# Chapter 7

## Strategies for closing the treatment gap of refractory epilepsy

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### Introduction

There are numerous therapeutic options for the management of chronic seizures and epilepsy. Seventeen approved antiepileptic drugs in the United States, one stimulation device, vagus nerve stimulation (VNS), epilepsy surgery for certain localization-related epilepsies and the ketogenic diet are all available. Despite the plethora of surgical and medical treatments, there remains a need for better therapies that fundamentally stop and cure epilepsy. Psychosocial consequences of epilepsy along with comorbid conditions of cognitive dysfunction, mood disorders and other concerns limit the benefit of current therapy. The goal for this chapter is to try to outline the treatment gap of epilepsy. To accomplish this goal, the discussion will center on the current state of epilepsy care followed by identification of three gaps. This chapter will discuss the current best evidence supporting various therapeutic options with the goal of closing the treatment gap.

### The state of epilepsy care in the United States

In 2005, the United States (US) Centers for Disease Control and Prevention (CDC) conducted surveillance work to assess the state of epilepsy and seizure care in the United States based on 19 reporting states [1] **(Ib/A)**. The US CDC worked with the Behavioral Risk

Factor Surveillance System and assessed a number of epilepsy and seizure-related variables to better characterize how well the US healthcare structure was handling epilepsy care. The Behavioral Risk Factor Surveillance System is an ongoing, state-based, random, digit-dialed telephone survey of non-institutionalized United States adults over the age of 18. The system collects information on health risk, behaviors, and preventive health services that relate to the leading causes of death and morbidity.

The surveillance system included a total of 2207 adults from 19 states, or 1.65% who reported a history of epilepsy [1]. 0.084% had active epilepsy defined as either a history of epilepsy and currently taking medications or reporting one or more seizures during the past 3 months [1]. 0.75% were classified as having inactive epilepsy or a history of epilepsy or seizure disorder but not currently taking medicine to control epilepsy and no seizures in the 3 months preceding the survey [1] **(Ib/A)**.

American adults with a history of chronic seizures were much more likely to report fair or poor health, being unemployed or unable to work. These individuals also lived in households with the lowest annual incomes, and had a history of concomitant disorders such as stroke or arthritis [1]. Adults with a history of epilepsy also reported significantly worse quality of life. Individuals with epilepsy were more likely to be obese, physically inactive and smoking [1]. In adults with epilepsy who have had recent seizures, 16.1% reported not taking their epilepsy medications and 65.1% reported having had more than one seizure in the past month [1] **(Ib/A)**.

Among adults with a history of seizures, almost 24% reported cost as a barrier to seeking care from a physician over the previous year [1]. A total of 35% of adults also reported not having seen a neurologist or an epilepsy specialist in the previous year [1] **(Ib/A)**. The study showed that seizures and epilepsy are frequent occurrences among the American population and there is a significant burden of disease that cannot be assessed from epidemiologic studies [1]. Even with multiple treatment options, a major gap exists between treatment and optimal quality of life.

## How well do seizure medications work?

This question was addressed in a seminal study by Brodie and Kwan in 2000 [2] **(IIa/B)**. Using newer agents Brodie and Kwan investigated 523 untreated patients with epilepsy. Of those 523 patients, 470 were drug naïve, 47% responded to their first antiepileptic drug and 13% were seizure-free on the second antiepileptic drug [2] **(IIa/B)**. Of the individuals whose seizures failed to respond to the first two agents, seizures in only 1% responded to the third choice of drug [2] **(IIa/B)**.

The study uncovered that there are two groups of epilepsy patients. There are those whose seizures can be managed with any seizure medication and will likely respond to the first or second agent presented to them in monotherapy. However, there is another group of individuals which are much more difficult to identify at an early point and whose seizures fail to respond to any drug. These cases are defined as refractory epilepsy patients who may

need to be assessed for surgical intervention at an earlier point in their course of epilepsy as opposed to committing them to multiple medication trials over extended periods of time.

To further underscore this point, the International League against Epilepsy recently created a new definition which better defines drug-resistant epilepsy [3] **(IV/C)**. The new operational definition is that a patient's seizures must have failed to be completely controlled with two antiepileptic drugs used in informative trials [3] **(IV/C)**. Success is defined as an appropriately selected antiepileptic drug used with complete cessation of seizures for more than 1 year or three times longer than the baseline inter-seizure interval, whichever is longer of the two with a minimum of a year to determine an effect [3] **(IV/C)**. This particular definition helps to define when a patient is likely not to be responsive to a seizure medication and more aggressive treatment is necessary [3].

## Defining gaps

If one were to best categorize the treatment gaps of refractory epilepsy, there would be three broad groups. The first is a diagnostic treatment gap, which pertains to identifying individuals with refractory epilepsy and denoting them at an earlier point in the course of the disease before the psychosocial problems have had life-altering consequences. Second is a medical treatment gap, defined as lack of use of new drug therapies. Lastly, a surgical treatment gap exists, which refers to leveraging potentially curative and disease-modifying tactics by the use of devices or surgery.

### *Diagnostic treatment gap*

One of the essential strategies in closing the treatment gap is to distinguish the 'at risk' population that will merit extra resources in order to better help them. Put another way, what are the biomarkers that will denote patients who may be in need of extra attention with regards to their condition? Table 1 shows helpful clinical historical biomarkers. Clinical historical biomarkers are helpful in predicting seizure remission. Such biomarkers with class 1 evidentiary support include: normal neurological and intellectual abilities; age of seizure onset less than 12 years of age; and infrequent or easily controlled seizures. If all three are present, there is an 80% remission rate. If none are present then there is a 20% remission rate [4, 5] **(I/A)**. Other consistent historical biomarkers for remission have included the presence of idiopathic epilepsy, a normal physical examination and an early response within 2 years of antiepileptic drug-induced remission [4, 5] **(I/A)**. Thus, the absence of these markers may portend a more difficult prognosis for the patient.

Modalities such as imaging have helped to find epileptogenic lesions, particularly those associated with heterotopia, low-grade neoplasms, and hemorrhagic infarctions, which are highly related to refractory epilepsy. Combining historical biomarkers with imaging may be potentially useful. Another helpful biomarker is electroencephalography (EEG). Although the EEG is useful in predicting which patients are likely to have seizure recurrence based on the presence of epileptiform discharges, there is a lack of specificity for predicting which patients

**Table 1. Clinical historical biomarkers suggesting seizure remission [4, 5].**

| Historical variable | Level of evidence |
|---|---|
| Seizure onset less than 12 years of age | Ia/A |
| Infrequent seizures | Ia/A |
| Normal examination | Ia/A |
| Idiopathic epilepsy | Ia/A |
| Early response to AED | Ia/A |

are likely to enter a seizure remission. In the future, it is possible that high frequency oscillations found on intracranial EEG recordings may be fruitful in helping to select which patients are likely to have ongoing seizures [6] **(IV/C)**.

One of the more exciting approaches to diagnostic aspects of closing the treatment gap is the concept of seizure detection and prediction (see also Chapter 8). Seizures are manifestations of increased network synchronies. Therefore, it is reasonable to assume that there are changes in activity potentially embedded within an EEG signal that will reflect these synaptic or network changes before an actual seizure occurs. Examination of interictal spikes has not convincingly shown that spike frequency increases prior to ictal initiations. However, there are subclinical seizures, bursts or 'chirps' that increase prior to clinical events [7]. The concept of these early changes, which could occur minutes or even hours before a clinical event, characterizes the pre-ictal state [7].

Thus a device could be created to link early seizure detection to therapeutic intervention. To provide meaningful benefit this would require an automated system with rapid response. Ideally the intervention would reduce seizure duration so that alteration of consciousness or secondary generalization did not occur. If a seizure prediction algorithm allowed identification of a pre-ictal state before a seizure, then a window for intervention could be noted, reducing the unpredictability of seizures.

Coupling a seizure detection device for early seizure detection to a drug delivery system could be a potent strategy. Using devices in rats, computerized detection of ictal onset triggered application of diazepam to experimental seizure foci [8, 9]. The application was administered quickly enough, less than 5 seconds after seizure onset, to produce a 64% reduction in seizure duration [8, 9]. If such a device could be coupled with a seizure prediction algorithm, greater reduction or even seizure prevention could result. Rapid cooling or hyperthermia has also been linked with early seizure detection devices [10].

There are thus a number of historical, electroencephalographic and potential imaging biomarkers which could help identify who are patients likely to have drug-resistant seizures early in their course, help to predict when seizures occur, and in essence transform the quality of life of patients with epilepsy.

### *AED treatment gap*

As one examines the current plethora of options available for epilepsy, one notes that most AEDs have been approved based on a limited understanding as to the mechanism of action of these various compounds. The current era of antiepileptic drug discovery was ushered in by Merritt and Putnam in 1937 when they demonstrated the feasibility of using a maximal electroshock (MES) seizure, or a MES model, to identify the anticonvulsive potential of phenytoin [11]. A number of other animal models have been employed in the search for more efficacious and tolerable AEDs. In the early 1970s, the National Institute of Neurological Disorders and Stroke embarked on a mission to encourage basic research aimed at a greater understanding of the factors that contribute to the initiation, propagation and amelioration of seizures. As part of this effort the Anticonvulsive Drug Development Program (ADD) was created to foster the development of new drugs for the treatment of epilepsy.

Since 1975 the ADD has accessioned more than 25,000 investigational anticonvulsant drugs from the academic community and the pharmaceutical industry. This has led to the identification and development of several new antiepileptic agents. It has fostered significant understanding not only of the therapeutic nature of various agents but also the basic science associated with epilepsy. As the understanding of the pathophysiology of acquired epilepsy at the molecular genetic level leads to the development of a new therapeutic approach, it is likely that drug development models will need to be refined in order to find better approaches for the management of epilepsy. The current approach for drug development is to identify agents that are effective for treating seizures but not likely to be disease-modifying or anti-epileptogenic as say an antibiotic or chemotherapy for an infection or neoplasms are, respectively. A discussion on future animal models for better AED identification is beyond the scope of this chapter and the reader is referred to other sources for a more comprehensive review of the topic [12].

## Complementary and alternative therapy for epilepsy

One strategy for potential benefit for refractory epilepsy is complementary and alternative medicine (CAM). CAM is defined by the National Institutes of Health (NIH) as “those health care and medical practices not currently an integral part of conventional medicine” [13]. It is estimated that anywhere between 42% of the US population, 48% of the Australian population and 70% of the Canadian population use complementary and alternative medicine for various health conditions [13-17]. There are 600 million visits to CAM practitioners per year in the United States at a relative cost of 30 billion dollars which is almost always paid as an out-of-pocket expense [13]. The NIH has created a national center for complementary and alternative medicine

at an initial budget of $100M per year to investigate potential therapies [17]. As a result, CAM has obtained a measure of legitimacy.

Several studies have explored the extent of CAM treatments in the United States. Sirven and colleagues surveyed 3100 members of the Epilepsy Foundation in Arizona in one of the first studies to address this issue [18] **(IIb/B)**. The results showed that about 51% had tried CAM for non-seizure-related conditions. These non-seizure-related conditions included memory loss, headaches, chronic pain, diabetes, and prevention of cardiac, cerebrovascular and neurodegenerative diseases. Forty-four percent of the respondents had used CAM specifically for their seizure control.

Several therapies are being used as CAM for seizures in epilepsy. The most commonly cited CAMs included acupuncture, botanical therapies (see also Chapter 11), chiropractic care, magnet therapy, prayer, stress management and yoga. The most commonly cited CAM procedure was prayer with 44% of individuals stating that they use prayer as treatment for their seizures [18] **(IIb/B)**. When asked whether CAM therapy benefited seizures, almost all respondents stated that each of the mentioned CAMs had positively benefited their seizures.

### *Evidence-based medicine supporting CAM treatments*

Table 2 illustrates the available evidence on CAM for epilepsy. No randomized controlled trials have evaluated the efficacy of various CAM treatments for epilepsy. This has been highlighted by several recent reviews on the topic showing the absence of evidence to support CAM efficacy despite the high prevalence of use of these treatments by epilepsy patients [19, 20]. Two Cochrane reviews highlighted this fact in assessing the current state of evidence for CAM treatments for epilepsy [19, 20] **(III/B)**. One Cochrane review examined five studies of yoga, none of which were randomized or controlled [19] **(III/B)**, and the other review evaluated 11 stress management studies [20] **(III/B)**. Stress management studies included aromatherapy, desensitization, relaxation, biofeedback, massage, yoga, and acupuncture. Based on observational data, there appears to be a beneficial effect on seizure frequency related to either yoga or stress management, but there was no level I/A evidence to support the use of either approach. A recent review of CAM treatment efficacy for epilepsy reported high response rates with therapies such as biofeedback, yoga, acupuncture and one

**Table 2. Evidence supporting CAM for epilepsy.**

| CAM | Study | Level of evidence |
|---|---|---|
| Yoga | Ramaratnam [19] | IV/C |
| Stress management | Ramaratnam [20] | IV/C |

botanical (*Cyanchum porophylum*) [21] **(IV/C)**. However, none of these response rates are based on randomized controlled trials. There is no evidence to support the use of other modalities such as chiropractic care or any of the current botanicals that are used by some patients for the management of epilepsy.

## Surgical gap: new devices for epilepsy

There is considerable hope and promise in devices for epilepsy. This section will address two modalities in late-stage pivotal randomized controlled trials. Table 3 addresses the current available evidence for new devices for epilepsy.

### *Deep brain stimulation for epilepsy*

Seizure suppression with electrical stimulation of deep brain structures is effective in animal models using various neural targets including the cerebellum, hippocampus, caudate nucleus, thalamus, subthalamic nucleus (STN), and mammillary nuclei. A randomized controlled trial investigated deep brain stimulation (DBS) of the anterior nucleus of the thalamus (ANT) [22, 23]. One hundred and ten patients were enrolled in the trial and randomized to treatment or control. Bilateral stimulation of the anterior nucleus of the thalamus resulted in a significant (29%) reduction of seizures in the treatment group compared to the placebo group. The effect lasted for at least 2 years [22, 23] **(Ib/A)**.

Animal studies investigating the efficacy of the ANT DBS for epilepsy primarily reflect the work of Mirski and colleagues [24]. Bilateral electrolytic lesions of the tracks connecting the mammillary bodies to the ANT in guinea pigs resulted in essentially complete protection from

**Table 3. Evidence supporting novel devices for epilepsy.**

| Device | Study | Level of evidence |
|---|---|---|
| Deep brain stimulation of anterior thalamus | SANTE [23] | Ib/A |
| Closed-loop stimulation of cortex (RNS) | RNS pivotal [28, 29] | Ib/A |
| Transcranial magnetic stimulation | Vonck [30] | IV/C |
| Trigeminal nerve stimulation | DeGiorgio [31] | IV/C |

pentylenetetrazole-induced seizure activity [24]. This finding was supported by observations of enhanced glucose metabolism in the ANT following administration of both pentylenetetrazole and ethosuximide in guinea pigs [24]. High frequency DBS of the ANT was shown to increase the clonic seizure threshold in a pentylenetetrazole-induced seizure model [25].

The SANTE trial evaluated patients with partial onset epilepsy with or without secondary generalization associated with frequent seizures, resulting in falls, injuries and impaired quality of life, refractory to at least two therapeutically dosed antiepileptic agents for a minimum of 12 to 18 months [22, 23] **(Ib/A)**. Patients were without evidence of progressive neurologic or systemic disease and many had not improved from surgical resection and/or vagal nerve stimulation. Pilot studies showed that there is significant individual variation in outcome but overall bilateral high frequency ANT DBS appears to be safe, well tolerated and effective in some subjects with inoperable refractory epilepsy. In a series of six various pilot studies with up to six patients, the reduction in seizure frequency ranged from 14% to 75% [26] **(III/B)**. The pivotal SANTE trial, as discussed above, however, identified that this modality was useful for refractory epilepsy [22, 23] **(Ib/A)**. Despite this positive trial, the US Federal Drug Administration requested further study. The European Union has approved the device for use in drug-resistant epilepsy.

### *Closed-loop stimulation in the control of focal epilepsy*

The only currently approved device for epilepsy management is vagus nerve stimulation (VNS). VNS is a cyclical type of open loop stimulation that has been shown to reduce seizures with statistical significance **(Ia/A)**. In 1999, a study of brief stimulation of induced afterdischarges showed that induced afterdischarges could be aborted [27]. Based on that study, investigators conceived the possibility that an implanted closed-loop device could both detect and abort epileptiform activity as opposed to the VNS or DBS approach of aborting activity without seizure detection. Currently, there is a device being investigated which is a closed-loop neurostimulation device termed responsive neurostimulation (RNS) [28]. The RNS system is comprised of an implantable pulse generator, depth electrodes and a programmer. The salient features of the RNS system is electrocorticography storage and algorithmic analysis so that ictal EEG recordings from the intracranial electrodes can be detected [28].

The neurostimulator utilizes one of three seizure detection tools, operating on one or two detection channels. The system is designed to detect a seizure when it occurs. The neurostimulator system can then deliver an electrical charge by phasic pulses with amplitude programmable between 0.5 milliamps to 12 milliamps with a duration programmable from 40 to 1000 microseconds at a frequency programmable from 1 to 330Hz [28]. Any of the electric contacts or the pulse generator housing may be programmed as anode or cathode. After a pulse-trained therapy has been delivered, a re-detection algorithm determines if the epileptiform activity is still present and if so up to four additional therapies may be delivered per episode. The neurostimulator system has a built-in charge density limit that allows no more than 25 micro-coulombs\cm$^2$\phase charge density to be delivered [28].

Recently the RNS investigators reported results from their multi-centered, double-blinded, randomized, controlled pivotal investigation of the RNS system for treatment of intractable partial epilepsy in adults [29] **(Ib/A)**. Eligible subjects were 18 to 70 years of age, had an average of three disabling partial seizures a month, had seizures that failed to improve from two or more antiepileptic medications and had seizure foci localized to one or two regions. Subjects completed a 3-month baseline to determine eligibility based on seizure frequency and were then given the option to have the RNS system neurostimulator leads implanted.

The neurostimulator was programmed to detect data on seizure detection 1 month postoperatively. Subjects were randomized 1:1 to receive sham or active responsive stimulation. Physicians responsible for acquiring data for the primary and secondary safety and efficacy outcomes were blinded to the randomization status. Seizure frequency was considered over the 84 days beginning 2 months after implantation. At completion of this blinded efficacy evaluation period, all subjects were able to receive stimulation until 2 years post-implant, then could transition into a 5-year open-label, long-term treatment trial [29].

As of 2009, 191 subjects had been implanted with the RNS neurostimulator across 29 United States sites. The mean age was 36 years, range 18 to 67, and 48% were female. The mean age of seizure onset was 14 years. Subjects were taking an average of 2.8 AEDs, 34% had previously been treated with VNS and 33% with epilepsy surgery. Sixteen percent had been treated with both VNS and surgery. Sixty percent had prior intracranial monitoring for localization of the epileptic focus [29]. Forty-six percent had ictal onset from mesial temporal structures only and 82% of these subjects had bilateral mesial temporal ictal onsets [29].

The trial demonstrated a statistically significant reduction in seizure frequency in the treatment group as compared to the sham stimulation group. During the last 2 months of the 3-month blinded evaluation period of the study, the treatment group experienced a mean percentage reduction of 29% in their disabling seizures compared to a 14% reduction for those in the sham stimulation group [29] **(Ib/A)**. In the long-term open-label period of the trial at least 12 weeks of data were available for 171 study participants; 47% of these subjects experienced a 50% or greater reduction of their seizure frequency based on their most recent 12 weeks of data as compared to their baseline [29].

The trial also demonstrated a serious adverse event rate less than the comparative surgical procedures. There were no serious, unanticipated device-related adverse events reported in the trial. There were no differences between the treatment and sham stimulation groups when comparing the rates of adverse events, including depression, memory impairment and anxiety. In summary, this particular study showed that there is significant improvement in seizures and is now being considered by the FDA for potential approval for its use in refractory partial epilepsy treatment in the United States.

### *Other forms of stimulation*

Transcranial magnetic stimulation is an extracranial form of neurostimulation therapy that transmits magnetic fields via a coil held over the scalp. This form of stimulation therapy influences both excitatory and inhibitory functions of the cerebral cortex and is currently being investigated as a possible treatment option for refractory epilepsy and depression [30] **(III/B)**. Trigeminal nerve stimulation involves the transcutaneous or subcutaneous stimulation of the infra-orbital or supra-orbital branches of the trigeminal nerve. A small pilot study evaluated the safety and efficacy of trigeminal nerve stimulation among patients with epilepsy and showed that four of seven patients had at least a 50% reduction in seizure frequency after 3 months of trigeminal nerve stimulation without significant pain or discomfort [31] **(III/B)**. Controlled and multicenter studies in larger patient groups are still necessary for all of these emerging therapies before their utility in the treatment of epilepsy can be established.

## Summary

There are many therapeutic options which hold promise in the future for closing the treatment gap of epilepsy. The ultimate goal for the management of epilepsy is to completely stop seizures with minimal impact on quality of life from those treatments. It is through rapid and early identification of patients who struggle with epilepsy that aggressive management can be most effective to avert psychosocial problems that are so common to this population. The goal is to determine how we can best utilize and harness the power of technology and science so that we can best improve the lives of our patients who suffer from this disabling condition. Hopefully as we look to the future we will see marked improvements in our approach to closing the treatment gap for those patients with epilepsy. Lastly, although this chapter has focused on the best evidence-based approaches to management of epilepsy, system-based processes need to be considered as well. The financing and access to healthcare are still essential elements for any successful treatment program. It is of no use to develop treatments for epilepsy if they cannot be accessed by all patients who could potentially benefit, regardless of their socioeconomic status. It is only by making certain that the economic and financial barriers to healthcare are erased that the rest of the treatment gaps of epilepsy can be addressed and significant strides can be made at the public health level for the management of epilepsy.

## Conclusions

The evidence suggests that reliable diagnostic markers for seizure remission include:

- seizure onset less than 12 years of age;
- infrequent seizures;

- normal examination;
- normal intellectual abilities.

There is an absence of randomized controlled data supporting the use of various CAMs for epilepsy.

There is evidence to support the use of vagus nerve stimulation and deep brain stimulation of the anterior thalamus for refractory epilepsy as adjunctive therapy. There is forthcoming evidence to address the use of the closed-loop stimulation system, RNS, for refractory epilepsy.

| Key points | Evidence level |
|---|---|
| ◆ There are clinical historical biomarkers that predict seizure remission. Absence of these factors may portend a poor prognosis. | Ia/A |
| ◆ There is an absence of clinical evidence to support the use of CAM for epilepsy. | IV/C |
| ◆ There is evidence to support the use of vagus nerve stimulation and deep brain stimulation of the anterior thalamus for refractory epilepsy as adjunctive therapy. | Ib/A |
| ◆ There are forthcoming randomized controlled trials addressing the efficacy of a novel closed-loop system of cortical stimulation for epilepsy. | Ib/A |
| ◆ There is no current evidence to support the use of transcranial magnetic stimulation or trigeminal nerve stimulation for epilepsy. | IV/C |

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