Treatment Options for Epilepsy in Adults

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Introduction

Epilepsy affects around 50 million people globally. Each year, about 40-190 people are newly affected by this ailment. The armamentarium for management of epilepsy in adults consists of both pharmacological and non-pharmacological options. Pharmacological therapy continues to be the mainstay of management of a large majority of persons with epilepsy (PWE). However, several pertinent issues need to be dealt with in the pharmacological treatment of epilepsy in adults. Some of these issues are- when should anti-epileptic AEDs be started, choice of the first AED, combination therapy, treatment of generalized versus partial seizures. The following sections will deal with the management of epilepsy in adults, both pharmacological and surgical.

Pharmacotherapy: When should AEDs be Started?

AED therapy is typically instituted for several years and sometimes for life. The decision to start AEDs should therefore be taken after considering the risk-benefit equation. After a first unprovoked seizure, the average risk of having a second seizure is 46%. However, the risk of subsequent seizures after the first seizure is 70% even in a cohort in which most patients were on treatment after their second seizure. On the basis of this increased risk, there is a consensus that treatment is definitely indicated after at least two unprovoked seizures. Risk factors for seizure recurrence include epileptiform electroencephalogram [EEG] discharges, an abnormal neurological examination, or other evidence of a structural CNS abnormality. In the presence of these factors, the risk of recurrence after one seizure may be as high as the risk of recurrence after two seizures. Early treatment might be justified in patients with a high recurrence risk, in particular if the consequences of further seizures are expected to be severe. Patients with a first unprovoked seizure after a stroke or a seizure caused by other identifiable lesions have a high recurrence rate, and fragile elderly patients are also likely to be more vulnerable if seizures recur. The choice to start or not too also has to be offered to the patient as the patient may not be able to risk having another episode.

Choice of the First AED

A number of factors govern the first choice of AED (Table 1). These include- drug efficacy for seizure type or types, adverse effects considering the patient profile, interactions with other medications, cost of medication, age and gender of patient (women of childbearing age), psychiatric co-morbidities, and co-medication. The proportion of patients who remain on the allocated AED for a period of time, often referred to as effectiveness, provides a combined measure of efficacy and tolerability although this parameter takes into consideration only the adverse effects which lead to drug discontinuation.

Some epilepsy syndromes may be responsive to specific anti-epileptic drugs. For example, juvenile myoclonic epilepsy responds to sodium valproate, and infantile spasms in tuberous sclerosis respond to Vigabatrin. Narrow spectrum agents, such as carbamazepine, phenytoin, gabapentin, pregabalin, and oxcarbazepine, can worsen myoclonic jerks and absence seizures. If seizure classification is uncertain or the patient exhibits multiple seizure types, a broad spectrum agent such as sodium valproate, topiramate, levetiracetam, or zonisamide may be the best choice. Levetiracetam is a highly efficacious broad spectrum agent that can be used for a number of seizure types including partial seizures, myoclonic seizures of JME, and generalised tonic-clonic seizures of pharmacokinetics, renal metabolism with minimal drug interactions, and multiple dosing preparations. A word of caution being few reports of seizure aggravation on the drug needing withdrawal.

Table 2 lists the broad classification for drugs effective in generalized versus focal epilepsy.

A systematic review comparing the efficacy and effectiveness of AEDs concluded that there are major weaknesses in the quality of the available evidence. It is not surprising, therefore, that recommendations for first line AEDs to be used in the treatment of focal epilepsy in adults differ in different guidelines.

Co-morbidities can influence the choice of AEDs in patients by proving efficacious in conditions other than epilepsy. For instance, in patients of migraine, valproate or topiramate may serve as good choice of anti-epileptic agent due to its dual role in epilepsy and migraine prophylaxis. Similarly, in patients of epilepsy with co-existing neuropathic pain, gabapentin or pregabalin may serve as a good anti-epileptic agent. The adverse effects of an agent may compel one to exclude it as a treatment option in certain cases. For instance, sodium valproate, carbamazepine, pregabalin, gabapentin, and vigabatrin are all associated with weight gain and may be best avoided in obese patients or in those with diabetes mellitus. On the other hand, patients wishing to gain weight may benefit from these agents.

Table 2: Efficacy spectrum of antiepileptic drugs against different seizure types in adults

| Effective against focal seizures and most generalized seizures | Valproate, benzodiazepines, Phenobarbital, primidone, lamotrigine, levetiracetam, topiramate, zonisamide, rufinamide, felbamate. |
| Primarily effective against focal seizures, with or without secondary generalization | Carbamazepine, phenytoin, gabapentin, lacosamide, oxcarbazepine, eslicarbazepine, pregabalin, tiagabine, vigabatrin. |
| Effective against absence seizure | Ethosuximide |
Table 3: Initial and maintenance daily doses and important side effects of commonly used AEDs

<table>
<thead>
<tr>
<th>AED</th>
<th>Starting dose in average adult</th>
<th>Maintenance dose in average adults (mg/day)</th>
<th>Important side effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carbamazepine (CBZ) 10-20 mg/kg</td>
<td>100 mg BID</td>
<td>400-1000</td>
<td>Sedation, dizziness, ataxia, skin rash (occasionally Steven-Johnson syndrome), hyponatremia, weight gain, seizure worsening in some epilepsy syndromes</td>
</tr>
<tr>
<td>Clobazam (CLB)</td>
<td>10 mg OD (HS)</td>
<td>10-30</td>
<td>Sedation, ataxia, somnolence, irritability, depression, weight gain, tolerance (reduced anti-epileptic effect)</td>
</tr>
<tr>
<td>Lamotrigine (LTG) 5 mg/kg with other AEDs 2.5 mg/kg with VPA</td>
<td>25 mg OD (HS) Lower dose with VPA</td>
<td>100-300</td>
<td>Sedation, ataxia, dizziness, skin rash (occasionally Steven-Johnson syndrome)</td>
</tr>
<tr>
<td>Levetiracetam (LEV) 20-40 mg/kg</td>
<td>250 mg BID</td>
<td>1000-3000</td>
<td>Somnolence, dizziness, cognitive slowing, psychosis</td>
</tr>
<tr>
<td>Oxcarbazepine (OXC) 15-30 mg/kg</td>
<td>150 mg BID</td>
<td>600-1800</td>
<td>Sedation, dizziness, ataxia, headache, hyponatremia, skin rash</td>
</tr>
<tr>
<td>Phenobarbitone (PB) 5-8 mg/kg</td>
<td>60-90 mg OD (HS)</td>
<td>60-180</td>
<td>Sedation, ataxia, depression, memory problems, skin rash, hyperactivity in children</td>
</tr>
<tr>
<td>Phenytoin (PHT) 5 mg/kg</td>
<td>200-300 mg OD (HS)</td>
<td>200-400</td>
<td>Ataxia, sedation, gum hyperplasia, coarsening of facial features, hirsutism, memory problems, osteomalacia and bone loss, skin rash</td>
</tr>
<tr>
<td>Valproate (VPA)</td>
<td>200 mg BID</td>
<td>500-2000</td>
<td>Anorexia, weight gain, nausea, vomiting, tremors, hair loss, polycystic ovarian syndrome, thrombocytopenia</td>
</tr>
<tr>
<td>Topiramate (TPM) 2-5mg/kg</td>
<td>25 mg OD</td>
<td>100-400</td>
<td>Sedation, somnolence, cognitive problems, weight loss, word finding difficulty, renal stones, seizure worsening</td>
</tr>
<tr>
<td>Zonisamide (ZNS) 4-5 mg/kg</td>
<td>50 mg OD (HS)</td>
<td>200-500</td>
<td>Sedation, anorexia, renal stones, forgetfulness, skin rash, weight loss, distal paraesthesiae</td>
</tr>
</tbody>
</table>

OD: Once daily; BID: Twice daily; HS: At night

Topiramate and Zonisamide increase cachexia and should be avoided in underweight patients. There is a relationship between Valproate intake and polycystic ovarian syndrome and it is essential to take a menstrual history and consider BMI and hirsutism when introducing this drug in a young woman. Valproate can also cause parkinsonism and tremor and is best avoided in patients with the above movement disorders. Topiramate and zonisamide have been associated with nephrolithiasis, especially in hot environments, so it may be fruitful to advise patients regarding adequate hydration before prescribing these agents. The use of agents like topiramate, zonisamide and levetiracetam has been associated with psychiatric disturbances and so, are best avoided in patients with current or previous psychiatric co-morbidity. Antiepileptic drugs should be chosen with caution in patients with hematological disorders as commonly used first line agents such as phenytoin, carbamazepine, and phenobarbitone and second line agents like oxcarbamazapine, eslicarbazapine, lamotrigine, and ethosuximide can cause bone marrow depression. In patients with prolonged QT syndrome or in those taking medication which can prolong the QT interval, lacosamide, rufinamide, and retigabine should be avoided.

In recent years, evidence has accumulated that people with newly diagnosed epilepsy respond to relatively low doses of AEDs – 400 mg per day for carbamazepine, 1000 mg per day for levetiracetam, 125-200mg per day for lamotrigine, and 600-1000 mg per day for Valproate. Should seizures occur at the selected initial maintenance dose, the dose should be appropriately increased to maximum tolerable doses (Table 3).

**What to do when Monotherapy Fails?**

Following the institution of the first AED for newly diagnosed epilepsy, about 60% of the patients are well controlled with the first AED prescribed. What happens to the remainder? When should AEDs be substituted or added in these patients? If initial monotherapy fails, the subsequent course of action should take into account the reason for failure. For instance, in case of failure due to an idiosyncratic reaction, the AED should be substituted with care, avoiding a drug which may have cross-reactivity with the first one. If the first AED is considered to have failed because of lack of efficacy, non-compliance must be excluded. If a change in AED is indicated, gradual substitution of the second drug must be done with slow withdrawal of the first. A second school of thought propounds that combination therapy can be tried earlier in severe epilepsies where the first AED seems to have been partially effective and well tolerated. An effort should be made to avoid using drugs with similar mechanisms of action. Often an agent with multiple mechanisms of action and a broad spectrum with minimum interactions will be chosen as first add-on.
Management of Drug Resistant Epilepsy

Patients who fail to attain seizure freedom after an adequate trial of at least two antiepileptics should be managed as drug refractory epilepsy (DRE). The rationale for this definition is that the probability of seizure freedom decreases in proportion to the number of drugs tried in the past and is less than 20% after the patient has failed two AEDs. Such patients should be referred to a specialist for reassessment to evaluate the cause of refractoriness and be evaluated for epilepsy surgery. However, disabling seizures should be identified much earlier for surgical candidacy. Likewise, in the presence of an identifiable substrate (like hippocampal sclerosis, cortical dysplasia etc) PWE should be evaluated early for the possibility of a surgical cure.

Mesial temporal sclerosis is the commonest indication for resective epilepsy surgery. The available procedures for extra temporal epilepsy account for less than half of all epilepsy surgery and can be either resective or palliative. Surgical procedures include hemispherectomy, corpus callosotomy and multiple sub-pial and lobar resections.

Surgery has now become the standard of care for adults with mesial temporal lobe epilepsy (MTLE) syndrome, with anterior temporal resection being the commonest procedure. Results of meta-analyses surveying the literature from 1985 to 2003 indicate that about two-thirds of patients are seizure-free in the first two to three years after surgery for MTLE.

Neurostimulation

There exist multiple types of direct or indirect neurostimulation methods for therapeutically altering brain activity. Such techniques include stimulating the brain indirectly, as with transcranial magnetic stimulation, stimulating the brain directly, as with deep brain stimulation, or affecting the brain indirectly via stimulation of peripheral nerves. Electrical neuromodulatory approaches to extratemporal epilepsy are indicated where epilepsy persists despite resection of epileptogenic foci or in the palliative circumstance where no seizure focus is demonstrated using scalp recording, non-invasive neuroimaging and invasive recording, described elsewhere. Neuromodulatory procedures useful in epilepsy include deep brain stimulation (DBS) and VNS (Vagal nerve stimulation). These however may not be more useful than an added new AED and come at a tremendous side effect of cost.

Vagal Nerve Stimulation

Stimulation of both the trigeminal and vagus nerves has been shown in multiple clinical trials to be anticonvulsant, and stimulation of these nerves at therapeutic levels does not cause pain or negatively affect brain function. Left sided VNS was approved by the USFDA in 1997 as an adjunctive treatment for medically refractory epilepsy in adults. It is useful in patients who have failed resection or in patients who are poor candidates for resection. The neurobiological mechanisms of VNS in epilepsy are incompletely understood, although it is hypothesized that VNS may desynchronize activity and decrease abnormal spiking patterns on the EEG. A meta-analysis of studies pertaining to VNS in epilepsy identified three blinded randomized controlled trials, two non-blinded randomized controlled trials and 10 studies reporting prospective data. Seizure reduction rates were 17%–55% after 3–64 months of VNS therapy, with 21% to 50% of patients experiencing ≥ 50% decrease in seizure frequency. Across all studies, VNS reduced seizure frequency by approximately 45%, although the rate of seizure reduction increased from 36% at the 3- to 12-month follow-up to 51% after > 1 year of therapy. Patients of post-traumatic epilepsy and tuberous sclerosis experienced the greatest seizure reduction following VNS. Hoarseness of voice was the most common side effect reported by 37%–62% of patients. Cough, paresthesia, pain, dyspnea, and headache were other side effects. Device site infection occurred in 4-6% cases, requiring device explantation. Asystole was reported in 5 cases (<0.1%), although it is unclear if stimulation directly lead to this occurrence. Although not yet approved for use in the pediatric population, VNS has shown efficacy similar to that in the adult population in pediatric series as well.

Deep Brain Stimulation

Deep brain stimulation is a neurosurgical procedure that enables brain structures to be stimulated electrically by a pacemaker implanted under the skin. Several targets, including the cerebellum, anterior thalamic nucleus, subthalamic nucleus, hypothalamus, caudate and hippocampus have been studied as targets for deep brain stimulation in patients of epilepsy. Despite initial reports of the efficacy of cerebellar stimulation in epilepsy, a double blind randomized trial consisting of 12 patients failed to show any improvement in seizure control. The Stimulation of the Anterior Nucleus of the Thalamus in Epilepsy (SANTE) trial, a double-blind trial of anterior nucleus DBS for refractory seizures, has suggested that targeting the anterior nucleus of the thalamus is effective for refractory epilepsy. No surgery related complications were reported, although two patients had stimulation induced seizures. A randomized, double-blind multicenter sham stimulation trial of the responsive neurostimulator system has been done in the United States. The responsive neurostimulator system is an implanted device designed to detect abnormal activity in the brain and respond, similar to an implantable cardiac defibrillator.

Ketogenic Diet

Ancient teaching advocates the benefits of fasting and prayer in epilepsy. The ketogenic diet is a high fat, low carbohydrate diet, induces a state similar to fasting. The classical ketogenic diet uses a 4:1 ratio in calories of fat to carbohydrate. The Atkins diet is a popular weight-reducing diet which has a 2:1 ratio in calories of fat to carbohydrate and is considerably less restricted. Although evidence about long term efficacy of the ketogenic diet is lacking and one study reports high attrition rates in the long term, at three months, the efficacy of the ketogenic diet is similar to that of antiepileptic drugs. For those with medically intractable epilepsy or those in whom surgery is unsuitable, a ketogenic diet could improve seizure control, but tolerability is poor.

To summarize, the majority of adult patients (two thirds) with epilepsy can be treated adequately with pharmacotherapy alone, using either a single drug or a rational drug combination. In a small section of patients who are not adequately controlled on medication, surgical options are available. Surgery has now become the standard of care in epilepsy attributable to conditions like hippocampal sclerosis, focal cortical dysplasia and gliotic pathologies.

Most of the treatment options are available in centers in India. A timely diagnosis, counseling a PWE to various medical and social aspects of epilepsy, apart from AED therapy are the
cornerstone of good epilepsy management in India. The senior author (MT) strongly recommends physicians are a pillar of support for the management of epilepsy in this country considering the burden and treatment gap a PWE faces. Reading the freely available online version of guidelines of epilepsy management in India will help achieve the goal of reducing the knowledge and practice gap this disease could face too.

References