of both hemispheres (inter-hemispheric synchrony). The frequency of this activity may be either in the 4-7 Hz (theta) range, 1-3 Hz (delta) range, or a mixture of theta and delta frequencies. More specific subtypes of bisynchronous slow activity include frontal intermittent rhythmic delta activity (FIRDA – FIGURE 7.3) and occipital intermittent rhythmic delta activity (OIRDA). These subtypes manifest as bursts of bisynchronous, intermittent, rhythmic 2-3 Hz activity that may predominate either in the “frontal” or “occipital” regions.

Bisynchronous slow activity is mechanistically derived from abnormal interaction between the cerebral cortex and distant, subcortical midline structures (i.e., brainstem, thalamus, mesial/orbital surfaces of the frontal lobe).<sup>7</sup> Because of the wide areas and varied substrates involved, several etiologies can be associated with bisynchronous slow activity, including: (1) diffuse cerebral disturbances (e.g., from metabolic encephalopathies or neurodegenerative conditions) that involve both cortical and subcortical gray matter, and are typically associated with slow theta and delta range activity that occurs in essentially all parts of the brain (FIGURE 7.4); or, (2) structural lesions (e.g., tumors or stroke) that directly involve the deep midline structures. However, it should be noted that such rhythmic slow activity may be seen in the EEGs of individuals who demonstrate no evidence of diffuse cerebral dysfunction, have normal brain imaging findings, and in whom the background EEG activity is otherwise normal. Also, such rhythmic slow activity is not infrequently present in the EEGs of patients with generalized epilepsy. It is important to remember that in the absence of definitive generalized spike-wave activity, such rhythmic slow activity occurring in isolation cannot be used to support the diagnosis of epilepsy.



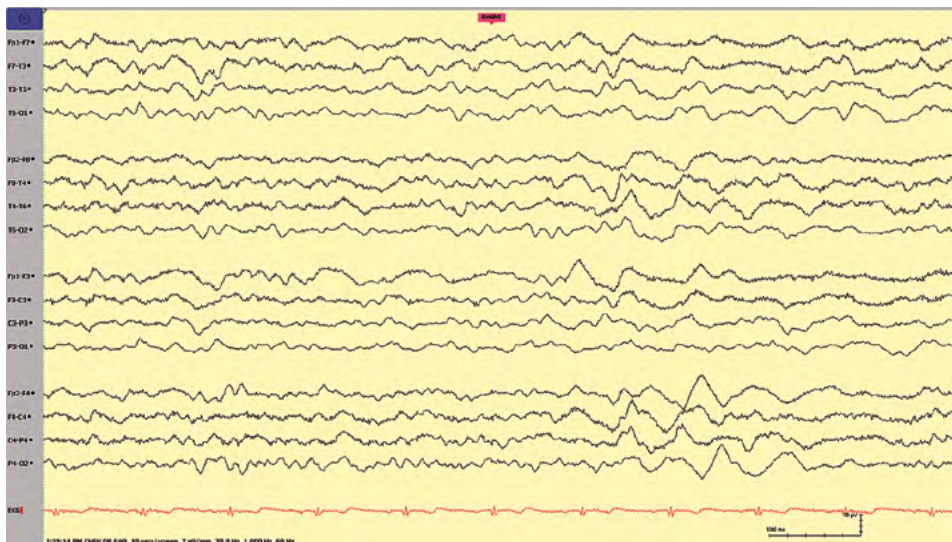
**FIGURE 7.2**  
**Burst of Generalized Spike-Wave Discharges**

A brief (1 second) burst of generalized, 3-4 Hz spike-wave discharges that demonstrate an anterior dominance.



**FIGURE 7.3**  
**Frontal Intermittent Rhythmic Delta Activity (FIRDA)**

An approximate 5-second burst of frontal intermittent rhythmic delta activity (FIRDA) that demonstrates the typical 2.5 to 3 Hz, relatively uniform slow wave patterns of frontal dominance.



**FIGURE 7.4**  
**Diffuse Background Slowing**

Diffuse background slowing is demonstrated by slower theta and delta activity that populates essentially all parts of the brain.

## Focal Polymorphic Slow Activity

A localized disturbance in cerebral function can be associated with focal slow activity in the theta or delta range. Focal slow activity in this setting usually demonstrates irregular morphology (polymorphic), variable duration, and variable frequency (arrhythmic) (FIGURE 7.5). Compared to focal polymorphic slow activity in the theta range, activity in the slower delta range suggests a more severe or more acute disturbance. Furthermore, focal polymorphic slow activity that is “continuously” present has a robust correlation with an underlying gross structural lesion. “Intermittently” present focal slow activity is less specific, being associated with either structural or physiologic (e.g., migraine, peri-ictal phenomena, transient cerebral ischemia) disturbances.

## Bitemporal Slow Activity

In the EEGs of patients over 50 years of age, intermittent, random polymorphic slow activity that occurs independently over the bilateral temporal regions may be evident. The frequency of this activity may be predominantly in the 4-7 Hz (theta) or 1.5-3 Hz (delta) range. Both frequencies may be present in apparently normal older individuals. Bitemporal intermittent slow activity in the theta range is usually interpreted as a nonspecific abnormality commonly seen individuals within this age group. This activity frequently is more pronounced on the left side. Bitemporal slow activity in the delta range should be interpreted as an abnormal finding that is more likely to be associated with a variety of

FIGURE 7.5

### Focal Slowing

Continuous focal, polymorphic, arrhythmic 2-6 Hz (delta and theta range) slow activity is present over the left temporo-central region.

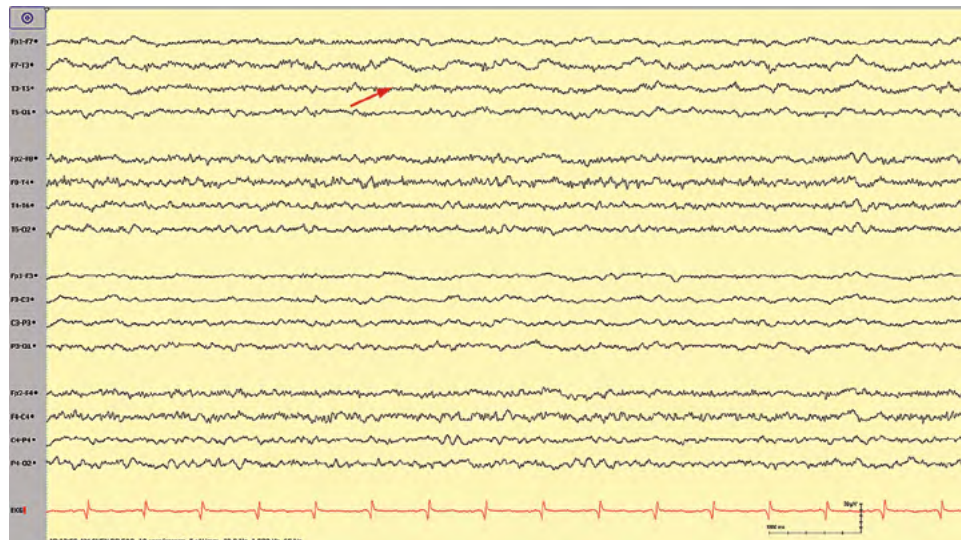
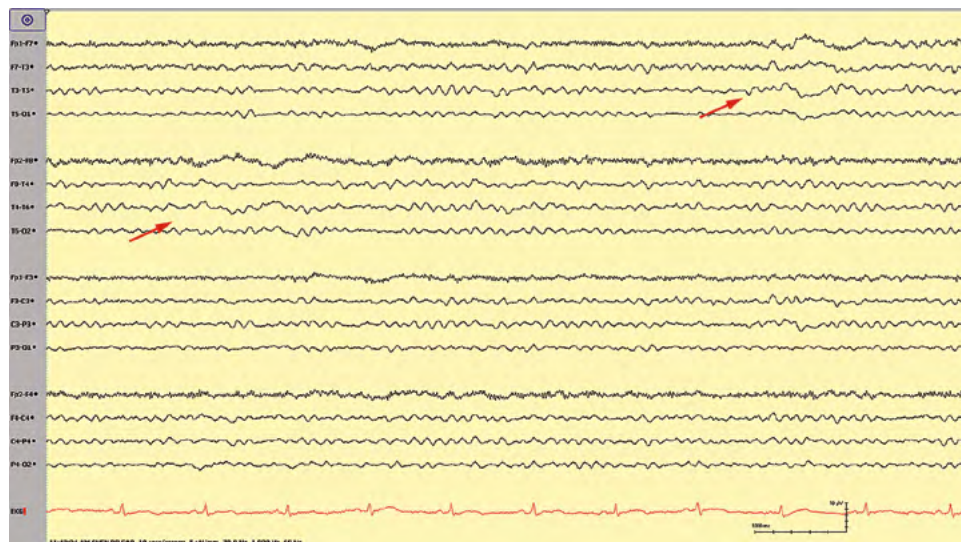


FIGURE 7.6

### Bitemporal Slowing

Intermittent and polymorphic 1.5-3 Hz delta focal slow activity occurs independently over the left and right temporal regions in this 78 year old elderly man.



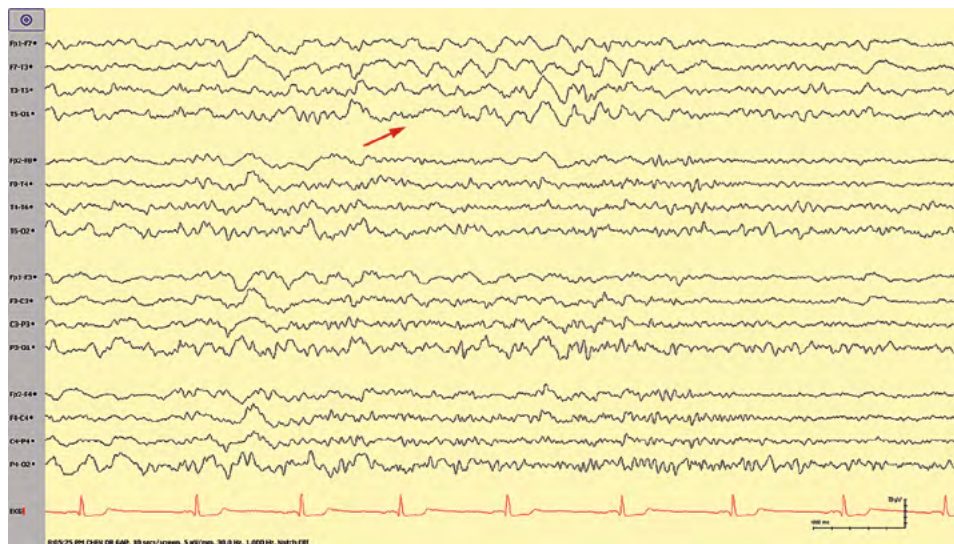
conditions including neurodegenerative processes and cerebrovascular disease (FIGURE 7.6). Bitemporal slow activity in either frequency range should not be interpreted in isolation as evidence of focal structural lesions or focal epileptogenic processes.

### **Focal Rhythmic Temporal Slow Activity**

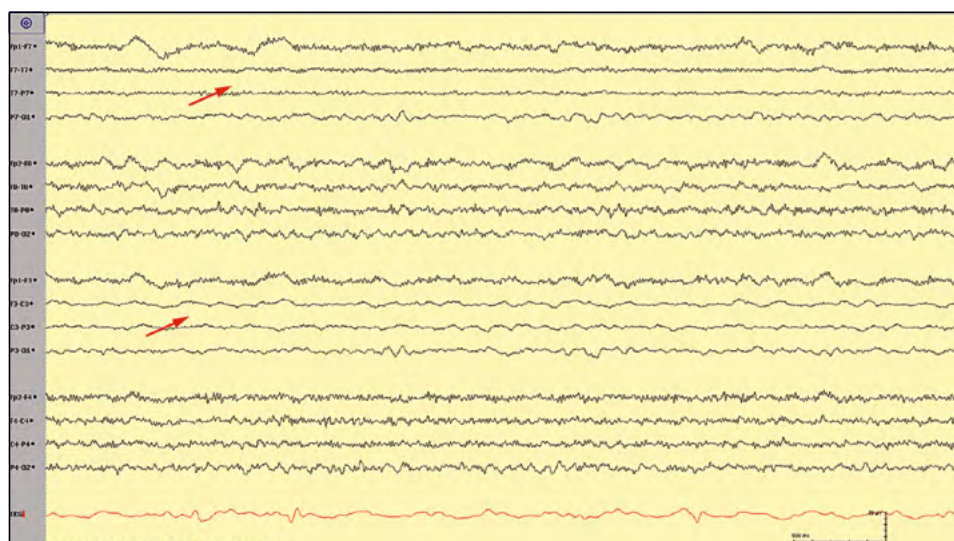
Another form of focal temporal slow activity occurs as intermittent rhythmical bursts with more uniform frequencies and morphologies. Temporal intermittent rhythmic delta activity (TIRDA) is the hallmark of this particular form of focal slowing (FIGURE 7.7). Compared to temporal arrhythmic and polymorphic slow activity, TIRDA is less common in prevalence but more specific in its pathological association with the presence of ipsilateral temporal lobe epilepsy. In fact, some investigators assert that the presence of TIRDA represents the same diagnostic significance as focal IEDs from the temporal region.<sup>3</sup>

### **Background Asymmetry**

The EEG background activity is considered to be asymmetric when the amplitude of the activity recorded from one area is more attenuated than the homologous area from the opposite hemisphere (typically >50% in amplitude difference between sides) (FIGURE 7.8). The voltage attenuation is strongly associated with a disturbance of the underlying



**FIGURE 7.7**  
**Temporal Intermittent Rhythmic Delta Activity (TIRDA)**  
TIRDA is illustrated by this brief 3-second burst of rhythmic and relatively uniform 3 Hz delta activity over the left temporal region.



**FIGURE 7.8**  
**Background Asymmetry**  
Background asymmetry is demonstrated by background voltage attenuation throughout the left hemisphere, when compared to corresponding regions on the right hemisphere.



cerebral cortex, either structurally (e.g., infarction) or physiologically (e.g., postictal phenomena). Additionally, the background activity may be attenuated if there is increased conduction barrier between the cortex and the recording electrode (e.g., subdural hematoma or scalp edema).

Conversely, the background activity can be enhanced by the loss of conduction barrier, as in the setting of known skull defects. Such activity is often sharply contoured and may be misinterpreted as abnormal sharp waves or spikes. This activity is frequently referred to as a breach rhythm (FIGURE 7.9).

## Ictal Patterns

### Focal Ictal Discharges

Focal ictal seizure discharges are usually distinct from interictal discharges. Rather than simply the conglomeration of “spikes” or “sharp waves,” focal ictal discharges more commonly emerge as a focus or region of rhythmic activity that evolves in amplitude, frequency, morphology, and distribution (modulation) (FIGURE 7.10). Postictally, the region of the ictal onset may show focal or regional attenuation of background rhythms and/or focal slow rhythms. In addition, there are characteristic ictal EEG patterns associated with two of the more common and important substrates of seizure origin: mesial temporal and neocortical ictal onset zones.

#### *Ictal Pattern for Seizures of Mesial Temporal Origin*

Studies have shown that a focal ictal rhythmic discharge of 5 Hz or faster (usually 5-7 Hz theta range), if maximally expressed over the anterior temporal region and if present within 30 seconds of the very first sign of EEG ictal change, strongly suggests seizure onset from the ipsilateral mesial temporal substrate (FIGURE 7.11).<sup>8</sup>

#### *Ictal Pattern for Seizures of Neocortical Origin*

Focal electrographic seizures of neocortical origin are suggested by the presence of initial higher frequency activities (usually beta range) at onset, with subsequent evolving changes (FIGURE 7.12).<sup>9</sup> Ictal fast frequency activity, in essence, indicates close proximity of the seizure generator to the electrodes recording the ictal activity. Conversely, ictal activity in the slower delta range at onset may suggest that the seizure generator is at some distance from the recording electrodes.

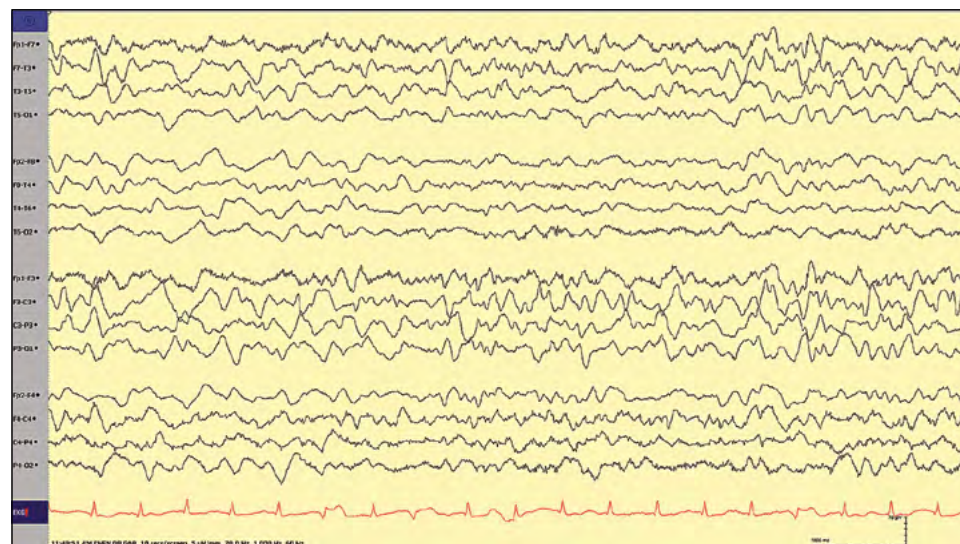
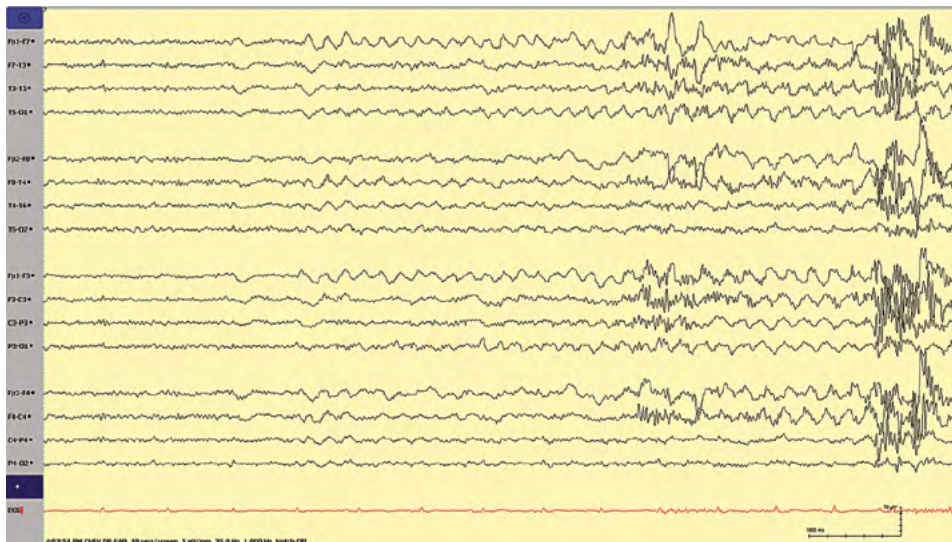


FIGURE 7.9

#### **Breach**

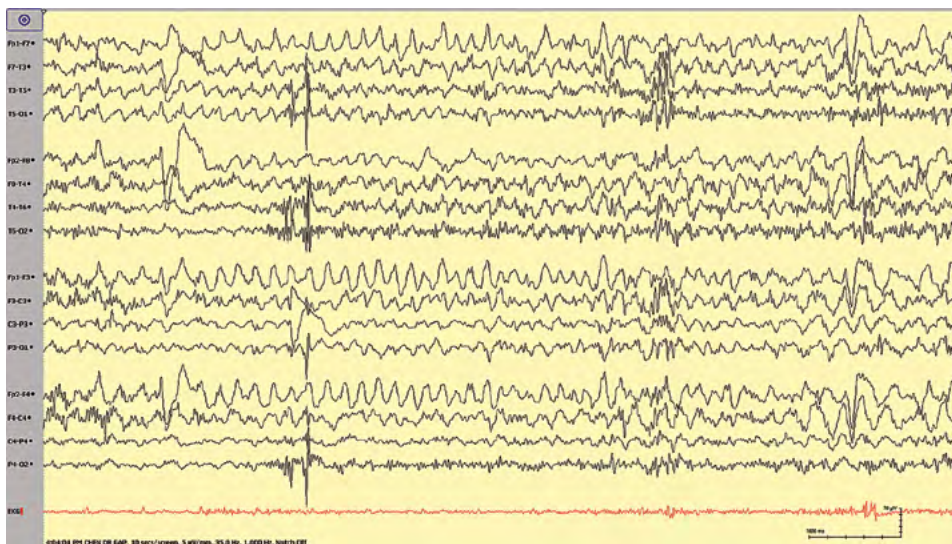
A left fronto-centro-temporal breach rhythm consists of sharply contoured and higher amplitude activity, reflecting enhancement of background activity consequent to a skull defect in close proximity.



**FIGURE 7.10A**

**Focal Seizure**

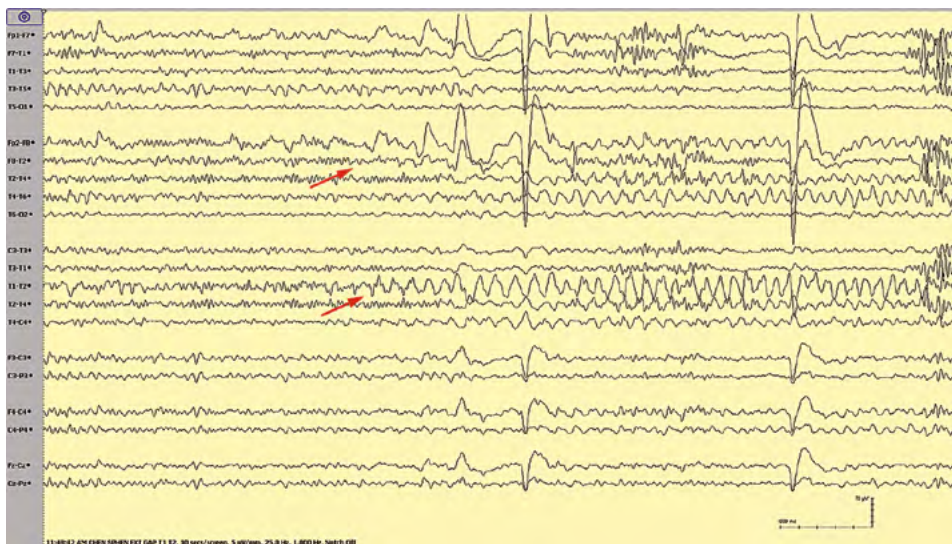
This EEG demonstrates the typical modulating features of a focal (left hemispheric) electrographic seizure as it evolves in amplitude, frequency, morphology, and distribution.



**FIGURE 7.10B**

**Focal Seizure**

Ten seconds later, further modulating features are evident.



**FIGURE 7.11**

**Mesial Temporal Seizure**

The early emergence of rhythmic 6-7 Hz ictal theta, within 30 seconds of electrographic ictal onset and preferentially expressed over the right anterior temporal region (T2), strongly supports an ipsilateral mesial temporal seizure focus.

# Generalized Ictal Discharges

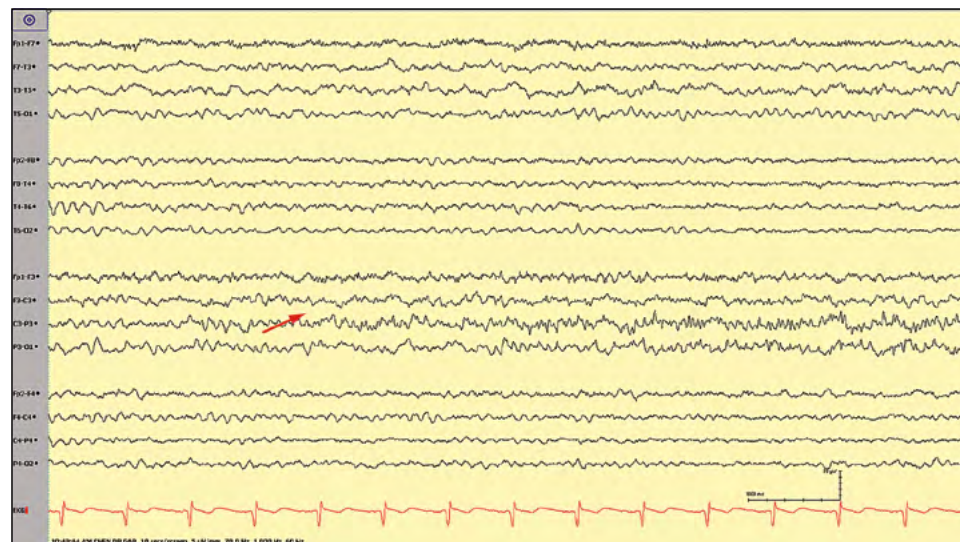
Generalized seizures demonstrate ictal electrographic correlates across all electrodes at onset. There are 3 important types of generalized ictal patterns: (1) spike-wave complexes; (2) recruiting rhythms; and (3) electrodecremental responses.<sup>10</sup>

## Spike-wave Complexes

The morphology of ictal generalized spike-wave complexes is similar to the morphology of interictal generalized spike-wave complexes.<sup>6</sup> Thus, the distinction between what are considered ictal vs interictal patterns can sometimes be rather ambiguous, especially when the correlating symptoms and behaviors are subtle or when bedside observations are insufficient. In patients with absence seizures corresponding to typical 3 Hz spike-wave discharges electrographically, the shortest duration of spike-wave activity associated with a clinically detected behavioral arrest is typically around 2-2.5 seconds (FIGURE 7.13). However, shorter bursts of spike-wave activity can be associated with observed eyelid myoclonia or myoclonic jerks (myoclonic seizures). At the end of the spike-wave burst activity, the frequency of the complexes may slow and the spike component of the complex may diminish or disappear, leaving only rhythmic slow waves (ringing effect).

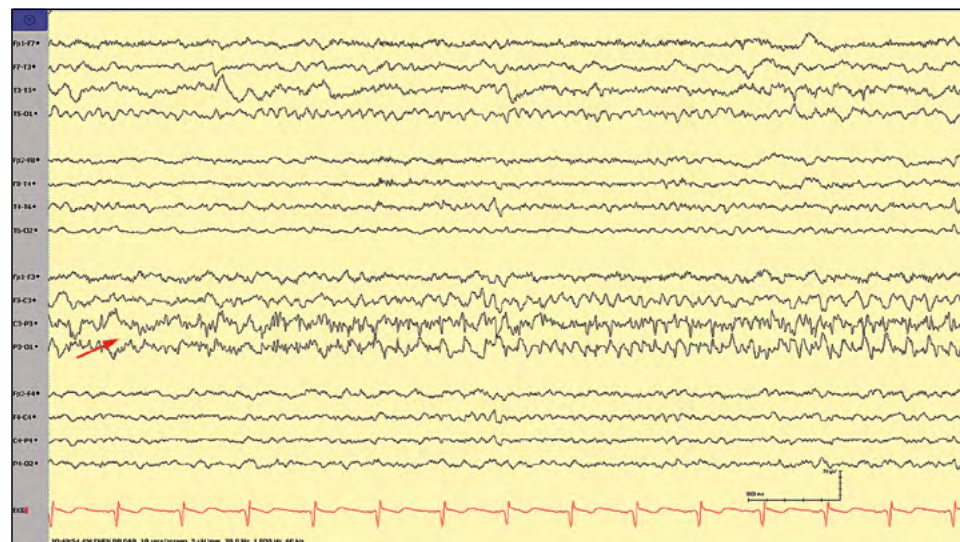
**FIGURE 7.12A**  
**Parietal Seizure**

This EEG illustrates a focal seizure arising from the left parietal convexity, as suggested by ictal fast frequency activity in the 15-18 Hz beta range from this region.



**FIGURE 7.12B**  
**Parietal Seizure**

Ten seconds later, further evolving features emerge.



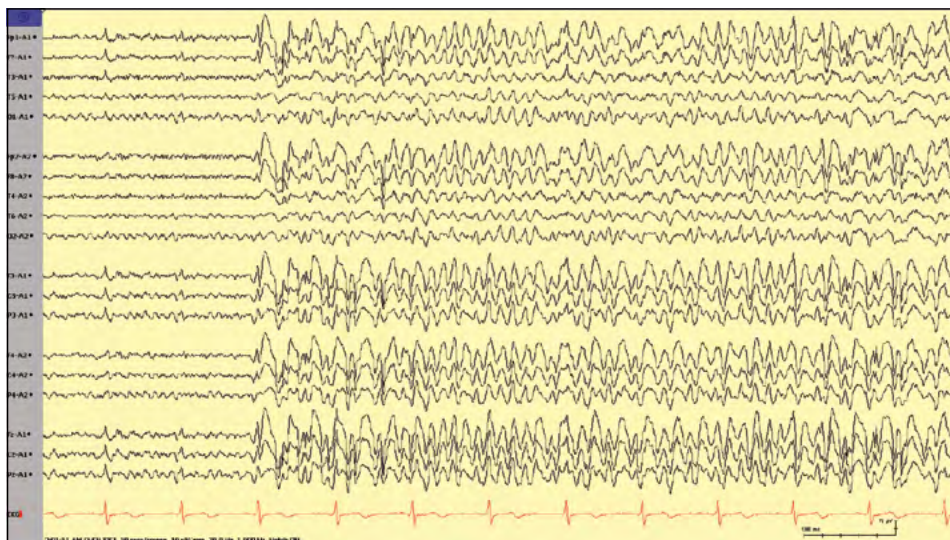
## Recruiting Rhythms

This ictal pattern is characterized by an abrupt onset of generalized, low to moderate amplitude, rhythmic (usually 10 to 13 Hz) activity. As the seizure evolves, this ictal pattern progressively increases in amplitude and slows in frequency (FIGURE 7.14).

Recruiting rhythms frequently correspond to the emergence of the tonic phase of generalized tonic-clonic convulsions. This ictal pattern can also be associated with tonic or atonic seizures occurring in isolation.

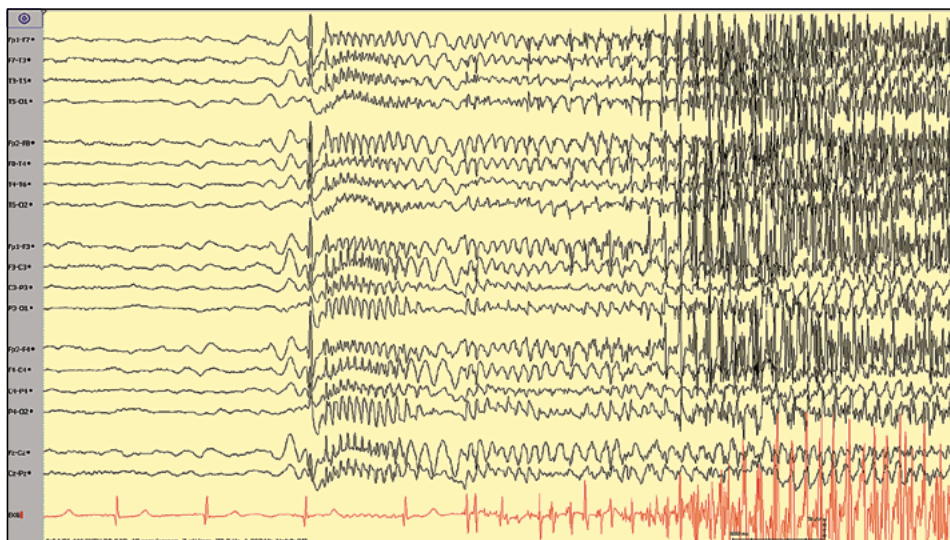
## Electrodecremental Responses

Electrodecremental responses consist of an abrupt and generalized attenuation of the background activity. The background can appear nearly isoelectric for several seconds, after which fast frequency and low voltage but discernible rhythmic activity may evolve. Some tonic or atonic seizures can be electrographically correlated with abrupt electrodecremental responses.



**FIGURE 7.13**  
**Absence Seizure**

An absence seizure is demonstrated as sustained run of generalized 3-4 Hz spike-wave discharges that clinically coincide with abrupt behavioral arrest.

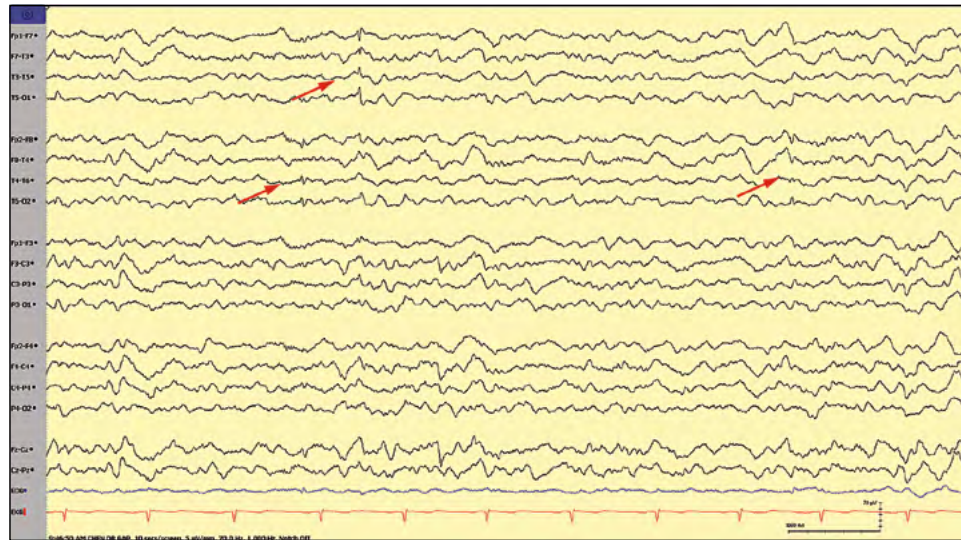


**FIGURE 7.14**  
**Primary Generalized Seizure**

A primary generalized tonic-clonic seizure emerges from onset as a recruiting rhythm of generalized, low to moderate amplitude, rhythmic 11-12 Hz activity.

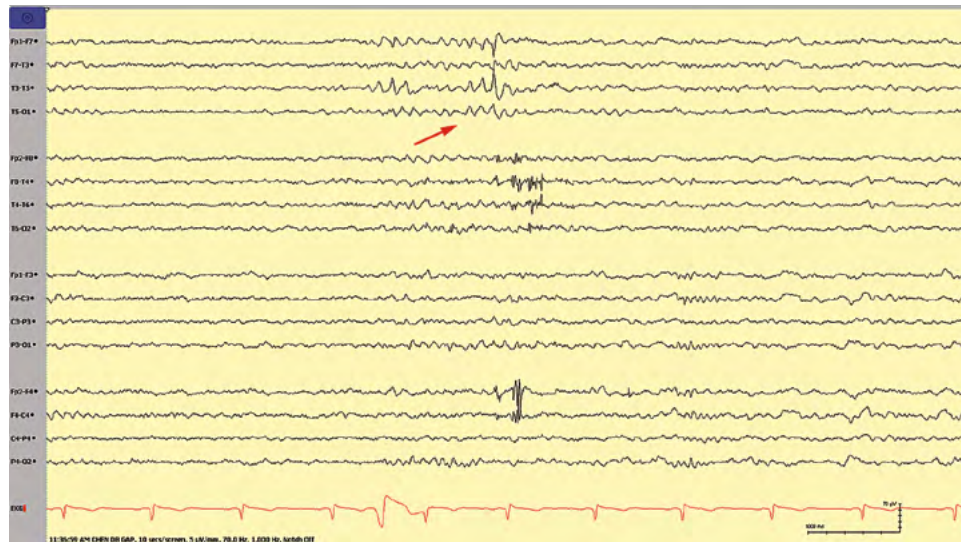
**FIGURE 7.15  
Benign Epileptiform  
Transients of  
Sleep (BETS)**

BETS consist of simply configured spike transients of low amplitude that typically populate over the right and left temporal regions independently during sleep.



**FIGURE 7.16  
Wicket Spike**

A wicket spike demonstrates simple waveform contours and does not disrupt the pre-existing background (6-7 Hz) rhythms, in contrast to a focal epileptiform spikes evident in FIGURE 7.1.



**FIGURE 7.17  
Rhythmic Midtemporal  
Theta Activity of  
Drowsiness (RMTD)**

RMTD of 5-6 Hz frequency is present over the right anterior to mid temporal region.



## Normal Variant Patterns

Normal variant patterns consist of several waveforms or rhythms that morphologically resemble interictal or ictal epileptiform abnormalities, but have no proven pathologic significance as they can occur in normal individuals. The appropriate distinction of normal variants from epileptiform abnormalities is therefore critical to the proper management of patients.

### Benign Epileptiform Sharp Transients of Sleep

Benign epileptiform sharp transients of sleep (BETS) are also referred to as small sharp spike (SSS) patterns by other authors. They are sharp but simply configured waveforms that demonstrate low amplitude (usually less than 90  $\mu\text{V}$ ) and short duration (usually less than 60 msec). Though broad in distribution, BETS are typically best expressed over the right and left temporal regions, either independently or bisynchronously (FIGURE 7.15). As their name describes, BETS occur exclusively during sleep, especially during stages 1 and 2, non-rapid eye movement sleep.

### Wicket Spikes

Wicket spikes are sharp but simply configured waveforms in the 6-11 Hz range that occur independently over left and right temporal regions. They are moderate to high amplitude potentials that may occur as a single transient in isolation, or in brief rhythmic trains. One important distinguishing feature from pathologic focal spikes is that wicket spikes do not disrupt the ongoing background rhythms (FIGURE 7.16). Although wicket spikes are typically seen over both temporal regions in an EEG, a strictly unilateral expression is also possible. Wicket spikes are present in relaxed wakefulness and activated by drowsiness and light sleep. In some patients, they are only seen during sleep.

### Rhythmic Midtemporal Theta Bursts of Drowsiness

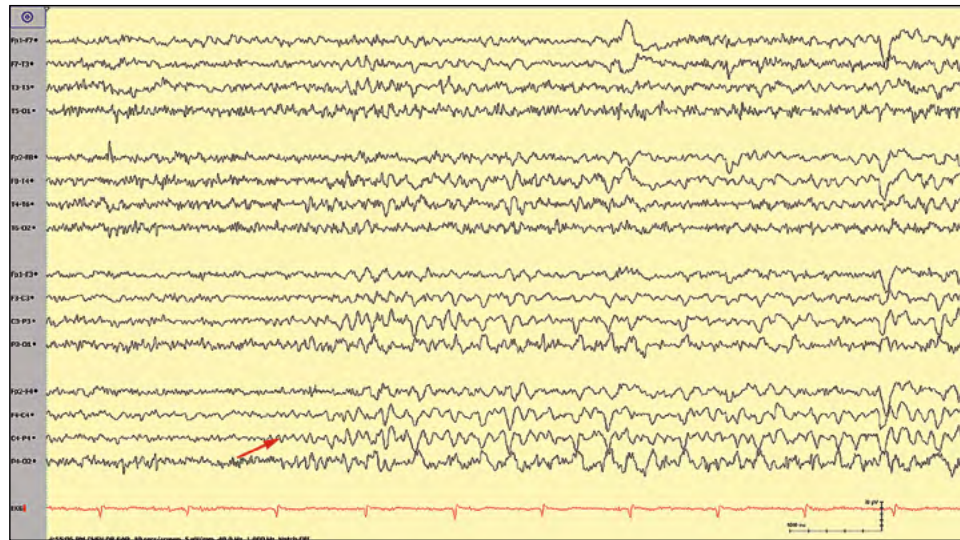
Rhythmic midtemporal theta bursts of drowsiness (RMTD) are also historically referred to as psychomotor variant. They consist of bursts of rhythmic, notched 4-7 Hz waveforms that are maximally expressed in the left or right midtemporal regions. RMTD typically occur independently on either side or on occasion, they may occur synchronously. The duration of these bursts is usually less than 1.5 seconds (FIGURE 7.17). When contrasted with focal electrographic seizure discharges, RMTD are briefer and highly regular, showing minimal variation in morphology and frequency throughout their duration. Also, this pattern has an abrupt onset and offset.

### Subclinical Rhythmic Electrographic Discharge of Adults

Subclinical rhythmic electrographic discharge of adults (SREDA) is typically characterized by broadly distributed rhythmic activity that is best expressed over the parietal and posterior temporal regions. SREDA is composed of rhythmic theta or delta activity that usually evolves in frequency and varies in the sharpness of waveforms (FIGURE 7.18). Therefore, although this is a relatively rare pattern, it is important to distinguish the rhythmic and evolving features of SREDA from true electrographic seizures. Other distinguishing characteristics for SREDA include: (1) the relative restriction of its topographic distribution to bilateral posterior regions, rather than spreading elsewhere; (2) the immediate resumption of previous background activity after the offset of SREDA, rather than the postictal EEG changes that commonly follow electrographic seizures; (3) the complete absence of accompanying clinical symptoms; (4) the absence of focal interictal spikes or sharp waves, and, (5) the known proclivity of SREDA to recur multiple times during a routine EEG study.<sup>7</sup> As indicated by its name, SREDA most commonly occurs in adults older than 50 years of age.

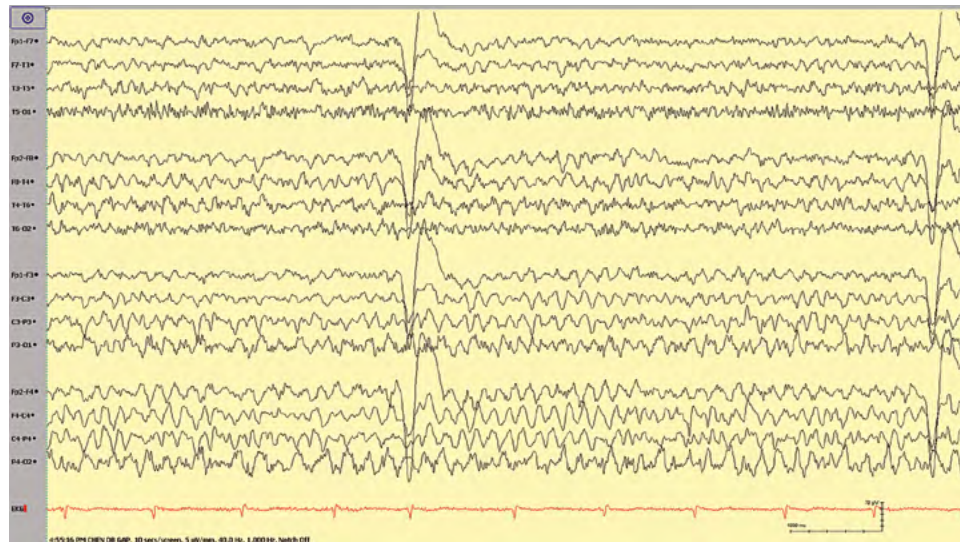
**FIGURE 7.18A**  
**Subclinical Rhythmic**  
**Electrographic**  
**Discharge of Adults**  
**(SREDA)**

This EEG illustrates an example of SREDA characterized by broadly distributed, mixed rhythmic frequencies that are best expressed over bilateral (right greater than left) parietal head regions.



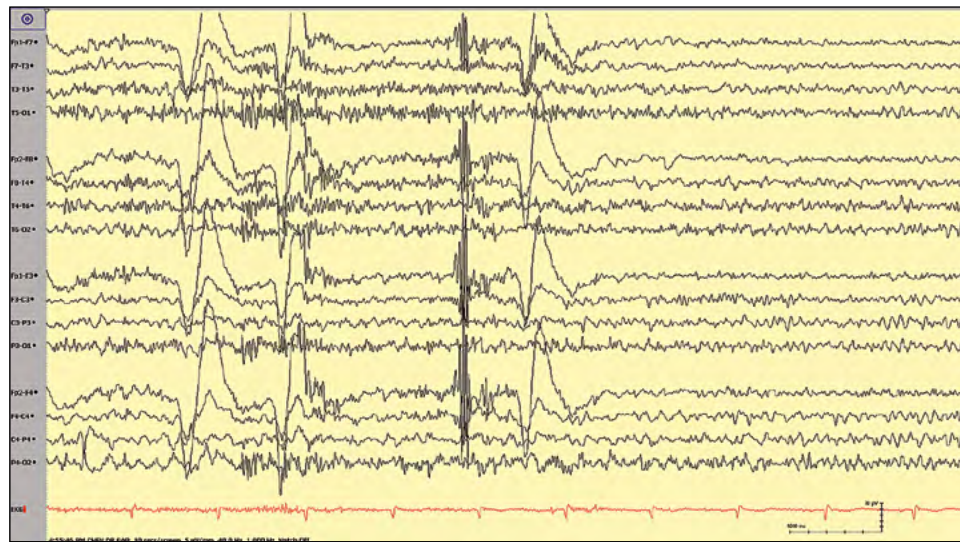
**FIGURE 7.18B**  
**SREDA**

As SREDA progresses, electrographic evolving features in terms frequency and sharpness of waveform contours become evident.



**FIGURE 7.18C**  
**SREDA**

After 50 seconds, SREDA approaches offset near end of this tracing. Subsequently, there is immediate resumption of previous background activity.



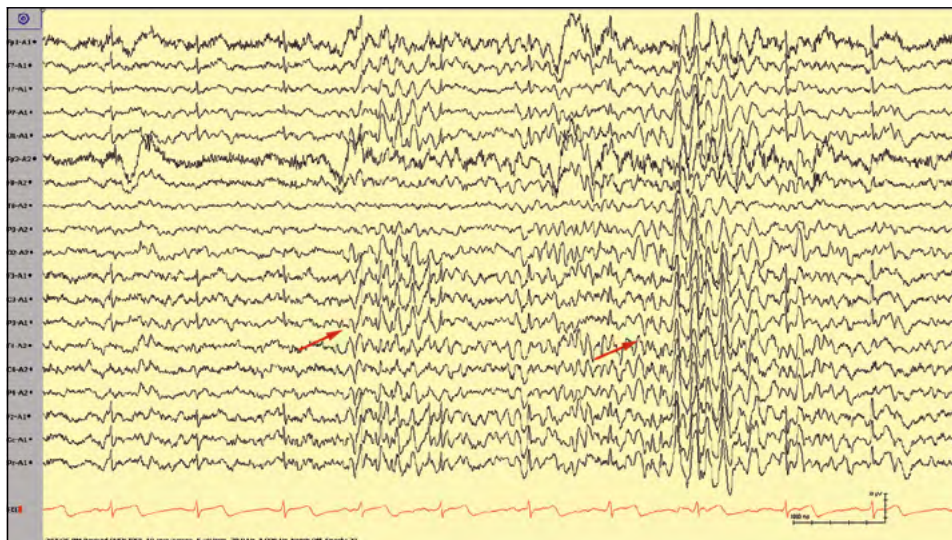
## Six Hz Spike-wave Pattern

The 6 Hz spike-wave pattern is also known as the phantom spike-wave discharges. This pattern consists of brief bursts (typically less than 1.5 seconds in duration) of spike-wave complexes whose frequency varies between 4-7 Hz, usually around 6 Hz, thus its name. The spike component of the complex is usually very low in voltage compared to the spikes seen with pathological spike-wave complexes. Phantom spike-wave discharges are typically expressed bisynchronously, with either an anterior or posterior predominance (FIGURE 7.19) and may be seen in wakefulness, sleep, or during hyperventilation.

## Other Abnormal Patterns

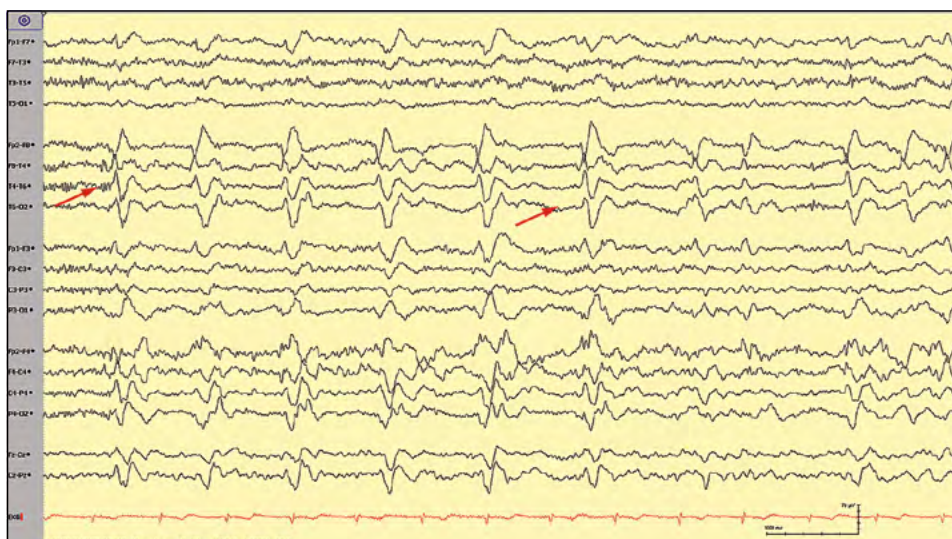
### Periodic Lateralized Epileptiform Discharges

Compared to focal IEDs, periodic lateralized epileptiform discharges (PLEDs) usually show wider distribution across one hemisphere, as well as a discharge recurrence pattern or periodicity that is mostly preserved throughout the EEG. The discharge periodicity is typically between 0.5 to 2 Hz, and PLEDs may occur either with a high degree of regularity or with some variations in the interdischarge interval or discharge morphology (FIGURE 7.20).



**FIGURE 7.19**  
**6 Hz Spike-Wave Pattern**

The 6 Hz spike-wave patterns are illustrated by brief bursts of 6-7 Hz, spike-wave complexes showing slight posterior dominance. The second 6 Hz spike-wave pattern (on the right side of figure) represents a relatively more bisynchronous and higher voltage variation.



**FIGURE 7.20**  
**Periodic Lateralized Epileptiform Discharges (PLEDs)**

This EEG demonstrates PLEDs that have a broad distribution over the right hemisphere and occur with a periodicity of about 1 Hz.



It has been hypothesized that the electrographic “periodicity” reflects marked underlying disruption that is severe enough to cause “disconnection” of the cortex from subcortical structures.<sup>7</sup> Therefore, PLEDs are usually associated significant cerebral insults of acute (stroke, seizures) or subacute (high grade tumors, encephalitis) nature. When PLEDs are present in these acute or subacute settings, the incidence of seizures ranges from 58% to 100% during active disease periods.<sup>11</sup> The time course of PLEDs is usually self-limited, remitting over the course of weeks to months. As the PLEDs resolve, the seizure propensity also wanes. Some controversies exist regarding whether PLEDs represent an ictal pattern.

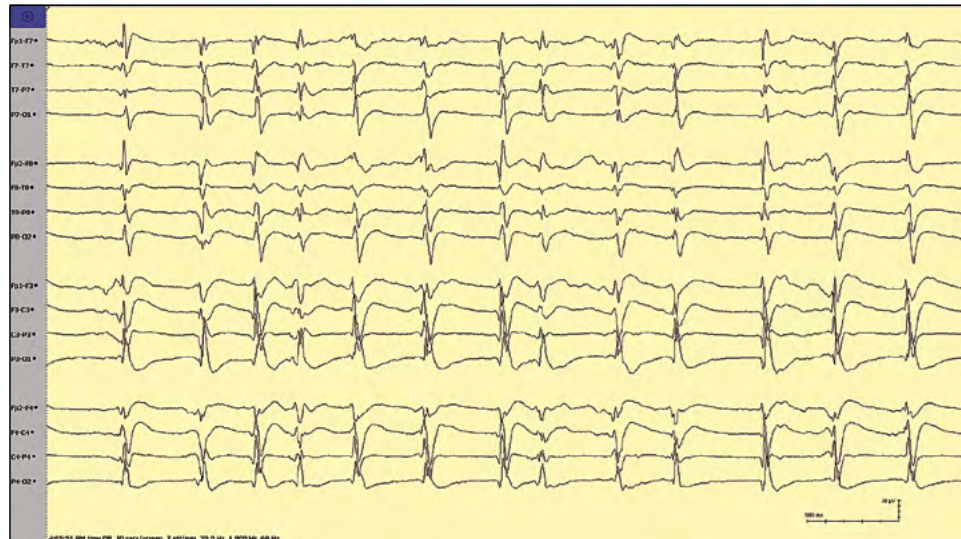
## Generalized Periodic Epileptiform Discharges

Generalized periodic epileptiform discharges (GPEDs) are characterized by periodic epileptiform discharges that occur symmetrically and synchronously across both hemispheres. Though generalized in distribution, GPEDs typically demonstrate an anterior dominance in expression. GPEDs usually recur with a periodicity of about 1 discharge every 0.5 to 3 seconds (FIGURE 7.21).

Similar to PLEDs, GPEDs are associated with significant CNS insults although usually of more diffuse nature (e.g., anoxia and CJD). GPEDs can also be associated with seizures during the active disease periods, but this risk is generally lower when compared to PLEDs. Notably, some cases of nonconvulsive status epilepticus (NCSE) can manifest

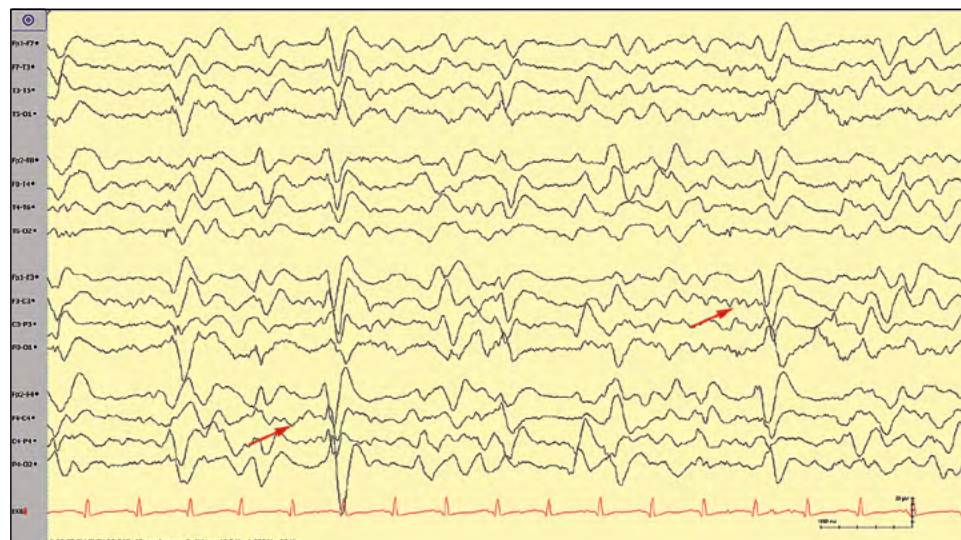
**FIGURE 7.21**  
**Generalized Periodic Epileptiform Discharges (GPEDs)**

This example of GPEDs demonstrates widespread and bisynchronous spike discharges that occur with a periodicity between 1-2 Hz.



**FIGURE 7.22**  
**Triphasic Waves**

Triphasic wave potentials are complex sharp waves with 3 phase elements that typically occur bisynchronously and predominate over the anterior head regions.



electrographically as GPEDs. In the setting of NCSE, the GPEDs periodicity is usually faster at  $>3$  Hz, while some electrographic evolving features in discharge frequency, morphology, amplitude, and/or distribution will likely be evident.

## Triphasic Wave Pattern

The typical triphasic wave pattern is a complex sharp wave with 3 phase elements as its name suggests.<sup>3</sup> The first phase is usually marked by negative (upward) and sharpest deflection among the 3 elements. A positive (downward) second phase represents the tallest element in terms of amplitude. The final third phase consists of a negative (upward) and longest component in terms of duration. Triphasic waves are typically bisynchronous and predominate over the anterior head, occurring either singly or in brief repetitive, 1.5-3 Hz trains (FIGURE 7.22). Less typical variants of triphasic waves can occur, such as those that show biphasic morphology, posterior dominance, or occur sporadically in isolation.

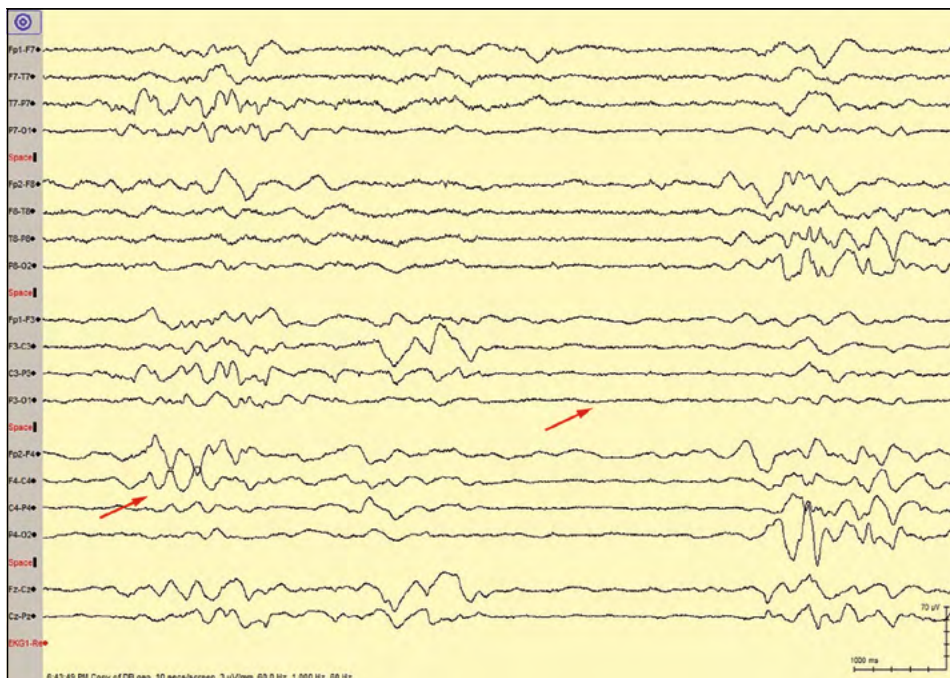
Although such waves are epileptiform in appearance, they usually occur in patients who do not experience seizures. This is because triphasic waves are usually associated with metabolic encephalopathies, such as from hepatic, renal, or anoxic derangements. However, they can also occasionally occur in other non-metabolic etiologies resulting in widespread CNS insults such as traumas, strokes, or the aftermath of significant seizure activity.

## EEG Patterns in Coma and Electrocerebral Inactivity

Coma has been identified as a major predictor of death and poor neurofunctional outcomes. EEG can complement the bedside clinical evaluation of comatose patients by informing the depth and severity of coma. Some EEG patterns may either support the etiology for the coma or have a role in prognostication. While the previously described periodic discharge and triphasic wave patterns can occur in comatose patients, the following discussions describe additional important EEG patterns in coma.

### **Burst suppression**

This EEG pattern consists of bursts of higher amplitude, polyfrequency activity and/or sharp wave activity alternating with segments of very low amplitude or suppressed background activity (FIGURE 7.23). Greater proportion of background suppression corresponds to more severe degree of encephalopathy. A burst suppression pattern that occurs in the setting of intoxication (sedative medications), anesthesia, or hypothermia protocol can be associated with a



**FIGURE 7.23**  
**Burst Suppression**  
**Pattern**

This EEG demonstrates 2-3 second bursts of admixed theta and delta activity of moderate amplitude, followed by 3-4 second segments of background suppression.

favorable prognosis. On the other hand, a monotonous burst suppression pattern that occurs in the setting of hypoxic-ischemic insult and persists for hours after the insult strongly portends adverse neurologic outcome in terms of meaningful functional recovery.<sup>12</sup>

In the treatment of refractory status epilepticus, pharmacologic sedation is titrated until the establishment of burst suppression pattern on EEG. This pursuit is guided by the observation of lower incidence of later breakthrough seizures when treatment target was EEG burst suppression, rather than simply seizure freedom.<sup>13</sup> However, aggressive burst suppression inducing treatment can be associated with notable morbidity and mortality, particularly in critically-ill patients.

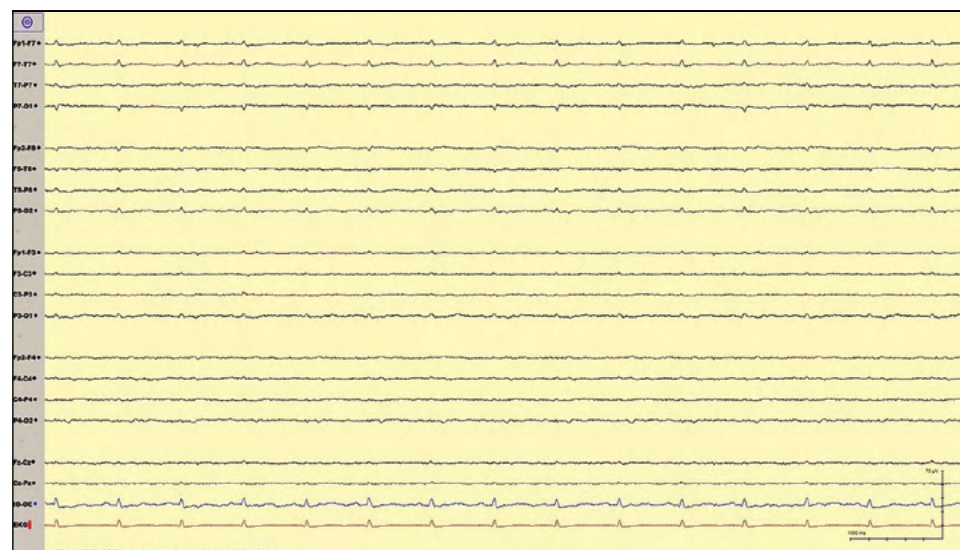
## Alpha coma

This EEG pattern is defined by persistent 8-13 Hz EEG activity that is unresponsive to eye opening or external stimulation. It differs from the posterior dominant rhythm in spatial distribution as well as its lack of reactivity. It is monorhythmic and can be diffuse or have an anterior or posterior accentuation. This EEG pattern can occur in the setting of intoxication (barbiturates, benzodiazepines, anesthetics, imipramine) for which the prognosis is favorable. However, occurrence in the setting of severe anoxic brain injury or acute brainstem lesions (ischemic stroke or hemorrhage) is associated with guarded prognosis in terms of meaningful recovery. The alpha coma pattern must be distinguished from the alpha frequency pattern seen in patients with de-efferented (locked-in) states. In such cases, the EEG pattern shows a posterior dominant alpha rhythm that is reactive to physical/photic stimulation.<sup>12</sup>

## Electrocerebral inactivity

An EEG background showing marked voltage attenuation that is diffuse and poorly differentiated throughout all recording regions represents another important pattern in comatose patients. Upon further deterioration of the patient's cerebral dysfunction, electrocerebral inactivity (ECI) can ensue. ECI is defined by the absence of EEG activity greater than 2  $\mu$ V (FIGURE 7.24). Activities lower than this amplitude cannot be reliably differentiated from electrical noise. In order for ECI to be formally interpreted, the EEG recordings must fulfill the minimum technical standards as proposed by the American Clinical Neurophysiology Society:<sup>14</sup>

- A complete complement of scalp electrodes
- Interelectrode impedances between 100 and 10,000 ohms
- Integrity of the entire recording system tested by touching each electrode individually to obtain appropriately located artifact potential
- Interelectrode distances of at least 10 cm

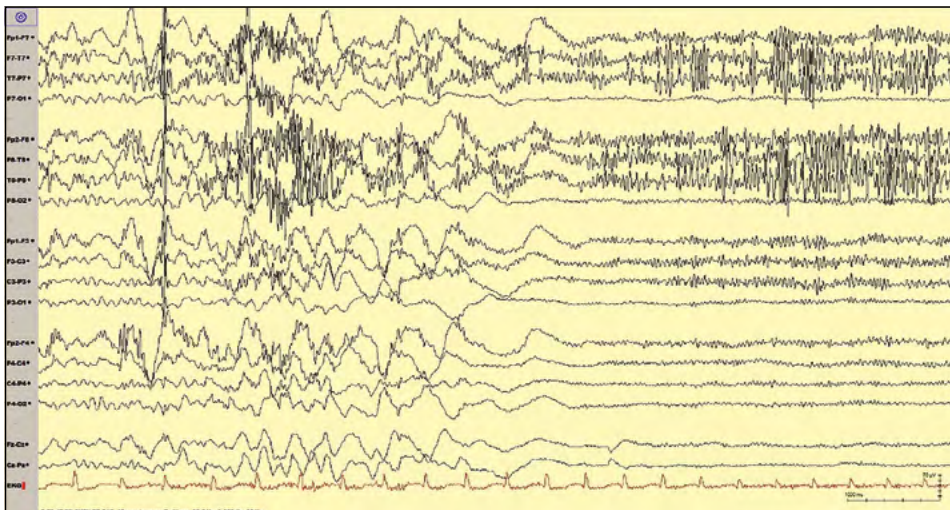


**FIGURE 7.24**  
**Electrocerebral Inactivity (ECI)**  
This EEG demonstrates ECI with no activity greater than 2  $\mu$ V.

- Sensitivity of at least 2  $\mu\text{V}$  for 30 minutes of the recording, with appropriate calibrations documented
- High-frequency filter (HFF) not set below 30 Hz and low-frequency filter (LFF) not set above 1 Hz
- Additional monitoring techniques used as necessary to eliminate or prove waveforms are artifactual
- No EEG reactivity to strong and thorough tactile, auditory, or visual stimulation
- Recording performed by a qualified technologist working under the direction of a qualified electroencephalographer
- If ECI in doubt, EEG repeated after an interval (suggested 6 hours)
- Record physiologic variables and medications

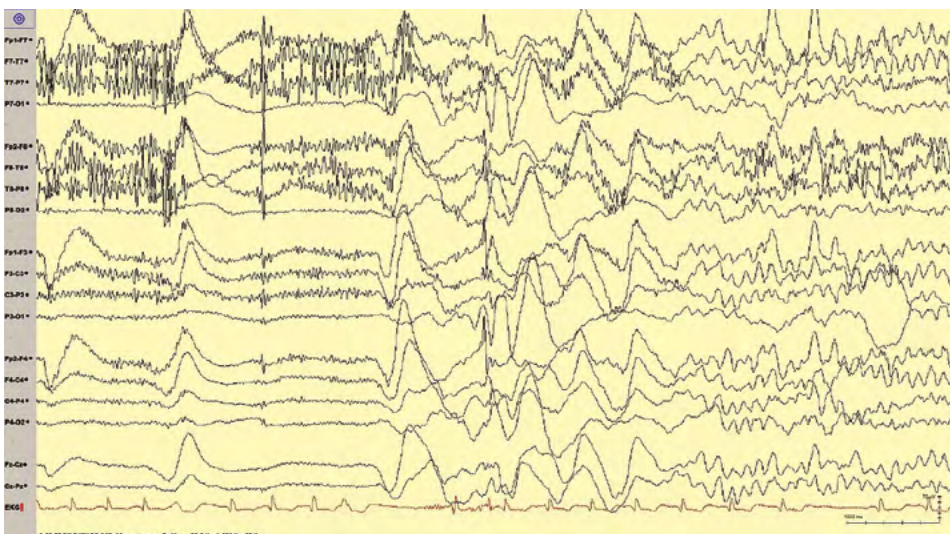
## Syncope

The EEG in syncope progresses through a stereotyped pattern, with each change corresponding to the extent of cerebral dysfunction related to blood flow reduction. This pattern is typically heralded by moderate to high amplitude, diffuse theta (4-5 Hz) slow activity, followed by even higher amplitude, diffuse slower activity in the delta range (1.5-3 Hz). Background slowing as such has been postulated to reflect an increasing failure of network activity as synaptic connectivity diminishes. Subsequently, complete network failure ensues should cerebral blood flow falls below 0.16 mL/g/min and is reflected by diffuse suppression of all EEG background activity. Upon restoration of cerebral blood flow, the EEG background progresses conversely from diffuse delta slow activity to theta slow activity, followed by relatively rapid recovery of the posterior dominant rhythm (i.e., neurophysiological marker of the resting awake state)<sup>15</sup> (FIGURE 7.25).



**FIGURE 7.25A**  
**Syncope**

This EEG is an example of cough syncope, showing an initial awake background admixed with coughing-related movement artifacts. Subsequently, the background progresses from diffuse theta slowing to diffuse delta slowing, followed by diffuse attenuation during which the patient loses consciousness.



**FIGURE 7.25B**  
**Syncope**

A few seconds later, delta slow activity reemerges, followed by recovery of theta and alpha faster frequencies as the patient returns to baseline functioning.

# Indications for Other Specialized EEG Methods

## Continuous Bedside Video-EEG Studies

This type of study entails recording of both video and EEG data continuously by either a portable EEG machine or a fixed EEG unit in specialized rooms dedicated to continuous video-EEG monitoring (e.g., some neuro-intensive care rooms). This recording method is frequently relevant for critically-ill patients whose severe medical conditions can sometimes be associated with highly recurring seizure activity. The continuous nature of this type of recording allows for detection and quantification of potentially recurring electrographic seizure activity. This recording method is especially useful for patients whose seizures correlate with very subtle or no visible manifestations to the bedside examiner.

In one recent study, it was reported that among critically-ill patients who received continuous video-EEG monitoring, 88% of those who experienced electrographic seizures demonstrated their first seizure within the first 24 hours of the recording. By 48 hours of continuous recording, 93% of these patients demonstrated their first seizure.<sup>16</sup> Therefore, it has been argued that the probability for NCSE diminishes if 48 hours of continuous recording yields no evidence for electrographic seizure activity. Furthermore, although continuous video-EEG bedside monitoring can help detect subclinical electrographic seizures in patients with depressed levels of consciousness, prospective studies are needed to demonstrate that such monitoring will ultimately affect the patients' long-term outcome.

## Epilepsy Monitoring Units

Epilepsy monitoring units (EMUs) refer to specially-equipped patient rooms with not only continuous video-EEG recording capacity, but also with provision for continued surveillance by a trained technician in a nearby control room. During a seizure, the EMU monitoring technician redirects the video to best capture the most relevant clinical manifestation, and performs a standardized set of bedside examinations. The availability of optimized video documentation and bedside ictal examination contributes to a more confident event characterization— as this information can sometimes help localize seizure focus, or distinguish epileptic from non-epileptic seizures. Therefore, when the clinical question is regarding need for detailed event characterization (beyond simply seizure identification or quantification), then EMU studies are better equipped to properly address this question (more so than continuous bedside video-EEG studies).

## Ambulatory EEG Studies

Ambulatory EEG represents an outpatient procedure in which the patient initially arrives at the EEG laboratory for electrode placement, and then returns home with a recording device that continuously records EEG data. The allotted duration of continuous recording depends on length of the battery life and capacity of data memory storage, but can be renewed if the patient is able to return for battery or memory storage replacement in midst of a longer planned study. Some ambulatory EEG devices have the capability for concurrent video recordings. However, because of the afforded patient freedom and hence less standardized recording settings of this method, the qualities of both the EEG and video data are quite variable as they are more prone to artifacts. Therefore, ambulatory EEG studies may be a less optimal initial method to investigate behavioral or EEG paroxysms of unclear etiology. Instead, ambulatory EEG studies can be highly useful to quantify the occurrences of behavioral or EEG paroxysms—once the EEG findings or behaviors have already been well documented by routine EEG or EMU studies.

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# Neuroimaging

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# Introduction

Seizures result from many medical and neurological causes. The initial diagnostic consideration is whether the seizures are provoked by systemic disturbances such as drugs, alcohol withdrawal, or metabolic disorders (eg, hypoglycemia or uremia), or whether they are due to disorders of the brain. Epilepsy is defined as recurrent seizures that are not provoked.

Imaging of the brain is an essential part of the workup and treatment planning for adults with seizures. Functional and anatomic imaging modalities are complementary. The appropriate choice of imaging modalities depends on the clinical scenario. This chapter provides a guide for stratifying patients into appropriate imaging categories that facilitate optimal therapy. Examples of pathology are provided in context within the discussion of each modality.

## Differential Diagnosis Considerations

Seizures encompass a broad range of pathology and can be a manifestation of many different types of epilepsy and epileptic syndromes.<sup>1</sup> In addition, seizures can occur as a result of metabolic disorders, such as uremia, or certain toxins, including some medications, and can be provoked by acute insults to the nervous system such as hypoxia, ischemia, and stroke. The underlying epileptic etiologies in adults include genetic, developmental, and acquired due an insult to the cerebral cortex. The most common genetic epilepsy in the Veteran population is benign JME. Most genetic epilepsies present in childhood, thus precluding military service, but benign JME often is discovered in early adulthood.

Developmental anomalies that can produce adult-onset epilepsy include vascular malformations and cortical dysplasia. Both may be asymptomatic until early adulthood. Rarely do these anomalies explain the onset of seizures after the age of 30. Cortical dysplasias can be detected with MRI but may be overlooked because they are small and may be difficult to differentiate from normal cortical structures.

Most of the epilepsies in the Veteran population are due to acquired insults to the brain. In younger Veterans, TBI is a common cause, most commonly due to moderate to severe blunt head trauma or penetrating injury.

Mesial temporal sclerosis (MTS) is among the most common lesions causing acquired epilepsy and can result from ischemia, hypoglycemia, or from prolonged seizures that become self-initiating. Febrile convulsion in childhood is one such insult that can progress to MTS. Although the vast majority of patients with febrile convulsions will not develop epilepsy, those patients that do have MTS have a high likelihood of having had febrile convulsions as a child and subsequently developing medically refractory seizures. MTS may present in childhood or as new onset seizures in the young adult.

Another common cause of acquired epilepsy in the young Veteran is central nervous system infection. Both viral encephalitis and bacterial or fungal meningitis can result in subsequent development of an epileptogenic focus.

Primary and metastatic brain tumors can cause new onset seizures at any age. Low-grade gliomas are most common among the primary tumors, but glioblastoma multiforme and primary central nervous system lymphoma may also present with seizure as their first clinical manifestation. Neoplasms that commonly metastasize to the brain include lung, breast, or melanoma. In addition, thyroid carcinoma and renal cell carcinoma metastases have a propensity to hemorrhage, which increases the likelihood that they may predispose to seizures.

Stroke is a common cause of new-onset seizures in the older adult, either in the acute setting or following development of surrounding gliosis at the site of remote stroke. Seizures in the setting of an acute stroke can be convulsive or nonconvulsive, and can result from thrombotic, embolic, or hemorrhagic forms. Subsequently, a chronic epileptogenic focus can develop weeks to years after infarction.

Brain imaging provides essential diagnostic information in the setting of new onset seizures, unexplained chronic epilepsy and unexplained increase in the frequency and severity of epileptic seizures. Brain imaging also is an important part of the workup of patients with medically refractory epilepsy to determine eligibility for seizure surgery and for presurgical localization of the seizure onset zone.

# Imaging Modalities

In general, cross-sectional imaging such as CT or MRI is most useful to assess for a structural abnormality such as neoplasm, infection, cortical dysplasias, heterotopia, or the presence of gliosis from any cause.<sup>2,3</sup> Mesial temporal sclerosis in its later stages can also be readily demonstrated with dedicated imaging through the temporal lobe, particularly with MRI.

Other modalities have a functional focus rather than strictly anatomical. Relative perfusion can be analyzed with SPECT, using either <sup>99m</sup>Tc-hexamethylpropyleneamine oxime (HMPAO) or <sup>99m</sup>Tc-ethyl cysteinate dimer (ECD). 18F fluorodeoxyglucose (FDG) PET localizes to areas of higher metabolic activity, and fMRI is also a perfusion-based modality that discriminates between areas of relative oxygen concentration. Any of these modalities may help distinguish normal from abnormal parenchyma. When appropriately performed, these have high sensitivity for localization of a potential seizure focus and may reflect changes even before the anatomic imaging.

Modern CT and MRI scanners also have the ability to acquire images so quickly that dynamic images can be obtained over time, enabling perfusion analysis following rapid bolus intravenous contrast administration. This allows for mapping out of relative perfusion or calculation of absolute perfusion parameters of different areas of the brain, and has the advantage of combining anatomic structural images with functional parameters in one scan.

## Computed Tomography

Computed tomography (CT) creates an image by rotating an electron beam around the patient and calculating relative absorption based on the amount of x-rays that are able to pass through. The image that is generated is based entirely on relative differences in tissue density. It shows variable light and dark shades of gray in areas where the beam is more or less attenuated, respectively. For example, dense bone absorbs more of the x-ray photons than soft tissue (eg, brain) and appears white, while the soft tissue appears as various shades of gray. Fat and air are of lower density than water-containing soft tissue, and appear darker. The appearance can also be changed by adjusting the “window” and “level” settings, which alter the relative on-screen lightness or darkness of a given density value.

### Noncontrast CT Imaging

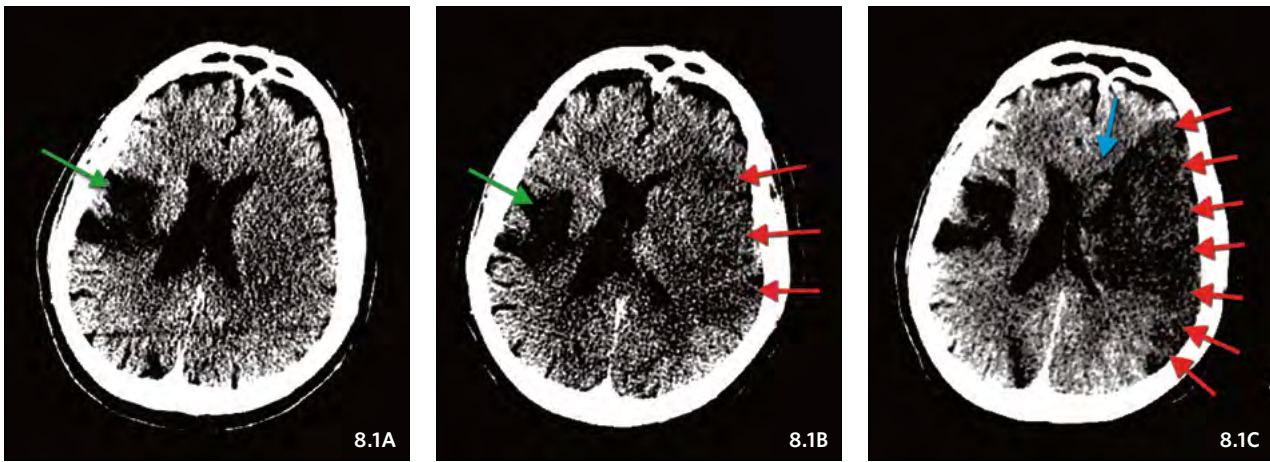
Noncontrast CT is often the first screening test for most patients presenting to the emergency department with any neurologic complaint including seizures, to assess for the presence of acute blood products, head trauma, herniation, or edema secondary to mass, abscess, or infarction. Seizure activity may have been unwitnessed or unrecognized, or may begin later secondary to the initial insult.

Normal gray matter is slightly higher in density than white matter even without contrast and appears as a lighter shade of gray. The presence of abnormal fluid is referred to as edema, and can be related to cytotoxicity, with cell death causing intracellular fluid accumulation, or can be interstitial related to vessel leak. Both cytotoxic and vasogenic edema cause decreased attenuation as the water content in the tissue increases.

In very early acute stroke, the noncontrast CT is normal until sufficient water seeps into the areas of tissue death to show up as decreased density of the gray matter. Subsequently, the early cytotoxic edema is seen as subtle decrease in attenuation of the gray matter, becoming the same density as white matter, and is described as loss of gray-white differentiation. As the cells continue to swell, there is associated sulcal effacement, and ultimately the infarction will progress to secondary vasogenic edema as the epithelial cells lining the blood vessels also die. At that point larger volumes of fluid contribute to significantly increased mass effect (FIGURES 8.1A, 8.1B, and 8.1C).

When evaluating a patient with new neurologic deficit, a careful inspection of the central vessels of the circle of Willis may demonstrate increased attenuation indicating acute thrombus within an artery (FIGURE 8.2). Similarly, a venous thrombosis appears as increased density and outward convexity of the dural venous sinus.

Vasogenic edema without stroke causes decreased attenuation of the white matter with preserved density of overlying cortical gray matter. This requires evaluation for an underlying parenchymal lesion that is disrupting the blood–brain barrier or causing neovascularity, which is more prone to fluid leakage (FIGURE 8.3).



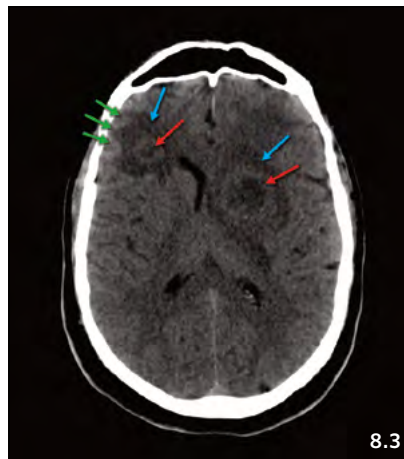
**FIGURE 8.1 Acute stroke in evolution**

A 65-year-old man presented with acute onset of slurred speech and right-sided weakness. His initial head CT in the emergency department (A) demonstrated the presence of a remote completed infarct in the right MCA territory (*green arrow*) but did not reveal left hemisphere pathology. Recombinant tissue plasminogen activator was administered, and 4 hours later the patient began having partial complex seizures localizing to the left hemisphere. Repeat imaging (B) at that time showed subtle cytotoxic edema with loss of gray-white differentiation and early sulcal effacement in the left temporal lobe (*red arrows*) but no hemorrhage. Follow-up exam 24 hours later (C) showed a dense area of infarction throughout the left MCA territory (*red arrows*) with increased sulcal and ventricular effacement.



**FIGURE 8.2 Hyperdense vessel sign**

In this patient with new left-sided weakness, there is acute thrombosis of the right MCA at the level of the proximal M1 segment (*red arrows*).



**FIGURE 8.3 Vasogenic edema on noncontrast CT**

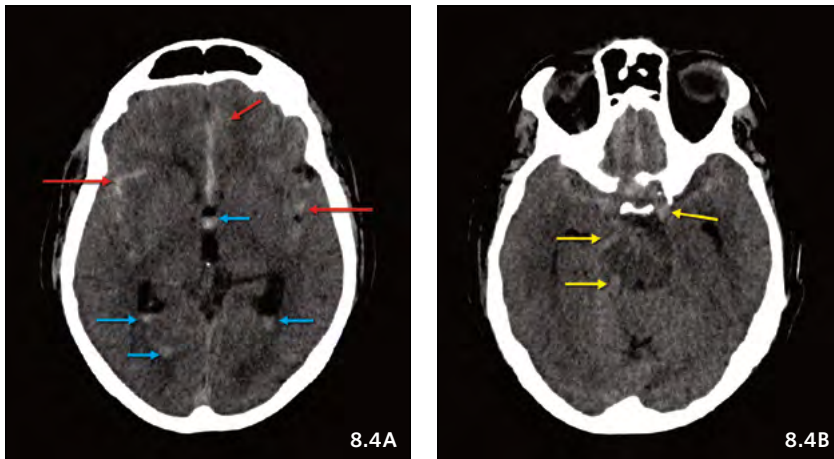
This gentleman had a history of previously treated esophageal carcinoma. Multiple lesions (*red arrows*) were seen on CT with significant surrounding vasogenic edema (*blue arrows*) causing regional mass effect. Note that the overlying cortex is displaced but maintains relatively normal gray matter density (*green arrows*).

Acute blood products appear hyperdense (whiter) relative to the brain parenchyma. The presence of acute subarachnoid blood products in the absence of trauma should prompt evaluation for vascular abnormality such as aneurysm (FIGURE 8.4).

Ultimately, whether the initial CT is positive or negative, most of the patients presenting with seizures will undergo additional imaging, especially in the absence of a known epilepsy history.

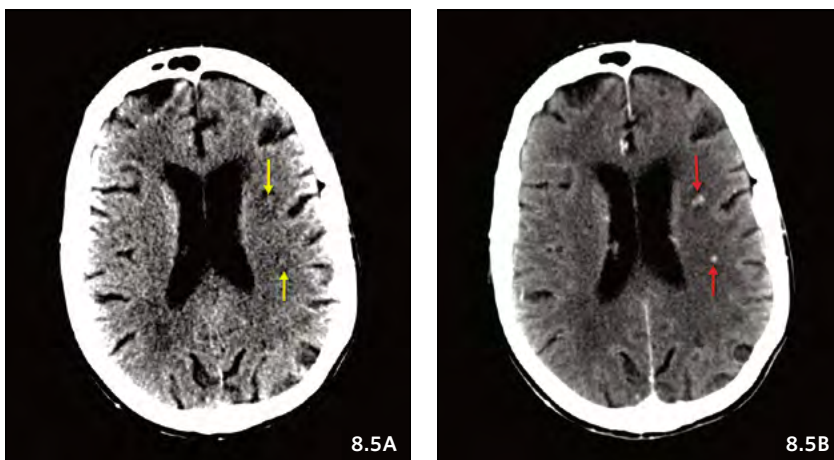
### Postcontrast CT Imaging

Iodinated intravascular contrast can be administered to increase conspicuity of lesions in the brain. The indications for a simple postcontrast CT are rather limited. The anatomic detail and contrast between gray and white matter are much lower than on MRI. Therefore, contrast-enhanced CT is reserved only for those patients who cannot have MRI (FIGURE 8.5).



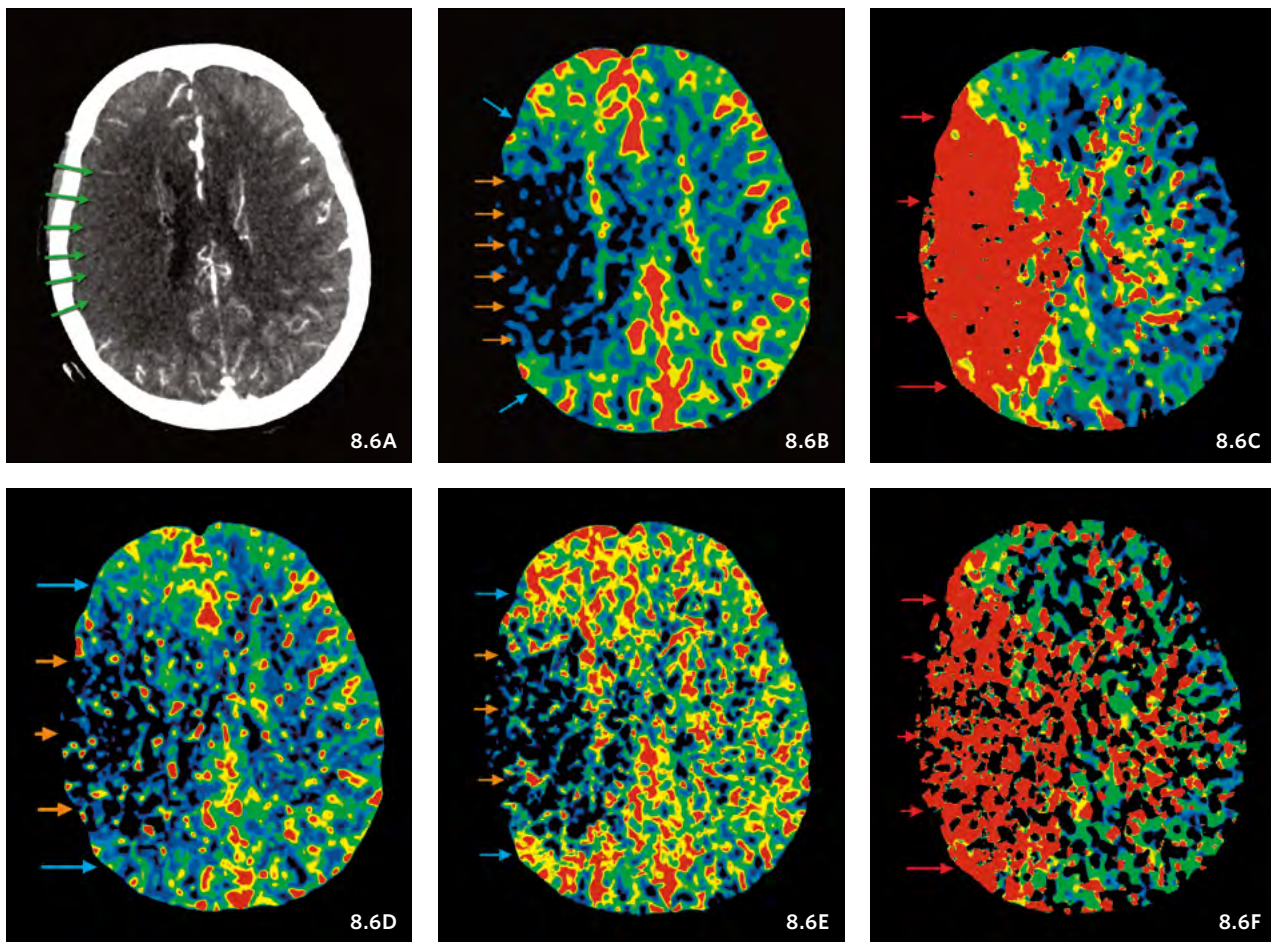
**FIGURE 8.4 Acute subarachnoid hemorrhage**

Acute blood products on CT are of higher attenuation than normal gray matter, and significantly higher than water (CSF). Subarachnoid hemorrhage is manifest as hyperdense blood filling the sulci (**red arrows, A**) and suprasellar and perimesencephalic cisterns (**yellow arrows, B**), and is in communication with the ventricular system (**blue arrows, A**). The accumulation of intraventricular blood predisposes the patient to acute ventricular obstruction by clot.



**FIGURE 8.5 Postcontrast CT showing multiple enhancing lesions**

This immunocompromised patient had multiple enhancing lesions (**red arrows**) with surrounding vasogenic edema, found to be nocardia abscesses. These are much more conspicuous on the postcontrast images (**B**) than the noncontrast sequence (**A**).

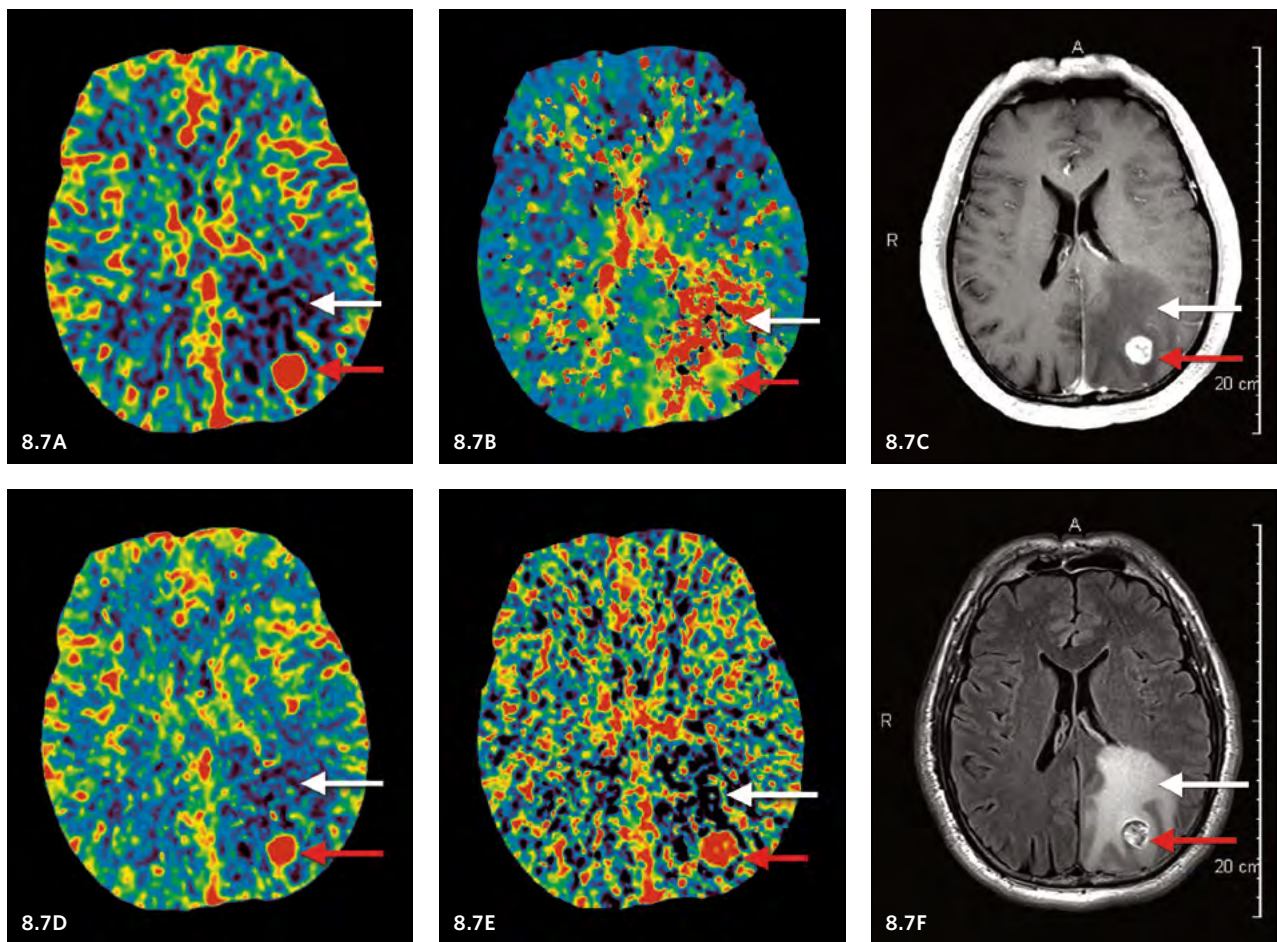


**FIGURE 8.6 Acute stroke on CT angiogram with perfusion**

CT angiogram perfusion maps are usually arranged with an axial maximum intensity projection slice (A), CBV (B), and TTP (C) along the top row; and CBF (D), MTT (E), and delay (F) maps along the bottom row. In this patient with acute right MCA infarct and hyperdense MCA sign seen in FIGURE 8.2, there is a large area of increased (*more red*) TTP and associated delay throughout the right MCA territory (*red arrows*) beyond the point of a proximal MCA occlusion. Diffusely decreased vascularity is seen throughout this region on the MIP CT angiogram image (*green arrows, A*). There is corresponding decrease in MTT through the capillary bed in the infarcted territory and subtly increased MTT in adjacent ischemic tissue. There is decreased CBF and CBV (*more blue*) in the areas of infarct core (*orange arrows*), but with preservation of normal CBF and CBV in the areas of surrounding ischemic penumbra (*blue arrows*).

### **CT Angiogram with Dynamic Perfusion Analysis**

Seizures can arise within areas of gliosis associated with previous stroke but may also occur in acutely insulted parenchyma. As discussed above, the noncontrast CT is initially normal in hyperacute infarct. Even before changes are seen on the noncontrast portion of the exam, however, the CT perfusion demonstrates a completed infarction as an area with delayed arrival of contrast to the tissue and increase in time to peak attenuation (TTP), slowing of mean contrast passage time (MTT) through the affected capillary bed ultimately progressing to no contrast passage time and a defect on the MTT maps, decreased cerebral blood volume (CBV) passing through the area, and decrease in calculated rates of cerebral blood flow (CBF). Ischemic penumbra that has not yet progressed to irreversible infarct has delayed MTT and increased CBF and CBV.<sup>4</sup> This is usually combined with CT angiography to evaluate for underlying vessel stenosis or occlusion (FIGURES 8.6A-8.6F).



**FIGURE 8.7 Tumor on CT angiogram with perfusion**

In this case, the CT angiogram maps demonstrated focally increased CBF (*D*) and CBV (*A*), with decreased TTP (*B*) but increased MTT (*E*) corresponding to a focal lesion (*red arrows*) in the left parietal lobe. The vasogenic edema (*white arrows*) caused perfusion delay in the surrounding white matter. Subsequent MRI confirmed the presence of the lesion and the adjacent edema on postcontrast (*C*) and FLAIR (*F*) images. Further workup determined that the patient had metastatic disease from a previously undiagnosed cancer.

In ictal patients the CT perfusion study may actually demonstrate an area of increased perfusion at the site of seizure focus.<sup>5</sup> Tumor with associated seizure may also be demonstrated as a mass lesion that is hyperperfused relative to normal parenchyma (FIGURES 8.7A-8.7F).

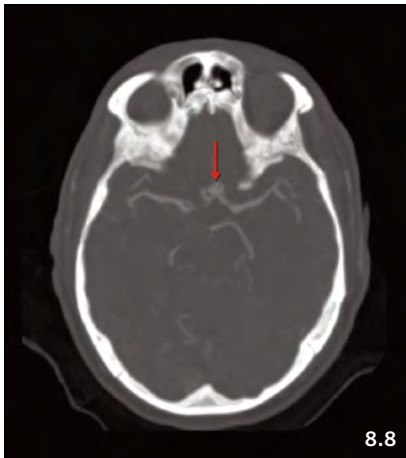
For patients with subarachnoid hemorrhage, CT angiography is often performed to evaluate for underlying vascular lesion, particularly aneurysm. Additionally, aneurysms may be found incidentally, and when one is present a diligent search may demonstrate multiple lesions. These occur most commonly at arterial branch points in patients with hypertension. Anatomic variants with altered flow may lead to saccular aneurysm as well, such as hypoplasia of an A1 segment leading to increased flow through the anterior communicating artery. Certain inherited conditions such as autosomal dominant polycystic kidney disease and Marfan syndrome also predispose to aneurysm formation (FIGURE 8.8).

## Magnetic Resonance Imaging

MRI of the brain has a much higher contrast resolution between gray matter and white matter as well as between normal and abnormal tissue. Therefore, it is the preferred modality in the workup of patients with seizures.<sup>6</sup> Different sequences are used in this process, detailed below.

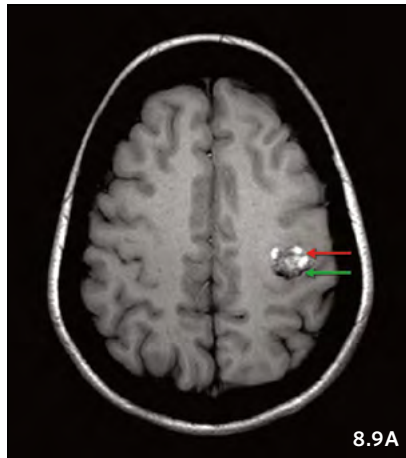
## T1-weighted Images

T1-weighted images are obtained with relatively short echo time (TE) and repetition time (TR). Bright signal on T1 is caused by fat, subacute blood products, hydrolyzed calcium, melanin, or highly proteinaceous material. Chronic blood products in hemosiderin stage, extracellular calcium, and CSF appear dark (FIGURE 8.9). Normal gray matter appears gray, and white matter is relatively brighter (more white) due to the presence of lipid within myelin. Gadolinium-based contrast also appears bright on T1-weighted sequences.



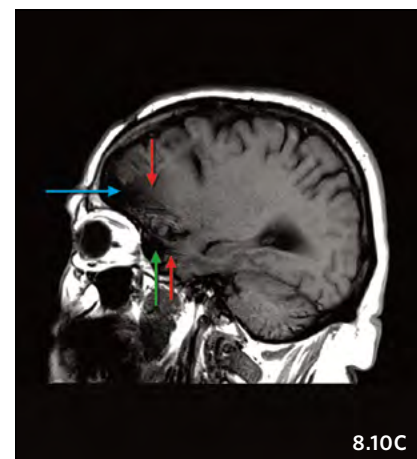
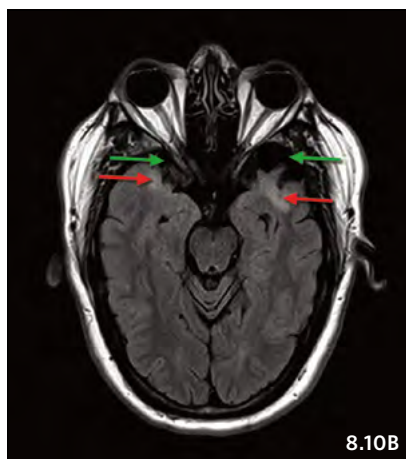
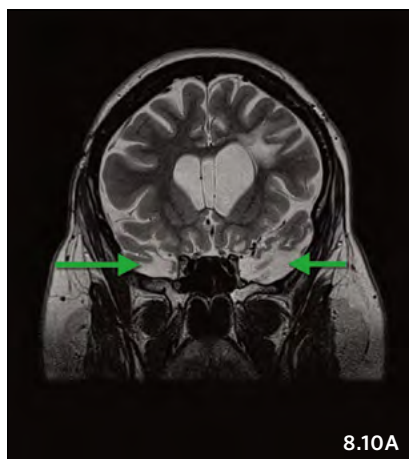
**FIGURE 8.8 Aneurysm on CT angiogram**

This patient presented with subarachnoid hemorrhage (FIGURE 8.4), and CT angiogram demonstrated the presence of an irregular bilobed aneurysm (*red arrow*) arising from the anterior communicating artery on the left.



**FIGURE 8.9 Subacute and remote blood on MRI**

As blood accumulates and then is broken down, it progresses through a variety of stages. In the brain, these have a predictable timeline as detailed in TABLE 8.1. The subacute blood products (methemoglobin) appear bright on T1-weighted images (*red arrow, A*). As they are further broken down, hemosiderin (*green arrow*) is seen as decreased T1 and T2 signal, starting at the periphery of the collection. This patient had a dominant cavernoma in the left frontoparietal region with associated gliosis (*blue arrow, B*).



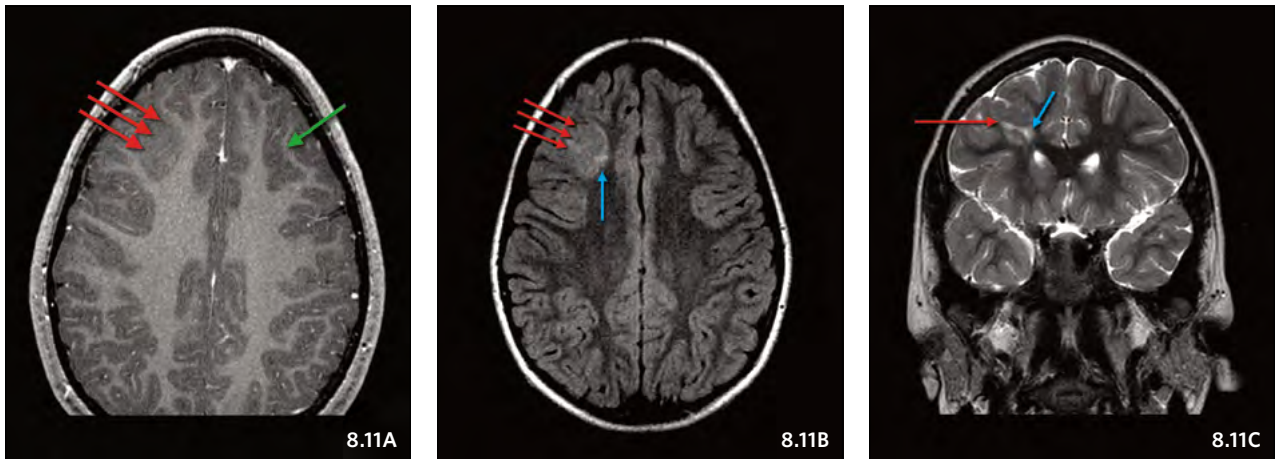
**FIGURE 8.10 Encephalomalacia and gliosis from prior trauma**

Fluid-sensitive sequences demonstrate increased signal in areas of gliosis (*red arrows*) at the periphery of encephalomalacic cavities on both T2-weighted (*A*) and FLAIR (*B*) sequences. T1 signal is decreased (*C*). The cavity itself (*green arrows*), filled with CSF, is suppressed on the FLAIR sequence and bright on the conventional T2 images. This patient also had encephalomalacia in the frontal lobes (*blue arrow, C*). The distribution is classic for a significant closed head injury.

## Fluid-sensitive Images

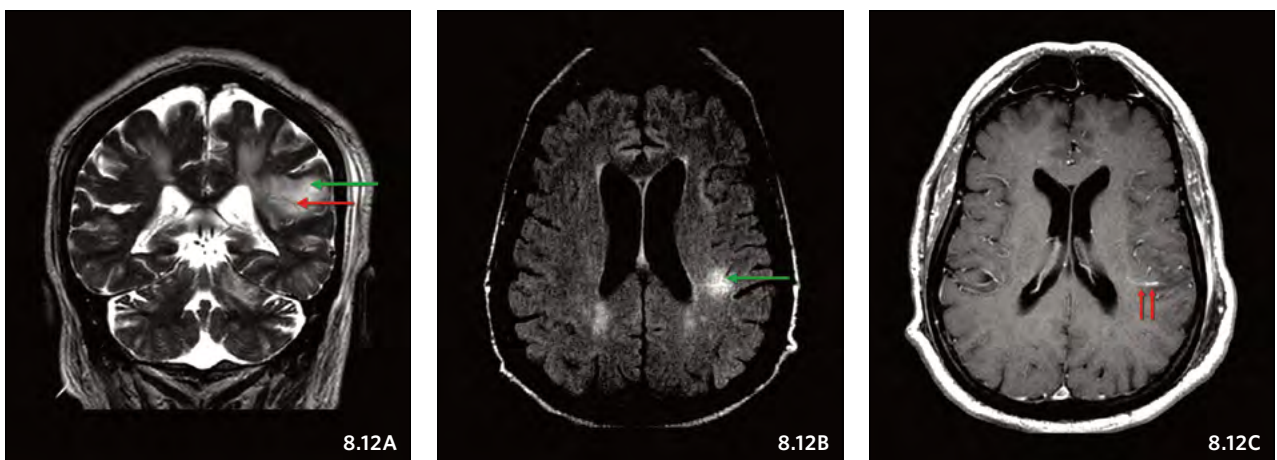
T2-weighted sequences have much longer TR and TE and demonstrate normal cortex to be brighter than the white matter. The T2-weighted images are considered “fluid sensitive”: edema, gliosis, or gliomatosis will appear bright. Blood products may be bright or dark depending on their age, and tumors generally display slightly higher signal than normal white matter but lower signal than the adjacent associated edema.

Fluid-attenuated inversion recovery (FLAIR)-weighted images essentially represent T2-weighted images with suppression of the CSF (FIGURES 8.10A and 8.10B). This leads to increased conspicuity of and sensitivity to parenchymal T2 signal abnormality from almost any cause. Gliosis and both cytotoxic and vasogenic edema are particularly highlighted when the CSF signal is suppressed (FIGURES 8.11A-8.11C and FIGURE 8.12).



**FIGURE 8.11 Cortical dysplasia on MRI**

Focal balloon cell cortical dysplasia demonstrates subtle regional thickening of the cortical gray matter (**red arrows**) with slightly increased T1 signal (**A**) in comparison with normal contralateral cortex (**green arrows**). There is adjacent FLAIR (**B**) and T2 (**C**) signal increase in the underlying subcortical white matter (**blue arrows**).



**FIGURE 8.12 Gliosis**

Gliotic change is the brain's equivalent to scar formation, and can be secondary to almost any remote insult. This demonstrates increased T2 (**A**) and FLAIR (**B**) signal surrounding the site of the insult. In this case, the patient had a developmental venous anomaly (**red arrows**) seen on the postcontrast images (**C**) without associated AVM or aneurysm. Typically, this is an incidental finding, but in this case there was surrounding gliosis (**green arrows**) indicative of scarring, suggesting some degree of parenchymal insult. In addition, no alternative cause for seizure was identified.



## Postcontrast Images

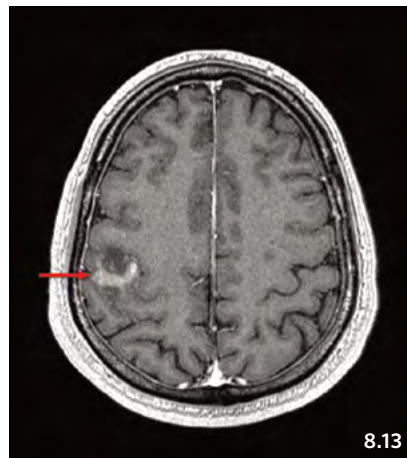
Gadolinium-based contrast agents are administered and remain in the blood pool, so that tissues that receive more blood are seen as enhancing on the postcontrast images. Vascular abnormalities such as aneurysm or arteriovenous malformations are especially bright on T1-weighted images acquired in an earlier (arterial) postcontrast phase, whereas most tumors tend to enhance more in a slightly later phase with similar timing to venous opacification (FIGURE 8.13).

## Diffusion-weighted Imaging (DWI)

DWI makes use of differential diffusion of water molecules when the local magnetic field strength is varied, typically in a gradient field strength of B800 to B1000, with a baseline referred to as B0. In tissues with higher cellularity or increased accumulation of fluid in the intracellular compartment, the free diffusion of water is “restricted” and shows up as bright signal on the high B-value images. The difference between the baseline and the higher field strength is calculated for each voxel as an apparent diffusion coefficient (ADC), and a map of this calculation shows decreased ADC values in areas that have restricted diffusion of water. The classic pathologic cause for “acute water restriction” is cytotoxic edema from ischemic infarct in either the acute or early subacute stages (FIGURES 8.14A and 8.14B).<sup>4</sup>

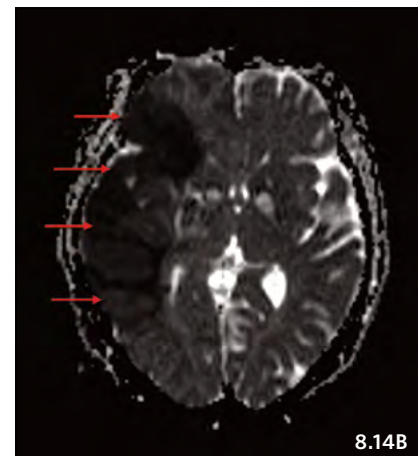
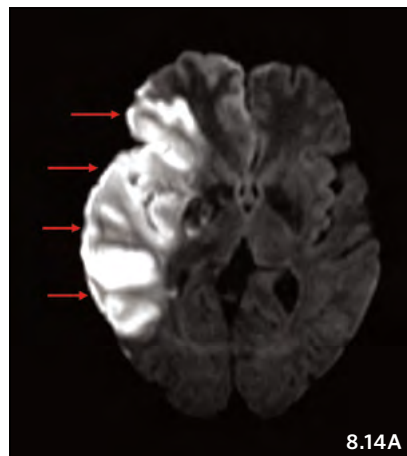
### FIGURE 8.13 Tumor on postcontrast MRI

Gadolinium-based intravenous contrast causes enhancement in areas of breakdown of the blood-brain barrier. In this case, the patient has an enhancing mass in the region of the right motor cortex (*red arrows*).



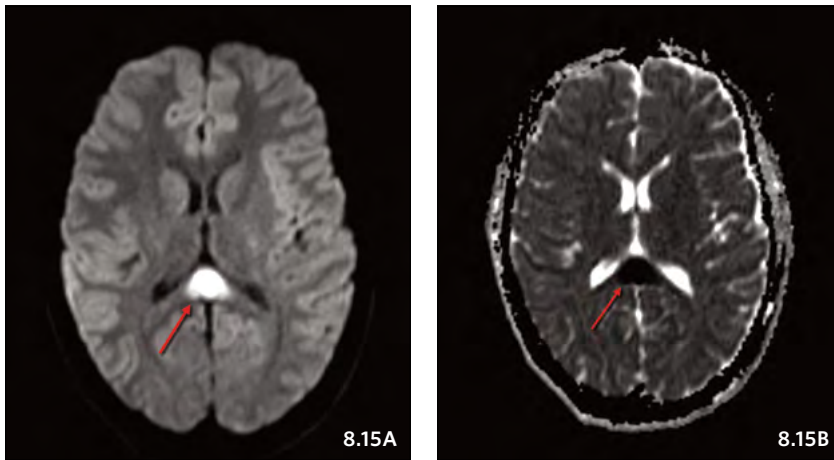
### FIGURE 8.14 Acute stroke on DWI MRI

In the patient with acute right MCA occlusion, diffusion weighted imaging confirmed acute water restriction throughout most of the MCA territory (*red arrows*). This is seen as bright signal on the B1000 images (A) and low signal on the map of ADC values (B).



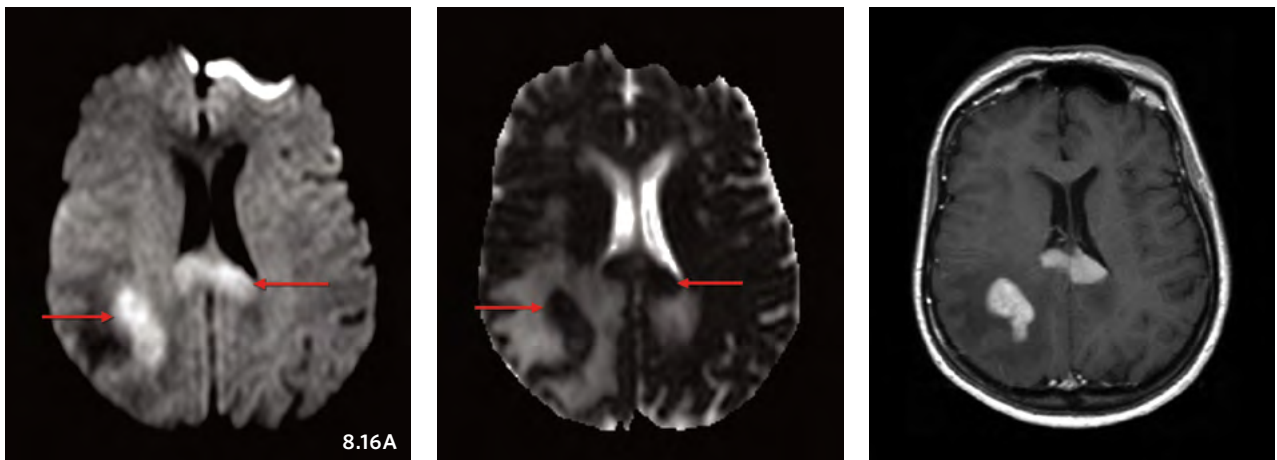
A patient with recent seizure activity may demonstrate subtle water restriction in the hippocampi, with progression to involve the cortex after prolonged seizures. In status epilepticus, there may be edema and DWI signal abnormalities in the splenium of the corpus callosum or the pulvinar of the thalamus (FIGURES 8.15A and 8.15B).

Tumors may also demonstrate restricted diffusion when they are highly cellular, particularly small round blue cell tumors such as primary central nervous system lymphoma or small cell lung cancer (FIGURE 8.16). Water restriction is also seen in abscess cavities. In the case of tumor restriction, the DWI abnormality should correspond to the areas of solid tumor with enhancement, whereas in abscess, the restriction is within the cavity rather than the organized rim (FIGURE 8.17). In severe encephalitis with necrosis and occasionally in posterior reversible encephalopathy syndrome, acute water restriction can also be seen (FIGURE 8.18).



**FIGURE 8.15 Acute water restriction in the splenium of the corpus callosum**

DWI abnormalities in the splenium of the corpus callosum (*red arrows*) may be seen in the setting of recent seizure, as well as the hippocampus or in the cortex.

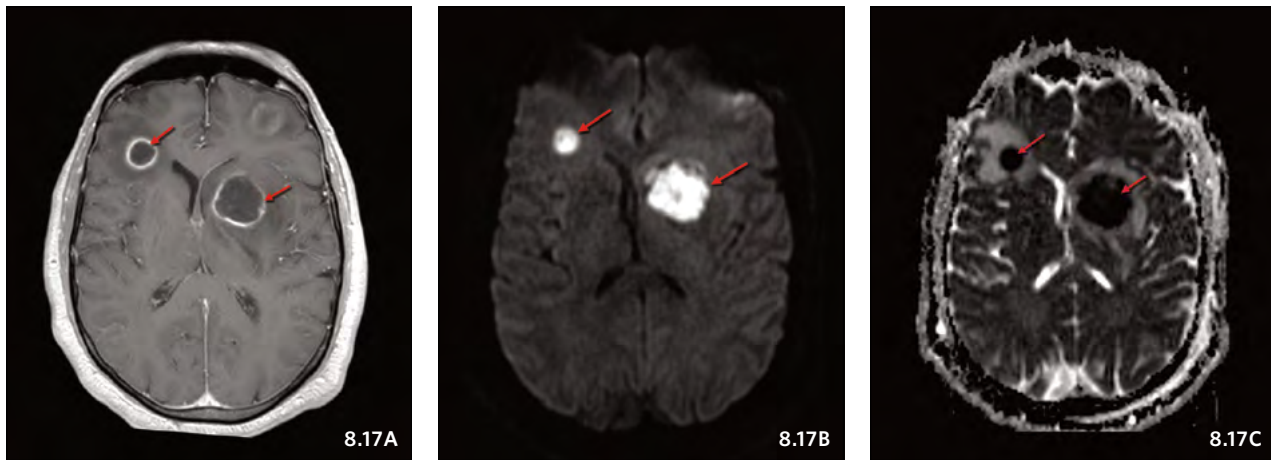


**FIGURE 8.16 Cellular tumor on DWI**

Small round blue cell tumors with relative low volume of intracellular fluid demonstrate restricted diffusion and bright signal on B1000 images (*A*) with low ADC values (*B*) in the solid enhancing components on the corresponding postcontrast images (*C*). These may also be hyperdense to normal brain parenchyma on noncontrast CT due to their dense cellularity. The classic examples of this include lymphoma as in this case, small cell lung cancer in adult patients, medulloblastoma, and neuroblastoma in children.

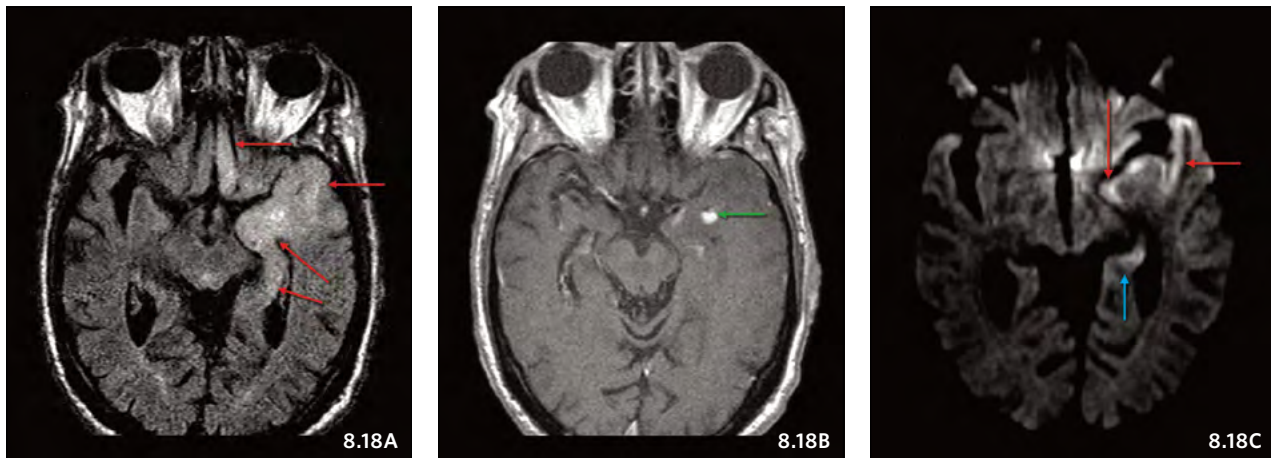
## Blood-sensitive Sequences

Paramagnetic substances have the ability to alter local field strength and cause signal dropout on conventional MR sequences secondary to susceptibility effects. The blood-sensitive sequences make use of this susceptibility effect from deoxyhemoglobin and hemosiderin to cause signal dropout in areas of acute or remote hemorrhage. While a punctate focus of old blood may be difficult to see on conventional images, gradient recalled echo (GRE) sequences are more susceptible to the local paramagnetic effects and show “blooming” of the signal dropout so that tiny foci become much more apparent. Newer scanners and coils allow for more specific susceptibility-weighted imaging (SWI), combining magnitude and phase data with even greater sensitivity for blood products.



**FIGURE 8.17 Restricted diffusion in intracranial abscess**

The patient imaged in FIGURE 8.3 went on to have MRI evaluation. The MRI better delineates the lesions (*red arrows*), which are ring-enhancing on post-contrast images (**A**) and uniformly demonstrate central water restriction on DWI (**B, C**). This pattern of water restriction is most suggestive of abscess. Tumor restriction is typically within the areas of enhancement rather than the central cavity. In a patient with unknown history found to have ring-enhancing lesions in the brain, considerations would include metastatic disease, abscesses, glioblastoma multiforme, late subacute infarct, demyelinating disease, or prior hemorrhage. In the immunocompromised patient, lymphoma and toxoplasmosis are the classic differential concerns.

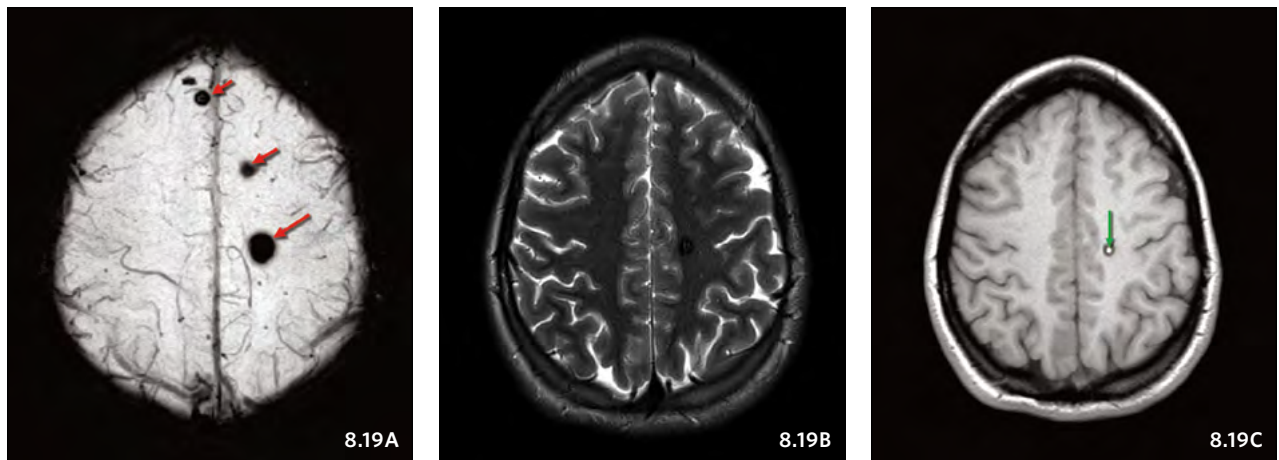


**FIGURE 8.18 Herpes encephalitis**

This patient demonstrated the typical temporal and frontal lobe involvement of herpetic encephalitis (*red arrows*), with edema manifest on the FLAIR images (**A**), patchy areas of enhancement (**B**), and restricted cortical diffusion (**C**). Note the edema and water restriction in the left hippocampus as well (*blue arrows*). This case was slightly atypical in that it was fairly unilateral—herpes, while often asymmetric, more commonly shows bilateral inflammatory change.

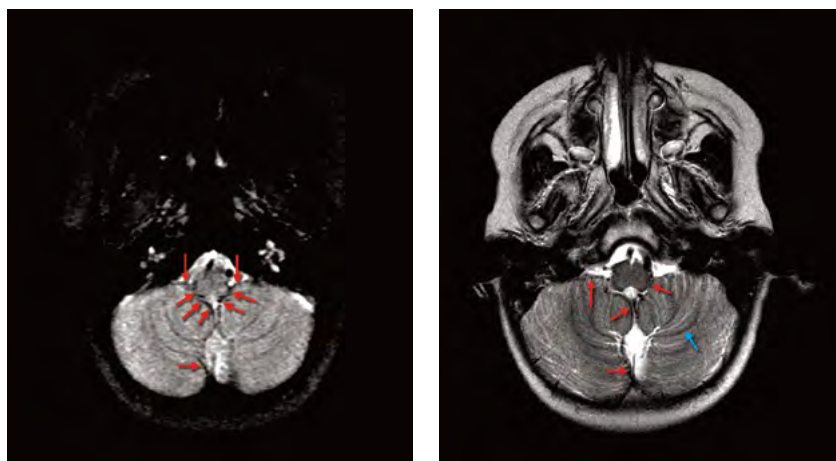
Multiple foci of intraparenchymal blood products showing blooming artifact and multiple “black dots” on SWI sequences raise suspicion for hemorrhagic metastases, multiple cavernomas, prior trauma, or amyloid angiopathy in the elderly population (FIGURE 8.19). Remote subarachnoid hemorrhage can cause diffuse leptomeningeal hemosiderosis reflected as dark outline along the sulci and cisterns, and should prompt workup for aneurysm or hemorrhagic lesions somewhere along the neuroaxis (FIGURE 8.20).

Blood products in the subacute (methemoglobin) stage are bright on conventional T1-weighted images, and also on SWI sequences (TABLE 8.1). One potential false positive that may be confused for hemosiderin with signal dropout on T1 and T2 sequences is the presence of calcification, but this does not induce as much blooming of signal dropout on the SWI images, and should have different phase characteristics.<sup>7,8</sup>



**FIGURE 8.19 Black dots on blood-sensitive sequences**

Multiple foci of hemosiderin are seen as black dots (*red arrows*) from susceptibility effect and blooming artifact on SWI. The tiny foci are much less conspicuous on the T2-weighted images (*B*) and the T1-weighted images (*C*), but the T1-bright methemoglobin (*green arrow*) confirms the presence of mixed blood products in this patient with multiple cavernomas.



**FIGURE 8.20 Hemosiderosis**

Remote subarachnoid hemorrhage results in hemosiderin staining of the leptomeninges, seen on MRI as a dark outline of signal dropout (*red arrows*), in this case seen on SWI (*A*) and T2-weighted (*B*) images around the brainstem and cerebellum. This can also be seen outlining the cerebellar folia (*blue arrow*).

TABLE 8.1 Evolution of Blood Products on Conventional MRI Sequences

APPROXIMATE AGE	STAGE	T1 SIGNAL	T2 SIGNAL
Hyperacute (<2 hours)	Oxyhemoglobin	Isointense	Hyperintense (bright)
Acute (2 hours to 2 days)	Deoxyhemoglobin	Isointense	Hypointense (dark)
Early subacute (2 days to 2 weeks)	Intracellular methemoglobin	Hyperintense (bright)	Hypointense (dark)
Late subacute (2 weeks to 2 months)	Extracellular methemoglobin	Hyperintense (bright)	Hyperintense (bright)
Chronic (> 2 months)	Hemosiderin	Hypointense (dark)	Hypointense (dark)

### Imaging the Hippocampi

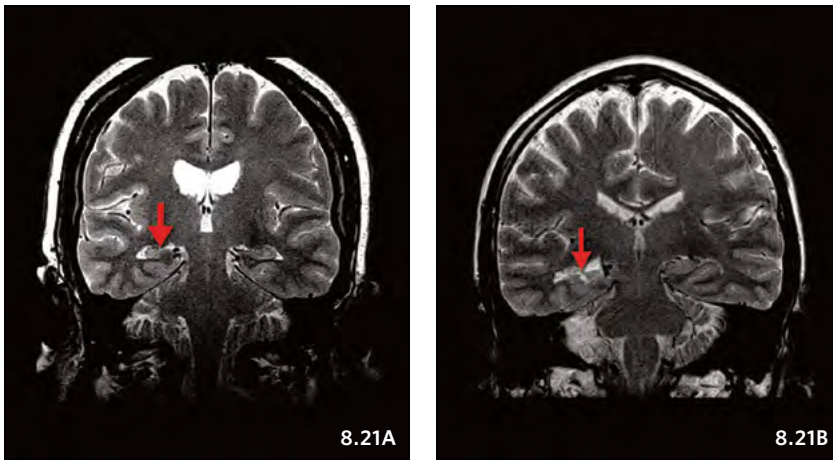
Fluid-sensitive images oriented perpendicular to the hippocampi (oblique coronal) give excellent detail of the hippocampal structures, particularly when acquired on magnets with higher field strength (3 Tesla). Such images through the hippocampi are a crucial part of seizure evaluation.<sup>9</sup> The hippocampal formations are typically the first area to demonstrate edema in the setting of recent seizure, and may also demonstrate acute water restriction. In the chronic setting, mesial temporal sclerosis manifests as abnormality in this area, classically described as a combination of increased T2 signal and decreased volume. The internal hippocampal white matter tracks (perforant pathways and Schaeffer's collaterals) are lost, and there is volume loss of the overlying cortical gray matter (FIGURES 8.2 1A and 8.2 1B).

### SPECT

HMPAO and ECD are used as perfusional agents to the brain that become entrapped within the brain parenchyma and reflect the relative perfusion to different areas. Gray matter has higher volume of flow than white matter, and shows increased accumulation of either radiotracer. These agents have the advantage of localization *at the time of injection* without redistribution, allowing them to be used for both interictal and *intraictal* examinations. Typically, seizure foci are relatively hyperperfused at the time of active seizure activity but are hypoperfused relative to normal brain if the patient is injected in a resting state.

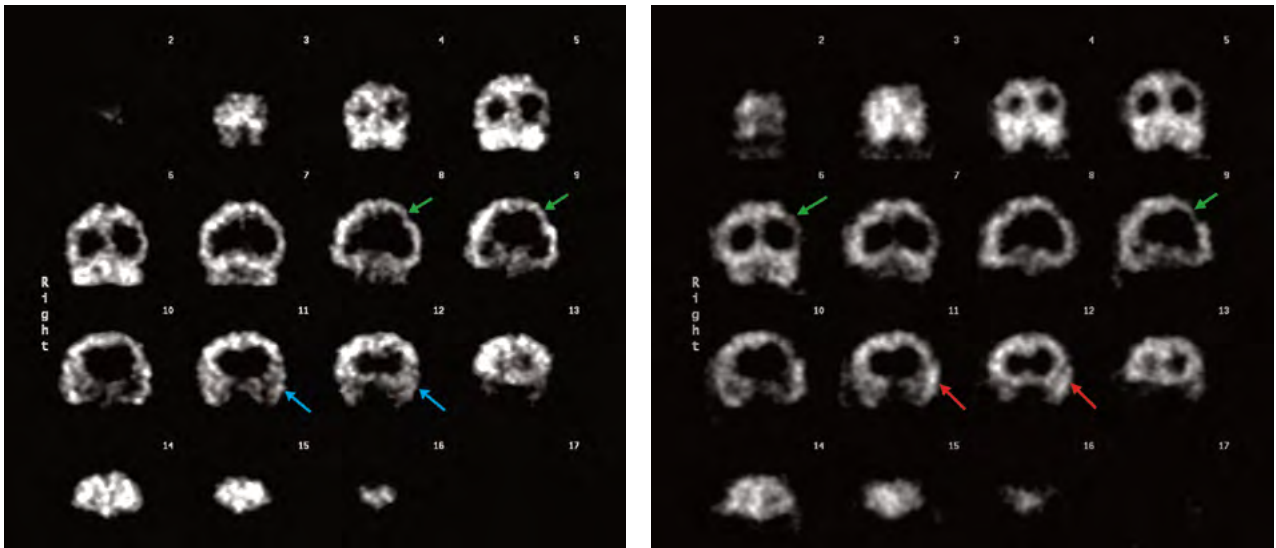
The acquisition of an ictal exam is dependent on rapid injection *during* clinical seizure activity, or within 30 seconds of completion, necessitating a readily available dose of radiotracer and staff to perform the injection.<sup>10</sup> This may also require EEG monitoring for patients with subclinical seizures.

Interictal studies are easier to acquire without specific planning or patient monitoring. However, these have largely been replaced by FDG PET (see next section), which is also obtained in the interictal period.<sup>11</sup> It has been shown that the combination of interictal and ictal examinations has a higher positive predictive value for seizure focus localization than interictal studies alone (FIGURES 8.2 2A and 8.2 2B).<sup>10</sup>



**FIGURE 8.21 MTS on MRI**

MTS is seen on coronal T2-weighted images as decreased volume and increased signal in the hippocampus, with loss of normal white matter lamellations. These two examples show the spectrum of disease from a more mild early stage of right-sided MTS (A) to a later stage (B).



**FIGURE 8.22 Interictal and ictal SPECT imaging**

The interictal ECD study (A) in this patient demonstrated two areas of decreased perfusion at baseline, one in the left frontoparietal region (*green arrow*) and one in the left temporal lobe (*blue arrow*). On ictal images (B), the left temporal region demonstrated relative increase in radiotracer accumulation (*red arrow*) consistent with "activation" of seizure focus.

## PET

FDG PET involves injection of a radioactive glucose, which becomes entrapped in the brain and other bodily tissues, with relatively greater uptake by areas that are more actively metabolizing glucose. This requires a time delay between injection and image acquisition, to allow the tracer to localize to the tissue. When imaging the brain, the study is almost always acquired as an interictal exam unless the patient is in known status epilepticus. In the interictal period, seizure foci tend to show decreased FDG uptake compared with normal metabolic activity in cortical gray matter, similar to a SPECT study.

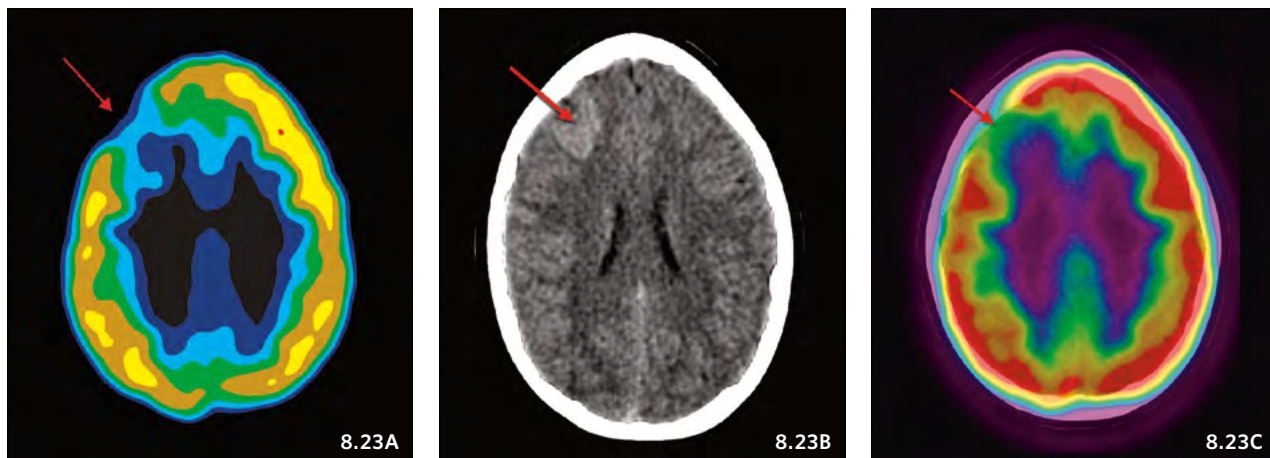
Most imaging centers now make use of combined PET/CT scanners for correction of inhomogeneous radiation attenuation (absorption) by the body. Although attenuation correction is not generally required for the head, the CT portion of the exam can provide some degree of very basic anatomic information, such as the presence of encephalomalacic defects that would be an alternative cause for areas of decreased perfusion (FIGURES 8.23A and 8.23B).

## Other Modalities and Future Directions

Functional MRI can be used for preoperative planning when there is concern for lesion proximity to eloquent areas. Typically, a patient is asked to perform a certain task while images are acquired, with relative oxygen levels within the tissue used as a marker of perfusion differences within the activated part of the brain. There is also some early research into mapping perfusion in the resting state (without assigning a particular task), similar to a SPECT or PET exam, to correlate with increased ictal and decreased interictal blood flow to epileptogenic foci.<sup>12</sup>

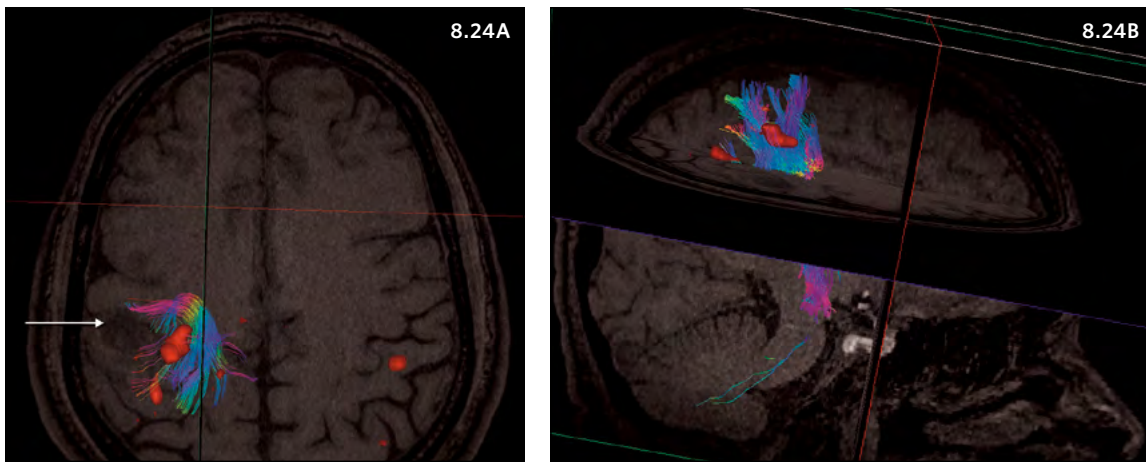
Diffusion tensor imaging (DTI) is also a newer modality that allows mapping of white matter pathways by charting the relative diffusivity of water molecules in multiple directions.<sup>13,14</sup> Conventional diffusion-weighted images are actually an average of data obtained in multiple planes, typically three, which are oriented orthogonal to each other. DTI data, in contrast, is acquired in at least 10 directions, and often up to as many as 64. Rather than averaging the data for one diffusion map, the directionality of diffusion can be determined. In the cerebral white matter, the presence of myelin sheaths causes relatively free diffusion of water along the path of the axon, whereas motion in other planes will be restricted. In addition, the fractional anisotropy (FA) values provide a numerical quantification of the relative degree of restriction, and color maps can be generated that incorporate both the directional information as red/yellow/green/blue as well as the FA values as color intensity. Alternatively, newer software allows the determination of tracks leading to or from a certain area of the brain, and can be helpful for evaluating whether the normal pathways are displaced or disrupted by an adjacent tumor (FIGURES 8.24A and 8.24B).

Other modalities that have been previously evaluated in the setting of seizure but are not in routine clinical practice include MR spectroscopy and MEG. MR spectroscopy evaluates the concentration of particular molecules within a region of interest, and may show abnormalities within seizure foci or the hippocampi.<sup>15</sup> MEG is a potential alternative to EEG for localizing and monitoring seizure.<sup>16</sup>



**FIGURE 8.23 Cortical dysplasia on PET/CT**

The same patient as in FIGURE 8.11 also underwent PET/CT, showing decreased FDG accumulation (A) in the dysplastic focus in relation to the normal surrounding gray matter. The cortical dysplasia is relatively well seen on the corresponding CT obtained for attenuation correction (B)—these are typically more subtle on CT. The fused images (C) confirm that the metabolic defect corresponds to the CT abnormality.



**FIGURE 8.24 fMRI and DTI for preoperative planning**

This patient's tumor (*white arrow*) appeared centered in the region of the motor cortex for the left hand. Prior to undergoing surgical resection, fMRI and DTI were performed for localization of the patient's motor function. The (*red*) activity seen on the functional exam during finger tapping is displaced anteriorly, and there is also displacement of the descending corticospinal track.

## Choosing the Appropriate Exam

With all of the imaging modalities available, it can be difficult to determine which exams are the most beneficial or which combination might be the most cost effective. In light of this, the American College of Radiology assembled expert multidisciplinary panels to address the relative appropriateness of a particular exam for a particular clinical scenario. These "appropriateness criteria" are meant to guide ordering physicians in requesting the most useful exams for their patients. The panel assigns numerical values to the relative appropriateness ranging from 0 to 9. In the setting of epilepsy, the criteria were initially outlined in 2008 and last updated in 2011.<sup>17,18</sup> The breakdown is as follows:

1. A patient with chronic epileptic seizures, refractory to medication, who is a potential surgical candidate. In this category, it is imperative to identify potential structural causes, including MTS, to guide the surgical planning.
2. A patient with new-onset seizures in the setting of alcohol or drug use. In this setting, the likelihood of a structural lesion is relatively lower, and a more generalized screening exam may be more appropriate if imaging is to be done at all.
3. A young adult (18 to 40 years old) with new-onset seizures not related to substance abuse or trauma and without focal neurologic deficit. For younger patients living in dormitory environments, there is a greater risk of contracting meningitis, and for those who are deployed there is a higher risk of exposure to certain infectious encephalopathies. Congenital abnormalities and vascular malformations may also present for the first time in these patients.
4. An adult over the age of 40 with new-onset seizures not related to substance abuse or trauma and without focal neurologic deficit. In this case, tumor and encephalitis are the main concerns that must be ruled out.
5. A patient with new onset-seizures not related to substance abuse or trauma, with a focal neurologic deficit. Such a localizing sign suggests an underlying insult to the brain with subsequent epileptogenic focus. Tumor and infection remain the primary concerns that must be excluded, but vascular malformation remains in the differential.
6. Adult with new-onset acute post-traumatic seizure. CT without contrast is the preferred initial examination for evaluation of hemorrhage and intracranial injury.



- Adult with new onset of seizures and subacute or remote history of trauma. This is a common scenario in the Veteran population, and the concern is for a focus of remote blood products or developing gliosis predisposing to seizures, which may become self-propagating over time. Since tumor and infection remain in the differential, contrasted MRI is the most appropriate.

These criteria and the weighted numerical values (0 to 9) for appropriateness of imaging studies are summarized in table form on the American College of Radiology website, which is also searchable for appropriateness criteria in other scenarios (APPENDIX 8.1).

## Conclusion

This chapter has presented a very basic introduction to brain imaging for the workup and treatment planning for patients with seizures. The most important distinguishing features of the various modalities are the inclusion of both anatomic or structural information as well as functional evaluation of the altered brain physiology in the sites of origin of seizure. ■

### APPENDIX 8.1 ACR Appropriateness Criteria®

VARIANT 1 Medically refractory epilepsy; surgical candidate and/or surgical planning.			
RADIOLOGIC PROCEDURE	RATING	COMMENTS	RRL*
MRI head without contrast	8		0
MRI head without and with contrast	8	See statement regarding contrast in text under "Anticipated Exceptions."	0
FDG-PET/CT head	7	May be helpful in preoperative planning.	☢☢☢☢
CT head with contrast	6		☢☢☢
MRI functional (fMRI) head without contrast	6	May be helpful in preoperative planning.	0
MEG/MSI	6	May identify IOZ in nonlesional patients (normal MRI), can provide confirmatory localization information, may guide placement of iEEG. May substitute for invasive testing, and may be useful when other tests are discordant.	0
Tc-99m HMPAO SPECT head	5	May provide confirmatory localization information.	☢☢☢☢
CT head without contrast	5		☢☢☢
CT head without and with contrast	4		☢☢☢

Rating Scale: 1,2,3 Usually not appropriate; 4,5,6 May be appropriate; 7,8,9 Usually appropriate

(\*) Relative Radiation Level

**APPENDIX 8.1 ACR Appropriateness Criteria® (continued)**

<b>VARIANT 2 New-onset seizure, unrelated to trauma. EtOH, and/or drug related.</b>			
<b>RADIOLOGIC PROCEDURE</b>	<b>RATING</b>	<b>COMMENTS</b>	<b>RRL*</b>
MRI head without and with contrast	8	In the acute or emergency setting, CT may be the imaging study of choice. See statement regarding contrast in text under " <i>Anticipated Exceptions.</i> "	0
MRI head without contrast	7	In the acute or emergency setting, CT may be the imaging study of choice.	0
CT head with contrast	6	In the acute or emergency setting, CT may be the imaging study of choice.	☼☼☼
CT head without contrast	5	In the acute or emergency setting, CT may be the imaging study of choice.	☼☼☼
CT head without and with contrast	3		☼☼☼
MRI functional (fMRI) head without contrast	2		0
Tc-99m HMPAO SPECT head	2		☼☼☼☼
FDG-PET/CT head	2		☼☼☼☼
MEG/MSI	2		0

Rating Scale: 1,2,3 Usually not appropriate; 4,5,6 May be appropriate; 7,8,9 Usually appropriate

(\*) Relative Radiation Level

<b>VARIANT 3 New-onset seizure, unrelated to trauma. Age 18-40.</b>			
<b>RADIOLOGIC PROCEDURE</b>	<b>RATING</b>	<b>COMMENTS</b>	<b>RRL*</b>
MRI head without contrast	8	In the acute or emergency setting, CT may be the imaging study of choice.	0
MRI head without and with contrast	7	In the acute or emergency setting, CT may be the imaging study of choice. See statement regarding contrast in text under " <i>Anticipated Exceptions.</i> "	0
CT head with contrast	6	In the acute or emergency setting, CT may be the imaging study of choice.	☼☼☼
CT head without contrast	5	In the acute or emergency setting, CT may be the imaging study of choice.	☼☼☼
Tc-99m HMPAO SPECT head	4		☼☼☼☼
FDG-PET/CT head	4		☼☼☼☼
CT head without and with contrast	3		☼☼☼
MRI functional (fMRI) head without contrast	2		0
MEG/MSI	2		0

Rating Scale: 1,2,3 Usually not appropriate; 4,5,6 May be appropriate; 7,8,9 Usually appropriate

(\*) Relative Radiation Level

APPENDIX 8.1 **ACR Appropriateness Criteria® (continued)**

**VARIANT 4 New-onset seizure, unrelated to trauma. Older than age 40.**

RADIOLOGIC PROCEDURE	RATING	COMMENTS	RRL*
MRI head without and with contrast	8	In the acute or emergency setting, CT may be the imaging study of choice. See statement regarding contrast in text under " <i>Anticipated Exceptions.</i> "	0
MRI head without contrast	7	In the acute or emergency setting, CT may be the imaging study of choice.	0
CT head with contrast	6	In the acute or emergency setting, CT may be the imaging study of choice.	☼☼☼
CT head without contrast	5	In the acute or emergency setting, CT may be the imaging study of choice.	☼☼☼
CT head without and with contrast	5		☼☼☼
Tc-99m HMPAO SPECT head	4		☼☼☼☼
FDG-PET/CT head	4		☼☼☼☼
MRI functional (fMRI) head without contrast	2		0
MEG/MSI	2		0

Rating Scale: 1,2,3 Usually not appropriate; 4,5,6 May be appropriate; 7,8,9 Usually appropriate

(\*) Relative Radiation Level

**VARIANT 5 New-onset seizure, unrelated to trauma. Focal neurological deficit.**

RADIOLOGIC PROCEDURE	RATING	COMMENTS	RRL*
MRI head without and with contrast	8	In the acute or emergency setting, CT may be the imaging study of choice. See statement regarding contrast in text under " <i>Anticipated Exceptions.</i> "	0
MRI head without contrast	8	If intravenous contrast is contraindicated. In the acute or emergency setting, CT may be the imaging study of choice.	0
CT head with contrast	7	In the acute or emergency setting, CT may be the imaging study of choice.	☼☼☼
CT head without contrast	6	In the acute or emergency setting, CT may be the imaging study of choice.	☼☼☼
CT head without and with contrast	3		☼☼☼
Tc-99m HMPAO SPECT head	3		☼☼☼☼
FDG-PET/CT head	3		☼☼☼☼
MRI functional (fMRI) head without contrast	2		0
MEG/MSI	2		0

Rating Scale: 1,2,3 Usually not appropriate; 4,5,6 May be appropriate; 7,8,9 Usually appropriate

(\*) Relative Radiation Level

**APPENDIX 8.1 ACR Appropriateness Criteria® (continued)**

<b>VARIANT 6 New-onset seizure. Older than age 18. Post-traumatic, acute.</b>			
<b>RADIOLOGIC PROCEDURE</b>	<b>RATING</b>	<b>COMMENTS</b>	<b>RRL*</b>
CT head without contrast	9		☼☼☼
MRI head without and with contrast	8	See statement regarding contrast in text under "Anticipated Exceptions."	0
MRI head without contrast	7	If intravenous contrast is contraindicated.	0
CT head with contrast	5		☼☼☼
CT head without and with contrast	3		☼☼☼
Tc-99m HMPAO SPECT head	2		☼☼☼☼
FDG-PET/CT head	2		☼☼☼☼
MRI functional (fMRI) head without contrast	2		0
MEG/MSI	2		0

Rating Scale: 1,2,3 Usually not appropriate; 4,5,6 May be appropriate; 7,8,9 Usually appropriate

(\*) Relative Radiation Level

<b>VARIANT 7 New-onset seizure. Older than age 18. Post-traumatic, subacute or chronic.</b>			
<b>RADIOLOGIC PROCEDURE</b>	<b>RATING</b>	<b>COMMENTS</b>	<b>RRL*</b>
MRI head without contrast	8	If intravenous contrast is contraindicated.	0
MRI head without and with contrast	8	See statement regarding contrast in text under "Anticipated Exceptions."	0
CT head without contrast	7		☼☼☼
CT head with contrast	6		☼☼☼
FDG-PET/CT head	5		☼☼☼☼
MRI functional (fMRI) head without contrast	4		0
CT head without and with contrast	3		☼☼☼
Tc-99m HMPAO SPECT head	2		☼☼☼☼
MEG/MSI	2		0

Rating Scale: 1,2,3 Usually not appropriate; 4,5,6 May be appropriate; 7,8,9 Usually appropriate

(\*) Relative Radiation Level

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9

# Evaluation for Epilepsy Surgery

**TUNG T. TRAN**



# Introduction

The majority of patients with epilepsy can be well controlled with AEDs. In fact, about half of all patients with epilepsy have successful seizure control with their first appropriately chosen and well-tolerated AED. Another 10% to 15% find success with a second appropriate AED. Unfortunately, after two appropriate AED trials, less than 5% achieve success with the addition of more medications.<sup>1</sup> Patients with epilepsy whose seizures are not well controlled despite multiple trials of AEDs, traditionally referred to as having intractable epilepsy, are currently described as having drug-resistant epilepsy (DRE). The ILAE's definition of DRE is "failure of adequate trials of two tolerated and appropriately chosen and used AED schedules (whether as monotherapies or in combination) to achieve sustained seizure freedom."<sup>2</sup> Risk factors for DRE include poor response to the first AED and signs of higher epilepsy burden, including frequent seizures, a long duration of epilepsy, and a history of status epilepticus.

There are multiple reasons a patient treated with AEDs continue to have seizures. One is DRE. Another is inappropriate or poorly tolerated AED treatment, discussed in another chapter. A third reason is misdiagnosis, discussed elsewhere in this text. In any of these cases, if seizures are not controlled, the patients should be referred to an epilepsy specialist. Diagnostic tests, such as an EMU admission, may have great impact on a patient's quality of life.

Partial seizures are generally more difficult to control with medications when compared to idiopathic generalized epilepsy. Fortunately, partial seizures are sometimes amenable to surgical resections while generalized seizures are not. The majority of this chapter describes the use of surgical resection for partial seizures. However, there are surgical treatment options for generalized seizures, including corpus callosotomies and vagus nerve stimulators, to be discussed in another chapter. Callosotomies, in particular, can be very useful for patients who fall and injure themselves. These patients often require helmets because of the severity of their falls. A callosotomy can reduce falls and injuries, if not necessarily seizures. Therefore, a referral to an epilepsy center should be considered for all patients with any persistent debilitating seizures.

## Referral for Epilepsy Surgery

All patients with debilitating partial seizures and DRE should be referred for epilepsy surgery workup, because DRE implies lifelong impairments. In these patients, epilepsy surgery may offer a possible cure. The goal for any patient with epilepsy is "no seizures, no side effects."

## Benefits

Patients with DRE have a multitude of complications. Persistent seizures mean increased risk of injuries from falls. Quality of life is often affected because driving, employment, social isolation, and stigma may be associated with intractable seizures. The continued use of AEDs may cause cognitive and mood impairments, as well as other long-term side effects associated with chronic medication use, such as impaired bone health. DRE patients are often on multiple medications, which can lead to toxicity effects. Furthermore, persistent seizures are related to increased mortality, whether due to status epilepticus or sudden unexpected death. These topics are discussed in other chapters, but both emphasize the motivation behind controlling seizures. This is especially important because many patients with DRE can potentially be cured: have no seizures and no side effects.

While surgery is often considered by patients and practitioners as a drastic measure, studies show that for select DRE patients the long-term benefits and tolerability of surgery are significantly better than prolonged unsuccessful treatment of DRE with AEDs. About 2 in 3 patients who undergo temporal lobe resections become seizure-free, with an additional percentage having significant improvement in their seizure frequency. Many of these patients, after surgery, can drive, work, and live lives relatively free from the persistent fear that a seizure can occur at any time. Some are weaned off of all seizure medications. These patients avoid the long-term side effects of chronic AED use. Also, from an economic standpoint, the up-front cost of surgery is much less than the cost of years of medications, seizures, emergency room visits, and loss of productive time.

Additional advantages of epilepsy surgery are discussed in a later section on positive outcomes, including persistent improvements in quality of life. The number of patients with drug-resistant temporal lobe epilepsy one needs to treat with epilepsy surgery before demonstrating an advantage over conservative treatment is only 2.<sup>3</sup> This demonstrates the high effectiveness of epilepsy surgery and is the reason it is considered the standard of care for many Veterans with seizures.

## Who Should Be Referred?

The American Academy of Neurology Clinical Practice Guidelines state that any patient with disabling complex partial seizures who has failed appropriate AED treatment should be considered for epilepsy surgery center referral.<sup>4</sup> In fact, anyone who continues to have partial seizures that affect their quality of life, despite their practitioner's best efforts, should be offered an evaluation for possible surgery. This may include patients with only simple partial seizures—frequent auras can sometimes have an impact on a person's life. Similarly, even one major seizure, however rare, can cause significant injury if it occurs at an inopportune time. Thus, there is no minimal criterion for seizure intensity or frequency with regards to epilepsy surgery, as long as epilepsy continues to have a negative impact on a patient's life.

Furthermore, referrals to epilepsy centers are not restricted by seizure type. While epilepsy surgery resection is restricted to patients with partial seizures, other advanced techniques, discussed in another chapter, may be very helpful. Also, sometimes secondarily generalized partial seizures may mimic primary generalized seizures. Prolonged video-EEG monitoring may help differentiate between them. If a practitioner is unable to satisfactorily control seizures, that is enough reason for an epilepsy center referral.

The Canadian Appropriateness Study of Epilepsy Surgery (CASES) group placed online at [www.epilepsy.cases.com](http://www.epilepsy.cases.com) a free, simplified questionnaire to evaluate the appropriateness of an epilepsy surgery referral. It is based on seizure characteristics such as type, severity, frequency, and first onset, along with treatment success, side effects, and prior diagnostic results.

For the purpose of encouraging patients to be seen at an epilepsy center, it may be helpful to know that certain characteristics correlate with patients have better outcomes with surgery. One is the identification of a focal brain lesion. Concordant imaging and EEG suggest a higher chance of seizure freedom after surgery. That said, sometimes lesions are not identified initially. With additional workup, surgery can often be successfully performed when a lesion was not initially seen.<sup>5</sup> Therefore, the absence of a documented focal brain lesion should not prevent one from being referred to an epilepsy center.

Other factors influence success of surgery. Along with imaging abnormalities, EEG abnormalities correlate to more positive outcomes. This suggests that better localization of epileptogenic regions lead to better results. On the other hand, not surprisingly, more severe preoperative seizures seem to relate to worse outcomes. Patients with secondarily generalized seizures have relatively decreased remission rates than those without. Patients with lower intelligence and comorbid psychiatric disease are also thought to have higher seizure recurrence rates after surgery. Another important predictor of surgery success is duration from time of onset. However, none of the above factors alone precludes a patient from getting an epilepsy surgery evaluation.

## When to Refer

If someone with DRE is a good surgical candidate, they should probably be referred for epilepsy surgery as soon as possible. In any case, after two appropriate AED treatment trials, there is little evidence that postponing surgery is helpful. Some patients with DRE may go months without a seizure, but the majority of them are very likely to have another seizure at some point.<sup>6</sup> Each seizure puts the patient at increased risk of brain and possibly bodily injury.

Multiple studies have suggested that the outcome of epilepsy surgery depends on the time from seizure onset; the less time to epilepsy surgery, generally the better the prognosis after surgery. Even for patients with disabling mesial temporal lobe epilepsy for not more than 2 years, a recent study showed that surgical therapy is better than medical therapy in terms of both seizure freedom and quality of life.<sup>7</sup> Based on all this, once a Veteran is thought to have DRE, discussion should be initiated with the patient regarding an epilepsy center referral.



## Obstacles to Referral

Despite a consensus that epilepsy surgery should be considered for patients with drug-resistant partial seizures, a large percentage of eligible patients are not referred to an epilepsy surgery center, and few are referred in a timely manner. Even after the release of clinical guidelines from the American Academy of Neurology in 2003, the average time from seizure onset to surgical evaluation remained about 18 years.<sup>8</sup> The number of epilepsy surgeries have not dramatically increased in the last few years.

Sometimes patients are not referred because they are thought not to be good surgical candidates. However, as discussed in a previous subsection, a wide range of patients with epilepsy might benefit from surgery—not necessarily limited by suspected seizure type, seizure frequency, or seizure characteristics. It is usually between the patient and their referring physician whether they are willing to take the next step. This should occur with the understanding that referral for epilepsy surgery is usually still a long way away from actual surgery, as an extensive workup must occur first.

Epilepsy referrals are particularly difficult in the VHA population. When compared to the private sector, there are fewer epilepsy referrals and a greater delay in EMU monitoring. There is some evidence that epilepsy referrals are less likely in minorities and those without private insurance,<sup>9</sup> but within the VHA system, insurance should not be a factor. Some of the problems with VHA referrals may be related to insufficient Veteran and practitioner education, ingrained attitudes about maintaining the status quo, or the inconvenience of finding and getting to an epilepsy surgery referral center. If the effectiveness and availability of epilepsy surgery is emphasized to more Veterans with drug-resistant partial seizures, more Veterans may agree to pursue this therapy, which can significantly improve their quality of life.

As it remains, epilepsy surgery is underutilized in the general population and particularly among Veterans.

## Where to Refer

The National Association of Epilepsy Centers (NAEC) defines guidelines and standards of care for epilepsy centers. Level 3 epilepsy centers provide basic noninvasive epilepsy care, sufficient for the phase 1 monitoring described in the next section. NAEC level 4 centers offer a more complete range of epilepsy treatment options, including phase 2 monitoring and epilepsy surgery.

Sixteen Epilepsy Centers of Excellence (ECoE) have been established within the VA Health Care system for the purpose of giving all Veterans access to the most advanced epilepsy care. As of 2012, 14 provide noninvasive video-EEG monitoring. Eight of these perform invasive monitoring and epilepsy surgery, the equivalent of a NAEC level 4 epilepsy center. In 2012, about a dozen epilepsy surgeries were performed within the ECoE. Given the number of Veterans with epilepsy, this is a very small number. Many Veterans who are candidates for epilepsy surgery are referred to neighboring academic hospitals—most of the time, the same physicians at these academic hospitals are managing the care of patients within the VHA system. It is the intent of the VHA and ECoE to offer equally outstanding epilepsy surgery care to all Veterans.

## Phase 1 Monitoring

The goal of surgical intervention is to remove all epileptogenic brain tissue, thereby hopefully eliminating all seizures. The purpose of the presurgical workup is to both identify the epileptogenic region and assess the risk of removing it. Identifying the seizure origin involves multiple electrophysiological and neuroimaging methods described below. Assessing the risk of surgical resection involves measuring the function of relevant regions of the brain.

Ideally, the epileptogenic region is a stable, single focus that can be removed without any deficit in the patient's function. A fluctuating lesion, on the other hand, may suggest a more systemic etiology that could recur despite resection. Similarly, multiple sources of seizures, particularly if coming from both hemispheres independently, would also suggest a poor surgical outcome. If a patient does not have a resectable epileptogenic region, other advanced therapies must be considered.

Surgical workup is commonly divided into phases. Phase 1 is noninvasive and involves electrophysiological monitoring, neuroimaging, and functional testing. Sometimes phase 1 testing is conclusive and sufficient, and the patient can proceed directly to surgical resection.

## **Electroencephalography and Neuroimaging**

Epilepsy resection surgery workup includes prolonged inpatient video-EEG monitoring in an EMU. The goal of monitoring is to capture as many seizures as needed in order to localize their site of origin.

Multiple seizures should be recorded, because a patient may have multifocal epilepsy, which is less amenable to surgical resection. Capturing only one or two seizures may miss different seizure foci. Also, seizures that occur close to each other in time may be the result of one persistent seizure event; seizures should be separated by several hours.

Ideally, for confident ictal localization, at least 4 to 5 independent seizures with the same EEG pattern should be recorded. If the EEG pattern is different, then there may be more than one site of seizure onset. Similarly, if the patient describes multiple seizure types, each type should be recorded, with the hope that they all arise from only one epileptogenic region.

Sometimes insufficient ictal recordings are captured. If this is the case, then ancillary data are used. Interictal discharges are often suggestive of an epileptogenic zone. For example, frequent spike-and-slow-wave discharges over right anterior temporal head regions, without discharges anywhere else, are suggestive of right temporal seizures. In addition, the semiology of seizures often reflects its origin, along with neuroimaging results, such as MRI, PET, SPECT, and fMRI. Of particular note, unilateral MTS when identified on MRI is particularly suggestive of a good surgical outcome.

In summary, concordant imaging, semiology, and interictal discharges greatly increase the confidence of seizure localization when combined with ictal EEG. On the other hand, if results are not concordant, then further discussion and possibly additional testing should be done before proceeding to surgery.

## **Neuropsychological Testing**

Neuropsychological testing involves a battery of cognitive tests used to quantify psychological function associated with neuroanatomical structures and pathways. Preoperatively, these provide two benefits with regards to epilepsy surgery evaluation. First, they can demonstrate that a particular brain region is impaired, which may suggest brain abnormality and possible seizure origin, much like imaging studies. Secondly, neuropsychological testing evaluates brain function, and thus it could possibly predict the cognitive deficits that would occur from removal of the examined brain regions. Cognitive skills testing includes memory, language, executive function, and visual-spatial perception. Impaired language skills, for example, might suggest a dominant hemisphere dysfunction. Presurgical testing is important for comparison to post-surgical testing, particularly with regard to measuring outcome. Neuropsychological testing is often an all-day process, as the battery of tests can be time-consuming.

## **Wada Test**

The Wada test involves temporarily impairing one hemisphere of the brain in order to assess language and memory dependency on that side. This is done, typically, by injection of sodium amobarbital by a neuroradiologist into the internal carotid artery via the femoral artery, one side at a time. This essentially puts one half of the brain “to sleep.” Once this happens, the patient is usually paralyzed on the contralateral side, sometimes with a visual field deficit. A series of brief tests are then performed in order to assess how memory and language are affected. The effects of amobarbital usually wear off quickly, so after about 30 minutes, the other side can be tested. EEG is often recorded during the exam, to document effects on brain wave activity. EEG and motor strength are often used to measure effectiveness of cortical anesthesia.

If injection into the left carotid artery greatly disrupts language and memory, but sequential injection into the right produces minimal abnormality, then the patient likely depends on their left hemisphere for language and

memory. They are likely left-hemisphere dominant, and memory is poorly supported by the right hippocampus, but well supported by the left. Resection of the right may not produce any significant cognitive deficit.

The Wada test is generally well tolerated. Complications may arise from application of the medication, but serious adverse effects, such as stroke, bleeding, or infection, are rare, occurring in less than 1% of patients.

## MEG and Other Tests

Unlike EEG, which measures electrical activity on the scalp, MEG measures magnetic fields around the scalp. These magnetic fields are generated by electrical activity in the brain, but are less distorted by structures like the skull and muscles. Therefore, magnetic fields are good at detecting electrophysiological activity deeper the brain such as cortical sulci. MEG electrophysiological detection is often complimentary to EEG detection.

Unfortunately, MEG machines are much more unwieldy and much less available than EEGs. They are large machines in specially isolated rooms. There are VHA hospitals affiliated with academic facilities performing MEG, but MEG is not available within the VHA system. MEG, unlike EEG, MRI, and neuropsychological testing, is not considered standard of care in epilepsy surgery evaluation. However, epilepsy centers may choose to use it if the additional information can affect treatment.

Along with MEG, several new diagnostic techniques are being developed for the evaluation of patients for epilepsy surgery. Some involve improved sensitivities of current tests, such as increased resolution of MRI. Others look at different modalities, such as the connectivity of white-matter tracts. Still other techniques incorporate multiple modalities to improve outcome. Given the changing nature of seizure diagnosis and treatment, a patient thought not to be eligible for surgical treatment might benefit from being reevaluated every few years.

## Phase 2 Monitoring

Sometimes noninvasive monitoring is not conclusive, and the patient may or may not be a good surgical candidate. In these cases, the patient must undergo intracranial monitoring before a resection can be recommended. This phase 2 monitoring involves surgical placement of electrodes directly on brain tissue. This is done after a plan is discussed between the epileptologist and neurosurgeon regarding where electrodes should be placed. Intracranial electrodes can almost never cover the entire brain, so seizures will be detected only where electrodes are placed—seizures cannot be found where no one is looking, resulting in some selection bias. It is the responsibility of the caring team to appropriately narrow the regions of interest. Sometimes this requires multiple stages of intracranial monitoring.

## Intracranial Electrodes

There are two standard intracranial electrode types: surface and depth electrodes. Surface electrodes are thin, flat disks, usually arranged in linear strips or grids, placed on the surface of the brain under the dura. They are usually positioned on the cortex where epileptogenic activity is suspected to occur. The goal is to cover all epileptogenic cortex as well as neighboring eloquent tissue. Ideally, by the end of phase 2 monitoring, the epilepsy team is able draw the boundaries of both tissues types and plan a resection to include all tissue of seizure origin, without removing important brain tissue. Common placements of surface electrodes include the lateral surfaces of the frontal, temporal, and parietal lobes; inferior surface of the temporal lobe; and sometimes the medial interhemispheric surface.

Electrodes may also be embedded in thin flexible wires that pierce the brain. These are referred to as depth electrodes, and they typically are used to measure electrographic activity deep in the brain. A common example is a depth electrode directed towards the hippocampus, a typical source for seizures. Depth electrodes are placed using stereotactic surgery, guided by coordinates determined by MRI and x-ray. They can be inserted through small burr holes, which involves less trauma to the skull and surrounding tissue. Compared to surface electrodes, they are also often better tolerated by the patient, and complications are generally lower. Placement of depth electrodes bilaterally can be used

to lateralize the hemisphere of seizure onset, and to identify deep borders of epileptogenic cortex. However, compared to surface electrodes, they usually cover less cortex, and they involve penetrating the brain. Sometimes a combination of surface and depth electrodes is used.

## **Disadvantages of Intracranial Monitoring**

Regardless of the type of electrodes used, surgical intervention is required to implant the electrodes, thus carrying the associated risks of general anesthesia, bleeding, and infections. The number of electrodes placed within the skull is limited by the volume electrodes occupy and the amount of brain exposure that is required. In general, more electrodes require more exposure and a higher risk of complications.

After electrodes are placed, in the OR, the patient is monitored in an EMU. Special conditions apply to phase 2 monitoring when compared with phase 1. First, special equipment is needed. Second, the monitoring team must manage general postsurgical symptoms, such as pain and nausea. They must monitor for common postsurgical complications, such as infections and atelectasis. Occasionally patients undergoing phase 2 monitoring have postsurgical nausea leading to a lack of oral intake, thus creating a ketosis-like state. This may decrease the chance of having seizures at one of the rare times where the patient is hoping to have seizures.

## **Advantages of Intracranial Monitoring**

The primary advantage of intracranial monitoring is increased proximity to epileptogenic tissue, and thus increased resolution of seizure-origin localization. That resolution depends on placement of the intracranial electrodes. Intracranial monitoring allows this to be customized based on prior results. It is generally limited by anatomical consideration.

Another advantage of having electrodes adjacent to cortex is better detection of high-frequency (>80 Hz) oscillations. There is some evidence that removal of all regions demonstrating these higher frequencies, which may be beyond the usually determined epileptogenic zone, correlates with better surgical outcome. Along with some of the advanced techniques mentioned previously, these new techniques bring hope that epilepsy surgery will continue to improve. However, more work needs to be done to prove a correlation between better technology and better outcome.

At least eight ECoE sites across the nation perform epilepsy surgery. Contacting any ECoE site can lead to contact with an epilepsy referral center. Particularly in the setting of VA networks established through the National VA Epilepsy Consortium and the advent of telemedicine, any Veteran who needs phase 2 intracranial monitoring should be able to get it.

## **Surgical Resection**

Once it is determined that a patient is a good surgical candidate, the treating healthcare team, including epileptologist and neurosurgeon, should discuss the options available to the patient. This includes a review of all prior workup and the implications, resection plan, expected outcomes, and possible complications. The patient should demonstrate understanding of the plan and its possible consequences. If phase 2 monitoring is required, this discussion may take place before intracranial electrodes are removed because often resection occurs in conjunction with removal of electrodes.

Once a plan for surgery is in place and the patient is informed and comfortable with it, surgery should be scheduled as soon as the patient is ready. In some institutions, cortical mapping may occur in the OR with resection, in order to confirm that important eloquent brain tissue is spared. However, if adequate preoperative testing was done, a standard temporal lobe resection is performed without additional mapping.

## **Complications**

Epilepsy surgery puts patients at risk of the typical neurosurgical complications, including stroke, hemorrhage, and infections. However, the most common concerns about removing brain tissue are the associated cognitive deficits.

Obviously, the presurgical evaluations discussed above provide some guidance on potential risks. Even so, despite Wada testing, neuropsychological testing, and language mapping, up to 40% of patients experience some difficulty with verbalization after dominant lobe resections.<sup>10</sup> Thus, dominant anterior temporal resections are usually more conservative, with the posterior margin of resection not being as far back as nondominant anterior temporal lobe resections.

Another functional deficit that may arise from temporal lobe resections is a superior quadrant visual field defect. Although this defect occurs in about half of such cases, the extent of this deficit is variable and often does not affect daily functions. Other less common complications include nerve palsies and hemiparesis. Fatality is extremely rare.

Despite the associated risks of an epilepsy surgery resection, the positive outcomes of surgery generally compensate for its complications, in the form of overall quality-of-life improvements.

## Positive Outcomes

The commonly used Engel Epilepsy Surgery Outcome Scale divides outcomes into four categories. Classes I and II mean seizure-free and rare disabling seizures, respectively. These are the best outcomes. Class III indicates worthwhile improvement, while class IV suggests no worthwhile improvement.

One completed randomized control trial and multiple other studies show that the percentage of patients seizure-free—Engel class I—after temporal lobe surgery is about 2 in 3.<sup>3</sup>

The success of epilepsy surgery often persists long term. About 75% of patients who are seizure-free after 2 years remain seizure-free after 15 years, and this is even more likely if the patient is seizure-free for 5 years.<sup>11</sup> About half of patients who have undergone an anterior temporal lobectomy are seizure free, and an additional 30% achieve intermittent seizure control. Only 20% never achieve any measure of seizure control.

While the majority of epilepsy surgeries are standard temporal lobectomies and most outcome studies are based upon these surgeries, extratemporal epilepsy is often also successfully treated with neocortical resection. While patients undergoing a temporal lobectomy have about a 67% chance of seizure-free outcome, patients undergoing extratemporal surgery enjoy a less than 50% chance of seizure freedom.

As important as seizure control is on a patient's well-being, their quality of life after surgery should also be considered. This is helped by the combination of AED reduction, or even elimination, with reduced seizures and their effects. These effects include improved independence, driving capability, employment opportunity, and overall social and lifestyle options. There is evidence that even mental health status can improve after surgery. Furthermore, the mortality risk after surgery is generally lowered and the vast majority of patients who undergo surgery say that they would repeat the process.<sup>12</sup> Sometimes, the most effective means of convincing a Veteran to undergo surgery is to get them in touch with someone who was in the same position in the past and underwent epilepsy surgery.

## Characteristics of Success and Failure

Success with regards to seizure control depends in part on the location of the epileptogenic zone. Temporal lobe resections are more successful than frontal lobe resections. This partially correlates with the difficulty of completely defining the extent of some epileptogenic zones, as better identification ensures resection of all epileptogenic tissue. Temporal lobe epilepsy surgeries are often successful because the epileptogenic zone is often isolated to medial temporal structures.

In general, a better baseline with regard to both seizure control and cognitive and mental health, along with an identified MRI abnormality, predict better postoperative quality of life.

Postoperative evaluations also may help predict surgery success. Not surprisingly, a lack of deficits and seizures postoperatively predicts better long-term outcome. More specifically, recurrent seizures in the first month to year after surgery predict worse long-term outcome.<sup>11</sup> There is some debate whether postoperative EEGs showing interictal epileptiform discharges also portend a worse result.

# Postsurgical Care

## Withdrawal of AED

Epilepsy surgery is intended improve seizure control. Particularly for the more severe cases, expectations of a cure should be tempered. The hope is to at least reduce seizure burden, and also possibly reduce treatment burden by using less AEDs. If there are no seizures, then there is even the possibility of totally eliminating all anticonvulsive medications.

Immediately after a resection, there is the risk of seizures due to the brain inflammation and trauma associated with surgery. AEDs are usually continued for at least 1 year after surgery. However, if a patient is seizure-free during that period, can they have AEDs decreased and eventually withdrawn for good? Ideally, epilepsy surgery reduces seizure risk enough that AEDs are no longer needed, but that is certainly not always achieved. Do the benefits of AED freedom outweigh the risks of getting another seizure and possibly losing seizure control?

While there is a correlation between how early AEDs are reduced and the likelihood of seizure recurrence, there is no clear evidence that early AED reduction predicts long-term seizure freedom in temporal lobe resections.<sup>13</sup> Reducing AED treatment earlier reveals persistent postoperative epilepsy earlier, but it does not seem to influence long-term prognosis. This is probably particularly true in cases where seizure freedom is more likely, but is less true when the probability of seizure freedom is less. In any case, if medication withdrawal is being considered, there may be evidence that doing this early is not harmful.

## Repeat Surgery

Sometimes surgery fails because a patient's epilepsy is actually not amenable to surgery, despite the presurgical estimation of success. Even so, sometimes the potential benefits and hope of success justify the attempt. This should always be made in conjunction of with the patient's full understanding and agreement.

Occasionally surgery fails because of technical limitations. For example, there may be complications that arise during surgery. The neurosurgeon may determine that a more extensive resection is not worth the risk. Resections may be incomplete because diagnostic testing suggests that a wider margin would cause functional impairments. In these cases, the patient may be a repeat surgery candidate. As medical technology improves, if any patient continues to have seizures, they should continue to follow up or revisit an epilepsy center at least every few years.

## Conclusion

When a patient with partial seizures has tried 2 appropriate and tolerated antiepileptic drugs and still has seizures that interfere with life in any way, they should be referred for consideration of epilepsy surgery. The goal of an epilepsy surgery workup is to identify the single source of all seizures and confirm that its resection would not dramatically affect function. Focal abnormalities on MRI and EEG, along with better baseline seizure control and general health, are positive predictors of epilepsy surgery success. Workup for epilepsy surgery includes phase 1 noninvasive EMU monitoring, MRI, and neuropsychological testing, along with possible PET, SPECT, and Wada testing. In some cases, phase 2 invasive intracranial EEG monitoring is required.

For most surgical-resection candidates, the benefits of surgery greatly outweighs its risks, in terms of both seizure control and quality of life. In general, early surgery is better than postponed surgery. The most common epilepsy surgical resections done are temporal lobe resections. Ideally, AEDs can be decreased and eventually stopped 1 to 2 years postoperatively, although this should not necessarily be expected.

There are 16 Epilepsy Centers of Excellence (ECoE) across the US that serve Veterans and can direct them to advanced epilepsy treatment options, including epilepsy surgery. ■

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# Principles of Treatment

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# Introduction

Epilepsy is relatively common in the VA population (~1%), and the lifetime risk of epilepsy is ~3.5%. The highest incidence of epilepsy is in the first decade of life and after the 7th hence many new cases of epilepsy begin in an elderly population. The most common acquired epilepsy in adulthood (20-60 years of age) is post-traumatic epilepsy, which is a concern in the VA population. Some of the most compelling studies in antiepileptic drug (AED) efficacy were done at the VA through the cooperative study mechanism.<sup>1-3</sup>

## First Seizure and Decision to Treat

In general a seizure is a symptom, and an etiology for a seizure should be investigated. Common causes of a provoked seizure include metabolic abnormalities, drugs, alcohol or drug withdrawal, acute cerebral injury or hemorrhage, infections, and neoplasms. Some of these conditions only produce seizures in an acute setting, e.g., metabolic causes or alcohol withdrawal. Recurrent unprovoked are considered to constitute the diagnosis of epilepsy. Many consider a first-time unprovoked seizure with a definite epileptiform EEG to be sufficient to initiate therapy with an AED. It is important to realize that a first-time seizure may not really be the first seizure, and the patient may have been having other paroxysmal symptoms that were consistent with focal seizures (e.g., déjà vu, fleeting sensory symptoms, or brief episodes of confusion, etc.).

Treatment may not be initiated unless there is reason to believe that the patient will experience recurrent seizures. Epidemiological evidence has demonstrated the risk of recurrent unprovoked seizures is approximately 33% at 5-year follow-up.<sup>4</sup> If there is a remote symptomatic cause, such a prior stroke or significant head trauma, there is a 2.5 increase in having a second seizure in 5 years (>66%), hence AED treatment would be initiated in this setting.

An EEG is a helpful tool to stratify recurrence risk. An epileptiform abnormality increases the risk of recurrence to 30-50% the first year and this may lead to the initiation of therapy. A caveat is that EEGs may be over-interpreted as epileptiform, so a clinical decision needs to be made as to whether treatment should be begun.

## Choosing which AED to Start

If seizures are recurrent and the diagnosis of epilepsy is made, then AED treatment should be initiated. The choice of which drug to start depends on the seizure type and what comorbidities the patient has. Currently available AEDs have similar effectiveness but differ in their side effects profiles. There is a strong correlation between side effects and AED discontinuation. This was demonstrated in the VA cooperative trials.<sup>1-3</sup> The initial VA Cooperative Trials compared first generation AEDs (carbamazepine, phenobarbital, primidone, phenytoin, and valproate). Phenytoin and carbamazepine were found to be superior to phenobarbital and primidone for new onset epilepsy primarily because of fewer side effects. Carbamazepine was found to be superior to valproate for the treatment of focal seizures that did not spread; however, valproate was equivalent to carbamazepine for controlling focal seizures that progressed to generalized seizures.

The most recent VA cooperative trial compared efficacy and side effects in a population of new onset epilepsy in those over 60 years old.<sup>3</sup> Carbamazepine, gabapentin, and lamotrigine were compared. This trial demonstrated that more patients stayed on gabapentin and lamotrigine than carbamazepine because of side effect profile. These three drugs could not be separated statistically in terms of efficacy.

These same associations have been demonstrated in non-VA sponsored trials. Kwan and Brodie evaluated the outcome of treatment success in a cohort of patients with a new diagnosis of epilepsy.<sup>5</sup> Overall the success rate of seizure freedom was 64%. The first drug used resulted in seizure freedom in 47%. The second drug resulted in seizure freedom in another 13%; therefore few patients became seizure free with subsequent medication trials. No drug appeared to increase the likelihood of being seizure-free. A later follow-up of this cohort showed that 68% were seizure-free, 64%

on monotherapy.<sup>6</sup> Of patients who initially did not become seizure-free, 22% later became seizure-free, and 25% never became seizure-free.

From a practical approach, the initial AED choice should be dictated by the seizure type (focal vs generalized) and the patient's comorbidities and concurrent medications (see TABLE 10.1). The enzyme inducers (carbamazepine, phenytoin, primidone, phenobarbital and to a lesser extent oxcarbazepine and topiramate) have drug interactions that may interfere with other medications including with coumadin, estrogen containing oral contraceptives, and statins. For focal seizures, first-line therapies are carbamazepine, gabapentin, lamotrigine, levetiracetam, oxcarbazepine, and zonisamide. For generalized tonic-clonic seizures, first-line therapies include lamotrigine, levetiracetam, valproate, and zonisamide. Not all of these FDA approved as initial therapies but may be considered reasonable firstline choices based on one of the author's experiences, clinical trial evidence and the American Academy of Neurology recommendation.<sup>7</sup> There are now many AEDs available and more study is needed to determine the optimal therapeutic choices for specific patient populations. TABLE 10.2 lists AEDs that have a broad spectrum that may be useful in both generalized and focal epilepsies and those that have a narrower spectrum of being effective in focal epilepsies.

TABLE 10.1 **Selecting an AED**

<p>AEDs are selected primarily based on the type of seizure(s) being treated and can be divided into broad-spectrum drugs (good efficacy in partial and generalized seizures) and narrow-spectrum drugs (typically effective in partial seizures with or without secondary generalization, somewhat effective in primarily generalized tonic-clonic seizures, and ineffective or may even worsen absence or myoclonic seizures).</p> <p>In addition to the AED's efficacy, other variables come into play when selecting the best medicine for a patient, including:</p> <ul style="list-style-type: none"> <li>▪ the type of seizure and how frequently the seizures occur</li> <li>▪ the individual's age, gender and lifestyle</li> <li>▪ the patient's genetic background</li> <li>▪ the patient's comorbidities</li> <li>▪ the likelihood of pregnancy for a woman</li> <li>▪ the comparative cost of the drug</li> <li>▪ the drug's ease of use</li> <li>▪ drug-drug interaction potential, especially in elderly patients</li> <li>▪ the drug's potential toxic reactions and side effects</li> <li>▪ the convenience of dosing</li> </ul>
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TABLE 10.2 **AED Choices**

SEIZURE TYPE	ANTIEPILEPTIC DRUG
<p><b>Broad spectrum</b> All seizure types (generalized from onset and partial onset seizures)</p>	<p>First line: lamotrigine, levetiracetam, valproate, zonisamide Second line: brivaracetam, topiramate, perampanel Third line: clobazam, felbamate, rufinamide</p>
<p><b>Narrow spectrum</b> Simple partial, complex partial, and secondarily generalized seizures</p>	<p>First line: carbamazepine, gabapentin, lacosamide, oxcarbazepine Second line: eslicarbazepine, phenytoin, pregabalin, primidone, phenobarbital Third line: tiagabine, vigabatrin</p>

Note that third line drugs may be effective but have potentially dangerous side effects (felbamate) or have narrow indications (rufinamide for Lennox-Gastaut syndrome).

Another practical approach is to select an AED based on the seizure type as well as comorbidities the patient has (TABLE 10.1). For example, in a patient with epilepsy and migraines, topiramate or valproate may also help prevent migraines. For painful neuropathy, gabapentin may help the neuropathy and control focal seizures. For comorbidity of mania, carbamazepine and valproate may be helpful. There are many ways to tailor AED therapy to individual patients.

Dosing of AEDs depends on pharmacokinetic and pharmacodynamic effects. Drugs should be given at intervals that correspond to their half-life, particularly when a serum concentration has been associated with efficacy. Dosing of lamotrigine will depend on whether the patient is taking an enzyme inducer or inhibitor (valproate) because the half-life is different. With an inducer the half-life is 12 hours so dosing is twice a day, whereas with valproate the half-life is 60 hours so can be once a day dosing. Some AEDs have a pharmacodynamic effect that does not match pharmacokinetics. For example, levetiracetam has a half-life of 6-8 hours, but is usually dosed twice a day because its pharmacodynamic effects are longer than its half-life.

## Side Effects

The VA cooperative studies and additional non-VA trials demonstrate that the most common reason for a drug to fail is side effects. Side effects include idiosyncratic side effects such as rash or hepatitis, or dose-dependent side effects like tremor, ataxia, nystagmus, sedation, or cognitive problems. Idiosyncratic side effects usually require stopping the AED whereas dose-dependent side effects can be remedied by dose reduction or dosing schedule. Slow-release preparations of AEDs often minimize peak-dose side effects. Some medications have more common side effects, for example renal stones are a more specific side effect for topiramate and zonisamide. Lamotrigine can cause rash and Stevens-Johnson syndrome, usually when an initial dose titration is too fast. Levetiracetam can cause irritability in a significant percentage of patients. Topiramate may cause cognitive changes such as difficulty with word finding, particularly at higher doses. Furthermore, concern of suicidal ideation associated with many of the newer AEDs needs to be considered. Side effects should be addressed at every visit for someone on AEDs.

## Therapeutic Monitoring of AEDs

Therapeutic drug monitoring (TDM) of AED medications is an important tool in the pharmacologic therapy of epilepsy (TABLE 10.3).<sup>8,9</sup> The use of TDM may be critical in the optimization of the therapeutic effects of AEDs while minimizing the side effects. It allows the health care provider to optimize the clinical outcome in patients by managing their medication with the assistance of measured drug levels. These measured levels can be used as: (1) a marker of compliance; (2) a tool to identify drug interactions with concurrent therapy; (3) provide a correlation to efficacy and safety in a particular patient; (4) monitor drugs with a narrow therapeutic index; (5) provide correlation to safe/effective levels of drug in cases where issues such as protein binding and hepatic induction/inhibition are important, and finally (6) provide a guide to use in specific seizure types.

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TABLE 10.3 **Therapeutic Drug Monitoring**

- Efficacy and side effects are patient specific and may not always correlate to the quoted laboratory normal range.
- Consider getting a blood level when the patient is well controlled to use as a comparator when breakthrough seizures or side effects occur or addition of medications that could have a drug interaction.
- Be sure to measure blood levels at comparable times in relation to dosing (peak or trough).
- Consider the impact of pregnancy, liver or renal dysfunction, concurrent medications on the blood levels, especially for AED which are highly bound to plasma proteins.

Seizure control can occur before the “minimum” of the published therapeutic range is achieved, and side effects can appear before the “maximum” of the range is achieved. While many practitioners may utilize therapeutic ranges as a hard and fast rule, it is important to note that each patient has their unique therapeutic range. Some patients may need and tolerate concentrations beyond the upper therapeutic range. The therapeutic range for AEDs can be different for different seizure types. Clinicians should define a therapeutic range for an individual patient above which there are side effects and below which the patient experiences seizures. Depending on the AED, serum levels can also be useful in patients with significant renal and/or hepatic disease, patients taking multiple drugs, and women who are pregnant or taking oral contraceptives (OCs) in the case of lamotrigine. Therapeutic concentration ranges have not been clearly defined for some of the second-generation AEDs.

Serum drug concentrations may fluctuate in compliant patients due to laboratory error, change in drug formulation (generic to brand, brand to generic, or generic to generic switch), drug interactions, variable absorption, and variable pill potency (e.g., some pills stored in warm, humid places may have reduced effectiveness). AED levels may change when volume of distribution changes as occurs during pregnancy.<sup>9</sup>

## The Great Debate: Brand versus Generic AEDs

The literature contains many discussions regarding the safety and efficacy of brand-to-generic conversions of AED therapies. It is important to understand the many issues which can play a part in these discussions.<sup>10-13</sup> First, an understanding of the terms and limits used by the FDA in regards to generic medications is important. In order for a generic drug to be given an AB rating by the FDA, several criteria must be met. First, it must contain the same active ingredient as the brand or innovator product. It must be identical in strength and dosage form. It must have adequate labeling, and it must be manufactured in compliance with good manufacturing process (GMP). The fundamental feature and perhaps the most important feature for clinicians is that the generic product be considered bioequivalent to the brand product. The presumption is that a generic product will be essentially pharmacokinetically similar to the branded or innovator product. It will have a similar area under the curve (AUC), which is a measure of systemic exposure of the drug, and it will have a similar maximal peak concentration (C<sub>max</sub>). In an ideal situation, a generic product and a branded product would display superimposable pharmacokinetic profiles. However, there will always be variance between individuals. This raises the question, how similar can a product be for it to be accepted as therapeutically equivalent. Standard testing methodology used in gaining an AB rating includes the following: (1) a group of healthy volunteers, usually between 20 and 30, (2) employing the fasted state, a single dose of the reference drug (branded product)—with subsequent measurement of serial plasma concentrations over time, and (3) these same normal volunteers are then given a single dose of the generic product, and the same measurements are repeated. In this manner, an AUC can be constructed as a measure of systemic exposure, as well as the peak concentration, C<sub>max</sub>. Statistics are used to determine bioequivalence, whether the rate and extent of absorption vary significantly from brand product.

Several years ago, the FDA considered a generic product bioequivalent to the branded product if the AUC and the C<sub>max</sub> differed between the brand and generic by plus or minus 20%. Currently, the criteria now are far more stringent. A ratio of the AUC of the brand product to the generic product and the 90% confidence interval of that ratio must fall between 80% to 125%. This may appear to be a subtle difference, but in reality, current bioequivalence standards criteria are far more rigorous than in previous years. The FDA states that using this approach, “there is no more than a 5% chance that a generic product is not truly equivalent to the reference product.”<sup>14,15</sup>

The FDA’s unequivocal position is that “products evaluated as therapeutically equivalent can be expected, in the judgment of FDA, to have equivalent clinical effect and no difference in their potential for adverse effects.” The FDA reiterated this position in a 1998 letter to health practitioners responding to concerns about the interchangeability of narrow therapeutic index (NTI) drugs.<sup>16</sup> The FDA stated, “there are no documented examples of a generic product manufactured to meet its approved specifications that could not be used interchangeably with the corresponding brand-name drug.” However, available evidence would support an informed provider/patient decision and continued monitoring in some cases. These might include drugs with non-linear pharmacokinetics, those with low solubility, or

complex drug interaction profiles and patients who have a difficulty to manage disease state. The VA is more rigorous than the private sector in ensuring a consistent generic equivalent drug for the duration of the contract with the generic producer, for periods of up to 5 years.

## Nonformulary

Formulary management is an integral part of the VA's comprehensive health care delivery process. The VA National Formulary (VANF) is the only drug formulary authorized for use in the VHA. The use of VISN formularies or local drug formularies at individual medical care facilities is prohibited. The formulary management process must provide pharmaceutical agents of the highest quality and best value, while ensuring the portability and standardization of this benefit to all eligible Veterans.<sup>17</sup> There are different status levels for the currently available AEDs. As part of formulary management, all new molecular entities approved by the FDA are reviewed by the National PBM for VANF inclusion. Until those reviews are complete, the AED would be available via the nonformulary request process. This applies to the following agents: clobazam, pregabalin and vigabatrin. Agents not currently included on the VANF are lacosamide and rufinamide.<sup>18</sup> Periodic reviews of these agents include new clinical trial data, guideline revisions, and usage characteristics. Changes to VANF status are discussed as determined by these reviews. Several of these agents are more suited to use by an epileptologist due to efficacy and safety concerns. Other than eslicarbazine, lacosamide, pregabalin, and zonisamide, these other agents probably should only be prescribed and managed by an epileptologist.

The nonformulary use procedure is the process by which providers request the use of drug or supply products that are not on the VANF. If the nonformulary request is approved, the product will be covered by the VA pharmacy benefits. A nonformulary request process must exist at each VA facility. The process should assure that decisions are evidence-based and timely. Nonformulary products may be approved under the following circumstances: contraindication(s) to the formulary agent(s); adverse reaction to the formulary agent(s); therapeutic failure of formulary alternatives; no formulary alternative exists; the patient has previously responded to a nonformulary agent and risk is associated with a change to a formulary agent (reference: (VHA Handbook 1108.08, paragraph 17.q. Refer to VHA Publications link for the handbook at <http://www1.va.gov/vhapublications/publications.cfm?pub=2>.)

Should a nonformulary request be denied, an appeal process is in place at each facility. Contact your Pharmacy Chief or P&T Chair to access the process for your facility. A new nonformulary request is not required for patients who have had pharmacotherapy initiated on a nonformulary agent at one VA facility, if their care has been transferred to another VA facility, or when care is transferred back to the primary facility. In some instances, patients may present prescriptions from an outside provider to their VA provider. The Dual Care Policy applies to these prescriptions.

## Discontinuing AEDs

Factors favoring successful withdrawal of AEDs include a seizure-free period of 2 to 4 years, complete seizure control within 1 year of onset, an onset of seizures after age 2 but before age 35, and a normal neurologic examination and EEG. Factors associated with a poor prognosis in discontinuing AEDs, despite a seizure-free interval, include a history of a high frequency of seizures, repeated episodes of status epilepticus, a combination of seizure types, and development of

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TABLE 10.4 **AED Withdrawal Summary**

- |  |
|--|
| <ul style="list-style-type: none"><li>▪ Discuss after at least two years of seizure freedom.</li><li>▪ Consider the chances of recurrence of seizures, may wish to obtain an EEG.</li><li>▪ Discuss impact on job, family/social life and driving privileges.</li><li>▪ Withdraw AED slowly.</li></ul> |
|--|

abnormal mental functioning. In children a 2-year seizure-free period is suggested for absence and rolandic epilepsy, whereas a 3-5 year seizure-free period is suggested for other focal seizures, and absence seizures associated with tonic-clonic seizures. AED withdrawal generally is not suggested for patients with juvenile myoclonic epilepsy, absence with clonic-tonic-clonic seizures, or clonic-tonic-clonic seizures. The American Academy of Neurology (AAN) has issued guidelines for discontinuing AEDs in seizure-free patients.<sup>19</sup> After assessing the risks and benefits to both the patient and society, AED withdrawal can be considered in a patient meeting the following profile: seizure-free for 2 to 5 years, a history of a single type of partial seizure or primary GTC seizures, a normal neurologic exam and normal IQ, and an EEG that has normalized with treatment. When these factors are present, the relapse rate is expected to be less than 32% for children and 39% for adults.

AED withdrawal should be done gradually (TABLE 10.4). Some patients will have a recurrence of seizures as the AEDs are withdrawn. Sudden withdrawal is associated with the precipitation of status epilepticus. Withdrawal seizures are of particular concern for agents such as benzodiazepines and barbiturates. Seizure relapse has been reported to be more common if these AEDs are withdrawn over 1-3 months compared to over 6 months.

## Special Cases

### Elderly

Epilepsy has a high incidence in the population over 60 years of age. The VA cooperative study on new-onset epilepsy in the elderly documented the sensitivity of the older population to side effects. The elderly often have side effects at lower concentrations of AEDs, and AEDs that are highly protein bound may have a higher free level in the elderly. Likewise drugs that are renally excreted need to be used at lower doses in patients with renal insufficiency.

### Women

The American Academy of Neurology has issued a number of guidelines regarding AED use in women, especially of childbearing age.<sup>20</sup> All the older AEDs are considered teratogenic, and valproate appears to have a number of detrimental effects on the fetus, particularly when used at higher doses.<sup>21</sup> The enzyme inducers can alter estrogen metabolism and make the lower-estrogen birth control pill ineffective. Also estrogen increases the clearance of lamotrigine, so pregnancy and estrogen oral contraceptives require a higher lamotrigine dose. Women with epilepsy should be on at least 0.4 mg of folate before they become pregnant. Breastfeeding is encouraged.

### Alcoholics

Alcohol withdrawal is a common cause of seizures in patients with and without epilepsy. Furthermore, alcoholics often have traumatic brain injury that can cause epilepsy. Heavy alcohol use is a risk factor for developing epilepsy. Lastly, alcoholics are often noncompliant. That being said, AED therapy should be instituted in alcoholics who have seizures that are not clearly provoked by withdrawal or who have an EEG or imaging study that suggests they have a likelihood of seizures. In general, alcohol enhances the side effects of AEDs and can lead to serious drug interactions with phenobarbital and benzodiazepines. ■

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# Antiepileptic Drugs: First Generation

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# Introduction

Epilepsy afflicts about 1% of the general population. Treatment with AEDs is the mainstay of therapy. Bromide salts were first used to treat seizures in the 19th century and were found to be moderately effective but produced intolerable side effects. In 1912 Alfred Hauptmann serendipitously discovered the anticonvulsant properties of phenobarbital. In 1934 Tracy Putnam set out to discover an AED that was less sedating than phenobarbital, and in 1936 he gave phenytoin to one of his young assistants, Houston Merritt, for clinical evaluation. Phenytoin was launched into the market by Parke, Davis & Co. in 1938. This was followed by introduction of primidone and ethosuximide in 1958. The next major AED to be approved was carbamazepine in 1963 followed by diazepam in 1965, clonazepam in 1975, and finally valproic acid in 1978. All of these AEDs are regarded as first-generation AEDs and will be discussed in this chapter.

## ■ PHENOBARBITAL

### Indication

Phenobarbital is a second-line treatment of partial onset and generalized seizures, in refractory idiopathic generalized epilepsy, and intractable secondarily generalized epilepsy syndromes. It is effective in the treatment of complex partial seizures (eg, psychomotor, temporal lobe), generalized tonic-clonic seizures (grand mal), and mixed seizure patterns that include the above or other partial or generalized seizures. Additionally, the injectable formulation of phenobarbital is considered a third-line drug for status epilepticus, to be used if benzodiazepines and phenytoin fail. Phenobarbital is not effective in treating—and may even worsen—absence, myoclonic, or akinetic seizures, and should be avoided in these patients.<sup>1-4</sup>

### Dosing

#### *Initial Oral Dosing*

The initial starting dose of phenobarbital in adults is 60 mg/day.<sup>1</sup> The dose can be titrated up to a target dose of 100 to 300 mg/day over several weeks. Most patients experience sedative side effects of phenobarbital. Excessive sedation can be minimized by gradually increasing the phenobarbital dose over a period of several weeks when initiating therapy. The typical practice is to begin phenobarbital with about 25% of the final planned daily dose every evening for 5 to 7 days, gradually increasing the dose by 25% increments every 5 to 7 days until the therapeutic goal dose has been achieved. The dose should be adjusted according to the patient's response and serum concentrations.

#### *Intravenous Dosing*

In status epilepticus it is recommended to load phenobarbital at a dose of 10 to 20 mg/kg followed by a maintenance dose of 1 to 3 mg/kg/day. The maximum rate of administration is 60 mg/min in adults. Patients receiving intravenous phenobarbital must have cardiovascular monitoring.<sup>5</sup>

#### *Adjunct Therapy*

If phenobarbital is being added to existing anticonvulsant therapy, it may be initiated at 30 to 60 mg/day and increased gradually by 30 mg every 2 to 4 weeks while the existing anticonvulsant is maintained or gradually decreased. The exceptions are phenytoin and lamotrigine, which may need their dosages adjusted prior to or during phenobarbital initiation due to induction of CYP metabolism and phase II glucuronidation.<sup>6,7</sup>

## **Discontinuation**

Therapy should be withdrawn gradually to minimize the potential of increased seizure frequency unless safety concerns require a more rapid withdrawal. Decreasing the dose every 2 to 4 weeks by 25% of total dose is acceptable for most patients.<sup>7</sup>

## **Pharmacology**

### **Mechanism of Action**

Phenobarbital potentiates the action of  $\gamma$ -aminobutyric acid (GABA) on GABAA receptors by prolonging the opening of the GABA receptor–chloride ionophore complex. It also depresses normal excitatory synaptic transmission by inhibiting glutamate release through an effect on P/Q type high-voltage activated calcium channels and blocking AMPA/kainite receptors.<sup>7,8</sup>

### **Metabolism**

Phenobarbital is hepatically metabolized by CYP2C9 (major), CYP2C19, and CYP2E1 to two inactive metabolites. Phenobarbital is an inducer of many CYP proteins, including CYP1A2, CYP2B6, CYP2A6, CYP2C8, CYP2C9, and CYP3A4, resulting in increased metabolism of any substrate that goes through these pathways. It also induces the metabolism of lamotrigine by inducing UGT1A4 enzyme. Phenobarbital has a long plasma half-life of 70 to 130 hours in adults. Approximately 25% of phenobarbital is cleared via the kidneys.<sup>7-11</sup>

### **Plasma Concentration**

Usual adult therapeutic levels of phenobarbital are between 10 and 40 mcg/mL. Toxic concentrations are most likely to occur at levels greater than 40 mcg/mL. Side effects including sedation occur commonly at higher dosage levels.<sup>9</sup>

## **Preparations Available**

Phenobarbital has been designated a Schedule IV drug. Generic phenobarbital is available at the VA for oral use in tablet and elixir form. It is also available in vials of sterile solution for injectable use. The tablets are available in the following strengths: 16.2 mg, 32.4 mg, 65 mg, 97.2 mg, and 100 mg. The elixir formulation is available as 20 mg/mL, and the injectable vials are available in two strengths: 65 mg/mL and 130 mg/mL. The injectable formulation must be diluted with normal saline for intravenous administration with a maximum concentration of 10 mg/mL.

## **Side Effects and Toxicity**

### **Side Effects**

Common side effects, particularly during the initial phases of therapy, are dizziness, drowsiness, unsteadiness, and sedation. To minimize these side effects, phenobarbital should be initiated at a low dosage.<sup>1,4,6,12</sup>

The most common side effects of phenobarbital are somnolence, dizziness, decreased coordination, impaired cognition, mental confusion, depressed affect, and behavioral problems most commonly seen in children.<sup>6,8</sup> Additionally, connective tissue disorders such as Dupuytren's contracture and frozen shoulder have also been reported.

Side effects associated with long-term phenobarbital therapy include osteomalacia, megaloblastic anemia, and folate deficiency. Serious side effects include hepatotoxicity and serious dermatologic reactions that include Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN). LFTs should be monitored, and phenobarbital should be discontinued at the first sign of rash.<sup>6,7,8,12</sup>

## **Overdose and Toxicity**

Initial toxic symptoms include sedation, dizziness, and impaired cognition. Other signs of toxicity are somnolence, slurred speech, confusion, and ataxia. Severe effects may include coma, hypotension, decreased myocardial contractility, diminished reflexes, hypothermia, and respiratory failure. Death can occur due to respiratory depression and cardiovascular collapse.<sup>6,7</sup>

## **Teratogenicity and Warnings**

Phenobarbital is FDA Pregnancy Category D. It is contraindicated in patients with a history or family history of acute intermittent porphyria, patients with marked liver dysfunction, respiratory disease, a history of sedative or hypnotic addiction, or a history of hypersensitivity to barbiturates.<sup>13,14</sup>

## **Drug Interactions**

### ***Drug Interactions with Other Antiepileptic Drugs***

Phenobarbital may affect the metabolism of other AEDs, including clobazam, midazolam, phenytoin, and lamotrigine. It enhances the metabolism of clobazam, midazolam, and lamotrigine, thereby decreasing their serum levels. The effect of phenobarbital on phenytoin is unpredictable; it may increase or decrease phenytoin serum levels.<sup>14,15</sup>

AEDs may affect the plasma concentration of phenobarbital as well. Felbamate, oxcarbazepine, phenytoin, and valproate may inhibit the metabolism of phenobarbital, thereby increasing its serum levels.<sup>14,15</sup>

### ***Drug Interactions with Common Drugs***

Common drugs that may interact with phenobarbital include amitriptyline, citalopram, cyclosporine, haloperidol, felodipine, nifedipine, propranolol, verapamil, and warfarin.<sup>14,15</sup>

## **Efficacy**

Phenobarbital is effective as monotherapy and as adjunct therapy.<sup>2,3</sup> Its efficacy as monotherapy against other AEDs has been evaluated in a handful of clinical trials. It has been found to be equally efficacious to phenytoin, carbamazepine, and valproate. However, phenobarbital was found to be less tolerable than these AEDs in clinical trials. A trial comparing phenobarbital to phenytoin, carbamazepine, and primidone was conducted in the Veteran population. At the end of 12 months, phenobarbital was effective in 36% of Veterans, carbamazepine in 47% and phenytoin in 38% of Veterans. Phenobarbital was found to be equally efficacious to although less tolerable than phenytoin, and less efficacious and less tolerable than carbamazepine. Several observational studies from developing countries have been conducted with phenobarbital, all demonstrating relatively similar efficacy rates of approximately 50% to 55% seizure control.<sup>2-4</sup>

## **Use in Special Populations**

### ***Renal Failure and Dialysis***

Phenobarbital is safe to use in mild to moderate renal failure. However in patients with severe renal failure (GFR < 10 mL/min) it is recommended that the dose is decreased or dosing interval increased. Dose supplementation is required following peritoneal dialysis and hemodialysis.<sup>9</sup>

### ***Hepatic Impairment***

Phenobarbital is contraindicated in patients with marked liver impairment. In mild liver impairment phenobarbital can be used with caution; the initial dose of phenobarbital must be reduced and patients need to be monitored for side effects and toxicity.<sup>9</sup>

## Geriatric Population

Phenobarbital should be used with caution in elderly patients as they may be more susceptible to the sedative and cognitive side effects of the drug, and dosage reductions may be necessary.

## ■ PHENYTOIN

### Indication

Phenytoin is FDA approved for the treatment of generalized tonic-clonic (grand mal) and complex partial (petit mal) seizures, including psychomotor and temporal lobe seizures. It is also approved for prevention and treatment of seizures occurring during or following neurosurgery (preoperative, perioperative, or postoperative prophylaxis and treatment). Phenytoin may worsen seizures in those with idiopathic or genetic generalized epilepsies such as absence and should be avoided in these patients.<sup>2-4,7</sup>

While not FDA approved for use in status epilepticus, phenytoin is considered one of the first-line drugs after lorazepam and now midazolam for the treatment of status epilepticus. This is in part due to the paucity of randomized controlled trials evaluating treatments for status epilepticus. Phenytoin—along with lorazepam, midazolam, and diazepam—is one of the few antiepileptic agents that have been evaluated in a randomized controlled fashion for the treatment of status epilepticus.<sup>5</sup>

Phenytoin is sometimes used for the treatment of alcohol withdrawal seizures. There is inconclusive evidence to support this use. Phenytoin therapy or other anticonvulsant therapy is not indicated for the treatment of alcohol withdrawal seizures unless the patient has a history of epilepsy or unprovoked seizures.

### Dosing

#### Intravenous Dosing

The recommended IV loading dose for phenytoin is 15 to 20 mg/kg. A common standard IV loading dose of 1,000 mg is often used. However, larger patients may require a larger loading dose. The maximum rate of administration is 50 mg/min in adults. Elderly patients and those with cardiac disease should receive phenytoin more slowly (eg, 20 mg/min). A 1,000-mg dose is usually given over 30 or 60 minutes.<sup>5,6</sup>

#### Oral Dosing

The oral loading dose for phenytoin is 15 to 20 mg/kg. Again a common standard oral loading dose of 1,000 mg is often used, and larger patients may require larger doses. Single oral phenytoin doses greater than 400 mg may not be completely absorbed and may increase risk of gastrointestinal adverse effects, so phenytoin oral loading doses are administered in three divided doses given every 2 to 4 hours. Either phenytoin immediate-release formulations (syrup or chewable tablets) or the more commonly prescribed phenytoin extended-release formulations (capsules, 30 mg and 100 mg) may be used for oral loading.

The usual maintenance dose of phenytoin can range from 200 to 600 mg given once daily as extended-release capsules. However, during the initial few days to 1 week, the phenytoin maintenance dose is often given in three divided doses to ensure adequate levels throughout the day while achieving steady state. After steady state is achieved the patient may then be switched to a once-daily dose usually given at bedtime. Any dose greater than 400 mg/day should be given as divided doses to ensure complete absorption and to reduce GI side effects. Doses greater than 600 mg/day are unusual.<sup>6</sup>

If used as adjunct therapy, phenytoin may be initiated at 100 mg/day and titrated up by 100-mg increments weekly to a maintenance dose of 300 mg/day given once a day with the phenytoin extended-release formulation. At

doses greater than 400 mg, consider dose adjustments in 30-mg increments due to increased risk of toxicity from saturable phenytoin protein binding.

## **Discontinuation**

Anticonvulsants should not be discontinued abruptly because of the possibility of increasing seizure frequency. Therapy should be withdrawn gradually to minimize the potential of increased seizure frequency, unless safety concerns require a more rapid withdrawal. Phenytoin may be decreased by 30 to 100 mg every 1 to 2 weeks.

## **Pharmacology**

### **Mechanism of Action**

Phenytoin is a sodium channel inhibitor. It stabilizes neuronal membranes and decreases seizure activity by increasing efflux or decreasing influx of sodium ions across cell membranes in the motor cortex during generation of nerve impulses.<sup>7,8</sup>

### **Metabolism**

Phenytoin is metabolized hepatically and is excreted as a glucuronidated product. Its clearance is highly variable depending on hepatic function and dose with a half-life ranging from 7 to 42 hours. Phenytoin is an inducer of CYP2C19 and CYP2C9 and a substrate of CYP3A4.<sup>7,10,11</sup>

### **Preparations Available**

Generic phenytoin is available through VA formularies as chewable tablets (50 mg), extended-release capsules (100 mg, 200 mg, and 300 mg), syrup (125 mg/5 mL), and an intravenous formulation. Branded phenytoin is no longer on formulary at the VA but is available commercially as Dilantin® chewable tablets (50 mg), extended-release capsules (30 mg and 100 mg), and syrup (Dilantin-125®, 125mg/5 mL). Phenytek® is available as extended-release capsules (200 mg and 300 mg).

### **Drug Plasma Concentrations**

Usual adult therapeutic trough levels of total phenytoin are between 10 and 20 mcg/mL. Fifty percent of patients show decreased frequency of seizures at concentrations above 10 mcg/mL. Eighty-six percent of patients show decreased frequency of seizures at concentrations above 15 mcg/mL. Levels are considered to be toxic at greater than 30 mcg/mL and lethal at greater than 100 mcg/mL. A therapeutic steady-state level of phenytoin is generally not achieved with phenytoin loading. However, loading the patient will aid in achieving a steady-state level more quickly with subsequent maintenance doses.<sup>6,7,9</sup>

Age, renal function, liver function, and comorbid disease states may affect protein status and alter the percent of total phenytoin that is unbound and therapeutically active. Although equations exist to estimate corrected total phenytoin levels in these disease states, free phenytoin levels may better reflect therapeutic phenytoin concentrations in blood. Usual adult therapeutic trough levels for free phenytoin are between 1 and 2.5 mcg/mL.<sup>9</sup>

## **Efficacy Data**

Phenytoin is effective as monotherapy and as adjunct therapy. Its efficacy against other AEDs as monotherapy has been evaluated in multiple trials. Approximately 80% of patients have been found to be adequately managed on phenytoin monotherapy similar to other AEDs. However, phenytoin may be less tolerable than some other AEDs in specific patients. Carbamazepine specifically may be more tolerable in a Veteran population.<sup>2-4</sup>

## Side Effects and Toxicity

The most common side effects of phenytoin are nystagmus, mental confusion, decreased coordination, dizziness, and sedation, which are dose related and may be transient. Side effects associated with long-term phenytoin therapy include osteomalacia, gingival hyperplasia, coarsening of the features, and a predominantly sensory polyneuropathy.<sup>7,8,12</sup>

Serious side effects include hepatotoxicity and serious dermatologic reactions include SJS and TEN. There may be a genetic susceptibility for serious skin reactions in patients of Asian descent. LFTs should be monitored and phenytoin should be discontinued at the first sign of rash.<sup>7,15</sup>

Initial toxic symptoms include ataxia and dysarthria. Other signs are tremor, hyperreflexia, lethargy, slurred speech, nausea, and vomiting. The patient may become comatose and hypotensive. Death is due to respiratory and circulatory depression.<sup>6,7</sup>

Some side effects are unique to the IV formulation. Serious side effects occur with rapid administration, including purple glove syndrome and cardiovascular events such as hypotension and severe cardiac arrhythmias (eg, heart block, ventricular tachycardia, ventricular fibrillation). Adverse cardiac events have been reported at or below the recommended infusion rate. Cardiac monitoring is necessary during and after administration of intravenous phenytoin. Oral phenytoin should be used whenever possible.<sup>6</sup>

## Drug Interactions

Phenytoin may affect the metabolism of other AEDs, including carbamazepine, phenobarbital, primidone, and valproate. Carbamazepine, ethosuximide, phenobarbital, primidone, and valproate may affect the metabolism of phenytoin. Drugs that may either increase or decrease phenytoin serum levels include phenobarbital, sodium valproate, and valproic acid. Similarly, the effect of phenytoin on phenobarbital, valproic acid, and sodium valproate serum levels is unpredictable. Other common drugs that may interact with phenytoin include warfarin, estrogens, cimetidine, rifampin, and theophylline.<sup>10,11,15</sup>

## Teratogenicity and Warnings

Phenytoin is FDA Pregnancy Category D.<sup>12</sup>

## Use in Special Populations

### **Renal Failure**

Monitoring of free phenytoin is recommended in renal failure. Supplemental dosages are not recommended in hemodialysis.<sup>9</sup>

### **Hepatic Impairment**

Phenytoin is safe in usual doses in patients with mild liver disease. However, phenytoin clearance may be substantially reduced in cirrhosis, and free phenytoin levels should be monitored.<sup>7,9</sup>

### **Asian Ancestry**

Asian patients with the variant HLA-B\*1502 may be at an increased risk of developing SJS or TEN.<sup>16</sup>

### **Tube Feedings**

Tube feedings decrease phenytoin absorption. To avoid decreased serum levels with continuous nasogastric tube feeds, hold feedings for 1 to 2 hours prior to and 1 to 2 hours after phenytoin administration.

## ■ CARBAMAZEPINE

### Indication

Carbamazepine is FDA approved for the treatment of complex partial seizures (eg, psychomotor, temporal lobe), generalized tonic-clonic seizures (grand mal) and mixed seizure patterns, which include the above or other partial or generalized seizures. Carbamazepine is not effective in treating—and may even worsen—absence, myoclonic, or akinetic seizures and should be avoided in these patients.<sup>2-4</sup>

### Dosing

#### Initial Dosing

The initial dose of carbamazepine is 400 mg/day. The dose may be increased by up to 200 mg/day at weekly intervals. It should be adjusted according to the patient's response and serum concentrations. For patients who need to get to therapeutic levels quickly, it is possible to increase the dose by 200 mg every few days. However, faster titrations may increase the risk for rash, including life-threatening rash. These patients should be closely monitored.<sup>6,7</sup>

The dosing schedule is determined by formulation. Immediate-release tablets are the most common formulation of carbamazepine available and used in the VA. Immediate-release tablets should be dosed 2 to 3 times a day. Although steady-state levels of twice daily and thrice daily dosage regimens are comparable, thrice-daily dosage regimens are more often recommended. This is especially true for those patients who have breakthrough seizures, so as to ensure adequate trough levels throughout the day.

Extended-release formulations should be dosed twice a day and give steady-state plasma levels comparable to carbamazepine immediate-release given four times a day. The suspension must be given 3 to 4 times a day. Although not completely bioequivalent, each of the above formulations may be started at the same total daily dose and increased slowly. If transitioning from one formulation from the other, a 1:1 conversion is acceptable.

The usual maintenance dose of carbamazepine is 800 to 1,200 mg. The maximum recommended dose is 1,600 mg. However, there are some patients who require up to 2,400 mg/day.

#### Adjunct Therapy

If carbamazepine is being added to existing anticonvulsant therapy, it may be initiated at 200 to 400 mg/day and increased gradually by 200 mg/day weekly while the existing anticonvulsant is maintained or gradually decreased. The exceptions are phenytoin, phenobarbital, lamotrigine, and valproate, which may need their dosages increased prior to or during carbamazepine initiation due to induction of CYP metabolism. Plasma drug level goal for carbamazepine adjunct therapy is 4 to 8 mcg/mL.<sup>6,7</sup>

#### Discontinuation

Therapy should be withdrawn gradually to minimize the potential of increased seizure frequency unless safety concerns require a more rapid withdrawal. Decreasing the dose 200 to 400 mg/day weekly is acceptable for most patients.

### Pharmacology

#### Mechanism of Action

Carbamazepine is a sodium channel inhibitor and limits influx of sodium ions across the cell membrane. It reduces polysynaptic responses and blocks post-tetanic potentiation. The principal metabolite of carbamazepine, carbamazepine-10,11-epoxide, also has anticonvulsant activity.<sup>6-8</sup>

## Metabolism

Carbamazepine is hepatically metabolized by CYP3A4 to the active epoxide metabolite carbamazepine-10,11-epoxide. Very importantly, carbamazepine is a major inducer of many CYP proteins, including, CYP2C19, CYP2C9, and CYP3A4, resulting in increased metabolism of any substrates that go through these pathways. It also induces P-glycoprotein. Carbamazepine's half-life is variable because of autoinduction, which is usually complete 3 to 5 weeks after initiation of a fixed carbamazepine regimen. Initially the half-life of carbamazepine is 25 to 65 hours. After multiple doses the half-life of carbamazepine is 12 to 17 hours. The half-life of the epoxide metabolite is initially 25 to 43 hours, and 6.1 hours after induction is completed.<sup>6,7,9</sup>

## Preparations Available

Carbamazepine is available at the VA as generic and as branded Tegretol® immediate-release tablets (200 mg), chewable tablets (100 mg), and suspension (100 mg/5 mL). Extended-release carbamazepine is nonformulary but available commercially as branded Carbatrol® capsules (100 mg, 200 mg, and 300 mg) and branded Tegretol-XR® tablets (100 mg, 200 mg, and 400 mg).

## Plasma Drug Levels

Usual adult therapeutic levels of carbamazepine are between 4 and 12 mcg/mL. Toxic concentrations are most likely to occur at levels are greater than 15 mcg/mL. Side effects including CNS effects occur commonly at higher dosage levels. If other anticonvulsants are given the therapeutic range has been recommended to be 4 to 8 mcg/mL.<sup>6,7,9</sup>

## Side Effects

Common side effects, particularly during the initial phases of therapy, are dizziness, drowsiness, unsteadiness, nonserious rash, and gastrointestinal side effects, including nausea and vomiting. To minimize these adverse reactions, carbamazepine should be initiated at low dosages.<sup>6-8</sup>

Carbamazepine causes syndrome of inappropriate antidiuretic hormone (SIADH) by stimulating the release of ADH and potentiates its action in promoting reabsorption of water, resulting in hyponatremia in some patients. The risk of hyponatremia may be increased in the elderly or in patients also taking diuretics, and may be dose dependent. Serum sodium levels should be monitored periodically.<sup>6,7,12</sup>

Serious hematologic adverse effects have been reported with carbamazepine, including agranulocytosis, aplastic anemia, and pancytopenia. The risk of developing these reactions is 5 to 8 times greater than in the general population. However, the overall risk of these reactions in the untreated general population is low. Hepatotoxicity has also occurred. Cell counts and liver function tests should be monitored periodically.<sup>6,7,12</sup>

Serious and sometimes fatal dermatologic reactions, including TEN and SJS, can occur with carbamazepine use at a frequency of about 1 to 6 per 10,000 new users in countries with mainly Caucasian populations. More than 90% of patients who experience TEN or SJS have this reaction within the first few months of treatment.

Those who inherited the variant allele HLA-B\*1502 have a much higher risk of TEN or SJS with carbamazepine therapy than those without. Asian populations have a much higher prevalence of this variant allele. Fifteen percent of the population in Hong Kong, Thailand, Malaysia, parts of the Philippines; 10% of the population in Taiwan; and 4% of the population in North China are positive for this variant. Two to four percent of South Asians are positive for this variant, while less than 1% of Japanese and Koreans are positive. Prior to initiating carbamazepine therapy, testing for HLA-B\*1502 should be performed in patients from populations with a high prevalence of this allele. Those positive for this allele should not be given carbamazepine therapy. The HLA-B\*1502 allele has not been found to be associated with risk for nonserious rash. However, the variant may be a risk factor for the development of TEN or SJS in patients taking other antiepileptic drugs.<sup>6,16,17</sup>



The risk of developing a hypersensitivity reaction may be increased in patients with the variant HLA-A\*3101 allele. This allele may occur more frequently in patients of African-American, Asian, European, Indian, Latin American, and Native American ancestry. Hypersensitivity has also been reported in patients experiencing hypersensitivity reactions to other anticonvulsants. The history of hypersensitivity reactions in the patient and their immediate family members should be reviewed. Approximately 25% to 30% of patients allergic to carbamazepine will also have reactions with oxcarbazepine.<sup>6,15</sup>

## Efficacy Data

### **Monotherapy**

Carbamazepine as monotherapy has been reported to be effective in controlling seizures in over 75% of outpatients, reducing seizure frequency by more than 75%. Patients with complex partial seizures have been reported to show greater improvement with carbamazepine than those with other types of seizures. In patients with secondarily generalized seizures, one study has shown that seizures may be better controlled in patients with a left-sided versus right-sided EEG focus.<sup>2-4,6</sup>

Carbamazepine is generally at least as effective as other AEDs in the treatment of complex partial seizures. Carbamazepine monotherapy has been reported to be as efficacious as monotherapy with clonazepam, gabapentin, lamotrigine, oxcarbazepine, phenobarbital, phenytoin, primidone, topiramate, valproate, or zonisamide. However, in comparison with phenobarbital, phenytoin, and primidone, carbamazepine appears to have the least effect on cognitive function and behavioral disturbances. Gabapentin and lamotrigine may be more tolerable than carbamazepine.<sup>2-4,6</sup>

Carbamazepine monotherapy with therapeutic levels in the range of 6 to 10 mcg/mL has been shown to be equally efficacious to polytherapy after temporal lobectomy in medically intractable temporal lobe epilepsy.

### **Adjunct Therapy**

Carbamazepine is effective as add-on therapy. When added to other AEDs that are susceptible to carbamazepine's inductive effect, it may be necessary to increase the dose of that AED to prevent breakthrough seizures during the carbamazepine titration period. This may be most notable with felbamate, lamotrigine, phenytoin, and phenobarbital. Valproic acid levels may also be decreased, and its dosage should be increased or its levels monitored.<sup>10,11</sup>

If AEDs with inductive or inhibitory effects are added to carbamazepine monotherapy, the carbamazepine dosage should be increased or decreased as appropriate, and/or levels should be monitored to prevent breakthrough seizures.<sup>10,11</sup>

## Teratogenicity and Warnings

Carbamazepine is FDA Pregnancy Category D.<sup>14</sup> It has black box warnings for serious dermatologic reactions with the HLA-B\*1502 allele and the risk of aplastic anemia and agranulocytosis.

## Drug Interactions

### **Drug Interactions with Other Antiepileptic Drugs**

Carbamazepine has inductive effects and may decrease levels of all hepatically metabolized AEDs, in particular felbamate, lamotrigine, phenobarbital, phenytoin (and fosphenytoin), primidone, and valproate. Dosage adjustments may be considered. The major active metabolite of oxcarbazepine and benzodiazepines may also be reduced. While carbamazepine is more likely to cause induction and decrease levels of other AEDs, it may also occasionally increase serum concentrations of AEDs such as phenytoin, possibly by competitive inhibition at sites of metabolism. Monitoring is recommended in these situations.<sup>10,11,15</sup>

Carbamazepine is susceptible to the inductive or inhibitory effects of other AEDs. Its levels may be reduced by inducers such as phenytoin and phenobarbital, or rise to toxic levels by interactions with inhibitors such as valproate.<sup>10,11,15</sup>

## **Drug Interactions with Other Common Drugs**

CYP3A4 inhibitors, including the commonly prescribed drugs cimetidine, macrolide antibiotics (eg, erythromycin and clarithromycin), and antifungals (eg, ketoconazole and fluconazole), inhibit carbamazepine metabolism and can increase plasma carbamazepine levels. CYP3A4 inducers such as rifampin and theophylline can reduce carbamazepine levels.<sup>10,11,15</sup>

Carbamazepine interacts with many HIV medications and may lower their efficacy. It is specifically contraindicated in combination with nefazodone and delavirdine. Carbamazepine is structurally similar to tricyclic antidepressants. Therefore, on theoretical grounds, carbamazepine use with MAO inhibitors is not recommended. MAO inhibitors should be discontinued for a minimum of 14 days prior to carbamazepine initiation. Carbamazepine may decrease plasma concentrations of hormonal contraceptives. Breakthrough bleeding or unintended pregnancy may occur, and alternate or backup methods of contraception should be considered.<sup>10,11,15</sup>

## **Special Populations**

### **Renal Failure and Hepatic Impairment**

Carbamazepine is dialyzable. No dosage changes are recommended by the FDA. However, some clinicians recommend that 75% of the dose be administered after dialysis for those on hemodialysis or peritoneal dialysis. No adjustment is needed for continuous renal replacement therapy. Carbamazepine should be used with caution in patients with hepatic impairment.<sup>6,7</sup>

### **Elderly**

Carbamazepine should be used with caution in elderly patients as they may be more susceptible to SIADH and hyponatremia. Sodium concentrations should be closely monitored with initiation and dosage adjustments in older adults. The elderly may also be at increased risk for carbamazepine activation of latent psychosis, confusion, or agitation.<sup>6,7</sup>

### **Patients of Asian Descent**

Patients of Asian descent should be screened for the variant HLA-B\*1502 allele prior to initiating therapy. This genetic variant has been associated with a significantly increased risk of developing TEN and SJS. Patients with a positive result should not be started on carbamazepine.<sup>16,17</sup>

## **■ ETHOSUXIMIDE**

### **Indication**

Ethosuximide is FDA approved for the treatment of absence seizures. Ethosuximide has little value in the treatment of generalized tonic-clonic seizures, simple partial seizures, and complex partial seizures. When used alone in mixed types of epilepsy, ethosuximide may even increase the frequency of generalized tonic-clonic seizures in some patients.<sup>2-4,6,7</sup>

### **Dosing**

The initial dose of ethosuximide is 500 mg/day. Ethosuximide has a long-half life (50 to 60 hours in adults) and may be administered as a single daily dose. However, it is usually administered in two divided doses to reduce the risk of nausea or drowsiness. The dose may be increased by 250 mg as needed every 4 to 7 days up to 1.5 g/day, although increasing the dose above 1 g/day does not generally add significant benefit. Doses greater than 1,500 mg/day should be used only with caution. Most of the dosing information comes from the pediatric literature. The usual maintenance dose is 20 mg/kg/day for pediatric patients.<sup>2-4,6,7</sup>

## Pharmacology

### Mechanism of Action

Ethosuximide inhibits low-threshold  $\text{Ca}^{2+}$  currents known as T currents in thalamic neurons. The T-current is a pacemaker type current important in the generation of 3-Hz spike-and-wave activity and subsequent rhythmic cortical discharges typical of absence seizures. Ethosuximide increases the seizure threshold and suppresses the above transmission to the motor cortex. Ethosuximide has no effect on the voltage dependence of steady-state inactivation or the time course of recovery from inactivation. It also does not inhibit sustained repetitive firing or enhance GABA response).<sup>7,8</sup>

### Metabolism

Ethosuximide is metabolized hepatically principally by hydroxylation. Eighty percent of the drug is metabolized to three inactive metabolites and 20% remains unchanged. It is excreted in the urine with a small amount excreted in the feces. The half-life in adults is approximately 50 to 60 hours. It is a major substrate of CYP3A4.<sup>6,7</sup>

### Preparations Available

Generic ethosuximide is available at the VA as oral softgel capsules (250 mg) and oral solution (250 mg/5 mL). The branded product, Zarontin<sup>®</sup>, is nonformulary at the VA but is available commercially in the above formulations as well as oral syrup (250 mg/5 mL).

### Plasma Drug Concentrations

The usual therapeutic range for ethosuximide is 40 to 100 mcg/mL. However, a relationship between ethosuximide toxicity and plasma levels has not been established. Levels as high as 160 mcg/mL have been tolerated without excessive side effects. Steady-state plasma drug levels are achieved within 4 to 7 days. Plasma drug levels are proportional to the dose given per unit of weight. Age does not alter this relationship.<sup>6,7,9</sup>

## Efficacy

Ethosuximide is generally considered first-line treatment for absence seizures. It eliminates the generalized 3-Hz spike-and-wave complexes of absence seizures and completely or almost completely controls absence seizures in approximately 50% of patients with absence epilepsy. Ethosuximide reduces the frequency of these seizures in another 40% to 45% of patients. Although valproic acid may be as effective as ethosuximide in treating absence seizures, valproic acid has a greater side-effect profile and is also more likely to interact with other antiepileptic drugs. Ethosuximide has been found to be more effective than clonazepam in the treatment of absence seizures.<sup>2-4,6,7</sup>

## Side Effects

Ethosuximide is generally well tolerated. The most common side effects of ethosuximide are gastrointestinal, including pain, nausea, and vomiting. These side effects can be avoided by starting therapy at low doses with gradual increases. Lethargy and fatigue are other dose-related side effects. Headache, hiccup, and euphoria are less common effects. Those who have a prior psychiatric history may be at increased risk for neuropsychiatric side effects such as sleep disturbance, night terrors, and aggression. Idiosyncratic adverse effects are extremely uncommon but include serious dermatologic reactions such as potentially fatal SJS and blood dyscrasias. Periodic blood counts should be performed to monitor for blood dyscrasias. Abnormal liver and renal function tests have been reported. Periodic renal and liver function tests are recommended.

Acute overdoses may produce nausea, vomiting, and central nervous system depression, including coma with respiratory depression.<sup>6-8,12</sup>

## Teratogenicity and Warnings

Ethosuximide is FDA Pregnancy Category C.<sup>14</sup>

Warnings for ethosuximide include blood dyscrasias, possible effects on liver and kidneys, and case reports of systemic lupus erythematosus.<sup>6,7,12</sup>

## Drug Interactions

### *Drug Interactions with Other Antiepileptic Drugs*

In general, ethosuximide has not been found to significantly interact with other AEDs.

AEDs that may affect ethosuximide include valproic acid, carbamazepine, phenobarbital, and phenytoin. Valproic acid has been found to increase ethosuximide levels, which may possibly increase risk for toxicity. As it is hepatically metabolized, ethosuximide may also be susceptible to the inductive effects of carbamazepine, phenytoin, and phenobarbital, although some studies have reported no effect when administered together.<sup>11,15</sup>

AEDs that ethosuximide may affect include valproic acid, phenytoin, and fosphenytoin. Ethosuximide may reduce valproic acid levels, and has been reported to increase phenytoin or fosphenytoin levels.<sup>11,15</sup>

### *Drug Interactions with Other Common Drugs*

Ethosuximide has few significant drug interactions. It may interact with other drugs that act on CYP3A4.<sup>11,15</sup>

## Use in Special Populations

### *Renal Failure and Hepatic Impairment*

Ethosuximide may be used in patients with renal failure. No dosage adjustment is necessary for patients with renal failure. Although 50% of ethosuximide may be removed during dialysis, no dosage adjustments are recommended. It may be used with caution in patients with hepatic impairment.<sup>6,7</sup>

## ■ VALPROIC ACID

## Indication

Oral valproic acid and divalproex are FDA approved as monotherapy or as adjunct therapy for complex partial seizures that occur in isolation, complex partial seizures that occur in association with other types of seizures, and simple and complex absence seizures, as well as adjunctively in patients with multiple seizure types that include absence seizures. Intravenous valproate sodium is FDA approved as an intravenous alternative in patients for whom oral administration of valproate products is temporarily not feasible. Oral valproic acid and oral divalproex have been found to be useful in almost all epilepsy types and are used off-label in almost all epilepsy types. Intravenous valproate sodium has been found to be useful in the treatment of status epilepticus.<sup>2,4,6,7</sup>

## Dosing

### *Initial Oral Dosing*

Oral valproic acid or divalproex therapy may be initiated at 10 to 15 mg/kg/day or at around 500 to 1,000 mg/day. The dosage should be increased 5 to 10 mg/kg/week or 250 to 500 mg/week to achieve optimal clinical response. Ordinarily, optimal clinical response and therapeutic plasma drug levels in the range of 50 to 100 mcg/mL are achieved with

doses below 60 mg/kg/day. Doses above 60 mg/kg/day have been used, but the safety of this is unknown. For larger patients, it is not uncommon to have doses of 4,000 to 6,000 mg/day.<sup>6,7</sup>

The daily schedule depends on the formulation. Valproic acid (brand name Depakene®) is an immediate-release formulation that should be dosed four times daily. Divalproex is composed of valproate sodium and valproic acid in a 1:1 molar relationship and is formulated as a delayed-release formulation (brand name Depakote DR®) and as an extended-release formulation (brand name Depakote ER®). The delayed-release (DR) formulation (divalproex EC in VA health system formularies), and the extended release (ER) formulation (divalproex SA), should be dosed 2 to 3 times daily and 1 to 2 times daily, respectively. However, many epilepsy specialists recommend the more frequent dosing schedules (three times daily for DR formulations and twice daily for ER formulations) to ensure adequate plasma drug levels throughout the day.

The bioavailability of divalproex is only 85% that of valproic acid. If switching from valproic acid therapy, divalproex sodium may be initiated at the same daily dose, while monitoring for increased breakthrough seizures. If switching from divalproex therapy, valproic acid may be initiated at the same daily dose as well, while monitoring for toxicity.

## **Intravenous Loading**

Valproate sodium may be intravenously loaded at a dose of 15 to 20 mg/kg. The recommended loading dose for status epilepticus is 20 mg/kg with a goal trough level of greater than 100 mcg/mL. Careful monitoring for dose-dependent side effects such as thrombocytopenia is necessary.<sup>6,7</sup>

## **Adjunct Therapy**

Oral valproic acid and oral divalproex may be added to the patient's regimen at a dosage of 10 to 15 mg/kg/day. The dosage may be increased by 5 to 10 mg/kg/week to achieve optimal clinical response. Of note valproate is an inhibitor of multiple CYP proteins. When adding valproate therapy to a regimen of AEDs that are metabolized by CYP proteins (eg, lamotrigine, phenytoin, phenobarbital, carbamazepine, or felbamate), these drugs may increase to toxic levels. Adjustments of carbamazepine and phenytoin dosages are generally not needed. However, plasma drug concentrations of these AEDs should be monitored closely during this period. Reduction of lamotrigine and felbamate dosages may be necessary prior to or during the valproate initiation period. Patients should be monitored closely during this period for signs of toxicity and for increased seizure frequency.<sup>6,10,11,15</sup>

## **Discontinuation**

Therapy should be withdrawn gradually to minimize the potential of increased seizure frequency unless safety concerns require a more rapid withdrawal. AED therapy can ordinarily be reduced by approximately 25% every 1 to 2 weeks. However, the speed and duration of withdrawal can be highly variable and patient dependent. Decreasing the dose 200 to 400 mg/day weekly is acceptable for most patients, while monitoring for increased seizure frequency. If alternate concomitant AED therapy is being initiated, the reduction of valproate may be started at the initiation of new therapy, or delayed by 1 to 2 weeks if there is concern for breakthrough seizure.

## **Pharmacology**

### **Mechanism of Action**

Divalproex is composed of sodium valproate and valproic acid in a 1:1 molar relationship. Divalproex dissociates to the valproate ion in the gastrointestinal tract. The mechanisms by which valproate exerts its therapeutic effects have not been established. It has been thought that its activity in epilepsy is related to increased brain concentrations of GABA. However, its antiepileptic effect may also be related to sodium channel inhibition.<sup>6-8</sup>

## **Metabolism**

Valproate is metabolized almost entirely by the liver. In adult patients on monotherapy, 30% to 50% of an administered dose appears in urine as a glucuronide conjugate. Mitochondrial  $\beta$ -oxidation is the other major metabolic pathway, typically accounting for more than 40% of the dose. The mean half-life for valproate monotherapy ranges from 9 to 16 hours. However, patients taking enzyme-inducing AEDs (carbamazepine, phenytoin, and phenobarbital) clear valproate more rapidly.<sup>6-8</sup>

## **Preparations Available**

Valproic acid is available as generic or branded Depakene® immediate-release tablets (250 mg and 500 mg) and immediate-release suspension (250 mg/5 mL). The divalproex delayed-release (DR) formulation (divalproex EC in VA health system formularies) is available as generic or branded tablets (250 mg and 500 mg). The divalproex extended-release formulation (divalproex SA in VA formularies) is available as generic or branded tablets (250 mg and 500 mg). Valproate sodium is available as branded Depacon® in an intravenous injection formulation.

## **Plasma Drug Concentration**

The therapeutic plasma drug concentration range in epilepsy is 50 to 100 mcg/mL of total valproate, although some patients may be controlled with lower or higher plasma concentrations. The relationship between dose and total valproate concentration is nonlinear. Concentration increases to a lesser extent than dose due to saturable plasma protein binding. Higher than expected free fractions of valproate occur in the elderly, hyperlipidemic patients, and patients with hepatic and renal disease.<sup>7,9</sup>

## **Efficacy**

### **Monotherapy**

Valproate's efficacy has been established as monotherapy for complex partial seizures. Patients who continued to experience 2 or more complex partial seizures per 4 weeks on prior AEDs (phenytoin, carbamazepine, phenobarbital, or primidone) were transitioned over to either low- or high-dose divalproex monotherapy and followed for as long as 22 weeks. Although less than 50% of the patients completed the study, those treated with high-dose divalproex had a significant reduction in seizure frequency at the end of the study compared to baseline. The mean total valproate concentrations were 71 and 123 mcg/mL in the low-dose and high-dose groups, respectively.<sup>2,4,6,7</sup>

### **Adjunct Therapy**

Valproate's efficacy has been established as adjunct therapy for complex partial seizures in a multicenter, randomized placebo-controlled trial. Patients who continued to experience 8 or more complex partial seizures per 8 weeks on prior phenytoin or carbamazepine monotherapy were treated adjunctively with divalproex. Forty-five percent of patients treated with divalproex had a  $\geq 50\%$  reduction in complex partial seizure rate compared with 23% of patients treated with placebo.<sup>4,6,7</sup>

### **Status Epilepticus**

Numerous studies have reported on the efficacy and safety of intravenous valproate in status epilepticus. However, valproate use has not been studied in a randomized placebo-controlled trial. It has been found to be possibly more efficacious than phenytoin as a first- or second-line drug in a small randomized trial with only 68 patients. In general, it is considered a second-line drug in status epilepticus.<sup>18</sup>

## Side Effects

The most common side effects are nausea, vomiting, and gastrointestinal distress, including indigestion and abdominal cramps. These effects are usually transient and are less likely to occur with divalproex DR or ER. Increased appetite and weight gain are common. Somnolence may occur but is more common in patients receiving combination therapy. Tremor and parkinsonism are not uncommon and may be dose related.<sup>6,7,12</sup>

Serious side effects include thrombocytopenia, hepatotoxicity, pancreatitis, and hyperammonemia with encephalopathy. The risk of thrombocytopenia increases significantly at total trough valproate plasma concentrations above 110 mcg/mL in females and 135 mcg/mL in males. Platelets are expected to return to normal in 50% of patient after discontinuation. Minor elevations of transaminases and lactate dehydrogenase are frequent and also may be dose related. However, potentially serious hepatotoxicity resulting in hepatic failure and fatalities may occur, usually in the first 6 months. Acute pancreatitis including hemorrhagic pancreatitis with fatalities has occurred. Asymptomatic elevations of ammonia are more common and, when present, require close monitoring of plasma ammonia levels. Concomitant administration of topiramate and valproic acid has been associated with hyperammonemia. Serious encephalopathy can occur.<sup>6,7,12</sup>

Overdosage with valproate may result in somnolence, heart block, and deep coma. Fatalities have been reported; however patients have recovered from valproate levels as high as 2,120 mcg/mL. In overdose situations, the fraction of drug not bound to protein is high and hemodialysis or tandem hemodialysis plus hemoperfusion may be of benefit.<sup>6,7,12</sup>

## Teratogenicity and Warnings

Divalproex is FDA Pregnancy Category D.<sup>14</sup>

It has black box warnings for hepatotoxicity, use in pregnancy, and pancreatitis. There is also a precaution for patients with HIV and cytomegalovirus; valproate has been found to stimulate replication of these viruses in vitro although the clinical significance of this is unclear.

## Drug Interactions

### *Drug Interactions with Other Antiepileptic Drugs*

Phenytoin, carbamazepine, phenobarbital, and primidone may elevate levels of glucuronosyltransferase and increase clearance of valproate. Felbamate may also increase valproate clearance, although by alternate mechanisms. These combinations should be monitored for decreased drug levels and breakthrough seizures.<sup>10,11,15</sup>

Valproate is an inhibitor of metabolizing enzymes and increases levels of many AEDs, including lamotrigine, phenobarbital, primidone, and ethosuximide. These combinations should be monitored for toxicity. Most significantly, valproate increases the half-life of lamotrigine by almost 165% and increases the risk of TEN and SJS. The dosage of lamotrigine should be decreased prior to valproate initiation.<sup>10,11,15</sup>

Valproate likely inhibits phenytoin and carbamazepine metabolism. However, dosage adjustments may not be required. Valproate may also displace phenytoin from protein-binding sites. Monitoring and adjusting for valproate-phenytoin and valproate-carbamazepine interactions may be necessary. Concomitant topiramate and valproate administration increases risk of hyperammonemia with or without encephalopathy.<sup>6,7,10,11,15</sup>

### *Drug Interactions with Other Common Drugs*

The antibiotics rifampin and carbapenem may increase clearance of valproate and lower valproate levels by a clinically significant degree. Valproate increases the unbound fraction of warfarin, although the clinical significance of this is unknown. Coagulation tests should be monitored. Inhibitors of CYP450 should not have significant effect on valproate clearance.<sup>10,11,15</sup>

**TABLE 11.1 Antiepileptic Drugs: First Generation**

DRUG	INDICATION	STARTING DOSE IN ADULTS	TYPICAL DOSE RANGE	MECHANISM OF ACTION	PREGNANCY CATEGORY
<b>Phenobarbital</b>	Complex partial seizures, generalized tonic-clonic seizures, status epilepticus	60 mg/day	100 to 300 mg/day	Potentiates action of GABA	D
<b>Phenytoin</b>	Generalized tonic-clonic, complex partial seizures including psychomotor and temporal lobe seizures, and seizures occurring during or following neurosurgery	Loading dose of 15 to 20 mg/kg followed by a maintenance dose of 200 to 600 mg per day	200 to 600 mg/day	Sodium channel inhibitor	D
<b>Carbamazepine</b>	Complex partial seizures (eg, psychomotor, temporal lobe), generalized tonic-clonic seizures, and mixed seizure patterns	400 mg/day	800 to 1,600 mg/day	Sodium channel inhibitor	D
<b>Ethosuximide</b>	Absence seizures	500 mg/day	500 to 1,500 mg/day	Inhibits calcium currents in thalamic neurons	C
<b>Valproic acid</b>	Complex partial seizures and absence seizures	10 to 15 mg/kg per day	15 to 60 mg/kg per day	Enhances GABA and sodium channel inhibition	D
<b>Clonazepam</b>	Lennox-Gastaut syndrome (petit mal variant), akinetic, myoclonic and absence seizures, primary generalized epilepsies and simple and partial epilepsies	1.5 mg/day	4 to 6 mg/day	Enhances action of GABA	D



TABLE 11.1 Antiepileptic Drugs: First Generation (cont.)

DRUG	COMMON SIDE EFFECTS	WARNINGS	COMMON DRUG INTERACTIONS
<b>Phenobarbital</b>	Somnolence, dizziness, decreased coordination, impaired cognition, mental confusion, depressed affect, and behavioral problems most commonly seen in children	Contraindicated in acute intermittent porphyria, liver dysfunction, respiratory disease, sedative or hypnotic addiction, and history of hypersensitivity to barbiturates  Monitor liver function; stop therapy in patients who develop a rash	Clobazam, midazolam, phenytoin, lamotrigine, felbamate, oxcarbazepine, valproate, oral contraceptive pills, amitriptyline, citalopram, cyclosporine, haloperidol, felodipine, nifedipine, propranolol, verapamil, and warfarin
<b>Phenytoin</b>	Nystagmus, mental confusion, decreased coordination, dizziness, and sedation  With long term use: osteomalacia, gingival hyperplasia, coarsening of the features, and sensory polyneuropathy  With IV formulation: purple glove syndrome, hypotension, and severe cardiac arrhythmias	Monitoring of free phenytoin recommended in renal failure  Monitor liver function  Monitor for rash. If rash develops discontinue phenytoin. Avoid use in Asians with HLA-B*1502 allele; they may be at an increased risk of developing Stevens-Johnson syndrome or toxic epidermal necrolysis.	Carbamazepine, phenobarbital, valproate, felbamate, lamotrigine, theophylline, warfarin, oral contraceptive pills, cimetidine, and rifampin
<b>Carbamazepine</b>	Dizziness, drowsiness, unsteadiness, nonserious rash, gastrointestinal side effects including nausea and vomiting, and hyponatremia	Monitor WBC; serious hematologic adverse effects including agranulocytosis, aplastic anemia, and pancytopenia have been reported with use of this agent  Monitor for rash; toxic epidermal necrolysis and Stevens-Johnson syndrome can occur, especially in those with the HLA-B*1502 allele  Monitor liver function for hepatotoxicity	Felbamate, lamotrigine, phenobarbital, phenytoin, primidone, valproate, oxcarbazepine, benzodiazepines, cimetidine, macrolide antibiotics, antifungals, rifampin, theophylline, nefazodone, delavirdine, TCAs, MAO inhibitors, and oral contraceptive pills
<b>Ethosuximide</b>	Gastrointestinal side effects, including pain, nausea and vomiting	Avoid in patients with history of psychiatric disease; they may be at increased risk of developing neuropsychiatric side effects such as sleep disturbance, night terrors, and aggression  Idiosyncratic adverse effects are extremely rare but include serious dermatologic reactions such as potentially fatal SJS and blood dyscrasias  Periodic blood counts should be performed to monitor for blood dyscrasias	Valproic acid, carbamazepine, phenobarbital, and phenytoin
<b>Valproic acid</b>	Nausea, vomiting, gastrointestinal distress, weight gain, hair loss, and tremor	Thrombocytopenia, hepatotoxicity, fatal hemorrhagic pancreatitis, and hyperammonemia with encephalopathy	Phenytoin, carbamazepine, phenobarbital, primidone, felbamate, lamotrigine, topiramate, aspirin, rifampin, carbapenem, antibiotics, and warfarin
<b>Clonazepam</b>	Sedation, incoordination, ataxia, memory impairment, and hyperactivity in children	Dependence, withdrawal symptoms, respiratory depression, and CNS depression  Clonazepam should not be abruptly discontinued	Phenobarbital, phenytoin, primidone, carbamazepine, amiodarone, and theophylline

## Special Populations

### Renal Failure

No dosage adjustments are required in renal disease. Hemodialysis typically reduces valproate concentrations by about 20%, but protein binding in these patients is also substantially reduced and total concentrations may be misleading.<sup>6,7,9</sup>

### Hepatic Impairment

The clearance of free valproate may be decreased by up to 50% in patients with cirrhosis and to a lesser extent in those with acute hepatitis. Additionally, protein binding is reduced due to decreased albumin concentrations. Valproate should be avoided in those with advanced liver disease, and must be used cautiously in patients with mild disease.<sup>6,7,9</sup>

### Elderly

A significantly higher proportion of elderly patients experience somnolence with valproate. Reduced nutritional intake and weight loss instead of weight gain is also more likely to occur in the elderly. Protein binding of valproate is also reduced in the elderly.<sup>6,7,9</sup>

## ■ CLONAZEPAM

### Indication

Clonazepam is FDA approved for the treatment of seizure disorders. It is approved as monotherapy or as adjunct treatment for the treatment of Lennox-Gastaut syndrome (petit mal variant), akinetic, myoclonic, and absence seizures.<sup>2,4,6,7</sup>

Clonazepam has also been found to be effective in other epilepsy types, including primary generalized epilepsies and simple and complex partial epilepsies. It can also help cluster seizures and nocturnal epilepsies, and has also been used in photic-stimulation-induced seizures.<sup>2,4,6,7</sup>

### Dosing

#### Initial Dosing

FDA labeling recommends that the initial clonazepam dose not exceed 1.5 mg/day divided into three doses, increased by 0.5 to 1 mg every 3 days until seizures are controlled, up to a maximum of 20 mg/day. Early studies report the optimal anticonvulsant dosing of clonazepam to be 0.1 to 0.2 mg/kg. However, current practice is to initiate clonazepam at much lower doses (eg, 0.5 mg/day). Furthermore, in recent surveys of epilepsy specialists, most recommended maintenance doses of no more than 4 to 6 mg/day and usually prescribed no more than 2 mg/day. Due to clonazepam's long half-life (20 to 40 hours), it can be given in one or two daily doses instead of three to aid in compliance, although most specialists prefer twice-daily dosing to ensure adequate levels throughout the day.<sup>6,7</sup>

Tolerance develops with clonazepam. Early studies suggested that up to 30% of patients showed a loss of anticonvulsant activity, often within 3 months of administration. In some cases increases in doses were required to re-establish efficacy.

#### Discontinuation

As with all anticonvulsants, withdrawal of clonazepam must be done with extreme caution. Clonazepam, like other benzodiazepines, may cause psychological and physiological dependence within 2 to 4 weeks. Withdrawal symptoms may occur if a dose is missed or reduced and may last for 8 to 10 days. Very gradual reduction of the benzodiazepine (often over many weeks or months) is recommended.

# Pharmacology

## Mechanism of Action

Although the exact mechanism of action is unknown, clonazepam is a benzodiazepine derivative. Like other benzodiazepines, it is believed to enhance the actions of GABA.<sup>6-8</sup>

## Metabolism

Clonazepam is metabolized in the liver by the cytochrome P450 system, and the metabolites are excreted by the kidneys. Clonazepam is approximately 85% protein bound. The half-life of clonazepam in multiple-dose studies is approximately 30 to 40 hours. The effects of age, gender, hepatic dysfunction, and renal dysfunction on the pharmacokinetics of clonazepam have not been well studied.<sup>6-8</sup>

## Preparations Available

Clonazepam is available as generic and branded Klonopin® immediate-release tablets (0.5 mg, 1 mg, and 2 mg). Clonazepam wafers, or orally disintegrating tablets, are available only as branded Klonopin® (0.125 mg, 0.25 mg, 0.5 mg, 1 mg, and 2 mg).

## Plasma Drug Concentrations

Plasma drug concentrations are not commonly monitored. However, the therapeutic concentration is believed to be in the range of 25 to 30 ng/mL. Lower plasma levels (20 ng/mL or less) have been shown to control myoclonic and self-induced photogenic epilepsy. The relationship between plasma levels and the dose is linear.<sup>6,7</sup>

## Side Effects

The most common side effects of clonazepam are sedation and incoordination, with up to 50% of patients reporting sedation and 30% reporting incoordination. Ataxia and memory impairment are also common. Hyperactivity commonly occurs in children (approximately 25%). These side effects are dose related and may lessen over time. They can be mitigated by reducing or splitting the total daily dose into more frequent doses, or shifting more of the total daily dose to bedtime, especially for those patients with nocturnal or early-morning seizures.<sup>6-8,12</sup>

Serious adverse effects include respiratory depression. Tolerance develops with clonazepam. Dosage increases may be necessary to a certain extent. However, adverse effects such as impaired memory may be greater than seizure control. Clonazepam, like other benzodiazepines, may cause psychological and physiological dependence within 2 to 4 weeks. Withdrawal symptoms may occur if a dose is missed or reduced, and may last for 8 to 10 days.<sup>6,7</sup>

## Efficacy

Clonazepam is an effective medication, but problems with tolerance and dependence keep it from being more widely used. It is usually used as an add-on medication for patients whose seizures are refractory. There have been few large, well-controlled studies of clonazepam's effectiveness. It is generally used to treat absence seizures, often in combination with valproate, and myoclonic seizures in patients with JME and progressive myoclonic epilepsy, also typically in combination with valproate. Children with Lennox-Gastaut syndrome may benefit from its use, though not all studies have found it helpful for long-term treatment. Clonazepam has also been effective in controlling sensory-precipitated epilepsy such as photomyoclonic or "reading" epilepsy. Partial complex seizures and focal seizures do not respond as well to clonazepam as to other drugs. It has not been found to be effective in postanoxic myoclonus.<sup>2,4,6,7</sup>

## Teratogenicity and Warnings

Clonazepam is FDA Pregnancy Category D.<sup>14</sup>

It has warnings for CNS and respiratory depression and should not be discontinued abruptly.

## Drug Interactions

### **Drug Interactions with Other Antiepileptic Drugs**

Clonazepam has relatively few drug interactions. The most significant interaction is additive respiratory depression with concomitant phenobarbital, primidone, or other benzodiazepine or barbiturate administration. Clonazepam metabolism may also be affected by inducers of CYP metabolism such as phenytoin, carbamazepine, and phenobarbital.<sup>10,11,15</sup>

### **Drug Interactions with Other Common Drugs**

Amiodarone may increase clonazepam levels and cause toxicity, with symptoms such as confusion, slurred speech, and enuresis. Theophylline may decrease benzodiazepine effectiveness.<sup>10,11,15</sup>

## Special Populations

Clonazepam dose adjustments are not necessary in renal failure or hemodialysis. However, dosage or dosing interval may need to be altered to compensate for impaired hepatic function. Lorazepam may be an alternative as it undergoes glucuronidation, and its half-life is only slightly altered in hepatic dysfunction. CNS side effect of benzodiazepines such as gait disturbances, incoordination, ataxia, and behavior changes may be exaggerated in elderly patients.<sup>6,7,10,11,1</sup> ■

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# Antiepileptic Drugs: Second Generation

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# Introduction

The goal of treatment with AEDs is seizure freedom. Toward this end, a primary factor in selecting an antiepileptic drug is its efficacy and spectrum of action—the type of seizures or epilepsy being treated. It is also important to consider the interactions with other medications, including other AEDs, tolerability, and comorbidities. Prior to the late 1990s, physicians had a limited armamentarium of AEDs, all of which were associated with significant drug interactions as well as significant neurotoxic and idiosyncratic side effects. Prescribers now enjoy considerable treatment options for their patients with epilepsy. In addition to having varied mechanisms of action, which may complement other medications in the setting of dual-AED therapy, many of these newer agents benefit from renal metabolism, minimal drug interactions, and improved safety and tolerability compared to older AEDs. Some of these AEDs are also effective treatments for conditions other than epilepsy. These newer, second-generation AEDs are particularly advantageous for patients seen within the VHA, who are typically older, with comorbid conditions and often using numerous prescription medications. Moreover, all of these second-generation AEDs are effective for focal-onset seizures, the seizure type for essentially all adult-onset epilepsy. This chapter reviews the properties and clinical uses of second-generation AEDs.

## ■ LAMOTRIGINE

Lamotrigine has demonstrated efficacy for controlling focal-onset seizures as well as primary generalized seizures. Lamotrigine is used as either add-on therapy or as monotherapy. Its wide spectrum of action and tolerability have made lamotrigine a first-line agent for new-onset seizures in older Veterans.<sup>1</sup>

### Dosing

Lamotrigine dose is titrated over several weeks to minimize side effects. This slow titration to therapeutic doses is perhaps the biggest disadvantage of this medication. Because of its metabolism, the lamotrigine titration schedule is influenced by other medications. TABLE 12.1 reproduces the manufacturer-recommended titration for monotherapy, for people taking enzyme-inducing medications, and for people taking valproic acid. Typical maintenance doses range from 150 to 400 mg daily in divided doses. Lamotrigine has a wide therapeutic index, and serum levels do not correlate well with clinical effect. For this reason, routine measurements of plasma concentrations are not recommended.

TABLE 12.1 Lamotrigine Dose Titration

	WEEKS 1-2	WEEKS 3-4	WEEK 5 ONWARDS	MAINTENANCE DOSE
<b>Monotherapy</b>	25 mg daily	25 mg twice daily	Increase by 50 mg/day every 1-2 weeks	200-400 mg/day in two divided doses
<b>Enzyme-inducing drugs</b>	50 mg daily	50 mg twice daily	Increase by 100 mg/day every 1-2 weeks	300-500 mg/day in two divided doses
<b>Valproic acid</b>	25 mg every other day	25 mg daily	Increase by 25 mg/day every 1-2 weeks	100-200 mg/day in two divided doses

## Pharmacology

### *Mechanism of Action*

Lamotrigine is believed to exert its antiepileptic effect via antagonism of voltage-gated Na<sup>+</sup> ion channels in neurons. This mechanism is shared with other AEDs, including phenytoin, carbamazepine, and lacosamide. Other ion channels are also modulated by lamotrigine, including Ca<sup>2+</sup> channels and hyperpolarization-activated cation channels (HCN channels).

### *Metabolism*

Lamotrigine has a two-step metabolism. It is conjugated to glucuronic acid in the liver by the enzyme UGT. The majority of lamotrigine is renally cleared as this glucuronidated metabolite; small amounts are cleared in feces as unchanged lamotrigine. The plasma half-life of lamotrigine is typically between 24 and 35 hours.

### *Drug Interactions*

Medications that induce hepatic enzymes (specifically UGT) will accelerate lamotrigine clearance, thereby shortening half-life and reducing plasma concentrations. Common AEDs with this effect include phenytoin, carbamazepine, and phenobarbital. Valproic acid inhibits many hepatic enzymes, including UGT, and causes an increase in lamotrigine concentrations. For this reason, it is recommended that if a patient taking lamotrigine is started on valproic acid, the lamotrigine dose be cut in half prior to initiation of valproic acid.

## Side Effects and Toxicity

Lamotrigine can produce dose-dependent neurotoxic side effects that include lethargy, somnolence, ataxia, double vision, and nausea. Because of the slow titration schedule used during the initiation of lamotrigine these effects are not commonly seen. Headache and insomnia are other common side effects. Like many other AEDs, lamotrigine rarely causes a paradoxical increase in seizures, an indication for discontinuation.

Lamotrigine is associated with potentially life-threatening adverse effects. The most notable of these are hypersensitivity reactions including Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN). The slow titration schedule has been shown to reduce the incidence of these hypersensitivity reactions. Lamotrigine can cause more typical and benign drug hypersensitivity and rash, but because it is not possible to distinguish between the more benign hypersensitivity and the fulminant, life-threatening conditions, any rash is indication to immediately discontinue lamotrigine. Lamotrigine has also been associated with reversible hematologic disorders including agranulocytosis, anemia, and leukopenia.

## Contraindications

Lamotrigine should be avoided in individuals with a history of drug hypersensitivity reactions, hepatic failure, or hematologic disorders. The FDA ordered a black box warning for all AEDs in 2008 regarding an increase in suicidal thoughts, so clinical decision-making is required when using lamotrigine in patients with depression.

## Use in Pregnancy/Teratogenicity

Lamotrigine is FDA Pregnancy Category C. It is believed to be safe, however, and is the preferred agent for women with epilepsy who require treatment during their pregnancy. Rates of major malformations with lamotrigine exposure in the first trimester of pregnancy were 3.8%, similar to the rates seen in general population (2.2%) or in women with epilepsy (6% to 9%).<sup>2</sup> The North American Antiepileptic Drug Pregnancy Registry data from Spring 2012 indicated that 2% of pregnant women taking lamotrigine had offspring with malformations, the lowest incidence of malformations for all



AEDs studied. Lamotrigine levels drop during pregnancy, so this is a situation where measurement of plasma concentrations and dose adjustments are indicated.

## Other Uses

Lamotrigine has been used extensively to treat psychiatric conditions, including bipolar disorder and refractory depression. There is also evidence that lamotrigine is effective for neuropathic pain, an effect that it shares with other Na<sup>+</sup> channel antagonists. Some practitioners use lamotrigine for migraine prophylaxis if other agents are ineffective or poorly tolerated, but it should be considered a third-tier drug for migraine prophylaxis.

## ■ LEVETIRACETAM

Levetiracetam has become a favorite choice for treating epilepsy in Veterans owing to its wide spectrum of action and ease of use. Levetiracetam is approved for add-on therapy for focal-onset seizures but is increasingly used as monotherapy and even as initial therapy for new-onset seizures. In addition to efficacy for focal-onset seizures, levetiracetam has been shown to reduce generalized tonic-clonic seizures and myoclonic seizures in individuals with primary generalized epilepsy syndromes when used as add-on therapy.

## Dosing

Levetiracetam therapy is initiated at doses of 250 to 500 mg twice daily. Typical maintenance doses are 1,000 to 2,000 mg/day in divided doses. Levetiracetam has a wide therapeutic index, and routine monitoring of plasma concentrations is not recommended. There is an intravenous formulation for levetiracetam. Doses can be converted on 1:1 basis. Because oral administration of levetiracetam achieves peak serum concentrations as quickly as IV administration, the IV formulation is most advantageous for patients who cannot take any oral medication.

## Pharmacology

### *Mechanism of Action*

Levetiracetam binds to a protein that is a component of synaptic vesicles in presynaptic terminals. This function of this protein, synaptic vesicle protein 2A (SV2A), is not completely understood but it influences neurotransmitter release. There is no compelling evidence that levetiracetam directly modulates neurotransmitter receptors or voltage-gated ion channels. This makes levetiracetam a mechanistically unique drug compared to other AEDs.

### *Metabolism*

Levetiracetam is almost exclusively renally cleared, so plasma concentrations and half-life are increased with renal impairment. There is biotransformation in the liver but the pharmacokinetics of levetiracetam and its metabolites are unaffected by mild to moderate hepatic impairment. Plasma concentrations and half-life are elevated in severe hepatic impairment. The half-life of levetiracetam in healthy individuals is between 6 and 8 hours but it is used as a twice-daily drug.

### *Drug Interactions*

Minimal protein binding and negligible hepatic metabolism of levetiracetam prevent any pharmacokinetic drug interactions. There are no clinically significant drug interactions identified to date with levetiracetam.<sup>3</sup> The absence of drug interactions makes levetiracetam a very easy drug to use in Veterans with epilepsy.

## Side Effects and Toxicity

In placebo-controlled trials the most common side effects of levetiracetam were asthenia, somnolence, dizziness, and headache. There was also an increased incidence of routine infections seen with levetiracetam. This effect was initially thought to be spurious, but subsequent trials on the long-acting form of levetiracetam made similar findings. The mechanism of this is not known.

There are several reports of mild leukopenia with levetiracetam use. This mild leukopenia does not appear to be progressive, and it reverses after discontinuation of levetiracetam. In some individuals with a mild, static leukopenia, levetiracetam therapy can be continued.

An important use-limiting side effect of levetiracetam is behavioral; there is an increased incidence of nervousness, emotional lability, and hostility with levetiracetam. It is important to counsel patients and family members about this “irritability” effect, which frequently requires discontinuation of levetiracetam.

## Contraindications

Severe renal impairment requires judicious use of levetiracetam, initiation at lower doses, and a slow titration. Individuals with premorbid psychiatric or personality disorders should avoid levetiracetam, but this is not an absolute contraindication.

## Use in Pregnancy/Teratogenicity

Levetiracetam is FDA Pregnancy Category C. No teratogenic effects were identified in animal studies, but there was slight reduction in fetal growth, and rib number abnormalities. Levetiracetam may be used in pregnancy when the perceived benefits outweigh the potential risks. The North American Antiepileptic Drug Pregnancy Registry data from Spring 2012 reported a malformation rate of 2.4% in offspring of women taking levetiracetam during their pregnancy.

## Other Uses

Levetiracetam has been used to treat some movement disorders, including tremor and myoclonus.

## ■ GABAPENTIN

Gabapentin is approved for use as add-on therapy for the treatment of focal-onset seizures with or without secondary generalization. Although gabapentin is often considered a poorly efficacious AED, studies of new-onset epilepsy in an older Veteran population indicated that gabapentin monotherapy was as efficacious as lamotrigine in preventing recurrent seizures.<sup>1</sup> Because of gabapentin’s excellent tolerability, it should be considered among the first-line agents to treat new-onset seizures in older Veterans.

## Dosing

Gabapentin therapy is initiated at doses of 300 to 900 mg/day in three divided doses. For antiepileptic effects, the dose should be increased to 1,800 mg/day within 3 to 7 days. Gabapentin has been used at doses up to 3,600 to 4,800 mg/day. It has a wide therapeutic index, and routine monitoring of plasma concentrations is not recommended.

## Pharmacology

### *Mechanism of Action*

Gabapentin was designed as an analog of the inhibitory neurotransmitter GABA but it does not appear to directly act on GABA receptors. Gabapentin does, however, increase brain GABA levels and enhance GABA release. Gabapentin also binds to a specific  $\text{Ca}^{2+}$  channel subunit ( $\alpha 2\delta$ ), and this action is believed to underlie its antinociceptive effects. The precise mechanism(s) underlying the antiepileptic effects of gabapentin are incompletely understood.

### *Metabolism*

Gabapentin is cleared exclusively by the kidneys and does not undergo significant hepatic metabolism in either experimental animals or humans.

### *Drug Interactions*

Minimal protein binding and negligible hepatic metabolism of gabapentin prevent any pharmacokinetic drug interactions. Gabapentin does not have any clinically significant drug interactions.

## Side Effects and Toxicity

In placebo-controlled trials the most common side effects of gabapentin were somnolence, dizziness, ataxia, fatigue, and tremor. Gabapentin has also been associated with mood or behavioral disturbances, including depression, and weight gain. Toxicity from gabapentin is characterized by lethargy and dizziness and resolves without sequelae once gabapentin is discontinued. More serious side effects with gabapentin are rare; reported conditions include gait disturbances, leukopenia, thrombocytopenia, and rash. The incidence of rash with gabapentin is lower than that with any other AED.

## Contraindications

Severe renal impairment requires judicious use of gabapentin; initiation of gabapentin should use lower doses and a slow titration. Individuals with premorbid depression or obesity should avoid gabapentin, but this is not an absolute contraindication.

## Use in Pregnancy/Teratogenicity

Gabapentin is FDA Pregnancy Category C. No teratogenic effects were identified in animal studies at therapeutic doses. Gabapentin may be used in pregnancy when the perceived benefits outweigh the potential risks.

## Other Uses

Gabapentin is effective for many other conditions and is used most frequently for indications other than seizures. Gabapentin is a first-line agent for the treatment of neuropathic pain, particularly diabetic neuropathy and post-herpetic neuralgia. It is effective for migraine prophylaxis and chronic daily headache. Gabapentin has been used effectively to treat some movement disorders, including essential tremor and restless legs syndrome, and has been shown to possess anxiolytic effects.

## ■ FELBAMATE

Felbamate is approved for use as monotherapy or adjunct therapy for the treatment of focal-onset seizures with or without secondary generalization. Although felbamate has documented efficacy in the treatment of focal seizures, it is rarely used because of its association with a potentially life-threatening, idiosyncratic side effect (aplastic anemia). The American Academy of Neurology Subcommittee on Quality and Standards recommends the use of felbamate only for medically refractory (intractable) focal epilepsy.

### Dosing

Felbamate therapy is initiated at doses of 1,200 mg/day in three or four divided doses. This dose can be increased to 2,400 mg/day after one week with a maximum dose of 3,600 mg/day. To minimize the risk of adverse effects the manufacturer recommends reducing the dose of other AEDs by 20% to 30% initially, and then reducing the dose of concomitant AEDs further as felbamate dose is titrated.

### Pharmacology

#### *Mechanism of Action*

Felbamate inhibits *N*-methyl-D-aspartate (NMDA) glutamate receptors.<sup>4</sup> It has also been shown to interact with other ion channels, including GABA<sub>A</sub> receptors, voltage-gated Na<sup>+</sup> channels, and voltage-gated Ca<sup>2+</sup> channels.

#### *Metabolism*

Felbamate is renally cleared as both unchanged compound (approximately 50%) and as metabolites (approximately 50%). Thus, felbamate undergoes some hepatic metabolism. It also is a mild inducer of hepatic enzymes (cytochrome P450). The half-life of felbamate is in the range of 16 to 22 hours.

#### *Drug Interactions*

Felbamate interacts with several other AEDs. It increases plasma concentrations of phenytoin and valproic acid. Felbamate reduces carbamazepine levels. Because felbamate undergoes partial metabolism in the liver, enzyme-inducing drugs (phenytoin, carbamazepine, and phenobarbital) accelerate felbamate clearance and reduce plasma levels.

### Side Effects and Toxicity

The most common side effects of felbamate are anorexia, nausea, vomiting, insomnia, and headache. These symptoms were more common during concomitant use of other AEDs. Neurotoxic symptoms such as ataxia, diplopia, and somnolence are also reported.

Felbamate is associated with potentially fatal idiosyncratic reactions. Aplastic anemia resulting from felbamate therapy resulted in the FDA issuing a black box warning. Use of felbamate requires signed written consent, frequent blood monitoring, slow dose escalation, and reduction of other AEDs. Eighteen cases of hepatotoxicity have been reported, four of which were fatal.

### Contraindications

Severe renal impairment requires judicious use of felbamate. Felbamate use is reserved for medically refractory epilepsy. Analysis of the cases of aplastic anemia has identified a patient profile at risk for this reaction; the majority of patients were female and using other AEDs, and a sizable percentage had a history of cytopenia or autoimmune disease.

## Use in Pregnancy/Teratogenicity

Felbamate is FDA Pregnancy Category C.

## Other Uses

There are no other indications for felbamate use outside of treatment for medically refractory epilepsy.

### ■ TOPIRAMATE

Topiramate is approved for use as monotherapy or adjunct therapy for the treatment of focal-onset seizures (with or without secondary generalization) and primary generalized seizures. Topiramate is considered a first-line agent for migraine prophylaxis.

## Dosing

Topiramate therapy is initiated at doses of 50 mg/day in two divided doses. To minimize side effects it is recommended that dose be slowly escalated by 50 mg/week towards a maintenance dose of 400 mg/day in divided doses. For migraine prophylaxis lower doses are used; doses above 150 mg/day have not been shown to provide additional benefit for the prevention of migraine.

## Pharmacology

### *Mechanism of Action*

Topiramate is believed to have multiple mechanisms of action that contribute to its antiepileptic effects. It inhibits voltage-gated Na<sup>+</sup> channels and reduces sustained repetitive firing of neurons. Topiramate also antagonizes non-NMDA glutamate receptors. It affects inhibitory neurotransmission by potentiating GABA<sub>A</sub> receptor responses and increasing whole brain GABA concentrations. Topiramate is a carbonic anhydrase inhibitor, which may contribute to some of its antiepileptic effects and is the cause of paresthesias (perioral or fingertip tingling) seen with its use.

### *Metabolism*

Topiramate is cleared primarily renally as the unchanged compound, and renal dysfunction increases topiramate levels and half-life. There is some hepatic metabolism of topiramate, but this pathway appears less important than renal clearance. Topiramate levels and half-life are only minimally affected in liver failure. However, some enzyme-inducing AEDs can reduce topiramate levels. The half-life of topiramate is approximately 21 hours.

### *Drug Interactions*

Topiramate levels are reduced by some enzyme-inducing AEDs (phenytoin and carbamazepine). It has not been shown to affect the clearance of other AEDs. Topiramate may alter the effectiveness of OCs, specifically by lowering the estrogenic components. Patients taking OCs should be counseled about this and instructed to report any changes in bleeding patterns.

## Side Effects and Toxicity

The most common and important side effects of topiramate are cognitive problems. These problems can manifest as confusion, difficulty concentrating, language problems, or nervousness. Anorexia, weight loss, and paresthesias are also commonly seen, and patients should be counseled about these side effects. Topiramate frequently causes a mild metabolic acidosis, but this typically does not limit its use.

Kidney stones can occur with topiramate, a consequence of carbonic anhydrase inhibition. Rare cases of acute angle closure glaucoma have occurred with topiramate use; patients should be instructed to stop the medication and contact their healthcare provider in the event of eye pain or vision problems.

## Contraindications

Severe renal impairment requires judicious use of topiramate and dose reduction. Topiramate should be avoided in individuals with history of renal stones.

## Use in Pregnancy/Teratogenicity

Topiramate is FDA Pregnancy Category D. It has been associated with midline craniofacial defects. The FDA recommends avoiding topiramate use in women of childbearing age.

## Other Uses

Topiramate is used for many nonepileptic neurological conditions, including migraine headache prophylaxis, chronic daily headache, pseudotumor cerebri, essential tremor, restless leg syndrome, and diabetic neuropathy. There is evidence that topiramate can be effective for bipolar disorder.

## ■ ZONISAMIDE

Zonisamide is approved for use as adjunct therapy for the treatment of focal-onset seizures (with or without secondary generalization) and primary generalized seizures. In Japan, zonisamide is approved for use as monotherapy.

## Dosing

Zonisamide therapy is initiated at doses of 100 mg/day. To minimize side effects it is recommended that the dose be escalated slowly by 100 mg/day every two weeks. Typical maintenance doses are 300 to 400 mg/day either as a single dose or in divided doses. Routine monitoring of plasma concentrations is not recommended.

## Pharmacology

### *Mechanism of Action*

The antiepileptic mechanism of zonisamide is incompletely understood but is believed to relate to antagonism of voltage-gated ion channels (Na<sup>+</sup> channels and T-type Ca<sup>2+</sup> channels).<sup>5</sup> Specifically, zonisamide inhibits sustained repetitive firing of neurons, an effect that suggests use-dependent block of voltage-gated ion channels. Zonisamide, like topiramate, has activity as a carbonic anhydrase inhibitor.

### *Metabolism*

Zonisamide undergoes renal clearance and hepatic metabolism. Approximately 30% of renal clearance is as unchanged parent compound, and the remainder undergoes hepatic biotransformation prior to renal clearance (acetylation or glucuronidation). Predictably, enzyme-inducing drugs accelerate zonisamide clearance and shorten the half-life. The half-life of zonisamide is in the range of 50 to 60 hours.

## **Drug Interactions**

Zonisamide clearance may be increased by some enzyme-inducing AEDs (phenytoin, phenobarbital, and carbamazepine), with suspected reductions in zonisamide levels. Zonisamide dose adjustment should be considered when starting or stopping an enzyme-inducing drug.

## **Side Effects and Toxicity**

The most common side effects of zonisamide are fatigue, somnolence, dizziness, anorexia, memory problems, and nausea. Owing to carbonic anhydrase inhibition, paresthesias (fingertip or perioral tingling) and metabolic acidosis may also occur with zonisamide.

More serious side effects include kidney stones, likely a consequence of zonisamide's inhibitory action on carbonic anhydrase. Zonisamide is a sulfa drug and has the capacity to cause hypersensitivity reactions and rash, including severe forms of hypersensitivity such as SJS and TEN. There are case reports of oligohidrosis and hyperthermia occurring with zonisamide use.

## **Contraindications**

Severe renal impairment requires judicious use of zonisamide and dose reduction. Zonisamide should be avoided in individuals with history of renal stones or prior reaction to sulfa drugs.

## **Use in Pregnancy/Teratogenicity**

Zonisamide is FDA Pregnancy Category C. It has produced teratogenic effects in animal models. Zonisamide should be used in pregnancy only if the benefits are felt to outweigh the potential risks.

## **Other Uses**

Zonisamide has been used for conditions other than epilepsy, including migraine headache prophylaxis, rest tremor in Parkinson's disease, and obesity.

### **■ TIAGABINE**

Tiagabine is approved for use as adjunct therapy for the treatment of focal-onset seizures with or without secondary generalization.

## **Dosing**

Tiagabine therapy is initiated at doses of 7.5 to 15 mg/day in divided doses. To minimize side effects it is recommended that dose be slowly escalated by 5 to 10 mg/day every week. Typical maintenance doses are 30 to 40 mg/day as divided doses. Individuals using enzyme-inducing drugs will require higher doses, up to 50 to 60 mg/day. Splitting the dose into a regimen of three or four times a day may minimize side effects.

## **Pharmacology**

### ***Mechanism of Action***

Tiagabine inhibits the uptake mechanism for the inhibitory neurotransmitter GABA (GABA transporter type 1, GAT1). This causes an increase in ambient GABA levels and can prolong inhibitory postsynaptic potentials.

## **Metabolism**

Tiagabine undergoes extensive hepatic metabolism with the majority of elimination occurring via feces (>60%). There is also renal clearance of tiagabine metabolites; less than 5% is renally cleared as unchanged compound. The half-life of tiagabine is approximately 7 hours. Predictably, enzyme-inducing drugs reduce tiagabine serum concentrations and shorten the half-life.

## **Drug Interactions**

Tiagabine clearance is increased by enzyme-inducing AEDs (phenytoin, phenobarbital, and carbamazepine), with reductions in tiagabine levels. Tiagabine dose adjustment may be required when starting or stopping an enzyme-inducing drug. Tiagabine is highly protein bound (>95%) and could affect the serum concentrations and clearance of AEDs and other drugs that are also highly protein bound (warfarin).

## **Side Effects and Toxicity**

The most common side effects of tiagabine are dizziness, nervousness, and tremor. Ataxia, difficulty concentrating, abdominal pain, and worsening depression are also reported.

Tiagabine increased seizure frequency in 23% of patients in one analysis of data from clinical efficacy trials. Tiagabine has also caused status epilepticus at therapeutic or toxic doses, even in people without epilepsy.

## **Contraindications**

Tiagabine increases seizure frequency in individuals with primary generalized epilepsy syndromes. It should not be used in patients with either absence or generalized tonic clonic seizures with a generalized spike-and-wave EEG pattern. Tiagabine should be used with caution and at lower doses in individuals with hepatic impairment, and should be used cautiously and at lower doses in patients with a history of depression or behavioral problems.

## **Use in Pregnancy/Teratogenicity**

Tiagabine is FDA Pregnancy Category C. It has produced teratogenic effects in animal models at toxic doses but not at nontoxic doses. There is insufficient evidence to recommend its use during pregnancy and tiagabine should be used in pregnancy only if the benefits are felt to outweigh the potential risks.

## **Other Uses**

Tiagabine use for conditions other than epilepsy is not established. Although its efficacy for conditions such as pain, migraine headache, and spasticity has been investigated, the use of tiagabine for these indications cannot be recommended.

### **■ OXCARBAZEPINE**

Oxcarbazepine is approved for use as adjunct or monotherapy for focal-onset seizures with or without secondary generalization. It is structurally similar to carbamazepine with similar mechanism of action and efficacy, but has unique pharmacokinetics, side-effect profiles, and metabolism. In addition, some patients may respond to one drug but not the other. For these reasons oxcarbazepine should be considered as a distinct drug.<sup>6</sup>



## Dosing

Oxcarbazepine therapy is initiated at doses of 150 mg/day. This can be increased by 150 mg/day every 2 to 4 days. Typical maintenance doses for use as monotherapy are 600 to 1,200 mg/day given in divided doses.

## Pharmacology

### *Mechanism of Action*

Oxcarbazepine is believed to exert its antiepileptic action by inhibiting voltage-gated ion channels and preventing sustained repetitive firing of neurons. This effect is primarily due to inhibition of Na<sup>+</sup> channels, but oxcarbazepine may also inhibit Ca<sup>2+</sup> channels and reduce excitatory glutamatergic synaptic transmission.

### *Metabolism*

Oxcarbazepine functions as a prodrug and undergoes hepatic metabolism to its monohydroxylated derivative (MHD). MHD is responsible for much of the antiepileptic action of oxcarbazepine. The majority of oxcarbazepine is renally cleared as MHD or as a glucuronidated metabolite of MHD. The half-life of oxcarbazepine is 1 to 4 hours. The half-life of the active metabolite MHD is 9 to 10 hours. Oxcarbazepine, in contrast to carbamazepine, has only a modest and clinically insignificant enzyme-inducing effect.

### *Drug Interactions*

Oxcarbazepine can increase the concentrations of phenytoin and phenobarbital. Conversely, these two drugs reduce the concentration of oxcarbazepine. Oxcarbazepine has no effect on warfarin actions (measured as changes in prothrombin time).

## Side Effects and Toxicity

The most common side effects seen with oxcarbazepine are somnolence, headache, dizziness, nausea, ataxia, and visual changes/diplopia. Rash is reported in up to 10 percent of patients in some studies. Hyponatremia frequently occurs with oxcarbazepine therapy. If this is mild it does not necessarily limit the use of oxcarbazepine.

## Contraindications

Oxcarbazepine should be used with caution in patients with hepatic or renal failure. In patients at risk for severe hyponatremia (elderly, diuretic use, nonsteroidal anti-inflammatory drug use) oxcarbazepine should be avoided. Oxcarbazepine should be avoided in patients with a history of rash with carbamazepine because of significant cross reactivity.

## Use in Pregnancy/Teratogenicity

Oxcarbazepine is FDA Pregnancy Category C. There is insufficient evidence to recommend its use during pregnancy, and oxcarbazepine should be used in pregnancy only if the benefits are felt to outweigh the potential risks.

## Other Uses

Oxcarbazepine has documented efficacy for treatment of psychiatric disorders including bipolar disease and acute mania. It is also effective for neuropathic pain and migraine headache prophylaxis.

TABLE 12.2 summarizes the indications, dosing, drug interactions, and metabolism of the second generation AEDs covered in this chapter. ■

TABLE 12.2 Antiepileptic Drugs: Second Generation

DRUG	INDICATIONS	STARTING DOSE	TYPICAL DOSE RANGE	MECHANISM OF ACTION
<b>Lamotrigine (Lamictal)</b>	Focal seizures Primary generalized epilepsy, including absence epilepsy	25 mg once or twice a day with slow titration (increase by 50 mg per day every 2 weeks)	150-400 mg per day in divided doses	Blocks voltage-gated ion channels (Na <sup>+</sup> channels)
<b>Levetiracetam (Keppra)</b>	Focal seizures Myoclonic seizures Generalized seizures	250-500 mg per day in divided doses	1,000-2,000 mg per day in divided doses	Binds to synaptic vesicle protein 2A (SV2A), affects neurotransmitter release and Ca <sup>2+</sup> channels
<b>Gabapentin (Neurontin)</b>	Focal seizures	300-900 mg per day in three divided doses	1,800-3,600 mg per day in three divided doses	Inhibits $\alpha 2\delta$ Ca <sup>2+</sup> channel subunits Increases brain GABA concentration Enhances tonic GABAergic inhibition
<b>Felbamate (Felbatol)</b>	Focal seizures	1,200 mg per day in three or four divided doses	2,400-3,600 mg per day	Inhibits NMDA-type glutamate receptors
<b>Topiramate (Topamax)</b>	Focal seizures Primary generalized seizures	50 mg per day in divided doses	300-400 mg per day in divided doses	Inhibits voltage-gated ion channels (Na <sup>+</sup> and Ca <sup>2+</sup> channels) Carbonic anhydrase inhibitor
<b>Zonisamide (Zonegran)</b>	Focal seizures Primary generalized seizures	100 mg per day as single or divided dose	300-400 mg per day as single or divided doses	Inhibits voltage-gated ion channels (Na <sup>+</sup> and Ca <sup>2+</sup> channels)
<b>Tiagabine (Gabitril)</b>	Focal seizures	7.5-15 mg per day in divided doses	30-60 mg per day in divided doses	GABA transporter type 1 inhibitor
<b>Oxcarbazepine (Trileptal)</b>	Focal epilepsy	150 mg per day	600-1,200 mg per day in divided doses	Inhibits voltage-gated ion channels (Na <sup>+</sup> and Ca <sup>2+</sup> channels)

CBZ: carbamazepine; PHB: phenobarbital; PHT: phenytoin; VPA: valproic acid.

**TABLE 12.2 Antiepileptic Drugs: Second Generation (cont.)**

DRUG	COMMON SIDE EFFECTS	PREGNANCY CATEGORY	WARNINGS	COMMON DRUG INTERACTIONS
<b>Lamotrigine (Lamictal)</b>	Neurotoxic side effects (somnolence, ataxia, dizziness) Headache Nausea	C (risk cannot be ruled out)	Stevens-Johnson syndrome	VPA (↑) PHT, CBZ, PHB (↓)
<b>Levetiracetam (Keppra)</b>	Behavioral/mood changes	C (risk cannot be ruled out)	Depression/psychiatric illness Increased suicidal thoughts	None
<b>Gabapentin (Neurontin)</b>	Somnolence Gait disturbances Depression Weight gain	C (risk cannot be ruled out)	Dose adjustment required with renal failure	None
<b>Felbamate (Felbatol)</b>	Neurotoxic side effects	C (risk cannot be ruled out)	Aplastic anemia, requires frequent monitoring Hepatotoxicity	PHT, CBZ, PHB (↓) Felbamate may increase PHT and VPA
<b>Topiramate (Topamax)</b>	Somnolence Cognitive problems Paresthesias Anorexia Metabolic acidosis	D (avoid in pregnancy)	Kidney stones Acute angle closure glaucoma	PHT, CBZ, PHB (↓) Topiramate may affect oral contraception
<b>Zonisamide (Zonegran)</b>	Somnolence Cognitive problems Paresthesias Anorexia	C (risk cannot be ruled out)	Kidney stones Rash (sulfa allergy) Stevens-Johnson syndrome	PHT, CBZ, PHB (↓)
<b>Tiagabine (Gabitril)</b>	Tremor Nervousness Ataxia Somnolence Increased seizures	C (risk cannot be ruled out)	Increased seizures in primary generalized epilepsy syndromes (eg, absence epilepsy) Status epilepticus	PHT, CBZ, PHB (↓)
<b>Oxcarbazepine (Trileptal)</b>	Somnolence Headache Ataxia	C (risk cannot be ruled out)	Rash Hyponatremia	PHT, PHB (↓) Oxcarbazepine can increase PHT and PHB

CBZ: carbamazepine; PHB: phenobarbital; PHT: phenytoin; VPA: valproic acid.

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# Antiepileptic Drugs: Third Generation

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# Introduction

The newest generation of AEDs endeavors to improve efficacy and to reduce side effects. While some of these medications are modifications of older AEDs, others work through novel mechanisms. Some of these medications are the result of rational drug design, with targets identified from humans with genetic epilepsy. While these newer generation AEDs have the potential for greater clinical utility, the dearth of experience with many of these medications keeps them from being clear first-line agents at this time.

## ■ PREGABALIN

### Pharmacology and Mechanisms of Action

Pregabalin is structurally related to gabapentin, and is approved as adjunct treatment of focal-onset seizures as well as pain associated with postherpetic neuralgia and diabetic neuropathy. From a pharmacological perspective, pregabalin appears to have a similar mechanism of action to gabapentin. Specifically, the drug binds to the  $\alpha^2\delta$  protein subunit of the voltage-gated calcium channel. This binding appears to result in the modulation of presynaptic neurotransmitter release, which would lead to reduced neuronal excitability, and therefore limit seizures.<sup>1</sup>

### Pharmacokinetics

Pregabalin is rapidly, and essentially completely, absorbed after oral administration. Unlike its structural analog, gabapentin, pregabalin displays nonsaturable, linear absorption across its approved dosage range. This would be expected to lead to more predictable bioavailability and less interpatient variability. Pregabalin is not bound to plasma proteins and is essentially completely eliminated unchanged by renal excretion (glomerular filtration). This drug does not undergo metabolism in either the gut or the liver.<sup>2</sup>

### Adverse Effects

Adverse effects of pregabalin include dizziness, somnolence, blurred vision, peripheral edema, and weight gain. Sedation may be particularly troublesome, especially when the drug is rapidly titrated. Weight gain may also be problematic, and does not appear to be related to dose.<sup>3</sup> With abrupt discontinuation, withdrawal reactions of increased anxiety, nervousness, and irritability have been reported.

### Drug Interactions

Pregabalin does not appear to cause pharmacokinetic interactions. It is neither an inducer nor inhibitor of either the cytochrome P450 or UDP glucuronyl transferase isozyme systems. Pregabalin also does not appear to alter function of drug transport proteins such as P-glycoprotein. Therefore the likelihood of this medication participating in kinetic interactions is quite low.

### Dosing and Administration

Pregabalin is initiated with a starting dose of 150 mg/day, divided into two or three daily doses. It may be titrated as tolerated to a target dose of 600 mg/day in two or three divided doses. In end-stage renal disease a single daily dose of 25 to 75 mg given after hemodialysis is recommended. Since this drug is renally eliminated, serum creatinine and an estimate of GFR will need to be monitored and dose adjustments made accordingly.

## Advantages

Pregabalin has modest adverse effects and is devoid of significant drug-drug interactions. It may be useful in treating comorbid conditions such as pain or anxiety. Rash is uncommon.

## Disadvantages

While adverse effects are generally modest, somnolence and weight gain may limit therapy. Pregabalin is a controlled substance (Schedule V).

## Place in Therapy

For focal-onset seizures, pregabalin is a second-line therapy. It may be useful in patients with comorbid chronic pain or anxiety.

### ■ LACOSAMIDE

## Pharmacology and Mechanisms of Action

Lacosamide is FDA approved as treatment for focal-onset seizures. Mechanistically, this agent appears to selectively enhance the slow inactivation of voltage-gated sodium channels. Pharmacologically, its mechanism differs from older medications such as carbamazepine, phenytoin, oxcarbazepine, or lamotrigine, which appear to work via enhancement of the fast inactivation of sodium currents in neurons.<sup>4</sup> While early laboratory studies suggested that lacosamide may also interact with collapsin response mediator protein-2, the evidence (and clinical significance) is conflicting.

## Pharmacokinetics

Lacosamide is rapidly, and essentially completely, absorbed following oral administration. Lacosamide undergoes hepatic metabolism and is also partially (40%) eliminated unchanged via renal excretion. Metabolism is mediated by the cytochrome P450 2C19 (CYP2C19) to inactive metabolites. No significant differences in lacosamide pharmacokinetics have been noted in either poor or extensive CYP2C19-metabolizer phenotypes.<sup>5</sup> Lacosamide binding to plasma proteins is negligible (<15%).

## Adverse Effects

Adverse effects of lacosamide include dizziness, nausea, diplopia, ataxia, and nystagmus. Adverse effects appear to occur more commonly in patients receiving concomitant treatment with other sodium channel blocking AEDs. Lacosamide may cause a 5- to 9-msec prolongation of the PR interval of the ECG, however QTc does not appear to be prolonged.

## Drug Interactions

Lacosamide is not known to affect other drugs. It does not appear to cause pharmacokinetic interactions. It is neither an inducer nor inhibitor of either the cytochrome P450 or UDP glucuronyl transferase isozyme systems. Lacosamide also does not appear to alter function of drug transport proteins such as P-glycoprotein. Therefore the likelihood of this medication participating in kinetic interactions is quite low. Lacosamide serum concentrations are decreased by 15% to 20% by enzyme-inducing AEDs (eg, carbamazepine, phenytoin, and phenobarbital), but the clinical significance of this is unclear.<sup>2</sup>



## Dosing and Administration

Lacosamide is initiated with a starting dose of 100 mg/day in two divided doses. The dose is increased by 100 mg/day every week for a target dose of 200 to 400 mg/day. Doses up to 600 mg/day may be efficacious and tolerated in some patients. In selected patients who require rapid titration, an intravenous dose of 400 mg may be given to start therapy, followed by 400 mg/day divided into two oral doses. Because a substantial fraction of lacosamide is renally eliminated, dosage must be modified in patients with creatinine clearance less than 30 mL/min (300 mg/day maximum recommended dose).

## Advantages

Lacosamide has a novel mechanism of action and minimal interactions with other drugs. Multiple dosage formulations are available including tablet, oral solution, and a parenteral formulation. These dosage forms are bioequivalent, so that no dosage adjustment is required when switching between formulations. The parenteral formulation is well tolerated, does not appear to cause either respiratory or hemodynamic effects, and offers minimal venous irritation. Lacosamide does not appear to cause changes in body weight. Rash does not appear to be a common adverse effect.

## Disadvantages

CNS adverse effects may be dose-limiting in some patients, particularly those receiving concomitant sodium channel blocking AEDs. No generic formulations are available.

## Place in Therapy

Until more evidence for monotherapy is available, lacosamide should be considered a second-line agent for focal-onset seizures

### ■ RUFINAMIDE

## Pharmacology and Mechanisms of Action

Rufinamide is a triazole-derivative drug that appears to work by prolonging the inactivation phase of voltage-gated sodium channels. Rufinamide does not appear to interact with other receptor systems. Currently, this agent is approved as adjunct treatment for focal-onset seizures and seizures associated with Lennox-Gastaut syndrome.

## Pharmacokinetics

Rufinamide displays what appears to be dose-dependent oral absorption, meaning that plasma concentrations do not appear to rise proportionately with increasing oral dose. Its estimated bioavailability is approximately 85%. Administration of rufinamide with meals (or at least within several hours of food consumption) appears to increase oral absorption. Rufinamide is extensively metabolized by carboxylesterase hydrolysis to inactive metabolites that are subsequently renally excreted. Rufinamide is not metabolized by the cytochrome P450 isozyme system. Rufinamide has an elimination half-life of approximately 10 hours, and is not extensively bound to plasma proteins.<sup>6</sup>

## Adverse Effects

The adverse effects of rufinamide include headache, dizziness, fatigue, somnolence, and nausea. In some cases rufinamide may worsen seizure frequency or induce status epilepticus. Multiorgan hypersensitivity has been reported in patients less than 12 years old. Rufinamide may shorten the PR interval of the ECG.

## Drug Interactions

Clinical evidence suggests that the carboxylesterases responsible for the hydrolysis of the carboxamide group on rufinamide are inducible. Serum concentrations of rufinamide are reduced (25% to 45%) by concomitant administration of carbamazepine, phenytoin, phenobarbital, and primidone. In contrast, coadministration of valproate can result in marked elevations of rufinamide serum concentrations. This apparent inhibitory effect is reportedly greater in children, with increases of 60% to 70% seen. In adults, the magnitude of this interaction is less, but increases of approximately 20% may still be seen. The mechanism of this interaction is unclear. Rufinamide is a modest inducer of CYP3A4 and UDP-glucuronyltransferase, and coadministration results in decreases the serum levels of carbamazepine, lamotrigine, phenobarbital, and phenytoin. Rufinamide does not appear to affect serum concentrations of topiramate, levetiracetam, or valproate.

## Dosing and Administration

Rufinamide is initiated with a starting dose of 400 to 800 mg/day in two divided doses. The dose may be increased by 400 to 800 mg/day every other day, for a target dose of up to 3,200 mg/day.

## Advantages

Rufinamide is effective for seizure control, especially tonic-atonic seizures, in Lennox-Gastaut syndrome without significant cognitive impairment. Rufinamide can be rapidly titrated to a therapeutic dose.

## Disadvantages

Rufinamide has multiple drug interactions and is currently FDA approved for treatment of focal-onset seizures only in patients with Lennox-Gastaut syndrome.

## Place in Therapy

Rufinamide is a second-line medication in Lennox-Gastaut syndrome. It is known to be efficacious in the treatment of tonic-atonic seizures. Until more data is available, rufinamide should be considered a third- or perhaps fourth-line agent in other cases.

## ■ VIGABATRIN

### Pharmacology and Mechanisms of Action

Vigabatrin is an irreversible inhibitor of the enzyme GABA transaminase, the enzyme responsible for the degradation of the inhibitory neurotransmitter GABA. Vigabatrin does not interact with any other known receptor or enzyme systems.

### Pharmacokinetics

Vigabatrin is rapidly absorbed after oral administration and has a bioavailability of approximately 80%. Vigabatrin is not metabolized, and it is eliminated unchanged via glomerular filtration. Vigabatrin is not bound to plasma proteins.

### Adverse Effects

Vigabatrin may worsen myoclonic and absence seizures. Vigabatrin causes progressive, irreversible, bilateral visual field constriction in perhaps up to one third of treated patients. The mechanism of this adverse effect is unclear, but may involve GABA toxicity to the retina. Adverse psychiatric effects can be seen in patients with a history of psychiatric illness. Vigabatrin may cause weight gain, edema, peripheral neuropathy, somnolence, and fatigue.

## Drug Interactions

Available data would suggest that vigabatrin is neither an inducer nor inhibitor of any drug-metabolizing enzyme system. Nonetheless, vigabatrin has been reported to decrease phenytoin levels by up to 20%, and may increase carbamazepine levels by up to 10%. The mechanisms underlying these interactions are not clear.

## Dosing and Administration

Vigabatrin is initiated with a starting dose of 1,000 mg/day in two divided doses. The dose is increased by 500 mg/day on a weekly basis to a target dose of 3,000 mg/day in two divided doses.

## Advantages

Vigabatrin has a unique mechanism of action and can be rapidly titrated to a therapeutic dose. The relative absence of drug interactions is also advantageous.

## Disadvantages

Vigabatrin has significant adverse effects, some of which are irreversible. The use of vigabatrin requires patients and providers to be registered and patients to undergo peripheral vision evaluations prior to, during, and after discontinuation of the medication.

## Place in Therapy

Vigabatrin is a third-line agent for adults with refractory focal-onset seizures. It may be considered earlier in blind patients.

## ■ CLOBAZAM

## Pharmacology and Mechanisms of Action

Clobazam has been shown to modulate GABAergic neurotransmission by positive allosteric modulation of GABA<sub>A</sub> receptors and to increase expression of transporters for both GABA and glutamate. The active metabolite *N*-desmethyloclobazam (norclobazam) also modulates GABA<sub>A</sub> receptors. Structurally this drug is a 1,5 benzodiazepine, and this difference from other marketed benzodiazepines (1,4 benzodiazepines) may confer a different pattern of sedation and muscle relaxant properties.

## Pharmacokinetics

Clobazam is well absorbed, and food does not appear to interfere with absorption. Clobazam is highly bound (80% to 90%) to plasma proteins. Clobazam is mainly metabolized by CYP3A4 to its active metabolite, *N*-desmethyloclobazam, which is subsequently metabolized by CYP2C19.<sup>7</sup>

## Adverse Effects

Adverse effects of clobazam include somnolence, lethargy, and aspiration. Aggressive behavior, mostly in pediatric patients, has also been reported.

## Drug Interactions

Clobazam is a weak inducer of CYP3A4. Importantly, this drug can also inhibit CYP2D6, so clinicians should monitor for potential interactions when using this agent with other medications metabolized by this enzyme. Given that

clobazam is metabolized by both CYP3A4 and CYP2C19, the potential for multiple interactions exists. Drugs that are inhibitors of either of these CYP isozymes may be expected to significantly increase clobazam serum concentrations.

## Dosing and Administration

Clobazam is initiated with a starting dose of 10 mg/day, given in two divided doses. The dose may be increased to 20 mg/day in one week and 40 mg/day after another week.

## Advantages

Extensive experience with clobazam is available from outside of the United States.

## Disadvantages

No generic formulation is available.

## Place in Therapy

Clobazam is a second-line therapy for seizures in Lennox-Gastaut syndrome. It may be useful in patients with seizures and anxiety, or in those already taking a benzodiazepine.

## ■ EZOGABINE

### Pharmacology and Mechanisms of Action

Ezogabine is a selective potassium channel ( $K_V7.2$  to  $7.5$ ) opener that was approved for adjunct treatment for focal-onset seizures but was withdrawn from the market in 2017. Information is presented for informational purposes. By enhancing neuronal potassium currents, this agent is thought to stabilize membrane resting potential and reduce cortical excitability.<sup>8</sup>

### Pharmacokinetics

Ezogabine has an oral bioavailability of approximately 60%. Food does not appear to influence overall extent of absorption, but taking ezogabine with meals does appear to increase peak serum concentrations by approximately 38%. Ezogabine is extensively metabolized by glucuronidation and acetylation. Ezogabine is not metabolized via the CYP isozyme system.

### Adverse Effects

Adverse effects of ezogabine include dizziness, somnolence, and fatigue. Urinary retention occurred in 2% of patients in clinical trials and monitoring for urinary retention is recommended, especially in patients with additional risk factors such as benign prostatic hypertrophy. Recent FDA warnings have indicated that in a small group of patients, retinal and skin pigment changes were noted following chronic (years) use of ezogabine. The mechanism of this adverse effect is still unclear. Retinal changes may result in changes in visual acuity.

### Drug Interactions

Ezogabine is not known to affect concentrations of other AEDs. The *N*-acetyl metabolite of ezogabine may interfere with the renal elimination of digoxin, so serum concentrations of this medication should be monitored. Given that

*(Ezogabine information continues on page 177)*

**TABLE 13.1 Antiepileptic Drugs: Third Generation**

<b>DRUG</b>	<b>INDICATIONS</b>	<b>STARTING DOSE</b>	<b>TYPICAL DOSE RANGE</b>	<b>MECHANISM OF ACTION</b>
<b>Pregabalin (PGB)</b>	Adjunct treatment of focal-onset seizures	150 mg/d, divided BID or TID	Increase to 600 mg/d, typically over two weeks; adjust dose in renal impairment	Binds to the $\alpha^2\delta$ subunit of the voltage-gated calcium channel
<b>Lacosamide (LCM)</b>	Treatment of focal-onset seizures	50 mg BID	Increase by 100 mg/d/wk, typical maintenance 200 to 400 mg/d; adjust dose in renal impairment	Sodium channel inactivator; enhances slow inactivation of voltage-gated sodium channels; may block neurotrophins via CRMP-2
<b>Rufinamide (RFN)</b>	Adjunct treatment for focal-onset seizures and seizures associated with Lennox-Gastaut syndrome	400-800 mg/d, divided BID	Increase by 400 to 800 mg every other day, with target dose of 3,200 mg/d	May prolong inactive state of sodium channels
<b>Vigabatrin (VGB)</b>	Adjunct treatment of focal-onset seizures	500 mg BID	Increase by 500 mg/d/wk, typical maintenance dose 1,500 mg BID; adjust dose in renal impairment	Irreversible inhibition of GABA transaminase
<b>Clobazam (CLB)</b>	Adjunct treatment in Lennox-Gastaut syndrome, $\geq 2$ years old	10 mg/d, divided BID	Increase by 10 mg/d/wk, up to 40 mg/d	Binds to the benzodiazepine site on GABA <sub>A</sub> receptor
<b>Ezogabine (EZG)</b>	Adjunct treatment for focal-onset seizures; withdrawn from market	100 mg TID	150 mg/d/wk to 200 to 400 mg TID	Enhances potassium channel opening (K <sub>v</sub> 7/KCQN)
<b>Perampanel</b>	Mono or adjunct therapy for focal-onset seizures and adjunct therapy for generalized seizures	2 mg QHS	Increase by 2 mg/d/wk to 4 to 8 mg QHS; adjust dose in hepatic impairment	Noncompetitive antagonist of AMPA-type glutamate receptor
<b>Eslicarbazepine</b>	Treatment for focal-onset seizures	400 mg once per day	Increase by 400 mg/d/wk to a maximum dose of 1,200 mg/day	Prolongs inactivation of voltage-gated sodium channels

CBM: carbamazepine; LTG: lamotrigine; PB: phenobarbital; PHT: phenytoin; PRM: primidone; VPA: valproic acid.

TABLE 13.1 Antiepileptic Drugs: Third Generation (cont.)

DRUG	COMMON SIDE EFFECTS	PREGNANCY CATEGORY	WARNINGS	COMMON DRUG INTERACTIONS
<b>Pregabalin (PGB)</b>	Somnolence, dizziness, peripheral edema, ataxia, and weight gain	C	Angioedema reported	None
<b>Lacosamide (LCM)</b>	Headache, nausea, vomiting, and diplopia	C	5- to 9-msec prolongation of the PR interval of the ECG	None
<b>Rufinamide (RFN)</b>	Somnolence, nausea, vomiting, and headache	C	May shorten the PR interval of the ECG	Clearance increased by CBM, PHT, PRM, PB; clearance reduced by VPA; RFN decreases serum levels of CBM, LTG, PB, and PHT
<b>Vigabatrin (VGB)</b>	Irreversible vision loss, tremor, headache, psychosis, and weight gain	C	Irreversible vision loss: requires vision testing before, during, and after treatment	May decrease PHT levels, may increase CBM levels
<b>Clobazam (CLB)</b>	Somnolence and sedation	C	None	CNS depressants, alcohol, CLB weakly induces CYP3A4 and inhibits CYP2D6, metabolized by CYP3A4 and CYP2C19
<b>Ezogabine (EZG)</b>	Retinal and skin changes with chronic use, dizziness, somnolence, confusion, and blurred vision	C	Pigment changes in retina and skin, and urinary retention	Interferes with elimination of digoxin; CBM or PHT decrease levels of EZG
<b>Perampanel</b>	Psychiatric, mood, and personality changes; dizziness, somnolence, and headache	C	Psychiatric and behavioral adverse reactions	The level of perampanel is reduced by inducers of CYP3A4
<b>Eslicarbazepine</b>	Dizziness, somnolence	(not available)	May increase the PR interval of the ECG	Level of eslicarbazepine is decreased by PHT; eslicarbazepine increases the level of PHT and clearance of oral contraceptives and simvastatin

CBM: carbamazepine; LTG: lamotrigine; PB: phenobarbital; PHT: phenytoin; PRM: primidone; VPA: valproic acid.

ezogabine is metabolized via glucuronidation, it is susceptible to enzyme induction. Coadministration of drugs such as carbamazepine or phenytoin results in about a 35% decrease in ezogabine serum concentrations. The clearance of ezogabine is increased by carbamazepine and phenytoin. Neither valproate nor oral contraceptive medications appear to alter the pharmacokinetics of ezogabine.

## Dosing and Administration

Ezogabine is initiated with a starting dose of 300 mg/day divided into three daily doses. The dosage is increased by 150 mg/day on a weekly interval, with a target dose of 600 to 1,200 mg/day.

## Advantages

Ezogabine has a novel mechanism of action.

## Disadvantages

Idiosyncratic pigment changes in the skin and retina may limit its use. Ezogabine requires dosing three times per day. Ezogabine is a controlled substance (Schedule V).

## Place in Therapy

This medication has been withdrawn from the market.

### ■ PERAMPANEL

## Pharmacology and Mechanisms of Action

Perampanel is a highly selective noncompetitive AMPA-type glutamate receptor antagonist that has recently been approved by FDA as mono or adjunct therapy for focal-onset seizures and adjunct therapy for generalized seizures.<sup>9</sup> Perampanel does not appear to interact with any other receptor systems.

## Pharmacokinetics

Following oral administration, perampanel is rapidly and almost completely absorbed. Perampanel is highly protein bound (95%). Perampanel is eliminated primarily via hepatic metabolism by CYP3A4 to inactive metabolite.

## Adverse Effects

Adverse effects of perampanel include an FDA black box warning pertaining to monitoring psychiatric, behavioral, mood, or personality changes, which may be life-threatening. Additional adverse effects include dizziness, somnolence, headache, and ataxia.

## Drug Interactions

Perampanel is metabolized via CYP3A4 and therefore serum levels of perampanel are markedly decreased by enzyme-inducing AEDs. Given by itself, perampanel has an elimination half-life of about 100 hours. Given with concomitant enzyme-inducing AEDs, perampanel's oral clearance is increased by two- to threefold. Perampanel displays modest enzyme-inducing properties at the high end of its typical dose range (12 mg/day).<sup>10</sup>

## Dosing and Administration

Perampanel is initiated with a starting dose of 2 mg/day, unless the patient is taking enzyme-inducing AEDs, in which case the starting dose is 4 mg/day. The dose is titrated by 2 mg/day on a weekly basis to a maximum dose of 12 mg/day. In hepatic failure, the dose should be increased every 2 weeks, and the target dose is decreased to 4 to 6 mg/day.

## Advantages

Perampanel has a novel mechanism of action. It can be dosed once per day.

## Disadvantages

Perampanel side effects include active psychosis with hostility and aggressive behavior.

## Place in Therapy

Perampanel is particularly useful when once-a-day dosing is needed, and when there is uncertainty about whether seizures are focal or generalized, as it has efficacy for both.

## ■ ESLICARBAZEPINE

### Pharmacology and Mechanisms of Action

Eslicarbazepine is approved as treatment for focal-onset seizures. It appears to work by prolonging the inactivation phase of voltage-gated sodium channels.<sup>11</sup>

### Pharmacokinetics

Eslicarbazepine acetate is a prodrug that undergoes hydrolysis to S-licarbazepine (also known as eslicarbazepine). This molecule is subsequently glucuronidated and then renally excreted. Eslicarbazepine is structurally similar to carbamazepine and oxcarbazepine but is structurally different at the 10,11 position. Therefore eslicarbazepine does not form carbamazepine-10,11-epoxide. Unlike oxcarbazepine, which is metabolized to both S- and R-licarbazepine, eslicarbazepine is extensively converted to S-licarbazepine. At steady state the half-life of eslicarbazepine is about 24 hours.<sup>12</sup>

### Drug Interactions

Eslicarbazepine is a modest inducer of CYP3A4 and UDP-glucuronyltransferase (glucuronidation). Eslicarbazepine increases serum levels of phenytoin, and serum levels of eslicarbazepine are reduced by phenytoin. Eslicarbazepine accelerates clearance of hormonal components of oral contraceptives and simvastatin. Its potential for drug interactions seems similar to that of oxcarbazepine.

### Adverse Effects

Adverse effects of eslicarbazepine include dizziness and somnolence. Hyponatremia is less common than with carbamazepine or oxcarbazepine. Eslicarbazepine may increase the PR interval of the ECG.

### Dosing and Administration

Eslicarbazepine is initiated with a starting dose of 400 mg as a single daily dose. It may be increased by 400 mg/day on a weekly basis to a maximum dose of 1,200 mg/day.



## Advantages

Eslicarbazepine has once-daily dosing and appears to be well-tolerated. It may cause less hyponatremia than oxcarbazepine. Eslicarbazepine has potentially less CNS adverse effects than oxcarbazepine; further evaluation is required.

## Disadvantages

Eslicarbazepine may cause hyponatremia, particularly in older patients. In women using oral contraceptive pills, it may cause contraceptive failure. Rash can also occur.

## Place in Therapy

Because of its long half-life, eslicarbazepine is particularly useful when once-a-day therapy is needed. ■

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# Advanced Therapies

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# Introduction

The goal of epilepsy treatment is for patients to become seizure-free. A patient who has tried at least two appropriate anti-epileptic drugs (AEDs) alone and in combination without achieving seizure freedom at reasonable doses is considered to have medically-refractory epilepsy. In this subset of patients, the likelihood of obtaining seizure freedom with each additional AED trial is only 5-10%,<sup>1</sup> and a variety of other treatment options should be considered. Referral to one of the VA Epilepsy Centers of Excellence (ECoE) for comprehensive evaluation is recommended for all patients with medically-refractory epilepsy.

Resective surgery may offer a chance at complete seizure remission in appropriate candidates. For medically-refractory patients who are deemed not to be candidates for resective surgery, treatment options include continued AED trials, implantation of a vagal nerve stimulator (VNS), responsive neurostimulation system (RNS), investigational device-based therapies, immunotherapy, dietary treatments, and other alternative therapies (herbals, behavioral approaches, yoga, meditation, acupuncture, acupressure, etc.). This chapter will review these treatment options.

## Epilepsy Surgery

There are several types of surgery that may help control seizures in patients with medically-refractory epilepsy. The most common types of epilepsy surgery performed are lobectomies and lesionectomies, though other procedures can be done including multiple subpial transections, corpus callosotomy, and hemispherectomies. Device-based therapies and minimally-invasive techniques also exist such as VNS, RNS, and investigational therapies including radiosurgery and deep brain stimulation.

The evaluation for epilepsy surgery is complex, and begins with testing to determine if there is a single focus causing seizures. Once that is established, another series of evaluations are done to evaluate the safety of surgery and risks of resecting the focus in question. Surgery may offer an excellent chance of achieving complete seizure remission in some cases. The risks of surgery depend largely on the area to be removed, whether it overlaps with areas of the brain that control critical functions such as language or motor control, also referred to as eloquent cortex, as well as other anatomical considerations. The ultimate goal is to remove the area causing seizures as completely as possible without causing new neurological deficits. Although resective surgery may lead to complete seizure remission, weaning AEDs should not be the primary goal of surgery. Most patients will remain on at least one AED indefinitely, though many patients can successfully have their AEDs reduced in number and dose several years after successful surgery.

An individualized approach is taken to determine the risk-benefit ratio, taking into consideration psychological stability and social support as much as other medical considerations. To be deemed a surgical candidate, a patient generally should: 1) fulfill the definition of having medically-refractory epilepsy, 2) have a single focus or lesion causing seizures not overlapping with eloquent cortex, and 3) have a relatively high seizure burden as it relates to seizure frequency and severity, psychological effects, and/or socioeconomic impact.<sup>2</sup> Please refer to CHAPTER 9 for further details on the evaluation for epilepsy surgery.

Patients with a single seizure focus are often divided either by the presence or absence of a radiographic lesion (lesional vs non-lesional), or by the location of the focus irrespective of presence of a lesion (temporal vs extratemporal). For the purposes of this discussion, the author will use the former distinction, but will discuss temporal lobe resections in the greatest detail. Of note, this chapter will not discuss surgery for lesions requiring urgent resection for reasons other than epilepsy such as malignant or progressively enlarging neoplasms and arteriovenous malformations.

## Lesional Resections

### Temporal Lobe Resections

The most common form of medically-refractory epilepsy is mesial temporal lobe epilepsy (MTLE) with hippocampal sclerosis (HS). Patients with this syndrome typically have a characteristic history of prior cerebral insult such as complex febrile seizures, central nervous system infection, or traumatic brain injury followed by delayed onset of temporal lobe seizures.<sup>3</sup> The delay may be as long as several decades in some cases. The exact mechanism underlying the development of HS remains elusive.

Despite being one of the most refractory forms of epilepsy, it is also the syndrome most commonly, and most effectively, treated by surgical resection.<sup>3</sup> As discussed in CHAPTER 9, the strongest candidates for temporal lobe resection undergo an evaluation demonstrating ictal onset in the mesial temporal region by scalp video electroencephalographic telemetry monitoring (VET) and concordant ipsilateral HS on MRI.

The first published randomized, controlled trial of surgery for temporal lobe epilepsy demonstrated that 58% of patients undergoing temporal lobectomy achieved remission from seizures impairing awareness compared to only 8% in those treated medically.<sup>4</sup> The patient population was relatively heterogeneous as it included patients with and without HS on imaging, as long as there were no additional lesions or brain lesions that required urgent surgery.

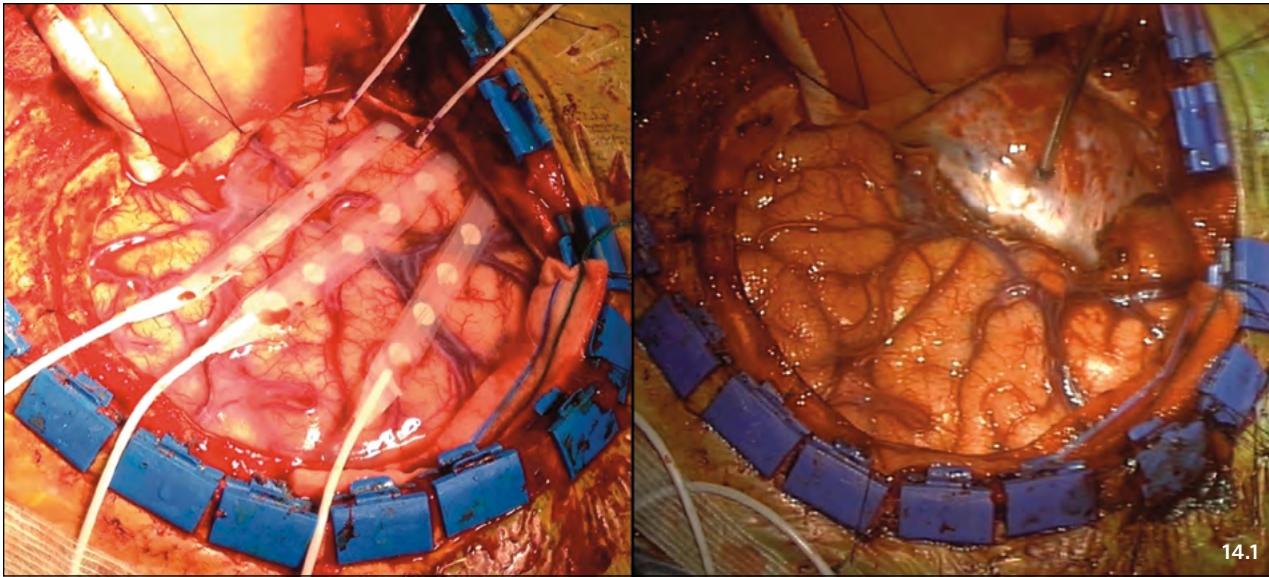
It had been hypothesized that surgery earlier in the course of the disease might yield similar or better rates of seizure remission, while avoiding long term psychosocial effects of having poorly controlled seizures for many years. The ERSET trial was designed to address this issue, and it showed a 73% rate of achieving seizure freedom in patients undergoing surgery within 2 years of epilepsy onset, while none achieved seizure remission in the medically-treated group.<sup>5</sup> All patients had signs of HS on brain MRI, which may have contributed to the higher rate of seizure remission. This study is particularly relevant, as many of the medically-treated patients had tried newer, second-generation AEDs that are used so commonly in current practice.

In both studies, a significant percentage of patients did not become seizure-free.<sup>4,5</sup> Although the reasons for surgical failure are not published in these series and may not be evident in individual patients, in the author's experience this may occur for a variety of reasons. Some patients may have had incomplete resection of the hippocampal tail due to anatomical constraints, such as intervening critical vascular structures. Others may have had occult bilateral HS caused by the original cerebral insult or by previous episodes of status epilepticus, but only unilateral HS on imaging. Finally, some may have undetected dual pathology, which refers to the coexistence of HS with an additional potentially epileptogenic lesion identified on neuroimaging or on pathology specimens.<sup>6</sup> These lesions most commonly include cortical dysplasia followed by low-grade tumors and, less commonly, vascular malformations, perinatal injury, or infarction. Failure to resect the co-existent pathology is the primary reason that medial temporal resection does not cure all patients.<sup>6</sup>

Risks of surgery include low rates of infection (superficial or meningitis), bleeding, and stroke. An anticipated complication is a homonymous superior quadrantanopsia due to interruption of the optic tract and radiations. This is usually asymptomatic and only detected on formal visual field testing. Cognitive outcomes and risks are highest in dominant temporal lobectomies, with risks to verbal memory in as many as 19-50% of patients.<sup>6</sup> Risks to language may be minimized in dominant hemisphere temporal lobectomies by performing pre-resection intraoperative language mapping and tailoring the resection to preserve critical areas identified. Mood disorders may improve in patients who achieve seizure remission as well, though the presence of preoperative psychiatric disorders may be a risk factor for post-surgical worsening of mood.<sup>6</sup> Health related quality of life typically improves after surgery, but most notably in those who achieve seizure remission.<sup>6</sup>

### SURGICAL APPROACHES FOR TEMPORAL LOBE RESECTIONS

There are several different approaches to performing resections for mesial temporal lobe epilepsy when there is evidence of hippocampal sclerosis on magnetic resonance imaging (MRI). Some centers perform selective amygdalohippocampectomy, in which the mesial limbic structures are resected while relatively sparing the remaining anterior and lateral temporal neocortex. The alternative surgery is a standard anterior temporal lobectomy (ATL), which includes resection of the same limbic structures along with the anterior pole of the temporal lobe and varying amounts of lateral



**FIGURE 14.1 Right Anterior Temporal Lobectomy**

Photographs of the right cerebral hemisphere during a tailored right anterior temporal lobectomy. The images are oriented in the inverted surgeon's view, with the superior margin of the surgical field at the bottom of each photograph, and the anterior margin of the surgical field at the left of each photograph. The left image shows the surface of the brain prior to resection with electrodes placed on its surface and inserted deep into the hippocampus for intraoperative electrocorticography recordings. The right image shows the same patient's brain with a prominent resection cavity after right anterior temporal lobectomy. [Author's photographs.]

temporal neocortex. Typically, the amount of lateral neocortex resected depends upon whether surgery is in the dominant or nondominant hemisphere (3-4.5 cm from the anterior pole in dominant hemisphere surgery, and 4-6.5 cm from the anterior pole in non-dominant hemisphere surgery). Many centers perform a tailored ATL, which is a standard ATL that is customized based on the presence or absence of abnormal epileptiform activity detected by electrocorticography recordings during surgery (see FIGURE 14.1). In dominant hemisphere ATLs, it may be further tailored by performing intraoperative language mapping to identify margins for safe resection sparing eloquent cortex.

Proponents of standard or tailored ATLs suggest there is a high incidence of dual pathology with coexistent temporal neocortical foci, and that removal of as much temporal lobe as is safely possible may be associated with higher rates of seizure remission. In contrast, proponents of selective amygdalohippocampectomy believe that sparing neocortical resection can minimize potential cognitive deficits post-operatively, such as verbal memory and language deficits in dominant hemisphere resections. In trials comparing these different surgical approaches, no significant difference is seen in the percentage of patients achieving seizure remission, nor is there any significant difference in post-operative language or verbal memory outcome.<sup>7</sup> Institutional experience and preference usually dictate which approach is used.

### **Other Lesionectomies**

Many patients with medically-refractory focal epilepsy may have a corresponding imaging abnormality that is either congenital or acquired, such as low-grade neoplasms, vascular malformations, and cortical migration abnormalities. These lesions may be quite subtle on imaging and indolent for many years, often leading to delay in identification of the lesion after years of having epilepsy. Even when a lesion is overt, if it has not grown or caused additional symptoms, surgical resection may not be indicated unless seizures become medically-refractory.

Some of these patients may also develop concurrent HS, which can be subtle or absent on imaging but present histologically (dual pathology). In these situations, it is not always clear which of the two lesions is the refractory seizure focus. It is critical to evaluate if the lesion is the seizure focus or if there is any suggestion that the seizure focus might be mesial temporal prior to planning a surgical resection. Clues may be that the semiology strongly resembles one of mesial temporal onset or propagation, or subtle findings of HS are present on imaging. If either of these clues is

present, a detailed evaluation is necessary to determine whether surgery should proceed as a pure lesionectomy or as a lesionectomy plus anterior temporal lobe resection.

If there is no evidence of concurrent mesial temporal lobe epilepsy or HS, surgery may be done to resect the lesion using a variety of surgical techniques dependent upon the location and type of lesion. A notable caveat to this statement is that in certain types of cortical migration abnormalities, the lesion as defined by MRI may grossly underestimate the true extent of the lesion pathologically. Resection of the lesion may be insufficient to cure epilepsy, and may require more advanced evaluation to better localize the seizure-onset zone within or around the lesion. If there is high suspicion that the lesion is a focal cortical dysplasia, the surgical evaluation is similar to that described in the forthcoming section on non-lesional epilepsy resections.

## **Nonlesional Epilepsy Resections**

Epilepsy surgery may be done in patients without obvious MRI abnormalities in two broad clinical contexts: those with clinical features of mesial temporal lobe epilepsy without MRI evidence of HS, and those with clinical features of neocortical focal epilepsy with either normal or subtle imaging abnormalities. A patient may have a normal MRI despite refractory temporal lobe epilepsy, even when the history and scalp-recorded video electroencephalography telemetry (VET) findings are strongly suggestive of seizures with unilateral mesial temporal onset. In these instances, ancillary tests such as positron emission tomography (PET), magnetoencephalography (MEG), or even ictal single-photon emission computed tomography (SPECT) may be done to gather data that may support temporal lobe dysfunction in order to proceed with surgery. Many of these patients ultimately proceed to temporal lobe resection with pathology proving HS despite the lack of imaging findings. In other patients, hippocampal imaging may be normal because the seizure focus is actually neocortical with rapid spread to limbic structures mimicking classic mesial temporal lobe seizures. The pathology of the neocortical focus may be microscopic gliosis from prior injury (vascular or traumatic), cortical migration abnormalities such as focal cortical dysplasia, vascular anomalies such as cavernous malformations, or low-grade glial or neuronal tumors. Many of these lesions are too subtle or diffuse to be well-defined on MRI.

If the accumulated tests do not provide enough concordant data to confirm a mesial temporal seizure focus, some of these patients may be offered a two- or three-stage surgical procedure if they are otherwise medically-refractory with features strongly suggestive of a single seizure focus. In patients with normal brain MRI, the likelihood of achieving seizure freedom is significantly lower than in patients with clear lesions or HS, but the overall seizure outcomes are still much higher than with medical therapy alone.<sup>8</sup>

## **Invasive Evaluation**

A chronic intracranial implantation requires a well-formulated hypothesis of the area(s) of interest where the intracranial recordings will be sampling from. These areas of interest are planned during a multidisciplinary meeting and determined based on concordant data of all noninvasive tests performed (such as EEG, MRI, SPECT, PET, MEG). The two most commonly used invasive methods used to record intracranially are stereotactic placement of stereoelectroencephalography (SEEG) depth electrodes and subdural electrodes. Depending on the hypothesis, these can be unilaterally or bilaterally placed.

The first stage of surgery is implantation of intracranial electrodes, and then admission/transfer to an epilepsy monitoring unit (EMU) to record seizures directly from the brain (chronic electrocorticography). The location of implanted electrodes is determined in advance with detailed interdisciplinary discussions between epileptologists, surgeons, radiologists, and neuropsychologists. After recording seizures and defining the seizure-onset zone, the epileptologist and surgeon discuss a plan for surgical resection or other intervention. Bedside or intraoperative language, motor, and sensory mapping may be performed if there is any concern that the planned resection might include or overlap with any of these eloquent areas. The patient then returns to the operating room for the second stage of surgery, the resection. Invasive monitoring can be performed unilaterally or bilaterally, and both methods are discussed in more detail below.

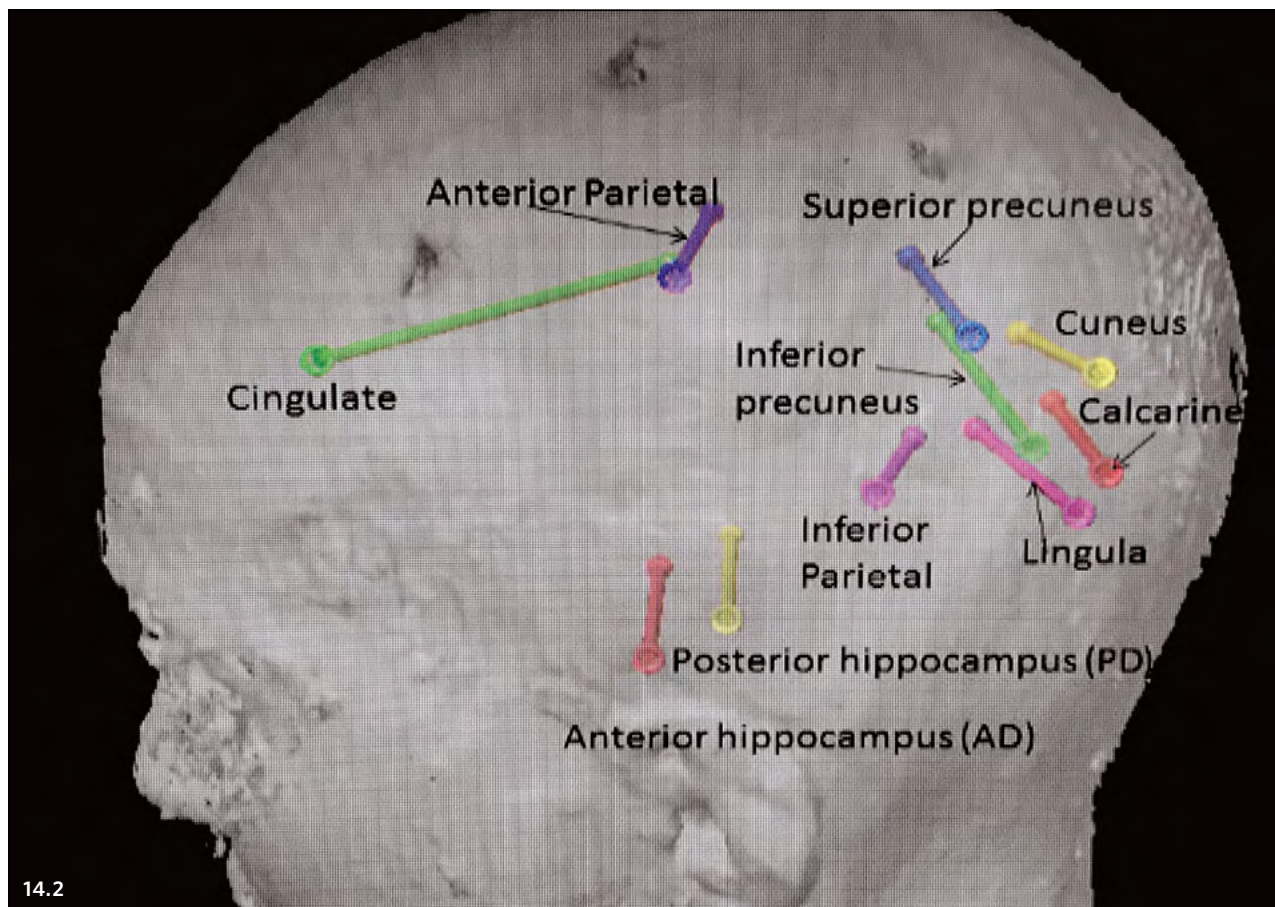
## BILATERAL INVASIVE RECORDINGS

This procedure may be done for patients who have focal onset seizure semiology without sufficient lateralizing and/or localizing data from scalp VET recordings, unremarkable or non-lateralizing brain MRI, and insufficient collateral data by PET, MEG, or SPECT further identifying the target hemisphere. This is done most commonly in patients with clinical features of temporal lobe seizures in which the scalp VET recordings show simultaneous bilateral mesial temporal epileptiform activity. This may happen because the mesial temporal limbic structures are quite deep and distant from scalp electrodes, and because epileptic activity can rapidly spread to ipsilateral, contralateral, or bilateral temporal lobes via limbic pathways. This may also happen in patients with bilateral HS and poorly lateralized seizure onset, or in patients with unilateral HS but conflicting scalp VET recordings suggesting contralateral temporal lobe seizure onset.

Stereoencephalography (SEEG) depth electrodes are available in various number of contacts with various lengths. The electrodes are implanted using either conventional stereotactic techniques using stereotactic frame or a more recent technique using the Robotic Stereotactic Assistance (ROSA) device to accurately place the electrodes in the area of interest with great precision (see FIGURE 14.2).

This technique enables precise recordings from deep areas. Another advantage is that allows for bilateral intracranial exploration without the morbidity of a large or bilateral craniotomy. The main disadvantage of SEEG comes from the lack of contiguous anatomical recording. Thus, SEEG lacks the ability to clearly delineate a continuous surgical border and it has limited capabilities for performing functional mapping. Although SEEG are known to have less complications, there is well documented calculated risk of hemorrhage per electrode of 0.18% that should be consider when planning the implantation.<sup>9</sup>

**FIGURE 14.2** Computer-generated representation of a patient with ten SEEG electrodes inserted into various locations in the left hemisphere. [Author's image.]



14.2

If SEEG electrodes are not available, traditional strips of platinum or stainless steel electrodes embedded in a thin plastic sheet may be used. These are inserted through burr holes and guided to rest on different areas of the brain (frontal, lateral temporal, subtemporal, etc.). Typically, two to four strips are placed on each hemisphere, which is usually sufficient to gauge the general seizure-onset area, but may not be adequate to localize the area very finely. In addition, wire-like depth electrodes may be inserted directly into the brain to record from deeper structures, such as the hippocampus and other limbic areas. The patient is then monitored either on a portable video EEG machine in the ICU, or in the EMU. Ideally, several seizures are recorded over the next several days by employing techniques to trigger seizures such as AED dose reduction and sleep deprivation.

If several typical seizures are recorded and they all begin in the same area of one cerebral hemisphere, the testing is complete. Furthermore, if the seizure onset is in a hippocampal depth electrode and/or subtemporal strip electrode, the patient may be able to proceed directly to temporal lobe resection either during the same admission or at a later date. However, if the seizure onset is either diffuse or focal in any other region, the patient may need to return for further invasive monitoring with surgical implantation of a subdural electrode grid (discussed in the following section) to better localize the seizure-onset zone prior to a definitive resection.

The main risks of performing this invasive monitoring are causing hemorrhage along the insertion track of depth electrodes, or causing subdural hematomas by disrupting bridging veins during insertion of subdural strip electrodes. There is also an increased risk of infection with chronically-implanted electrodes and direct access of pathogens to the brain. The risk rises the longer the electrodes remain implanted. It is also important to consider the risks of a patient having a focal or convulsive seizure while the invasive electrodes are in place. Some patients may be confused, agitated, or even violent after a seizure, and may pull on the electrodes, increasing the risk of bleeding. Several techniques for securing the electrodes may reduce this risk, as well as having a staff member and/or family member constantly present.

## UNILATERAL INVASIVE RECORDINGS

Patients with focal onset seizure semiology with cumulative data lateralizing but not localizing the seizure-onset zone may undergo unilateral subdural grid, subdural strip and depth electrode placement for long term monitoring. This is done commonly in patients with unilateral temporal lobe seizures on scalp VET recordings, but with normal imaging and ancillary testing. It may also be done in patients with well-localized scalp VET recordings and concordant abnormal imaging when the target area overlaps with suspected eloquent areas or the imaging abnormality is too diffuse or poorly defined. Finally, it may be done in patients with lateralized invasive bilateral VET recordings where further localization is needed.

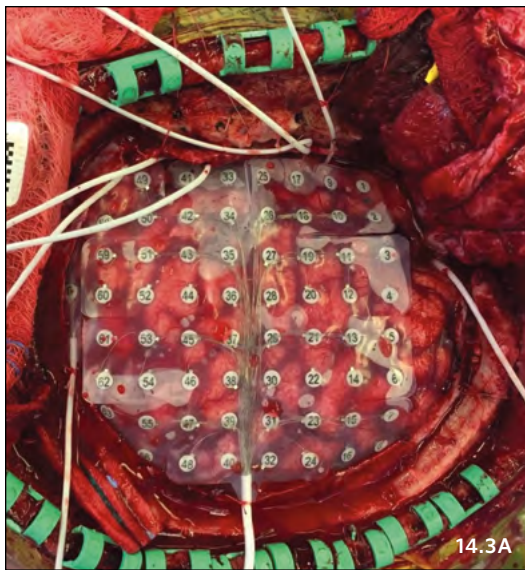
Subdural electrodes consist of discs embedded in either sheets forming an array or strips that are implanted over the cortical surface. The incision and/or craniotomy should be large enough to facilitate the placement of the electrodes in the correct location. The wires are secured to the nearest dural edge with a stitch (see FIGURES 14.3A and 14.3B). Depth electrodes and/or subtemporal subdural strip electrodes are also placed if there is suspicion that the seizure focus may be hippocampal or mesial temporal.

The main advantage of the subdural method is it allows one to record contiguous anatomical areas in order to visualize spread of ictal patterns in the surrounding region and to be able to delineate clear resective surgical borders. Another advantage is the ability to functionally map eloquent cortex and identify the areas of motor, sensory, and language.

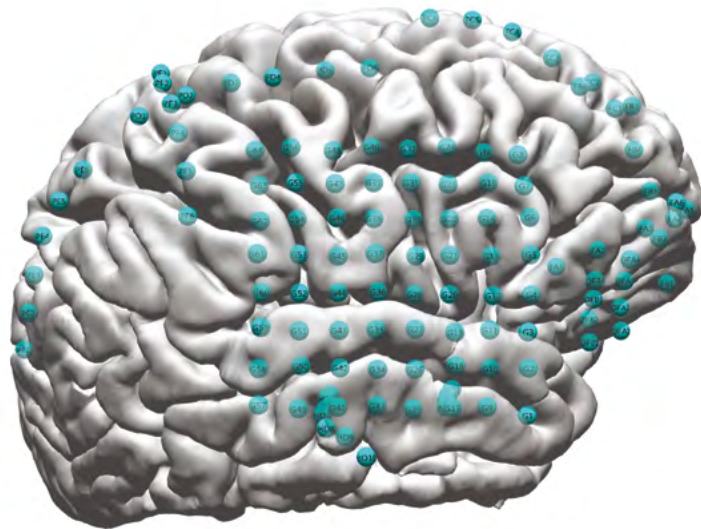
There are limitations to this approach that must be considered. One limitation is the inability to record inter-hemispheric and deep three-dimensional areas, such as focal cortical dysplasia, heterotopias, encephalomalacia, etc. Another limitation is the surgical morbidity risk of the procedure. Two large retrospective studies documenting the major complication rates found infection rates from 2.5-12.1%.<sup>10,11</sup> In addition, there is an 8.6% risk of all hematomas, and 6% risk of symptomatic hematoma. Other complication rates include DVT (1.5%) and permanent neurologic deficits (1.5%).<sup>11</sup>

After electrode implantation, the patient is transferred to the ICU or EMU for monitoring, just as described in the previous section on bilateral invasive monitoring. The goal is to record several seizures to localize the seizure-onset





**FIGURE 14.3A** Photograph of the left cerebral hemisphere with a 64-contact subdural grid of electrodes. The images are oriented in the inverted surgeon's view, with the superior margin of the surgical field at the bottom of the photograph, and the anterior margin of the surgical field at the right of the photograph. [Author's photograph.]



**FIGURE 14.3B** Computer reconstructed images of the right surface of the brain with superimposed invasive electrodes in a different patient with medically refractory seizures lateralized to the right hemisphere by scalp VET, but with negative brain MRI and PET. [Author's image.]

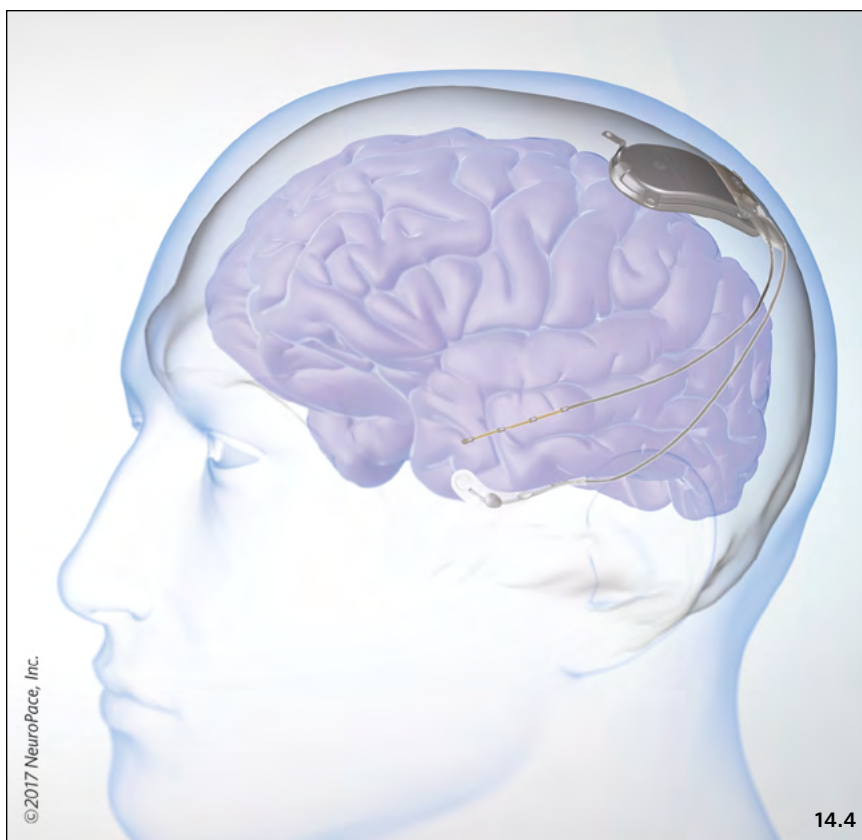
zone, and to perform bedside language, motor, and sensory mapping in appropriate patients to define eloquent areas. The recording period typically ranges from a few days to a few weeks, though the longer durations may be associated with increased risk of infection. Once seizures are recorded, the patient returns to the operating room for removal of the electrodes and definitive resection of the seizure-onset zone.

In some patients, the seizure-onset zone overlaps with eloquent cortex, and resection of the seizure focus is not possible. In these circumstances, a palliative technique called multiple subpial transections (MSTs) may be performed. This technique aims to disconnect cortical areas from lateral connections in the brain without disrupting vertical connections to subcortical structures. Theoretically, this would preserve the function of the tissue, but reduce the likelihood that a seizure generated in that tissue could recruit adjacent areas of tissue. Some patients may undergo implantation of chronic electrodes for responsive neurostimulation (RNS) as discussed in the next section.

## Responsive Neurostimulation (RNS)

NeuroPace developed the first and only responsive (closed loop) neurostimulation system (RNS® System) and was granted approval in 2013 by the FDA for use as an adjunctive therapy in adults with medically refractory epilepsy. The RNS system is often considered in patients with multifocal epilepsy and in those with ictal onset from eloquent cortex or cortex not amenable to resection. Localization of the seizure onset zone may require pre-surgical evaluation including subdural grids or stereo EEG (SEEG). The RNS System is complimentary to antiepileptic medications and not a replacement.

The RNS system consists of a small battery-operated device which is placed under the scalp and sits within a ferrule seated in the skull. Connected to the neurostimulator are up to two intracranial leads, four-contact depth or strip leads which are placed in or over the seizure onset zone (see FIGURE 14.4).<sup>12</sup> The implanted electrodes sense and record chronic electrocorticography (ECoGs) and are also used to deliver electrical stimulation. Samples of ECoGs,



**FIGURE 14.4** The implantable RNS® System components consist of a neurostimulator which is placed in a ferrule seated in the skull, hidden under the scalp, and intracranial depth or cortical strip electrodes which are placed at the seizure onset zone (in this image in the patient's left temporal lobe) by a neurosurgeon. [Image used with permission from NeuroPace, Inc.]

specifically those corresponding to electrographic seizures, and other device data may be downloaded and stored in a provided programmer laptop and uploaded to a secure web-based database for further review. The epileptologist uses the stored ECoGs to identify patient-specific electrical patterns of interest. The RNS system is then programmed to provide electrical stimulation to the electrodes in response to the patient-specific electrical activity in an attempt to prevent or abort the seizure as early as possible. The responsive stimulation is often provided prior to the aura or other clinical symptoms and is not perceived by the patient. Based on clinical response, detection algorithms and responsive stimulation parameters are iteratively changed during routine office appointments.

In clinical trials, the median percent seizure reduction was 44% at 1 year and 72% at year 7, compared to their pre-implant baseline.<sup>13,14</sup> During the 7th year 30% of patients had a 90% or greater reduction in disabling seizures.<sup>14</sup> However, patients should be cautioned regarding expectation of complete seizure freedom. While 29% had at least one 6-month period of seizure freedom, only 16 % had one or more periods of a year or longer without seizures.<sup>14</sup>

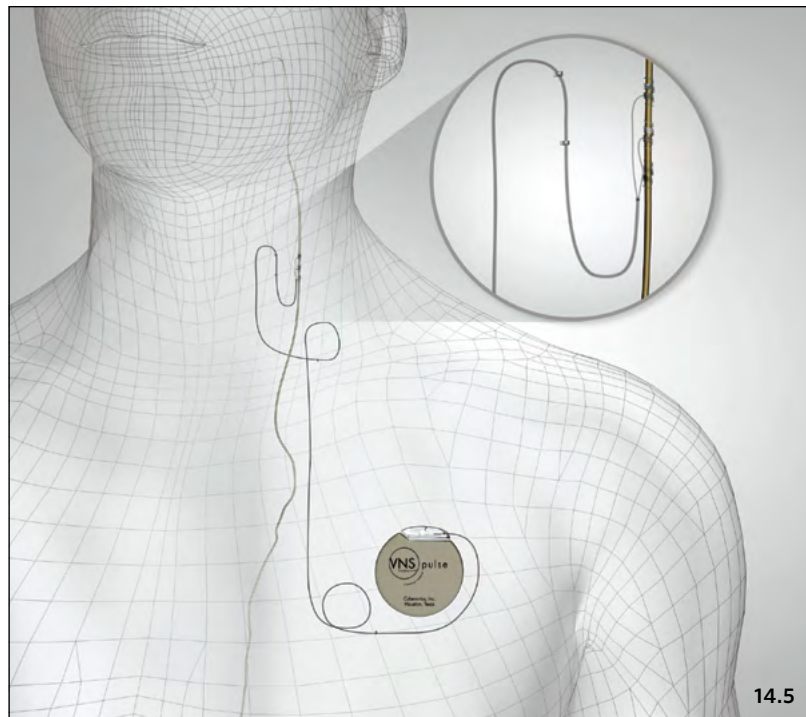
Electronics such as cell phones and computers, and airport security screening process do not interfere with the RNS System though patients should be advised to let TSA personnel know that they have an implanted device.<sup>15</sup> As of this publication, the RNS System is not compatible with magnetic resonance imaging (MRI), electroconvulsive therapy (ECT) and transcranial magnetic stimulation (TMS).

## Vagal Nerve Stimulation

The vagus nerve has multiple functions. Its main efferent functions, or signals leaving the brain and traveling to the body, include parasympathetic innervation of internal organs including the heart, lungs, blood vessels, gastrointestinal tract, and genitourinary tracts. Its afferent functions, or signals entering the brain from the body, include general, visceral, and special sensation. These afferent fibers ascend via several tracts to the brainstem and cortex. The right vagus nerve carries the vast majority of the efferent fibers, while the left vagus nerve carries the vast majority of the afferent fibers.

## FIGURE 14.5 Vagal Nerve Stimulator (VNS)

Artistic representation of implanted VNS device with close up showing electrodes encircling the vagus nerve. There are several loops and turns of the tunneled lead to reduce tension and prevent breaks in the lead. [Image courtesy of Cyberonics, Inc, Houston, TX.]



In animal models, stimulation of the vagus nerve in a repetitive pacemaker-like fashion has been associated with reducing seizure threshold and frequency and aborting seizures. The mechanism of action is not well-established, but there are several theories suggesting it increases cortical inhibition via desynchronization of cortical electrical activity, increasing inhibitory neurotransmitters, and/or altering cerebral blood flow to various regions of the brain.<sup>16</sup>

The VNS device consists of positive and negative stimulating electrodes encircling the left vagus nerve in the carotid sheath in the neck, a programmable generator implanted subcutaneously in the left chest wall, and a tunneled lead connecting the generator to the electrodes (see FIGURE 14.5). After implantation, the device can be programmed and interrogated with an external wand and portable computing device. Programmable variables include intensity of the electrical current, stimulation frequency, pulse width, and cycling parameters (on and off time). An external magnet may also be used to trigger the device to deliver additional current for a separately programmable current strength, frequency, and duration. A new model of the device includes a heart rate detection algorithm that can be programmed to deliver additional stimulation, thereby potentially treating ictal tachycardia automatically.

The left vagus nerve is always chosen for implantation since it carries the majority of afferent fibers, leading to greater potential efficacy and fewer efferent adverse effects. The negative electrode is placed proximally, and is the depolarizing electrode. The distal position of the positive electrode theoretically blocks some of the efferent transmission of the action potential. Potential advantages of VNS over AEDs include a lack of drug-drug interactions, fewer systemic side effects, and programmed stimulation that does not depend on patient adherence. The major disadvantages of VNS are its cost and that it requires invasive procedures for implantation and battery replacements, carrying risks of anesthesia and surgery.

## Outcomes of VNS

After study in humans, vagal nerve stimulation (VNS) was approved by the FDA in 1997, for adjunctive therapy in adults and adolescents with refractory partial-onset seizures, but is also frequently used in younger children and in patients with generalized epilepsy syndromes. Two pivotal randomized, controlled studies of VNS therapy in patients over 12 years of age with refractory partial-onset epilepsy showed an average reduction of 24-28% in total seizure frequency compared to 6-15% of active-control patients with implanted devices set to very low stimulation parameters.<sup>16,17</sup>

VNS therapy is currently regarded as a reasonable treatment option for patients with medically-refractory epilepsy, particularly in patients who are not candidates for resective surgery or in patients who have failed surgical resection and aggressive medical therapy. VNS therapy is not considered in patients who are good candidates for resective surgery, as the latter offers a much greater chance of achieving complete seizure remission.

Common side effects can include hoarseness, throat tingling or pain, and coughing. Most patients adapt to the side effects over time at typical stimulation parameters. Rare adverse effects include aspiration, infection, and cardiac conduction effects—though the latter are almost never seen since most efferent fibers to the heart descend along the right vagus nerve.

One concern with VNS implantation is the safety of magnetic resonance imaging (MRI). Current safety guidelines allow for brain and extremity MRI scans using send-receive coils only with magnets no stronger than 3 Tesla. Body MRI is not recommended as send-receive coils are not used, and is absolutely contraindicated in the region of the device (neck and chest). If the device is ineffective, it can be inactivated and left in place, or it may be explanted surgically. Surgical explantation consists of removing the pulse generator and lead wire, while leaving the electrodes encircling the vagus nerve behind. If the device has been explanted with less than 2 cm of the lead wire remaining, patients may undergo MRI of the brain, body, and extremities. There is inadequate safety data to allow any MRI scanning in patients with greater than 2 cm of remaining lead wire.

## **Programming**

Typical goal stimulation parameters include current strength of 1.5 to 3.0 milliamperes (mA) after an initial slow titration beginning with 0.25 mA, frequency of 20-30 Hz, pulse width of 250-500 microseconds, and cycling on for 30 seconds every 5 minutes. These parameters can be adjusted to increase efficacy by increasing the current strength, or by increasing the percentage of time the device is on during slow or rapid cycles. Decreasing current strength, frequency or pulse width can help combat side effects.

## **Investigational Treatments**

One additional device that has shown positive results in randomized trials is deep brain stimulation of the anterior nucleus of the thalamus (DBS). DBS provides continuous cyclical stimulation of the target tissue with the idea that this may impact thalamo-cortical circuits and potentially reduce seizure genesis or propagation.

Although DBS has positive results, the overall effectiveness of the devices was only slightly superior to VNS during the blinded phases of these studies.<sup>18</sup> As of August 2017, DBS is only approved for use in Europe, and has yet to receive FDA approval for use in the United States.

Stereotactic radiosurgery is a technique of focusing ionizing radiation to various targets within the brain to damage the target tissue.<sup>19</sup> It is commonly used to treat deep lesions, or those that are otherwise difficult to access, such as tumors and vascular malformations. It has been investigated recently for use in MTLE, with a pilot trial showing safety and efficacy comparable to open surgery,<sup>20</sup> and an ongoing subsequent phase 3 multicenter randomized trial.<sup>19</sup> Its main potential advantages would be lower cost, less invasiveness, and potentially better neurocognitive outcomes.<sup>20</sup> Laser surgery is another surgical technique in early investigation for treatment of refractory epilepsy, but used more widely for other approved indications.

## **Dietary Treatments**

Dietary treatments for epilepsy have been used regularly since the 1920s. These treatments fell out of favor with the introduction of AEDs such as phenytoin in 1938, but their popularity returned in the early 1990s. Since then, several published randomized and unrandomized trials have established the efficacy of dietary treatments, the most notable being the ketogenic diet.<sup>21</sup> Although used more often in children, these diets can be used in adults as well.

## The Ketogenic Diet

The ketogenic diet consists of a high fat, low carbohydrate, and adequate protein diet designed to mimic the starvation state. It increases the body's utilization of fatty acids rather than glucose for energy, and leads to many alterations in metabolism. Its mechanism(s) of action are unknown but have been proposed to be related to alterations in acid-base balance, water and electrolyte balance, energy balance, hormonal balance, neurotransmitter levels, neuropeptide function, lipid composition, blood brain barrier permeability, or even direct interaction with ion channels. It is unclear whether these effects are modulated by ketones or by other mechanisms.<sup>22</sup>

### ***Efficacy and Indications***

Most randomized trials showing efficacy of the ketogenic diet have been done in children, but adults have been studied in nonrandomized open-label prospective studies with promising results. In children, about half of patients experience greater than 50 percent seizure reduction, and up to 30 percent may have greater than 90 percent seizure reduction.<sup>21</sup> The percent of medically-refractory epilepsy patients achieving seizure freedom remains quite low, so the ketogenic diet is considered inferior to epilepsy surgery in appropriate surgical candidates.<sup>22</sup> In the past, it has been considered second-line to AEDs because it is difficult to implement and maintain, and has poorly-characterized long-term effects; however, it is a valid option for many.

There is no data to support a difference in efficacy among patients with refractory focal or refractory generalized epilepsies, but it may be particularly effective in children with specific inborn errors of metabolism such as glucose transporter protein deficiency and pyruvate dehydrogenase complex deficiency as it provides the brain with the alternative energy source of ketones rather than glucose.<sup>22</sup> The most applicable condition in the veteran population is the tuberous sclerosis complex, as it may be present in adults with normal intelligence.

Once ketosis is achieved, the effect of seizure control can be seen quite rapidly, often within weeks or months of initiating the diet. If seizure control does not improve within three months with maintained ketosis, it may be discontinued.<sup>16</sup> The diet may be continued for up to two years if effective, though some patients have maintained it for longer periods without major adverse effects. If the decision is made to discontinue the diet due to side effects or prolonged seizure-freedom, it is typically weaned by gradually reducing the fat to carbohydrate/protein ratio. It may be discontinued more rapidly if it has been ineffective.<sup>22</sup>

### ***Contraindications and Adverse Effects***

Just as the ketogenic diet can be particularly effective for patients with certain metabolic disorders or syndromes, it is absolutely contraindicated in several other disorders affecting long chain fatty acid metabolism such as primary and secondary forms of carnitine deficiency, fatty acid oxidation defects, and pyruvate carboxylase deficiency.<sup>22</sup> These disorders are not likely to be seen in the veteran population, as clinical features typically include cardiac and skeletal muscle dysfunction from childhood; however, the diet may also exacerbate acute intermittent porphyria.

The ketogenic diet is associated with a number of relatively common adverse effects such as gastrointestinal upset (nausea, vomiting, constipation, diarrhea), hyperlipidemia, metabolic acidosis, weight loss or failure to thrive, osteopenia/osteoporosis, kidney stones, pancreatitis, iron-deficiency anemia and minor bruising and bleeding.<sup>22</sup> The incidence of kidney stones and weight loss may be even higher in patients concurrently taking topiramate, zonisamide, or acetazolamide.<sup>21</sup> Concurrent use of valproate may be associated with the increased risk of pancreatitis.<sup>22</sup>

Vitamin deficiencies can develop, but a daily carbohydrate-free multivitamin, calcium and vitamin D are recommended to minimize these effects. Long-term maintenance of the diet can lead to osteopenia despite supplementation.<sup>22</sup>

## Initiation and Maintenance of the Diet

At several institutions, the diet may be initiated as an inpatient after a 1-2 day period of fasting with IV fluids and glucose monitoring. It may also be started as an outpatient in close conjunction with a skilled dietitian.<sup>22</sup> After obtaining a detailed food history, a dietitian can assist in meal planning based on caloric needs, weight, and activity level. In adults, typically a 3:1 ratio of fat to carbohydrates/proteins is the goal. Any special dietary requirements or preferences, and cultural/religious dietary needs should be reviewed. Most of these can be accommodated, though it can be particularly challenging to initiate and maintain ketosis with a purely vegan diet. The amount of carbohydrate fillers in AEDs and other medications should be evaluated and included in the total daily carbohydrate calculations.

During the maintenance phase, patients should have urine ketones checked several times a week to ensure ketosis is being maintained. This is easily done at home with commercially available testing strips, and the diet can be adjusted if there is decreased ketosis. In addition, calorie intake and weight require frequent monitoring. Laboratory studies including complete blood count, electrolytes, liver transaminases, bilirubin, glucose, serum calcium, fasting lipid profile, and urinalysis are recommended every 3 months. All patients should receive supplementation daily with a sugar-free multivitamin, calcium, and vitamin D.<sup>22</sup>

## Other Diets

There are several alternative diets, but the most common one used in adults is the Atkins diet or modified Atkins diet as they are less restrictive than the ketogenic diet.<sup>22</sup> These diets are similar to the ketogenic diet with high fat intake and restricted carbohydrates, but with fewer restrictions on protein, fluid, and total caloric intake. It may be started easily as an outpatient without a fast.<sup>21</sup> The efficacy in adults is modest, but notable with 29% of patients having >50% reduction in seizures, and 10% of patients having >90% reduction in seizures.<sup>22</sup> The risks are relatively low (weight loss, constipation, hypercholesterolemia, and gastroesophageal reflux), so treatment with the diet is a reasonable adjunct to AEDs. Caution should be used if considering this diet in patients concurrently taking medications that inhibit carbonic anhydrase activity (topiramate, zonisamide, acetazolamide, furosemide, etc.).

## Immunotherapy

Autoimmune encephalitis is characterized by the presence of neurological symptoms and neuronal antibodies in CSF and/or serum. Seizures and status epilepticus usually represent the acute symptomatic stage of the encephalitis. A multicenter study on patients with NORSE (New Onset Refractory Status Epilepticus in adult or children), in whom a cause could not be determined within the first 48 hours of presentation, found that in 40% the etiology was autoimmune (60% remained unknown).<sup>23</sup> The risk of developing chronic epilepsy, after the treatment of the encephalitis is less than 15%. However, autoimmune epilepsy is often underrecognized and its true incidence and prevalence is unknown. Prompt identification of an autoimmune etiology in patients with otherwise cryptogenic epilepsy and initiating treatment has a favorable seizure outcome.

There is no standardized or evidence based guideline for the treatment of autoimmune epilepsy; however, the main stay recommendation remains immunotherapy. In the presence of high clinical suspicion, CSF suggestive of inflammation and no other etiology; immunotherapy with intravenous (IV) methyl prednisolone or IV Immunoglobulins (IVIg) should be considered while awaiting results of the autoimmune panels. Screening for malignancy, and treatment if detected, should also be added to the work up. Presence of antibodies should prompt the consideration of more aggressive immunotherapy in non-responders to steroid or IVIg. Plasma exchange, rituximab or cyclophosphamide have been suggested, particularly in those with a syndromic presentation, status epilepticus, coma and antibodies strongly associated with autoimmune epilepsy/encephalitis.<sup>24</sup> Early initiation of immunotherapy and presence of anti-cell-surface antibodies (compared to those with antibodies targeting intracellular antigens or those with T-cell autoimmunity or seronegative) are thought to predict a favorable outcome.<sup>23,24,25</sup>

## Other Alternative Treatments

In addition to standard Western medical therapies, a wide variety of complementary and alternative medicines (CAMs) exist that may benefit patients with epilepsy. Most of these approaches are not well-studied or rigorously tested scientifically, but have anecdotal reports of efficacy in case reports and case series. These treatments may be utilized by patients with medically-refractory epilepsy, or even by patients who are not medically-refractory, to combat medication side effects, to reduce the total daily dose of AEDs needed to achieve seizure-freedom, or to combat comorbid conditions. These treatments include non-Western medical traditions like traditional Chinese medicine, botanicals, homeopathy, and Ayurveda, but also include vitamins, supplements, behavior therapies, acupuncture, yoga and meditation. These treatments will be discussed here briefly.

Several herbal medicines with known sedative or anxiolytic effects may potentially reduce seizure frequency. Chamomile, kava, passionflower, and valerian have been best studied in animal models, with possible benefit to seizures at least on theoretical grounds.<sup>26</sup> The sedative effects may be pronounced, and several of these compounds may reduce attention and concentration, quite reminiscent of the side effects seen with many traditional AEDs. Furthermore, concurrent use of these compounds with AEDs may potentiate side effects or lead to significant drug-drug interactions.<sup>27</sup>

Ephedrine and caffeine-containing compounds may potentially exacerbate seizures.<sup>27</sup> Gingko and ginseng herbs are commonly used to improve memory and cognition, but the former has been associated with several case reports of seizures.<sup>27</sup> St. John's wort, an herb commonly used to treat depression, may have drug-drug interactions with several AEDs, though these have not been examined in detail.<sup>27</sup> In general, it is the authors' recommendation that healthcare providers review with patients any herbal treatments being used to evaluate potential risks and better guide therapy.

There are a multitude of compounds used to treat epilepsy in traditional Chinese medicine and in Ayurveda, but many are combinations of several herbs, making it difficult to ascertain which components at what doses might be effective, and for which types of seizures. Several have been studied in animal and in vitro studies, showing potential anticonvulsant properties, but rigorous evidence is lacking in humans with controlled trials.

Significant attention has been given to cannabis in the current climate of legal medical use in several states, though federal law prohibits prescription by VA medical centers. Initial case reports suggest a potential anti-epileptic effect at least with some strains of cannabis in a few patients.<sup>28</sup> Research is still needed to better elucidate which components of cannabis might have pro- or anti-convulsant effects, and to determine how the timing of exposure might impact epileptogenesis. Results of a large open-label clinical trial of oral synthetic cannabidiol in a group of children and young adults with severe, intractable, childhood-onset, treatment-resistant epilepsy show a 36.5% median reduction in monthly motor seizures.<sup>29</sup> Common adverse effects included somnolence, anorexia, diarrhea, and fatigue. Randomized controlled trials are recommended to further characterize the safety and efficacy of this compound in this population as well as in populations with adult-onset intractable epilepsy.

Acupuncture may be prescribed alone or in combination with herbs used in traditional Chinese medicine. It, too, has been studied in epilepsy without clear evidence of benefit in rigorous randomized trials using sham acupuncture as a placebo.<sup>30</sup> It has proven much more difficult to conduct randomized, double-blinded studies of various psychological therapies and mind-body techniques such as cognitive behavior therapy, progressive relaxation, yoga and meditation to determine if there is a clear benefit in patients with epilepsy.<sup>30</sup> Despite the lack of evidence, these psychological therapies and techniques carry minimal risk, so patients may be encouraged to explore these.

## Summary

A wide variety of advanced treatments are available for patients with medically-refractory epilepsy. A number of investigative treatments will potentially become available in the near future as well. These patients should be referred to a VA Epilepsy Center of Excellence for evaluation and consideration of these options as adjuncts to traditional medical therapy with AEDs. ■

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# Status Epilepticus

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# Introduction

Status epilepticus (SE), including convulsive and nonconvulsive SE (NCSE), are not infrequently encountered in the care of Veterans. SE is a condition with high morbidity and mortality,<sup>1,2</sup> especially in the elderly. Most often it is a critical condition that requires extended ICU care with airway protection, in a state of induced coma by anesthetic agents, especially when the SE becomes refractory or super-refractory.<sup>3</sup> This chapter reviews the current literature on this topic, and discusses the management methods. The basic mechanism of SE is briefly discussed to elucidate the important concepts and principles behind the development of current and future management methods. One important understanding is the time-dependent and quick development of resistance to anticonvulsants in SE.<sup>1</sup> Newer and nonstandardized emerging therapies are also discussed because the standardized therapies, based on the VA cooperative study, are known to have high mortality rate, and are clinically not sufficient for managing the refractory and super-refractory cases.<sup>4,5</sup> Continuous EEG monitoring in the ICU setting to diagnose SE and guide pharmacotherapy is also discussed. The issue of how and when to withdraw support—a complex issue that should be carefully evaluated case by case—is briefly touched upon. Finally, the long-term outcome after a successful remission of SE is addressed in light of the importance of neuroprotection during treatment.

## History and Definition of SE

SE was first known to be described in the tablets of the Sakikku cuneiform during 718 to 612 BC. In 1876, Bourneville defined SE as “more or less incessant seizures.” Clark and Prout described the natural course of SE in 38 patients without pharmacotherapy and recognized three phases: an early pseudostatus phase (described as aborted, imperfect, or incomplete), convulsive status, and stuporous SE.<sup>1</sup>

The challenge in defining SE is expressed by Gastaut’s statement, “there are as many types of status as there are types of epileptic seizures.” He defined SE as “a term used whenever a seizure persists for a sufficient length of time or is repeated frequently enough to produce a fixed or enduring epileptic condition.” Gastaut commented on what constitutes “a sufficient length of time” as about 30 to 60 minutes (min). However, the lack of a well-defined time parameter led to several decades of academic debates on what is the universally acceptable “sufficient length of time” to constitute SE. Research with animals shows that repetitive seizures can become self-sustaining and pharmacoresistant within 15 to 30 min, and the development of neuronal injury has the same timeframe. Driven mostly by the clinical necessity for early treatment to abort SE and to prevent neuronal death, the duration of what is accepted as SE has been progressively shrinking from 30 min in the guidelines of the Epilepsy Foundation of America’s Working Group on Status Epilepticus to 20 min to 10 min in the Veterans Affairs Status Epilepticus Cooperation Study, and to 5 min in the Santa Monica Meeting.<sup>1</sup>

## Stages of SE

The modern definition of SE was adopted in the 1962 Xth Marseilles Colloquium as “a term used whenever a seizure persists for a sufficient length of time or is repeated frequently enough to produce a fixed or enduring epileptic condition.” The duration of this sufficient length of time was not defined, which renders the definition of SE impractical in a clinical situation, in which overwhelming evidence mandates an early intervention to abort SE as soon as possible to prevent neuronal injuries. Over the decades since the Xth Marseilles Colloquium, “sufficient length of time” underwent several modifications. Shortening the time definition of SE to 5 minutes could fulfill the clinical needs to intervene early, but defies the observations that at this early stage of time, SE might not have been fully established. This creates problems for clinical trials and epidemiological studies because the cases of impending SE and established SE are included together for data collection. It is accepted now to describe the early phase of convulsive SE, before it is fully established, as impending SE to fulfill the clinical needs for early intervention to start the first-line drugs. Impending convulsive SE is defined as “continuous or intermittent seizures lasting more than 5 minutes, without full recovery of consciousness between seizures.”<sup>1</sup> Five minutes was chosen because it is 18 to 20 standard deviations removed from

the average duration of a single convulsive seizure, rendering it a new identification on a path transforming into established SE.<sup>1</sup> In NCSE, there is probably also an impending phase, but it is less clinically important because NCSE is rarely detected in its early stages—for most cases, the onset time is unknown. Based on our data, it is estimated that if a complex partial seizure lasts for a period of more than 15 minutes, it can constitute a rare and unusual event, and is probably on the transformation pathway to NCSE.

The definition of established SE is “clinical or electrographic seizures lasting more than 30 minutes without full recovery of consciousness between seizures.” There are overwhelming animal and human data to support the adoption of 30 minutes as a practical cutoff time point. The transformation from impending SE to established SE is probably a continuum, and can be modeled by a single exponential curve. The time constant of this exponential curve is estimated to be 30 minutes, suggesting that at 30 minutes, about two thirds of continuous seizing cases have become established SE. Once the SE is established, following a hospital SE protocol, the first-line and second-line therapies should be given as soon as possible; at this stage, SE can easily become refractory or super-refractory. The concept of established SE is the foundation for defining refractory and super-refractory SE, which is based on the lack of therapeutic response in an established SE.

Refractory SE is defined as SE that has not responded to first-line therapy (benzodiazepine) or second-line therapy, and which, according to the treatment protocols, requires the application of general anesthesia.<sup>3</sup> Super-refractory SE is the “SE that continues or recurs 24 hours or more after the onset of anesthesia, including those cases in which SE recurs on the reduction or withdrawal of anesthesia.”<sup>3</sup>

## Classification

Despite the truth in Gastaut’s statement that “there are as many types of status as there are types of epileptic seizures,” it may obscure the possibility that most cases of SE could ultimately share a common basic mechanistic pathway, in contrast to their corresponding discrete seizures. The classification of SE remains an ongoing academic endeavor. There is no current, universally accepted classification system due to confusion in the historical nomenclature and the lack of a universally accepted way to define all types of SE.<sup>6</sup> However, most agree that SE can be roughly divided into convulsive SE and NCSE, mostly due to the differences in clinical presentation and management. Convulsive SE is self-evident in that it is SE with convulsions. NCSE is less straightforward because the diagnosis is based on the clinical presentation of coma, lack of convulsion, and incessant epileptic discharges seen on the EEG recording—and the EEG patterns may be sufficiently ambiguous that different EEG readers might disagree on whether the patterns represent SE. For example, rhythmic slow wave discharges with electrodecremental responses could be interpreted as SE by one EEG reader but not by another. Response to treatment, such as a 2-mg IV injection of lorazepam, is often used at this point to tease out whether the EEG pattern is SE, but a lack of response could be because the SE is refractory. Response does not always rule in SE, either; certain non-SE EEG patterns (such as bilateral periodic epileptiform discharges—BiPEDs) may be suppressed by anticonvulsants. In addition, using the presence of convulsions is not an optimal way of classifying SE; this type of categorization gives too much weight to the involvement of the motor cortex, and ignores the fact that the lack of convulsions does not necessarily mean all nonconvulsive SE should be categorized together. In fact, the NCSEs consist of a very diverse group in SE, as long as the epileptic network spares the motor cortex. Because there is no universally accepted classification system at the present time, however, this article will use the convulsive vs nonconvulsive concepts to discuss treatment options for SE.

## Epidemiology

Three population-based prospective studies investigated the incidence of SE. The first study, around Richmond (VA, USA), demonstrated an overall incidence of 41 per 100,000 individuals per year, with a rate of 27 per 100,000 per year for young adults and 86 per 100,000 per year in the elderly. Mortality was higher in the elderly: 38% for people aged 60 years and older vs 14% for adults aged 16 to 59 years. The incidences from two prospective studies in Europe were 17.1 per 100,000 per year in Germany and 10.3 per 100,000 per year in the French-speaking part of Switzerland.<sup>1</sup>

## Etiology

Any normal brain can generate seizures if sufficiently perturbed. When the conditions are right, the seizures can become incessant. It is not uncommon to see SE in a patient without a prior history of epilepsy. The most commonly noted etiologies for SE include low AED blood levels in patients with chronic epilepsy (often due to a rapid cessation of anticonvulsants without a taper), anoxia/hypoxia, metabolic derangements, intoxication, trauma, stroke, and alcohol or drug withdrawal.<sup>1</sup>

## Characteristics of SE, Based on Basic Mechanisms

In managing SE, it is important that a treatment plan be formulated based on a standardized protocol, which can then be modified as needed for each case by the understanding of the pathophysiology of the SE. A standardized SE treatment protocol provides a timely response to any new-onset SE, which offers the best chance of aborting SE early, before it becomes refractory and then super-refractory. An example of a standardized protocol is discussed in the treatment section. In this section, the characteristics of SE are discussed based on the current understanding of the basic mechanisms of SE.

The major difference between a discrete seizure and SE is that a discrete seizure terminates spontaneously, whereas SE is self-sustaining. Exactly what happens at the basic mechanistic level is still not completely understood, but several lines of evidence show that in transformation to SE, at least at the cellular level, the normal inhibitory GABA<sub>A</sub> receptors are downregulated, and the excitatory glutamate receptors are upregulated. This process probably occurs within seconds to minutes after ongoing seizure activity. This major transformation could have significant clinical implications: GABAergic drugs could become less effective over time if the GABA system has been downregulated, and inhibition of glutamate receptors, especially via NMDA-receptor blockade, could prove to be a crucial component in the suppression of SE, especially in refractory and super-refractory cases.<sup>1</sup>

Probably within minutes to hours, increases in gene expression and new synthesis of the proconvulsant neuropeptides (substance P and neurokinin B) with decreased availability of some inhibitory neuropeptides (dynorphin, galanin, somatostatin, and neuropeptide Y)<sup>4</sup> occur to further enhance excitability. The important clinical implication is that in the future newer anticonvulsants with mechanisms modulating such proconvulsant and anticonvulsant neuropeptides might be crucial in SE management.

Over the course of hours, days, and weeks following SE, long-term changes in gene expression take place as late sequelae of repeated seizures, seizure-induced neuronal death, and neuronal reorganization and neurogenesis. This process might be also important for epileptogenesis. The clinical implication is that this process should be managed with measures providing neuroprotection to reduce neuronal death, and measures to reduce epileptogenesis to prevent development of epilepsy after SE. This part of a management plan has important implications for the long-term outcome after a successful remission of refractory and super-refractory SE.

Another commonly observed phenomenon in animal research is the time-dependent development of pharmacoresistance during SE. This is not limited to GABAergic drugs but potentially occurs for all anticonvulsants, except drugs that block NMDA receptors. The clinical implication is that “Time is Brain in treating SE!” Clinicians should understand that using combination therapy at the onset of SE is probably more sensible than using single anticonvulsants sequentially. The sequential approach is too slow and loses precious time before pharmacoresistance develops. NMDA-blocking agents should be incorporated in the management of super-refractory SE, because they are less likely to lose effect due to time-dependent pharmacoresistance.<sup>1</sup>

## Treatment

### Treatment of Impending SE (Convulsive and Nonconvulsive)

Important therapeutic principles to adhere to in treating SE include the following<sup>1</sup>:

1. Treat early and vigorously to abort seizures.

2. Maintaining homeostasis is essential to prevent iatrogenic complications such as hypoxic/anoxic brain injury, stroke, and myocardial infarction.
3. Treatment should be initiated immediately after a clinical diagnosis of impending convulsive SE or EEG diagnosis of NCSE. The diagnostic workup should not delay initiation of treatment.
4. The first phase of treatment should follow a defined protocol. This includes the prehospital treatment, treatment in the ER, and early hospital treatment.

At this stage, the goal is to give IV or intramuscular (IM) anticonvulsants as soon as possible to suppress seizure activity but not to sedate to an extent precipitating the need for intubation.

## Prehospital Treatment

Several validated treatment options at this stage that could be safely given by paramedics to patients in impending or established SE. Any one—and only one—of the options listed below can be given to the patient in the prehospital setting, ideally after learning whether there is a history of allergic reactions to these medications:

- Diazepam rectal gel 15 to 20 mg
- IV lorazepam 2 mg; may repeat once
- IV diazepam 5 mg; may repeat once
- IM midazolam 10 mg (preferably with an autoinjector)

## ER and Early Hospital Treatment

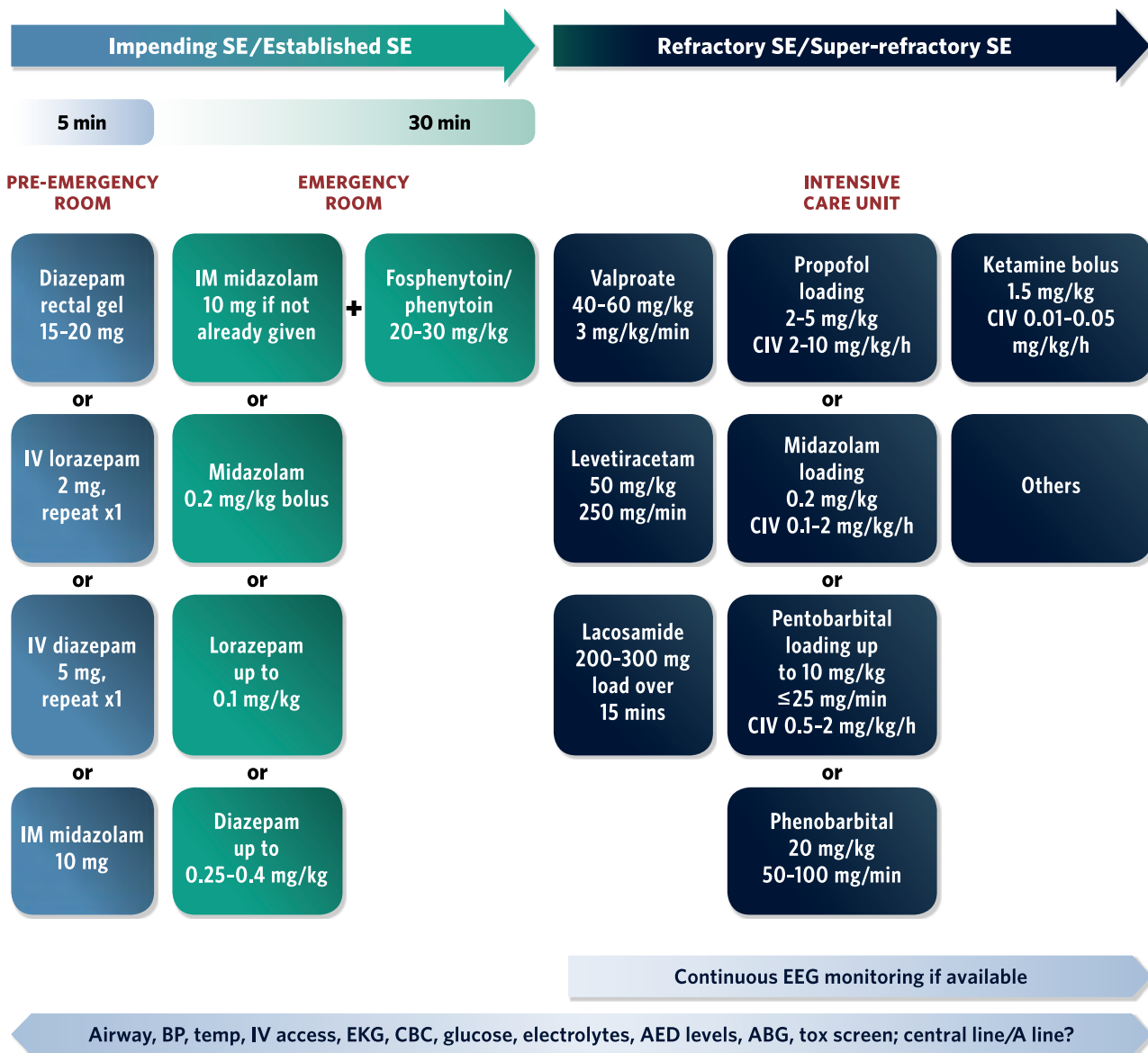
Every VA ER should develop a protocol for treating SE. The clinicians should move down the steps as long as seizure is continuing or the patient has not fully regained consciousness due to continuous epileptic discharges. The protocol could be similar to the following (see TABLE 15.1 and FIGURE 15.1 for medication dosage):

1. Use one of the prehospital treatment options as the first-line treatment if none was given yet in the prehospital setting.
2. Establish IV access.
3. If benzodiazepine has not yet been administered, start therapy with two IV anticonvulsants, such as a benzodiazepine (midazolam, lorazepam, or diazepam) plus a hydantoin (phenytoin or fosphenytoin). If a prehospital dose of benzodiazepine was injected, repeat up to 8 mg lorazepam or 20 mg diazepam or midazolam, and proceed with the hydantoin of choice (usually fosphenytoin).
4. At the same time, check vitals, airway, EKG, CBC, glucose, electrolytes, AED levels, toxic screen, and ABG.
5. If seizure does not stop, add other IV anticonvulsants, such as IV valproic acid, levetiracetam, or lacosamide. These agents may be added sequentially. A neurologist should be called to evaluate the patient, and a stat EEG requested if available.
6. If seizures do not stop, the SE is considered refractory. The patient should then be intubated and transferred to the ICU for treatment with anesthetic agents such as continuous IV midazolam, propofol, pentobarbital, ketamine, or phenobarbital.
7. Spot EEG study must be converted to continuous EEG monitoring to guide pharmacotherapy for refractory SE in the ICU.
8. Central line, PICC line, and arterial lines could be considered based on the clinical scenario. The decision should be made with the understanding that it may require days, weeks, or even months to treat super-refractory SE.
9. Vasopressors may be needed to maintain adequate BP for brain perfusion under anesthetic agents to suppress SE.
10. If SE does not remit, consider using other nonstandardized treatment options (discussed in the following section).

# Treatment of Refractory SE and Super-refractory SE: Newer and Nonstandard Therapies

An estimated 23% to 43% of patients with SE have persistent seizures despite adequate treatment with benzodiazepine and one antiepileptic agent.<sup>7</sup> These patients are classified as having refractory SE (RSE), which carries a mortality of 35% and considerable morbidities.<sup>8</sup> The optimal treatment strategy for RSE remains unclear. While general anesthesia remains a conventional foundation of treatment,<sup>3</sup> multiple other pharmacological and nonpharmacological approaches have also been described. This section will elaborate on some of these treatments. None of the regimens discussed in this section are indicated for SE based on FDA-approved labeling.

FIGURE 15.1 Brief Sample Treatment Algorithm in SE



Adapted from Chen JW, Wasterlain CG. Status epilepticus: pathophysiology and management in adults. *Lancet Neurology*. 2006;5:246-56.

TABLE 15.1 Medications for Treatment of Status Epilepticus

PREHOSPITAL MANAGEMENT: "impending status epilepticus" (5 to 30 min)	
MEDICATION	DOSAGE
Diazepam rectal gel	15 to 20 mg
OR	
IV lorazepam	2 mg, may repeat once
OR	
IV diazepam	5 mg, may repeat once
OR	
IM midazolam	10-mg injection

HOSPITAL/ICU MANAGEMENT: "refractory status epilepticus," early	
MEDICATION	DOSAGE
IV valproic acid*	40 to 60 mg/kg load (at 3 mg/kg/min), only if not already given previously
AND/OR	
IV levetiracetam*	3,000 to 4,000 mg load (at 100 mg/min)
AND/OR	
IV lacosamide*	200 mg or 300 mg load (over 15 minutes)

\*These are followed by maintenance doses if desired to be continued.

INITIAL ER MANAGEMENT: "impending" (5 to 30 min) OR "established status epilepticus" (>30 min)	
MEDICATION	DOSAGE
Midazolam	10-mg IM injection (if not already given). Alternatively, 0.2-mg/kg IV bolus.
OR	
IV lorazepam	Up to 0.1 mg/kg
OR	
IV diazepam	Up to 0.25 to 0.40 mg/kg

+

IV fosphenytoin/ phenytoin*	20 to 30 mg/kg load
AND/OR	
IV valproic acid*	40 to 60 mg/kg load (at 3 mg/kg/min)

\*These are followed by maintenance doses if desired to be continued.

ICU MANAGEMENT: "refractory status epilepticus," late	
MEDICATION	DOSAGE
IV propofol	2 to 5 mg/kg load, followed by 2 to 10 mg/kg/hr infusion
OR	
IV phenobarbital	20 mg/kg load (rate not to exceed 100 mg/min), which should result in plasma level of around 20 mg/L; usually followed by maintenance dosing Q 8 hours. (Note: if patient on ventilator, serum levels >40 mg/L can be targeted if vitals are stable and SE persists.)
OR	
IV midazolam	0.2 mg/kg load, followed by 0.1 to 2 mg/kg/hr infusion
OR	
IV pentobarbital	5 to 10 mg/kg load (≤25 mg/min), followed by 0.5 to 2 mg/kg/hr infusion
AND, if still unsuccessful, consider:	
IV ketamine	1.5 mg/kg load, followed by 0.01 to 0.05 mg/kg/hr infusion

Adapted from Chen JW, Wasterlain CG. Status epilepticus: pathophysiology and management in adults. *Lancet Neurology*. 2006;5:246-56.



## Pharmacological Agents

### AEDs

In addition to standard initial medications used for SE, more recent studies have investigated the use of valproic acid, levetiracetam, lacosamide, and topiramate as adjunct therapies for RSE. Valproic acid, levetiracetam, and lacosamide have IV formulations permitting relatively rapid loading, while topiramate is available only as an enteral formulation. AEDs such as felbamate, which has NMDA-receptor-blocking properties, may also have utility in the treatment of RSE.<sup>9</sup>

Multiple characteristics of intravenous valproate make it quite desirable as a potential first-line treatment for SE, but robust, high-quality data to support this use are lacking.<sup>9,10</sup> IV valproate is rapidly loadable and differs from phenytoin, benzodiazepines, and barbiturates in that the side effects of hypotension, cardiac arrhythmias, and respiratory depression are uncommon even with rapid infusions.<sup>9</sup> While one unblinded randomized trial suggested significantly greater efficacy of valproate in the first-line treatment of SE when compared with phenytoin, methodological issues have been raised about the true clinical significance of these findings.<sup>9</sup> Another trial using IV valproate or diazepam to treat RSE, in children failing initial treatment with diazepam and phenytoin, found valproate to be as efficacious as diazepam for controlling seizures in SE; this study may also have been affected by similar methodological issues.<sup>9</sup> The efficacy of valproate has been observed in multiple types of SE<sup>10</sup> but appears to wane with delayed initiation, with maximal effectiveness possibly within the first 3 hours.<sup>9</sup> Chief side effects of valproate include potential hepatotoxicity and hematotoxicity, especially in individuals with underlying mitochondrialopathies. Induction of SE has also been reported.<sup>9</sup>

Levetiracetam has also been used in RSE with reported response rates of 65% to 70%, although the medication is not FDA labeled for this use, and the results are based on nonrandomized retrospective studies that may be subject to publication bias.<sup>9,11,12</sup> Advantages of levetiracetam include low hepatic metabolism with few drug interactions and lack of centrally depressing effects, although psychiatric side effects may occur.<sup>9,11</sup> An initial intravenous loading dose of 3,000 to 4,000 mg (or up to 50 mg/kg) is typically used,<sup>11</sup> after which initial maintenance is usually continued intravenously (bioequivalence to the enteral formulation has been demonstrated). It has been suggested by experimental models that while levetiracetam is more effective in later stages of SE, it may either be less efficacious or lack efficacy for treating acute seizures.<sup>11</sup> Thus, levetiracetam may be a very reasonable option to consider once the initial SE has progressed to early stages of RSE.<sup>9</sup>

Lacosamide is a newer agent that enhances slow inactivation of sodium channels and is approved as an adjunct AED for focal-onset seizures. Prior recent studies suggested its efficacy in the treatment of SE, though experience is limited.<sup>12</sup> A more recent comparative cohort study demonstrated higher odds of seizure control in RSE in patients receiving intravenous lacosamide.<sup>13</sup> Seizure control was achieved in 91% of patients receiving lacosamide as the last AED, suggesting that lacosamide was responsible for this effect. No adverse effect related to lacosamide occurred in this study, although angioedema on lacosamide has been described.<sup>8</sup>

Topiramate is a broad-spectrum agent whose actions include ionotropic glutamatergic AMPA-receptor blockade, which may be important for the treatment of SE.<sup>14</sup> In one observational cohort study, 71% of seizures terminated within 72 hours following the addition of enteral topiramate.<sup>14</sup> Patients received variable daily dosages ranging from <400 mg to ≥800 mg. The response rate stabilized at 67% even when topiramate was used as the fourth, fifth, sixth, or even seventh AED. No directly attributable serious adverse events occurred, though slight hyperchloremic acidosis and hyperammonemia were noted when topiramate was used in conjunction with valproate. The authors concluded that adjunct treatment of RSE with enteral topiramate was feasible and had an appropriate safety profile.

Felbamate is a medication with NMDA-receptor-blocking properties, which may be an important target in the treatment of RSE given the increase in NMDA receptors observed with continuing seizures.<sup>9</sup> Such NMDA-receptor blockade may also confer neuroprotective effects.<sup>3,9</sup> While studies in animal models of SE have been promising, data on the use of felbamate in human RSE are lacking. Potentially serious side effects such as aplastic anemia and hepatic failure may preclude its consideration as an early treatment for RSE.

Both topiramate and felbamate should be reserved only for super-refractory SE.

## CONTINUOUS ANESTHETIC AGENTS

Anesthetic agents are a mainstay of the treatment of RSE, with other AEDs also being continued during the period of continuous anesthesia. A conventional approach is to initiate anesthesia for 24 hours in RSE, and then wean the anesthetic.<sup>3</sup> If seizures recur, then the anesthetic can be reinitiated with weaning trials attempted every 24 to 48 hours. If seizures still persist upon weaning, the anesthetic can be continued for 5 to 7 days with subsequent weaning trials attempted at these intervals. There is no consensus on the optimal degree of EEG suppression during the period of continuous anesthesia, or regarding whether burst-suppression or simply seizure control should be the goal.<sup>7,12</sup>

Conventional anesthetic agents used in RSE include midazolam, propofol, and barbiturates.<sup>7</sup> While such agents at sufficient dosages ultimately control seizures, attaining these dosages may be limited by side effects, including hypotension or cardiorespiratory depression.<sup>8</sup> Midazolam is often used as a first-line anesthetic, with its otherwise short half-life (90 min) potentially increasing to 6 to 50 hours with prolonged administration or in the setting of liver disease. However, tachyphylaxis commonly occurs within 24 to 48 hours, necessitating increased dosages of this medication.

Propofol has multiple mechanisms of action that may be desirable in the treatment of RSE.<sup>7</sup> In addition, its short half-life allows the medication to be rapidly initiated and withdrawn. However, with prolonged use, propofol may also result in the potentially fatal propofol infusion syndrome (PRIS), especially in younger individuals. As a result, propofol infusions of >48 hours at rates of >5 mg/kg/hour are to be used with extreme caution, and serum lactate levels, liver and kidney function, potassium levels, creatine kinase levels, and triglycerides should be closely monitored for early detection of PRIS.<sup>7,15</sup> In addition, propofol has been demonstrated to result in neuronal apoptosis and long-term cognitive deficits with repeated exposure in some animal models,<sup>16</sup> also supporting a need for its judicious use.

Barbiturates used for RSE include pentobarbital and thiopental (not available in the United States), and it has been suggested that given their long washout periods their use be reserved for cases failing the other anesthetic agents. These considerations, as well dosing recommendations for these anesthetic agents, are discussed in detail in the excellent review by Rossetti and Lowenstein.<sup>7</sup>

Other, less standard anesthetic agents for RSE include ketamine and inhalational anesthetics such as isoflurane and desflurane. A recent retrospective multicenter study comprising 58 subjects noted permanent seizure control in 57% of RSE episodes in which ketamine was administered, with ketamine felt to have contributed to the permanent control in 32% of the total RSE episodes.<sup>17</sup> No likely responses to ketamine were noted with infusion rates <0.9 mg/kg/hr, addition of ketamine at least 8 days after SE onset, or after 7 or more AEDs had already failed. Ketamine was discontinued in 5 patients due to potential adverse events, mainly cardiac arrhythmias. The authors concluded that ketamine appeared to be relatively effective and safe for treating RSE.

Ketamine's mechanism of action as an NMDA antagonist blocks runaway excitation resulting from seizure-induced increase in synaptic NMDA receptors during SE,<sup>18</sup> and this medication has also been shown to be effective late in the course of SE in experimental models.<sup>19</sup> By contrast, the sensitivity to GABA agonists diminishes in prolonged seizures.<sup>20</sup> The paucity of cardiorespiratory effects of ketamine is another potential advantage over other anesthetic agents. Some have suggested ketamine therapy be combined with benzodiazepines to obtain synergy from the combination of NMDA antagonism and GABA agonism.<sup>7</sup> It should be noted that ketamine may have potential psychiatric side effects,<sup>8</sup> possibly related to blockade of both intra- and extrasynaptic NMDA receptors,<sup>7</sup> although the NMDA-receptor blockade may also be neuroprotective.<sup>3</sup>

Isoflurane and desflurane are considered later-line agents; they have been noted to have high rates of complications including hypotension, infection, atelectasis, paralytic ileus, and deep vein thrombosis when used in the treatment of RSE.<sup>8</sup> In addition, high rates of seizure recurrence have been noted following discontinuation of these inhalational agents.<sup>8,12</sup>

## IMMUNOMODULATION

Immunomodulation is very effective in SE mediated by anti-NMDA-receptor antibodies,<sup>21</sup> and might be considered in otherwise cryptogenic RSE, even in the absence of a clearly established immunological basis for the SE. The rationale for this is based on the increased recognition of antibody-associated SE (especially anti-NMDA-receptor antibodies)

as a relatively common etiology for SE, raising the possibility that other, still unknown antibodies may have a pathogenic role in certain cases of RSE.<sup>3</sup>

A recent study<sup>22</sup> demonstrated dramatic improvement following plasma exchange (PLEX) in patients with new-onset RSE resistant to treatments with multiple seizure medications and general anesthesia; despite extensive workup, no etiology for the SE was ultimately found in any of these patients. One approach to immunomodulation, after exclusion of infection,<sup>7</sup> may be to initiate treatment with high-dose IV steroids and then assess for response, followed by a trial of PLEX or IV immunoglobulin (Ig) if no response occurs, or a more prolonged course of steroid followed by PLEX or IV Ig, and then longer-term immunomodulatory agents such as cyclophosphamide or rituximab if response is noted.<sup>3</sup> However, the PLEX approach is a diversion from the continued management of SE with AEDs and anesthetics.

## OTHER PHARMACOLOGICAL AGENTS

Additional nonstandard pharmacological agents in the treatment of RSE include lidocaine, verapamil, magnesium infusion, furosemide, mannitol, and pyridoxine.

Lidocaine is a sodium channel modulator that can itself cause seizures at sufficient concentrations.<sup>7</sup> Multiple case reports and series have supported its use in RSE, and its efficacy has been demonstrated in pediatric populations not responding to barbiturates,<sup>23</sup> or as a rescue medication in phenytoin-resistant SE.<sup>7</sup> Cardiac monitoring is required during lidocaine administration given its potential for inducing arrhythmias.

Verapamil is a calcium channel blocker (without antiseizure effects of its own) with few case reports detailing its use in RSE.<sup>7</sup> It appears safe in dosages of up to 360 mg/day, and may act via inhibition of drug transporters, thereby improving the CNS availability of other AEDs.<sup>3,7</sup>

Magnesium infusion is frequently given in RSE associated with eclampsia even when magnesium deficiency is not present.<sup>8</sup> While magnesium blocks NMDA receptors, the published data regarding its effects on controlling RSE are extremely limited. Data on efficacy remain unconvincing even at high serum concentrations,<sup>7,8</sup> perhaps because it crosses the blood–brain barrier poorly. Moreover, high serum concentrations of magnesium can result in neuromuscular blockade and carry cardiovascular risks.

Diuretics that inhibit the neonatal form of the cation-chloride cotransporter may have a role in neonatal SE, but the evidence for their usefulness in adults is limited. An experimental study in which a single injection of 20 mg furosemide or 50 g mannitol was administered to patients undergoing surgery for intractable epilepsy<sup>24</sup> demonstrated significant decrease in both spontaneous epileptiform activity and spread of electrically evoked epileptiform activity while leaving normal electrographic activity essentially intact. The authors postulated that furosemide, which antagonizes cation-chloride cotransporter, and mannitol, which is an osmotic diuretic, exert their antiepileptic effects through alterations of electrical properties of the extracellular space, thereby conferring the potential advantage of largely sparing normal synaptic activity. These interventions may thus also be considered in persistent RSE.

Pyridoxine is a medication typically administered in super-refractory SE in the pediatric population as part of the diagnosis and treatment of pyridoxine-dependent seizures, which result from inborn errors of metabolism of pyridoxine.<sup>8,25</sup> Pyridoxine is a cofactor for glutamic acid decarboxylase (GAD),<sup>25</sup> responsible for converting excitatory glutamate to GABA. In this condition, insufficient levels of inhibitory GABA are present, thereby presumably resulting in recurrent seizures. Only isolated case reports exist pertaining to the use of pyridoxine in patients with non-pyridoxine-dependent seizures.<sup>8</sup> In these instances, the patients already had low pyridoxine levels due to other conditions and, despite initial seizure control following pyridoxine, they also received other AEDs, which raised ambiguity as to the effect of pyridoxine in seizure control. However, pyridoxine may nonetheless be an empiric consideration in super-refractory SE in adults, considering relative depletion of GABA due to the SE and the known progressive loss of GABA responsiveness in prolonged SE. Pyridoxine is typically nontoxic at regular doses in adults, but rare potential risks of infusion may include bradycardia, hypotension, and anaphylaxis (depending on the formulation), and so the patient should be monitored at least during the time of initial infusion.

## Other Treatment Options

### SURGERY

Emergency surgery has been used in RSE, provided a definite single seizure focus involving noneloquent cortex can be identified.<sup>3,7</sup>

### NEUROSTIMULATION

Neurostimulation for RSE encompasses several different modalities including vagus nerve stimulation (VNS), repetitive transcranial magnetic stimulation (TMS), electroconvulsive therapy (ECT), and deep brain stimulation. These modalities are not at all conventional, and it has been suggested that these therapies cannot be recommended, on the basis of considerable risks and lack of sufficient efficacy.<sup>8</sup> That said, acute VNS implantation with up-titration of the output current has been suggested to be effective in several cases, and while the implantation is invasive the device also permits long-term use.<sup>7</sup> Repetitive TMS is a noninvasive modality noted to have transient success for simple partial SE. However, there was loss of response after initial stimulations suggesting that TMS treatments may need to be repeated for efficacy.<sup>7</sup> While ECT itself induces seizures, treatment consisting of several daily sessions of ECT in patients with very resistant RSE was reported to result in permanent control in some patients via unclear mechanisms.<sup>7</sup> Data are limited regarding deep brain stimulation to unconventional targets in RSE,<sup>8</sup> and thus this modality is not recommended as a practical consideration at this time.

### OTHER

Several additional treatment modalities for RSE include initiation of the ketogenic diet or hypothermia. While multiple other types of therapies including drainage of cerebrospinal fluid<sup>8</sup> and the use of classical music<sup>7</sup> in RSE have been reported, these will not be discussed further due to their exceedingly small modern evidence base.

The ketogenic diet is typically implemented as chronic therapy of refractory epilepsy in pediatric populations, but it may also be used acutely in RSE, with ready-made 4:1 solutions such as KetoCal provided via nasogastric tube.<sup>8</sup> Acute initiation of the ketogenic diet may be a promising intervention in both children and adults, with effects in RSE seen within several days.<sup>7</sup> Glucose should be completely avoided at the outset, and the ketogenic diet should not be used in patients with disorders of fatty-acid oxidation.<sup>8</sup> While the precise mechanism of action of the ketogenic diet for seizure control remains a topic of debate, it has been suggested that the resultant metabolic acidosis contributes to its effects.<sup>7</sup> A dietician familiar with the ketogenic diet as well as assessments for ketonuria are needed.<sup>7</sup>

While animal models have demonstrated beneficial effects of hypothermia in SE both from electrographic and pathological standpoints, the experience in patients is not robust.<sup>7</sup> The optimal level of hypothermia is unknown, although success with mild hypothermia (31°C to 36°C) has been reported.<sup>7,8</sup> Induced hypothermia has the potential for major side effects, including electrolyte imbalances, various coagulopathies, infections, cardiac arrhythmias, and even paralytic ileus<sup>3</sup>; moreover, seizures may recur following rewarming.<sup>7</sup> Hypothermia should be reserved as adjunct, later-line intervention for RSE not responsive to medications.

## Special Considerations in the Treatment of NCSE

Complex partial SE (CPSE) is an interesting type of NCSE. Historically, an interesting case of CPSE was described in a patient named Dr. Z by John Hughlings Jackson in 1894.<sup>26</sup> Dr. Z would enter into hours of a “dreamy state,” during which he was still noted to be able to continue his work as a physician, giving diagnoses, prescriptions, and admission orders and later awakening to learn those tasks were accomplished during his dreamy state. Autopsy showed that Dr. Z had a lesion in his left uncus. Earlier, Prichard (1822) described CPSE<sup>6</sup> as “a state of epileptic ecstasy and somnambulism, patient wandering in a confused state....” A similar description was found in a patient described by Samuel Wilks (1878), “In the condition which is popularly called ‘lost’; he is scarcely conscious of acts ... continue walking in a given direction.... He is in a dreamland ... the same state as a somnambulist.”

Many different nomenclatures were used to describe NCSE: epileptic twilight state, complex partial SE, petit mal status, status psychomotoricus, and temporal lobe SE, just to name a few. Based on epidemiologic studies, NCSE constitutes from 30% to 63% of total instances of SE.<sup>2</sup> However, there is no universally accepted definition and classification of NCSE. There is still no standard for the minimal duration of nonconvulsive seizures needed to qualify as NCSE. In addition, the actual time of onset of NCSE is often difficult to determine. NCSE might encompass a component of encephalopathy, which makes it difficult to utilize a classification system that is modified from the traditional classification of seizures. Continuous EEG might be the best method to detect and make the diagnosis of NCSE, but different EEG interpreters may interpret equivocal EEG patterns differently, because there is still no conformity on what constitutes the EEG patterns of NCSE.

The most commonly seen subtypes of NCSE are complex partial SE (CPSE) and absence SE (ASE). NCSE can be further classified based on whether or not there is an associated encephalopathy with the SE.<sup>6</sup>

Because all the nonconvulsive types of SE are lumped together as NCSE, subtypes of SE span a huge spectrum ranging from the “walking wounded” in a dreamy state to patients in deep coma in the ICU. Accordingly, it is extremely difficult to recommend a standardized treatment plan that fits the clinical needs of all cases of NCSE.

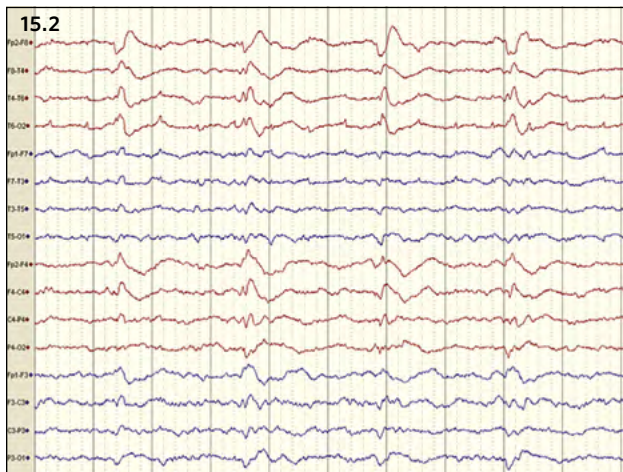
The biggest confusion occurs in cases that are refractory and super-refractory to treatment. For those refractory and super-refractory walking CPSE, it remains a conundrum as to whether induced coma with anesthetic agents is more beneficial to the patients than non-coma-inducing anticonvulsant therapy. The authors have seen cases of super-refractory CPSE in which therapy with coma-inducing anesthetic agents was ultimately discontinued with resultant return to the baseline of walking CPSE. In the authors’ speculation, these patients might have formed a very robust cerebral epileptic network that hardened structurally over a long duration of months to years to sustain the CPSE. The medical management discussed in this article might not be able to break such fortified networks with structural changes.

CPSE is not necessarily refractory to treatment. The authors have encountered patients who have a long history of intermittent CPSE but remain sensitive to benzodiazepine. Resolution of epileptic discharges on EEG can be achieved by using benzodiazepine alone without the need of airway protection. Discussion with the family members to understand their expectations is key to managing CPSE optimally in each clinical scenario.

## Continuous EEG Monitoring

Continuous EEG (cEEG) monitoring is recommended in the management of refractory and super-refractory SE for three reasons: diagnosis, guiding pharmacotherapy, and prognosis. EEG can be used to make a diagnosis of NCSE or confirm the clinical diagnosis of convulsive SE. In addition, it can provide localizing information pertaining to the seizure focus. During the treatment of refractory and super-refractory SE, cEEG can be used to guide pharmacotherapy. Specific EEG patterns may have prognostic value in SE patients. For instance, prominent discontinuous patterns or nonreactivity could imply poor prognosis.<sup>27</sup> A few examples of cEEG findings in SE are demonstrated in FIGURES 15.2, 15.3, and 15.4.

cEEG is crucial in the detection and diagnosis of NCSE. A review of 236 patients monitored by cEEG as part of their coma evaluation showed that 8% of the patients in the series had NCSE.<sup>28</sup> In 570 consecutive critically ill patients monitored with cEEG, 19% of the patients were found to have electrographic seizures, and of these patients 92% had exclusively nonconvulsive seizures.<sup>29</sup> In 124 critically ill neurological patients with cEEG, 35% of the patients had nonconvulsive seizures and of these 76% were considered to have NCSE.<sup>30</sup>

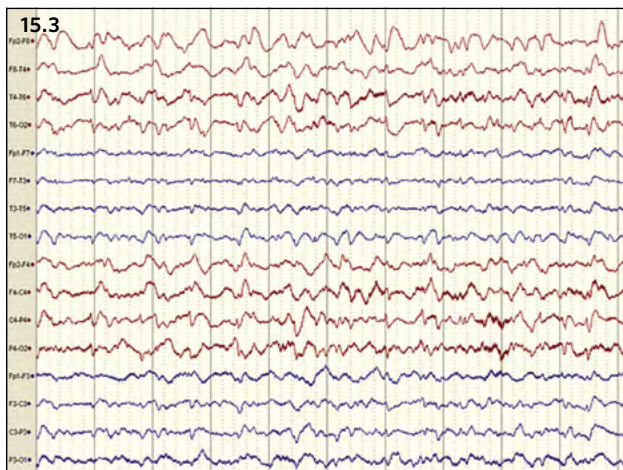


**FIGURE 15.2 Periodic Lateralized Epileptiform Discharges (PLEDs)**

The patient is a 60-year-old man with a history of end-stage renal disease on hemodialysis, coronary artery disease status-post recent STEMI and PCI to right coronary artery, ischemic cardiomyopathy with ejection fraction of 25%, and peripheral artery disease status-post recent thrombolysis for left lower leg. He presented to ER with generalized malaise over the past several days and had a seizure. He was later intubated and treated with propofol and other anticonvulsants.

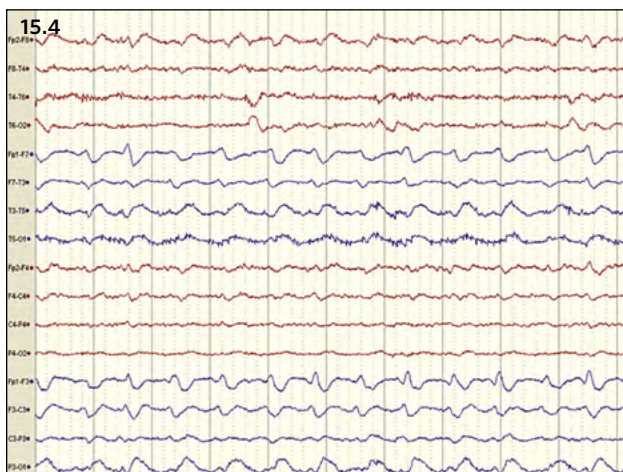
The EEG shows very frequent periodic, focal, lateralized sharp and slow-wave discharges in the right hemisphere with a right temporal lobe focus. These epileptiform discharges (PLEDs), when intense, spread to the left hemisphere as shown here and in FIGURES 15.3 and 15.4.

EEG Setting: Low-Frequency Filter 1 Hz, High-Frequency Filter 70 Hz, Timebase 30mm/sec, Bipolar "Double Banana" montage.



**FIGURE 15.3 Right Temporal Seizure**

The EEG shows the intermittent transformation of the PLEDs (as in FIGURE 15.2) into electrographic seizures with a right temporal lobe focus.



**FIGURE 15.4 Left Hemisphere Seizure**

Evolution of the PLEDs over the left hemisphere was noted with faster rhythms, higher amplitude and more prominent posterior spread when compared with FIGURE 15.3. These activities are likely seizures predominantly over the left hemisphere arising from the PLEDs.

# Team Approach for Managing Refractory and Super-refractory SE

The optimal setting for the management of refractory and super-refractory SE is in the neuro ICU, by a team led by a neurointensivist who is also board certified in EEG interpretation. However, at the present time, most VA medical centers do not have dedicated neuro ICU. In addition, most critical care neurologists do not have adequate training to read cEEG. At the WLA VA Medical Center, as in many other VA medical centers, refractory and super-refractory SE are managed by collaborative efforts among the ICU team, the inpatient neurology team, and the EEG/epilepsy team. The ICU team is in charge of the critical care component, the neurology team is in charge of managing the treatment for SE, and the EEG/epilepsy team is responsible for providing daily cEEG interpretation. In addition, at WLA VA Medical Center, the clinical neuropharmacists are closely involved in managing each case of refractory and super-refractory SE.

In this setting, we have observed several principles necessary for making this collaborative effort work:

1. Clear leadership from the neurology team on actively managing the SE
2. Daily cEEG interpretation early in the day, with the EEG findings conveyed to the neurology team in person; cEEG should be reviewed quickly after each change of pharmacotherapy
3. An ICU team responsive to the directives of the neurology team, such as promptly instituting major changes of pharmacological treatment during the day to avoid undetected BP drops due to new medications started in the middle of the night
4. An unremitting sense of urgency and willingness to move on to new treatments if SE continues
5. A complete neurological examination performed on a daily basis to facilitate detection of new stroke, anoxia, critical care myopathy or neuropathy, or other signs that could indicate complications during the treatment of SE
6. Good communication among the care providers, with conveyance of messages to the family with a unified voice

## Long-term Outcome after Successful Treatment of Refractory and Super-refractory SE

There are no good prospective data to show the long-term outcome after a successful remission of SE. The surviving patients are commonly noted to be encephalopathic long after the remission of refractory SE. However, several lines of evidence show that good outcomes can be achieved even after over 7 days of refractory SE. A recent study showed that 66% survived to discharge, with 10% of patients achieving a good outcome without significant disability, and 8% with only mild disability.<sup>31</sup> However, all patients with good outcomes were younger than 70 years old. A recent meta-analysis showed that 35% of patients returned to baseline.<sup>8</sup> The authors believe that a constant awareness of neuroprotection during the treatment of SE—by maintaining adequate cerebral perfusion, suppression of epileptiform discharges, and including drugs that might have neuroprotective effect in the regimen, such as drugs with mechanism in blocking the glutamate receptors—might be important in achieving a good long-term outcome.

## Withdrawal of Support or Comfort Care

Withdrawal of support or comfort care might be indicated in certain cases. For instance, if the patient is in super-refractory SE but cannot maintain adequate blood pressure with a coma-inducing anesthetic agent, even with high dose of vasopressors, comfort care might be indicated. If the Veteran has no family, consultation with the bio-ethics committee is required. On the other hand, a protracted treatment course alone should not be the ground for discontinuation of

treatment with anesthetic agent. Even for SE that lasts for weeks or longer, if the patient has relatively normal neuroimaging, is younger than 70 years old, and has no other major life-threatening medical conditions, it is advised to continue the treatment. Whether to withdraw support and only provide comfort care should be evaluated carefully, case by case, based on the patient's advance directives, long-term outcomes, and family's expectations. A consultation with the bioethics committee should be sought in equivocal cases.

## Conclusion

SE is a medical emergency with high morbidity and mortality, especially in the elderly. A transformation, not fully understood, occurs in the brain that makes it proconvulsant and hyperexcitable. SE can quickly develop pharmacoresistance to most if not all pharmacological agents, including anesthetics. Early treatment, including prehospital management with IV, IM, or rectal benzodiazepine by paramedics, and a quick response in the emergency room following an SE treatment protocol, is crucial to abort SE in the impending phase, before it is fully established. Once SE is established, the treatment often requires transfer to the ICU, with continuous EEG monitoring and ventilation support. SE can easily become refractory or super-refractory. Vasopressors may be needed due to tendency of anesthetics to cause cardiovascular suppression and hypotension. A well-organized team approach among the members of the ICU, neurology, EEG/epilepsy specialists, and the clinical neuropharmacist is crucial to manage refractory and super-refractory SE successfully.

On a special note, whether to aggressively treat super-refractory CPSE should be decided case by case. Due to the general poor outcome, especially in the elderly, withdrawal of support for comfort care might be considered for certain cases, but this requires a stringent process, including consultation with the bioethics committee. A protracted treatment course alone, even after weeks or months of treatment, should not constitute grounds for discontinuing treatment. Although less likely, good long-term outcome with no significant disability may still occur in super-refractory SE after a remission of SE. ■

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# SUDEP and Other Risks of Seizures

**JOSÉ E. CAVAZOS**



# Introduction

Patients with recurrent seizures have an increased risk for accidental injury and/or fatality as well as an increased risk for sudden unexplained death. Sudden unexplained death in epilepsy (SUDEP) accounts for up to 17% of all cases of death in people with epilepsy, which increases the rate of sudden death by 2.3 compared with the general population.<sup>1</sup> SUDEP is defined as an unexpected death in a person who has epilepsy with no other obvious cause of death.<sup>1</sup>

The importance of discussing SUDEP, and other accidental risks of seizures, with people with epilepsy is that these potential risks are a major drain on their quality of life, by creating barriers for independent living, employment, and self-esteem, as well as other social impacts.<sup>2</sup> Seizures are unpredictable in occurrence. It is their unpredictability that casts a shadow in the minds of people with epilepsy, and places limitations in their activities. The existence of these potential risks must be discussed frankly with the patient and family to encourage adherence to medical treatment—increased seizure frequency and the presence of convulsions are associated with SUDEP. In addition, epileptologists often discuss these risks when surgical interventions are being considered, because the continuing risk for SUDEP, and other accidental morbidities associated with recurrent seizures, might resolve with a successful curative epilepsy surgery, or these potential risks persist if the patient declines surgical intervention or the surgery is not successful.<sup>3</sup> In a sense, the potential risks for injury or mortality is what offsets the surgical risk for potentially curative epilepsy procedures.

## Definitions

SUDEP is defined as an unexpected death in a person who has epilepsy with no other obvious cause of death.<sup>1</sup> Usually, the victim was in relatively good health, and the death may or may not be caused by seizure. If postmortem examination is obtained and no evidence for other causes of death is found, the case is considered definite SUDEP. If the occurrence meets all above criteria, but autopsy was not performed, then it is considered probable SUDEP. Over the last two decades, there has been increased interest in SUDEP, but the literature consists primarily of epidemiological studies and case reports. Only recently, experimental models revealed compelling details about potential mechanisms of SUDEP, beginning to broaden our limited understanding of the pathogenesis and mechanisms of SUDEP, as well as offering hope to prevent its occurrence.<sup>2</sup>

## Risk Factors for SUDEP

The most consistent risk factors for SUDEP are<sup>4</sup>:

- Poor compliance with antiepileptic medication
- Young age (>40 years of age)
- Early age of onset of seizures (>5 years of age)
- Increased refractoriness of epilepsy
- Presence of generalized tonic-clonic (GTC) seizures
- Male
- Prolonged postictal suppression in the EEG

In recent years, there has been concern that several medications and/or devices for epilepsy are associated with an increased incidence of SUDEP.<sup>5</sup> A major confounder on the data is that randomized, controlled trials are performed in people with refractory epilepsy in whom multiple anticonvulsants have failed to offer seizure control. The FDA has now required obtaining information about frequency of SUDEP for several medications and devices. Warnings about SUDEP have been included in the FDA packet inserts for lamotrigine, topiramate, and the vagal nerve stimulator. However, the rates of SUDEP observed during the treatments with these medications or device are within the published frequency of SUDEP expected for the population of refractory epilepsy patients, who are the subjects of these randomized, controlled studies.

## Epidemiology

Studies have shown that the incidence of SUDEP is about 0.5 per 1,000 patient-years (1 in 2,000 per year).<sup>6</sup> This is about 2.3 times higher than the rate in the general population, a risk often called standardized mortality ratio (SMR).<sup>6</sup> Patients with refractory epilepsy in whom at least 3 anticonvulsants have failed to yield seizure control have an incidence of SUDEP of 4.0 per 1,000 patient-years (1 in 250 per year), and the risk of SUDEP can be as high as 9.3 per 1,000 patient-years (1 in 100 per year) for patients with medically intractable epilepsy who were epilepsy surgery candidates.<sup>6</sup> Remarkably, those patients who undergo successful curative epilepsy surgery experience a normalization of the rate of sudden death that is indistinguishable from the general population.<sup>3</sup>

## Pathophysiology

There are several proposed pathophysiological mechanisms of SUDEP, including ictal arrhythmias, ictal or postictal central apnea, acute neurogenic pulmonary edema, and autonomic dysregulation.<sup>7</sup> Case reports for each potential mechanism have been described, but there is lack of a unifying mechanism for SUDEP.<sup>8-10</sup>

Central apnea and acute neurogenic pulmonary edema have been documented by clinical and postmortem observations in humans with SUDEP.<sup>11-13</sup> Ictal oxygen desaturation has been observed in about one third of patients with intractable epilepsy in the EMU, and hypoventilation in two case reports of SUDEP with physiological monitoring in the EMU.<sup>9,10</sup> Several types of ictal arrhythmias including third-degree atrioventricular block and ventricular tachycardia have also been described.<sup>14</sup>

Studies in experimental models of intractable epilepsy have suggested that brainstem centers involved in the neural regulation of autonomic and cardiorespiratory reflexes are likely involved in the pathophysiology of SUDEP.<sup>7</sup> A potentially important observation is that the presence of serotonin reuptake inhibitors such as fluoxetine confers protection from SUDEP in an audiogenic-evoked seizure model of epilepsy.<sup>7</sup> The NIH recently convened a workshop on SUDEP to focus research efforts and determine benchmarks for further investigations.

## Other Risks of Epileptic Seizures

Patients with seizures are exposed to other risks for accidental morbidity and mortality.<sup>6</sup> Most of these risks stem from the occurrence of seizures that have an impairment of consciousness or loss of motor control while the patient is in a precarious situation. The major problem for patients with seizures is the unpredictability of the next seizure.

Trauma is not uncommon among people with GTC seizures.<sup>6</sup> Injuries such as ecchymosis, hematomas, abrasions, and tongue, facial, and limb lacerations often develop as a result of the repeated tonic-clonic movements. Atonic seizures are also frequently associated with facial and neck injuries. Worldwide, burns are the most common serious injury associated with epileptic seizures. Accidental death is most often associated with drowning, and occasionally with driving motorized vehicles.

To prevent injury, educate patients who have lapses of consciousness during wakefulness, and in whom seizures are suspected, about seizure precautions. Most accidents occur when patients have impaired consciousness. This is one of the reasons for restrictions on driving, swimming, taking unsupervised baths, working at significant heights, and the use of fire and power tools in people who have epileptic seizures and other spells of sudden-onset seizures.

The restrictions differ for each patient because of the individual features of the seizures, the degree of seizure control, and, in the United States, state laws. Other countries have more permissive or more restrictive laws regarding driving. Check the local laws for driving before making recommendations.

The Epilepsy Foundation of America has a large library of educational materials available to healthcare professionals and the general public. The American Epilepsy Society is the professional organization of people who take care of patients with epilepsy, and its website provides a large amount of credible information for the public and physicians.

# Seizure Precautions

Clinicians should discuss five types of seizure precautions with patients who have epileptic seizures and other sudden-onset spells:

- Driving
- Heights
- Working with fire or cooking
- Using power tools
- Water (eg, unsupervised baths or swimming)

These lifestyle precautions are clearly more applicable to some patients than others. Clinicians should be documenting in the patient's chart that driving and occupational hazards for people with seizures were discussed. In some parts of the United States, clinicians must notify the Department of Motor Vehicles of patients who are still driving with seizures. Unfortunately, this requirement can have an impact on the open communication of possible spells by patients.

Safety must be balanced with the risk for seizures. A patient with many poorly controlled, diurnal seizures may need to exercise more caution than a patient who has only nocturnal seizures. Encourage the use of helmets to prevent head trauma while the patient is biking, skiing, riding a motorcycle, or participating in other activities.

The restrictions differ for each patient because of the individual features of the seizures; the degree of seizure control; and, in the United States, state laws.

## Driving Motorized Vehicles

Recommendations vary depending on state laws and on whether the patient has seizures that occur exclusively during sleep. Consult current state and federal laws and regulations. For example, to resume commercial driving across state lines, a patient must have a 5-year seizure-free period. Other countries have more permissive or more restrictive laws regarding driving. Physicians should be aware of the local regulations regarding driving, which vary considerably among states and nations. The recommendation for driving cars and trucks extends to the operation of other motorized vehicles, such as boats, motorcycles, and snowmobiles. Commercial aircraft pilots are typically no longer permitted to fly.

## Water Precautions

Common sense dictates that patients who have seizures should not swim alone, and they should be in the presence of an adult lifeguard or other adults who can pull them out of the water if needed. Wearing a life jacket in a boat is important. Activities as simple as taking a bath may be risky, because a patient can drown with as little as an inch of water during the flaccid postictal phase. Leaving the bathroom door unlocked may limit a patient's sense of independence, but it is a recommendation that should be discussed. Accidental drowning has an SMR in epilepsy patients of 8.2 times that in the general population.<sup>6</sup> In addition, patients with seizures can suffer hot-water burns as they might turn up the hot water first, while waiting for the water to warm up or during the seizure.

## Heights, Fire, and Power Tools

Patients with seizures might experience an episode in situations such as trying to fix a roof or during another activity at a considerable height. Inquiring about occupation is important—construction workers, house painters, and tree-branch cutting could expose people with epilepsy to unnecessary risks. In addition, burns from injuries related to cooking are not uncommon. The SMR for fatal accidents with fire or burns in people with epilepsy is 10.3 times that in the general population.<sup>6</sup> Injuries can also occur with the use of power tools, when people continue to hold or grab these tools while suffering. Adult supervision is advised when power tools are used, and the use of safety devices, such as automatic shutoff switches, is recommended.

# Conclusion

Seizures occur unpredictably. Despite their brief duration, this unpredictability is a major source of disability and loss of personal independence. Open discussion about risks of accidental morbidity and mortality is essential.<sup>15</sup> Discuss these five seizure precautions with patients: driving, heights, water, fire, and power tools. SUDEP must be discussed with patients, not least in order to encourage compliance with anticonvulsant treatments. ■

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# Post-traumatic Seizures

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# Introduction

An estimated 1.7 million people each year sustain a TBI, including 52,000 deaths and 275,000 hospitalizations, with the remaining 80% treated and released from emergency departments. Among the survivors of TBI, a sizable number remain with important medical and neurological sequelae, including seizures and epilepsy.<sup>1</sup>

## Definitions

An epileptic seizure is a clinical manifestation presumed to result from an abnormal and excessive discharge of a set of neurons in the brain. The clinical manifestation consists of sudden and transitory abnormal phenomena, which may include alterations of consciousness, motor, sensory, autonomic, or psychic events, perceived by the patient or an observer. Epilepsy is a condition characterized by recurrent (two or more) epileptic seizures, unprovoked by any immediate identified cause.

Post-traumatic epilepsy (PTE) is a disorder characterized by recurrent late seizure episodes, not attributable to another obvious cause, in patients with TBI. Post-traumatic seizures (PTS) denote a single or recurrent seizures occurring after TBI and are commonly classified into early (less than 1 week after TBI) and late (more than 1 week after TBI).

## Precipitants

Seizures occurring among patients with TBI may be the result of precipitants unrelated to mechanisms currently linked with post-traumatic epileptogenesis. Seizure precipitants have been defined as any endogenous or exogenous factor that promotes the occurrence of epileptic seizures. Examples of seizure precipitants among patients with TBI include hydrocephalus, sepsis, hypoxia, metabolic abnormalities, and mass-occupying lesions. Among epileptic patients, more than half cite precipitants among recurrent seizures they experience.<sup>2</sup>

Drugs—including alcohol, prescribed psychotropic agents, and recreational/illicit drugs—are common seizure precipitants among patients with TBI. Antidepressants are implicated with increased seizure occurrence, including tricyclic agents and immediate and sustained-release formulations of bupropion. SSRIs appear to be relatively safe and are the drugs of choice for patients with comorbid epilepsy and depression.<sup>3</sup> Certain antipsychotic drugs, including newer atypical antipsychotic agents, particularly clozapine, may induce EEG abnormalities and seizures. Antibiotics, particularly imipenem and quinolone agents, have been associated with seizures. Seizure risk is generally elevated among critically ill patients, and proper dose adjustment for renal clearance may mitigate much of the risk attributed to antibiotic administration. Bromocriptine and amantadine, used to treat impaired arousal after TBI, have been implicated as seizure precipitants, although this association presently appears to be largely anecdotal. Recreational and illicit stimulants with well-known seizure-inducing properties include cocaine. Amphetamine and related drugs rarely induce epileptic seizures at therapeutic doses. Opioid analgesics, especially meperidine, have been implicated in lowering the seizure threshold.<sup>4</sup>

## Classification

Seizures and epilepsy are classified according to their clinical and electroencephalographic characteristics, as developed by the Commission on Classification and Terminology of the ILAE. This classification is currently undergoing revisions. Seizures can be divided into two categories, based primarily on pattern of onset. These include partial focal seizures and generalized seizures. Generalized seizures denote those that are bilaterally symmetrical in origin without apparent focal onset. The most commonly recognized example is the generalized tonic-clonic (GTC) or generalized convulsive seizure. Generalized-onset seizures or focal-onset seizures with secondary generalization are reported in approximately half of patients with PTS, and appear more frequently in patients with nonpenetrating TBI and among children.<sup>5</sup>

Partial or focal seizures originate in a localized area of one cerebral hemisphere. Focal seizures are further classified according to whether consciousness is maintained. In simple partial seizures (SPS) consciousness is maintained, whereas it is impaired in complex partial seizures (CPS). In the revised classification, these terms are being replaced by the more descriptive terms of focal seizures associated with alteration of consciousness for CPS, and focal seizures (motor, sensory, psychic, and other seizures), without alteration of consciousness, for SPS. Characteristics of both vary, depending on the location of the seizure activity within the brain. Twelve percent of focal seizures with alteration of consciousness in the general population may be attributable to TBI. Focal-onset seizures are observed in slightly more than half of all patients with PTS, and appear more frequently in adults, patients with early seizures, focal lesions on CT, penetrating TBI (PTBI), and nonpenetrating TBI of greater severity. Seizure evaluations that incorporate video (video EEG) are more likely to detect subtle clinical signs that may indicate focal-onset PTS.

Epilepsy and seizures can be characterized by their underlying etiology, and fall into three categories: genetic, structural/metabolic, and unknown.<sup>5</sup> Genetic epilepsy is the direct result of a known or presumed genetic defect. Previously, genetic epilepsies were known as idiopathic. Structural/metabolic epilepsies, also known as symptomatic epilepsies, are considered to be the consequence of a known or suspected disorder of the central nervous system, such as TBI, stroke, or infection. Recurrent late post-traumatic seizure, or post-traumatic epilepsy, is a common and important type of structural epilepsy, accounting for 20% of all lesional epilepsies in the general population. Structural/metabolic epilepsies comprise syndromes of great individual variability, based mainly on seizure type and anatomic localization. Epilepsies are designated as cryptogenic or “unknown” when the nature of the underlying cause is not yet known.<sup>5</sup>

## Manifestations of Post-traumatic Seizures and Epilepsy

Seizures may present with a variety of manifestations, including cognitive, behavioral, and affective changes that may not be attributed to an underlying epileptic disorder. Patients with severe TBI may exhibit cognitive, behavioral, and affective sequelae that potentially confound attribution of episodic behavioral changes to an underlying epileptic disorder. The varied semiology of seizures that originate in the frontal or temporal lobes, and their associated ictal or postictal alteration of consciousness, justify their consideration in the differential diagnosis of any TBI patient with episodic (especially stereotypic) changes in mental status. Given the propensity of TBI contusion localization to the frontal and temporal lobes, it is not surprising that these regions are the most frequent sites of origin for video-EEG-verified partial onset PTE. Presumed or pathologically confirmed post-traumatic seizure foci, however, have been described in all major lobes of the brain.<sup>6</sup>

Patients with frontal lobe epilepsy may exhibit complex, semipurposeful, complex motor automatisms such as kicking, screaming, and thrashing episodes. Frontal lobe interictal and postictal manifestations also include cognitive or affective symptoms, such as confusion, anger, hostility, and hallucinations. Complex partial seizures of temporal lobe origin may also present with emotional symptoms such as fear or panic, followed by periods of postictal confusion and amnesia. Seizure-related aggression, however, is rare. It is usually associated with postictal confusion, particularly while the patient is being restrained. Reports of aggression are more frequent among epileptic patients, particularly with younger age, male gender, psychopathology, and prior brain injury. Conventional interictal scalp EEG may of limited diagnostic value in such cases. In these instances, video EEG may be indicated to make the diagnosis.<sup>6</sup>

The presence of focal motor, sensory, or language deficit of new onset should alert the clinician to the possibility of a recent unwitnessed PTS. Todd's postictal paresis (PP) is defined as a transient focal deficit that may follow a seizure of focal onset. It is a recognized postictal manifestation of PTS and does not reflect permanent structural damage but rather represents transient postictal disruption of function that typically resolves within 24 to 48 hours. In one video-EEG study, PP was found in 13.4% of patients and was always unilateral and contralateral to the seizure focus. The duration of the PP ranged from 11 seconds to 22 minutes.<sup>7</sup>

Psychogenic nonepileptic seizures (PNES), often called pseudo-seizures or psychogenic seizures, refers to episodic behavioral events that superficially resemble epileptic attacks but are not associated with paroxysmal activity within the brain. PNES must be differentiated from other nonepileptic events such as syncopal episodes and cardiac events. PNES is not uncommon in neurologic settings, and may coexist with epileptic seizures in patients with epilepsy. The differentiation between nonepileptic and epileptic seizures cannot be made on the basis of clinical characteristics alone. EEG monitoring, particularly with video, is often helpful in establishing a diagnosis. Postictal prolactin (PRL) measurement may provide additional diagnostic information if significant elevations are observed, suggesting that an epileptic seizure has occurred within 1 hour. The utility of this test to discriminate between epileptic seizures and PNES has been questioned, however, as a subset of patients with video-EEG-documented PNES have also been reported to experience an increase in PRL, particularly if the sample is obtained within 10 to 20 minutes of a suspected PNES.<sup>6</sup> While recognized to occur among patients with TBI, relatively few studies address post-traumatic PNES. Hudak et al reported that one third of patients with moderate-to-severe TBI undergoing video EEG for diagnosis of epilepsy were found to have PNES. When nondiagnostic video-EEG studies were excluded, patients with NES comprised 40% of the TBI sample.<sup>8</sup> Barry et al described the characteristics of 16 patients thought to have PTS, who actually had PNES, as confirmed on video-EEG monitoring. Patients with PNES were characterized by injuries of much milder severity, although the disability associated with the PNES was pronounced. The patients usually had manifestations of other conversion disorders as well, and psychiatric histories that preceded the TBI.<sup>9</sup> In a study comparing Veterans and civilians admitted to the EMU, PNES was identified in 25% of Veterans and 26% of civilians. Fifty-eight percent of Veterans with PNES were thought to have seizures related to TBI. In the Veteran group, PNES was the single most common discharge diagnosis and more common than the discharge diagnosis of epilepsy. Post-traumatic stress disorder (PTSD) has also been shown to be a significant risk factor for developing PNES.<sup>10</sup>

## Epidemiology of Post-traumatic Seizures

TBI is an important cause of epilepsy, accounting for 20% of structural epilepsies observed in the general population, and 5% of all epilepsy. TBI is the leading cause of epilepsy in young adults. Many studies addressing the relationship between TBI and epilepsy came from observations of Veterans sustaining PTBI on the battlefield. Studies in civilian settings generally appeared later and reflect a larger patient population with nonpenetrating TBI. The observed results vary, reflecting differences in inclusion and exclusion criteria, methods for evaluation and description of seizure phenomena, attention to confounding variables, duration of follow-up, and patient population. Nevertheless, these studies provide useful information regarding the incidence, risk factors, and natural history of PTS/PTE.<sup>6</sup>

In summary, the overall incidence of late seizures in hospitalized patients following non-penetrating TBI is approximately 4% to 7%, varying with the injury and patient characteristics. Late seizures are observed less frequently among children. The incidence of PTS among patients with nonpenetrating TBI observed in the rehabilitation setting appears substantially higher than that reported in other civilian settings, approximately 17%. This is probably a reflection of the increased severity of injury and concurrence of multiple risk factors encountered among inpatients in these settings. In contrast, the incidence of seizures among adults after mild TBI is slightly greater than that observed in the general population. PTS will be observed in approximately 35% to 65% of patients with PTBI.<sup>6</sup>

The incidence of early seizures is approximately 5% among all patients with nonpenetrating TBI and is higher in young children, among whom the incidence is approximately 10%. However, continuous EEG monitoring of patients with severe TBI in the ICU suggests that the incidence of early convulsive and nonconvulsive PTS may be considerably higher than initially believed, approximately 22%. Immediate seizures, which make up 50% to 80% of early post-traumatic seizures (EPTS), are more frequent among children with severe TBI. EPTS are occasionally observed among children with mild TBI, but are comparatively much less frequent among adults with mild TBI. Early seizures among these adults warrant investigation for an underlying intracranial hemorrhage.

Approximately one half to two thirds of patients who suffer PTS experience seizure onset within the first 12 months, and 75% to 80% by the end of the second year following the trauma. After 5 years, adults with mild TBI do not appear to have a significantly increased risk relative to the general population. However, patients with moderate or severe TBI and PTBI continue to remain at an increased risk of developing PTS many years after the injury.

Seizure recurrence is a crucial factor in determining subsequent disability and quality of life (QOL). Increased seizure frequency significantly correlates with lower employment rates, increased healthcare costs, and lower measures of QOL. Recent studies addressing late post-traumatic seizure (LPTS) recurrence indicate that many patients with severe TBI continue to experience recurrent seizures. Semah et al investigated the relationship between prognosis for seizure recurrence and the etiology of epilepsy.<sup>13</sup> Among 50 patients with remote symptomatic (lesional) epilepsy with history or radiographic evidence of TBI, only 30% of those with partial epilepsy experienced seizure-free durations of greater than 1 year without recurrence. Haltiner and colleagues followed 63 adults with moderate or severe TBI, who developed LPTS during the course of participation in a randomized, placebo-controlled study of the effectiveness of phenytoin prophylaxis for prevention of LPTS.<sup>11</sup> The cumulative incidence of recurrent late seizures was 86% by 2 years. However, 52% experienced at least 5 late seizures, and 37% had 10 or more late seizures within 2 years of the first late seizure.<sup>11</sup>

Pohlmann-Eden published results of a PTE study population derived from a tertiary referral epilepsy clinic.<sup>12</sup> Fifty-seven patients with PTE were compared with 50 age- and sex-matched control patients with severe TBI. Of all PTE patients, 35% became seizure-free (no seizures within the last 3 years), 3.5% without any treatment. Twenty-one percent experienced more than 1 seizure per week. The most important risk factors for poor seizure control were missile injuries, “combined seizure patterns,” high seizure frequency, AED noncompliance, and alcohol abuse.

In summary, recent evidence suggests that while patients with EPTS experience a late seizure in 20% to 30% of cases, seizure onset after the first week is associated with a much higher likelihood of seizure recurrence. Seizure frequency within the first year after injury may be predictive of future recurrence, particularly with PTBI. Persistent PTS may be more common in focal seizures, and less common in generalized seizures. Immediate post-traumatic seizures (IPTs) are generally believed to carry no or little increased risk of recurrence. On the other hand, between one fifth and one third of patients with LPTS experience frequent recurrences, apparently refractory to conventional AED therapy. Some of these patients may be helped with surgical intervention.<sup>11</sup>

## Complications and Consequences of PTS

Potentially significant complications accompany seizures in the patient with TBI. Recurrence of seizures is an important cause of nonelective hospitalization and death among patients with severe TBI. Among patients with newly diagnosed or chronic structural epilepsy, persistent seizures are associated with increased mortality, particularly among individuals with status epilepticus (SE) or generalized convulsions. An appreciation of these potential complications is useful when evaluating risk/benefit relationships for decisions regarding AED therapy.

Manifestations of PTS include cognitive and behavioral dysfunction. Evidence of cognitive impairment may occur or persist during the interictal state, when the patient is not actively manifesting seizures. Persistent behavioral abnormalities and a significantly higher incidence of psychiatric-related hospitalizations have been noted among patients with PTS when compared with nonepileptic controls with PTBI. Mazzini et al found that disinhibited behavior, irritability, and aggressive behavior were significantly more frequent and severe among rehabilitation inpatients with PTE, when compared with TBI patients without seizures.<sup>14</sup>

Recurrent PTS may exert an adverse impact upon functional status among adults and children with TBI, independent of that attributable to the severity of injury. Among patients with PTBI in the Vietnam Head Injury Study, PTS was one of seven impairments that independently and cumulatively predicted employment status.<sup>15</sup> PTS and increasing brain volume loss have been noted to exert independent and profound effects on cognitive performance among patients with restricted frontal lobe lesions due to PTBI.<sup>16</sup>

However, studies among patients with nonpenetrating TBI less clearly discriminate the influence of seizures on functional prognosis and cognition from those of injury. Haltiner examined the relationship of LPTS to neuropsychological performance and aspects of psychosocial functioning.<sup>17</sup> While patients with LPTS demonstrated greater impairment than those without seizures, after adjusting for injury severity, there were no significant differences in outcome at 1 year as a function of seizures. The authors concluded that poorer outcomes encountered among patients with PTS 1 year after injury reflect the severity of injury and not the effects of LPTS per se. Asikainen noted that patients with PTS had poorer outcome as measured by the Glasgow Outcome Scale (GOS), a gross global outcome measure, but no significant differences in employment outcome when compared with nonepileptic patients with TBI.<sup>18</sup> Mazzini also found that PTS correlated with significantly poorer outcome, as measured by the GOS, disability rating scale, functional independence measure, and subscales of the neurobehavioral rating scale at 1 year after severe TBI.<sup>19</sup>

SE is the most clinically significant manifestation of PTS, and carries the greatest risk of adverse outcome. The Working Group on Status Epilepticus defines SE as more than 30 minutes of continuous seizure activity or two or more sequential seizures without full recovery of consciousness between seizures. More recent publications define SE as seizures that persist for shorter durations, based upon estimates of the duration necessary to cause injury to central nervous system neurons.<sup>20</sup> Because the duration of most seizures is generally no longer than 3 minutes, it is felt that treatment for SE should be instituted after 5 to 10 minutes of continuous seizure activity. SE must be distinguished from other terms describing multiple seizure episodes, including serial seizures and acute repetitive seizures. Serial seizures are two or more seizures occurring over a relatively brief period (minutes to many hours) but with the patient regaining consciousness between the seizures. Acute repetitive seizures are clusters of seizures that appear to increase in frequency or severity over a short time. Acute repetitive seizures may become SE, but the frequency of this occurrence is unclear.

Clinical manifestations of SE vary, and may include clinically obvious tonic-clonic movements, or small amplitude twitching movements of the eyes, face, or extremities. Some patients have no observable repetitive motor activity, and the detection of SE requires EEG. Studies employing continuous EEG monitoring suggests that NCSE may not be rare, occurring in perhaps as many as 6% of patients with severe TBI despite “therapeutic” levels of AED prophylaxis. Moreover, SE among patients early after TBI is associated with a very high mortality risk. SE is usually attributable to another cause, such as AED withdrawal, acute systemic or neurologic injury (such as anoxic encephalopathy or stroke), sepsis, metabolic derangements, or a combination of these conditions. Deaths associated with SE are usually attributable to the disorder that precipitated it, comorbidities, and the age of the patient.<sup>21</sup>

Sudden unexpected death in epilepsy (SUDEP) accounts for 18% of all deaths among patients treated in major epilepsy centers. SUDEP can be defined as a sudden unexpected death in people with epilepsy occurring in the absence of an obvious medical cause.<sup>22</sup> Walczak noted that occurrence of tonic-clonic seizures, treatment with more than two AEDs, and full-scale IQ less than 70 are independent risk factors for SUDEP.<sup>23</sup> Tonic-clonic seizure frequency may be a risk factor, but only in women. In summary, sequelae associated with isolated LPTS are comparable to those found in any seizure. Isolated or infrequent late seizure episodes are generally associated with relatively little risk. Increasing frequency and severity of seizure disorders, including SE, carry greater associated risks of increased morbidity or mortality, and worsened cognitive and functional prognosis.

## Blast Neurotrauma

TBI is considered the “signature injury” of the wars in Iraq and Afghanistan. Improvements in body armor and the ability to quickly evacuate wounded soldiers from the battlefield resulted in better survival rates, even for those who suffered from TBI. Many of the casualties were caused by an explosive blast, usually secondary to an improvised explosive device (IED). In Operation Enduring Freedom (OEF) and Operation Iraqi Freedom (OIF) blast injuries accounted for an estimate >60% of combat injuries. Blast TBI (bTBI) may also be associated with secondary, tertiary, and quaternary blast effects that may also contribute to a patient’s presentation. The precise mechanisms of primary bTBI remain unknown and the current understanding is incomplete.<sup>24</sup> The incidence of seizures in this population is not known and is currently the subject of ongoing research.

# Risk Factors for PTS Development

Methods have been proposed to improve identification of those patients at risk for PTS development, and therefore with most to gain from its prevention or potential recurrence. These include assessment of the clinical characteristics of the patient and injury, as well as information yielded by neuroimaging and electrophysiologic assessment techniques.

## Patient Characteristics

Age, history of alcohol abuse, and family history represent the patient characteristics most frequently cited as factors influencing subsequent seizure risk. Patients with histories of alcohol abuse, particularly chronic alcoholism, demonstrate an increased risk of early and late seizure development and recurrence following TBI. Patient age appears to exert a strong influence on PTS risk. Children demonstrate markedly lower risk for LPTS and considerably higher risk for IPTS and EPTS, when compared with adult patients with comparable injury severity. Some studies suggest that age at onset of injury or seizures may influence susceptibility to seizures later in life. Some authors note a modestly increased incidence of PTS among patients with nonpenetrating TBI and a family history of seizures. This has not been consistently observed, suggesting that the influence of a family history of seizures appears weak when compared to the effects of extensive cerebral trauma. However, Diaz-Arrastia noted that inheritance of the apolipoprotein E (APOE) allele was significantly associated with development of late seizures, but not poorer outcome, after moderate and severe TBI.<sup>25</sup> These findings indicate that genetic influences may ultimately be found to have an important role in post-traumatic epileptogenesis. The identification of specific biomarkers for PTE has been limited but remains a particularly important area for future research.

## Injury Characteristics

Certain injury characteristics show an increased frequency resulting in LPTS (TABLE 17.1). There is almost uniform agreement regarding observations of markedly increased seizure risk among patients with PTBI. Blood appears to have an irritating effect on cortical neurons, as demonstrated by increased seizure incidence among TBI patients with intracranial bleeding, particularly with subdural hematoma.<sup>6</sup>

There is a general consensus of increased PTS risk in patients with TBI characterized by focal neurologic deficits, depressed skull fractures, cerebral contusions, and retained fragments. Lesion location may affect incidence, type, and possibly frequency and treatment response of PTS. The presence of multiple risk factors is associated with increased seizure risk.

TABLE 17.1 Risk Factors for Late Post-traumatic Seizures

	PATIENT CHARACTERISTICS	INJURY CHARACTERISTICS	OTHER
<b>RISK FACTOR</b>	Age	Bone/metal fragments	Early post-traumatic seizures
	Alcohol use	Depressed skull fracture	
	Family history	Focal contusions/injury	
	APOE allele	Focal neurological deficits	
		Lesion location	
		Dural penetration	
		Intracranial hemorrhage	
		Injury severity	
		Focal hypoperfusion	

Modified from Yablon and Towne, 2013.<sup>7</sup>

LPTS rarely occurs after mild TBI. Among adults, trivial blows to the head almost never result in seizures, but they may occur in the presence of preexisting or concurrent brain lesions. Despite their rarity, PTS and even recurrent PTS do occur after mild TBI, but their presence in the adult patient should prompt an investigation for a precipitating cause, such as an intracranial mass lesion. Moreover, frequent LPTS after mild TBI should also prompt careful evaluation for PNES.<sup>26</sup>

## EEG

The interictal EEG is a poor predictor of subsequent PTS/PTE. It is frequently abnormal in patients with TBI, both with and without PTS, reflecting the severity of brain damage sustained. Sleep-deprivation activation procedures similarly do not appear to differentiate between patients with and without PTS. The rare change of focal slow-wave activity to focal spike discharges, particularly during the first month after injury, or persistence of focal spike or sharp-wave discharges, may be suggestive of increased seizure risk. However, such discharges may be observed on the EEG of nonepileptic patients. Conversely, a normal EEG may precede PTS onset, although this finding is more frequently associated with a favorable prognosis. EEG findings should be evaluated in context with other clinical risk factors when assessing the likelihood of PTS onset.

The EEG provides valuable information in focus localization, seizure persistence, and severity prognostication once PTS has been observed. In addition, the EEG may identify the presence of nonconvulsive seizures among patients with impaired consciousness.

## AED Prophylaxis: Clinical Trials and Guidelines

Numerous studies of anticonvulsants have sought to determine whether they prevent the development of epileptic foci in animals and humans. Numerous trials indicate that early AED prophylaxis is not accompanied by a reduction in LPTS, mortality, or neurological disability. In contrast, AED prophylaxis does reduce the incidence of EPTS. Treatment failure among trials conducted thus far should not imply that future trials are similarly destined to fail. Different approaches are currently under investigation. These include the use of available AEDs that have not been previously studied for prophylaxis of PTE, different timing of administration (eg, < 12 hours after injury), and development and investigation of new AEDs.

# Management of Post-traumatic Seizures and Epilepsy

## Diagnosis

An initial step in the management of suspected seizures is establishing whether seizures are present. In many cases, a diagnosis can reliably be made from clinical observations of the event, a complete history, and electrographic studies. Classification of the observed seizures is similarly important, as categorization can have significant prognostic and therapeutic implications.

There are situations, however, where the diverse or subtle clinical presentations of PTS complicate diagnosis. As noted earlier, epileptic manifestations (particularly those of CPS) may not be recognized in patients with significant cognitive and behavioral dysfunction. Alternatively, nonepileptic phenomena such as PNES and syncopal episodes may be mistaken for PTS. Clinical observations alone may be insufficient to render or rule out a diagnosis of PTS, prompting the use of other diagnostic options.

The EEG is the single most informative laboratory test for the diagnosis of epileptic disorders and should be obtained in any patient with suspected PTS. The EEG may assist in assessing the likelihood of an underlying seizure when correlated with the clinical diagnosis, or in localization of the seizure focus. Although interictal epileptiform activity is apparent in only approximately 50% of single awake recordings in adults with epilepsy, this proportion rises

to approximately 80% to 85% if sleep is included. Two recordings obtained while the patient is awake demonstrate epileptiform activity in 85% of individuals with epilepsy, and this rises to 92% of persons within four recordings. In patients who manifest only generalized seizures, interictal discharges are bilateral, symmetrical, and synchronous, generally of greatest amplitude over the frontal regions but sometimes located posteriorly. In patients with partial seizures, discharge topography more or less closely corresponds to that of the focus from which seizures arise. These focal interictal discharges may spread, producing secondarily generalized spike-and-slow-wave activity. If the generalization is rapid, the focal onset may be difficult to detect.<sup>27</sup>

There are limitations in the diagnostic sensitivity of the standard interictal EEG, however, and absence of EEG abnormalities does not exclude the presence of seizures. When initial standard evaluations fail to resolve the clinical diagnosis, long-term EEG monitoring techniques, including ambulatory EEG monitoring or inpatient video-EEG telemetry, are effective and clinically valuable methods. Ambulatory EEG monitoring offers an intermediate-level option for recording while the patient conducts normal activities at home, work, or school. It is most useful for investigating the patient in a natural environment. A patient or observer log is maintained to identify the times and descriptions of behavioral episodes suspected of representing seizure activity. Video EEG in an EMU using telemetry with video monitoring provides the best opportunity to obtain an artifact-free EEG while observing and evaluating associated clinical behavior. Computerized automatic seizure detection often identifies important events, particularly at night, that are not reported by the patient or nursing staff. Definitive diagnosis requires recorded examples of all seizure types experienced by the patient.

## Treatment

It is beyond the scope of this chapter to discuss all the treatment modalities that can be employed in the treatment of PTE. However, some broad concepts for patient management are discussed.

While there is general agreement regarding the appropriateness of AED treatment among patients who manifest two or more unprovoked seizures, debate remains concerning the benefits of treatment in reducing recurrence risk following a first seizure. Overall, about 33% of patients with a first unprovoked seizure can be expected to have a second within the subsequent 3 to 5 years. This risk varies considerably, depending on clinical characteristics of the patient. Increased risk is observed among patients with remote lesional (symptomatic) epilepsy. Approximately 44% to 48% of patients with a first remote, lesional seizure experience a second seizure in the next 3 to 5 years. Of the patients with a second seizure, almost 87% will experience a third seizure by 5 years.<sup>28</sup> Seizures occurring immediately after acute TBI carry a lower risk of recurrence than late seizures.<sup>29</sup>

Once a decision has been reached that pharmacological treatment of a patient with PTS is indicated, a primary goal is to attain control of seizures with one medication. The decision of which specific agent to use reflects the type of post-traumatic seizure, the route and frequency of drug administration, the anticipated adverse effects, and comorbidities. Among patients with structural or lesional epilepsy, including patients with TBI who manifest seizures of focal onset, extended-release carbamazepine remains a commonly preferred drug. Patients with tonic-clonic seizures of generalized, secondarily generalized, or multifocal onset respond well to valproate. While generally effective for seizure control, the utility of phenobarbital is limited by prominent adverse effects on cognition and behavior.<sup>6</sup>

Neurologists increasingly employ newer, second-generation AEDs in symptomatic management of selected patients with PTE. A recent review of the effectiveness and safety of antiepileptic medications in patients with epilepsy compared the newer and older AEDs. There was no significant difference in efficacy when the newer AEDs were compared with phenytoin, carbamazepine, or valproate. The older AEDs had more adverse events but did not lead to a higher rate of withdrawal.<sup>30</sup> Two previous expert consensus panels address the use of the newer AEDs as initial monotherapy, including patients with symptomatic localization-related epilepsy (SLRE) and symptomatic generalized epilepsy (SGE).<sup>31,32</sup> The Quality Standards and the Therapeutics and Technology Assessment Subcommittees of the American Academy of Neurology published a practice parameter summarizing an evidence-based assessment regarding the efficacy, tolerability, and safety of seven new AEDs in the management of new-onset partial or generalized epilepsy, including gabapentin, lamotrigine, topiramate, tiagabine, oxcarbazepine, levetiracetam, and zonisamide. They found



evidence that gabapentin, lamotrigine, topiramate, and oxcarbazepine are effective as monotherapy in newly diagnosed adolescents and adults with either partial or mixed seizure disorders but not generalized epilepsy syndromes. No specific guidelines were provided regarding AED use in remote symptomatic epilepsy or PTE.<sup>32</sup> Karceski et al employed an “expert consensus method” to survey epilepsy specialists regarding AED preference in specific clinical scenarios.<sup>31</sup> The survey revealed a preference for carbamazepine as the initial AED for management of symptomatic epilepsies. Phenytoin, oxcarbazepine, and lamotrigine were also cited as initial first-line agents for SLRE manifested by simple partial seizures or complex partial seizures. For management of SLRE with secondarily generalized seizures, phenytoin, oxcarbazepine, lamotrigine, and valproate were identified as initial first-line AEDs. A limitation of this consensus statement is that it does not address the place of some of the newest AEDs, such as zonisamide, lacosamide, or levetiracetam, as these agents were not in wide use at the time the survey data were obtained.

## **Adverse Effects of AED Therapy**

AEDs commonly employed in the treatment of PTS may be associated with significant idiosyncratic and dose-related adverse drug reactions,<sup>32</sup> requiring their discontinuation or substitution in as many as 20% to 30% of patients. These include hematologic, dermatologic, hepatic, neurologic, endocrine, urologic, and teratogenic adverse effects.<sup>32</sup> Transient or persistent leukopenia and thrombocytopenia may be observed in patients taking phenytoin and carbamazepine, although idiosyncratic aplastic anemia is extremely rare. Rashes are occasionally encountered with many AEDs, and severe dermatologic reactions more rarely noted with lamotrigine and phenytoin.<sup>32</sup> Hirsutism and gingival hyperplasia may be seen in patients treated with phenytoin. Weight gain has been associated with valproate and gabapentin treatment, and weight loss reported with zonisamide and topiramate. Elevations of hepatic enzymes are reported to occur in patients receiving phenytoin, carbamazepine, and valproate. Frequent routine laboratory monitoring—aside from baseline determination of hematologic, chemistry, and liver function—is not necessary for most AEDs (with the notable exception of felbamate). These typically do not provide meaningful protection from rare and potentially life-threatening manifestations. Appropriate counseling for the patient, family, and caregivers regarding potential complications and symptoms that might herald an adverse event is far more useful and important.<sup>6</sup>

Cognitive effects of AEDs warrant particular attention in the patient with TBI. Newer AEDs have superior cognitive adverse-effect profiles and tolerability when compared with older agents.<sup>6</sup> In contrast, older AEDs—particularly phenobarbital, phenytoin, and carbamazepine—significantly impair memory performance in double-blind crossover trials among healthy adults.<sup>33</sup> Patients with severe TBI already have significant cognitive impairment. AEDs may exert independent and additional adverse cognitive effects on the patient with TBI who is receiving chronic therapy.<sup>34</sup> Among patients with severe TBI participating in the landmark prophylaxis trial of Temkin et al, a significantly greater proportion (78%) of individuals treated with phenytoin demonstrated cognitive impairment sufficient to preclude testing at 1 month after injury.<sup>35</sup> This was observed in only 47% of corresponding patients treated with placebo.<sup>34</sup>

Among older established AEDs, most studies demonstrate no comparative advantage in cognitive adverse-effect profile between carbamazepine, phenytoin, or valproate, although few include subjects with TBI. Smith found no significant difference in cognitive testing results among patients randomized to withdrawal from phenytoin and carbamazepine prophylaxis.<sup>36</sup> Only 13 of the 82 patients studied sustained severe TBI, however, with the remainder receiving prophylaxis following craniotomy or mild/moderate TBI. There remains considerable evidence suggesting that phenytoin provides a relatively unfavorable cognitive side-effect profile among patients with severe TBI.<sup>34</sup> Patients randomized to receive 6 months of valproate for prophylaxis of LPTS following severe TBI demonstrated no evidence of adverse cognitive effects when compared with those receiving 1 week of phenytoin.<sup>37</sup> In contrast, an earlier study among comparably injured patients receiving phenytoin prophylaxis yielded unequivocal evidence of cognitive impairment among AED-treated patients.<sup>34</sup>

While attention regarding adverse drug effects frequently focuses upon observable phenomena, such as lethargy, the influence of AED therapy upon the course of postinjury neurologic recovery also warrants consideration. Certain drugs, including AEDs, impair recovery after brain injury in laboratory animals.<sup>38</sup> Schallert et al demonstrated that diazepam administered to rats within 12 hours of neocortical damage delayed recovery indefinitely, whereas delayed

administration of diazepam resulted in only transient reinstatement of neurologic deficit.<sup>38</sup> This and other studies suggest that AED administration with diazepam or phenytoin during certain crucial periods following brain injury may exert a deleterious effect on subsequent neurologic recovery.

In summary, dose-related and idiosyncratic adverse effects occur among a substantial subset of treated patients, particularly with older AEDs. Cognitive adverse effects may be particularly bothersome, particularly with the older established agents, limiting long-term tolerability. The cited studies serve as a reminder that decisions regarding chronic AED treatment, and especially prophylaxis, cannot be considered solely on the merits of effectiveness in seizure prevention. Consideration must also be given to potentially significant adverse effects and toxicities of the AED regimen.

### **Duration of AED Therapy**

No clinical studies specifically address the duration of AED therapy for patients with recurrent LPTS. In general, it is reasonable to consider AED withdrawal in patients with epilepsy after a 2- to 4-year period free of seizures.<sup>6</sup> Reported rates of relapse vary considerably, and reflect the type of seizure disorder being treated. The risk of seizure recurrence under a policy of slow AED withdrawal is still substantial when compared with a policy of continued treatment, particularly during the first year of withdrawal.<sup>39</sup> Increased risk of recurrence has been reported among patients with a history of more frequent seizures, treatment with more than one AED, a history of GTC seizures, and abnormal or epileptiform discharges on prewithdrawal EEGs.<sup>39</sup> Among patients for whom the risk of relapse after discontinuation appears low, the psychosocial benefits of discontinuation may be considerable. There is no consensus regarding the ideal period over which AEDs should be withdrawn in patients with recurrent seizures, but a conservative estimate would be over a period of 6 to 12 months. Other authors consider seizure freedom after patients have gone without seizures for a period equal to 3 times the preintervention interseizure interval. Although, in certain cases, it may be necessary to wait up to 6 times this interval to confirm seizure freedom.<sup>40</sup>

### **Surgical Treatment of Post-traumatic Seizures**

For those patients who continue to experience frequent seizures despite various AED monotherapy or polytherapy combinations, early surgical treatment options should be considered.

There is now growing sentiment among epileptologists that surgical treatment for refractory epilepsy is underused. In the first randomized study comparing surgical and medical treatment for temporal lobe epilepsy, 58% of surgically treated patients were free of disabling seizures at 1 year, compared with only 8% of those assigned to receive medical treatment.<sup>41</sup> Significant improvements in outcome were observed in measures of quality of life, as was a positive trend with respect to social functioning.<sup>41</sup> The Multicenter Study of Epilepsy Surgery similarly reported that resective surgery significantly reduced seizure recurrence after medial temporal (77% 1-year remission) and neocortical resection (56% 1-year remission).<sup>42</sup> In light of such findings, the American Academy of Neurology, in association with the American Epilepsy Society and the American Association of Neurological Surgeons, published a practice parameter supporting the benefits of anteromesial temporal lobe resection for disabling complex partial seizures. It further recommended referral of patients with these seizures to an epilepsy surgery center.<sup>43</sup>

Surgical excision of the seizure focus also provides an important treatment option for carefully selected patients with refractory PTE. Favorable responses, including seizure freedom, have been described among selected patients with PTE treated with resective surgery.<sup>44</sup> Patients with unilateral post-traumatic frontal lesions who undergo complete resection of perilesional encephalomalacia or gliosis and adjacent electrophysiologically abnormal tissue respond particularly well to surgery.<sup>45</sup> The cumulative experience described in published studies, however, also highlight the challenges accompanying accurate identification of the seizure focus in patients with severe TBI, who often demonstrate bilateral and multifocal injury.<sup>25</sup> Marks described 25 patients with PTE treated in their tertiary epilepsy center, 21 of whom were treated surgically. Of the 21 patients treated with surgery, only 9 (43%) had favorable outcomes, those with well-circumscribed hippocampal or neocortical focal lesions.<sup>46</sup> Schuh and associates reported on 102 patients who underwent anterior temporal lobectomy. A history of TBI, alone or in combination with other factors was significantly correlated with continued seizures after surgery.<sup>47</sup>

VNS is an alternative to pharmacologic treatment of seizures in patients in whom conventional pharmacotherapy has failed, either due to lack of efficacy or adverse effects. VNS is approved by the FDA for adjunct treatment of intractable partial seizures in patients over 12 years old. Based on controlled, randomized trials, approximately 30% of these patients can be expected to have an at least 50% decrease in overall seizure frequency.<sup>48</sup> Many patients with VNS continue to need AEDs for maximum seizure control, but medications can usually be reduced, resulting in less adverse-effect burden. Efficacy in LPTS has not been specifically studied. While this technique is invasive, no intracranial surgery is required, and surgical morbidity and mortality are limited. Common adverse effects include hoarseness and cough.

While numbers of patients treated with this technique are limited compared to AED therapy, in 1999, the American Academy of Neurology Therapeutics and Technology Subcommittee classified VNS as safe and effective for intractable partial seizures, based on sufficient Class I evidence.<sup>49</sup> VNS is considered to be an appropriate therapy for patients with medically refractory epileptic seizures who are not optimal candidates for resective epilepsy surgery.

A potential advantage to the use of VNS in the context of LPTS is the relative absence of cognitive adverse effects. Still, the role of this technology in the treatment of epilepsy in the context of TBI remains to be delineated.

## Consultation and Referral

Generally, the first step for individuals experiencing an initial seizure or seizures is to consult their primary care physician. The primary physician may then choose to manage the patient or refer to a neurologist for consultation. If seizures continue to occur after 3 months, a referral to a neurologist is indicated. When the seizures are controlled, many patients return to the care of their primary physicians, with follow-up with the neurologist as needed. If seizure control is not achieved, referral to a center that offers comprehensive diagnostic and treatment services to patients with intractable seizures is indicated.

## Conclusion

Epilepsy is the nation's fourth most common neurological disorder, after migraine, stroke, and Alzheimer's disease. An estimated 2.2 million Americans have epilepsy, with approximately 150,000 new cases diagnosed in the United States each year. Approximately 1 in 26 people develops epilepsy at some point in life.<sup>50</sup> TBI is an acknowledged and preventable cause of seizures, and is responsible for 20% of lesional/structural causes of epilepsy and 5% of all epilepsy. In patients with TBI, chronic AED prophylaxis of LPTS is unjustified, and with few exceptions no AED therapy is provided unless late seizures are reported. Exceptions to this general rule may include anticipated intracranial surgical procedure within the next 7 to 14 days, EEG findings consistent with epileptiform activity, and electrographic seizures.

If a late post-traumatic seizure is observed, an identifiable seizure precipitant is sought, including neuroimaging study of the brain. If no obvious correctable seizure precipitant is identified, establishment of a diagnosis of seizure disorder ideally precedes initiation of AED therapy. Clinical description of the episode alone, provided by a family member or other witnesses, may be sufficiently convincing to initiate AED therapy. The patient and family are given instructions for keeping a "seizure logbook," and more frequent follow-up visits are often warranted. If LPTE has been documented, selection of an AED for symptomatic seizure management is usually initiated. AED selection is influenced by various factors, including the patient's cognitive and behavioral status, the type or manifestation of the seizure, the perceived need for rapid achievement of a therapeutic dose, and whether the patient has already been started on another AED, for example, in the emergency department. If the patient has received an AED in the emergency department and seizures are well controlled, the patient may be maintained on this medication if there are no adverse effects. An alternative AED may be substituted at the earliest suitable point if side effects or a particular contraindication to the AED appears.

Postinjury prophylaxis of EPTS may be justified in patients with severe TBI belonging to high-risk groups. The patient is at their highest risk for seizure development at a time when they can least afford to endure complications

from a seizure. Prophylaxis may be continued for approximately 1 week if seizures are not observed, and then tapered gradually. Again, this should take place in a setting in which close observation can be provided. The risks incurred with such a short duration of treatment currently appear minimal and acceptable.<sup>6</sup>

Insufficient data exist to definitively guide AED therapy among patients whose only manifestation of seizures is EPTS. Most published reports exclude these patients from further study, thereby losing valuable information regarding the influence of continued AED therapy on LPTS recurrence risk. Issues to consider include onset (day 1 vs day 7 or later), severity (particularly SE), recurrence frequency, and clinical risk factors for recurrence. Factors favoring continuation of AED therapy would include later time of seizure onset, documented episodes of SE, persistent epileptiform activity or electrographic seizures on EEG, multiple seizure episodes throughout the first week of injury, and the presence of multiple risk factors suggestive of high risk for LPTS occurrence, such as penetrating TBI. In contrast, it may be reasonable to consider a monitored withdrawal of AED therapy in selected patients with isolated EPTS, particularly those with IPTS. Most patients with nonpenetrating TBI and isolated EPTS tolerate discontinuation of AED therapy without seizure recurrence.

Important research questions remain, and involve a broad range of topics pertinent to the diagnosis and treatment of PTE. Investigation must be directed towards identifying laboratory models that reflect human response to prevention of initial or recurrent PTS. Further study is needed to clarify the natural history of PTE, the prognostic implications of single or isolated seizures, and the effect of AED therapy upon recurrence risk. Assessment of each patient's risk and suitability for treatment must be made on an individual basis, guidelines or algorithms notwithstanding. Even with the publication of guidelines addressing the issue of AED prophylaxis, discussion of issues related to PTE with the patient and family members is useful and important. Moreover, the clinician should be aware of the prevailing regional standards of care regarding symptomatic management. Lastly, in instances where questionable or repeated seizures occur, engaging the expertise of an epileptologist with a specific interest in the unique management issues of this patient population can be invaluable. ■

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# Psychogenic Nonepileptic Attacks

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# Introduction

Psychogenic nonepileptic attacks (PNEA) is the most common misdiagnosis of epileptic seizures, and as such neurologists are inevitably involved. In one study, about 90% of those misdiagnosed with epilepsy actually had psychogenic nonepileptic attacks.<sup>1</sup> It is considered a somatoform disorder (DSM-IV) or (DSM-V) and is not associated with any abnormal electrographic changes or any abnormal neuronal discharges.<sup>2</sup> PNEA is typically not considered a factitious disorder or malingering, which both imply intentional feigning, but it is instead considered an unconscious production of physical symptoms.<sup>3</sup> In the DSM V criteria, symptoms described as “attacks or seizures” are specifically listed under “conversion disorder” also known as Functional Neurological Symptom Disorder.<sup>4</sup> As such, patients with PNEA are not considered to be “faking” or purposefully trying to obtain a secondary gain, though that distinction is difficult to make in individual cases even for mental health professionals.

Of the patients referred to epilepsy centers, at least 20%-30% are found to have PNEA.<sup>3</sup> While it is difficult to estimate, the overall prevalence is about 2-33/100,000.<sup>5</sup> Annual incidence of PNEA was estimated to be 1.4/100,000,<sup>6</sup> and a more recent study shows incidence of PNEA is 4.9/100,000 a year.<sup>7</sup> Assumingly, the incidence may be even higher now, which may partly be due to increased recognition of the diagnosis. About 75% of PNEA patients are women.<sup>8</sup> Eighty percent of patients with PNEA are initially diagnosed with epilepsy and treated with anti-epileptic drugs.<sup>9</sup> On average, there is a 7-year delay in diagnosing PNEA, and one correlation to the delay is the number of anti-epileptic medication trials that were tried. This suggests trials were continued despite no response and supports the notion that patients with presumed seizures should be referred to an epilepsy center after two failed AEDs.<sup>10</sup> Studies have shown there is a longer delay to diagnosis in Veterans than civilians; one study showed Veterans were diagnosed with video-EEG on average after 5 years from start of clinical presentation versus civilians, who were diagnosed by a year. This a 4-year discrepancy and has led to 4 times greater cumulative AED treatment in Veterans.<sup>11</sup>

## Semiology of PNEA

PNEA has been studied extensively over the past several years. The advent of video-EEG monitoring has made it possible to describe differentiating characteristics of PNEA compared to epileptic seizures. This is especially useful as the EEG can be at times completely obscured by excessive electromyographic (EMG) artifact. Furthermore, certain types of seizures often have no clear discernible ictal surface-EEG change, and one must rely solely on the ictal semiology to make the correct diagnosis.

Common behaviors encountered in PNEA are out-of-phase clonic activity of the extremities; vocalizations such as weeping, screaming, wrenching, and grunting; pelvic thrusting; and violent high-amplitude side-to-side head movements.<sup>3</sup> Other features commonly seen in PNEA are long and fluctuating ictus, very gradual onset and termination,<sup>4</sup> opisthotonic posturing (back arching), and stuttering.<sup>5</sup> Eye closure is a relatively easy historical question that can with high degree of certainty differentiate PNEA from epileptic seizures. Ictal eye closure is highly associated with PNEA with a sensitivity of 96% and specificity of 98%. Conversely, eye opening has a sensitivity of 98% and specificity of 96% in diagnosing epileptic seizures.<sup>6</sup> With the widespread use of mobile phones, most patients' family members can even show a video of the episodes in question in clinic, which minimizes recall bias on the part of the observer.

This chapter discusses how to identify and manage PNEA, but also focuses on the special circumstances that arise in Veterans.

## Problem with Misdiagnosis

As is the case with any disorder, misdiagnosis delays the appropriate treatment needed to provide relief to the patient. For example, in the case of PNEA, a completely different therapeutic approach is needed (vs epileptic seizures),

including psychotherapy and psychiatric medications as will be discussed further below. In addition, treatments are not without side effects. Anti-epileptic drugs (AEDs) are no exception. AEDs used in patients who do not need them place an unnecessary risk of common and rare side effects of the drugs.

## What causes PNEA?

Simply stated it is a manifestation of psychological distress. One thought is patients with PNEA or conversion disorder in general have the inability to rationalize and understand their “feelings” and emotions, which is also known as alexithymia. This lack of emotional identification can cause misplacement or “misattribution” of “autonomic symptoms” of anxiety to a true organic disease.<sup>12</sup> It is as if to provide oneself an explanation and reconcile the inexplicable anxiety one experiences. PNEA has been considered a defense mechanism, and there is discussion of the importance of dissecting the underlying defense mechanism as the different types may require unique therapies.<sup>13</sup>

## Provocative Measures

### History

Initial suspicion for PNEA should arise from clinical presentation with thorough history and examination.<sup>14</sup> The past medical history, including social and sexual history, can be particularly useful in raising suspicion for PNEA when certain psychiatric comorbidities are present. Greater than 40%-80% of PNEA can have other psychiatric conditions such as somatoform disorders, affective disorders, personality disorders, post-traumatic stress disorder, and anxiety related disorders. In the same study, 87% of patients had a history of trauma with greater than 60% with a traumatic history of sexual or physical abuse.<sup>8</sup> These become the “pertinent positives” in the history taking. Other risk factors include concurrent diagnoses of what are considered “functional somatic syndromes” such as “fibromyalgia, chronic fatigue syndrome, chronic pain syndrome, tension headaches, IBS, asthma, migraines and GERD.”<sup>15</sup>

Post-traumatic stress disorder, as well as mental health illness, is a very prevalent issue in Veteran population. A study looked at 50 Veterans with PNEA and 37 with epileptic seizures. Seventy-eight percent of the PNEA patients had a mental health disorder and 62% of the epileptic seizure patients. PTSD preceded respective diagnoses in 58% of patients with PNEA when compared to only 13.5% with epileptic seizures. Major depression disorder was diagnosed in 46% of PNEA patients.<sup>16</sup>

Another study comparing characteristics in male Veterans with PNEA versus epileptic seizures revealed those with PNEA were approximately 10 years younger, had more frequent episodes and were more likely to have normal brain imaging. They were also more likely to receive monotherapy when compared to veterans with epileptic seizures.<sup>17</sup>

### Clinical Presentation

As one delves further into the history, details of the semiology of the attacks are brought to light and can aid in PNEA diagnosis. Persistent stress related triggers such as pain, getting angry, certain sounds/movement resulting in an attack should also raise suspicion.<sup>14</sup> One study attempted to classify PNEA by semiology and describe common clinical presentation during the event and including auras prior to the event. Classifications included abnormal motor phenomena such as asynchronous “violent thrashing, grabbing and kicking movements” and other examples included pelvic thrusting, whole body jerking/flaccidity. An example of partial motor phenomena is head shaking. Affective/emotional behavior phenomena included “grimacing, gasping, choking feeling, and coughing.”<sup>18</sup>

Another type was characterized as “dialeptic,” and patients were unresponsive and “flaccid” throughout the entire event. There was even description of nonepileptic auras with “dizziness” as one example. Other symptoms noted were a stop and go pattern with “cessation or decrease in intensity during the events” as well as “stereotypy” and “variability.” “Vocalizations” prior or during the event were described as “moaning, grunting, screaming/shouting, gasping

and sorting.” Fifty patients in the study had “forceful eye closure,” and some had staring with lateral movements of the eyeballs. Hyperventilation and abnormal breathing pattern were also noted in some patients.<sup>18</sup> Even if the classification is not implemented in clinical practices, this study provides a very thorough and descriptive portrayal of the common red flags that can help identify PNEA.

The duration of the ictal period can further provide a hint to help differentiate epileptic versus nonepileptic event. Generally, PNEA activity lasts significantly longer than epileptic seizures. Events lasting greater than 5 minutes are 24 more times likely to be PNEA.<sup>19</sup> As also stated in the study, this is a problem since status epilepticus is also defined as seizure activity >5 minutes. This can result in intubation, sedation and treatment with intravenous AEDs for PNEA patients, exposing yet another reason how PNEA can be easily misdiagnosed as epilepsy.

Can the underlying psychiatric condition cause a unique PNEA presentation? One study revealed the traumatic experience underlying a Veteran’s PTSD could change the clinical presentation of PNEA. In the study, there was no significant difference between how PNEA in those with PTSD presented versus those without. However, combat related PTSD was more likely to manifest into hypomotor PNEA (91%) when compared to non-combat related PTSD (around 42%). Non-combat related PTSD referred to trauma not associated with military operations, but could still have occurred during though not limited to active duty, for example physical or sexual abuse. Hypomotor semiology referred to as altered awareness with mild motor movements if any at all, for example, trembling. This is in stark contrast to the hypermotor PNEA, which predominantly consists of, as the name suggests, motor movements such as “pelvic thrusting, head movements, or posturing mannerisms.” Interestingly, service connection rate had no significant impact on any of the outcomes.<sup>20</sup>

## Examination

Examination and observation can also help in suspecting the diagnosis. Give-way weakness, overdramatization and histrionic demeanor can all be clues.<sup>14</sup> Many patients will have events in the office, and in one study 10 of 13 patients with spells during the office visit turned out to have PNEA.<sup>21</sup>

## Confirming a Diagnosis

By definition, PNEA does not have epileptic electrographic correlation on EEG. During movements of PNEA, as is expected with any movement including epileptic activity, muscle artifacts can be seen in varying frequencies and amplitudes. Interestingly, “hypermotor” and “partial motor” PNEA could be differentiated on EEG by the characteristics of muscle artifact.<sup>18</sup> Muscle artifact may also obscure epileptic activity, however in PNEA after cessation of abnormal motor activity, no postictal changes were seen on EEG<sup>18</sup> as would be expected in epileptic seizures.

The question becomes which type of EEG should be used. Typically, long term video monitoring EEG is recommended, and not ambulatory or routine EEG. The issue with ambulatory EEG is that often it is without video. Video of the actual event allows interpreting physicians to review the entire event and correlate it with the EEG to ensure no electrographic changes concerning for seizure occurred. Additionally, reviewing the semiology of the event on video, allows for the clinical confirmation that patient is not having frontal lobe seizures and other small epileptic seizures that are not always detected on EEG.<sup>22</sup>

Repeated normal routine EEGs can raise suspicion, but diagnosis remains unconfirmed if episodes are infrequent and not captured during a short, limited routine EEG. <sup>22</sup> However, a recent study did show short-term video-EEG monitoring, defined as less than 24 hours accurately provided diagnosis 57% of the time for epilepsy and PNEA. Of those that were sent with a presumed diagnosis of PNEA, 54% were definitively diagnosed after having provoked events from activation.<sup>23</sup> Another study specifically studying short-term video-EEG in a Veteran Administration population found in 67%, the habitual events were captured on a short-term video-EEG. In this study, short-term video-EEG was defined as 1-2 hours long. Seizure like episodes were induced by provocative measures, including hyperventilation, photic activation, and verbal suggestions.<sup>24</sup>

A long-term EEG is on average takes about 5.6 days, but can be as long as 2 weeks. A routine EEG is about 20-30 minutes, and as mentioned before may not capture the event.<sup>25</sup> Short-term video-EEG is an option in between routine and long-term EEG. It is not only time efficient, but patients who do not want to be hospitalized for days to over a week, may be more amenable to coming in for observation for less than a full day. It can be a consideration to start with short-term EEG monitoring especially in patients who have frequent episodes that were not captured on routine EEGs.

## Management

### Role of the Neurologist

Of course, diagnosis of PNEA is the initial role for neurologists, but there is a continued obligation in management.

The first step in management and often the most difficult part, is presenting the diagnosis of PNEA to patients and their families. Given many patients were initially misdiagnosed and treated for epileptic seizures, it can be challenging to reverse the epilepsy diagnosis and provide an alternative disorder, especially one associated with mental health. In Veterans, this may be especially a sensitive topic as that underlying mental health issue, namely PTSD, may be directly related to active duty. Inquiring about it may be viewed as provoking and may invoke traumatic memories. Moreover, the Veteran patient should never feel unappreciated for his or her service, which may have resulted in the very mental health issues that manifest itself as PNEA.

Since commonly it is the neurologist who confirms the diagnosis clinically and with video-EEG, it becomes the neurologist's role to tell the patient. The diagnosis should be clearly stated with compassion but without ambiguity in terms that the patient can clearly understand. For example, patients should be told using words such as "psychological" or "stress induced".<sup>22</sup> Patients should leave the conversation without feeling accused of "faking" it or trying to obtain secondary gain.

Terminology and semantics are important. For example, throughout this chapter we have referred to these nonepileptic episodes as PNEA or psychogenic nonepileptic "events" rather than PNES that is, psychogenic nonepileptic "seizures." Referring to the attacks or events as seizures can be misleading to patients, and they may associate it with epileptic seizures regardless of the "nonepileptic" adjective. Avoiding the term seizure is one way to prevent room for ambiguity and the most "dreaded" question after a lengthy discussion on PNEA diagnosis: "So I still have seizures, right?"<sup>26</sup> Anecdotally, stating it as an uncontrollable symptom or manifestation of anxiety, depression or stress as can be seen with palpitations or gastrointestinal distress can be relatable to patients and can alleviate the stigma associated with mental health.

Part of the discussion should include driving recommendations. Despite episodes not being epileptic, as discussed above, PNEA can occur on a subconscious level thus potentially posing the same risks as epileptic seizures. There are not very clear data regarding driving and PNEAs. On a questionnaire for physicians, out of 37 physicians who responded, 49% felt driving restrictions should be the same as epileptic patients, 32% thought there should be no restrictions. Nineteen percent thought it should be decided on an individual basis.<sup>27</sup>

### Role of Mental Health Professional

Psychologists, psychiatrists and other mental health professions should play a long-term role after patient has been diagnosed with PNEA.

The psychiatrist's role is not only to prescribe medicinal therapies as treatment for PNEA is not limited to psychotropic drugs and are inclusive of psychotherapy. One study took 37 patients with PNEA confirmed on video-EEG, who were all initially treated for refractory epilepsy with aggressive anti-epileptics. They underwent individualized psychoanalytic therapy after correct diagnosis of PNEA. Eleven of these patients had complete resolution of their events, and the remainder showed decrease in frequency.<sup>28</sup>

It is imperative to recognize other concurrent psychiatric disorders that are playing a role and manifesting itself as PNEA. Specific psychiatric conditions or underlying defense mechanisms as mentioned above will have unique therapies.<sup>13</sup> For example, in another case study,<sup>29</sup> prolonged exposure was used to treat patients specifically with concurrent post-traumatic stress disorder (PTSD) and PNEA. Prolonged exposure therapy generally is a method used to treat patients with PTSD. The modifications made in this study for concurrent PNEA included psychoeducation, including breathing and other “grounding” techniques exercised even during the actual nonepileptic attack. Additionally, other “in-vivo” exercises including exposures to scenarios, situations, locations and events that were intentionally and at times, irrationally avoided by patients with PTSD as they presented a reminder of their traumatic events. Of the 16 patients to complete the study, 13 had complete resolution of PNEA with these techniques and the remainder had decreased seizure frequency.

## Roadblocks to Management

There are roadblocks to successful management from both a patient and a physician perspective. In addition to discussing what can be a daunting diagnosis, physicians also feel frustration due to limited evidence based treatments. There is fear in losing the patient’s trust/loyalty or being unable to communicate the diagnosis to the patient.

One issue from a patient’s perspective, specifically Veteran, is service connection. There are patients who are 100% service connected due to their disabilities from PNEA<sup>30</sup> initially mistaken for epileptic seizures. Does a “psychogenic” diagnosis change their service connection? Will they continue to remain 100% connected because the underlying psychiatric illness may be service related? It is hard to say, but these are questions both providers and patients will have to consider.

Another roadblock is if the physicians involved do not accept the diagnosis. It is critical that the psychiatrist believes the diagnosis before treating a patient, as it is common for the psychiatrist to question the neurologist’s diagnosis even after video-EEG has confirmed it. This can obviously hinder treatment. To prevent such discrepancies, it is recommended to take a multidisciplinary approach with diagnosis and involve the psychiatrist during diagnosis.<sup>30,31</sup>

There is an inherent discomfort with approaching psychiatric illness with patients as discussed above as well as specific concern that the patient may be “faking it” or malingering when somatoform disorders are discussed given many mimic organic conditions.<sup>32</sup> Additionally, there may be a lack of interest on the part of the American Psychiatric Association and American Psychological Association.<sup>33</sup> The omission does not appear accidental given the comprehensive nature of these organizations covering rarer conditions. Additionally, a search of a large psychiatric journal in 2011 showed no articles under “somatoform or conversion,” but many on depression and anxiety.<sup>33</sup> This raises concern of ignorance of the topic in the mental health profession, whether it be a lack of interest, ignorance or discomfort. Perhaps the issue is a lack of ownership, given for somatoform disorders, organic disorders must be excluded which requires non-psychiatric work up. For example, for diagnosis of PNEA, epileptic seizures must be excluded. While the neurologists are responsible to rule out epileptic seizures, they are not equipped to manage psychiatric illness, and it is imperative that psychiatrists and psychologists recognize, accept and manage PNEA.

## Prognosis

Adequate treatment allows complete resolution of seizure like activity in 60-70% of patients diagnosed with PNEA.<sup>9</sup> One study specifically aimed at the early outcome of PNEA noted employment was related to a better prognosis. Interestingly, in the same study, 24 of the 27 patients in the study to become spell free occurred almost immediately after patient was informed of the diagnosis, suggesting that an early diagnosis and appropriate discussion may lead to a better prognosis.<sup>7</sup> Notably, Veterans had a reduction of PNEA related outpatient visits after diagnostic studies, namely, video-EEG confirmed diagnosis<sup>34</sup> suggesting that appropriate diagnosis presumably leads to proper treatment thereby reducing utilization of outpatient resources.

# Conclusion

Generally, it seems recurring events that occur periodically, episodically, and intermittently are commonly mistaken for seizures, especially those associated with abnormal movements, loss of awareness, confusion for seizure. The differential diagnosis includes a wide variety of disorders, however PNEA is the most common. This is especially in Veterans, a population where PTSD is prevalent. PNEA should be considered in the forefront when evaluating a patient for seizure like activity with a history of PTSD and other red flags that were discussed. On the flip side, Veterans may also have strong risk factors for epileptic seizures with TBI, strokes, etc. Special considerations in Veteran patients include service connection, the underlying traumatic experience, whether it be combat or noncombat related and delicately but concurrently without ambiguity providing the diagnosis. Prompt and accurate diagnosis is crucial. Veterans have a longer delay in diagnosis when compared to the civilian population, which leads also to a delay in appropriate psychiatric treatment. Moreover, it avoids unnecessary, and at times, lifelong treatment with AEDs and their associated side-effects. ■

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# Psychiatric Comorbidities

**SCOTT D. MOORE**





# Introduction

Neurobehavioral disorders, including convulsions, have been described in writings since antiquity. However, until the advent of widespread use of the electroencephalogram (EEG) and other advances in brain sciences, little attempt was made to distinguish epilepsy from other disorders currently considered to reside in the domain of psychiatry.<sup>1</sup>

Recent studies suggest that psychiatric disorders may be diagnosed in 25%-50% of patients with epilepsy, at rates 3 to 5 times that of the general population.<sup>2</sup> This very broad range reflects considerable variability in the methodologies and diagnostic classification schema across multiple studies. In patients with poorly controlled seizures, the prevalence is higher.<sup>2,3</sup> Psychiatry disorders may also be more prevalent in epilepsy with a localized focus, particularly temporal lobe epilepsy (TLE),<sup>4</sup> although this remains controversial. However, multiple studies suggest that psychiatric disorders in patients with epilepsy are often undiagnosed or undertreated.<sup>5,6</sup> There is a critical need to address this, as presence of comorbid psychiatric disorders are clearly associated with much poorer quality of life and poorer compliance with treatment.<sup>7,8</sup> Patients with epilepsy and untreated psychiatric disorders have worse prognoses for their seizure disorder, poorer tolerance of antiepileptic medication, and overall increased morbidity and mortality than patients receiving adequate treatment.<sup>9</sup>

The reasons for the high association of epilepsy and psychiatric disorders appear to be very complex. There is evidence that pre-existing epilepsy may predispose to the development of affective and anxiety disorders, while affective and attentional disorders are associated with increased risk of developing epilepsy. The high comorbidity of epilepsy and these disorders also suggests the possibility of a common underlying pathology.<sup>7,10</sup> Some psychiatric symptoms are closely associated temporally with seizures (including preictal and postictal periods), suggesting causality; other symptoms clearly exist independently of ictal events.<sup>11</sup> In addition, there are documented effects, both negative and positive, of antiepileptic pharmacotherapy on mood and anxiety symptoms.

## Affective Disorders

Affective disorders, particularly major depression, represent the most common psychiatric disorder associated with epilepsy, with prevalence rates between 20% and 45%.<sup>12</sup> Depression may be more common in seizure patients with temporal or frontal lobe foci and in the context of poorly controlled seizures.<sup>2</sup> Untreated depression in the context of epilepsy is associated with poorer adherence to treatment, poorer seizure control and poorer quality of life.<sup>5,13</sup> Presence of depression is also associated with increased seizure frequency, while effective antidepressant treatment may reduce seizure frequency.<sup>14</sup> Newer studies associate pre-existing depression with an increased risk of developing a seizure disorder (including worse seizure outcomes), suggesting the possibility of overlapping neurobiological etiologies.<sup>15,16</sup> Bipolar affective disorder may be present in patients with epilepsy at prevalence rates of up to 13%, compared to 1-2% in the general population.<sup>17</sup> In a veteran population with epilepsy, the association with depression and insomnia was found to be stronger in white Veterans than black Veterans, although the exact reasons for this finding are unclear.<sup>18</sup>

Depressive episodes may occur as preictal or postictal symptoms, and preictal dysphoria may last from hours to days preceding a seizure.<sup>2</sup> Ictal dysphoric symptoms as an expression of partial simple epilepsy have been described, although the actual prevalence is unknown.<sup>2</sup>

## Anxiety Disorders

Although less well studied, rates of comorbid anxiety disorders with epilepsy are nearly as high as affective disorders, and the two disorders frequently occur together.<sup>19,21</sup> Panic disorder (with or without agoraphobia) and generalized anxiety disorder appear to be the most prominent among the various disorders associated with epilepsy.<sup>2</sup> However, panic attacks may resemble temporal lobe seizures and should be differentiated.<sup>20</sup> Like affective disorders in the context

of epilepsy, anxiety disorders also have a similarly high association with poor life quality.<sup>19</sup> Due to the distress associated with seizures, patients with epilepsy may develop a specific fear of seizure episodes.

The most frequent ictal psychiatric presentation is fear or panic. It is associated typically with simple partial seizures or partial complex seizures and generally has a temporal lobe focus.<sup>2</sup> Due to the deep location of temporal lobe structures involved, such as the amygdala, epileptiform activity inducing ictal fear may not be easily detectable with surface EEG electrodes. Use of sphenoidal electrodes may assist with the diagnosis.<sup>2</sup>

## Post-traumatic stress disorder (PTSD)

An association between PTSD and epilepsy has not yet been well studied. In contrast, there is a wealth of data regarding PTSD and psychogenic nonepileptic seizures (PNES), see below. However, in a population of Veterans with epilepsy with any psychiatric disorder, 28% self-reported PTSD.<sup>8</sup> In addition, there is an established connection between even mild traumatic brain injury and PTSD,<sup>22</sup> suggesting a high probability of development of PTSD following post-traumatic seizures.

## Psychosis

Psychosis associated with epilepsy is generally classified according to the temporal relation of the psychotic episodes with seizures.<sup>11</sup> The appearance of psychotic symptoms rarely may occur when seizures are suppressed (termed “forced normalization”).<sup>23</sup>

Optimal treatment involves controlling the seizures with anticonvulsant medication. Antipsychotic medication may be used to treat interictal and postictal psychosis, although their use should be balanced against their proconvulsant effects (particularly clozapine).<sup>11</sup> However, antipsychotic medication may be necessary in cases with severe psychopathology or aggressive behavior and violence.<sup>11</sup>

## Attentional Disorders

Attention deficit hyperactivity disorder (ADHD) occurs with epilepsy at a prevalence rate of 12-37%, approximately three times that of the general population.<sup>2</sup> Epilepsy is overrepresented in ADHD of the inattentive subtype. Data on comorbidity of ADHD and epilepsy is largely derived from pediatric populations, and little is known about the persistence of ADHD symptoms into adulthood with this group. Treatment of ADHD in the context of epilepsy generally entails psychostimulant medication just as with attentional disorders in the nonepileptic population.<sup>2</sup>

## Substance-use Disorders

There are very few studies of the prevalence of comorbid alcohol and drug abuse with epilepsy.<sup>11</sup> This is particularly unfortunate given the documented effects of alcohol use and withdrawal on risk of seizures. A recent study of Veterans indicated that among epilepsy patients with a mental illness, nearly 38% reported substance abuse.<sup>8</sup> Although many patients with epilepsy consume small quantities of alcohol without negative sequelae, excessive and prolonged use, as well as withdrawal, may result in seizures.<sup>24</sup> Additionally, chronic excessive alcohol use may predispose to noncompliance with treatment. Self-reported alcohol use is frequently subject to minimization, and corroboration from family or friends may be beneficial in accurately assessing a potential alcohol-use disorder.<sup>24</sup>

Opiates lower seizure thresholds in temporal lobe structures, though this has rarely been clinically significant even in overdose. On the other hand, psychostimulants such as cocaine and amphetamine may induce seizures. Psychostimulants may reduce seizure threshold by direct toxic effects, but also indirectly by disturbing sleep and poor compliance with anticonvulsant medications.<sup>19</sup>

## Suicide

Meta-analysis indicates a significantly higher rate of completed suicide among persons with epilepsy, with a mean of 12% compared to 1.1-1.2% in the general population.<sup>26,27</sup> Data on rates of attempted suicide are unclear. In epilepsy patients with suicidal ideation, a psychiatric diagnosis was reported in 94% of the sample, with nearly half diagnosed with depression.<sup>26</sup> It remains unclear as to whether epilepsy increases risk for suicide independently of comorbid psychopathology. As with the general population, elevated risk for suicide is also associated with positive family history, physical health issues, prior suicide attempts and access to firearms.<sup>26</sup> Presence of active suicidal ideation warrants immediate psychiatric consultation and possibly involuntary hospitalization.

## Psychogenic Nonepileptic Seizures (PNES)

Psychogenic Nonepileptic Seizures (PNES) refer to episodes of altered mental status and/or stereotypic motor movements suggestive of an epileptiform event, but in the absence of documentable abnormal brain electrical activity. Video-monitored EEG is considered the “gold standard” for diagnosis, and recent studies suggest that the reliability of this method is quite good. Studies also indicate that 10-25% of persons with PNES have comorbid epilepsy.<sup>28</sup> PNES is generally considered to be indicative of an underlying psychological disorder, with comorbid psychiatric disorders present in 43-100% of cases.<sup>11</sup> In a study of Veterans, psychogenic seizures were associated with PTSD at a significantly higher rate than were epileptic seizures.<sup>29</sup> Both were frequently associated with comorbid major depression and alcohol-use disorders. Effective treatment of PNES typically entails addressing underlying psychiatric issues and psychological stressors; use of anticonvulsant medication is generally not indicated.<sup>30</sup>

## Diagnosis of Psychiatric Disorders in the Neurology Clinic

Given the markedly increased risk of suicide in patients with comorbid epilepsy and mood disorders, neurologists should be able to incorporate screens for mood and anxiety disorders in their patient population.<sup>31</sup> Typical screening questions may include inquiries regarding a personal history of depression and/or anxiety, history of any psychiatric treatment, history of alcohol or illicit drug use, and family history of psychiatric disorders. Additional screening specific to epilepsy patients may include questions regarding the patient’s understanding of their seizure disorder and the perceived impact on their quality of life. Among the many brief screening tools available, one has been developed specifically for use in epilepsy patients: the 6-item Neurological Disorders Depression Inventory for Epilepsy (NDDI-E).<sup>14,32</sup> The advantage of the NDDI-E is that the items are not confounded by possible cognitive effects of the underlying seizure disorder or by side effects of anticonvulsant medication.<sup>32</sup> Although the NDDI-E remains the “gold standard,”<sup>33</sup> newer versions (e.g., the NDDI-E2) are being developed that may require less time for the patient and clinician.<sup>34</sup> Any indicator of significant ongoing depressive symptoms should be followed up with questions regarding suicidality, and possibly referral to a psychiatric consultation.

## Treatment Considerations

As stated above, poorly controlled seizures are associated with significantly increased rates of psychiatric disorders and poorer quality of life. However, any anticonvulsant medication may be also associated with adverse effects on mood.<sup>35,36</sup> Barbiturates, in particular, are associated with depression.<sup>35</sup> Although the FDA issued a warning in 2008 regarding a possible association between anticonvulsant medication use and suicidality, a subsequent expert consensus statement indicated that risk to be quite low.<sup>27</sup> However, suicide-related behaviors in elderly Veterans receiving monotherapy were found to be elevated.<sup>38</sup> In any case, the risk to the patient of withholding or stopping effective anticonvulsant treatment is far higher.

Depression in epilepsy may be treated safely and effectively with antidepressant medications.<sup>5</sup> The goal of effective treatment should be an abatement of depression and a return to functionality, rather than simply a reduction in the intensity of depressive symptoms.<sup>5,39</sup> When adequate antidepressant treatment is provided, rates of response in patients with epilepsy are comparable to those of nonepileptic depressed patients,<sup>5</sup> whether or not there is a concomitant decrease in seizure frequency.<sup>40</sup>

With the exception of bupropion, newer antidepressants are considered to have minimal effects on seizure threshold. Older antidepressants associated with decreased seizure threshold include maprotiline, amoxapine and clomipramine.<sup>2</sup> Due to low toxicity and favorable side-effect profile, selective serotonin reuptake inhibitors (SSRIs) are often the first-line choice for treating depression in epilepsy. Animal studies using pentylenetetrazole-induced kindling suggest little difference in safety profiles of newer antidepressant medications; however, the antidepressants venlafaxine and mirtazapine may actually enhance efficacy of antiepileptic medications.<sup>41</sup> Safety of newer antidepressants at standard doses has been corroborated in human studies, although toxic doses may lower seizure threshold.<sup>42</sup> Tricyclic antidepressants and monoamine oxidase inhibitors may also be used safely, though initial dosing should start low and increase cautiously. Patients should be monitored for response and for potential side effects that may negatively affect compliance.

Before initiating antidepressant treatment, the possibility of bipolar disorder should be ruled out based on family or personal history of mania or hypomania, as antidepressant medications may induce mania in predisposed individuals. In this circumstance, lithium or a mood stabilizing anticonvulsant (valproate, carbamazepine, or lamotrigine) may be started in conjunction with the antidepressant. For individuals failing to respond to an adequate trial of antidepressant treatment, psychiatric consultation may be considered. Electroconvulsive therapy is not contraindicated in epilepsy and does not increase spontaneous seizure frequency,<sup>14</sup> but its use may be limited if there is a need for continue anticonvulsant medication. Additionally, counseling and psychotherapy may be beneficial in helping patients with epilepsy handle stress and improve quality of life.<sup>43</sup>

Anticonvulsant medication may be particularly useful in the treatment of bipolar disorder, as either monotherapy or augmentation. Currently, only valproate, carbamazepine and lamotrigine are approved for this use. However, nearly every anticonvulsant medication has been tried for off-label use for multiple psychiatric disorders, despite lack of controlled data verifying efficacy.<sup>44</sup> Despite the combined anticonvulsant and mood-stabilizing effects, it should not be assumed that these medications at doses that control seizures in epilepsy patients are also necessarily stabilizing the psychiatric disorder.

Antidepressant and anticonvulsant medication have clear pharmacokinetic interactions. Metabolism of antidepressants increases in the presence of anticonvulsants that induce liver enzymes, primarily phenytoin, carbamazepine, phenobarbital and primidone, and to a lesser extent oxcarbazepine and topiramate.<sup>2</sup> Valproate acid may inhibit liver enzymes, thus increasing serum concentrations of antidepressants. In addition, newer antidepressants such as fluoxetine, paroxetine and fluvoxamine inhibit isoenzymes of the cytochrome P450 system, and may thereby affect serum concentrations of anticonvulsant medication.<sup>2</sup> Medications such as citalopram and sertraline have minimal effect on the cytochrome P450 system.

Anxiety disorders associated with epilepsy, including panic disorder and generalized anxiety disorder, may be optimally treated with an SSRI,<sup>20</sup> although these medications may have minimal beneficial effects on preictal or postictal fear symptoms.<sup>2</sup> Benzodiazepines such as clonazepam are very effective in treating anxiety acutely, although long-term

use is to be discouraged due to concerns regarding dependence, tolerance, sedation and cognitive impairment. Although not systematically studied, many anticonvulsant medications may also alleviate anxiety in epilepsy patients.<sup>19,20</sup>

## Conclusion

There is a critical need to address comorbid psychiatric conditions in patients with epilepsy, as when left untreated they result in poorer compliance with medication and poorer seizure control, significantly poorer quality of life and increased risk for suicide. Although depression and epilepsy have received considerable attention, comorbid anxiety has been less well studied despite being almost as prevalent and equally disabling. Prevalence of comorbid PTSD and substance abuse with epilepsy have received scant attention, although both are critically important issues in the Veteran population. ■

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# Epilepsy, Migraines, and Cognition

**STEPHEN HOLLOWAY**





# Migraines

Migraine headaches and seizures are distinct disorders but have a similar time course: both can have aura, ictus, and resolution. The pathophysiology underlying a migraine is a spreading cortical depression. The pathophysiology underlying a seizure is a spreading rhythmic cortical excitation. The clinical characteristics of each disorder are usually distinct enough to allow the clinician to make the correct diagnosis.

The comorbidity of migraine and epilepsy is significant and can be complex. TBI is a risk factor for both epilepsy and headache. In the VA population it is not uncommon for patients to have TBI and to have both epilepsy and headaches. Similarly, a structural brain lesion such as an arteriovenous malformation may lead to both disorders. Even without a predisposing condition, the prevalence of epilepsy in patients with migraine is 5.9%, compared with 0.5% in the general population.<sup>1</sup>

Postictal headaches are common. Forty percent of patients report a headache after a seizure.<sup>2</sup> In temporal lobe epilepsy the headache is most often ipsilateral to the seizure onset.<sup>3</sup> Ictal headaches have been reported in a small number of patients.<sup>4</sup> In rare patients a seizure may follow the migraine aura.<sup>5</sup>

A genetic link is suggested by familial studies.<sup>6</sup> A linkage study of a family with occipitotemporal lobe epilepsy and migraine showed a susceptibility focus on chromosome 9q21-q22.<sup>7</sup> Thus, it has been hypothesized that migraine and epilepsy may have shared genetic links that alter cerebral excitability.

The same medication used to reduce seizure frequency may also reduce headache frequency. This dual effectiveness is often considered in choosing an AED if both disorders are present. Divalproex, topiramate, and gabapentin have been shown to be effective both as an anticonvulsant and for migraine prophylaxis, but the doses that are effective for migraine are generally lower than those used for epilepsy. Because many VA patients with TBI, epilepsy, and headaches also have cognitive and impulse-control problems, this may also be a factor considered in choosing an AED. Note that divalproex should be avoided in women of childbearing age.

# Cognition

Cognitive complaints are common in patients with epilepsy, and include mental slowness, impaired memory, impaired problem solving, excessive sleepiness, and impaired attention.<sup>8</sup> Many factors may contribute, the most significant of which are the etiology of the epilepsy (such as TBI) and AED. Comorbidities such as depression<sup>9</sup> or other sedating medications may also contribute. Patients whose epilepsy is related to a developmental cause, mental retardation, or childhood disorder, such as Lennox-Gastaut syndrome or West syndrome, may also have substantial cognitive impairment. Most of these patients do not get into the military and therefore are not commonly seen in the VA population.

TBI is a common cause for developing epilepsy in the VA population. Cognitive impairment from TBI may be mild or severe, and is usually related to the severity of the head injury, as is the likelihood of developing epilepsy.<sup>10</sup> Impairment may involve memory, attention, or problem solving. The location of the injury and epilepsy may also be a factor. For example, left temporal lobe dysfunction may affect primarily verbal memory and impair language, while right temporal dysfunction affects visuospatial memory. Frontal lobe lesions may affect problem solving and attention. Similarly, structural brain injury from other causes—such as aneurysm rupture, a subdural hematoma, or surgical resection—can cause both the epilepsy and the cognitive impairment.

AEDs reduce neuronal excitability. Medications can have a considerable impact on cognitive function, and it is often greater in patients with structural lesions such as TBI. It also may be more significant in the elderly patient. Barbiturates and benzodiazepines have been particularly implicated in cognitive complaints.<sup>11</sup> Newer medications, such as lamotrigine or levetiracetam, are claimed to have less impact on cognition than phenytoin, carbamazepine, and valproic acid; the extended-release formulations for these medications can reduce the peak toxicity effects. Extensive individual variability is seen. One medication may cause considerable cognitive dysfunction in one individual and have little impact on another. Trying a different AED, if one is poorly tolerated, may lead to improved tolerance.

The dose of the medication is an important factor. Patients usually tolerate a low dose of an AED with only mild cognitive side effects, but cognitive complaints often develop at higher doses.<sup>11</sup> Using multiple AEDs, or

polypharmacy, is associated with a greater deleterious effect on cognition. Balancing medication side effects with seizure control may be necessary to maximize a patient's quality of life—in some cases a patient may better tolerate an infrequent seizure than the daily impairment of cognition, particularly if at higher doses seizure freedom is not obtained. The goal, however, is always complete seizure control with minimal side effects.

Staring spells may be epileptic seizures, but with an increasing AED dose, staring spells that are nonepileptic may develop due to cognitive slowing. Patient with TBIs may also have nonepileptic staring spells, which could lead to an increase in AED dose. With escalating doses, the patient may eventually have even greater cognitive impairment and continuing frequent spells. A multiday video EEG with dose reduction in a safe, inpatient setting may be needed to differentiate epileptic seizures from nonepileptic staring spells caused by excessive medications. With reduction of medication, the staring spells may be eliminated, and cognition and quality of life improved.

Patients with idiopathic epilepsy may have little or no cognitive dysfunction from the epilepsy but may have cognitive impairment from other conditions such as depression, PTSD, or other psychiatric disorders. The medication used to treat those disorders may cause cognitive impairment, and the effect may be additive to that of AEDs. A similar pattern may occur with patients in pain who are using narcotics or other sedating medication.

It is often difficult to determine whether cognitive impairment is due to epilepsy, brain injury, AEDs, comorbidities, or the medications used to treat the comorbidities. Reviewing medications and their risk/benefit ratios is always necessary in optimizing treatment. Depending on the type and degree of impairment, rehabilitation therapy and a structured environment may help to maximize the patient's quality of life.

## Summary

Migraines and epilepsy are distinct disorders with many similar features. They have similar time course, both may respond to the same antiepileptic medications, and both may be sequelae of TBI.

Cognitive impairment with epilepsy can be multifactorial. It may be related to medications, comorbidities such as depression, or the common etiology of TBI. ■

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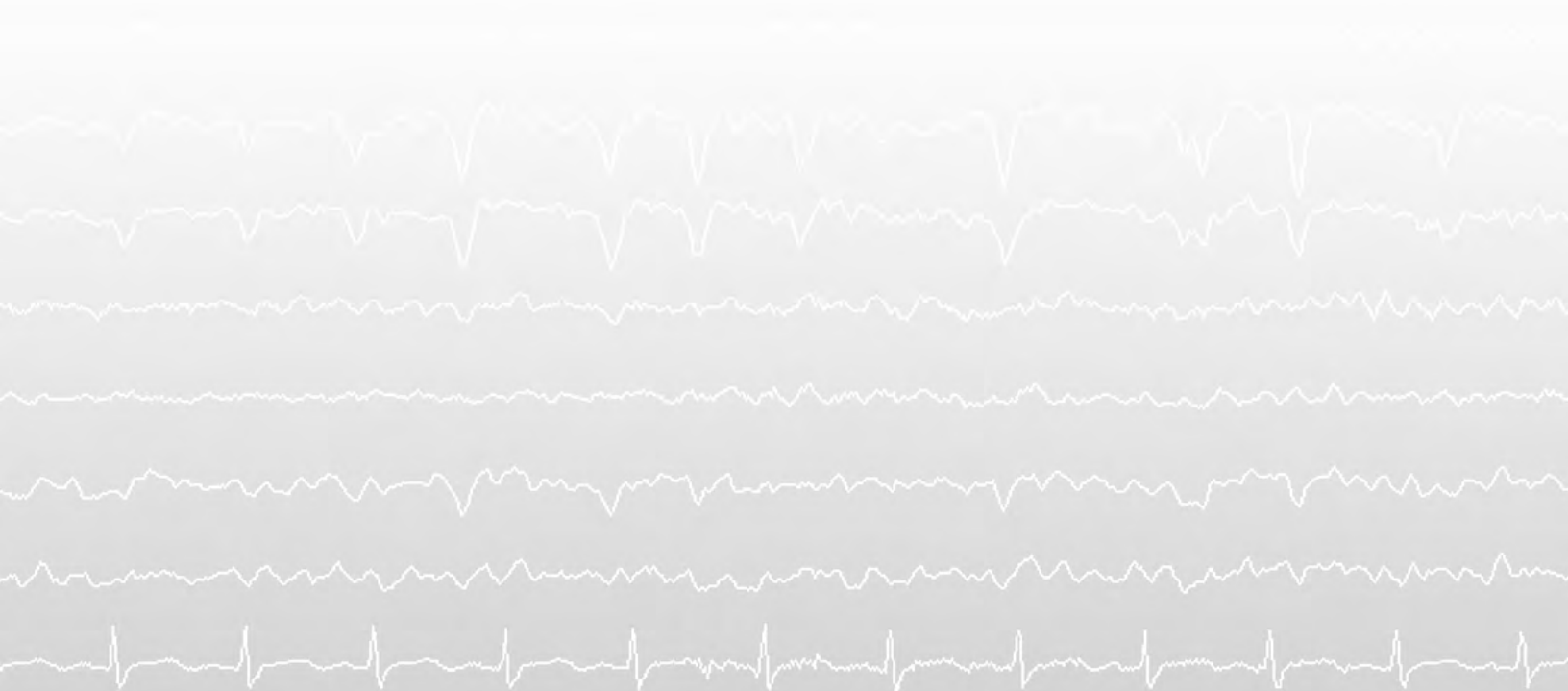
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# Reproduction Issues and Bone Health in Epilepsy

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# Introduction

Reproductive dysfunction is relatively common in women and men with epilepsy.<sup>1</sup> This may result from the effects of epilepsy itself or from the use of AEDs, both of which can adversely affect reproductive hormone secretion.<sup>1</sup> Hormonal disturbances in women can manifest as infertility, menstrual disorders, polycystic ovarian syndrome, sexual disturbances, and galactorrhea.<sup>2</sup> In men, reproductive dysfunction manifests as sexual disturbances and abnormal spermatogenesis, sperm morphology, and function. While certain AEDs play a pathogenic role, sexual disturbances also occur in men with epilepsy on no medication.<sup>1</sup> Many factors affect the low rate of reproduction in people with epilepsy, such as partial onset seizures, onset before 20 years of age, and reduced marital rates.<sup>3</sup>

The relationship between epilepsy and hormonal disturbances is bidirectional: they each affect the other. In this chapter we review the principal pathogenic, clinical, and therapeutic aspects of reproductive disturbances in patients with epilepsy (PWE).

Bone health is a common problem in PWE. It has been recognized in particular among patients who have been treated with enzyme-inducing AEDs (eg, phenytoin, barbiturates, and carbamazepine). This topic is also addressed in this chapter.

## What Reproductive Hormones Do to Epilepsy

Sexual hormones have a direct effect on epilepsy. Indeed, estrogens have been associated with proconvulsant effects and progesterone with anticonvulsant effects. For example, women may be more prone to experience epileptic seizures with high relative ratios of estrogen over progesterone, as seen during ovulation and the menstrual period.

### Catamenial Epilepsy

Under normal conditions, serum estrogen concentrations are higher than those of progesterone in the days leading up to ovulation and immediately before menstrual bleeding. Catamenial epilepsy is defined as >70% of seizures occurring around the menstrual period and/or ovulation,<sup>4,5</sup> the phases of the cycle associated with an elevated serum-estrogen-to-progesterone (E-P) ratio. Herzog has suggested three types of catamenial epilepsy: type I, when seizures increase or occur perimenstrually, type II before ovulation, and type III throughout the luteal phase of the cycle (eg, second half). Catamenial epilepsy occurs in approximately 50% to 70% of women with epilepsy (WWE) and is not restricted to any particular type of epileptic syndrome. In such cases, therapy with natural (but not synthetic) progesterone has been found to reduce seizure frequency. This phenomenon also explains the need to avoid therapy with estrogens without concomitant progesterone in WWE.

### Anovulatory Cycles

The presence of anovulatory cycles is suspected in women with menstrual cycles lasting more than 40 days. Low progesterone secretion from the ovaries has been identified in such women, who in turn are more likely to have more frequent seizures during the luteal phase of the cycle. In fact, one third of women with temporal lobe epilepsy experience anovulation over three cycles compared with fewer than 10% of control subjects or women with primarily generalized epilepsy.<sup>6</sup> Anovulatory cycles are an expression of the impact of epilepsy on the secretion of sexual hormones.

### Menopause

The impact of menopause on epilepsy varies among WWE, with one third experiencing an increase in seizure frequency, one third a reduction, and no effect in the remaining third. The hormonal changes during menopause may account for this phenomenon. For example, during the premenopausal period seizure frequency increases in women with catamenial epilepsy and improves (or remits) after menopause.<sup>7</sup>

# What Epilepsy Does to Sexual Hormones

In patients with idiopathic generalized epilepsy and focal epilepsy of temporal lobe origin (right > left), interictal epileptiform activity has been associated with a dysfunction of the hypothalamic-pituitary-gonadal axis resulting in an abnormal secretion of gonadotropic hormones, which in turn have an impact on the secretion of estrogen, progesterone, and testosterone. This may result in hypothalamic hypogonadism and the following families of disorders:

- Menstrual disturbances
- Infertility
- Sexual disturbances

## Menstrual Disturbances

Menstrual disturbances include amenorrhea and oligomenorrhea, which occur in idiopathic generalized and focal epilepsies but are more frequently seen in focal epilepsy of temporal lobe origin (reported in up to 70% of patients). Menstrual disturbances, however, can also be the expression of an iatrogenic phenomenon, especially with the use of valproic acid, in particular in those who go on to develop polycystic ovarian syndrome. This condition has been associated with exposure to valproic acid between the time of menarche and the age of 26 years old. Women with idiopathic generalized epilepsy have been thought to be at greater risk of this condition, although this observation has not been accepted universally.

## Infertility

Infertility is a relatively frequent comorbidity, seen in 15% to 30% of WWE. There are several causes, which have been reviewed above and include anovulatory cycles and polycystic ovarian syndrome.

## Sexual Disturbances

Sexual dysfunction occurs in 1 of every 3 WWE; this prevalence is higher than that reported in other chronic neurologic disorders.<sup>8</sup> It can be manifested as decreased libido, anorgasmia, vaginismus, decreased lubrication, and dyspareunia. While sexual dysfunction has been associated with abnormal secretion of sexual hormones, it may result from an iatrogenic effect of enzyme-inducing AEDs, which decreases the free fraction of sexual hormones through the synthesis of sex hormone-binding globulins (SHBG). In addition, comorbid depressive and anxiety disorders have been recently identified as a major cause for sexual disturbances.

Recommendations:

- Avoid exposure to valproic acid in WWE of childbearing age
- Avoid enzyme-inducing AEDs, which decrease the free fraction of estrogen and testosterone
- In women with suspected anovulatory cycles, measure serum progesterone concentrations mid cycle; this diagnosis is supported with concentrations < 5 mg/mL
- Screen for sexual disturbances with ASEX (TABLE 21.1)
- Screen for anxiety and depressive disorders with NDDI-E and GAD-7 (see below)

The Arizona Sexual Experiences Scale (ASEX) is a 5-item self-rating scale that quantifies sex drive, arousal, erection or vaginal lubrication, ability to reach orgasm, and satisfaction from orgasm. The Neurologic Depressive Disorders Inventory in Epilepsy (NDDI-E) has been developed to identify patients with epilepsy who are suffering from major depressive episodes. It consists of 6 items scored from 0 to 4 in a Likert scale; a score > 15 suggests this diagnosis with a sensitivity of 84% and specificity of 90%. It takes 3 minutes to complete. The Generalized Anxiety Disorder-7 is a 7-item self-rating instrument, developed to identify patients with generalized anxiety disorders. It takes 3 minutes to complete as well. Each item is scored from 0 to 3, with a score > 10 suggestive of this condition.

TABLE 21.1 **Arizona Sexual Experience Scale**

QUESTION	EXTREMELY EASY SCORE 1	VERY EASY SCORE 2	SOMEWHAT EASY SCORE 3	SOMEWHAT DIFFICULT SCORE 4
How strong is your sexual drive?				
How easily are you sexually aroused?				
Can you easily get and keep an erection?/How easily does your vagina become moist or wet during sex?				
How easily can you reach an orgasm?				
Are your orgasms satisfying?				

## Epilepsy and Pregnancy

When WWE contemplate pregnancy or become pregnant, the following issues must be addressed:

- The impact of the pregnancy on seizure control
- The impact of seizures on the pregnancy
- The choice and dosing of AEDs during pregnancy and in the postpartum period
- The effects of AEDs on the fetus

### Impact of Pregnancy on Seizure Control

In general, seizure frequency is unchanged in 50% to 60% of pregnant women with epilepsy (PWWE). Worsening of seizures occurs in approximately 15% to 32%, while in 20% seizures may improve or even remit. This increase is unrelated to seizure type, duration of epilepsy, or change in seizure frequency in previous pregnancies. Seizure freedom for at least 9 months prior to pregnancy is probably associated with a high likelihood (84% to 92%) of remaining seizure-free during pregnancy.

Several factors can worsen seizures, including:

- Increased clearance of AEDs resulting from an increase in the metabolic rate (eg, lamotrigine) or increase in renal flow (eg, levetiracetam); monthly measurements of serum concentrations are recommended so doses can be adjusted to maintain appropriate serum levels
- Impaired medication absorption as a result of nausea or vomiting
- Poor patient compliance with AEDs, because of fear that exposure to these drugs can affect the baby
- Sleep deprivation

Labor and delivery are associated with an increased risk of seizure occurrence, with an estimated 2% to 5% of WWE having seizures at these times.

### Impact of Seizures on Pregnancy

Most women with epilepsy can conceive and bear normal, healthy children, but their pregnancies can be associated with an increased risk of complications, resulting primarily from the occurrence of seizures. For example, generalized tonic-clonic seizures have been associated with maternal (and fetal) hypoxia and acidosis, leading to a negative impact on the fetal heart rate. In addition, the trauma resulting from these seizures can yield obstetric complications, including premature labor.

While uncommon, status epilepticus carries a high mortality rate for both mother and fetus. Death or permanent brain damage from seizures is rare but can occur, usually resulting from prolonged anoxia.

For a long time, complex partial seizures were not considered to affect the fetus's heart rate. Case reports have suggested the opposite, but the data are still scant, and additional research is needed to answer this question.

For WWE taking AEDs, there is probably a slightly increased risk (>2 times expected) of caesarian delivery or late pregnancy bleeding, and of premature contractions or premature labor and delivery (>1.5 times expected). In contrast, there is possibly a substantially increased risk of premature contractions and premature labor and delivery for WWE who smoke.<sup>9</sup>

## AEDs in Pregnancy

Most pregnancies—50% to 70%—are unplanned. Therefore, WWE are encouraged to use effective birth control methods until they decide to get pregnant. Furthermore, in women taking AEDs with higher teratogenic risks (eg, valproic acid, phenytoin, phenobarbital, or topiramate), careful planning can allow for a safe conversion to other AEDs with lower teratogenic effects. Stopping AEDs after the patient becomes pregnant is not recommended; the fetus is by then already exposed to the drug during pivotal stages of organ development, and abrupt discontinuation of AEDs places the mother at significant risk of seizure, including status epilepticus.

Recent guidelines emphasized the achievement of a seizure-free period of at least 9 months prior to pregnancy, because this increases the likelihood of remaining seizure-free during pregnancy (84% to 92%).<sup>10</sup>

Major malformations can result from a combination of risk factors, including family history of congenital malformations, age of the mother at conception, type of pharmacologic regimen (monotherapy vs polytherapy), and type of AED.

## Impact of AEDs on the Fetus

Specific major congenital malformations are associated with specific AEDs (TABLE 21.2).

Avoid valproic acid, if possible, in women with epilepsy who are of childbearing age. If it must be used, try to keep doses below 1,000 mg/day and/or serum concentrations below 50 mg/L.

## Management of Pregnancy in WWE

PWWE require closer monitoring of the seizure disorder, and the pregnancy should be followed by an obstetrician specializing in high-risk pregnancy. Monthly prenatal visits are needed. Management requires the use of multivitamins and folic acid supplementation, screening for congenital malformations, monthly monitoring of plasma AED levels, and the administration of Vitamin K before delivery. Folic acid supplementation may be effective in preventing congenital malformations in the offspring of women with epilepsy taking AEDs, and there may be an additional benefit with the use of preconceptional folic acid for WWE. However, use of high doses as an “antidote” for teratogenic risks of AEDs has not been proven and may be potentially hazardous. If seizures are exacerbated, investigate sleep deprivation, recurrent vomiting, and noncompliance with medications.

There is insufficient evidence to determine whether the risk of neonatal hemorrhagic complication is substantially increased in the newborn of WWE taking AEDs. Still, most physicians recommend the administration of prophylactic Vitamin K (10 to 20 mg/day) during the last month of pregnancy in PWWE treated with AEDs to protect the child against bleeding. There is a higher deficiency in Vitamin K–dependent clotting factors when enzyme-inducing AEDs are being administered (eg, phenobarbital, phenytoin, and carbamazepine). All newborns receive intramuscular 1 mg of Vitamin K at birth as routine practice, and fresh frozen plasma can be given if bleeding occurs.<sup>11</sup>



**TABLE 21.2 Seizure Medication Considerations in Women**

1. Women with epilepsy of childbearing age should be educated early in life, and choices reviewed annually.
2. Epilepsy treatment should be optimized **before** family planning since teratogenesis occurs during the first 4 weeks of pregnancy, before most women know they are pregnant.
3. Valproate can cause anovulatory cycles/amenorrhea, sexual dysfunction, and polycystic ovarian like syndrome.

<b>Hormonal contraceptives</b>	<ul style="list-style-type: none"> <li>▶ 1 out of 4 pregnancies are unplanned due to contraception failure in women with epilepsy.</li> <li>▶ Antiepileptic Drugs (AEDs) have potential drug interactions with hormonal contraceptives (HC) including combined oral/patches/emergent, vaginal rings and progesterone implants.</li> <li>▶ AEDs that induce liver enzymes lead to fast metabolism of sex hormones and decreased contraceptive effectiveness:</li> </ul>																												
	<p style="text-align: center;"><b>Decreased Effectiveness of HC (Enzyme Inducing AED)</b></p> <table border="1"> <tr> <td>Carbamazepine</td> <td>Oxcarbazepine</td> <td>Rufinamide</td> </tr> <tr> <td>Clobazam</td> <td>Phenobarbital</td> <td>Topiramate (doses &gt;200 mg/day)</td> </tr> <tr> <td>Eslicarbazepine</td> <td>Phenytoin</td> <td></td> </tr> <tr> <td>Felbamate</td> <td>Primidone</td> <td></td> </tr> </table>			Carbamazepine	Oxcarbazepine	Rufinamide	Clobazam	Phenobarbital	Topiramate (doses >200 mg/day)	Eslicarbazepine	Phenytoin		Felbamate	Primidone		<p style="text-align: center;"><b>No Effect on HC</b></p> <table border="1"> <tr> <td>Acetazolamide</td> <td>Lacosamide</td> <td>Valproate/</td> </tr> <tr> <td>Clonazepam</td> <td>Lamotrigine</td> <td>Divalproex</td> </tr> <tr> <td>Ethosuximide</td> <td>Levetiracetam</td> <td>Vigabatrin</td> </tr> <tr> <td>Gabapentin</td> <td>Pregabalin</td> <td>Zonisamide</td> </tr> </table>			Acetazolamide	Lacosamide	Valproate/	Clonazepam	Lamotrigine	Divalproex	Ethosuximide	Levetiracetam	Vigabatrin	Gabapentin	Pregabalin
Carbamazepine	Oxcarbazepine	Rufinamide																											
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	<ul style="list-style-type: none"> <li>▶ Estrogen lowers lamotrigine levels. Adjust lamotrigine dosing accordingly with any start/stop of estrogen-containing therapies or pregnancy.</li> <li>▶ Better emergency contraceptive options within 120 hours of unprotected sex include a single 3 mg dose of levonorgestrel OR placement of a copper IUD.</li> </ul>																												
<b>Phenytoin</b>	▶ Orofacial cleft	▶ Growth retardation	▶ Microcephaly	▶ Mental deficiency																									
<b>Phenobarbital</b>	▶ Low birth weight	▶ Microcephaly																											
<b>Teratogenicity</b>	<ul style="list-style-type: none"> <li>▶ AED teratogenicity is reinforced by polytherapy and/or folate deficiency.</li> <li>▶ Valproate/Divalproex is the only AED definitively associated with significantly increased risks of major congenital malformations/autism spectrum disorders. If it cannot be avoided, doses of 500 mg/day or less should be used.</li> <li>▶ Topiramate, phenytoin, carbamazepine, and phenobarbital have been associated with malformation at lower rates and appropriate counseling needs to be provided. Early reports suggest pregabalin may carry similar risks.</li> <li>▶ Lamotrigine and levetiracetam carry the lowest risk of overall malformations.</li> </ul>																												
<b>Pregnancy</b>	<ul style="list-style-type: none"> <li>▶ Increased drug clearance is common during pregnancy. This fact is especially relevant with lamotrigine (often requires 3x doses divided every 6-8 hours).</li> <li>▶ Frequent visits and AED levels are recommended to maintain seizure control during the entire pregnancy. Free and total AED levels are useful for older drugs that are highly protein-bound.</li> <li>▶ Lamotrigine and levetiracetam levels may need to be monitored monthly, while other AEDs may be monitored each trimester and 1-2 weeks post-partum.</li> </ul>																												
<b>Post-pregnancy</b>	<ul style="list-style-type: none"> <li>▶ Increased drug clearance during pregnancy gradually reverts to baseline over 2-4 weeks.</li> <li>▶ AED doses should be reduced to prevent toxicity, but with a slightly higher target than pre-pregnancy dose to balance the increased sleep deprivation.</li> </ul>																												
<b>Folate supplementation</b>	<ul style="list-style-type: none"> <li>▶ Folate supplementation is recommended for <b>all</b> women who may become pregnant at no less than 1 mg/day.</li> <li>▶ Women prescribed valproate/divalproex or enzyme-inducing AED may be prescribed 2 mg/day.</li> <li>▶ Women with history of prior pregnancy with neural tube malformation may be prescribed 4 mg/day.</li> </ul>																												
<b>Lactation</b>	<ul style="list-style-type: none"> <li>▶ Breastfeeding is generally promoted regardless of AED as the benefits outweigh known risks. Levels in milk do not necessarily correlate with any known clinical significance.</li> <li>▶ Premature and term neonates exposed to benzodiazepines and barbiturates throughout pregnancy are at risk of withdrawal, especially if formula-fed. Neonates/infants may need to be monitored for sedation and apneas if breastfed.</li> <li>▶ Lamotrigine present in breastmilk may predispose premature neonates to sedation due to immature hepatic function (glucuronidation).</li> </ul>																												

The ECoE Women Veterans with Epilepsy Workgroup developed this document and updates it annually. Consult an ECoE, or visit [www.epilepsy.va.gov](http://www.epilepsy.va.gov) if you have questions. Last revised February 2017.

## Breastfeeding and Women with Epilepsy

Mothers with epilepsy are often concerned about breastfeeding their babies for fear that they are exposing them to AEDs. It may help to note that AED exposure occurred throughout pregnancy at even higher concentrations; AEDs do pass through breast milk in small amounts, but generally the benefits of breastfeeding outweigh any side effects or feeding difficulties for the baby. However, breastfeeding should be undertaken with caution by women on phenobarbital or primidone because of the risk of infant sedation. In the case of certain AEDs, such as lamotrigine, the liver enzymes systems of the newborn may not be mature enough to metabolize the drug at the appropriate rate. It is therefore recommended that serum concentrations and liver function tests be performed for the first 2 weeks of life in full-term babies. In premature babies, however, there are no data on the ability of babies' livers to metabolize this AED at the expected rates.

## Epilepsy in Childbearing Age

There are currently at least 1 million WWE in the United States, and for many of them the contemplation of a possible pregnancy is fraught with issues. Whether pregnancy is an option or not, all women must be placed on folate supplementation and MVI, and their seizure disorder must be treated as often as possible with monotherapy regimens using AEDs that have no or minimal teratogenic risks (eg, lamotrigine or levetiracetam).

Women must be reminded that the majority of pregnancies are unplanned, and effective birth control methods used by the patient or her sexual partner are of the essence. The barrier method cannot rely solely on condoms, which have a 20% to 25% failure rate. Therefore, double-barrier methods (eg, condoms + diaphragm and/or vaginal ring) must be considered.

## Interactions of AEDs and Contraceptive Medications

Unwanted pregnancy is a potential risk for women taking birth control pills and enzyme-inducing AEDs (TABLE 21.3), which accelerate the metabolism of the contraceptives. Indeed, women on enzyme-inducing AEDs have an at least fivefold increase in failure rate with oral contraceptive agents. To counteract this effect, a higher dose of oral contraceptives (at least 50 micrograms of estrogen) or a second contraceptive method is recommended.

Enzyme-inducing AEDs also decrease the efficacy of levonorgestrel implants, and cause unplanned pregnancies by lowering the plasma concentration of the progestin-only contraceptive. In contrast, valproic acid and felbamate,

TABLE 21.3 Enzyme-Inducing AEDs

CYP 3A4 INDUCERS	PROTEIN BINDING %	HALF-LIFE (h)
Carbamazepine	75	9-15
Felbamate	25	13-22
Oxcarbazepine	40	9
Phenobarbital	45	75-110
Phenytoin	90	10-15
Primidone	20	10-15
Topiramate	15	12-24

TABLE 21.4 Second-Generation AEDs

CYP 3A4 NONINDUCERS	PROTEIN BINDING %	HALF-LIFE (h)
Ethosuximide	0	9-15
Gabapentin	0	5-7
Lamotrigine	55	12-62
Levetiracetam	<10	6-8
Pregabalin	0	6-7
Tiagabine	96	7-9
Valproate	90	6-18

both hepatic inhibitors, slow the metabolism of contraceptive hormone and have not been associated with unplanned pregnancies. However, as stated above, valproic acid should be avoided as much as possible.

Second-generation AEDs (TABLE 21.4) are not steroid-hormone enzyme inducers and would likely not interact with oral contraceptives. On the other hand, birth control pills accelerate the metabolism of lamotrigine, as estrogen accelerates glucuronidation, which is the primary metabolic pathway of this AED.

Topiramate (at doses >200 mg/day) and oxcarbazepine (at doses >900 mg/day) are weak inducers of cytochrome P450 enzymes, and can decrease estradiol concentration and contraceptive efficacy.

Recommendation:

- The estrogen dose of oral contraceptive agents must be increased to compensate for the effect of enzyme-inducing AEDs.
- An additional contraceptive method is recommended to avoid contraceptive failure.

## Menopausal Woman and Epilepsy

### Impact of Epilepsy on Menopause

WWE have increased risk of experiencing an early onset of perimenopausal symptoms, which may be the result of epilepsy itself or the use of AEDs, in particular enzyme-inducing drugs, and disruption of hypothalamic-pituitary-gonadal function. For example, there is a significantly higher risk of developing early menopause in WWE.<sup>12</sup>

### Impact of Menopause on Epilepsy

Menopause is associated with an improvement in seizure frequency in one third of WWE, a worsening in one third, and no effect the remaining third. Worsening of seizures has been attributed to changes in the estrogen/progesterone ratio, as discussed above.

The perimenopausal period is particularly associated with hormonal fluctuations that can worsen the seizure frequency, especially in women with catamenial epilepsy, and that revert during the postmenopausal period.

### Hormone Replacement Treatment (HRT) in WWE

Administration of HRT to relieve the menopausal symptoms in WWE may worsen seizure control. If HRT is to be used, natural progesterone and an estrogen compound such as 17- $\beta$ -estradiol should be considered.

## Reproductive and Sexual Dysfunction in Men with Epilepsy

Reproductive and sexual dysfunction in men is attributed to multiple mechanisms, including AED use and epilepsy itself.

Enzyme-inducing AEDs increase the synthesis of SHBG, leading to an increased binding of free testosterone (FT), which may account for decreased libido and infertility. Chronically low FT leads to testicular failure and hypergonadotropic hypogonadism with elevated luteinizing hormone (LH). The use of certain AEDs may impair spermatogenesis, reduce sperm motility, and induce sperm abnormalities, which can obviously have direct effects on fertility in men.

In epilepsy itself, altered modulation of the hypothalamus by medial temporal lobe limbic structures and especially the amygdala can create a hypothalamic-pituitary dysfunction that leads to a chronic state of low LH and to hypogonadotropic hypogonadism.

# Bone Health in Epilepsy

## How AEDs Affect Bone Health

Enzyme-inducing AEDs can affect bone health, causing osteoporosis through multiple mechanisms such as inactivation and acceleration of Vitamin D metabolism, reduction of intestinal calcium absorption, and decreased absorption of hormones such as estrogen, calcitonin, and insulin-like growth factor—reducing the calcium level and promoting bone loss.

## Supporting Bone Health in WWE

For patients taking enzyme-inducing AEDs, it is recommended to take 1,000 mg of calcium and 400 IU of Vitamin D daily. Screening DXA scans are also recommended in PWE taking enzyme inducing AEDs and valproic acid.

The severity of osteoporosis is related to the duration of AED treatment and the use of multiple AEDs. Postmenopausal epileptic WWE are a population at higher risk of osteoporosis; they have been found to have twice as many hip fractures compared to the general population, and should be treated with non-enzyme-inducing AEDs.

Other protective factors against developing osteoporosis include changes in lifestyle by increasing physical activity, preventing falling, cessation of smoking, and avoiding excessive intake of caffeine.

## Conclusion

Reproductive dysfunction is relatively common in women and men with epilepsy, the result of either epilepsy itself or the use of antiepileptic drugs. Hormonal disturbances can manifest as fertility disorders or sexual disturbances. The relationship between epilepsy and hormonal disturbances is bidirectional. Impaired bone health is a common problem in Veterans with epilepsy. ■

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# Social Issues

**DENISE RILEY  
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## Public Attitude

Epilepsy has affected individuals since the dawn of man. Unfortunately, misconceptions about epilepsy and prejudice towards people with epilepsy have existed since then and continue to this day. Epilepsy has been mentioned in the annals of history for centuries. It was associated with either possession by spirits or magical powers. During the last century in the United States, people with epilepsy were forbidden to marry or become parents, and in some states their sterilization was permitted. The last law forbidding marriage of people with epilepsy was repealed in 1980, and the last sterilization law was repealed in 1985.<sup>1</sup>

Although people with epilepsy have more freedom today, discrimination against them abounds. A survey of 19,000 American high school students showed that 19% thought that epilepsy was a mental illness, and 30% were unsure.<sup>2</sup> Another survey examining the perception between violence and seizures was conducted in 1981 and again in 2006. The general population was surveyed, including medical students and physicians. The results from 1981 found that 40% of the general population and medical students answered incorrectly to the questions while physicians answered incorrectly 20% of the time. When the same survey was given again in 2006, the authors found the same error rate among medical students and physicians despite advances in knowledge and epilepsy during the 25-year gap between administration of the surveys.

## Psychological Impact of Epilepsy

A recent systematic review and meta-analysis of depression in patients with epilepsy showed a 23.1% overall prevalence of active depression and a 13% overall prevalence of lifetime depression.<sup>3</sup> Factors that contribute to depression in patients with epilepsy include higher rates of unemployment, increased family discord due to shifted domestic roles, a smaller support and social network, chronic stress from living with a chronic disease, and learned helplessness from recurrent and unpredictable seizures. Neurobiological factors such as subclinical neural discharges in the brain or side effects of AEDs may predispose people with epilepsy to depression.

Due to the high rate of PTSD in our Veteran population and high comorbidity of other psychiatric illnesses, it is imperative that every Veteran with epilepsy be screened for depression at least once a year. Veterans who screen positive for depression can be referred to the robust social work and mental health network within the VA. Resources available to Veterans include one-on-one therapy, group therapy, social work evaluations, and epilepsy support groups.

## Alcohol, Drugs, and Epilepsy

Standard practice during patient visits is to discourage the use of any alcohol, but studies have shown that alcohol intake in small amounts (1 to 2 drinks per day) usually does not increase seizure frequency or alter serum levels of AEDs.<sup>4</sup> In fact, the seizure threshold may actually be raised due to the GABAergic effect of alcohol levels. There is little evidence to support that well-controlled epilepsy patients need to completely abstain from alcohol.<sup>5</sup>

Chronic alcohol ingestion, however, may increase seizure risk. Hypokalemia and head injuries from falls, possible consequences of chronic alcohol abuse, can lower seizure threshold and raise the risk of prolonged seizures. Alcohol-induced stupors may contribute to noncompliance with AEDs and therefore put the patient at risk for more seizures. Because a large proportion of our Veteran population has alcohol- and substance-abuse issues, a thorough assessment of alcohol use is important.

Some animal studies have shown anticonvulsive effects of cannabis.<sup>6</sup> In a recent study, cannabis consumption had no effect on seizures in 84.1% of study participants who were using marijuana. However, marijuana use can lead to forgetfulness, which may lead to AED nonadherence and breakthrough seizures. More clinical trials are needed to clarify the potential therapeutic role for cannabis in epilepsy.<sup>7</sup> The same study showed that frequent use of drugs other than cannabis worsened seizures in 80% of participants.

## Patient and Family Education

Many Veterans with epilepsy and their families feel isolated and stigmatized. There is a wealth of resources available to help answer any questions they may have and to connect them with others in similar situations. Patients with good epilepsy knowledge and coping skills have higher quality-of-life scores. In a recent study, poor epilepsy coping skills led to frequent, worse seizures and poor clinical trajectory of the disease.<sup>8</sup> In light of these findings, it is important for the Veteran's healthcare team to recognize that connecting patients with resources to improve chronic disease self-management skills is just as important as treating them with AEDs.

Veteran quality of life affects family life as well. The severity of tonic-clonic seizures in epilepsy patients was highly correlated with depression and anxiety of family members.<sup>9</sup> A study showed that family members of people with epilepsy wanted more information about epilepsy from healthcare professionals, and appreciated more opportunities to talk about stigmatization and lifestyle changes.<sup>10</sup> As part of a comprehensive epilepsy plan, VA healthcare providers should always offer and provide patient and caregiver education resources.

## Driving

Driving is integrally tied to employment, socialization, and self-esteem, making it a top concern for people living with epilepsy.<sup>11</sup> Driving restrictions for people with active seizures exist in all 50 states, and each state maintains rules about when and how to obtain a driver's license. A person with epilepsy may be held civilly or criminally accountable for motor vehicle accidents caused by seizures.<sup>12</sup> Typical requirements for driving include a period of freedom from seizures that impair consciousness ranging from 3 months to 1 year, as well as written confirmation by a medical provider that seizures are controlled and the citizen does not represent an unreasonable risk to public safety.<sup>12</sup>

Authorization to drive is governed by the laws of the state lived in, not the provider directly. Six states (California, Delaware, New Jersey, Oregon, Pennsylvania, and Nevada) require reporting of patients with seizures to the state, usually the Department of Motor Vehicles (DMV). In all other states, it is the responsibility of patients to report themselves to the DMV and abide by state-established guidelines. Providers are not typically held liable for driving recommendations to the state DMV if based on reasonable care, and always retain the right to report in cases of imminent danger to the public.<sup>11</sup>

A 3-month seizure-free interval is recommended by the American Association of Neurology, American Epilepsy Society, and the Epilepsy Foundation as the optimum balance between preventing motor vehicle accidents and imposing undue hardship on people with epilepsy who would not crash.<sup>11</sup> State law criteria are often not entirely specific to epilepsy, including any medical condition that prevents reasonable control over a motor vehicle; nonepileptic spells, syncope, or spells due to other etiology often fall under these criteria.

Some states permit driving in cases of recurrent seizures that do not impair consciousness or control of movement, occur only at night or at a predictable time of day, or are preceded by an aura. Breakthrough seizures that occur in the setting of extenuating circumstances, such as medication changes as prescribed by a provider or unusual stress, may provide grounds to appeal DMV policy. Some states permit restricted driving privileges. Periodic medical reports are typically required until seizures have stopped or have been controlled for 3 to 5 years.

Federal law prohibits drivers of commercial vehicles, such as delivery trucks, with epilepsy from driving across state lines unless they have been seizure-free off AEDs for 10 years. People with epilepsy may also have difficulty obtaining affordable auto insurance, and false information provided to an insurer may void coverage.<sup>11</sup>

More up-to-date information regarding state-specific driving and epilepsy may be found at the State's DOT or at the Epilepsy Foundation's driving-laws page: <https://www.epilepsy.com/driving-laws>.



## Seizure Precautions

Seizure precautions are guidelines patients can observe to mitigate the risk of injury during a seizure. Prior to any activity, a patient should ask him- or herself, “What would happen if I had a seizure during this?”<sup>13</sup>

**Bathroom safety:** Shower instead of bathing in a tub. If falls occur with seizures, a shower seat with a safety strap may be used. Use nonskid strips in the shower. Do not use electrical equipment near the water. Consider changing shower stall doors to shatterproof glass.<sup>13</sup>

**Kitchen safety:** When alone, use a microwave. Otherwise, cook when someone is nearby. Use the back burners of the stove. Limit time using knives or other sharp kitchen objects. Use shatterproof containers as much as possible.<sup>13</sup>

**Home safety:** Do not smoke or light fireplace fires while alone. Avoid the use of space heaters that can be accidentally overturned. Avoid the use of ladders and stepstools. Purchase power tools and equipment with a safety switch that will stop the machine if the handle is released.<sup>13</sup>

**For parents:** Feed, nurse, dress, or change infants on the floor. Childproof the home as much as possible. As the child grows, explain what seizures mean, and teach them to call 911 in an emergency. Parents can practice “seizure drills” to prepare children for what to do in the event of a seizure.<sup>13</sup>

## Leisure/Sports

People with epilepsy can safely engage in most sports, and many studies conducted over the past 15 years have shown that physical activity does not worsen epilepsy and may even improve seizure control.<sup>14</sup> Engaging in regular physical exercise not only confers cardiovascular, metabolic, cognitive, and emotional benefits but may counteract certain adverse effects of AEDs, such as weight gain and bone weakening.<sup>14</sup> People who get seizures are advised to avoid swimming, doing water sports, or hiking alone. Sports that are not recommended due to extreme risk should a seizure occur include hang-gliding, scuba diving, downhill skiing, horseback riding, free climbing, car/motorcycle racing, sky diving, and high-altitude mountain climbing. No special precautions exist against participation in contact sports such as football, basketball, or soccer with respect to seizures, although risks of head injury should be considered.<sup>14</sup>

It is especially important to avoid dehydration, hypoglycemia, electrolyte imbalances, or hyperthermia, which can provoke seizures, and to exercise on soft surfaces when possible. A person with poorly controlled seizures is at heightened risk of having a seizure during exercise purely by chance. While certain seizure types can rarely be exacerbated by physical activity, people with epilepsy can excel in sports and achieve high levels of physical performance.<sup>14</sup>

## Social Isolation

Epilepsy can lead to psychosocial dysfunction, a restricted lifestyle, and unsatisfactory quality of life. Because seizures can be unpredictable, people with epilepsy restrict or even withdraw from social activities, in part because of fear or embarrassment about having a seizure in public. They can also be subject to negative feelings from the general public due to a lack of knowledge about the disease and fear of not knowing what to do when a person has a seizure.

Studies have shown that people with epilepsy since childhood have a lower incidence of dating, marrying, or having children than those who developed epilepsy at an older age. The reasons can vary, but one thought is that people with epilepsy since childhood have had difficulty making friends and have had challenging social interactions, whether resulting from comorbidities of epilepsy, the seizures themselves, or side effects of medications.<sup>15</sup>

In older patients, epilepsy can lead to social isolation due to stigma, injury, loss of driving privileges, depression, reduced independence, and subsequent premature admission to a nursing home.

## Job Discrimination

Employers can have apprehensions about hiring someone with epilepsy, although people with epilepsy can perform many jobs productively. People with uncontrolled epilepsy, however, should not perform certain jobs, such as welding, construction, or firefighting. Stressors and irregular hours can act as triggers for breakthrough seizures. Other jobs, such as piloting an airplane, with a high potential for risk to public safety have established limitations as to who can perform them.

The Americans with Disabilities Act (ADA) of 1990 prohibits private employers, state and local governments, employment agencies, and labor unions from discriminating against qualified individuals with disabilities in job application procedures, hiring, firing, advancement, compensation, job training, and other privileges of employment.<sup>16</sup> The ADA covers employers with 15 or more employees.

An individual with a disability is a person who has a physical or mental impairment that limits one or more major life activities, has a record of such impairment, or is regarded as having such impairment.

A qualified employee or applicant with a disability is an individual who, with or without reasonable accommodation, can perform the essential functions of the job in question. Reasonable accommodation may include making existing facilities readily accessible to and usable by persons with disabilities, job restructuring, modifying work schedules, reassignment to a vacant position, acquiring or modifying equipment or devices, and adjusting or modifying examinations, training materials, or policies.

An employer is required to make a reasonable accommodation to the known disability of a qualified applicant or employee if it does not impose an undue hardship on the operation of the employer's business. An employer is not required to provide a reasonable accommodation if it imposes an undue hardship. Undue hardship is defined as an action requiring significant difficulty or expense that can affect the size, financial resources, and nature of an employer's operation.

An employer is not required to reduce quality or production standards to make an accommodation. An employer generally does not have to provide a reasonable accommodation unless an individual with a disability has asked for one.

More information on the ADA can be found at the Department of Justice's website: <https://www.ada.gov/employment.htm>.

## School

Some people with epilepsy perform well in school while others do not, just as in the general population. When people with epilepsy do not perform well in school, some of the mitigating factors can include neurobiological (interictal seizure activity, neuronal loss, hippocampal damage), medication (older vs newer seizure medications, polytherapy vs monotherapy, serum levels), or psychosocial factors (anxiety, depression, sleep disorders). Most colleges now have an Office for Student Disabilities, and Veterans returning to school are encouraged to register with them and obtain accommodations that can lead to a successful completion of studies.

## Sex and Relationships

Epilepsy can have an impact on libido or sexual performance in both men and women. Reasons include the psychosocial impact of epilepsy, the effect of epilepsy on brain mechanisms responsible for sexual interest and performance, and the side effects of medications.<sup>15</sup>

Sexual activity in and of itself is not known to be a seizure trigger, but the emotional context in which it occurs, coupled with fear that a seizure may occur, can trigger a seizure.

People with epilepsy should tell others about their diagnosis when they are ready to. It is difficult to say exactly when is appropriate, but letting others know provides an opportunity for educating them about epilepsy. It should also make the person with epilepsy more comfortable in the relationship knowing that, should a seizure occur, friends and loved ones know what to do and how to help.

## Insurance Issues

Receiving medical care at a VA is an entitlement, not insurance, and requires that certain criteria are met (J. Stepp, personal communication, March 5, 2013). These criteria include type of military discharge, time in service, and service connection, as well as assets. Pending results of review, the Veteran is assigned to an enrollment priority group as follows:

- **Enrollment Priority 1:** Veterans with service-connected disabilities rated 50% or more
- **Enrollment Priority 2:** Veterans with service-connected disabilities rated 30% or 40%
- **Enrollment Priority 3:** Former POWs, Veterans awarded the Purple Heart, Veterans whose discharge was for a disability that was incurred or aggravated in the line of duty, and Veterans with service-connected disabilities rated 10% or 20%
- **Enrollment Priority 4:** Veterans who are receiving aid or household benefits; Veterans who have been determined by VA to be catastrophically disabled
- **Enrollment Priority 5:** Nonservice-connected Veterans and noncompensable service-connected Veterans rated 0% disabled whose annual income and net worth are below the established VA Means Test thresholds; Veterans receiving VA pension benefits; Veterans eligible for Medicaid benefits
- **Enrollment Priority 6:** Mexican Border War Veterans; WW I Veterans; compensable 0% service-connected Veterans; Veterans seeking care solely for disorders associated with exposure to herbicides while in Vietnam, exposure to ionizing radiation during occupation of Hiroshima and Nagasaki, disorders associated with service in the Gulf War, illness possibly related to participation in Project 112/SHAD, or illness associated with service in combat after Gulf War or during a period of hostility after 11/11/98
- **Enrollment Priority 7:** Veterans who agree to pay specified copays with income and/or net worth above the VA Means Test threshold and income below the HUD geographic index
- **Enrollment Priority 8:** Veterans who agree to pay specified copays with income and/or net worth above the VA Means Test threshold and the HUD geographic index

Pending the assigned Priority group, Veterans receiving outpatient basic care service are charged a copay of \$15 per visit. Veterans receiving outpatient specialty care service (eg, surgeon, neurologist, cardiologist, or advanced imaging services) are charged a copay of \$50 per visit. The copay is limited to a single charge per visit regardless of the number of healthcare providers seen in a single day and is based on the highest level of service received. There is no copay requirement for preventive care services such as screenings and immunizations.

Veterans in Priority groups 2 through 6 pay \$8 for 30 days or less of medication for treatment of nonservice-connection conditions. Veterans in Priority groups 7 and 8 pay \$9 for 30 days or less of medication for treatment of nonservice-connected conditions.

There is an annual medication copay cap of \$960 for Veterans enrolled in Priority groups 2 through 6. An annual medication copay cap was not established for Veterans enrolled in Priority groups 7 and 8. Veterans who are former POWs are exempt from medication copays. Veterans in Priority group 1 receive outpatient care and medications at no charge.

Veterans in all Priority groups (except group 6) who have insurance have that insurance billed for any VA encounter if care was rendered for a nonservice-connected condition. There is no balance billing to the Veteran.

A Veteran can request a Compensation and Pension eligibility examination at any time through their Service Officer, who collects medical records for review and determination of service-connected conditions.

# Resources for Veterans with Epilepsy

A plethora of resources are available for Veterans living with epilepsy and their caregivers in varying formats and modalities.

## Support Groups

Support groups for Veterans with epilepsy or their caregivers may typically be found through local Epilepsy Foundation chapters or VA medical center educators.

## Online Resources

### ■ VA EPILEPSY CENTERS OF EXCELLENCE [www.epilepsy.va.gov](http://www.epilepsy.va.gov)

Offers information about services available to Veterans at the 16 Epilepsy Centers of Excellence sites located in the VA system. Patient education video and audio lectures about epilepsy are available for patients and their caregivers. There are live patient and caregiver conference calls every other month where patients are able to ask questions. A clinician lecture series is also offered. The Durham VAMC in 2013, for example, hosted a day-long symposium for Veterans and families and covered topics relevant to Veterans.

### ■ "HEADS UP FOR VETS" PROGRAM [www.epilepsy.va.gov/ECofE\\_Kaufmann.asp](http://www.epilepsy.va.gov/ECofE_Kaufmann.asp)

The Epilepsy Centers of Excellence and the Anita Kaufman Foundation, a nonprofit organization working to educate the community about epilepsy, have worked in collaboration to develop this program. The program is designed to provide Veterans returning from military duty information about epilepsy, seizure recognition, and first aid. Also offered are links to social support, employment, transportation, and opportunities to become involved in the epilepsy community as an advocate, volunteer, or educator.

### ■ EPILEPSY FOUNDATION [www.epilepsyfoundation.org](http://www.epilepsyfoundation.org)

The mission of the Epilepsy Foundation is to stop seizures and SUDEP, find a cure, and overcome the challenges created by epilepsy through education, advocacy, and research.

### ■ EPILEPSY.COM [www.epilepsy.com](http://www.epilepsy.com)

The Epilepsy.com website is an initiative of the Epilepsy Foundation. It is a comprehensive website offering clinical information, online forums, chat rooms, e-newsletters, podcasts, and blogs. The site includes a forum devoted to Veterans with seizures.

### ■ DEFENSE AND VETERANS BRAIN INJURY CENTER [www.dvbic.org](http://www.dvbic.org)

DVBIC's mission is to provide service to active-duty military, their beneficiaries, and Veterans with traumatic brain injuries through state-of-the-art clinical care, innovative clinical research initiatives, and educational programs.

### ■ EPILEPSY ADVOCATE [www.epilepsyadvocate.com](http://www.epilepsyadvocate.com)

A community of advocates and caregivers that lets people with epilepsy connect with those who share the same goal of achieving additional seizure control.

### ■ WEBEASE: A WEBINAR FOR PEOPLE WITH EPILEPSY [www.epilepsyfoundation.org/livingwiththeepilepsy/Webease/](http://www.epilepsyfoundation.org/livingwiththeepilepsy/Webease/)

WebEase (Web Epilepsy, Awareness, Support, and Education) is an interactive, on-line self-management program for people with epilepsy.

- MANAGING EPILEPSY WELL NETWORK [www.sph.emory.edu/ManagingEpilepsyWell/](http://www.sph.emory.edu/ManagingEpilepsyWell/)

The Managing Epilepsy Well (MEW) Network is composed of individuals interested in the care of people with epilepsy.

- SEIZURE TRACKER [www.seizuretracker.com](http://www.seizuretracker.com)

An online tool to help patients log and track seizure activity, appointments, and medication schedules through a simple calendar interface from their computer or mobile phone.

## Smartphone and Tablet Apps

- EPILEPSY SOCIETY APP FOR ANDROID OS AND IPHONE

Developed by the Epilepsy Society, the app includes medication reminders, medication lists, first-aid information for seizures, and a seizure diary to track events, triggers, and medication side effects.

- SEIZURE TRACKER APP FOR IPHONE/IPAD

Similar to the Seizure Tracker website described above but available on iPhones and iPads.

## Resources for Caregivers of People with Epilepsy

- NATIONAL MILITARY FAMILY ASSOCIATION [www.militaryfamily.org](http://www.militaryfamily.org)

This organization educates military families concerning rights, benefits, and services available to them.

- STRONG BONDS [www.strongbonds.org](http://www.strongbonds.org)

Strong Bonds has specialized programs for single soldiers, couples, and families. The program empowers soldiers and their loved ones with relationship-building skills, and connects them to community health and support services.

- THE NATIONAL ADULT DAY SERVICES ASSOCIATION [www.nadsa.org](http://www.nadsa.org)

877-745-1440. Helps caregivers find adult day care services that fit their Veteran's needs.

- FAMILY CAREGIVER ALLIANCE [www.caregiver.org](http://www.caregiver.org)

415-434-3388 or 800-445-8106. Offers a caregiver support group

- NATIONAL FAMILY CAREGIVERS ASSOCIATION [www.nfcacares.org](http://www.nfcacares.org)

800-896-3650

- NATIONAL FAMILY CAREGIVERS SUPPORT PROGRAMS [aoa.gov/aoa\\_programs/hcltc/caregiver/](http://aoa.gov/aoa_programs/hcltc/caregiver/)

800-896-3650

## Conclusion

Living with epilepsy is not easy. Epilepsy is a lifelong problem that affects both Veterans and their families. The unpredictability of when and where the next seizure may occur leaves people with epilepsy and their families in constant fear of the unknown. Not only must patients and families handle the complex demands of a chronic illness, they must also cope with prejudice in physical activities, employment, and education.

Veterans and their families often look to their healthcare team as a resource. As healthcare providers in the VA, we know that seizures are not the only problem, and treatment of seizures is not the only help patients and families need. Our goal in writing this chapter is to help VA providers start discussions with patients, answer questions about the socioeconomic issues related to epilepsy, and connect patients with appropriate resources. ■

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# VHA Benefits

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**PAMELA R. KELLY**





# Introduction

This chapter offers a brief synopsis of the Veteran disability process. To gain more detailed information about the Veteran compensation and pension process, consult the Veteran government website ([www.va.gov](http://www.va.gov)) or call toll-free (1-800-827-1000) with specific questions. Additionally, many Veterans need advocates that can assist them in contacting people in the community who can help locate and complete VA forms. State service officers, from all service organizations, are available to sponsor Veterans in the enrollment and disability processes. These services are free to the Veteran. Posting the VA website and the telephone number (noted above) in the office would be a welcome act of humanitarianism toward the Veteran community, which is often victimized by confidence schemes.

## Overview

In accordance with the laws originating in response to President Lincoln's declaration "to care for those who have borne the battle," Veterans qualify for healthcare services. After a Veteran applies for enrollment in the VA system, he or she is assigned to one of eight category groups, designated Priority 1 through 8, with 1 being the highest priority. Category assignments are used to determine enrollment but should not affect treatment by providers of patients after enrollment is complete. The category assignments are identified using factors associated with service-connected disabilities, disability ratings, era of service, and other special eligibility classification. Detailed category listings can be found on the VA website.

Veterans with service-connected disabilities rated 50% or more are considered category 1 Veterans. Veterans with less than 50% can be assigned to category 2 or 3. Categories 4 through 6 are used to identify Veterans with 0% compensable service connections. Veterans assigned to categories 7 and 8 agree to pay copayments based on income and/or net worth. It is important that providers ensure that medical records and documentation note clear relationships or associations with diseases or injuries—some Veterans (category dependent) are responsible for payment of healthcare for nonservice-connected injuries and diagnosis. An administrative review of records for diagnostic coding is used to determine copay requirements for the Veteran as well as billing and insurance coverage, a process similar to that in civilian healthcare organizations.

A Veteran's condition is considered service-connected if there is a relationship between the particular disability condition and military service time. The condition referenced must have begun during service, be a pre-existing condition that was permanently worsened, or considered due to the statutory presumptions. In the instance of statutory function there is a preconceived but not necessarily proven notion that the condition is most probably a result of or related to an activity or potential exposure occurrences (eg, agent orange).

There are four ways to establish service connection: direct, aggravation, presumptive, and secondary. Service time is a significant factor in the adjudication decision for each of the four ways identified (TABLE 23.1).

- **Direct:** There is a direct relationship between the disability and an injury or incident of service while on active duty, such as confirmed epilepsy or seizures as a result of a traumatic brain injury.
- **Aggravation:** A pre-existing disability that becomes worse during service as result of injury or incident, such as periodic headaches that progress to periodic migraines that can be associated with activities of service (eg, working in engine room).
- **Presumptive:** There is a list of specific chronic and tropical diseases that are presumed to have begun during service and manifested to a compensable degree over time (if there is no prior evidence of the disease before service time).
- **Secondary:** A new condition directly and proximately caused by an established service-connected disability, such as a knee injury that affects gait for a significant length of time and results in back disability.

Service connection may not be established for any disease or injury that is not incurred or aggravated in the line of duty or that is a result of willful misconduct. Service record documentation, Veteran statements, and medical documentation are all used to determine original disability rating, and subsequent reviews can result in changes in the rating. At the time of adjudication, paperwork will note a timeline for future reviews as deemed appropriate. Re-evaluations are scheduled based on defined timelines of reviewers or at the request of a Veteran that feels that his or her disabilities have worsened.

In summary, a Veteran wishing to file a service-connected disability claim is responsible for providing evidence and insuring that all information to be considered is in the record at the time of the decision. There are three evidentiary points that **MUST** be met:

1. Medical evidence of a disability
2. Incurrence or aggravation of condition while on active duty or within one year of service
3. A link from the incident or occurrence referenced in point 2 to the disability referenced in point 1

Specific documents are required to initiate a disability claim. VA forms are available at [www.va.gov/vaforms/contact.asp](http://www.va.gov/vaforms/contact.asp) or by contacting one of the service organizations for help. Key documents for entering a claim are listed below:

- DD214
- VA Form 21-22
- VA Form 21-526
- VA Form 21-527 EZ
- Current medical evidence confirming disability
- SSNs of dependents
- Marriage certificate (current spouse)
- Divorce decrees or death certificates of previous spouses
- Birth certificates of dependents or adoption papers for minor children

## Seizure Benefits

As previously noted, medical documentation in patient records is essential in the disability claims review. In addition to the providers' notes, admissions, and other materials that can be found in the patient's record, some medically diagnosed conditions require that additional forms be completed. For claims review of seizure disorders, the following information is important for the determination of disability rating:

- VA Form 21-0960C-11, Seizure disorders (epilepsy) disability benefits questionnaire
- Rating determination
- Global Assessment of Functionality (GAF) score
- Number of seizures
- Type of seizures

Although all claims are reviewed individually, and there are no guarantees about rating results, there are general guidelines used by VA claims raters. The guidelines focus on the type and number of seizures over time (TABLE 23.2).

A patient may not clearly fall into any of the medical descriptive categories, and the guidelines are not expected to be a template for provider notation. Your responsibility as a clinician does not extend beyond the general quality of practice of evidence-based medicine with accurate and clear documentation. VA Form 21-0960C-11 (FIGURE 23.1) is the required documentation form used to highlight medical information that should already be in the patient's record. Section 1 refers to the specifics of the diagnosis. Sections 2 and 3 are completed using record review and history. The diagnostic code in the 38 C.F.R. for Epilepsy is 8911.

It is important to note that guidelines for adjudication determinations are reviewed periodically per schedule or for cause. Approved changes are documented and communicated with specific guidance for implementation time-lines that can include options for retroactive applicable factors. Veterans should read all materials received thoroughly and take action as deemed appropriate. Providers should ensure that the adjudication documentation forms completed are the most current ones. Rating formulas and forms are readily available online. To ensure that Veterans in your care are well informed and receiving the assistance needed beyond their clinical healthcare, it is important that Veterans are directed to the available resources.

**TABLE 23.1 Length-of-Service Requirements**

TYPE OF SERVICE CONNECTION	SERVICE TIME
<b>Direct</b>	No minimal length of time
<b>Presumptive (chronic or tropical)</b>	90 consecutive days during wartime or after January 31, 1946
<b>Presumptive (disease and disability for POW)</b>	Dependent on specific disability or incarceration period

**TABLE 23.2 General Rating Formula for Epileptic Seizures**

MEDICAL DESCRIPTION	RECOMMENDED RATING
Averaging at least 1 major seizure per month over the last year	100%
Averaging at least 1 major seizure in 3 months over the last year, or more than 10 minor seizures weekly	80%
Averaging at least 1 major seizure in 4 months over the last year, or 9 to 10 minor seizures per week	60%
At least 1 major seizure in the last 6 months or 2 in the last year, or averaging 5 to 8 minor seizures weekly	40%
At least 1 major seizure in the last 2 years, or at least 2 minor seizures in the last 6 months	20%

This is only a guide. All cases are reviewed, and determinations are made on the basis of individual circumstances and documentation.

FIGURE 23.1 Form 21-0960C-11: Seizure Disorders (Epilepsy) Disability Benefits Questionnaire

OMB Approved No. 2900-0781  
Respondent Burden: 15 minutes

<b>Department of Veterans Affairs</b>	<b>SEIZURE DISORDERS (EPILEPSY) DISABILITY BENEFITS QUESTIONNAIRE</b>
<b>IMPORTANT - THE DEPARTMENT OF VETERANS AFFAIRS (VA) <i>WILL NOT PAY</i> OR <i>REIMBURSE</i> ANY EXPENSES OR COST INCURRED IN THE PROCESS OF COMPLETING AND/OR SUBMITTING THIS FORM. PLEASE READ THE PRIVACY ACT AND RESPONDENT BURDEN INFORMATION BEFORE COMPLETING FORM.</b>	
NAME OF PATIENT/VETERAN	PATIENT/VETERAN'S SOCIAL SECURITY NUMBER
<b>NOTE TO PHYSICIAN -</b> Your patient is applying to the U.S. Department of Veterans Affairs (VA) for disability benefits. VA will consider the information you provide on this questionnaire as part of their evaluation in processing the veteran's claim.	
<b>SECTION I - DIAGNOSIS</b>	
<b>1A. DOES THE VETERAN HAVE OR HAS HE OR SHE EVER BEEN DIAGNOSED WITH A SEIZURE DISORDER (epilepsy)? (This is the condition the veteran is claiming or for which an exam has been requested)</b> <input type="checkbox"/> YES <input type="checkbox"/> NO <i>(If "Yes," complete Item 1B)</i>	
<b>1B. SELECT THE APPROPRIATE DIAGNOSIS: (check all that apply):</b>	
<input type="checkbox"/> TONIC-CLONIC SEIZURES OR GRAND MAL EPILEPSY <i>(generalized convulsive seizures)</i> <input type="checkbox"/> ABSENCE SEIZURES OR PETIT MAL OR ATONIC SEIZURES <i>(generalized non-convulsive seizures)</i> <input type="checkbox"/> JACKSONIAN <i>(simple partial seizures)</i> <input type="checkbox"/> FOCAL MOTOR <input type="checkbox"/> FOCAL SENSORY <input type="checkbox"/> DIENCEPHALIC EPILEPSY <input type="checkbox"/> PSYCHOMOTOR EPILEPSY <i>(complex partial seizures, temporal lobe seizures)</i> <input type="checkbox"/> OTHER <i>(specify)</i> Other diagnosis #1 _____ Other diagnosis #2 _____	ICD Code: _____    Date of diagnosis: _____ ICD Code: _____    Date of diagnosis: _____ ICD Code: _____    Date of diagnosis: _____ ICD Code: _____    Date of diagnosis: _____ ICD Code: _____    Date of diagnosis: _____ ICD Code: _____    Date of diagnosis: _____ ICD Code: _____    Date of diagnosis: _____ ICD Code: _____    Date of diagnosis: _____ ICD Code: _____    Date of diagnosis: _____
<b>1C. IF THERE ARE ADDITIONAL DIAGNOSES THAT PERTAIN TO SEIZURE DISORDERS (epilepsy), LIST USING ABOVE FORMAT:</b>	
<b>SECTION II - MEDICAL RECORD REVIEW</b>	
<b>2. INDICATE MEDICAL RECORDS REVIEWED IN PREPARATION OF THIS REPORT:</b> <input type="checkbox"/> C-FILE (VA ONLY) <input type="checkbox"/> OTHER, DESCRIBE: _____	
<b>SECTION III - MEDICAL HISTORY</b>	
<b>3A. DESCRIBE THE HISTORY (including onset and course) OF THE VETERAN'S SEIZURE DISORDER (epilepsy) (brief summary):</b>	
<b>3B. IS CONTINUOUS MEDICATION REQUIRED FOR CONTROL OF EPILEPSY OR SEIZURE ACTIVITY?</b> <input type="checkbox"/> YES <input type="checkbox"/> NO <i>(If "Yes," list only those medications required for the veteran's epilepsy or seizure activity)</i>	
<b>3C. HAS THE VETERAN HAD ANY OTHER TREATMENT (such as surgery) FOR EPILEPSY OR SEIZURE ACTIVITY?</b> <input type="checkbox"/> YES <input type="checkbox"/> NO <i>(If "Yes," describe):</i>	
<b>3D. HAS THE DIAGNOSIS OF A SEIZURE DISORDER BEEN CONFIRMED?</b> <input type="checkbox"/> YES <input type="checkbox"/> NO <i>(If "Yes," describe):</i>	
<b>3E. HAS THE VETERAN HAD A WITNESSED SEIZURE?</b> <input type="checkbox"/> YES <input type="checkbox"/> NO <i>(If "Yes," describe, including relationship of witnesses to veteran):</i>	

FIGURE 23.1 Form 21-0960C-11: Seizure Disorders (Epilepsy) Disability Benefits Questionnaire (cont.)

SECTION IV - FINDINGS, SIGNS AND SYMPTOMS	
<p>4. DOES THE VETERAN HAVE OR HAS HE OR SHE HAD ANY FINDINGS, SIGNS OR SYMPTOMS ATTRIBUTABLE TO SEIZURE DISORDER (<i>epilepsy</i>) ACTIVITY?</p> <p><input type="checkbox"/> YES   <input type="checkbox"/> NO   (<i>If "Yes," check all that apply</i>)</p> <ul style="list-style-type: none"> <li><input type="checkbox"/> Generalized tonic-clonic convulsion</li> <li><input type="checkbox"/> Episodes of unconsciousness</li> <li><input type="checkbox"/> Brief interruption in consciousness or conscious control</li> <li><input type="checkbox"/> Episodes of staring</li> <li><input type="checkbox"/> Episodes of rhythmic blinking of the eyes</li> <li><input type="checkbox"/> Episodes of nodding of the head</li> <li><input type="checkbox"/> Episodes of sudden jerking movement of the arms, trunk or head (myoclonic type)</li> <li><input type="checkbox"/> Episodes of sudden loss of postural control (akinetic type)</li> <li><input type="checkbox"/> Episodes of complete or partial loss of use of one or more extremities</li> <li><input type="checkbox"/> Episodes of random motor movements</li> <li><input type="checkbox"/> Episodes of psychotic manifestations</li> <li><input type="checkbox"/> Episodes of hallucinations</li> <li><input type="checkbox"/> Episodes of perceptual illusions</li> <li><input type="checkbox"/> Episodes of abnormalities of thinking</li> <li><input type="checkbox"/> Episodes of abnormalities of memory</li> <li><input type="checkbox"/> Episodes of abnormalities of mood</li> <li><input type="checkbox"/> Episodes of autonomic disturbances</li> <li><input type="checkbox"/> Episodes of speech disturbances</li> <li><input type="checkbox"/> Episodes of impairment of vision</li> <li><input type="checkbox"/> Episodes of disturbances of gait</li> <li><input type="checkbox"/> Episodes of tremors</li> <li><input type="checkbox"/> Episodes of visceral manifestations</li> <li><input type="checkbox"/> Residuals of Injury during seizure</li> <li><input type="checkbox"/> Other</li> </ul> <p><i>(For all checked conditions describe):</i></p>	
SECTION V - TYPE AND FREQUENCY OF SEIZURE ACTIVITY	
<p>5.A. DOES THE VETERAN HAVE OR HAS HE OR SHE EVER HAD ANY TYPE OF SEIZURE ACTIVITY, INCLUDING MAJOR, MINOR, PETIT MAL OR PSYCHOMOTOR SEIZURE ACTIVITY?</p> <p><input type="checkbox"/> YES   <input type="checkbox"/> NO   (<i>If "Yes," complete Items 5B through 5H</i>)</p>	
<p>5B. PROVIDE APPROXIMATE DATE OF FIRST SEIZURE ACTIVITY (<i>Month, Year</i>) _____</p> <p>PROVIDE DATE OF MOST RECENT SEIZURE ACTIVITY (<i>Month, Year</i>) _____</p>	
<p>5C. HAS THE VETERAN EVER HAD MINOR SEIZURES (<i>characterized by a brief interruption in consciousness or conscious control associated with staring or rhythmic blinking of the eyes or nodding of the head ("pure" petit mal) or sudden jerking movements of the arms, trunk or head (myoclonic type) or sudden loss of postural control (akinetic type)</i>)?</p> <p><input type="checkbox"/> YES   <input type="checkbox"/> NO   (<i>If "Yes," complete the following</i>):</p> <p><b>Number of minor seizures over past 6 months:</b></p> <p><input type="checkbox"/> 0-1</p> <p><input type="checkbox"/> 2 or more</p> <p>If 2 or more over the past 6 months, indicate the average frequency of minor seizures:</p> <p><input type="checkbox"/> 0-4 per week   <input type="checkbox"/> 5-8 per week   <input type="checkbox"/> 9-10 per week   <input type="checkbox"/> More than 10 per week</p>	
<p>4D. HAS THE VETERAN EVER HAD MAJOR SEIZURES (<i>characterized by the generalized tonic-clonic convulsion with unconsciousness</i>)?</p> <p><input type="checkbox"/> YES   <input type="checkbox"/> NO   (<i>If "Yes," complete the following</i>):</p> <p><b>Number of major seizures:</b></p> <p><input type="checkbox"/> None in past 2 years   <input type="checkbox"/> At least 1 in past 2 years   <input type="checkbox"/> At least 2 in past year</p> <p><b>Average frequency of major seizures:</b></p> <p><input type="checkbox"/> Less than 1 in past 6 months</p> <p><input type="checkbox"/> At least 1 in past 6 months</p> <p><input type="checkbox"/> At least 1 in 4 months over past year</p> <p><input type="checkbox"/> At least 1 in 3 months over past year</p> <p><input type="checkbox"/> At least 1 per month over past year</p>	

FIGURE 23.1 Form 21-0960C-11: Seizure Disorders (Epilepsy) Disability Benefits Questionnaire (cont.)

SECTION IV - TYPE AND FREQUENCY OF SEIZURE ACTIVITY <i>(Continued)</i>																		
<p>5E. HAS THE VETERAN EVER HAD MINOR PSYCHOMOTOR SEIZURES (<i>characterized by brief transient episodes of random motor movements, hallucinations, perceptual illusions, abnormalities of thinking, memory or mood, or autonomic disturbances</i>)?</p> <p><input type="checkbox"/> YES <input type="checkbox"/> NO (<i>If "Yes," complete the following</i>):</p> <p><b>Number of minor psychomotor seizures over past 6 months:</b></p> <p><input type="checkbox"/> 0 <input type="checkbox"/> 1 <input type="checkbox"/> 2 or more</p> <p>If 2 or more over the past 6 months, indicate the average frequency of minor psychomotor seizures:</p> <p><input type="checkbox"/> 0-4 per week  <input type="checkbox"/> 5-8 per week  <input type="checkbox"/> 9-10 per week  <input type="checkbox"/> More than 10 per week</p>																		
<p>5F. HAS THE VETERAN EVER HAD MAJOR PSYCHOMOTOR SEIZURES (<i>major psychomotor seizures are characterized by automatic states and/or generalized convulsions with unconsciousness</i>)?</p> <p><input type="checkbox"/> YES <input type="checkbox"/> NO (<i>If "Yes," complete the following</i>):</p> <p><b>Number of major psychomotor seizures:</b></p> <p><input type="checkbox"/> None in past 2 years  <input type="checkbox"/> At least 1 in past 2 years  <input type="checkbox"/> At least 2 in past year</p> <p><b>Average frequency of major psychomotor seizures:</b></p> <p><input type="checkbox"/> Less than 1 in past 6 months  <input type="checkbox"/> At least 1 in past 6 months  <input type="checkbox"/> At least 1 in 4 months over past year  <input type="checkbox"/> At least 1 in 3 months over past year  <input type="checkbox"/> At least 1 per month over past year</p>																		
<p>5G. HAS THE VETERAN EVER HAD EPILEPSY ASSOCIATED WITH A NONPSYCHOTIC ORGANIC BRAIN SYNDROME?</p> <p><input type="checkbox"/> YES <input type="checkbox"/> NO (<i>If "Yes," describe</i>):</p>																		
<p>5H. HAS THE VETERAN EVER HAD EPILEPSY ASSOCIATED WITH A PSYCHOTIC DISORDER, PSYCHONEUROTIC DISORDER OR PERSONALITY DISORDER?</p> <p><input type="checkbox"/> YES <input type="checkbox"/> NO (<i>If "Yes," the appropriate Mental Disorder Questionnaire must ALSO be completed</i>)</p>																		
SECTION VI - OTHER PERTINENT PHYSICAL FINDINGS, COMPLICATIONS, CONDITIONS, SIGNS AND/OR SYMPTOMS																		
<p>6A. DOES THE VETERAN HAVE ANY SCARS (<i>surgical or otherwise</i>) RELATED TO ANY CONDITIONS OR TO THE TREATMENT OF ANY CONDITIONS LISTED IN SECTION I, DIAGNOSIS?</p> <p><input type="checkbox"/> YES <input type="checkbox"/> NO</p> <p>(<i>If "Yes," are any of the scars painful and/or unstable, or is the total area of all related scars greater than or equal to 39 square cm (6 square inches)</i>)?</p> <p><input type="checkbox"/> YES <input type="checkbox"/> NO (<i>If "Yes," also complete the VA Form 21-0960F-1, Scars/Disfigurement Disability Benefits Questionnaire</i>)</p>																		
<p>6B. DOES THE VETERAN HAVE ANY OTHER PERTINENT PHYSICAL FINDINGS, COMPLICATIONS, CONDITIONS, SIGNS AND/OR SYMPTOMS RELATED TO ANY CONDITIONS LISTED IN SECTION I, DIAGNOSIS?</p> <p><input type="checkbox"/> YES <input type="checkbox"/> NO (<i>If "Yes," describe (brief summary)</i>):</p>																		
SECTION VII - DIAGNOSTIC TESTING																		
<p><b>NOTE</b> - If diagnostic test results are in the medical record and reflect the veteran's current seizure (epilepsy) disorder, repeat testing is not required.</p>																		
<p>7A. HAVE ANY IMAGING STUDIES OR DIAGNOSTIC PROCEDURES BEEN PERFORMED?</p> <p><input type="checkbox"/> YES <input type="checkbox"/> NO (<i>If "Yes," check all that apply</i>)</p> <table style="width: 100%; border: none;"> <tr> <td style="width: 40%;"><input type="checkbox"/> Magnetic resonance imaging (MRI)</td> <td style="width: 20%;">Date: _____</td> <td style="width: 40%;">Results: _____</td> </tr> <tr> <td><input type="checkbox"/> Computed tomography (CT)</td> <td>Date: _____</td> <td>Results: _____</td> </tr> <tr> <td><input type="checkbox"/> Cerebrospinal fluid CSF examination</td> <td>Date: _____</td> <td>Results: _____</td> </tr> <tr> <td><input type="checkbox"/> Electroencephalography (EEG)</td> <td>Date: _____</td> <td>Results: _____</td> </tr> <tr> <td><input type="checkbox"/> Neuropsychologic testing</td> <td>Date: _____</td> <td>Results: _____</td> </tr> <tr> <td><input type="checkbox"/> Other (<i>describe</i>): _____</td> <td>Date: _____</td> <td>Results: _____</td> </tr> </table>	<input type="checkbox"/> Magnetic resonance imaging (MRI)	Date: _____	Results: _____	<input type="checkbox"/> Computed tomography (CT)	Date: _____	Results: _____	<input type="checkbox"/> Cerebrospinal fluid CSF examination	Date: _____	Results: _____	<input type="checkbox"/> Electroencephalography (EEG)	Date: _____	Results: _____	<input type="checkbox"/> Neuropsychologic testing	Date: _____	Results: _____	<input type="checkbox"/> Other ( <i>describe</i> ): _____	Date: _____	Results: _____
<input type="checkbox"/> Magnetic resonance imaging (MRI)	Date: _____	Results: _____																
<input type="checkbox"/> Computed tomography (CT)	Date: _____	Results: _____																
<input type="checkbox"/> Cerebrospinal fluid CSF examination	Date: _____	Results: _____																
<input type="checkbox"/> Electroencephalography (EEG)	Date: _____	Results: _____																
<input type="checkbox"/> Neuropsychologic testing	Date: _____	Results: _____																
<input type="checkbox"/> Other ( <i>describe</i> ): _____	Date: _____	Results: _____																
<p>7B. ARE THERE ANY OTHER SIGNIFICANT DIAGNOSTIC TEST FINDINGS AND/OR RESULTS?</p> <p><input type="checkbox"/> YES <input type="checkbox"/> NO (<i>If "Yes," provide type of test or procedure, date and results (brief summary)</i>):</p>																		

**FIGURE 23.1 Form 21-0960C-11: Seizure Disorders (Epilepsy) Disability Benefits Questionnaire (cont.)**

<b>SECTION VIII - FUNCTIONAL IMPACT</b>		
8. DOES THE VETERAN'S EPILEPSY OR SEIZURE ( <i>epilepsy</i> ) DISORDER IMPACT HIS OR HER ABILITY TO WORK? <input type="checkbox"/> YES <input type="checkbox"/> NO    ( <i>If "Yes," describe the impact of the veteran's seizure (epilepsy) disorder, providing one or more examples:</i> )		
<b>SECTION IX - REMARKS</b>		
9. REMARKS ( <i>If any</i> )		
<b>SECTION X - PHYSICIAN'S CERTIFICATION AND SIGNATURE</b>		
<b>CERTIFICATION</b> - To the best of my knowledge, the information contained herein is accurate, complete and current.		
10A. PHYSICIAN'S SIGNATURE	10B. PHYSICIAN'S PRINTED NAME	10C. DATE SIGNED
10D. PHYSICIAN'S PHONE AND FAX NUMBER	10E. PHYSICIAN'S MEDICAL LICENSE NUMBER	10F. PHYSICIAN'S ADDRESS
<b>NOTE</b> - VA may request additional medical information, including additional examinations, if necessary to complete VA's review of the veteran's application.		
<b>IMPORTANT</b> - Physician please fax the completed form to: _____ <div style="text-align: center;"><i>(VA Regional Office FAX No.)</i></div>		
<b>NOTE</b> - A list of VA Regional Office FAX Numbers can be found at <a href="http://www.benefits.va.gov/disabilityexams">www.benefits.va.gov/disabilityexams</a> or obtained by calling 1-800-827-1000.		
<b>PRIVACY ACT NOTICE:</b> VA will not disclose information collected on this form to any source other than what has been authorized under the Privacy Act of 1974 or Title 38, Code of Federal Regulations 1.576 for routine uses (i.e., civil or criminal law enforcement, congressional communications, epidemiological or research studies, the collection of money owed to the United States, litigation in which the United States is a party or has an interest, the administration of VA programs and delivery of VA benefits, verification of identity and status, and personnel administration) as identified in the VA system of records, 58/VA21/22/28, Compensation, Pension, Education and Vocational Rehabilitation and Employment Records - VA, published in the Federal Register. Your obligation to respond is voluntary. VA uses your SSN to identify your claim file. Providing your SSN will help ensure that your records are properly associated with your claim file. Giving us your SSN account information is voluntary. Refusal to provide your SSN by itself will not result in the denial of benefits. VA will not deny an individual benefits for refusing to provide his or her SSN unless the disclosure of the SSN is required by a Federal Statute of law in effect prior to January 1, 1975, and still in effect. The requested information is considered relevant and necessary to determine maximum benefits under the law. The responses you submit are considered confidential (38 U.S.C. 5701). Information submitted is subject to verification through computer matching programs with other agencies.		
<b>RESPONDENT BURDEN:</b> We need this information to determine entitlement to benefits (38 U.S.C. 501). Title 38, United States Code, allows us to ask for this information. We estimate that you will need an average of 15 minutes to review the instructions, find the information, and complete the form. VA cannot conduct or sponsor a collection of information unless a valid OMB control number is displayed. You are not required to respond to a collection of information if this number is not displayed. Valid OMB control numbers can be located on the OMB Internet Page at <a href="http://www.reginfo.gov/public/do/PRAMain">www.reginfo.gov/public/do/PRAMain</a> . If desired, you can call 1-800-827-1000 to get information on where to send comments or suggestions about this form.		

## Summary

Veterans with healthcare needs are encouraged to enroll in the VHA. Veterans wishing to file a claim for compensation and or pension are encouraged to see their local County Veteran Service Officer (CVSO) and/or state Veteran Service Officer (VSO) representatives. Information identifying these representatives can be found on the VA or state-specific government websites. Charges for healthcare are based on the Veteran's category of enrollment and whether the services required are related to service-connected injuries or diagnoses. Seeking healthcare in the VHA (enrollment) and applying for disability benefits are two independent processes. Veterans should complete appropriate paperwork and submit to the VBA for ruling on adjudication. There is no timeframe for submission on a service-connected benefit. Specific to epilepsy, VA Form 21-0960C-11 should be submitted along with appropriate paperwork for benefits. Veterans requiring assistance with VBA or VHA documents should be directed to local or state offices. Several recognized service organizations assist Veterans free of charge; a list of those organizations can be found on VA Form 21-22. ■

## REFERENCE

[www.va.gov](http://www.va.gov)





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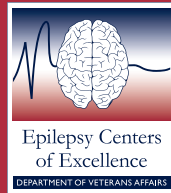
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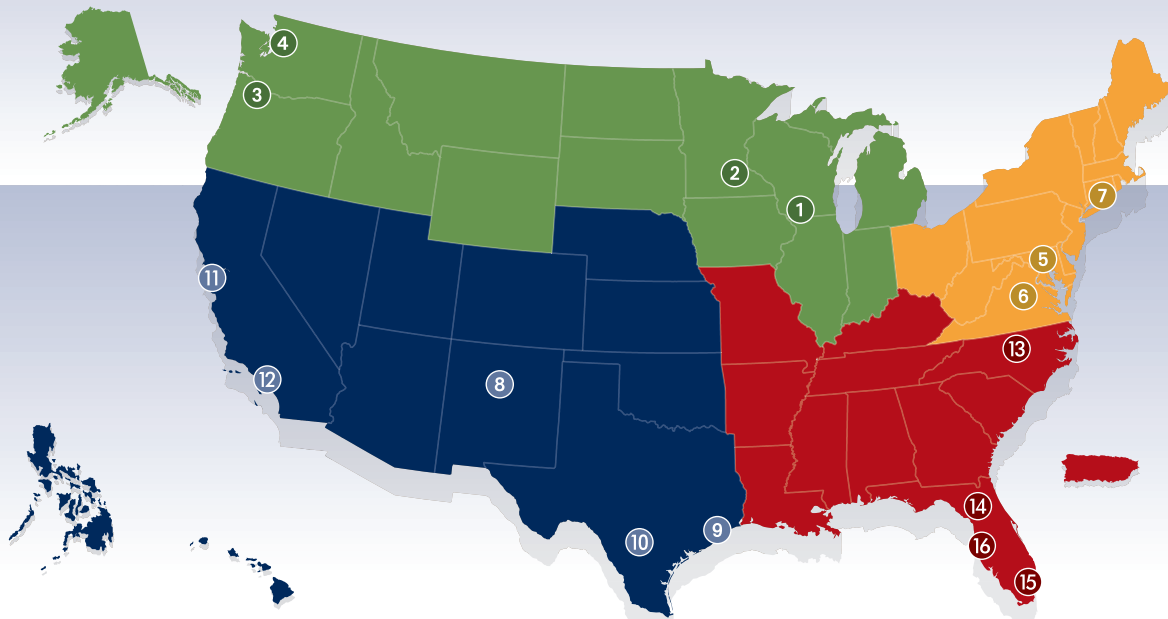
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