Aligning the Language to Advance Care and Science in Epilepsy

Twenty years ago, there were only a few medications available to treat epilepsy, and of patients treated with drugs, around 30% saw no decrease in seizures. We now have approximately twenty-five medications to choose from, and the newer medications tend to have fewer side effects than the older options.[1]

Still, the number of non-responders remains roughly the same, at about 30%. [1] This a large number, as prevalence of epilepsy in the US is 3.4 million, or 1.2 percent of this population, with more than 65 million affected worldwide.[2] Untreated epilepsy can lead to a multitude of unwanted consequences, including social stigma and decreased quality of life, injuries from falls, damage to the brain and even death. Limiting seizures in children is especially crucial as repeated epileptogenic activity can lead to epileptic encephalopathy, causing developmental deficits and even regression.[3]

Since the 1940s, some patients with refractory epilepsy were (and still are) treated with open brain surgery, which might involve resecting a focal portion or even a hemisphere. However, of patients who have open brain surgery, only 60 to 70 percent become seizure-free after surgery. [1] It is also a highly invasive surgery with potentially devastating side effects and complications.

Thus, there continues to be a large unmet need for many patients with drug-resistant epilepsy. However, in recent years, several avenues of therapy have been explored and developed, with some innovative options approved just this year,[1] providing new hope for many.

Of course, a patient needs a correct diagnosis first. This can be difficult to obtain, as there are myriad types of epilepsies, seizures, and syndromes, and in spite of our abilities to image the brain, the science is not developed enough to serve as a basis for classification.[4] Instead, the cumulative experience and consensus of experts is relied upon to define a classification system which facilitates best care practices.[4]

According to The International League Against Epilepsy (ILAE), a seizure is defined as "a transient occurrence of signs and/or symptoms due to abnormal excessive or synchronous neuronal activity in the brain."[5] In 2014, ILAE proposed an overall definition of epilepsy as a brain disease involving any of the following:

1) At least two unprovoked (or reflex) seizures occurring >24 h apart
2) One unprovoked (or reflex) seizure and a probability of further seizures similar to the general recurrence risk (at least 60%) after two unprovoked seizures, occurring over the next 10 years
3) Diagnosis of an epilepsy syndrome.

Epilepsy can be considered "resolved" in people who have outgrown an age-related (self-limited) syndrome, and in those who have been seizure-free for the last ten years and off AEDs for five or more years.[6]

ILAE created a taxonomy of seizure and epilepsy types in 1981, revised in 1989, which has largely remained in use to this day. The taxonomy is applied after the seizures are determined to be truly epileptic and not caused by some other disease process. In 2017, ILAE updated the guidelines and produced a three-part set of papers defining the categories of seizures[4] and epilepsy types, [7] with a third paper detailing how to apply the categories and terms.[8] This "user's manual" contains a glossary, maps new terms to old, and provides case-study examples which clearly illustrate appropriate implementation of this "operational classification system". [8]

As the authors of ILAE state, "One of the major problems is our lack of understanding of the processes that underlie the production of different types of seizures and so we are usually treating the

symptoms and not the cause of the problem. Nevertheless, if we are to eventually understand these processes, we will all need to speak the same language, e.g. identify correctly the seizure types and epilepsy syndromes, wherever the affected person comes from around the world."[9]

Gap #1: The diagnosis and classification of epilepsy can be challenging to clinicians, limiting the implementation of appropriate, effective therapies and impeding patient's quality of life.
LO #1: Improve the diagnosis and classification of epilepsy by incorporating evidence-based guidelines and seizure detection techniques

As per the 2017 ILAE guidelines update, the diagnostic process consists broadly of three levels of refinement, including seizure type, epilepsy type, and, if applicable, epilepsy syndrome. The new taxonomy does not classify epilepsy syndromes but drilling down on the seizure and epilepsy type can reveal elements of a known syndrome. The diagnosis may contain more or less information based on what is available, and the classification system is designed to provide a framework for making clinical predictions and decisions; hence it is an "operational classification." [4]

The update was due because, despite tweaking over the years, some of the precepts from the standing version had become obsolete due to advances in knowledge. In other cases, it was found that some of the terms were unclear, misleading, or even offensive or unnerving to patients. The aim of renaming terms was to introduce and reinforce the use of a universal and transparent language for describing epilepsy, for the purposes of patient care, research, and policy making.

Seizure onset is important as it is determined by where the seizure originates structurally, which in turn can point the way to a correct diagnosis and treatment. Seizure onset can be surmised by closely noting the initial seizure signs and symptoms, or it may be visualized in imaging or localized via EEG pattern. While the terms "partial onset "and "generalized onset" are traditional, the update calls for the replacement of "partial" with "focal" to describe onset that occurs in one part or hemisphere of the brain. "Focal" more clearly describes a structural location for the seizure onset, whereas "partial" misleadingly suggests the seizures are "less than" generalized seizures in some way. [7]

Level of awareness is an important qualifier of focal seizures and can be incorporated into the label. A patient who maintains awareness of self and environment during the seizure is classified as having a "focal aware" seizure, even if they are unable to speak or move during the episode; a patient who has greatly altered or loss of consciousness is said to have a "focal onset impaired awareness seizure".[4] These terms replace the old terms; "simple partial" is now "focal aware" and "complex partial" is "focal impaired awareness".[4] Awareness is not used when classifying generalized seizures, as these usually, although not always, involve loss of consciousness.[10]

Focal onset seizures are defined by the first prominent symptom that occurs and is qualified as that even if the seizure is followed by other symptoms. For example, a seizure that starts with déjà vu is classified as a "focal cognitive seizure" even if motor symptoms follow. New descriptors were added to refine the classification of focal onset seizures, including "behavior arrest", "automatisms", "hyperkinetic", "autonomic", "cognitive", "sensory", and "emotional". Certain terms were discarded as vague or misleading, these include "dyscognitive" and psychic". Focal, as well as generalized seizures, may include the labels "atonic", "clonic", "myoclonic" and "tonic, and "epileptic spasms". Any seizure can be described as motor or non-motor if appropriate. The term "non-motor", if referring to a generalized seizure, is equivalent to the traditional "absence seizure."[4]

A new category called "focal to bilateral tonic-clonic" replaces the "secondarily generalized seizure." This seizure pattern is common enough to warrant a clear descriptive name. This seizure has a focal

onset, but propagates to become a bilateral tonic-clonic event. [4] In contrast, primary generalized seizures have a diffuse bilateral onset.

New generalized seizure types have been named, including “non-motor with eyelid myoclonia”, “myoclonic absence”, “myoclonic-atonic”, and “myoclonic-tonic-clonic.”[10]

The category of “unknown onset” was added, but these seizures may still have features that can be classified, or a seizure can be of unknown onset and labeled “unclassified”; for example, an unobserved first seizure reported by a patient who lost consciousness during the seizure must be documented, even if there is simply not enough information to classify it .[7]

After classifying seizure type, epilepsy type may or may not be classified. “Generalized Epilepsy” and “Focal Epilepsy” continue to be used, but there is the new category “Combined Generalized and Focal Epilepsy, as there are some epilepsies that involve both types of seizures. There is also an “Unknown” category that can be used, even if the type of seizure is classified. [10]

The 2017 ILAE guidelines emphasize the importance of identifying etiology while classifying seizure and epilepsy type. Etiology categories include structural, genetic, metabolic, immune, infectious, and unknown, and can provide clues as to what kind of treatments might be effective. To illustrate, one study found that after two AED failures, 25% of pediatric patients with epilepsy of unknown cause responded favorably to a third AED, compared with only 7.8% of patients with structural or metabolic etiologies.[11] Imaging, blood tests, EEG results, genetic studies, and thorough medical interviewing can all provide clues for determining etiology.[8]

Gap #2: Identifying the appropriate treatment strategy relative to seizure type and patient-related factors can be daunting, with a significant number of clinicians indicating that they lack confidence in their ability to manage epilepsy.

LO #2: Formulate an individualized course of treatment for epilepsy in children and adults that considers mechanism of action, safety/efficacy/tolerability

After an epilepsy diagnosis is established, AEDS are introduced one at a time. A staged approach is used, and if one medication doesn’t work, or the side effects are not tolerable, the medication is replaced with another. If the seizures improve but not completely, an adjunct medication may be added, and some patients may be on 3 or more medications. AEDs suppress the seizure symptoms but do not treat the underlying cause.[12]

A longitudinal study followed a cohort over a 30-year period and found that despite the availability of many new drugs over the years, there was no improvement in seizure-freedom rate. The study found that 63.7% of patients were seizure-free after one year on AEDs, and 86.8% of these patients achieved seizure freedom on monotherapy. It was also found that with each failed drug trial, the probability of seizure freedom dropped precipitously. [12] This observation justifies the 2010 ILAE definition of drug-resistant epilepsy as following failure of two well-tolerated and appropriate AED regimens. [13] It also shows that more options are needed for at least a third of epilepsy patients.

Designer molecules, CRISPR technology, cannabinoid derivatives, all provide hope of expanding medication treatment options. Drugs can also be repurposed, and several established drugs have been found to treat underlying causes; for example, the mTOR inhibitor, tacrolimus, inhibits the cell proliferation of tuberous sclerosis and also inhibits seizures, while immune suppressants can be used on epilepsy with an autoimmune etiology. [14] Classifying epilepsy types is the first step in developing innovative treatments tailored to individual patients. [14]

Several new medications have emerged very recently for the treatment of specific epilepsy types. Cenobamate works on both GABA-A receptors and sodium channels, and is now in phase 3 trials for treatment of focal-onset seizures in adults.[15] Perampanel, an AMPA receptor antagonist, has recently received an expanded application approval for the treatment of focal onset and focal to bilateral tonic-

clonic seizures, in children as young as 4 years old. A missed medication dose is the primary cause of breakthrough seizures, and perampanel has once-a-day dosing and a long half-life which facilitates adherence and provides longer seizure coverage if a dose is missed. [16] Perampanel has also shown promise as treatment for generalized seizures.[17]

With drug-refractory epilepsy, surgical options can be considered. Fortunately, improvements in imaging and surgical techniques mean that highly invasive techniques such as hemispherectomy and corpus callosotomy may be avoided in favor of less risky options.

Again, correct diagnosis is essential. To illustrate, epileptic spasms can have a focal or generalized onset, and the distinction is especially important in children, as shorter time to diagnosis and control of epileptic spasms improves outcomes in young children. Correctly diagnosing focal onset epileptic spasm can lead to the search for and identification of the structural abnormality, and can facilitate a successful surgical dissection of the causative lesion.[18] Other known associations that may point to a surgical solution include mesial temporal seizures with hippocampal sclerosis and gelastic seizures with hypothalamic hamartoma. [10]

MRI-guided laser ablation is a newer technique which allows for pinpoint accuracy and minimal damage to surrounding tissue, and has been found especially effective on refractory mesial temporal lobe epilepsy.[19] Vagus-nerve stimulation (VNS) via an implanted device is approved for refractory focal epilepsy in adults and children over 4.[20] Responsive neurostimulation (RNS), was approved in 2013 for the treatment of refractory focal and focal to bilateral seizures in adults. It works like a pacemaker in that it can detect prodromal changes in electrical impulses and discharges within milliseconds to intercept the seizure.[21] A new Deep Brain Stimulation (DBS) device was recently approved and made commercially available for treatment of adults with focal onset epilepsy refractory to three or more AEDs; it delivers pulsed stimulation to the anterior nucleus of then thalamus and in clinical trial patients had a median reduction in seizure frequency of 75% after 7 years.[22]

Patients with refractory epilepsy are at high risk for cluster seizures, which are three or more seizures in <24 hours. Cluster seizures can progress to status epilepticus, which is a medical emergency. !5 % of patients with epilepsy will experience status epilepticus. Status epilepticus can cause permanent brain damage or be fatal, so the goal is to stop the seizure as quickly as possible. Seizures that continue for more than an hour lead to death in 38% of adults. [23]

Patients at risk for cluster seizures are usually prescribed a rescue medication, most likely a benzodiazepine for oral, buccal, or rectal administration. Adherence to a rescue regimen has been shown to be low (20%)[24] among patients and their caregivers, and may be due, in part, to delivery methods. Oral meds are hard to deliver to a seizing patient, and rectal meds may be slightly easier to administer, but social reticence with this method is highly understandable. To address this issue, there are now benzodiazepines that can be administered intranasally. Intranasal midazolam has been approved for cluster seizures in adults and children over age12,[25] and an intranasal diazepam is under review by the FDA for the rescue treatment of patients age 6 and above.[26]
An alprazolam inhaler using an innovative fast delivery device is in phase 2 trials and could become the first rescue medication that can stop a seizure that has already started. [27]

Gap#3: Epilepsy is a life-long disease that requires an emphasis on long term, team delivered care that includes partnership of specialist care with the patient and with primary care, sharing information, supporting, and empowering patients, and aiming for their increasing independence

LO#3: Integrate a team approach to the management of epilepsy

Many patients with epilepsy can be managed by a general neurologist, but for the 30% presenting with intractable epilepsy, it is imperative that they be treated at a comprehensive epilepsy center. Here, the combined expertise of practitioners can ensure that a patient will receive a thorough exam, accurate diagnosis, and best treatments. It has been found that 15% of people who have seizure-freedom after surgery averaged 15 years before being referred to a specialty center.[9] This is unacceptable; even more so when the patient is a child, as development is impacted by frequent seizures. Crucial physical and occupational therapies can be accessed at a center. Some patients may benefit from a ketogenic diet, and a nutritionist is thus essential. The wide variety of presentations and the fact that many epilepsy syndromes are extremely rare, as well as devastating, points to the need for the highest level of coordinated care. Specialty centers have access to newer treatments and surgical expertise and capabilities.

Psychological services can be found at specialty centers, and this is crucial as patients frequently have comorbid psychological and learning difficulties, including depression, intellectual disabilities, autism, sleep disorders, and psychosocial concerns.[28] It has been found that having epilepsy increases a patients risk of suicide five-fold.[29] Patients and families can also find support from the other patients and families living with similar conditions.[10] Indeed, social support is essential as, although epilepsy is no longer thought to be caused by “demonic possession, mental infirmity, or moral laxity”, patients still report feeling limited by social stigma, and stigmatization reduces quality of life as much as physical symptoms.[28]

All parties caring for a patient with epilepsy need to be consistent in their communications with each other and with patients and caregivers. Patients with epilepsy, especially those with learning or cognitive difficulties, may be at increased risk of med errors caused by unclear and inconsistent instructions from multiple providers.[30] Communication between providers is most likely improved at specialty centers, where all the providers are working under the same roof. Similarly, the assimilation of common terms, such as those promoted in the ILAE guidelines, can be more easily reinforced when all the actors are in close proximity.

New technologies continue to be developed which can empower patients with epilepsy to live as independently as possible. For example, seizure alert devices can be used at home to set off an alarm when seizures are detected, so that caregivers can be called to assist. Many of these devices are not tested; however, there are a couple that have been recently approved by the FDA. The Embrace2 is the first FDA approved “smartband”, and can detect tonic-clonic seizures by sensing changes in movement, electrodermal activity, change of position, and skin temperature.[16]

It is reported that more than 3,000 people in the US die each year from sudden unexpected death in epilepsy (SUDEP).[16] A seizure alert system could prevent some of these deaths if assistance is provided in time. Even better would be a device that can predict seizures before they happen. In Australia, scientists have developed a wearable device that uses artificial intelligence (AI) to predict seizures and alert the patient. And here in the US, an app for the Apple Watch, which can track seizures and record other pertinent data, is being used by researchers at John’s Hopkins, to learn what triggers seizures. [31]

All the new technology does not replace human creative intelligence, and understanding is increased by refinement of language; the ILAE classification system is a means to better understanding of all the nuances of this disease. Indeed, in 1983, a researcher diagnosed Fyodor Dostoevsky, more than a hundred years after his death, with “an ecstatic aura” and “partial complex epilepsy with secondarily generalized nocturnal seizures.”[32] The terminology would be a little different now, and the diagnosis

would be “focal emotional onset seizures with impaired awareness” and “nocturnal focal to bilateral tonic-clonic seizures.” This diagnosis was based on astute discernment of the “data” and did not even include an EEG, as that hadn’t been invented yet; the language of the ILAE diagnostic system describes the diagnosis vividly.

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