

## Current Developments in Epilepsy Treatment

a report by

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Epilepsy includes a heterogeneous group of disorders, affecting approximately 0.8% of the population, and sharing in common the presence of recurrent seizures. Most patients with epilepsy can be controlled with anti-epileptic drugs (AEDs), and many of them can eventually discontinue their medication. However, seizures cannot be controlled in approximately 30% of patients. As multiple molecular mechanisms are involved in the generation of epileptic seizures there are no expectations that a single therapeutic approach will ever be effective in all types of epilepsy. In addition, personal susceptibility to different agents further supports the need for multiple therapies to treat people with epilepsy. Therefore, current development in epilepsy treatment follows different approaches and lines of research, and when available for clinical use, new therapeutic approaches provide benefit to a group of patients, sometimes in clinical situations that were not initially considered the therapeutic target. Application of available therapies is usually different in new onset epilepsy than in patients with difficult to treat epilepsy.

### First Seizure and New Onset Epilepsy

When a patient has suffered the first epileptic seizure, a decision whether to treat or not is based on the risk of seizure recurrence and individual characteristics. A recent study demonstrates that initiating AEDs after a first seizure reduces the risk of seizure recurrence and generalised tonic-clonic seizures during the period of treatment, and concludes that treatment after a first seizure may be advised in patients with abnormal neurological examination, intellectual disability or an abnormal electroencephalogram (EEG). This approach to patients with a first seizure is further supported by a new definition of epilepsy from the International League Against Epilepsy. According to this definition, epilepsy is 'a disorder of the brain characterised by an enduring predisposition to generate epileptic seizures and by the neurobiological, cognitive, psychological and social consequences of this condition. This definition

requires the occurrence of at least one epileptic seizure.' Diagnosing the type of epilepsy after a first seizure is possible in 75% of patients, while in the remaining 25% it is not possible to determine whether it is a focal or generalised epilepsy. The distinction is clinically relevant since patients with idiopathic generalised epilepsy can suffer seizure worsening and even non-convulsive status epilepticus when treated with certain AEDs, mostly carbamazepine and phenytoin. Therefore, it is usually advised to initiate treatment with broad-spectrum AEDs in patients in whom the diagnosis of the epilepsy type is in doubt. In addition to valproic acid, lamotrigine, levetiracetam and topiramate are broad spectrum AEDs licensed for initiation of treatment in new onset epilepsy. Other drug and patient characteristics should be considered at the time of selecting an AED; important factors are co-morbidity, drug interactions, age, sex and weight status. In fact, differences in efficacy among AEDs are small, while differences in side effect profile and potential interactions are more pronounced, representing a more important factor at the time of AED selection. Among these, cognitive side effects are especially important to consider; however, no adequate comparative studies are available to determine with the highest degree of clinical evidence which AEDs have less cognitive side effects. In this scenario a pragmatic approach is recommended; this includes monitoring cognitive function and side effects when initiating treatment and considering AED substitution when cognitive or other problems are identified. Based on clinical observation, gabapentine, lamotrigine, levetiracetam, oxcarbazepine and tiagabine are considered to have a lower risk of causing cognitive side effects compared with other AEDs.

### Medically Refractory Epilepsy

Identification of the epilepsy syndrome and the aetiology of epilepsy are especially important in the assessment of prognosis. In a study of 2,200 adults, seizure control was achieved in 82% of patients who had idiopathic generalised epilepsy, 35% with

**Table 1: Antiepileptic Drugs in Advanced Stage of Development**

<b>AED</b>	<b>Special characteristics</b>	<b>Mechanism of action.</b>
Brivaracetam	Superior potency to levetiracetam	Union to glycoprotein SV2A2
Eslicarbazepine	One dose per day	Sodium channel blockade
Lacosamide	Epilepsy and pain	Unknown
Retigabine	Epilepsy and pain	Potassium channel modulation
Rufinamide	Efficacy in Lennox-Gastaut syndrome	Unknown
RWJ-33369	Highly effective in photoparoxysmal response	Felbamate analogue, glutamate blockade
Talampanel	Potential neuroprotective effect	AMPA antagonist

symptomatic partial epilepsy, 45% with cryptogenic partial epilepsy and 11% with partial epilepsy associated with mesial temporal sclerosis. Epilepsy should be considered to be refractory when seizures cannot be controlled after one year of treatment or when at least three AEDs have been tried without success. Prior to establishing a diagnosis of medically refractory epilepsy, other clinical conditions should be considered, of which psychogenic non-epileptic events is a clinical problem frequently confused with epilepsy, and should be ruled out in all patients considered for other therapeutic approaches. Once medically refractory or difficult to treat epilepsy is diagnosed, a variety of therapies can be considered.

also be controlled in approximately 70% of cases. The efficacy of surgery decreases to approximately 50% in patients with extratemporal epilepsy with normal brain MRI or extensive lesions that cannot be completely removed during the operation. As surgery is very effective when it is an option, it should be considered early in patients whose seizures are not controlled with AEDs.

### Stereotactic Radiosurgery

The efficacy of stereotactic radiosurgery has been explored in patients with epilepsy associated with small structural abnormalities. In an open study, complete seizure control was achieved in almost 80% of patients with mesial temporal sclerosis. The procedure was not associated with major complications; however, a disadvantage was that onset of effect was not observed until six to eighteen months after therapy. Other investigators have reported similar findings, while in different studies this rate of seizure control was not achieved, probably because of differences in patient selection, radiation to a smaller volume of the hippocampal formation or using a lower dose of radiation. Stereotactic radiosurgery has also been applied in patients with epilepsy secondary to hypothalamic hamartoma, small benign tumours and cavernous angioma. Series on

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### Epilepsy Surgery

Approximately 10% of patients with medically refractory epilepsy can be improved or become seizure free with epilepsy surgery. Surgical evaluation always includes the analysis of seizures recorded with video-EEG monitoring, neuropsychological testing and high definition brain magnetic resonance imaging (MRI). In cases of mesial temporal sclerosis, surgery can provide complete or almost complete seizure control in 70% of patients; the rate is lower in cases of temporal lobe epilepsy with normal brain MRI. A controlled study in patients with temporal lobe epilepsy demonstrated the superiority of epilepsy surgery over continued medical treatment without surgery. Patients with focal seizures secondary to a small lesion that can be resected with surgery can

gamma-knife therapy in the treatment of epilepsy have demonstrated some relevant aspects: delayed onset of its effect is probably related to the time mitotic cycles occur in susceptible tissues, such as the endothelium of small vessels and capillaries and astrocytes; occurrence of an increased frequency of brief simple partial seizures is common at the time of tissue changes seen in brain MRI, and this is probably related to earlier involvement of white matter pathways – those that participate in seizure propagation; and differences in individual susceptibility to radiation may explain failure of treatment in some patients. Stereotactic radiosurgery can be considered in patients with mesial temporal sclerosis, hypothalamic hamartoma and other small epileptogenic lesions that refuse standard surgery or have medical conditions that contraindicate it.

### Vagus Nerve Stimulation

Vagus nerve stimulation (VNS) was approved for treatment of medically refractory epilepsy in the 1990s after two open studies and one randomised controlled trial showed efficacy of the procedure. Patients treated with VNS had a mean seizure reduction of 31%, and 39% of patients had a 50% or higher reduction in seizure frequency; these efficacy rates are similar to those observed during clinical trials with AEDs. In addition, small open studies suggest a higher efficacy in secondary and cryptogenic generalised epilepsies. The device can be placed during a relatively simple procedure. Complications are very rare and include transient arrhythmia, persistent hiccups, damage to the facial nerve, migration of the battery and electrode rupture. Studies with depression scales have shown mood improvement in patients with epilepsy and depression, and additional studies further supported this effect in patients with depression not associated with epilepsy. Since responder rate to VNS is similar to AEDs and the procedure has demonstrated to be safe and cost effective, an ongoing study is exploring the benefits of earlier treatment. VNS should be considered in patients with medically refractory epilepsy who are not candidates for epilepsy surgery.

nucleus stimulation was initially explored in a European centre, showing improvement in seizure frequency in a small series of patients with refractory focal epilepsy. Bilateral hippocampal electrical stimulation was also explored in Europe in three patients from a larger number of non-lesional temporal lobe epilepsies studied with hippocampal depth electrodes. Those patients in whom the surgical evaluation was not able to identify the epileptogenic zone were treated with chronic electrical stimulation using the same intracranial electrodes that had been placed for diagnostic purposes. These patients had improvement in their seizure frequency and could have their anti-epileptic medication reduced. Although the number of patients treated in this study was small, it opened a practical approach for evaluating the efficacy of cerebral electrical stimulation in patients with medically refractory epilepsy.

### Anti-epileptic Drugs in Development

Despite the increase in therapeutic options for patients with epilepsy, a significant number still remain refractory to all available therapies. New AEDs are in an advanced stage of development, and many of them have new mechanisms of action that may eventually prove to

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### Deep Brain Stimulation

Deep brain stimulation has recently re-emerged as a therapeutic option for patients who are not candidates for resective epilepsy surgery. The centromedian and anterior nuclei of the thalamus, the subthalamic nucleus and the hippocampal formation are targets that have been explored in different types of epilepsy. Centromedian nucleus stimulation appears to be more effective in Lennox-Gastaut syndrome, where up to 80% responder rates have been reported in small studies. Two different trials explored the efficacy of electrical stimulation of the anterior nucleus of the thalamus, showing a 45–55% seizure reduction in patients with refractory focal epilepsy. Results from these small studies lead to a large multicentre trial currently ongoing in North America. Subthalamic

be effective in certain epilepsy types or better tolerated for some patients.

### Conclusions

Current management of epilepsy requires knowledge of a large number of AEDs, their efficacy profile and potential adverse events. Early recognition of medically refractory epilepsy is usually possible, and in these patients epilepsy surgery can be highly effective. For those patients who are not surgical candidates, further attempts to control seizures with available AED and VNS may improve their seizure control and quality of life. On-going trials with different modalities of deep brain stimulation and new AEDs may also prove their efficacy, adding new therapeutic options for people with epilepsy. ■