Epilepsy in the Oral and Maxillofacial Patient: Current Therapy

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Epilepsy is a common disease often encountered in the practice of oral and maxillofacial surgery. The worldwide prevalence has been estimated to range from 0.5% to 0.9% in the general population, affecting approximately 50 million individuals.[1] The periods of highest incidence occur in patients younger than 1 year and in patients older than 75 years.[2] Using antiepileptic medications, 50% to 65% of these patients become seizure free. Oral and maxillofacial surgeons treat patients on a regular basis for routine dentoalveolar surgery, as well as managing facial trauma sustained secondary to falls during seizures. The pathophysiology, classification, and treatment of seizures are discussed here, as are alterations in management for the oral and maxillofacial surgeon.

A *seizure* is defined as an episodic disturbance of movement, feeling, or consciousness that can be caused by sudden synchronous, inappropriate, and excessive electrical discharges that interfere with the normal function of the brain.[3] The term *epilepsy* is defined as a disease of frequent seizures that do not have a reversible metabolic cause.[4] Epilepsy can be caused by either abnormal neuronal membrane function or an alteration between the excitatory and inhibitory neurons. The postictal period is the time immediately following the seizure when there is a depression in the neurologic function. The interictal period refers to the time when the individual is at baseline neurologic function.

In approximately 70% of all epilepsy cases, the specific etiology cannot be determined. These cases are classified as idiopathic or primary epilepsy.[1] Seizures with known causes are termed acquired or secondary epilepsy. Secondary epilepsy can be a result of a wide range of metabolic, genetic, structural, and functional abnormalities.[5] Metabolic disturbances that cause seizures include electrolyte imbalances, acidosis, hyperglycemia, hypoglycemia, hypoxia, alcohol and barbiturate withdrawal, dehydration, and water intoxication.[4] Systemic disorders that can cause seizures are sepsis, systemic lupus erythematosus, hypertension, and diabetes. The remaining cases are caused by cerebral blood vessel malformations, brain tumors and hamartomas, hypoxic-ischemic lesions, and infectious processes.[6]

The etiologies of seizures in adults are only identifiable in one third to one half of cases. Cerebrovascular disease is the most common cause and accounts for 40% of all cases. The second most common cause consists of primary and metastatic brain tumors.[7] Pediatric epilepsies are normally idiopathic and are thought to be genetically determined.

Most inheritable epilepsies are transmitted in a complex, multifactorial nature. Epilepsy genes are related to mutations that result in abnormal brain development, neurodegeneration, and abnormal function. Several hereditary epilepsies have been related to genes that encode ion channels or functionally related proteins. Three forms of autosomal dominantly inherited human epilepsy have been localized (Table 1). These are benign familial neonatal convulsions, generalized epilepsy with febrile seizures, and a partial epilepsy syndrome. A benign familial neonatal convulsion arises in infants with mutations of voltage-gated potassium channels and presents with the onset of convulsions a few days after birth. This disease usually disappears by the sixth week of life. Generalized epilepsy with febrile seizures is an epilepsy syndrome characterized by heterogeneous phenotypes including febrile seizures and mild to severe generalized epilepsies (to be defined later). These seizures follow an autosomal dominant inheritance pattern with a 60% penetrance.[8] A partial epilepsy syndrome, which is also autosomal dominant, is associated with a mutation in a central nicotinic acetylcholine receptor and presents with a nocturnal frontal-lobe epi-

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Table 1. INHERITABLE SEIZURE DISORDERS

Benign familial neonatal convulsions
Generalized epilepsy with febrile seizures
Partial epilepsy syndrome/nocturnal frontal lobe epilepsy

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lepsy. This type of inheritable epilepsy does not present until later on in the child's development and can persist into adulthood. This disorder is characterized by the onset of typical absence seizures (to be defined later) in healthy children. It initially presents between the ages of 4 and 8 years, with a seizure frequency ranging up to hundreds per day. The absence seizures tend to remit in adolescence.

Classification

Seizures are, in part, classified by the clinical manifestations of a seizure (Table 2). Seizures that are initiated in a discrete area of the cerebral cortex are termed partial seizures. Seizures involving both cerebral hemispheres initially are termed generalized seizures. These attributes are based on electroencephalographic (EEG) signs and clinical symptoms. Partial seizures can remain focal during the event or may spread along the neuronal pathways to various regions of a hemisphere. Partial seizures that propagate to involve the 2 hemispheres are defined as being secondarily generalized.

The signs and symptoms related with a partial seizure are dependent on the affected cortical regions. Most partial seizures have the duration of 1 to 2 minutes but may be correlated with an increased postictal period. Partial seizures are defined as simple when there is no effect on patient consciousness. They are further defined as complex when consciousness is altered. Amnesia of the ictal event is the feature of a complex partial seizure. Confusion in the postictal period is associated with complex partial seizures but also, in a lesser amount, for a simple partial seizure. Simple partial seizures can transform into complex partial seizures, and both types can change into a secondarily generalized form.

Motor symptoms that occur during partial seizures depend on the anatomic location within the motor cortices. Jacksonian seizures are those that occur when the seizure spreads to adjoining cortical areas, producing a progressive involvement. They were first described by John Hughlings Jackson in the late 19th century. A Todd paralysis was first described by Robert Bentley Todd in the mid 19th century and is defined as a paralysis that occurs following prolonged focal seizure activity. It may have a duration ranging from several minutes to several hours.

The Lennox-Gastaut syndrome has a poor prognosis and is associated with multiple medication refractory seizures, mental retardation, and specific EEG findings. Trauma, intracranial hemorrhage, cerebral infections, and tuberous sclerosis can all cause Lennox-Gastaut, and it usually presents between ages 1 and 6. Lennox and Davis first observed the slow spike-and-wave EEG pattern with a set of clinical manifestations in 1950.[9] In 1966, Gastaut described the clinical manifestations and EEG patterns of 100 patients with slow spike-and-waves and called it childhood epileptic encephalopathy with diffuse slow spike-and-waves, or Lennox syndrome.[10]

Table 2. CLASSIFICATION OF SEIZURE DISORDERS

I. Generalized seizure	Both cerebral hemispheres affected synchronously
A. Generalized tonic-clonic seizures	A diffuse disturbance of cortical function, with a muscular movement component to the seizures
B. Atonic	Abrupt failure of muscle tone
C. Absence seizures	
1. Typical	Typically manifest as a brief staring spell that lasts 5 to 20 seconds
2. Atypical	Produce motor signs that last from 10 to 25 seconds
II. Partial seizures	Localized to only one region of the cortex
A. Simple partial seizures	Seizures do not involve loss of consciousness
1. Simple partial seizures with motor signs	Clonic or tonic movements of a discrete body part
2. Simple partial seizures with sensory symptoms	Sensory cortex is involved in seizure discharge
3. Autonomic simple partial seizures	Limbic structures are involved in seizure process and produce epigastric effects, nausea, or lightheadedness
4. Psychic simple partial seizures	Limbic and association cortex, with features of psychiatric disorders
B. Complex partial seizures	Duration of 30 seconds to several minutes and are initiated with an aura or a simple partial seizure, which then progresses to a loss of consciousness
C. Secondarily generalized tonic-clonic seizures	A partial seizure that progresses to a generalized seizure
III. Status epilepticus	A seizure of sufficient duration to provide an enduring epileptic condition

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Niedermeyer first coined the term Lennox-Gastaut syndrome in 1969.[11]

Generalized Seizures

GENERALIZED TONIC-CLONIC SEIZURES

The most common generalized seizure is the generalized tonic-clonic, also known as the grand mal, seizure. In generalized seizures, there is a diffuse alteration of cortical function, which affects both hemispheres simultaneously. An aura may present prior to seizure that may consist of headache, insomnia, mood alteration, and irritability. This seizure is characterized by a sudden tonic contraction of muscles followed by a loss of consciousness. A stridor occurs because sudden contraction of the respiratory musculature produces an explosive expiration through a constricted larynx. This is followed by the tonic phase, which is a stiffening of the body for 10 to 20 seconds. Prolonged tonic contraction can result in cyanosis, involuntary micturation, as well as biting of the lateral tongue and buccal mucosa. A clonic phase follows with characteristic jerking movement of the extremities for an additional 30 to 40 seconds. Grunting or labored respiratory sounds are occasionally heard between the seizure-induced movements, and frothing of the saliva may occur. The clonic movements continue to desynchronize in an irregular pattern between the 2 sides of the body. In the postictal phase, the patient may remain unconscious for variable duration, but the cyanosis usually resolves.

ATONIC SEIZURES

Other generalized seizures are the atonic seizures, which present with a sudden failure of muscle tone resulting in an acute downward collapse. When these seizures occur as short events, they are known as drop attacks and can result in severe injuries, including maxillofacial trauma. Atonic seizures are further subdivided into myoclonic and akinetic forms

A myoclonic seizure is distinguished by a sudden, excessive movement of the body and/or the extremities. These seizures are very short and can occur in clusters. Myoclonus is an involuntary, short contraction generated from the central nervous system. Myoclonus originating from a seizure may involve only 1 limb (focal), may involve 2 adjacent areas (regional), or may involve the whole body (generalized). This type of seizure involves a complete, sudden loss of muscle tone, resulting in bodily collapse. Consciousness quickly returns and normal activity can be resumed immediately. The less severe akinetic form involves a brief loss of muscle tone without the subsequent fall.

ABSENCE SEIZURES

Absence seizures are a generalized seizure that usually occurs in children and were formally termed petit mal seizures. There are two types of absence seizures: typical and atypical. Typical absence seizures are characteristic of the idiopathic generalized epilepsies, whereas atypical absence seizures are seen in the symptomatic generalized epilepsies.[12] Typical absence seizures are induced by hyperventilation, particularly with hypoglycemia. The seizures may stop as the child matures, or they may transform into another seizure type. The typical presentation is a short staring spell of a duration of 5 to 20 seconds and is usually accompanied by other signs and symptoms, including auras, altered behavior, or confusion following the seizure.

Absence seizures are associated with a multitude of signs and symptoms that have subtle presentations, such as clonic movements, changes to postural tone, automatisms, and autonomic changes. Automatisms include facial movements or a more purposeful rocking of the body. Autonomic signs related with absence seizures include pallor, pupillary dilatation, flushing, piloerection, tachycardia, increased salivation, and occasionally urinary incontinence.[12]

Atypical absence seizures usually produce motor signs, especially alterations in muscular tone. These can last from 10 to 25 seconds and can be followed by postictal confusion, unlike typical absence seizures. Atypical absences usually occur on awakening but are not initiated by hyperventilation. Patients normally present with episodes of inactivity, staring, and occasional myoclonic activity of the face and upper extremities. There also may be an extremely brief loss of consciousness. When left untreated, the seizures may occur with a frequency of up to hundreds of times a day and can be triggered by hyperventilation and flashing lights. Large amounts of medication may be necessary to eradicate absence seizures.

Partial Seizures

Partial seizures begin in a specific area of the cortex, as designated by the EEG and clinical manifestations. Partial seizures may be subdivided into 3 types: simple partial, complex partial, and secondarily generalized seizures. Simple partial seizures are when consciousness and ability to interact with the external environment is intact. Complex partial seizures are when consciousness is impaired. Impaired consciousness is defined as the inability to respond normally to external stimuli because of altered awareness.[12] Secondarily generalized partial seizures are those in which consciousness is impaired and tonic-clonic movements occur or when the cortical discharges

spread to involve the entire brain, causing a generalized tonic-clonic seizure.

SIMPLE PARTIAL SEIZURES

Simple partial seizures do not precipitate a loss of consciousness, with a normal duration of 1 minute. They frequently entail motor, sensory, or autonomic phenomena or a combination thereof. The discharge is normally isolated to a single lobe or hemisphere, and the symptoms are specific to the focal cortical region. It is the failure of the cortical discharge to extend throughout the remaining portions of the brain that prevents loss of consciousness. As with other types of seizures, the diagnosis of simple partial seizures is based on the history of symptoms and EEG readings, although it is only abnormal in approximately 25% of simple partial seizures and is not a reliable diagnostic test if the EEG is negative.[13] There are 4 main types of simple partial seizures: simple partial seizures with motor signs, simple partial seizures with sensory symptoms, autonomic simple partial seizures, and simple partial seizures with psychic symptoms.

SIMPLE PARTIAL SEIZURES WITH MOTOR SIGNS

These seizures usually begin with clonic or tonic movements of a discrete body part. The seizure can progress in a Jacksonian fashion, with a discharge that spreads in a sequential fashion along the precentral gyrus. In general, ictal discharges in frontal cortex trigger several muscle groups to produce complex actions like rotation of the head, eyes, or body to one side and posturing of one or more extremities. Involvement of the supplementary motor cortex results in the rotation of the head and eyes, with a bilateral proximal limb movement. Other manifestations of simple partial seizures with motor signs include aphasia, when language areas are involved, and ocular twitching initiated from frontal or occipital foci.

SIMPLE PARTIAL SEIZURES WITH SENSORY SYMPTOMS

Sensory simple partial seizures occur when the various sensory cortices are involved in a seizure disorder. Thus, localized paresthesias occur with seizures initiated from the parietal lobe, formed visual hallucinations occur with seizures associated with the occipital or posterior temporal, and objectionable olfactory, gustatory, and auditory hallucinations from temporal or frontal cortex.

AUTONOMIC SIMPLE PARTIAL SEIZURES

These seizures are caused by seizure involvement of limbic regions in the mesial temporal and frontal lobes that are associated with the hypothalamus, producing epigastric rising or distress, nausea, or lightheadedness. Other signs and symptoms include pallor, flushing, sweating, piloerection, pupillary dilatation, cardiac arrhythmias, and incontinence.

PSYCHIC SIMPLE PARTIAL SEIZURES

Psychic simple partial seizures are associated with the limbic and association cortex and present with features of psychiatric disorders. These include feelings of *deja vu jamais vu* (familiar acts that feel like they are being performed for the first time), forced thinking, cognitive disturbances, depersonalization, and affective syndromes.

COMPLEX PARTIAL SEIZURES

Complex partial seizures are the most common seizure type. They are often localized in descending order to the temporal, frontal, parietal, and occipital lobes. Complex partial seizures range from 30 seconds to several minutes and are initiated with an aura or a simple partial seizure, which is then followed by a loss of consciousness. An amnesic effect occurs in a majority of patients during the seizure. Postictal confusion and malaise follow, although exceptions may be seen, particularly in seizures initiated from the frontal lobe. Partial seizures with complex symptoms can have a multitude of behavioral, emotional, affective, and cognitive functions. The location of the discharging focus is usually in the temporal lobe, thus the historical term of temporal lobe seizure.[13]

SECONDARILY GENERALIZED TONIC-CLONIC SEIZURES

A secondarily generalized seizure has multiple presentations. Seizure initiation can occur without premonition; others can arise with either a simple partial or complex partial seizure that progresses to tonic-clonic activity. The tonic-clonic movements are normally asymmetric in secondarily generalized partial seizures, which is in contrast to the symmetry of primary generalized tonic-clonic seizures. This is followed by a predictable series of motor and autonomic phenomena.[12]

Status Epilepticus

Status epilepticus has been defined as a seizure of sufficient duration to provide an enduring epileptic condition, and it can be life threatening if it is untreated.[14] The defining feature occurs when the mechanisms involved in seizure termination are impaired or malfunction to such a degree that seizures continue indefinitely.[15] The first priority in treatment of a status epilepticus is ensuring an adequate airway, although most will breathe spontaneously if the airway is patent. Oral or nasopharyngeal devices with oxygen delivered are usually adequate to maintain

oxygenation. A prolonged seizure can lead to loss of pharyngeal patency and increase the risk of aspiration. Intubation can be difficult for patients with generalized clonic seizures and may require neuromuscular blockade. Adequate peripheral intravenous access is needed to provide drugs and fluid resuscitation. All patients should have continuous pulse oximetry and electrocardiographic monitoring. Routine laboratory evaluation includes serum electrolytes, glucose, magnesium, calcium, liver function tests, complete blood cell count, creatine kinase, toxicology screen, and antiepileptic medication levels. Initial management should be lorazepam 2 to 4 mg or diazepam 5 to 10 mg. Patients should be transferred to the emergency department or directly to the intensive care unit, where further dosing of lorazepam (0.1 mg/kg) or diazepam (0.15 mg/kg) should be continued. A phenytoin, fosphenytoin, or phenobarbital drip is then indicated. Further management is with either a benzodiazepine, a barbiturate, or propofol until the seizure is interrupted.[15]

MISDIAGNOSIS

Conditions that are commonly mistaken for seizures are syncope and excessive daytime sleep. Syncope can resemble the middle portion of a generalized tonic-clonic seizure. Excessive daytime sleep superficially resembles temporal lobe seizures or absence attacks. A significant majority of nonepileptic seizures are associated with psychiatric disorders, including conversion disorder, malingering, affective disorders, panic disorder, and personality disorders.[16] In the adolescent population, misdiagnoses include vasovagal attacks, classic migraine, nonepileptic/pseudoepileptic attacks, and substance abuse. The false diagnosis rate of epilepsy has been reported as 10%.[17]

EVALUATION

Electroencephalography

The electroencephalogram monitors cerebral function by recording electrical activity of the brain and displaying fluctuating electrical field potentials produced in the cortex as a function of time. The resultant patterns provide information regarding normal and abnormal brain activity. The electroencephalogram is the most common neurodiagnostic test performed to evaluate patients with suspected seizures and is still considered the gold standard when it is recorded in conjunction with observed seizures.[18] Video-EEG monitoring can be useful in classifying seizure types and determining focal point localization. The sensitivity and specificity of EEG recordings during clinical episodes is superior to those of the routine electroencephalogram.[19] The nonvideo or regular electroencephalogram is sufficient to classify seizure types and initiate medical therapy, although 20% of these are erroneously referred for seizure management and actually may have other physiologic or psychologic disorders.[20] Artifacts arising from swallowing, eye movements, body movements, sweating, and pulse can also cause misdiagnosis of seizure activity. In addition to noncerebral artifacts, EEG transients and patterns not associated with seizures can be mistaken for seizure patterns.[21]

Imaging

Neuroimaging studies used in evaluation of seizure patients are computed tomography (CT) and magnetic resonance imaging (MRI). MRI is preferred over CT due to its greater sensitivity in detecting small lesions. MRI is the most suitable imaging technique in the initial investigation of patients with epilepsy and is the most sensitive technique for the diagnosis of sclerosis, tumors, and congenital malformations. Other imaging techniques such as positron emission tomography (PET) and single-photon emission computed tomography are reserved for patients with intractable epilepsy when surgery is contemplated.[22]

MANAGEMENT

Pharmacotherapy

Historically, epilepsy management relied on 1 of 6 antiepileptic drugs (AEDs), used singularly or in combination, but in recent times, the number of AEDs has increased, making treatment more effective but also more complex (Table 3). The classic AEDs are phenobarbital, phenytoin, carbamazepine, ethosuximide, valproate, and the diazepam family. AEDs exert their effects on the cell membrane by inhibiting sodium and calcium channels, modulating the inhibiting γ-aminobutyric acid (GABA) receptor, excitation at the glutamate receptor, and by other unknown mechanisms. The goal of pharmacologic treatment of epilepsy is to control seizures without adverse medication-related side effects.[23] The majority of AEDs are partially bound to serum proteins; equilibrium exists between the concentration of protein-bound drug and the unbound drug concentration in plasma, with the unbound drug crossing the membranes that surround receptor sites.

Patients starting on an AED may complain of fatigue, dizziness, dyscoordination, and cognitive impairment. In general, these side effects lessen with continued use. All AEDs are capable of this effect, although phenobarbital and other barbiturate medications are the most evident. Severe, life-threatening reactions are rare but can also occur. Classic AEDs have been implicated with Stevens-Johnson syndrome, as has the newer AED lamotrigine. Valproate has been associated with pancreatitis and hepatic

failure in pediatric patients. Felbamate is associated with aplastic anemia and hepatic failure in rare cases.

Teratogenicity of AEDs

Most AEDs have the ability to cause teratogenic damage when used in pregnant patients. This effect has been referred to as fetal AED syndrome. This syndrome can include craniofacial abnormalities like cleft lip and palate, hypertelorism, ventricular septal defects, and dysplasia of the digits. Valproate and carbamazepine have been associated with a risk of neural tube defects when used in the first trimester. The risk of teratogenesis can be minimized by using monotherapy at the lowest effective dose and administering folate.

Bone Density

AEDs such as phenytoin, phenobarbital, carbamazepine, and primidone have been associated with decreased bone density and an increased risk of fractures. These AEDs act as inducers of cytochrome P450, which directly leads to the inactivation and degradation of vitamin D. It has also been speculated that vitamin D and calcium supplementation could actually worsen the osteoporosis in patients receiving valproate and other AEDs, by further increasing the hypercalcemia, leading to further inhibition of parathyroid hormone secretion and 1,25-(OH)2D production.[24]

Principles of AED Management

INITIATING TREATMENT

The goal of the medical management of seizures is to completely eliminate the onset of seizure with one medication. Adjunctive use of a second agent is usually not necessary. If seizure control is not obtained with a single medication, a different type of drug is attempted for monotherapy. If this proves unsuccessful, an additional second drug is added for polytherapy.

ACUTE MANAGEMENT

Management of a patient following a first seizure depends on clinical analysis and EEG findings. The past medical history should include incidences of febrile seizures, complications during delivery, head trauma, cancer, cerebrovascular disease, infectious disease, and substance abuse. Family history may include a history of febrile convulsions, epilepsy in relatives, and other neurologic diseases. During the physical examination, the cranium should be evaluated for signs of head trauma, past or current head and neck infections, congenital abnormalities, neurologic abnormalities, substance abuse, and signs of malignancy.

A complete blood cell count, blood chemistries, liver enzymes, toxicology screen, and urinalysis should be done to exclude metabolic disorders. Imaging with CT or MRI should be performed for all initial seizures to exclude any extrinsic lesion. A lumbar puncture for spinal fluid analysis should be performed if infection or malignancy is suspected. About 8% of patients with a first seizure have a brain tumor.[25]

TERMINATION OF PHARMACOLOGIC MANAGEMENT

Patients who have been seizure free for 2 to 5 years may be safely weaned from AED therapy. The benefits of the withdrawal of AEDs must be compared with the morbidity associated with seizure occurrence. The adult relapse rate ranges from 26% to 63% within 1 to 2 years after medication cessation.[23] In the pediatric population, a normal neurologic examination, in conjunction with a normal or improved electroencephalogram, and a history of early onset of seizures are associated with a lower incidence of relapse after medication withdrawal. Therapy termination should not proceed faster than a 20% dose reduction every 5 half-lives to avoid a withdrawal seizure. Withdrawal seizures commonly occur with barbiturates and benzodiazepine-type medications.

VAGAL NERVE STIMULATION

The Food and Drug Administration approved the use of an implantable vagal nerve stimulator (VNS) in 1997 for patients aged 12 and older. The left vagus nerve is stimulated with a pacemaker-like device that allows for adjustment of current, frequency, train duration, pulse width, on-time, and off-time. The electrical generator is placed subcutaneously over the left chest wall or placed under the left pectoralis muscle. The leads are then connected to the vagus nerve. The device is expensive and requires periodic modification, particularly in the immediate months after implantation.

The exact mechanism of action of VNS is unknown, although there are some hypothetical models that deal with the nucleus of the tractus solitarius. Patients usually do not become seizure free, but they do have a less frequent and milder course of seizures. VNS is an alternative treatment of medically refractory epilepsy, but it does not replace epilepsy surgery.

VNS is typically well tolerated. During stimulation, the patient may experience tightness in the throat and hoarseness, which are not disabling. The most common adverse effects associated with VNS are hoarseness (28%), aresthesias (12%), and dyspnea (3.2%).[26]

Cerebellar stimulation also may reduce seizure frequency through inhibitory interconnections to various regions of the brain and brainstem. Cerebellar stimulation is not presently considered effective for the treatment of epilepsy; however, additional re-

Table 3. ANTISEIZURE MEDICATIONS

Name	Half-life	Mechanism of Action	Side Effects
Phenytoin	22 hours, with a range of 7 to 42 hours	Regulates neuronal excitability of sodium channels, and its effects are mediated by its actions on calmodulin and cyclic nucleotides	Ataxia, nystagmus, dysarthria, incoordination, drowsiness, gingival hypertrophy, hirsuitism, coarsening of facial features, and acne
Carbamazepine	10 to 20 hours	Membrane stabilizing effect by altering ionic conductance of the sodium channel. Behaves as an adenosine agonist, noradrenergic stimulator	Cognitive slowing, fatigue, dizziness, diplopia, and dyscoordination
Ethosuximide	40 hours	Related to inhibition of thalamic synchronizing influences by reduction of calcium ionic currents and catecholamines	Gastrointestinal upset and photophobia with rare reports of aplastic anemia
Valproate	9 and 18 hours	Increases neuronal GABA concentrations	Idiosyncratic fatal hepatic necrosis, anorexia, nausea and vomiting, fine distal tremor, reversible dose-related alopecia; females may develop hirsuitism, acne, and menstrual cycle disturbances secondary to androgen elevation
Phenobarbital	90 hours in adults: shorter in children and longer in the geriatric population	Modulation of the inhibitory postsynaptic neurotransmitter GABA and the excitatory postsynaptic actions of glutamate	Sedation, irritability, depression, abnormal collagen deposition, nystagmus, ataxia, and hyperactivity in children
Clonazepam	24 to 48 hours	GABA-mediated inhibition, increasing chloride permeability, which leads to cellular hyperpolarization and inhibition of neuronal firing	Sedation, incoordination, and ataxia, hyperactivity in children, depression in the elderly
Diazepam	2 to 10 hours Diazepam is used in the treatment of status epilepticus due to its rapid onset and availability.	Same as for clonazepam	Same as for clonazepam
Lorazepam	24 hours	Same as for clonazepam	Same as for clonazepam
Felbamate	20 to 23 hours	Multiple mechanisms of action including membrane stabilization, GABA potentiation, and glutamate inhibition	Weight loss, nausea, and insomnia. Critical side effects of aplastic anemia and hepatic failure may be as high as 1:2,000
Gabapentin	Elimination half-life is 5 to 7 hours	Gabapentin was developed as a structural analog to GABA but appears to display very few GABAnergic effects. The mechanism of action has not been thoroughly established	Somnolence and fatigue that lessen with continued use
Lamotrigine	Varies with age	Effect on voltage-sensitive calcium channels that prevents the release of excitatory neurotransmitters	Dizziness, ataxia, somnolence, and headache Stevens-Johnson occurs in 1:300 adults and 1:100 children
Levetiracetam	7 ± 1 hour	Unknown	Asthenia, dizziness, headache, and somnolence
Oxcarbazepine	5 to 11 hours	Unknown	Dizziness, somnolence, diplopia, and, rarely, hyponatremia

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Table 3. ANTISEIZURE MEDICATIONS (Cont'd)			
Name	Half-life	Mechanism of Action	Side Effects
Tiagabine	5 to 13 hours	GABA reuptake blocker that increases intrasynaptic GABA concentrations	Dizziness, asthenia, nervousness, tremor, difficulty concentrating, depressed mood, and word-finding difficulties
Topiramate	20 to 30 hours	Carbonic anhydrase inhibitor modulates voltage-dependent sodium and calcium channels, GABA potentiation, and blockade of excitation at non-NMDA receptors	Dizziness, fatigue, nausea, weight loss, nephrolithiaisis, somnolence, and impared mental activity
Zonisamide	50 to 80 hours	The mechanism of action is not known but appears to include sodium channel blockade and T-type calcium channel blocking	Fatigue, somnolence, cognitive slowing, and anorexia with weight loss
Fosphenytoin	8 to 15 minutes	Fosphenytoin is a prodrug of phenytoin, and accordingly, its anticonvulsant effects are attributable to phenytoin	Adverse tissue effects have not been reported

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search is indicated to resolve the conflicting results of these studies.[27,28]

SURGICALLY REMEDIABLE EPILEPSY

The definition of medical intractability has historically been the therapeutic failure of 3 sequential AEDs. Currently, there are no firm guidelines that can be applied due to the need to individualize therapy, although there are some general considerations: seizure type and frequency, the amount of past medical therapy, and the psychologic and social aspects of epilepsy on the quality of life. A recent controlled study of adults showed that temporal lobectomy is superior to medical therapy for seizures that arise from the temporal lobe.[29] When drugs fail, the patient may be a candidate for epilepsy surgery, such as mesial temporal lobe resection, lesionectomy, neocortical resections, subpial transection, corpus callosotomy, and hemispherectomy.

MESIAL TEMPORAL LOBE RESECTIONS

Patients for whom medical management of their complex partial seizure fails are possible candidates for a mesial temporal lobe resection, which has a high rate of seizure-free outcomes.[29] The temporal lobe is the most common seizure focus site targeted for resection surgery, specifically the mesial structures like the amygdala and hippocampus. Resection of any brain tissue to treat epilepsy can cause damage to the functions mediated by the resected brain regions. Following dominant temporal lobe epilepsy surgery, patients can have a significant decline in verbal mem-

ory function.[30] The most devastating complications of temporal lobe epilepsy surgery can result from injury of adjacent vascular structures or mechanical disruption of the optic tract. Approximately 1% to 2% of patients develop a permanent homonymous hemianopsia as a consequence of damage to the anterior choroidal artery or branches of the posterior communicating artery.[31] Homonymous hemianopsia is a visual defect that effects both eyes equally, and it occurs to either the left or the right of the midline of the visual field.

LESIONECTOMY

A lesionectomy is a surgical procedure that removes specific, abnormal, seizure-initiating tissue. When removal of a lesion is being considered, the relationship of the seizures and the lesion must be accurately established if successful seizure control is to be achieved. Vascular pathologies, parenchymal surgeries, and surgery performed in adjacent locations increase the potential risks of complications and new seizure foci.

NEOCORTICAL RESECTIONS

Patients with intractable epilepsy with a seizure focus outside the mesial temporal lobe have a poor outcome when treated with surgery.[30] Modern neuroimaging devices have assisted in the identification of structural malformations of cortical development or the diagnosis of benign tumors in many new-onset epilepsy patients. Unfortunately, many patients with extratemporal lobe epilepsy have anatomically nor-

mal neuroimaging, leading to the inability to localize their seizure focus. Extratemporal neocortical resections for nonlesional epilepsy or malformations of cortical development achieve seizure freedom in only 50% of patients, although most do have some improvement in their seizure control.[30]

MULTIPLE SUBPIAL TRANSECTIONS

Many functionally defined regions, that is, the extremities and language regions, cannot be safely resected. The multiple subpial transections (MST) method is based on the theory that abnormal propagation of seizure activity is dependent on horizontal spread of cortical activity, whereas the normal functions of the cortex are largely mediated by activity within vertical columns.[30] MSTs are the creation of small incisions in the gyrus, with the intention to interrupt the intracortical fibers and disrupt seizure propagation.

CORPUS CALLOSOTOMY

The function of the corpus callosum is to allow communication of action potentials between the 2 hemispheres. This conduit also allows transmission of seizure activity between both hemispheres. Historically, a variety of disconnection procedures have been used to disrupt the propagation of seizure activity, including sectioning the corpus callosum, interhemispheric commissures, the massa intermedia, and the fornix.[30] Now, the only midline disconnection procedure that is considered for the treatment of epilepsy is the callosotomy. There are no clear benefits to resecting additional midline structures.[30]

Sectioning the corpus callosum does not eradicate seizure activity; it just inhibits transmission between the hemispheres. If the patient has a focal seizure disorder, it is important to identify the epileptic focus and eliminate it with a neocortical resection procedure. Nonlocalized seizures with synchronous, bilateral loss of motor tone and posture control may benefit from callosal sectioning. These patients present with falling spells and akinetic seizures. More than 65% of patients who undergo callosotomy experience a substantial diminution in the frequency or complete elimination of these drop attacks.[30]

HEMISPHERECTOMY

Hemispherectomy is an effective procedure for intractable seizures associated with multilobar hemispherical pathology. The benefit of a reduction of seizures and the elimination of medications on the individual's quality of life should be carefully considered against the known mortality and significant morbidities associated with the operation. Children with intractable partial seizures of all types who have a structural abnormality that involves most or all of one hemisphere and who are already hemiparetic with a homonymous hemianopsia are considered for hemispherectomy.[32]

Oral and Maxillofacial Considerations

Oral and maxillofacial surgeons treat seizure patients on a regular basis for routine surgery as well as managing their facial trauma sustained secondary to falls during seizures. In an elective outpatient evaluation of the patient, multiple issues must be taken into consideration. Preoperatively, the standards for determining the appropriate AED serum level are clinical and consist of a seizure free recent history and the absence of medication-related reactions. Because of the effectiveness of the AEDs, acquiring serum levels of seizure medications as a routine nature is often unnecessary. Presurgical medication levels can be helpful for comparative reasons if intrasurgical or postsurgical seizures occur. They can also help in elucidating the development of unexplained behavioral or neurologic findings. These signs can represent medication toxicity.

AEDs should generally be continued without alteration presurgically and postsurgically. Epileptic patients require no specific anesthetic management, although the use of benzodiazepines as an anesthetic agent seems prudent.[33] Vagal nerve stimulators should also have the power turned off prior to surgery.

Epileptic patients can be at an increased risk of fracture because both phenytoin and phenobarbital, the most commonly prescribed antiseizure medications, increase the metabolism and clearance of vitamin D and have been associated with frank osteomalacia. The high rate of fracture in institutionalized epileptic patients suggests that some form of prophylaxis, including calcium and vitamin D, should be considered.[34-36] Management of maxillofacial fractures should take into consideration the need for access to the airway, especially in patients with poorly controlled seizures. Consideration should be given to open reduction and rigid fixation of mandibular and maxillary fractures and MMF should be avoided. Postoperatively, AED levels should once again be evaluated prior to discharge to prevent further seizure-related injuries. Consultation of the treating neurologist should be obtained throughout management of the patient.

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