6 Pre-ictal Seizure Detection and Demand Treatment Strategies for Epilepsy

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6.1 TYPES OF EPILEPSY AND INITIAL TREATMENTS

Mechanisms of epilepsy have been explored through a variety of animal models as well as detailed human studies, for more than 70 years.[1–3] Through the animal models, a large number of contributing factors leading to epilepsy have been demonstrated, including conditions that lead to the intermittent, enhanced synchrony leading to partial or generalized seizures. While animal models still have only moderate predictive validity for anticonvulsant therapy development, the mechanisms may potentially apply to the human situation. However, in general, most animal models involve acute seizure development, mirrored in humans as acute convulsions, usually due to systemic or CNS irritants or toxins. For example, a classic convulsion may be seen with an overdose of penicillin or meperidine, and convulsions are characterized by a high degree of neuronal electrical synchrony throughout the brain.

In contrast, most human seizure disorders are intermittent (i.e., a few seizures a month), potentially have irregular or variable starting locations, and may involve relatively large "epileptic" zones. The concept of an epileptic focus in humans has come under considerable scrutiny, and a minimum volume of cerebral cortex appears necessary for seizure onset. Once a seizure starts, inherent mechanisms within the brain can either constrain or enhance the spread, often into a generalized tonic–clonic convulsion. Such seizure pathways include the substantia nigra reticulata (SNr), which may be responsible for one part of the generalization. Additionally, the thalamus may enhance synchrony between the two frontal lobes.

Two basic types of spontaneous seizure disorders are recognized: partial and generalized.[1] Partial seizures emanate from specific regions of the brain, for example, partial motor seizures arise from the motor cortex. Partial seizures may be either simple (awareness and memory are maintained) or complex (awareness and memory are lost for a period of time).

Mesial temporal or frontal structures are thought to be involved during a complex partial seizure. A partial seizure may secondarily generalize, resulting in a generalized tonic–clonic seizure, often with versive head or eye movements. The operational definition in epilepsy surgery of the volume of brain important in seizure onset has been defined as how large a brain area must be resected to significantly decrease seizure frequency. For mesial temporal origin seizure disorders, most of the temporal lobe must be resected, including the central gray matter such as amygdala, entorhinal cortex, and hippocampus, for adequate seizure relief.

For neocortical partial seizures, the area may be smaller or difficult to define, depending on the region of cortex involved. However, many partial seizure disorders can be treated by surgical resection if a specific location can be found for the seizures, the area is resectable without too many neurological burdens (speech difficulties, weakness, memory loss) for the patient, and the seizures are not bilateral in origin. Only a small percentage of patients with refractory partial seizure disorders are amenable to resection or are referred at an appropriate age for resection.

The second type of seizure disorder is generalized and is thought to arise from the entire brain simultaneously. These seizures are more common in children and may represent diffuse abnormalities in many regions of the cerebral cortex. For example, some childhood epilepsies may result from subtle (but pervasive and widespread) changes in ion channels regulating inhibition, particularly potassium channels. Many of these channel abnormalities are due to gene mutations, and thus may be hereditary. They may also be developmental in the sense that as the channels change with development, other channels may substitute, so the seizures resolve spontaneously. This type of epilepsy is called an idiopathic generalized seizure disorder. Other types of generalized seizure disorders are designated symptomatic generalized and are due to widespread brain damage; much of the cerebral cortex is diffusely involved, giving rise to multifocal seizures or multiple seizure types. The seizures may worsen with time or respond to various treatments.

Drug treatment is the mainstay of therapy in epilepsy. Many patients take at least one medication. All the available anticonvulsants act primarily to suppress seizures, and none is known to prevent the formation of the epileptic condition, such as epilepsy after a head injury or central nervous system insult. However, most drug

treatment interferes with fine cognition, particularly memory and complex thinking skills during growing and learning, thus inhibiting social skills and acquisition of learning skills. Additionally, many patients (potentially as many as 25%) fail to have their seizures controlled by drug treatment and are considered refractory to medical therapy. Even a single occasional seizure prevents activities such as driving a vehicle or pursuing many occupations.

The goal of therapy is to have rare or no seizures, if possible. Therefore, surgical treatment for intractable patients should become a consideration usually when they are children or young adults, when it is beneficial to increase participation in society, and it is clear that medical therapy is not successful. For most epilepsy surgical centers, surgical candidacy is considered after a patient has failed adequate trial with two or more standard medications and had seizures for 2 years or longer. Initial considerations for surgery are detailed localization of seizure onset and laterality and determination of the types of seizures to investigate the feasibility of localizing and removing an epileptogenic zone within the brain.[4]

6.2 SURGICAL TREATMENT

Surgical treatment for seizures began with tumor and obvious lesion resections to remove the irritating sources. However, in many instances the cortex generating the seizures was at a distance from a lesion such as a tumor, so the seizures did not necessarily improve with lesion resection. After the electroencephalogram (EEG) and direct electrocorticogram (ECoG) of the surface of the brain were developed, this technique provided a method to determine localization of brain function, as opposed to structural lesions. By the early 1930s, abnormal areas in the brain could be determined by EEG before the procedure and by ECoG during surgery, and resections of the functionally abnormal areas of the brain could be performed. This technique of preoperative or intraoperative localization of an epileptogenic zone based on an abnormal EEG still constitutes the standard form of epilepsy surgery, including temporal lobectomy procedures and neocortical resections.

A large number of patients present difficult localizations (too diffuse or in a critical area of eloquent cortex, not amenable to resection) or bilateral (multifocal) localization of seizure onset and abnormality. In addition, surgical resectioning of brain areas, even if abnormal, invariably leads to new deficits, however subtle. For many years, numerous attempts have been made to devise alternative surgical procedures that may be less invasive or may achieve benefits in patients not amenable to traditional EEG-guided resections.

These novel treatments fall into two main categories: (1) past treatments, many of which have now been abandoned, and (2) new translational treatments, still in the process of testing and development. Many of these treatments have underlying hypotheses of action not necessarily proven valid in a treatment sense.

Most current medical and surgical treatments for epilepsy are empirical in that they were not hypothesis-based at the time of human application.[1] Drugs are still screened with a basic convulsion model (electroshock therapy in rodents) used to assess ability to prevent death (ED_{50} dose). Many current surgical treatments such as vagus nerve stimulators have no known mechanisms of action.[5–7] The mechanisms

of action of most anticonvulsants were studied after their utility in humans was demonstrated, so standard anticonvulsants such as phenytoin, lamotrigine, and carbamazepine, for example, change the properties of the sodium channel involved with action potential generation to favor single action potentials over bursts or groups of potentials. While vagus nerve stimulation appears to have a mild effect on seizure suppression (rather than complete seizure prevention), its mild effect fortunately is balanced by a very low risk profile.

Resective surgery (such as temporal lobectomy) is based on the hypothesis of removing an autonomous, epileptic zone so that abnormal output from the zone cannot influence the remainder of the brain as a result of removing the epileptic influence. Presumably over time more information may be realized about the mechanisms of action of empiric treatments.

6.3 PAST SURGICAL TREATMENTS

One interesting approach stemmed from a basic neuroscience observation: while recording single neurons from nonhuman primate cortex, any neuron could be trained by the animal to respond at a certain rate of neuronal action potential firing.[8] This rate-training capability through biofeedback is now a well-known capability of the brain and it has been extended to EEG biofeedback training. Since neurons in epileptiform regions in the brain tend to have too-high firing rates and fire in abnormal patterns or bursts, considerable effort was made to try to alter the firing rates (and hence suppress the tendency toward seizures) using biofeedback techniques in nonhuman primates with induced seizure disorders.

Although the hypothesis was excellent, the afferent pathways to these abnormal neurons appear to have been altered by the process of seizure disorder induction. Thus, less brain control (and hence less biofeedback control) can be exerted over neurons in epileptic zones. The concept was foiled by the nature of the epileptic process, although much was discovered about afferent denervation in epilepsy from this research. Since then, the concept that an epileptic region is autonomous from normal brain control has developed.[9]

Other observations about epilepsy include the efficacy of a ketogenic diet, usually for childhood epilepsy. A ketogenic diet is characterized by enhanced ketone bodies in the blood stream and decreased glucose. Interestingly, ketone bodies are taken up into the brain via one form of a monocarboxylate transporter (MCT). MCT transporter levels fall rapidly after the neonatal period and weaning because a mother's milk has a high content of ketone bodies and lactate, both requiring MCT-based transport. Thus, in early childhood, uptake of ketone bodies into the brain is lower; the uptake can be upregulated over time on the ketone diet. The mechanisms of the moderate suppression of the ketogenic diet on epilepsy still remain elusive although a switch in central nervous system (CNS) metabolism, possibly to enhanced gamma aminobutyric acid (GABA) levels, may be critical.[10]

Additional conceptual treatments include focal cooling because direct brain cooling at the time of a craniotomy may successfully abort seizures. Other local factors important in suppressing or aborting seizures include enhanced sensory input.

Patients may occasionally be able to abort focal motor seizures by increasing sensory input to the affected part of the body, which may suppress the motor cortex through increased inhibition.

One treatment approach that evolved over time is stimulation therapy with electrical current or magnetic flux applied directly to the brain or across the skull. Although cortical stimulation (particularly in regions of hyperexcitable brain) can initiate seizures, cerebellar surface stimulation was suggested initially as a treatment for cerebral palsy and abnormal movement disorders.[11] This technique followed the partial effects of destructive lesions of the dentate nuclei of the cerebellum in cerebral palsy. However, although cerebellar surface stimulation applied to the anterior lobe and placed under the tentorium had little effect on movements, it was noted to have a partial effect on reducing the rate of generalized seizures.

While this effect was empirical initially, numerous stimulators were implanted through the 1970s. Although a randomized trial published later showed minimal clinical benefit, the concept was established that CNS stimulation had potential to improve seizure control.[11] Follow-up nonhuman primate studies showed that the primary effect was on enhancing alertness, and was a direct stimulation effect equivalent to enhancing brainstem reticular system function. Because many seizures occur in a hypnagogic state (toward sleep onset), enhanced alertness may exert a mild anticonvulsant effect. This is an example of a purely empirical treatment (with many advocates), with some insight into potential mechanism of action achieved through basic science studies. It is the complete opposite of a translational approach where ideally the hypothesis is developed first and treatment is second.

Direct cerebellar stimulation waned after demonstration of lack of efficacy (as happens with many empirical clinical treatments), but the concept that nonspecific brainstem stimulation may result in a mild, anticonvulsant effect persisted. Another technique to promote such stimulation is vagus nerve stimulation, which was tested and approved by the U.S. Food and Drug Administration (FDA) based on the earlier concept.[7,12] Although the mechanism is not known (and presumably relates to the same type of nonspecific brainstem effect seen for cerebellar surface stimulation), this empiric treatment has little risk and is well tolerated. However, vagus nerve stimulation is not likely to make an intractable patient seizure-free. It may merely decrease the number of seizures and perhaps their severity. Investigations regarding the relative worth and specific indications for vagus nerve stimulation are ongoing. Despite mild efficacy and lack of a specific hypothesis, the technique has numerous advocates.

6.4 NEW SURGICAL TREATMENTS IN CLINICAL TRIAL OR PRECLINICAL EVALUATION

The vagus nerve stimulator is an example of an open-loop system that is constantly stimulated (at some rate, frequency, and periodicity) without conscious or subconscious feedback from the patient to indicate whether the stimulation is effective.[12] Several other open-loop systems are now anticipated and are in clinical trials, particularly subthalamic nucleus (STN) stimulation and thalamic stimulation.[13–18]

The success of the standard, open-loop deep brain stimulator (DBS) systems from Medtronics for tremor and Parkinson's disease led to many other conceptual uses of the device. STN stimulation may lead to SNr suppression; the SNr is important as a common mediatory for the motor output of a generalized seizure. Thus, constant STN stimulation has been suggested and tested, similar to the type of stimulation used for Parkinson's disease.[13] However, very little is known about the EEG and cortical effects of STN stimulation or its role in mediating seizures in patients that will require study with implanted EEG electrodes. This type of study has been performed with vagal nerve stimulation.[19,20]

Although STN stimulation may result in acute cortical and possible seizure suppression, chronic stimulation may actually result in circuitry changes that are potentially proconvulsant. Thus, intermittent stimulation may be critical, highlighting the sparseness of knowledge about effective stimulation patterns for various uses. Theoretically, an STN system may work best in demand mode, in which some event (e.g., the patient senses an aura or seizure prelude) may trigger the stimulation to prevent a seizure.[21]

Other regions suggested as showing anticonvulsant effects with open-loop stimulation include several areas of the thalamus. The thalamus is known to aid propagation from one hemisphere to another, in other words synchronizing seizures, particularly frontal lobe seizures. Anterior thalamic lesions were suggested to improve generalized (frontal lobe-based) seizures. Following in this vein, DBS of anterior and medial thalamus is now in initial clinical trials to analyze whether any anticonvulsant effects arise within different regions.[16,17,21,22]

Hippocampal stimulation has also been suggested for partial complex seizures of hippocampal origin. These treatment sites use some form of intermittent (but still open-loop or constant) stimulation, theoretically blocking seizure throughput. It is unclear whether thalamic projections to the cortex may also result in some form of long-term suppression of a seizure tendency in the cortex as well.

Other types of treatment in clinical trials include stereotactic radiosurgery for temporal lobe seizures.[23] The dose of the radiation in this case is similar to single-dose treatments for tumors and produces some initial irritation of the brain areas and perhaps mild destruction without necrosis. This treatment is currently in clinical trials at several epilepsy centers; the trial format compares the new treatment to the standard current clinical treatment of temporal lobectomy. Other types of clinical trials also include various approaches to temporal lobectomy, and optimal methods to manage childhood seizures. A number of treatments, particularly for temporal lobe-mediated seizures, are not in small initial clinical trials.

6.5 CLOSED-LOOP OR DEMAND EPILEPSY FEEDBACK SYSTEM

A need still exists to develop alternative methods for controlling chronic epileptic seizures. The concept of an unsupervised method for detecting and treating epileptic activity automatically, in other words a demand system, has been widely proposed.[13,21,24–27] In many ways, such a system is equivalent to a demand for a heart pacemaker or defibrillator. This visionary event-controlled approach is rad-

ically different from and inherently more powerful in scope and application than any current treatment for chronic epilepsy.

A seizure feedback system could be an effective treatment scheme for focal seizure disorders, or potentially even for more diffuse generalized seizures, if applied to an output system that controls diffuse propagation. Such a system would function with an afferent limb able to sense the pre-ictal state in a local region of the brain, using either implanted or surface EEG electrodes or multiple single-unit electrodes. Clearly the seizure detection arm would require evaluation of the best area for electrode placement, similar to current invasive schemes. Once the pre-ictal state is reliably detected and processed, then an efferent limb in the region of the seizure can be used to cancel or convert an early pre-ictal rhythm into a less synchronized state.[28–33]

The clinical applicability of this type of system depends on detecting the pre-ictal state before any clinical manifestations occur and converting the state locally into one less likely to lead to seizure occurrence, in other words preventing the seizure from developing. Additionally, this type of system should not introduce any conscious awareness of the efferent treatment effect, such as pain, which would preclude general usefulness. The clinical applicability and current state of development of this type of system will be reviewed.

6.5.1 Demand Epilepsy Treatment System: Implementation

A definitive treatment scheme[21,34,35] involves three main parts (Figure 6.1):

1. A method to detect pre-ictal activity that is representative (specific and sensitive) to the pre-ictal epilepsy state for any patient, usually with implanted electrodes on the surface of the brain or within the brain
2. A technique to process information from these electrodes and generate an output signal with a threshold to indicate a possible seizure state in development
3. An efferent or control method to take the output signal and generate a subconscious effect that would abort or stop the seizure in germination so that it would not occur

The critical aspect of these aims of an ideal system is that the patient should not know about the detection or treatment; if a seizure occurs, the system is a clinical failure. While it is much easier to detect a highly synchronized seizure event, once a seizure has started treatment is too late because the patient has already lost awareness and the clinical implications have already occurred. However, in some seizure states, the goal is not necessarily to prevent all seizures; the goal may be to reduce the number significantly, similar to vagus nerve stimulation.

The need for a demand or feedback control system remains controversial, particularly because several (completely empirical) open-loop stimulation studies in humans (constant anterior or medial thalamus stimulation, constant or intermittent STN stimulation, and vagus nerve stimulation) are currently in progress. The consensus is that constant stimulation is theoretically much less effective than some

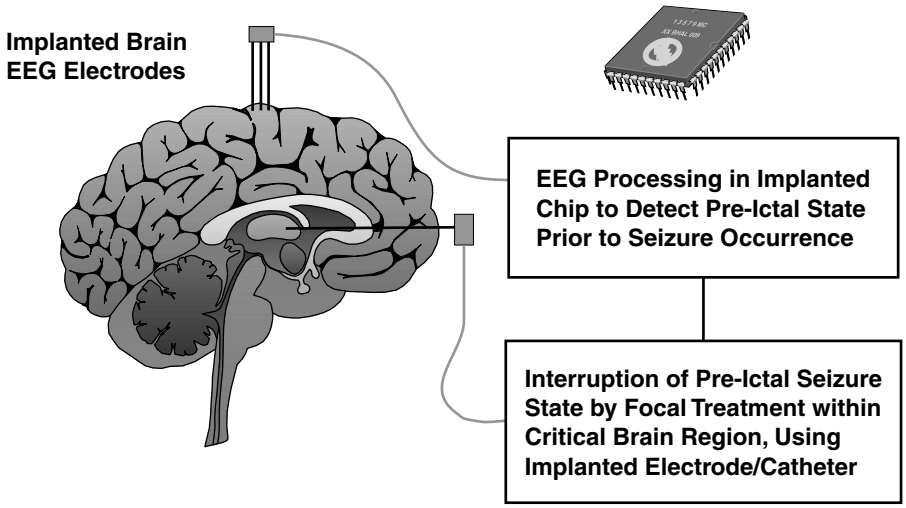

FIGURE 6.1 (See color insert following page 146.) The critical elements of a demand or feedback system for epilepsy include three major components: (1) a sensing arm or group of macro (EEG) electrodes on the brain surface or implanted near the maximally abnormal area that are critical for detecting both the pre-ictal state and the transition into seizure; (2) EEG processing for the detection of the pre-ictal state, usually considered optimal when the seizure is still building and the state can be interrupted in a subconscious fashion; and (3) stimulation or medical treatment to interrupt the seizure. The final component may be most efficient if administered near the origin of the seizure, but could also be a systemic injection, for example.

form of intermittent stimulation because the networks excited by the stimulation may become refractory and may not provide the necessary inhibition sufficient to prevent seizure development. However, a demand system requires the hypothesis that the development of a seizure may be both detectable and also critically interrupted during the build-up period, before an inter-ictal hyperexcitable occurrence generalizes to include more and more cortex. These aspects will be individually reviewed.

6.5.2 Detection Schemes and Electrodes

EEG and ECoG analysis paradigms have been more or less successful in detecting pre-ictal activity, particularly increased synchronization and decreased level of complexity of the EEG signal (i.e., less chaotic). [24–26,36–40] However, many of these have not been tried in significant animal models or on humans and the effects of noise and extraneous signals have not been adequately included. The location of such electrical recordings depends upon the level at which ictal activity is to be interrupted. For example, if a seizure is already generalized throughout much of the cortex and is bilateral, almost anywhere over the scalp or deep structures may be sufficient because the signal is highly propagated. However, at this late stage, the brain has

already been significantly involved with the seizure and will undergo interruption of ongoing function and post-ictal changes.

The more desirable detection would reside in a region close to the hyperexcitable zone, such as hippocampal depth electrodes for mesial temporal lobe complex partial seizures. An event should be detected before the patient becomes aware that a seizure is starting, and the detection method should abort even local seizure propagation. This would allow more subtle methods to be used to control or terminate an event (since less brain is involved), particularly at the subclinical level. These detection algorithms clearly need analysis and assessment.

The critical issues to be resolved for individual patients include electrode placement and how to determine optimal placement, particularly for invasive, implanted electrodes, because all of the envisioned systems would be required to be completely internalized (but with some external remote control possible, similar to current DBS systems). Because epileptogenic zones are often difficult to localize to small regions of the brain, the localization of sufficient electrodes to bracket areas of the brain critical for ictal onset is a continuing challenge.

Detection depends on monitoring sufficient areas of the brain so that all possible pre-ictal states may be recorded, particularly in patients with multiple seizure types. This localization approach is radically different from current epilepsy monitoring, where the point is to localize an epileptogenic zone to a sufficiently small region that a resection may be feasible. These seizure detection electrodes would optimally be near a hyperexcitable region associated with seizure onset (as determined by surface or depth electrodes). For permanent purposes, an implanted depth electrode located near the zone of seizure origin (Figure 6.1) and optimized for EEG detection or stimulation (or both combined in one electrode set) would be ideal.

6.5.3 Processing System

Processing and detection systems are commonly linked to a variety of dynamical approaches where changing ongoing activity slightly may deter the system from proceeding to seizure.[21,25,26,28,31,33,36,38,39,41] The disadvantage of most systems is that the processing time to detect a pre-ictal state is too long for real-time use. In many cases, realistic human data (usually from invasive recordings) has not been used to analyze how successful the various algorithms may be. However, a large variety of approaches, depending on the baseline and ictal activities in particular regions of the brain, may be chosen.

Detection systems may have to cope with a wide variety of pre-ictal and ictal onset patterns, many of which are already well characterized in EEG studies. For example, in many cases temporal lobe seizures involve a desynchronized state before the highly synchronized ictal state appears and many other variations may also exist. This variability in pre-ictal onset, depending on location in the brain and type of seizure, and the likelihood of noise added to any EEG/ECoG system, may contribute to difficult pre-ictal or seizure detection. However, both Litt and Iasemidis suggested that a seizure state may actually be developing for several hours, which may provide sufficient opportunity for perturbing this ictal development at an early stage.[25,37,38] Although may reports have focused on direct ictal detection and subsequent seizure

disruption,[28,29,30] some comparative studies are trying different algorithms to assess relative efficacies of seizure detection schemes.[24,26]

Further developments may require multiple detection algorithms employed within a single system. Although it is proprietary, the current Medtronics system in clinical trials uses alternative detection schemes with an external processing box because of the space required for the computer. However, it is anticipated that an internalized system will be critical, although the types of computer processor and algorithm to be used have not yet been confirmed. Clearly, the simpler the algorithm (and the more likely to function in real time), the more likely it will fail or not be applicable to a wide range of pre-ictal states. Thus, the development of small, totally implantable computer systems that can handle these challenges will require sophisticated biomedical engineering support.

6.5.4 Method of Seizure Termination

Many modes of electrical feedback have been applied in both slices and *in vivo* cortex to try to terminate seizures, which usually involve invoking some form of surround inhibition or reversing polarity of an ongoing event. These work far better on a local basis instead of on larger areas of brain.[28–32] Any form of stimulation can also trigger a seizure because the stimulation is usually anticipated to be applied to an epileptogenic zone. Thus, gradients of stimulation current sufficient to disrupt an ongoing ictal build-up and too small to generate a seizure may be required. Local stimulation with a clearly defined regional onset may be most beneficial to smaller regions of brain. Stimulation may also be patterned in such a way as to minimize seizure onset and to maximize seizure disruption, if possible.

There is a large question of the importance of the SNr in the motor output of a generalized seizure, but the effects of stimulation of this region on cortical areas responsible for the seizure or involvement of the cortex in general are unclear. It may be less than helpful to suppress only the motor output of a seizure if the entire cortex has already become involved in a generalized seizure; this will not improve cortical functioning and may only serve to limit damage. This is similar to the role of corpus callosotomy, following which individual cortical areas remain active and undergo ictal events but cannot generalize due to the lack of commissural connections. Cortical functioning (i.e., memory, cognitive functioning) does improve even though safety may not improve due to persistent (and more focal) seizure activity.

Likewise, several areas now suggested for stimulation to prevent seizure are highly nonspecific. Older studies of cerebellar and brainstem stimulation were shown only to heighten awareness via reticular activation. Vagus nerve stimulation may also function in this manner (although it is not well elucidated). Anterior thalamic stimulation may primarily serve to prevent commissural spread in the frontal areas; how it will affect cortical functioning remains unclear. Does a need exist for further empiric studies on alternative nonspecific sites that may lead primarily to mild suppression of diffuse cortical dysfunction? Pursuing a specific therapy that may function on a subclinical level with a feedback or demand loop would seem to be

more logical, particularly with the goal of arresting a local positive feedback loop before a significant region of the brain is involved.

Methods to arrest local development of a seizure could also include local parenchymal, intracerebroventricular or system delivery of drugs although few drugs are approved for intrathecal or parenchymal delivery and diffusion is limited.[41,42] The proposed and patented Ludvig system involves local detection and local drug application in a demand sense but, of course, any direct brain delivery of medication will require rigorous study for FDA approval.[41] Systemic delivery of a drug may be effective but would also produce generalized effects. Electrical stimulation of a focal region is attractive, but it would exert a limited field of effectiveness, and if ill-timed could heighten hyperexcitability and thus aggravate seizure activity.

Cardiac demand systems in current clinical use appear to be highly effective at detecting abnormal rhythms and generating sufficient electrical pulses to abort abnormal rhythms and restart more normal beats. It is tempting to suggest that some of this technology could also be applied to pre-ictal detection of seizures. Other modes of diffuse stimulation could include cranial nerve inputs such as trigeminal[30] or the current vagus nerve stimulation, but in intermittent stimulation mode. Magnetic stimulation to some regions may also be inhibitory, as may many of the current sites in thalamus, STN, or hippocampus. Many proprietary systems in development, which are neither publicized nor published, may overcome some of these difficult challenges. However, many of these systems may not become general knowledge unless they are effective or FDA approval is gained.

6.6 REQUIREMENTS FOR CLINICAL APPLICABILITY

One approach is to use current patients who are undergoing video EEG monitoring and add various stimulation sites for short-term assessment of efficacy and cortical effects of a feedback system. This would allow testing of all three aspects of a demand system. Many patients undergoing video EEGs also have implanted depth electrodes, and stimulation of the depth electrodes is currently underused as a possible method for seizure control.

Such research studies would have to be added after sufficient clinical information is garnered to localize seizures. However, pre-ictal detection could be determined *post hoc* with application of known algorithms to optimal EEG or depth electrode signals. The cortical effects and clinical effects of stimulation or medication at different sites could also be determined on a short-term level, with possible targets:

1. Near the seizure initiation zone, such as in the hippocampus
2. The subthalamic nucleus with unilateral or bilateral implanted electrodes
3. The trigeminal nerve if a suitable location could be found for stimulation within or adjacent to the nerve
4. Rapid systemic medication delivery

In addition to short-term studies, a combination of detection, processing, and suppression methods could be tested using a number of types of seizures. It is difficult now to argue for long-term implantation of stimulation electrodes at any of these

sites until short-term data on clinical effects and side effects can be obtained. In addition, the stimulation level at which seizures can be suppressed will be critical as will the feasibility of suppression prior to clinical expression of a seizure in a subconscious pre-ictal state.

Clearly, one long-term goal is to design, develop, and clinically test an "intelligent brain-pacemaker" device to detect neural activity preceding clinical manifestations of an epileptic seizure and disrupt this pathological brain state through intermittent electrical stimulation of a brain region or a peripheral cranial nerve.[34,35] Like a modern demand heart pacemaker, a brain pacemaker would operate autonomously to interrupt the development of an epileptic seizure at a critical early time period without intervention from the patient, physician, or other individuals.

6.7 CONCLUSIONS

A number of advances in epilepsy treatment are already in development or are undergoing clinical trials at a time when a large number of new drugs that may decrease the need for new surgical interventions are also available. Additionally, childhood and neonatal seizures and status epilepticus are more aggressively treated early now, as better protocols for status are now in use.

As episodes of febrile seizures and status decline, significantly fewer patients may experience later complex partial seizures because in many instances mesial temporal sclerosis appears to have arisen from early episodes of febrile seizures that terminated in status epilepticus. Thus, better early medical treatment may prevent the development of later intractable epilepsy, and could eventually decrease the population for whom surgical therapy of any type is considered.

Despite a number of new modalities of treatments on the horizon, an ideal system would consist of pre-ictal seizure detection in a critical area of the brain, and then a counteracting influence (local or systemic drug injection, local or diffuse electrical stimulation, etc.) to prevent ictal onset completely. From a clinical perspective, the only effective surgery is one that completely prevents seizure, avoids social stigmas attached to patients with the disorder, and maintains optimal neurological functioning.

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