# Managing Epilepsy I: Medical Management

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Treatment of epilepsy has improved with advances in neurodiagnostic procedures, addition of newer antiepilepic drugs (AEDs), and proper selection of cases for early surgical treatment. Control of seizures with vagus nerve stimulator, approved by FDA, has provided a new tool for the treatment of difficult to control cases and there is a prospect for development of more effective devices in future. Monotherapy with appropriate AEDs for seizure types and epileptic syndrome, is the initial treatment of choice. The concept of " Rational Polytherapy" is a reality now and is advocated in those failing with monotherapy and substitution therapy. Refractory cases to medical therapy should be referred to neurosurgical centers for the better control of seizure.

**Key Words:** antiepileptic drugs, epilepsy, monotherapy, rational polypharmacy

Epilepsy is the commonest disorder encountered in neurological practice affecting individuals of all age groups irrespective of their gender and socioeconomic status. It adversely affects the education, employment, marriage and social functioning of the affected individual thus affecting the overall quality of life. Moreover, it encompasses a broad range of epileptic syndromes with variable presentation,[8] often making the diagnosis problematic. During the last decade many gaps in our knowledge have been filled.[44] Since 1993 many new AEDs have been approved and some older AEDs (i.e. carbamazepine, ethosuximide, phenobarbital, phenytoin, primidone, and valproate) continue to be widely used. However, availability of newer drugs has not made the matter easy as (a) these drugs are expensive and are beyond the reach of the majority of patients with epilepsy in developing countries,[62] (b) despite the promise, not all patients who have not responded to standard AEDs become seizure free with treatment with newer AEDs,[67] (c) in developing countries treatment by the primary and secondary physician without special training and expertise has resulted in indiscriminate use of AEDs in incorrect combinations,[49] and (d) availability of an ideal AED (i.e. a cheap drug available in both oral and parenteral formulation, having broad spectrum activity, wide therapeutic range, long half life and lacking drug interactions and significant organ toxicity and ability to reverse the epileptic process ) is still a distant dream.[58] In this review the important problems associated with treatment of epilepsy are addressed and literature is reviewed.

## Medical Treatment of Epilepsy

The goal of therapy is to enable the patient to live a life style consistent with his or her capabilities by (a) obtaining a seizure free state with rapid and sustained control of seizures, (b) maintenance of seizure control with easily manageable drug regime without toxicity, and (c) modification and reversal of the epileptic process by targeting the fundamental cause of epilepsy and preventing the manifestation of epilepsy (i.e. epilepsy cure). Three levels of diagnosis should be considered in all patients with epilepsy i.e. etiological diagnosis, diagnosis of seizure type and epilepsy syndromes. To achieve the above goals the physician is required to have (a) an accurate knowledge of seizure types and epileptic syndromes, (b) he or she should be conversant with the pharmacology of AEDs and have working experience with their therapeutic application, (c) he or she should be able to differentiate between the seizure disorders with single specific etiology and epileptic encephalopathy where the epileptic process itself leads to cerebral dysfunction,[13] and (d) he or she should be able to educate the patients and involve them in all decision processes for the success of therapy.

### Patient With First Seizure: To Treat or not to Treat?

The question to start AEDs for patients who have had only one seizure is controversial. Unanswered questions are whether approach should be the same for both generalized and partial seizures? What are the chances of a single seizure recurring? And do patients ever present with a single absence attack or a single myoclonic seizure?

Berg and Shinnar,[4] in a meta-analysis of 17 studies on seizure recurrence after first unprovoked seizures, reported 3 studies in children where seizure recurrence at 2 years was 58% when electroencephalogram (EEG) showed specific epileptiform abnormalities while 37% of patients with non-epileptiform abnormalities in EEG and 27% with a normal EEG record respectively had recurrence of seizures. Although magnetic resonance imaging (MRI) was not considered in any of the studies, the pooled risk of recurrence at 2 years was 57% in patients with a known cause (remote symptomatic) and 32% for patients with idiopathic first seizures. A similar high relapse rate was noted by others,[66,55] when EEG was abnormal. Data on partial seizure is lacking. Most epileptologists presume that (a) a generalized tonic clonic seizure is always recognized while first partial seizure event when detected may not be the first episode as they may quite easily go unnoticed, especially if they occur infrequently, (b) a significant number of patients with solitary generalized seizures have no recurrence and have only toxicity to gain from medication, (c) the decision to treat or not to treat a single generalized tonic clonic seizure should be taken after considering other factors i.e. presence or absence of obvious focal brain pathology, presence or absence of prominent epileptiform EEG abnormalities and social factors, and (d) while all partial seizures should be treated as such, seizures are more likely to continue unless treated.

**Treatment of Newly Diagnosed Cases of Epilepsy**

As treatment with a single AED (i.e. monotherapy) has fewer side effects including teratogenecity, absence of drug interactions, improved compliance, lower cost of therapy,[47] most epileptologists believe that monotherapy is the appropriate choice for newly diagnosed epilepsy. Nearly 75% of newly diagnosed epilepsy cases achieve one year seizure freedom with an appropriate single AED.[37, 51] Because of adverse effects on cognitive functions due to their sedative-hypnotic effects, the barbiturates and benzodiazepines are not the first choice for monotherapy except when patients have myoclonic epilepsy and when patients are intolerant to usual baseline drugs. Hence only 4 primary drugs i.e. phenytoin, carbamazepine, sodium valproate, and ethosuximide are available for initial monotherapy. The choice of AEDs is based on seizure type **(Table 1)**. In genral, once selected, the AED should be started with a gradual increase of the dose. The changes in drug doses should be done according to their half-life, as time to steady-state level is dependant on the half-life of the drug rather than the increase in daily dose. Roughly, it takes 5 times the half-life to reach 97% of a new steady-state plasma drug level **(Table 2)**. Use of initial loading dose of AEDs with long half-life reduces the long time needed for reaching the steady–state level stage.[47] Only drugs available for intravenous use (i.e.phenytoin, phenobarbital, sodium valproate) can be given as loading dose for rapid control of seizure. Phenytoin is the drug of first choice for this indication as intravenous (IV) loading dose of phenobarbital is sedating and experience with the use of IV sodium valproate is lacking. Fosphenytoin sodium is an alternative to phenytoin and has the advantage that it can be given intramuscularly. The exception is the use of benzodiazepine derivatives (diazepam & lorazepam) for treatment of status epilepticus. At higher plasma levels, changes should be made slowly and in small increments to avoid or minimize the dose related toxicity.[47] Drugs with short half-life are given frequently while drugs with long half-life can be given once a day or twice a day. A number of extended release formulations (ERF) of AEDs have been developed and have the advantage that ERF (a) provide steady serum levels with lesser peak fluctuations thereby minimizing peak dose related side effects and break through seizures and (b) improve compliance resulting in better seizure control.[9] Many long acting formulations of carbamazepine and sodium valproate are available. The equivalent dose of ERF is 20-30% more than the conventional form.[12]

| Seizure type | First line drugs | Second line drugs |
|---|---|---|
| Partial(SPS:CPS) &generalized | DPH, CBZ, VPA | PRM, CZP, CLB, TPM, LTG |
| Absence | VPA, ESM | LTG, CLB, CZP |
| Atypical absence | VPA | CBZ, DPH, PB, CZP, LTG |
| Myoclonic | VPA | CZP, CLB, LTG, PB, PRM, Levetiracetam |

*AEDs, antiepileptic drugs; CBZ, carbamazepine; CLB, clobazam; CPS, complex partial seizure CZP, clonazepam; DPH, phenytoin; ESM, ethosuximide; LTG, lamotrigine, PB, phenobarbital; PRM, primidone; SPS, simple partial seizure; VPA, valproic acid

*Table 1. Efficacy of AEDs according to seizure type**

**When Monotherapy Fails: Substitution or Add on Therapy?**

It is estimated that approximately 30% or more of patients remain refractory to first monotherapy.[7] As 20% of referrals for refractory epilepsy are wrongly diagnosed,[56] and noncompliance is responsible for failure in over one third of patients,[33] management of such cases requires review of the diagnosis and exclusion of noncompliance. The next step is either to change to a second monotherapy or to add a second drug.[31] There are no randomized control trials in patients who have failed on monotherapy. Hakkareinen [22] and Mattson ,et al.,[37] reported better seizure control in one third and in 46% cases respectively with substitution of failed monotherapy with a second drug. Kwan and Brodie[31] in a prospective study of 248 cases, found similar outcome in patients receiving either substitution or add on therapy following failed first monotherapy. The selected second drug should be gradually added and after its optimum dose is reached, the first drug is withdrawn gradually in order to minimize the cost and the adverse effects.

| Drug | Dose in milligram/Kg | Adult dose in gram/day | Half life (hours)* | Time to reach steady state | Effective level µg/ml** | Toxic level µg/ml |
|---|---|---|---|---|---|---|
| Carbamazepine*** | 10-20 | 0.8-1.2 | 12 | 3 days | 4-10 (7) | >8 |
| Valproate*** | 20-60 | 1-2 | 12 | 3 days | 5-100 (80) | >100 |
| Primidone | - | 0.75-1.5 | 12 | 3 days | 5-15 (10) | >1.2 |
| Phenytoin | 4-8 | 0.3-0.6 | 24 | 5days | 10-20 (18) | >20 |
| Ethosuximide | 20 | 1-1.5 | 48 | 10 days | 50-100 (80) | >100 |
| Phenobarbital | 3-5 | 0.09-0.1 | 96 | 3 weeks | 10-40 (>35) | >40 |

*Half life is shorter if co-administered with enzyme inducing drugs.
**Levels which should be achieved in refractory epilepsy. A higher level can be achieved without toxicity when drug is given as monotherapy.
*** Carbamazepine doses are lower in elderly; phenytoin dose is higher in children; Valproate dose is higher with polypharmacy.
**** Primidone dose in children: < 2years 200-500mg/day: 2-5 years 500-750 mg/day: 6-9 years 0.75- 1g/day

*Table 2. AEDs: dose, plasma half life & effective drug level (Porter et al 1989)*[47]

Though monotherapy has definite advantages and is a preferred mode of therapy when treating newly diagnosed cases, polytherapy may occasionally be superior to monotherapy. Veteran's Administrative study [37] showed that 40% of the cases not controlled on monotherapy improved with polytherapy and 11% became seizure free. Mattson[36] reported that the addition of a second drug improves the seizure control in 20 to 25% of the cases with 5 to 10% of patients becoming seizure free. A further addition of a third AED further improves the seizure control in another 10% of cases. With the availability of newer AEDs **(Table 3)** with lower side effect profiles, the role of polytherapy is increasingly considered in treating the cases, uncontrolled with monotherapy (i.e. difficult to treat cases or refractory cases) leading to introduction of term "Rational Polytherapy" as a system for planning treatment.

## Rational Polytherapy

The term Rational Polytherapy implies " selection of drug combinations that would produce optimal seizure control with a minimum of adverse effects[15,16]" and "as a minimum combination of AEDs as would enhance the antiepileptic actions without increasing the adverse effects peculiar to each drug.[69]" Many drug combinations have been suggested, i.e. combinations using conventional AEDs, combinations of conventional and newer AEDs and combinations of only newer AEDs.[17]

The key principles of rational polytherapy, based on pharmacodynamics and pharmacokinetic knowledge of AEDs, are:

**(a) Selection of AEDs- drugs with different mechanism of action based on mechanism of seizure initiation and spread and arrest of seizure activity**. Sodium channels and calcium conductance is important in initiation and maintenance of seizure activity and potassium conductance is important in arrest of seizure activity.[17, 39] The mechanism of action of AEDs depends upon binding to inactivated channels, modification of GABA- mediated chloride conductance, elevation of GABA levels or action on T-calcium channels. While the combination of carbamazepine or lamotrigine or phenytoin with gabapentin, levetiracetam, tiagabine or topiramate is a most useful combination (different mechanism of action), the combinations of carbamazepine, lamotrigine or phenytoin and the combination of tiagabine and vigabatrin are least useful as they have similar mechanism of action.[34] Deckers, et al.,[10] reviewed 39 papers on the combination of two AEDs and reported that the combination of a GABA-minergic drug and a sodium channel blocker is better than two GABA minergic drugs which in turn are better than two sodium channel blockers.

**(b) Combination of AEDs having complex pharmacokinetic drug interaction, similar side effects and enzyme inducers to be avoided.[34]** Gabapentin and levetiracetam are notable for lack of drug interactions and form the most useful combination with any other AEDs. Another useful combination is of lamotrigine and valproate as they have a favorable interaction (i.e. valproate reduces the dose of lamotrigine by inhibiting metabolism of lamotrigine). Least useful combinations are (i) carbamazepine with phenytoin (i.e. phenytoin addition leads to induction of carbamazepine metabolism increasing its requirement while phenytoin withdrawal may induce carbamazepine toxicity by suddenly increasing its blood level), (ii) carbamazepine and lamotrigine (i.e. lamotrigine elevates the level of carbamazepine epoxide increasing risk of side effects), (iii) phenobarbital with carbamazepine or phenytoin or valproate (i.e. induction of hepatic Cytochrome P-450 system by phenobarbital), (iv) valproate and phenytoin ( i.e. both competing for protein binding sites effecting the value of total drug measurement) and (iv) felbamate with phenytoin, or carbamazepine or valproate because of many drug interactions.

**(C) Drugs with severe side effects are to be avoided:** Though effective as an add-on drug the use of the following

| Drug | Initial dose | Dose increment | Maintenance | How given |
|---|---|---|---|---|
| **Gabapentin*** | | | | |
| Adults | 300 mg/day | 300 mg/day | 0.9-2.4 gm/day | 3 divided doses |
| Children | 20 mg/kg/day | 10mg/kg/day | 40 mg/kg/day (3-5 years), 25-35 mg/kg/day (> 5 years) | ——do—— |
| **Lamotrigine*** | | | | |
| Adults | 25 mg/day | 10-25 mg/1-2 week | 100-200 mg/day | 2 divided doses |
| Children | 0.6 mg/kg/day | 1.2 mg/kg/day | 5-15mg/kg/day | ——do—— |
| **Felbamate** | | | | |
| Adults | 1.2 g/day | 600 mg weekly | 2.4-3.6g/day | 3 divided doses |
| Children | 15 mg/kg/day | 15 mg/kg/week | 45 mg/kg/day | ——do—— |
| **Oxacarbamazepine** | | | | |
| Adults | 600 mg/day | 300-600 mg/week | 600-1200 mg/day | 2 divided doses |
| Children | 8-10 mg/kg/day | 10 mg/kg/week | 40 mg/kg/day | ——do—— |
| **Topiramate*** | | | | |
| Adults | 25 mg/day | 25-50 mg/1-2 week | 200-400 mg/day | 2 divided doses |
| Children | 25 mg/day | 1-3 mg/kg/week | 5-9 mg/kg/day | ——do—— |
| **Vigabatrin** | | | | |
| Adults | 1.0 g/day | 0.5 g/week | 3 g/day | 2 divided doses |
| Children | 40 mg/kg/day | | 10-15 kg, 0.5-1g/day<br>15-30 kg, 1-1.5 g/day<br>>30 kg, 1.5-3 g/day | ——do—— |
| **Zonisamide** | | | | |
| Adults | 100 mg/day | 100 mg/week | 400-1000 mg/day | once a day |

*Available in Nepal

*Table 3. Newer antiepileptic drugs (adapted from Sweetman (2002)[59]*

drugs are restricted for use in selective severe epilepsy cases only, e.g. felbamate due to toxic effects of aplastic anemia and liver failure and vigabatrin due to side effects such as optic neuritis respectively.

**(d) Close monitoring of cases on polypharmacy should be done:** All patients on polypharmacy should be re-evaluated periodically both clinically and by monitoring drug levels. Although polypharmacy may be responsible for the seizure control, it is also possible that one of the AEDs alone may be effective. In a study from South India with a 'switch over' to monotherapy from polytherapy resulted in reduction of side effects from 29-20%, seizure control increase to 45% from 29% and with net saving of RS 750/- (approximately US$ 10.00) per month. [32] However, one should be aware of complex drug interactions as mentioned in sub paragraph. Drug level monitoring is essential when using polypharmacy.

## Treatment of epilepsy in Geriatrics

The elderly population, age more than 65 years, is the most rapidly growing segment of population. The incidence of epilepsy in them is approximately twice that in the younger population. They present special problems of altered pharmacokinetics, presence of co-morbid conditions requiring multiple medications (i.e. more chances of drug interaction) and misinterpretation of the interaction) and misinterpretation of the symptoms of drug toxicity as symptoms of co-morbid condition (i.e. Alzheimer's disease, stroke or metabolic encephalopathy). Hence proper selection of AEDs with optimal drug characteristics (i.e. no drug metabolism, a high therapeutic index and lack of drug interaction) is needed in elderly epileptics.[35] General rules are:

(a) Phenobarbitone and Primidone should not be used in elderly patients because of their sedative affects and adverse effect of cognition and mood to which this population is more sensitive. Of newer AEDs felbamate (hepatic toxicity and aplastic anemia) and vigabatrin (optic neuritis) should be avoided due to the side effects.

(b) Appropriate drugs for use in elderly epileptics are carbamazepine (with dose adjustment due to altered protein binding and altered hepatic metabolism), gabapentin (no drug interaction but dose is adjusted to renal functions), levetiracetam (no metabolism in liver, less protein bound i.e < 10%, lack of drug interaction, but dose to be adjusted to renal function), and lamotrigine (no dose adjustment required as hepatic glucuronide conjugation is only slightly diminished with age).

(c) Due to altered pharmacokinetics (i.e. altered protein binding & hepatic metabolism) the dose of phenytoin, carbamazepine, and valproate should be reduced. The frequency of administration should also be reduced when using drugs with short half-life, e.g. carbamazepine. Dose of AEDs having renal route of elimination ((e.g. gabapentin, levetiracetam) and both hepatic and renal elimination (e.g. topiramate, zonisamide) should be adjusted accordingly.

(d) The choice of AEDs is different in elderly epileptics with and without co-morbid medical problems. While carbamazepine, phenytoin, valproate, gabapentin, levetiracetam, lamotrigine, oxacarbamazepine, topiramate, tiagabine, and zonisamide are good AEDs for elderly epileptics without any other medical problems, gabapentin, levetiracetam, tiagabine and zonisamide only can be used for those with co-morbid conditions. AEDs are to be used carefully in this group (discussed later).

(e) Drug level monitoring, including estimation of free components, should be done especially when using polypharmacy and when co-morbid conditions are present.

## Treatment of women with epilepsy

Treatment of epilepsy in female patients needs special consideration as female hormones (i.e. estrogen and progesterone) by affecting neuronal excitability may alter seizure frequency. Cataminal epilepsy is a special problem in women. AEDs produce special problems in them (i.e. alteration in reproductive hormones producing anovulatory cycle, infertility and polycystic ovarian syndrome, aggravation of osteoporosis in elderly females by adversely affecting bone metabolism, potential teratogenicity, effect on the newborn as they cross into breast milk). In addition, pregnancy presents its own problem of unpredictable changes in seizure frequency, seizure recurrence related complications on pregnancy and altered drug pharmacokinetics.[43]

### Women with epilepsy during pregnancy

Special care should be taken in pregnancy in selection of AEDs to avoid harmful effect to fetus. Recommendations are:

(a) In pregnancy single AED (i.e. monotherapy) in the lowest effective dose and selection of AEDs which are most effective for seizure type and having least teratogenic effects should be used. There is no sufficient data to identify such AEDs. Teratogenicity is noted with higher dose of AEDs and when polypharmacy is used.[27] All older AEDs are teratogenic. There is little information on the teratogenicity of newer AEDS. These are labeled as risk "Category C" by Food and drug Administaration(FDA), USA.. When there is positive family history for neural tube defects carbamazepine and valproate should be avoided as incidence of these defects is 0.5-1% with carbamazepine and 1-2% with valproate respectively.

(b) Change in medication whether dose modification or substitution should be done prior to conception to avoid breakthrough seizures and to avoid exposing the fetus to additional AEDs.

(c) All women of childbearing age should receive folic acid supplementation as it has been reported to prevent occurrence of neural tube defects.[2, 64]

(d) All pregnant epileptics should receive vitamin $K_1$ (10 mg /day) over the last month of gestation to prevent hemorrhage secondary to AEDs related vitamin K deficiency and reduced vitamin K dependant factors.[63]

(e) As pharmacokinetics of AEDs is altered in pregnancy there should be compulsory drug monitoring to avoid using excessive doses. As protein binding and protein level decrease in pregnancy free fraction should also be determined.

(f) Prenatal screening for neural tube defects should be done with alpha fetoprotein screening and level II (anatomic) Ultrasonography at 14-18 weeks and may be supplemented by amniocentesis.

(g) Even though all AEDs cross into breast milk to variable extent, the best advice is to continue breast-feeding. Once it is started the infant should be observed for weight gain and sleep cycles. As metabolism and clearance of AEDS is increased as long as breast feeding is done, mothers may be advised to adjust the dose when breast feeding is stopped.

(h) As there are reports of long lasting neurodevelopmental or neurocognitive effects of AEDs in children exposed in utero, the children born to such mothers should be followed up carefully.

### Female patients on oral contraceptives

The problem of drug interaction should be anticipated and addressed in women on oral contraceptives. AEDs causing hepatic cytochrome P 450 enzyme induction (e.g., phenytoin, primidone, phenobarbital, carbamazepine, oxacarbamazepine, topiramate and felbamate) increases metabolism of oral contraceptives resulting in their failure.[38] To prevent this, women taking such AEDs should receive at least 50 microgram of estrogen component,[2,70] and should use barrier contraceptives if pregnancy is contraindicated. Valproate, gabapentin, lamotrigine, levetiracetam, tiagabine, and zonisamide have no effect on this enzyme system.

### Obese females with epilepsy

This is of special concern in females as AEDs have potentials to increase body weight, which is maximum with valproate and gabapentin followed by carbamazepine, tiagabine and vigabatrin. While phenytoin, lamotrigine and levetiracetam are devoid of this action, topiramate, zonisamide and felbamate often produce weight loss. Weight gain is maximum after 6 months of therapy presumably due to its effect on fatty acid metabolism.[19] Topiramate significantly produces weight loss (i.e. average 11%) and reduces food intake,[57] which is, most evident in obese epileptics. In addition, it produces beneficial changes in metabolic profiles in them (i.e. lowering of blood sugar, insulin and triglyceride levels). This metabolic effect is not seen in non-obese epileptics. Topiramate thus seems to be an ideal drug for use in obese epileptics.

### Epilepsy in females with irregular menstrual cycles

Women with epilepsy have higher incidence of reproductive and endocrine disorders, infertility, disturbance in sexual arousal, vaginismus and lack of vaginal lubrication),[40] menstrual cycle dysfunctions ( abnormal cycle length, frequent mid cycle bleeding, metrorrhagia [41] and anovulatory cycles). AEDs may

contribute to sexual dysfunctions directly or indirectly by altering hormonal effects on sexual behaviour.[41] A higher incidence of polycystic ovarian syndrome (PCOS) is reported in women with epilepsy,[25] especially those on valproate monotherapy and is attributed to initial weight gain, increased insulin resistance leading to hyperinulinemia, increased insulin like growth factor, decreased insulin like growth factor binding protein and sex hormone binding globulin - protein [29], and resulting in hyperadrogenism (i.e. increased synthesis of gonadal steroids and an increase in unbound testosterone). Hyperandrogenism may cause anovulation by direct effect on the ovary or by negative feed back on FSH secretion,[25] and is reversed by replacing valproate with lamotrigine[29] a view contested by others. Recommendations, though not evidence based, are that one should be aware of this problem and should monitor the female patients for possible symptoms and signs of POCS and when detected replace valproate with an alternative AEDs [4] especially enzyme inducing AEDs which by inducing hepatic enzymes lowers the androgens levels by increasing their metabolism. The problem of PCOS is well discussed by Polson (2003).[46]

### Women with cataminal epilepsy

Many women have seizures that cluster around menstrual cycles with reproducible patterns and differing between ovulatory and anovulatory cycles.[24] In ovulatory cycles seizures occur approximately 3 days before the onset of flow and persist for 6 days and at midcyles and are related to perimenstrual progesterone withdrawal and LH induced midcycle estrogen surge respectively. In anovulatory cycles they are more frequent and dispersed throughout the cycles, as estrogen level in them remains high throughout the cycle. With menopause there is improved control of cataminal seizures while during perimenopause the seizures may increase in frequency and their pattern may change due to fluctuations in gonadal steroids. Hormonal replacement therapy (HRT) in them adversely affects the seizure control.[23] The anticonvulsant properties of progesterone have been known since 1942, though the mechanism underlying this observation was a mystery. In the mid 1980s it was found that progesterone metabolites i.e. allopregnanolone (neurosteroids) have powerful anticonvulsant properties and modulate $GABA_A$ receptors. Its low level subsequent to reduced progesterone levels may be responsible for cataminal epilepsy. The treatment of cataminal seizures includes monotherapy with most effective AED with adjunctive therapy consisting of: (a) Intermittent therapy with carbonic anhydrase inhibitors acetazolamide (Diamox) 250-1000 mg/day given intermittently for 10-14 days surrounding the time of seizure vulnerability. It acts by the inhibition of carbonic anhydrase in glial cells and anticonvulsant properties may be related to production of mild metabolic acidosis. When oral dose is not possible similar dose can be give by IV route. (b) Progesterones such as medroxyprogesterone given in large doses to produce amenorrhea; natural progesterone given over early luteal phase in the dose of 100-200 mg three to four times a day (average dose 600 mg/day) to obtain a level of 5-25 ng/ml; prometrium 100 mg a day with progesterone topical cream. (c) Testerogens have been studied in the treatment (clomiphene, though effective, is associated with potential side effects of hot flushes, polycystic ovarian cysts, and unplanned pregnancy).[24] (d) Treatment with synthetic or natural neurosteroids and many antiesterogens are under study and may find a role in future.[42, 50]

### Women with epilepsy and bone metabolism

Cytochrome P450 hepatic enzyme inducing AEDs (i.e., phenytoin, Phenobarbital, Primidone, carbamazepine) are usually associated with bony changes and metabolic abnormalities and increased incidence of fractures by effecting vitamin D metabolism.[6,21] Many biochemical abnormalities are present in epileptics and are related to duration of AEDs exposure, number of AEDs used and the type of AEDs used and include a decrease in calcium and phosphorous levels, raised alkaline phosphatase, elevated parathyroid hormone and reduced levels of vitamin D and its metabolites along with markers of bone formation and bone resorption. Other suggested mechanisms are direct effect on bone cells including impairment of absorption of calcium, inhibition of response to PTH, hyperparathyroidism and deficiency of calcitonin. Hypocalcemia may adversely affect the seizure control and if not recognized, further increasing the dose of AEDs will further increase the seizure frequency setting a vicious cycle. Recently valproate has also been incriminated even though it has no enzyme inducing properties.[52] The mechanism by which it affects bone metabolism is not understood. Sato, et al., [52] found increased concentration of ionic calcium and suggested that negative feed back via calcium reduces secretion of PTH, which suppresses formation of active vitamin D metabolite 1,25 –(OH)2 D. Hence, addition of calcium is not required and in fact it may worsen osteoporosis. There is little information on newer AEDs. Recommendations are that all women with epilepsy should receive vitamin D and calcium supplementation (except when taking valproate) and do active exercise. The menopausal women with epilepsy should be regularly screened for bone mineral density.

## Special problems with AEDs

### Hyponatremia

Hyponatremia, seen with treatment with carbamazepine and oxacarbamazepine,[65] is mild (i.e. serum sodium levels between 125-135 mEq/L) and develops slowly. Though the mechanism is not understood, it is presumed that these AEDs produce this effect by increasing the sensitivity of osmo receptors to antidiuretic hormone (ADH) or by direct effect of the receptors of distal convoluted tubules or collecting duct leading to water retention. The risk factors include, elderly patients, menstruating women, high fluid intake and renal failure, in postoperative period and concomitant use of medications causing SIADH (e.g. diuretics, antipsychotic drugs and antidepressants).[68] It manifests with lethargy, dizziness, alteration in higher functions and seizures. Recommendations are that serum sodium level to be assessed after 3 months of treatment or

earlier when risk factors are present. When sodium levels are below 125 mEq/L the drug doses should be reduced, water intake is restricted and all drugs, which may cause SIADH, should be withdrawn. Rarely slow infusion of hypertonic saline may be needed. No action is needed if sodium levels are more than 130 mEq/L.

**Drug Rash**

AEDs induced drug rash is the most common idiosyncratic reaction seen within 4 weeks of AEDs therapy and manifests as maculopapular rash, erythema multiforme, Stevens Johnson syndrome or as life threatening Lyell's syndrome. These are unpredictable, are not dose dependent and signs of systemic involvement are absent. The drug induced hypersensitivity syndrome is less common and occurs after 2-8 weeks and are accompanied by fever and internal organ involvement (i.e. nephritis, hepatitis, eosinophilia and lymphadenopathy). Aromatic AEDs (i.e. phenytoin, phenobarbital, primidone, carbamazepine, oxacarbamazepine, lamotrigine and zonisamide) are frequently associated with drug rash. There is cross reactivity between phenytoin, phenobarbital and carbamazepine and between carbamazepine and oxacarbamazepine. Whether newer AEDs (lamotrigine and zonisamide) also have risk of cross reactivity is not known. Recommendations are to withdraw the drug immediately and to use AEDs with least risk of producing drug reactions i.e. valproate, topiramate, gabapentin, tiagabine or levetiracetam in patients with a history of drug rash.[3]

## Special problems: Co-morbid conditions in epileptics

A judicious use of AEDs is needed when other co-morbid conditions, a common occurrence in elderly patients, are present [35] e.g. (a) valproate should be avoided in Parkinson's patients (worsening of tremors), (b) carbamazepine and oxacarbamazepine (pro-arrhythmic action), are contraindicated in patients with cardiac arrhythmia, (c) in hepatic failure the drugs undergoing extensive hepatic metabolism (i.e. carbamazepine, valproate and phenytoin and tiagabine) should be avoided while in renal failure AEDs exclusively eliminated by renal route i.e. gabapentin, vigabatrin and topiramate (when used alone) are to be avoided and if in use require dose adjustment. Other AEDs are eliminated by both routes. In the presence of myxedema valproate is the drug of first choice as other drugs, phenytoin and carbamazepine and to lesser extent barbiturates, interact with thyroid hormone.[1,11,26] Cognitive dysfunctions are common in epileptics and are further compromised by adverse effects of AEDs and individual's susceptibility. It may remain undetected as this toxicity of AEDs is often mild and develops slowly. AEDs with potentially significant adverse effects on cognitive functions (i.e. phenobarbital, primidone and topiramate) should be avoided while drugs having some effect on cognitions (i.e. phenytoin, carbamazepine, valproate and zonisamide) should be used with caution.[3] Gabapentin is the drug of choice for seizure control in porphyria .[60]

## Difficult to Treat Epilepsy: Surgical Treatment or Neurostimulation?

Patients whose seizures are not controlled with adequate polypharmacy should be referred to specialized neurological centers. Patients should not wait indefinitely for trials of various drug combinations. In general, patients who continue to exhibit one or more disabling seizures per month for a period of 2 or more years despite supervised trials (6 months each), twice with monotherapy and once with polytherapy, are candidates for presurgical evaluation.[48] The cases of refractory epilepsy are further evaluated by history and clinical examination supplemented by simultaneous video and EEG recordings (for correct diagnosis of seizure type/epileptic syndrome) and localization of focal epileptic lesion with application of sphenoidal and depth electrodes electroencephalography, MRI, MR spectroscopy, ictal single photon emission computerized tomography (SPECT), positron emission tompraphy (PET) and by estimation of neurotransmitters through microdialysis technique. In partial epilepsy the epileptogenic lesion is excised to control the seizures.[14] In selected cases of generalized epilepsy, corpus callosotomy may control or reduce the seizure frequency.[18] At present, surgical techniques can be used to abolish the epilepsy and in controlling the clearly defined syndromes e.g. mesial temporal sclerosis. The cases of infantile spasm may be considered for surgery when refractory to medical treatment (i.e. ACTH or Prednisone, plus trial of conventional AEDs), have a definite zone of cortical abnormality with evidence of diffuse brain injury due to hypoxic brain damage or metabolic or storage disease.[54] However, not all cases respond to surgical treatment. Moreover, the surgery is not without risks.

Many investigators have investigated the possibility of seizure control by neural stimulation. Of many sites targeted (i.e. cerebellum, thalamus, locus coeruleus and subthalamic nucleus), stimulation of vagus nerve was approved by FDA in 1997 for the treatment of partial refractory epilepsy. The mechanism of its action is not known. It is presumed that stimulation of vagus nerve through its rich interconnection in brain stem and thalamus can influence the entire cerebral cortex. Stimulation of vagus increases cerebrospinal fluid (CSF) GABA concentration while decreasing the level of excitatory amino acid aspartate, thereby inhibiting cerebral cortical excitability and influencing the seizure generation and propagation. Three types of vagal nerve stimulators (VNSs) (i.e. model NCP100, model NCP 101 and model 102) are available. The newer model 102 is small with a battery life of eight and a half years and is attached using a single pin. The generator is placed subcutaneously over the left chest wall and leads are tunneled to the neck where the left vagus nerve is exposed and helical lead is attached. The commonly used pulse width and frequency are 500 microseconds and 30 Hz respectively. The usual settings are 30 seconds on and 5 minutes off. If patients do not respond then the duty cycle is increased by reducing the intervals between the stimulation (i.e. rapid cycle). The

seizure control was higher when a high dose or rapid cycle was used. It is presumed that advances in our knowledge of epilepsy will lead to stimulation of particular regions more effective to special types of epilepsy, finding optimal parameters of stimulation and development of better-designed and more effective devices that can respond to or anticipate the occurrence of seizures. The subject has been excellently reviewed by Karceski (2002). [30]

## Drug Monitoring [20, 47]

Drug level monitoring is invaluable especially when the patient is taking multiple drugs (i.e. rational polypharmacy with AEDs or due to co-morbid conditions) and when there is altered drug pharmacokinetics (i.e. renal failure, hepatic diseases, pregnancy or old age). If utilized correctly it helps in better seizure control, establishes drugs responsible for toxicity and helps detect and minimize the problem of drug interactions. In addition it helps to detect the cause of poor response to AEDs (i.e. poor drug compliance, malabsorption of drug or altered bioavailability due to changes in drug formulations). Because of its long half life, non-linear saturation kinetics of its metabolism, and narrow therapeutic index, drug level monitoring is reliable and indicated when using phenytoin as AED. Serum level monitoring is less dependable for carbamazepine because of the wide variation in its levels between patients and is markedly influenced by other enzyme inducing drugs. As sodium valproate has a wide therapeutic range, measuring of its drug level has little clinical significance. There is little experience of therapeutic serum levels of newer AEDs. **A reliable laboratory and timing of sample collection is critical to proper interpretation of results**. Many factors (i.e. time taken to achieve a steady-state blood level, phenomenon of auto induction and timing of blood collection) affect the drug levels. The blood is collected after three weeks (time for achieving a steady-state level) while using constant doses of phenytoin (long half life) and carbamazepine (auto induction of metabolism). Timing of sample collection is also important. Recommendations are that blood should be collected in morning hours for phenytoin (less fluctuations in serum level due to long half life), 4-6 hours after dosing for carbamazepine and sodium valproate (wide fluctuations due to short half life) and at the time of maximum symptoms for detecting toxic drug levels.[45] Except in special metabolic circumstances, the need of estimating free drug level remains in doubt. [47]

## Withdrawal of AEDs, when and how?

The decision to withdraw AEDs is dependant on risk or consequence of seizure recurrence. It is the duty of the treating neurophysician to provide this information to the patients and his or her relatives. This is important in women and children because of AEDs' effects on pregnancy and cognitive functions respectively. Present data suggest that nearly 75% of patients with epilepsy become seizure free with AEDs treatment within a few years and that more than 60% of seizure free patients remain seizure free when medication is withdrawn.[36, 51] Berg and Shinnar [5] in a metanalysis of 5000 cases reported recurrence of seizures within 2 years after starting AEDs withdrawal in 29% of cases. In most cases it occurs in the first 9 months. The good prognostic indicators are a normal IQ and neurological examination, a normal EEG, a seizure free interval of 2 years and absence of complex epilepsies e.g. juvenile myoclonic epilepsy.[32] A slow rate of withdrawal, not less than 2 months, is recommended. In patients on polytherapy, withdrawal of AEDs are done more slowly. Sedative AEDs e.g. phenobarbital and primidone are withdrawn more slowly. Tennison, et al., [61] found no difference in 6 weeks versus a 9 months withdrawal in 1333 seizure free children.

## Conclusions

Treatment of epilepsy is a complex and challenging problem. Selection of AEDs should be appropriate to patient, seizure type and epileptic syndromes. Application of pharmacokinetic principles while administering these drugs is an essential requirement. The ultimate goal of reversing and preventing the manifestation of epilepsy (i.e. epilepsy cure) is still not an obtainable target with AEDs. There is resurgence of "Rational polypharmacy" in the treatment of epilepsy. Other modes of therapy, including surgery, are still needed in those remaining refractory to medical treatment.

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