

Management of Epilepsy: Overview

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Introduction

Epilepsy is a common world-wide health problem. Its life time prevalence in Thailand is 1.3 percent that means nearly one million Thai people suffer from epilepsy.¹ Epilepsy occurs in all age groups with a higher incidence in neonate and the elderly. Epilepsy is actually not a disease. It is a group of syndromes or brain disorders with seizure manifestation. Its nature is complex. Many issues are to be individually considered after making the correct diagnosis, for examples, indications for treatment, treatment variables, initiating and discontinuing treatment, choice of antiepileptic drugs, treatment in special epileptic patient groups. Basic science and clinical research in various fields of epilepsy have been carried out. These research findings have progressively improved fundamental knowledge and clinical application in managing epilepsy.

Levels of diagnosis

Epilepsy is just a manifestation of brain disorders or syndromes. It is now classified according to the International League against Epilepsy (ILAE) classification with consideration on epilepsy etiology, seizure type and established epilepsy syndrome. This universal classification is intended to make meaningful diagnosis for better management of epilepsy. Therefore, levels of diagnosis in patients with epilepsy can conveniently be divided into three fundamental categories: (a) the diagnosis of epilepsy etiology, (b) the diagnosis of seizure type, and (c) the diagnosis of epilepsy syndrome. To control seizure is just symptomatic treatment. Every patient deserves a rational search for the epilepsy etiology. Even though a substantial proportion of this effort will be unsuccessful, some epilepsy etiologies are devastating if neglected such as brain tumour, arteriovenous malformation, etc. This etiologic diagnosis should be done in order to get an appropriate specific therapy for epilepsy etiology. Definitely, the correct seizure type diagnosis indicates the correct choice of therapy and choice of antiepileptic drug. The epilepsy syndrome diagnosis also helps to predict the prognosis and duration of therapy.

Goals of therapy

As epilepsy is a chronic brain disorder with unpredictable attacks, it greatly affects patients, family and society. Treatment options and goals for management of epilepsy should be discussed with the patient and family early after correct diagnosis has been done. In the beginning, all are

striving for cure or seizure-free without or with few adverse effects. After some treatment period, an amount of patients may not become seizure-free. Initial goals should be modified and other treatment variables may be considered. However, new antiepileptic drugs with fewer side effects and higher efficacy are being tested. In addition, other treatment modalities, for examples, deep brain stimulation, and new surgery techniques, may be developed. The goals of therapy, therefore, may be re-adjusted again. The primary goal of treatment is to improve patients' quality of life. Treatment of epilepsy should always be tailored to the individual patient, taking into account medical, financial, family, social and psychological needs. The patient should be kept independent and be fully involved in all aspects of management as much as possible.

Indications for treatment

Epilepsy is a manifestation of many brain disorders and epilepsy syndromes. They have a widely varying natural course. Some epilepsy may be easy to control while others may be difficult to control or even intractable to pharmacological treatment. For frequent recurrent seizures, there is no problem in deciding to start treatment. However, some epilepsy may be self-limited. Some epileptic patients may have only one or two seizures in their life. Some patients may have only nocturnal seizures and some patients may never lose consciousness during seizure attacks. Some patients are under supervision all the time. Additionally, individual perception and consequences of treating or not treating also vary. Some treatment options and some antiepileptic drugs can cause serious or even fatal side effects. Whether to treat these epileptic patients with a benign natural course is still a controversial issue. Given these considerations, indications for treatment vary. No single formula can be justifiably applied to all cases. In fact, decision making needs to be done individually based on different issues including the consequence of individual decision making. The best suggestion is to offer prognosis, variable treatment options including efficacy and side effects, risks and benefits, and consequences of any decision to the patient and family and to have them fully involved in all interactive decision-making.

Indications for treatment are based on assessing how seizures interfere with a patient's ability to function, quality of life, and health and well-being. Nature and severity of consequences of seizures vary widely on seizure type,

TABLE 1. Choice of antiepileptic drug according to seizure type²

Seizure type	Choice of antiepileptic drug	
	First choice	Second choice or add-on
Absence	Valproic acid	Topiramate, lamotrigine, levetiracetam
Myoclonic	Valproic acid	Phenobarbital, topiramate, lamotrigine, levetiracetam
Generalized atonic, Generalized tonic, Generalized tonic-clonic, Partial	Phenytoin, carbamazepine, phenobarbital, valproic acid	Topiramate, lamotrigine, levetiracetam, oxcarbazepine
Infantile spasm	ACTH, prednisolone, vigabatrin, valproic acid	Nitrazepam, clonazepam, clobazam

epilepsy syndrome, timing and frequency of attack, age and condition of patients, response of patient, family and society to seizures, type of employment, driving license, consequence of treatment, etcetera.

Choice of antiepileptic drugs

Since phenobarbital, the first antiepileptic drug was discovered a hundred years ago, many antiepileptic drugs have been continuously becoming available. A lot of antiepileptic drugs are now being developed and tested. They can be divided into old or first-line antiepileptic drugs, i.e. phenobarbital, phenytoin, carbamazepine, sodium valproate and acetazolamide, and new or second-line antiepileptic drugs such as lamotrigine, topiramate, gabapentin, vigabatrin, oxcarbazepine, levetiracetam, pregabalin, tiagabine, zonisamide, etcetera. Actually, the new antiepileptic drugs are not more effective than the old ones and cost much more. However, they carry less side effects. They, therefore, are regarded as second line drugs.

In order to choose an appropriate antiepileptic drug, one must consider drug efficacy, side effect and cost as well as guidelines. International and national epilepsy guidelines including the Thai epilepsy guideline are now available. Because health economics and health policies vary among individual countries, guidelines are just a guide or suggestion for management. Guidelines are not mandatory treatment options. They must be tailored to each individual situation and be intermittently updated according to new evidence.

All available antiepileptic drugs are effective in controlling seizures, however, they cannot prevent or cure epilepsy. Those epileptic patients who are seizure-free after taking antiepileptic drugs for years and can finally discontinue antiepileptic drugs are probably not cured by drugs. In fact, they are free from epilepsy because the

natural course of their epilepsy is self-limited.

Factors affecting antiepileptic drug choice are epilepsy syndrome and seizure type. Epilepsy syndromes are first subdivided into two etiologic categories, that is primary/idiopathic (genetic in etiology) or secondary/symptomatic (lesion). Each of these subdivisions is further subdivided into localization-related (partial) or generalized. For idiopathic and symptomatic localization-related epilepsy, most antiepileptic drugs are effective. Sodium valproate is drug of choice for idiopathic generalized epilepsy. Idiopathic generalized epilepsy is also responsive to lamotrigine, topiramate, levetiracetam, zonisamide, etc. Most symptomatic generalized epilepsy is intractable and requires a combination of antiepileptic drugs with different modes of action and without drug induced seizure. Some types of symptomatic generalized epilepsy are responsive to steroids such as West syndrome, Landau-Kleffner syndrome and epileptic status in slow-wave sleep.

Regarding to seizure type, antiepileptic drugs should be considered on whether it is partial or generalized seizure. For partial seizure, the drugs of choice are phenytoin and carbamazepine. However, most antiepileptic drugs are effective in controlling partial seizure. For generalized seizure, sodium valproate is the drug of choice. Other antiepileptic drugs are also effective. For examples, absence can be treated with ethosuximide, lamotrigine, topiramate, levetiracetam and zonisamide. Myoclonic seizure is well controlled by phenobarbital, lamotrigine, topiramate and levetiracetam. There are some reports that some antiepileptic drugs can induce absence such as phenytoin, carbamazepine, phenobarbital and some antiepileptic drugs can induce myoclonic seizure which are phenytoin, carbamazepine.

Individual seizure type and epilepsy type are reported to be responsive to many antiepileptic drugs. However, with unknown factors an individual epileptic patient with

TABLE 2. Side effects of antiepileptic drugs²

Antiepileptic drug	Dose-related	Idiosyncratic/metabolic
Carbamazepine	Dizziness, ataxia	Rash, Steven Johnsons' syndrome, hepatitis
Clobazam	Drowsiness	
Clonazepam	Drowsiness	
Gabapentin	Drowsiness, dizziness	Weight gain
Lamotrigine	Drowsiness, dizziness, ataxia	Rash, Steven Johnsons' syndrome
Levetiracetam	Drowsiness, dizziness, ataxia	Asthenia, headache
Oxcarbazepine	Dizziness, drowsiness, ataxia	Rash, Steven Johnsons' syndrome, hyponatremia
Phenobarbital	Drowsiness, dizziness, ataxia	Rash, Steven Johnsons' syndrome
Phenytoin	Dizziness, ataxia	Rash, Steven Johnsons' syndrome, hepatitis, hirsutism, gum hypertrophy
Pregabalin	Drowsiness	
Sodium valproate	Increased appetite, tremor, alopecia	Hepatitis, pancreatitis, weight gain
Topiramate	Decreased appetite, cognitive impairment, paresthesia, drowsiness, ataxia	Weight loss, renal stone, glaucoma
Zonisamide	Anorexia, drowsiness, impaired concentration	Rash, renal stone

TABLE 3. Antiepileptic drug profile²

Antiepileptic drug	Dosage		Therapeutic range (ug/ml)	Half life (hours)	Doses given per day	Time to reach steady state (day)
	Adult (mg/d)	Children (mg/kg/d)				
Carbamazepine	600-2,000	10-25	4-12	5-25	2-4	3-6
Clobazam	5-20					
Clonazepam	1-10	0.025-0.1	6.3-56.8	20-60	2-4	6-10
Gabapentin	900-3,600		4500	5-7	3-4	1-2
Lamotrigine	100-400			10-50	2	2-10
Levetiracetam	1,000-3,000			7	2	2
Oxcarbazepine	600-1,200			Active metabolite 10-25	2-3	2-5
Phenobarbital	60-240	4-8	15-40	50-160	1-2	> 20
Phenytoin	150-600	5-15	10-20	9-140	1-2	6-8
Sodium valproate	500-3,000	15-40	50-100	9-21	2-4	2-4
Topiramate	300-600			18-23	1-2	5
Vigabatrin	1,000-3,000	80-100		5-7	2-4	1-2
Zonizamide	200-600		7-30	5-70	1-2	2-15

the same seizure type or even with the same epilepsy type will respond better to different antiepileptic drugs. It is better to try and observe drug response.

Even though new antiepileptic drugs claim that they carry less side effects, they still have some intolerable or even serious adverse effects. Treating physicians have to inform patients and family about drug side effects.

Initiating antiepileptic drugs

After choosing an appropriate antiepileptic drug, the drug pharmacokinetic and pharmacodynamic are to be considered next in initiating that drug. An antiepileptic drug with a long half life such as phenytoin can start at once at an effective dose while an antiepileptic drug with a short half life such as carbamazepine must be slowly titrated up to an effective dose within days or weeks to eliminate side effects.

Antiepileptic drugs with a long half life can be given once or twice a day with better drug compliance. However, some short half-life antiepileptic drugs are now modified in their preparation such as sodium valproate chrono form, or carbamazepine controlled release form in order to be given once or twice a day.

Individual patients will respond to different dosage. Therefore, it is advised to start low and titrate up to the minimum effective dose and then monitor its efficacy.

Maintenance therapy

If there is another seizure attack after reaching the minimum effective dose, slowly stepping dosage up to the effective dose is needed. To allow appropriate evaluation time for drug efficacy according to the drug profile and to be certain that there is no precipitating factor or poor drug compliance these must be taken into consideration before adjusting dosage. Drug dosage should be gradually titrated up to the lowest effective dose. However, when a seizure-free is not achieved despite reaching the maximum tolerated dose, that is intolerable side effect appears, another antiepileptic drug should be switched to.

There is no guideline for antiepileptic drug substitution. For a fatal side effect such as drug rash (Steven Johnsons' syndrome threatening) the antiepileptic drug should be discontinued immediately and replaced with another drug. For none serious side effects, lowering the dosage to the previous dose without side effects and substituting with another drug is recommended before tapering off the

previous ineffective drug.

Combination therapy (rational polytherapy)

Based on research evidence, it is now accepted as a guideline that epileptic patients should be treated with monotherapy first. Most patients will be under control with monotherapy. For the minority of patients, two or three antiepileptic drugs may be tried before concluding that they do not response to monotherapy.

To choose an appropriate combination therapy, that is rational polytherapy, drug efficacy and profile is taken into account. Drugs with different modes of action will be first considered, for example a combination of phenytoin and sodium valproate. Side effects and cost are then to be concerned, for example drugs with a sedative side effect may not be able to be used together.

For polytherapy, it is recommended that two or not more than three antiepileptic drugs are combined because additional seizure-free achievement of the second and the third add-on antiepileptic drug is reported to be modest.³ Treatment with a combination of four or more drugs is unlikely to be successful and will have much more intolerable side effects. There is no guide for the optimal time and way to combine antiepileptic drugs, however, excessive drug load should be avoided.

Long-term monitoring strategies

Most antiepileptic drug side effects are individually dose-related and serious or fatal side effects are idiosyncratic. Therefore, regular monitoring side effects may not be able to predict or prevent idiosyncratic serious or fatal side effects. It is reasonable to determine bone marrow, renal and liver functions prior to initiating an antiepileptic drug. The information on these functions assists in selecting an appropriate drug with safe drug profile. To cost-effectively employ laboratory tests, drug side effects should be provided to the patients and family and suitable laboratory tests are requested if patients, family or physicians are concerned of side effects.

An antiepileptic drug's therapeutic range is just a guide for a clinician in treating epileptic patients. Individual patient response differently to different dosages of an antiepileptic drug despite similar epilepsy or seizure type. It is suggested to treat patients, do not treat drug level. Drug level should be applied with specific indication, for examples: to ensure drug compliance, to document drug

toxicity, to guide in dose adjustment, to guide in treating status epilepticus.

For patients who take a combination of antiepileptic drugs or polypharmacy, drug to drug interaction must be taken into account. In addition, epileptic patients with other medical illnesses tend to have more side effects. It may be worthy to perform laboratory tests randomly in these patients for earlier detection of serious side effects.

Discontinuing antiepileptic drugs

Approximately, 60-70% of newly diagnosed epileptic patients will be finally seizure-free and 60-70% of these patients will successfully discontinue use of an antiepileptic drug. Discontinuation of AED can be justified after achieving a seizure-free period of, at least, two years or more.⁴ Practically, 3-year seizure free is more widely applicable. However, approximately, 20-30% of these epileptic patients will have chronic active epilepsy⁴. There is no best way to predict whose epilepsy will be definitely in remission. Epileptic patients with the following conditions tend to have a recurrent seizure after antiepileptic drug withdrawal, such as Juvenile myoclonic epilepsy, some brain pathologies like cortical dysplasia, and difficult-to-control epilepsy for example Lennox-Gastaut syndrome. For epileptic patients who have ever had status epilepticus, they have a similar prognosis on seizure relapse after drug discontinuation. However, if they have recurrent seizure, they have more chance to have status epilepticus.

To discontinue antiepileptic drug or not should be a decision making by patients and family with given information on risk and benefit of either treatment option.

To abruptly withdraw an antiepileptic drug is not advised as it can induce drug withdrawal seizure. Most antiepileptic drugs can be withdrawn within several weeks to a few months. Phenobarbital and benzodiazepine are reported to have tendency of drug withdrawal seizure, so these two drugs should be withdrawn over a long period.

Vagus-nerve stimulation

Vagus-nerve stimulation (VNS) is effective in controlling seizure. The mechanism of action is not fully understood. It is suggested that VNS activates neuronal networks in the thalamus and other limbic structures and that norepinephrine may mediate its antiseizure activity.⁵ VNS may cause some side effects, for examples: cough, voice alteration, dyspnea, pain, paresthesia, headache, etc. Most side effects will gradually subside after long-term use.

VNS is now an accepted treatment option for patients with pharmacoresistant epilepsy. There is strong evidence (level I) that VNS is an effective treatment for patients with partial-onset seizures.⁵ There is level II evidence that VNS is also effective in most seizure types indicating a broad range of activity. However, VNS is a high-cost treatment and is usually indicated as an add-on therapy for refractory epilepsy that is not a candidate for epilepsy surgery.

Epilepsy surgery

For symptomatic epilepsy with brain pathology which requires surgery such as brain tumour, neurosurgery must be consulted. In addition, some chronic active epileptic patients are candidates for epilepsy surgery. Epilepsy surgery can be divided into two categories.

1. Curative epilepsy surgery: This surgery type is to cure or to absolutely control seizure. It can be performed if the epileptic focus can be identified

and totally removed without neurological deficit, for example mesial temporal sclerosis.

2. Palliative epilepsy surgery: Some refractory epilepsy can diminish their severity by surgery such as, corpus callosotomy, or multiple subpial transection.

Special therapeutic considerations

- Treatment of provoked seizures
- Treatment of single seizures
- Intractable epilepsy
- Antiepileptic drug treatment in pregnant women with epilepsy
- Antiepileptic drug treatment in the elderly patients

Treatment of provoked seizures

Provoked seizure is seizure that occurs in patients without epilepsy. It results from temporary brain dysfunction from a provoking factor. Usually, it will not recur after the provoking factor is alleviated. Generally, provoked seizure does not required an antiepileptic drug. However, if seizures recurs during treating the provoking factor, short-term antiepileptic drug may be justified.

Treatment of single seizures

From epidemiologic data, not all single seizure will recur. Current available antiepileptic drugs can just control seizure, not cure or prevent epilepsy. In addition, there is no really safe antiepileptic drug. Treatment of single seizure is, thus, no longer automatic. Many factors have to be taken into account including tendency of seizure recurrence, consequence of seizure recurrence, the effects of treatment, patient and family's perception and desire. Even in patients with multiple risk factors for seizure recurrence, a single unprovoked seizure remains an isolated event. Generally, it is recommended that treatment be delayed unless the patient has an abnormal electroencephalography or an associated medical or neurological condition that increases the risk of further seizures weighed on the consequence of seizure recurrence and a drug's side effects.

Intractable epilepsy

The minority of epileptic patients will be difficult to treat. These patients should be referred to epileptologists or neurologists. Their diagnosis and treatment will be reviewed. Some of them are finally able to control after adjusting antiepileptic drugs or undergoing epilepsy surgery. However, some epilepsy is really refractory to pharmacotherapy and surgery or some patients are unable to endure surgery.

For definite intractable epilepsy, the emphasis of treatment is then modified. Pharmacotherapy should be simplified and with less toxicity. Antiepileptic drugs with a sedative effect should be withdrawn or substituted. Intensive psychosocial support will benefit patients with refractory epilepsy, as they usually have many psychological and social problems.

Antiepileptic drug treatment in pregnant women with epilepsy

For epileptic patients who desire to have a baby, if they achieve seizure-free and are able to discontinue taking a drug, they are advised to wait until drug withdrawal is successful. However, some women with epilepsy may need to stay on an antiepileptic drug. The main concerns are maternal and fetal risks from uncontrolled seizures

and teratogenic side effects. The majority remain in control whereas worsening occurs in a fraction of childbearing women with epilepsy. Many factors associated with pregnancy may have a negative impact on epilepsy. A careful analysis in those who deteriorate should be carried out. Emotional and behavioral influence, including insufficient sleep and treatment non-compliance, as well as physical factors, such as emesis and pelvic distortion, should be reviewed. Most antiepileptic drugs' serum concentration decreases during pregnancy particularly drugs metabolized by glucuronidation. However, inter-individual variability is pronounced. In highly protein-bound drugs, such as phenytoin, unbound drug is less affected than total concentrations. Close follow-up tailored to individual needs and supported by therapeutic drug monitoring should be performed. In order to diminish teratogenicity, there are some suggestions to try before becoming pregnant:

1. Try switching to another antiepileptic drug with less teratogenicity such as carbamazepine, lamotrigine
2. Try monotherapy
3. Try to decrease drug as low as possible to control epilepsy
4. As sodium valproate carries a high risk of neural tube defect, try dosage not more than 1,000 mg per day with or without another safer add-on antiepileptic drug.

It is recommended that an antiepileptic drug should not be discontinued or substituted if the patient has already been pregnant, otherwise, drug withdrawal seizure may attack and may injure the fetus or the patient.

To screen neural tube defect and other fetal anomalies, ultrasonography should be performed at a gestational age of 16-20 weeks. In some institutes, amniotic alpha-fetoprotein level can be tested to support the diagnosis of neural tube defect.

Antiepileptic drug treatment in the elderly patients

From epidemiologic study, the elderly is one of the two age groups with a higher incidence of epilepsy. Despite the higher incidence of epilepsy, the elderly patients were not recruited into most research. Drugs efficacy, side effects, and pharmacokinetics may not be similar to those in younger age groups. The elderly tend to have deterioration of liver and renal function, therefore, antiepileptic drug metabolism and excretion will be slower than those in

other age groups. A number of elderly patients may have poor nutritional status with a low serum protein level that affects the proportion of active unbound drug form. Some elderly patients have other concurrent medical illnesses and take many kinds of medication. Adverse effects and drug to drug interaction are, therefore, to be more concerned. Drugs with mild sedative effect can affect balance and cause a fall in the elderly. In addition, drug caused cognitive impairment may considerably affect their daily activity function. Overall, there is no ideal antiepileptic drug for the elderly patients. Selecting an antiepileptic drug according to type of epilepsy or seizure with tolerable side effects and less drug to drug interaction and close monitoring of drug efficacy and side effects would be the best suggestion.

Epilepsy and legal issues

Epileptic seizures may attack at anytime, mostly without warning, accidents are, sometimes, unavoidable. Traffic accidents are more widely concerned particularly large-sized vehicles or mass transportation. Therefore, in some countries, there is a law on epilepsy and driving that treating physicians and epileptic patients must follow. This legal issue is in process in Thailand.

CONCLUSION

Treating epilepsy involves many issues and is both art and science. The growing research findings in the field of epilepsy will make a better quality of life for patients with epilepsy. Physicians should keep updating the knowledge in this field.

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