Evidence Report

Chapter 1. Introduction

Scope and Objectives of this Report

The objective of this report is to evaluate and synthesize, in an evidence-based fashion, the published literature on the management of treatment-resistant epilepsy. Epilepsy is a condition characterized by recurrent, unprovoked seizures. The term "seizure" is an inclusive generic term that encompasses the clinical manifestations of epilepsy as well as other disorders. Epileptic seizures arise from the abnormal discharge of electrical activity by cerebral neurons, and result in loss of consciousness, alterations in perception or impairment of psychic functions, convulsive movements, disturbances of sensation, or some combination of these events.[1] Nonepileptic seizures (NES), such as psychogenic (hysterical) seizures and seizures associated with syncope, are not caused by an abnormal neuronal discharge.

The first part of this Evidence Report deals with how the published literature defines "treatment-resistant" epilepsy. An acceptable definition for treatment-resistant epilepsy could aid in the identification and management of these patients. The terms "medically intractable" epilepsy and "refractory" epilepsy are frequently used to describe patients with uncontrolled seizures that do not respond to appropriate antiepileptic drugs (AEDs).[2,3] Other terms, with or without descriptive details, are also used.

This Evidence Report then considers the methods of diagnosis used to determine if a patient has treatment-resistant epilepsy. This section examines the possibility that some patients diagnosed with treatment-resistant epilepsy in fact have conditions other than epilepsy. We assessed diagnostic procedures that differentiate epileptic seizures from nonepileptic seizures and diagnostic procedures that aid in the diagnosis of epilepsy. Diagnostic procedures used to localize epileptogenic foci prior to surgery are not addressed in this report.

An evaluation of treatment interventions for patients with treatment-resistant epilepsy, specifically pharmacological and surgical procedures, as well as some nondrug/nonsurgical interventions, comprises a large part of this report. Rather than evaluate separate drugs, this report looks at which drug treatment strategy (sequential monotherapy, polytherapy, or optimized current therapy) may benefit patients with treatment-resistant epilepsy. In addition, we also examined a variety of surgical procedures and nondrug, nonsurgical interventions.

The final sections of this Evidence Report examine the potential impact of special services on patients with treatment-resistant epilepsy and the effect of treatment-resistant epilepsy on employment, education, and mortality. These areas are critical in the continuing management of patients with treatment-resistant epilepsy and in evaluating interventions beyond their effect on seizure frequency. The literature was examined for information on occupational, speech, and physical therapies, patient education, neuropsychological evaluation, and psychiatric consultation and treatment.

This report was prepared at the request of the Centers for Disease Control and Prevention and the Social Security Administration in an effort to evaluate the diagnostic procedures available for identifying patients with treatment-resistant epilepsy, identify the characteristics of patients with treatment-resistant epilepsy that interfere with employment and schooling, and assess the potential benefits of the available medical and nonmedical interventions for patients with treatment-resistant epilepsy. The patient population of interest in this report includes infants, children, and adults with treatment-resistant epilepsy.

Epilepsy and Treatment-Resistant Epilepsy

Neurobiology

An epileptic seizure can be defined clinically as an intermittent, stereotyped, disturbance of consciousness, behavior, emotion, motor function, or sensation that results from abnormal cortical neuronal discharge and recur without provocation.[4] The discharge may result in an almost instantaneous loss of consciousness, alteration of perception or impairment of psychic function, convulsive movements, disturbance of sensation, or some combination of these events.[1] The onset of the abnormal neuronal discharge may be widespread and bilateral or it may be localized. In the latter instance, the abnormal discharge arises from an assemblage of excitable neurons, called a focus, in any part of the cerebral cortex that may or may not be associated with a visible lesion.[a] Cortical excitation may then spread to the adjacent cortex and to the contralateral cortex through interhemispheric pathways as well as to subcortical areas such as the basal ganglion, thalamus, and brainstem. Clinical manifestations of a seizure occur when the excitation reaches these areas. In rare instances, death may occur due to sustained cessation of respiration, derangement of cardiac action, or some unknown cause.

Etiology and Pathology of Epilepsy

The focal cortical lesions responsible for the abnormal discharges associated with epileptic seizures may arise from a variety of causes. Epilepsies in which no pathological lesion can be found are referred to as primary or idiopathic epilepsies and include certain generalized tonic-clonic and absence seizure conditions.[1] The underlying cause of these seizure types is probably genetic. Secondary or symptomatic epilepsies are associated with a discernable lesion. Secondary epilepsies include simple partial seizures and complex partial seizures. The lesions may be zones of neuronal loss and scarring (sclerosis or gliosis), vascular malformations, tumors, or cortical dysplasia. Many patients with temporal lobe epilepsy have a condition called mesial temporal sclerosis (MTS) that is characterized by a loss of volume and scarring in the hippocampus and adjacent gyri on one or both sides. Posttraumatic epilepsy may occur after head trauma, brain surgery, and various infections that are responsible for creating focal lesions that result in epilepsy.

Signs, Symptoms, and Characteristics of Epilepsy and Treatment-Resistant Epilepsy

Epilepsy seizures may be classified according to etiology, site of origin, clinical form, frequency, or electrophysiologic characteristics.[1] Classification schemes have repeatedly changed, but the most commonly used scheme is the one adopted by the Commission on Classification and Terminology of the International League Against Epilepsy.[5] This classification is based primarily on the clinical form of the seizure and its electroencephalographic (EEG) features. Seizures are divided into partial seizures (a focal or localized onset can be discerned) and generalized seizures (bilateral origin and diffuse cerebral cortical involvement from the onset). Partial seizures that develop into generalized seizures are

[a] Why neurons in or near a focal cortical lesion discharge abnormally is not fully understood.

referred to as secondarily generalized seizures. Partial seizures (also called focal seizures) are further classified as simple when consciousness is maintained, and complex if consciousness is altered or lost. Simple partial seizures can be motor, sensory, autonomic, or psychic. Simple partial seizures are also called auras and may be a precursor to a complex seizure or may constitute the entire seizure. Generalized seizures may be convulsive or nonconvulsive. The common convulsive type is the tonic-clonic seizure and the common nonconvulsive type is the absence seizure that is characterized by a brief lapse of consciousness.

Patients with treatment-resistant epilepsy may experience one or more of the various types of epileptic seizures depending on the etiology of their condition. The following is a brief description of the clinical characteristics of each type of epileptic seizure that a patient with treatment-resistant epilepsy may experience. Adams and Victor's Principles of Neurology was used a guide in preparing these descriptions.[1]

Generalized tonic-clonic seizures are sometimes preceded by subjective phenomena (prodromes) that may take the form of psychological changes or myoclonic jerks of the trunk or limbs. Most often, the seizures occur without warning and the patient loses consciousness and falls to the ground. The seizure starts with an initial flexion of the trunk, opening of the mouth and eyelids, and upward deviation of the eyes. The tonic phase follows with protracted extension of the back and neck and then the arms and legs. Breathing is also impaired. The tonic phase lasts for 10 to 20 seconds. The clonic phase follows the tonic phase with a mild generalized tremor that represents relaxation of the tonic contractions. The rate of contractions gradually lessens over 30 seconds. Breathing is still impaired until the end of the clonic phase. Finally, all movements end. Upon regaining consciousness, the patient usually experiences a period of disorientation and/or fatigue.

Absence seizures are very brief, always associated with impaired consciousness, and may or may not have accompanying abnormal motor activity. Some are so short as to resemble daydreaming. The seizure comes without warning and consists of a sudden interruption of consciousness. These patients usually do not fall. After 2 to 10 seconds the patients become conscious again and resume their preseizure activity. Absence seizures are the most common form of epileptic seizure of childhood and rarely begin before 4 years of age or after puberty. Absence seizures tend to occur frequently, with as many as several hundred occurring in a single day. This type of seizure may be the only type seen in childhood and the attacks diminish in frequency with age and eventually disappear. However, absence seizures may be replaced in some instances by generalized tonic-clonic seizures.

Partial seizures are the product of focal abnormalities in some part of the cerebral cortex. Such lesions are often associated with focal EEG abnormalities. Simple partial seizures most often derive from a focal area in the sensory and motor cortex, while complex partial seizures most often derive from the temporal lobe of one side. Somatosensory seizures usually have a focus in the precentral or postcentral convolution. The sensation is described as numbness or tingling that usually starts in the lips, fingers, or toes and spreads to adjacent parts of the body. Visceral seizures (vague feelings in the thorax and abdomen) are some of the most frequent simple partial seizures. Other less common types of simple partial seizures include visual seizures (sensation of darkness and flashes of light), auditory hallucinations (buzzing or roaring in the ears), vertiginous sensations, and olfactory hallucinations (abnormal odors).

Loss of consciousness distinguishes complex partial seizures from simple partial seizures. However, unlike generalized tonic-clonic seizures, the patient suffers a period of altered behavior and consciousness with no later recollection, instead of a complete loss of control of thought and

action. Any type of complex partial seizure may develop into other forms of secondary generalized seizures. Complex partial seizures are not exclusive to any age group but show an increased incidence in adolescence and adult years.

The Lennox-Gastaut Syndrome is a neurological syndrome characterized by frequent seizures of various types. These patients have intellectual impairment and serious neurologic disease. The syndrome is usually diagnosed between 2 and 6 years of age.

Temporal lobe epilepsy, which is typically manifested by complex partial seizures described above, commonly starts before 10 years of age. By adolescence or early adulthood, this condition often becomes treatment-resistant.[6] Recurrent seizures may cause damage in the hippocampus resulting in a progressive loss in hippocampal volume as long as the seizures persist.[7]

Arroyos, Brodie, Avanzini, et al.[3] suggest that treatment-resistant epilepsy may be a distinct condition within epilepsy characterized by progressive neuronal, cognitive, and psychosocial deterioration. These authors point out that several markers have been advanced as indicators of treatment-resistant epilepsy. These include age at onset younger than 1 year, type of epilepsy (partial epilepsies or catastrophic epilepsies of childhood), failure of the first AED, use of more than two drugs, duration of treatment without achieving control, and specific pathologies. However, these markers may not be especially sensitive or specific for treatment-resistant epilepsy.[3]

Epidemiology of Epilepsy

Epilepsy is among the most common serious neurologic condition, with a prevalence rate 10 times higher than multiple sclerosis and 100 times higher than motor neuron disease.[8] An International League Against Epilepsy (ILAE) Commission Report from 1997 gives the prevalence of active epilepsy as 40 to100 in 10,000.[9] The ILAE prevalence and incidence rates are based on a review of selected studies, mostly from developed countries, by Sander and Shorvon .[10] Both rates varied widely among the studies included in this review. Their review found prevalence rates that ranged from 1.5 to 31 per 1,000 and incidence rates that varied from 11 to 134 per 100,000. The authors believe that the highest prevalence and incidence rates are more accurate because studies with these findings used more intensive and sophisticated case ascertainment methods. They further state that the low rates found in some studies were probably due to deficiencies in patient reporting (physical manifestations are transient and not observed by a clinician, patients are unaware of or deny their condition) and in diagnosis of epilepsy (syncope and psychogenic seizures are misdiagnosed as epilepsy, diagnostic criteria are unspecified or loosely defined). Sander and Shorvon[10] also believe that retrospective review of patient medical records in most case ascertainment studies also leads to an underestimate of prevalence and incidence.

Burden of Illness

In addition to the immediate effects of seizures, patients with epilepsy may also have to contend with the following burdens:[4,11,12]

- interference with normal activities
- increased possibility of accidental injury and even death (addressed in Key Question 8 in this report)

- impaired physical, psychological, and social functioning
- economic loss
- diminished quality of life
- psychiatric disorders, in particular, anxiety and depression[13]

Technologies Assessed in this Report

In this report, we considered 49 different technologies. These are comprised of 14 diagnostic technologies, 5 drug treatment strategies, 7 types of surgery, 10 nondrug, nonsurgical interventions, and 13 service-related interventions. For each of these technologies, we considered 16 different patient-oriented outcomes (for a list of these outcomes, see the Article Inclusion Criteria in the Methodology section of this Evidence Report). However, there was sufficient literature to address only ten of these technologies. Table 1 lists each of the technologies considered in this Evidence Report. The technologies for which there was sufficient literature are shown in bold italicized type.

Table 1. Technologies addressed

Drug Strategies	Surgery	Nondrug, Nonsurgical	Service-related Interventions	Diagnostics
Sequential monotherapy	***Temporal lobe***	***Vagal nerve stimulation (VNS)***	Multidisciplinary neurobehavioral treatments	***Blood prolactin***
Polytherapy	***Hemispherectomy***	Ketogenic diets	EEG biofeedback	Routine-EEG
Drug reduction	***Corpus callosotomy***	Chiropractic	Epilepsy education	Video-EEG
Maximum tolerable dosage	***Multiple subpial transection***	Acupuncture	Vocational services	Ambulatory-EEG
Dose frequency optimization	***Frontal lobe***	Hyperbaric oxygen	Physical exercise	Blood creatine kinase
	Parietal lobe	Herbal medicine and homeopathy	Medical resonance therapy music	Computed tomography
	Occipital lobe	Cranial realignment	Sahaja yoga	Magnetic resonance imaging
		Magnetic therapy	Meditation	Single Photon Emission Computed Tomography
		Electrical brain stimulation	Self-help group (group therapy)	Minnesota Multiphasic Personal Inventory
		Vitamin B_6	Counseling	Provocation techniques
			Progressive muscle relaxation	Tilt table
			End-tidal CO_2 biofeedback	Auditory evoked potentials
			Systematic desensitization	Hypnotic recall
				Tongue biting

Note: Bolded, italicized technologies are those addressed in this report. The remaining technologies were not addressed due to insufficient literature