

MANAGEMENT OF CHILDHOOD EPILEPSY

-Dr Vrajesh Udani

This review focuses on the practical aspects of management of childhood epilepsy. It combines what is well documented in the world literature with the author's personal observation, which may at times appear anecdotal. It is structured such that important questions are first asked about aspects of the day-to-day care of such patients and rational answers are then attempted.

Prerequisites to Starting Treatment

Before writing a prescription for any antiepileptic (AED), the physician must attempt to answer certain questions regarding the different levels of diagnosis. This would help decide not only drug management issues but also shed light on what other problems are likely to be encountered as well as final outcome in terms of seizure control, quality of life etc.

Nonepileptic events

These must be excluded usually clinically. A detailed history of the actual event, precipitating condition, etc are usually sufficient. Among the important differentials at different ages are conditions like neonatal sleep myoclonus, breath holding spells, migraine variants, syncope and pseudoseizures. The mistakes most often made are relying on EEG and imaging findings to reach the diagnosis. Often these may be coincidentally abnormal or may be wrongly interpreted.

Seizure type

This is the second important diagnostic level helping not only in epileptic syndromic and etiological diagnosis but also in choosing the most appropriate AED. Again the history is most helpful and this should be obtained not only from the caregiver/witness but also the child. Often even very young patients can describe auras or other phenomena if simple questions are asked.

Epileptic syndrome diagnosis

This refers to collation of information on seizure type and semiology, age at onset, associated handicaps/symptoms, EEG findings etc leading to a more informed decision making process. This helps in delineating etiology, need for further investigation, needs for treatment, choice of drug, ease of seizure control, length of treatment and evolution of other handicaps. For example benign rolandic epilepsy may not need treatment or investigations beyond an EEG and prognosis is always excellent for complete control and remission. Infantile spasms being a heterogeneous condition needs investigations for etiology and specific AEDs like steroids or Vigabatrin. It may also be difficult to control and may have associated conditions like autism and mental retardation. It must be emphasized that a syndromic diagnosis may not always be possible especially at the initial visit and a diagnosis may evolve over time.

Etiological diagnosis

An etiological diagnosis must be rigorously attempted in all cases. This may be surmised only from the history as a familial syndrome like childhood absence or febrile seizures or may need sophisticated imaging and biochemical techniques for conditions like neurocysticercosis, tuberous sclerosis cortical dysplasia, biotinidase deficiency etc. The etiological classification can then be **symptomatic** indicating a clear-cut cause or **idiopathic** which usually means familial.

Cryptogenic refers to presumption of a cause but an inability to document it with presently available diagnostic techniques.

Acute symptomatic seizures must be differentiated from unprovoked seizures, as the long-term management would differ in most cases. The former are seizures secondary to acute brain events like trauma or hypoxic, ischemic encephalopathy (HIE), meningoencephalitis, hypocalcemia, hypoglycemia etc. Even febrile seizures and seizures secondary to neurocysticercal granulomas should probably fall into this category. Most neonatal seizures likewise would be acute symptomatic seizures. These seizures do not necessarily lead to chronic epilepsy i.e. recurrent unprovoked seizures and the overall risk of such a long-term outcome is only around 10-15%.

Goals of Therapy -

what are we trying to achieve?

The doctor must have a clear idea of the goals of treatment in different types of cases and this must be clearly explained to the patient at the outset. Unrealistic patient expectations and poor doctor communication is the major reason for 'doctor shopping' so prevalent in India.

Seizure control

This is the most obvious goal AED therapy. A balance has to be achieved between seizure control and drug toxicity. Seizure control is important in those epilepsies where prolonged convulsive seizures and status epilepticus are frequent. It is also important in disabling drop attacks causing injury. Subtle and subclinical absence seizures in normal children should also warrant an attempt at maximal control as these interfere with school performance. However brief myoclonias or absences need not be totally controlled in a severely handicapped child where the seizures are just one of the many manifestations of a diffuse neurologic illness.

Ensuring normal development and learning

This aspect is not always in our control; however every attempt should be made to safeguard cognitive and higher functions for a more optimal long-term outcome. Development and learning could be affected the basic neurologic substrate, by the neuropsychologic adverse effects of AEDs, by frequent seizures, status epilepticus and when there are bilateral and/or diffuse epileptiform EEG abnormalities. Examples of the latter are infantile spasms, Lennox-Gastaut syndrome and the epileptic (Landau-Kleffner syndrome, Electrical Status in Slow wave Sleep.).

These so-called 'epileptic encephalopathies' may have few obvious or subtle clinical seizures and seizure control alone without normalization of the EEG would not be enough to ensure a good cognitive outcome. Every attempt should be made to choose the most appropriate AED with the neurobehavioral side effects as monotherapy; polytherapy has been regularly shown to increase these problems. Frequent episodes of status can lead to diffuse injury or more focal injury (e.g: hippocampal sclerosis) leading to irreversible cognitive impairment.

Quality of life

Such issues are often overlooked. These would be different in different situations. For example an adolescent who wants to drive may want AED control of even a single generalized seizure while a young infant/child with infrequent seizures in a supervised home environment may be spared the toxic effects of long term AEDs. Often unnecessary restrictions are placed on the child by the parents, sometimes on the advice of the physician. This leads to overprotection by the parents, loss of self-esteem and overdependence in the child, etc which becomes more of a problem than the seizures themselves. Often we forget the impact of this diagnosis on the family. Parents become overanxious and sometimes sit up all night looking for any slight twitch, which is then reported to the doctor who increases the AEDs dosage in a knee jerk reaction. Sibs often feel neglected and resentful.

This complete disruption of family dynamics is often not communicated to the physician in the busy consulting room. As physicians we should reassure parents about the benign nature of most childhood epilepsies and downplay the seriousness of the more difficult to control epilepsies without compromising on the truth. In the intractable and serious epilepsies the author prefers to spread the prognostic implications over a few visits so that time is given to the parents to adjust to the diagnosis and all its implications.

Who Needs Treatment?

Does treatment alter natural history?

The answer to the first question has changed as the natural history of the various epilepsy syndromes has been delineated and the adverse effects of the various AEDs elucidated more fully. The impact of seizures varies a great deal depending on patient age, type and timing of seizure, frequency of attacks and most important the family's and sometimes the child's attitude and reaction to the illness.

This question is most relevant for three groups of patients: those with

1. a first seizure
2. acute symptomatic seizures and
3. benign epilepsy syndromes in childhood.

First seizures

Historically, seizures were thought to beget more seizures and hence were always treated as soon as the diagnosis was made.

This concept has changed radically and several studies have shown that AEDs do not alter the natural history or prognosis of epilepsy—they have no effect on epileptogenesis, only on recurrence rates.

This discussion is not applied to myoclonic or absence seizures as by the time medical help is sought many seizures have already occurred. The same may apply in convulsive first seizures. Often on history minor complex partial episodes preceding the first generalized convulsive seizure may have been missed by the patients and/or parents. In those with the true first seizure several studies have shown relapse rates as low 23% to as high as 71%. This is not surprising, as epilepsy being a heterogeneous disorder, the relapse rate would differ between different groups. The most consistent risk factors across studies predicting recurrence are

1. **abnormal epileptiform EEG**
2. presence of underlying etiology i.e. **symptomatic seizures.**

The risk is lowest (24%) with idiopathic seizures with normal EEG, intermediate (48%) with either abnormal EEG or with underlying etiology and highest (65%) when both risk factors are present.

Other less consistent risk factors include :

1. sleep related seizures
2. positive family history
3. partial as opposed to generalized seizures. Gender and status epilepticus are not associated with an increased risk of recurrence. Age at onset of seizures may be relevant as a recent study of first seizures in Italy found higher rates in children & adolescents, as opposed to adults.

In summary, the overall risk of recurrence of a first seizure is about 38%. An abnormal EEG and symptomatic first seizures have higher relapse rates and if present, make many physicians inclined to treat. In our situation many a normal pediatric EEG is often misinterpreted as 'abnormal' and this should be considered before reaching a decision.

Acute symptomatic seizures

As mentioned earlier, these lead to chronic epilepsy in only 10- 15% and AEDs do not influence this from happening. This process of epileptogenesis takes from a few months to a few years to develop. This was well studied using phenytoin 'prophylaxis' in patients with significant head trauma. It was found that phenytoin is useful in preventing recurrence in only the first week after the trauma and did not influence the development of epilepsy. It is therefore recommended that all acute symptomatic seizures be treated either with short term AEDs till such time that the acute event is resolved. This usually means discontinuing the AEDs at discharge or within a few months.

Benign epilepsy syndromes

In childhood these are age-limited time-bound disorders with natural resolution within a few years of onset in the majority.

They include febrile seizures, benign partial epilepsies with centrotemporal spikes (BECTS) and with occipital paroxysms (BEOPS). The latter often have very abnormal EEGs that do not necessarily correlate with occurrence of clinical seizures. Often these syndromes have only infrequent recurrences, many of them at night. Also many children are young and parental supervision is already in place. These various factors lead most neurologists to suggest a withholding of treatment after the first or even subsequent seizures.

In clinical practice other non medical factors often influence decision making. Parents may be very anxious or may be working and hence want immediate treatment. Sometimes medical help is far away as in rural areas and may influence this decision. Also some patients, especially teenagers want treatment as they want to drive etc.

In case no treatment is given parents should be instructed on how to use rectal diazepam in case of a recurrence. As the maximum risk is within one year, it is reasonable to supervise or restrict activities like swimming, cycling on the road driving for this period.

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Choice of antiepileptic drug

Since the last few years there are new molecules being introduced every few months in the Indian market and the pediatrician is faced with a hitherto unavailable choice of which agent would be best suited for particular patient. This discussion is an attempt to rationalize this decision using both literature review and personal observations.

Important factors to consider in this decision include the following :

1. Epilepsy syndrome diagnosis if possible
2. Type of seizure/seizures
3. Age and gender of the patient
4. Premorbid conditions/disorders
5. Cost of therapy.

Epilepsy syndromes

Drug research and development has only recently targeted specific epileptic syndromes and diseases, providing us with invaluable data on which specific drugs help which syndromes. Felbamate (FBM) and Lamotrigine (LTG) have been shown in double blind randomized trials to be extremely effective in the Lennox-Gastaut syndrome of multiple seizure types. Similarly Vigabatrin (VGB) has been shown to be more than 90% effective in infantile spasms due to tuberous sclerosis (TS). A brief summary of the appropriate drugs in specific syndromes follows

Neonatal seizures

This is discussed elsewhere. It is important to emphasize that most are acute symptomatic seizures and will need specific management and only short term AEDs. Parenteral phenobarbital (PB) and phenytoin (PHT) either alone or sequentially control most seizures if appropriate doses are given; inadequate doses are the usual reason for failure. It must be also stressed that overdose may occur due to decreased hepatic and renal clearance in neonates with HIE or other systemic ailments.

Infantile spasms (IS)

ACTH is probably the drug of first choice being some-what more effective than prednisolone. They have been shown to stop the spasms, reduce or reverse the cognitive decline/epileptic encephalopathy and reduce possibly the risk of long-term epilepsy. Recently it has been demonstrated that low doses (20- 40 IU) are as effective as high doses. The problem in India is availability, making prednisolone the drug of choice. Recently European data supports the use of oral hydrocortisone in refractory cases. VGB is a strong competitor for this condition and has established itself as the drug of choice in IS due to TS. The benzodiazepines (BZDs) are next with nitrazepam (NZP) being the most effective and tolerated. Side effects and the phenomenon of tolerance limit clonazepam (CLP). Though there were good reports of valproate (VPA) in IS our experience has been disappointing. Higher doses may be useful but the price of GI side effects limits its use.

Febrile seizures

This is discussed elsewhere in detail. Suffice it to emphasize that this rarely needs long-term treatment and should be managed with parental reassurance and/or intermittent BZD therapy with either diazepam (DZ) or clobazam (CLB). Rectal DZ is probably more effective than oral; however ease of administration makes the oral preferable. If long term treatment is planned VPA and PB are effective. Carbamazepine (CBZ) and PHT do not help and in our experience at least, CBZ might worsen the seizures in a few children.

Lennox-Gastaut syndrome(LGS)

As mentioned earlier, LTG and FBM are most effective. The former has just been introduced and the latter has fallen out of favor because of bone marrow and liver toxicity. At present we start with VPA and add CLB in case the seizures do not get controlled.

LTG is the rational next step. Though CBZ and PHT may be useful for associated partial seizures there is a real risk of pushing these children into minor absence or myoclonic status and hence those should be avoided. BZDs may increase seizures as well because of their sedative effects. Many children are poorly controlled and alternative therapies like the ketogenic diet and epilepsy surgery (corpus callostomy) should be considered early.

Childhood absence epilepsy

The drugs of choice are either ethosuccimied (EBM) or VPA. The former is not easily available and does not control the associated generalized tonic-clonic seizures (GTCs), which sometimes occur. In fact ESM may actually precipitate GTCs especially in older children. Low doses of VPA are sufficient in most cases however in some, higher doses also are ineffective, especially absences associated with myoclonias-the so called 'myoclonic absence epilepsy'. In such cases BZDs notably CLP may help. Recently however the second drug of choice is LTG, which acts synergistically with VPA.

Benign partial epilepsies of childhood

The most common of these are the BECTS and the BEOPS. The seizures are infrequent and remit easily especially in the former, despite significant EEG abnormalities. Often no treatment is needed. However in case treatment is given, CBZ and VPA are the drugs of choice according to the literature. Our experience is better with VPA because of the tendency of CBZ to increase the generalization of epileptiform discharges and possibly induce language and cognitive problems. This atypical evolution of benign partial epilepsy has been recently reported in six patients, five of whom were on CBZ, CLB and Gabapentin (GBP) are two new AEDs that are being tried in these conditions.

Landau Kleffner and Related Syndromes (LKS)

This syndrome of epilepsy and aphasia has been extensively studied. The language disturbance appears to be due to epileptic dysfunction of bilateral posterior temporal & parietal cortex and usually involves auditory comprehension first. Later the aphasia progresses to mutism. Initial expressive language disorders have been noted rarely when the epileptic abnormalities are more in the rolandic areas. Clinical seizures are not really much of a problem and in fact may never occur. Steroids are the mainstay of therapy and do lead to remission in some. Repeated courses may be needed. The remission is often associated with normalization of the EEG. The long-term course is variable; some children with persistent aphasia benefit from surgery. For seizures, CBZ should be avoided as the language disturbance might worsen. VPA or CLB are useful. A closely related disorder is the ESES syndrome (Electrical Status in Slow Wave Sleep) where again the language, cognitive and behavioral regression is more prominent than the seizures. These are usually myoclonic in nature. Steroids are used with a poorer response rate and BZDs (not VPA) are the drug of choice for the myoclonias.

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Primary generalized epilepsies of adolescence

This encompasses several distinct syndromes with significant overlap the Juvenile Myoclonic Epilepsy (JME), Juvenile Absence Epilepsy (JAE), the early morning GTC seizures on awakening and others. Of ten patients have components of all three. VPA is the drug of choice and using the other drugs like CBZ, PHT & PB leads to intractability. Acetazolamide (AZ) and LTG are other choices. Treatment is usually needed for prolonged duration. Many less common syndromes are beyond the scope of this discussion.

Only 50% of cases or less can be classified into such specific syndromes. In the remaining the prominent seizure type helps decide the appropriate therapy.

Seizure type

The two broad classifications of seizures are:

Partial seizures

These are also known as localization-related and are divided into simple, complex partial and secondarily generalized seizures.

CBZ, PHT, PB & Primidone (PM) have been shown to be equally effective in newly diagnosed adults. However the percentage of adults dropping out because of side effects was more in the PB and PM groups thereby suggesting that CBZ and PHT should be first choice due to their more favorable side-effect profile. VPA was compared to CBZ in another study in adults and though both were equally effective in controlling generalized seizures, CBZ was superior in controlling purely partial seizures. In young children our experience has been slightly different, in that seizures with a prominent motor component, either generalized or partial, respond better to VPA; purely complex or simple partial seizures, especially in older children and adolescents, appear to respond well to CBZ. The new AEDs with a strong anti-epileptic effect in partial seizures are CLB and VGB. These have been tried even as first line monotherapy with efficacy equivalent to CBZ. LTG and GBP have a weaker effect. Topiramate (TPM) and Tiagabine (TGB), (still not available in India) are fairly effective drugs, though their use is mainly as adjunctive therapy in refractory seizures.

Generalized seizures

These include GTC, myoclonic, absence and atonic seizures occurring either alone or in combination as part of the primary idiopathic or secondary cryptogenic or symptomatic epilepsies. VPA being a broad spectrum drug has become the mainstay of therapy in this group. Though high dose VPA therapy had become fashionable in difficult to control seizures most authorities do not recommend going too high, because of the risk of a dose related encephalopathy-parkinsonism syndrome associated with brain atrophy. ESM is still a preferred drug in pure absence epilepsies though there is a risk of precipitating GTC seizures.

The BZDs are also broad-spectrum agents with fairly rapid response rates in many of the generalized and partial epilepsies. However CLP is limited by a high degree of tolerance within a few months and also by its myriad side effects especially on cognition and behavior. CLB being a slightly different BZD has however become a major drug, as side effects and tolerance rates are acceptably

low. LTG is another drug with a high therapeutic index in the generalized epilepsies with a strong effect on all types. It is especially effective in combination with VPA.

Age and gender considerations

We do not use CBZ in infants as far as possible. There is a risk of inducing generalized seizures in this age group especially when there are multiple seizure types. An attractive hypothesis to explain this phenomenon may be the tendency of CBZ to induce generalized spike and wave discharges in young children who have profuse synaptic connections, making secondary bilateral synchrony that much easier. This might lead to language and cognitive deterioration in some children. PB is very useful in young infants with partial and secondarily generalized seizures, and the adverse effects in this age group are much less than in the toddler and school going child. Though PHT has excellent efficacy, the formulations available in India i.e. suspensions and

capsules make this a difficult drug to use in young children. Also absorption and drug clearance is fairly variable and hence drug levels fluctuate widely leading to erratic seizure control. VPA was not preferred in infants because of the risk of fatal liver disease. However this appears to have been overstated and is really a problem only if the child has a metabolic disorder like a mitochondrial cytopathy or a Beta-oxidation defect. VGB is a good drug even in infants; however recent reports of field defects in those using high doses chronically is a cause for concern because of the difficulty of doing perimetry in this group. CLB and LTG are well tolerated.

In the school-age child, where learning is a priority, PB, PM, BZDs GBP and even VGB can cause significant neurobehavioral side effects which can interfere with academic performance. CBZ and VPA are the mainstays of first line therapy. Adolescents tend to medicate themselves and therefore it is preferable to use once or twice a day dosing as they often forget the afternoon dose and do not like to take this dose in front of their peers. Sustained release CBZ, PHT & CLB are good choices. In the primary generalized epilepsies where VPA is needed there are sustained release preparations, available only abroad. In most however, twice daily dosing is adequate.

We try and avoid PHT in girls-especially adolescents because of the cosmetic side effects, which may become irreversible. Coarsening of the facies, gum hyperplasia and hirsutism are commonplace with long term phenytoin.

Premorbid disorders/diseases

This is an important consideration when choosing an appropriate drug in an effort to minimize adverse effects. Children who are already retarded and who have behavior and school problems, are more prone to aggression and hyperactivity, as compared to those who are normal in neurobehavior at baseline. PB, VGB, BZDs and GBP are all drugs with an adverse effect on behavior and hence must be used cautiously in this group. The BZDs may adversely effect children with in-coordination and problems in motor skills. Those with tremors and fine motor problems may be worsened by high doses of VPA. BZDs may worsen the problem of drooling in-patients with cerebral palsy.

Obese children may gain significant weight with the use of VPA, VGB and more recently CLB, such that the weight gain may become the major problem rather than the seizures. Infants with GE reflux and recurrent vomiting are often made worse with the VPA in liquid form, as it may cause gastritis and more reflux. Those with sleep disorders, common in autistic children, are significantly worsened by the use of BZDs and PB.

Infants with diagnosed or suspected metabolic disorders are more prone to the liver toxicity of VPA and this is relatively contra- indicated.

Cost and availability of drugs

This is probably the most important determinant of which drug to use. Older drugs like PB and PHT are cheap and are available even in rural areas. VPA and CBZ are now reasonably priced and widely available; this may not hold true when the dosage is high, as VPA costs about a rupee a tablet and sometimes the dosage in teenagers may be around 6-8 tablets/day leading to a cost of Rs 180-240/- a month. The newer ADEs are obviously more costly. CLB is around Rs 4/- and LTG about Rs 3/-. The availability of these medicines in small towns and villages may not be regular, leading to forced noncompliance. Then there are drugs like VGB, which are still not marketed in India and available in the gray market for as much as RS 30/- per tablet. Obviously these are available only at certain chemists in metro cities and their availability is erratic.

How to Use Antiepileptic Drugs

General principles

1. Dose introduction and titration

It is important to realize that seizure control may occur at a variety of doses in different individuals. A lot of importance is given to mg/kg dosed and many attempts are made to reach these dosages; seizure control should be the yardstick to decide dosage increases. The method now preferred is introduction of the lowest dose possible and titrating it upwards till seizure control is achieved or side effects occur. This may be a gradual process, if seizures are infrequent and can be fairly rapid when they occur often. Drug steady state should be optimally reached before increasing the doses and this might vary from a few days as in the case of VPA to 3-4 weeks of PB.

One of the mistakes often made is to increase doses according to body weight even in fully controlled individuals. Introduction at the lowest possible dose reduces the chances of adverse effects. CBZ, PB & BZDs at full dosages often cause unacceptable drowsiness and lead to noncompliance. Slow introduction avoids these problems. PHT can be rapidly loaded within a day especially if rapid control is desired. VPA can also be introduced at the maintenance dose without significant problem. LTG should be introduced at very low doses and titrated upwards over a few months if the dreaded rash is to be avoided.

2. Dosage intervals

For maximum compliance once or twice daily dosing is optimal. Pharmacokinetic considerations make this possible with PB. PHT in young children as opposed to adults is cleared very rapidly and may have to be given three to four times a day. VPA, CBA & CLP are also optimally given three to four times a day; recent introduction of extended release preparations may obviate this problem. It is best to give the drug at mealtimes so that compliance is easier. This is especially true of VPA to minimize gastric effects. It is not necessary to give these doses at exact intervals and as far as possible the child's routine should not be disturbed. Of the newer drugs CLB, VGB & LTG can be given in twice daily dosages, as their half-lives are long. GBP has to be given three times daily.

3. Monitoring

Clinical monitoring of seizures and adverse effects is usually all that is needed. Initially, patient visits should be at one month intervals and later, after stabilization, patients could be monitored only every three to six monthly. There was a lot of interest in monitoring blood counts with CBZ and liver functions with VPA to try and predict the rare bone marrow and liver toxicity. However what is now apparent is that mild leucopenia and rises in liver enzymes are commonplace and have no predictive value, making them pointless and expensive exercises. Similarly plasma drug level monitoring came into vogue in eighties in the west and recently in India and physicians started doing routine monitoring.

However it has now become apparent that this is wasteful practice, as it does not improve seizure control. Situations where blood levels may be useful include monitoring during treatment of status epilepticus to guide further therapy; confirmation of toxicity especially when there is polytherapy, and ruling out noncompliance. Some do it before changing the drug to confirm that the drug is truly ineffective even at good levels. The main advantage of blood levels is that it has helped understand pharmacokinetics and drug interactions and has helped us in rationalizing treatment plans. Monitoring EEGs are not required in routine epilepsy. However if seizure control is poor or the child is deteriorating in school performance or in language and other cognitive skills, this must be done to exclude an evolving epileptic encephalopathy.

4. **Monotherapy**

This became the watchword in epilepsy management in the eighties and is now standard practice, even in India (though there are still combination pills available in rural markets). Single drug therapy has the advantage of fully exploiting the therapeutic effect of the drug. It obviates the need for drug levels in monitoring efficacy and adverse effects and reduces the risk of drug interactions and neuropsychological side effects which maybe additive in polytherapy. If at maximal doses the drug is ineffective, a new drug should be introduced with simultaneous withdrawal of the old drug. One of the common mistakes made is to continue the ineffective drug along with the new addition. It must be realized that changing the drug is effective in controlling the seizures in only 30% of patients who fail the first drug. This figure is probably only true if the first drug was truly appropriate for the patient's seizure or syndrome type.

5. **'Rational polytherapy'**

This has now come into vogue in intractable epilepsy. The word rational denotes using not more than two drugs at a time and avoiding drugs with similar mechanisms of action i.e. PB & BZDs, PHT & CBZ. Certain combinations like VPA and CLB or LTG may have synergistic actions.

6. **Pharmacokinetic considerations**

As mentioned earlier, half-lives and clearance rates decide dosing intervals and steady state (usually 5 half-lives) decides time to maximum efficacy. Absorption characteristics and bioavailability decide average doses. These pharmacokinetics change with age and co-administration of other AEDs. Neonates absorb drugs like PHT poorly and erratically with gradual improvement with age. Clearance rates are slow in neonates which might lead to toxicity, especially if renal and hepatic systems are disturbed as occurs in neonatal HIE. In infants and toddlers clearance rates increase to higher than adult rates e.g. PHT, which makes it necessary to give the drug more frequently. PHT also has zero order kinetics, which means that the drug level does not linearly increase with dosage increases. At higher doses small increases in dose lead to rapid increases in levels, causing toxicity.

Drug interactions are most frequent with enzyme inducers like PHT, PB, PM and CBZ, leading to increased clearance for co-administered drugs and decreased levels. VPA decreases clearance of drugs like PB and LTG increasing their levels and hence appropriate dosage reductions are in order. Newer drugs like VGB & GBP have little interactions and are ideally suited if polytherapy has to be used. Another mechanism for drug interactions is an increase in free levels, as occurs with PHT when VPA is given primarily because of increase in the unbound fraction. Also active drug metabolites may increase causing adverse effects in spite of 'normal' drug levels. This is classically seen with an increase in CBZ-epoxide levels when VPA is given with CBZ. As can be seen drug interactions make management unpredictable and necessitate routine monitoring of blood levels. It is therefore wise and less expensive to try and use monotherapy.

7. **Adverse effects**

A complete list of side effects of all the drugs is beyond the scope of this review. However the most common and also the most subtle are the cognitive and behavioral effects which are most often overlooked. PB, PM, BZDs (CLB is better than CLP & NZP) and the newer drugs like VGB and GBP may cause these problems. Aggression and other severe behavior problems may sometimes be more difficult to manage than the seizures, especially in mentally handicapped children. CBZ may cause language and attention problems if the EEG worsens on it. VPA is fairly safe though at high doses can cause a full-blown encephalopathy. The same applies to PHT. LTG may actually improve neuropsychologic performance. Other neurologic side-effects like sedation are

common with CBZ/PM and sometimes with the BZD & PB. The latter more often cause sleep disturbances, that is a special problem with mentally handicapped patients.

Ataxia is really a problem with higher doses of CBZ and PHT, while diplopia is with CBZ. Tremor may be a handicap with VPA. Paradoxical increase in both generalized and sometimes partial seizures is redominantly a problem with CBZ and sometimes PHT. VGB increases myoclonic seizures and LTG may worsen some syndromes like severe myoclonic epilepsy of infancy. Dermatological side effects are sometimes seen in CBZ,PHT and PB and may necessitate discontinuation. Many can be restarted after a brief gap without recurrence of a rash. LTG is probably the one drug with maximal dermatological adverse effects especially if given with VPA and if rapidly increased. Systemic side effects like bone marrow suppression has been overstressed with CBZ and is really a problem only with FBM. Thrombocytopenia is regularly a problem with high doses of VPA though it is most often asymptomatic.

Liver disease is mainly a problem with FBM and again has been over emphasized with VPA. Weight gain or loss can occur with VPA - the former in older children and the latter in infants given the syrup, which often cause gastritis and persistent anorexia and nausea. This regularly responds to antacids.VGB, CLB and sometimes CBZ cause weight gain as well and this is especially a problem in adolescence. Constipation occurs sometimes with CBZ, CLP and NZP cause significant increase in oral and respiratory secretions, causing a problem in handicapped patients. In summary adverse effects are plenty and need to be monitored closely.Fortunately though one-third of patients develop side effects, only 5-10% discontinue the drug due to this.

EPILEPSY - MYTHS AND FACTS

-Dr Navneet Kumar

What should the patient, his family and his school know; what can't he do?

Epilepsy is probably the most stigmatizing disease and parents and families go to extraordinary lengths to conceal this from their family and even the school authorities. Though it is easy to make a blanket statement that this is just another disease and everybody should be informed it is sometimes difficult to convince parents of this. What the author does is to inform the patient what epilepsy is and reassure them of the benign nature and outcome of most epilepsies starting in childhood. At every visit it is stressed that epilepsy is a just another disease and nothing to be ashamed of. Once patients understand how common this is, they tend to treat it just like other diseases. **Samman** is an epilepsy support group in Mumbai that helps this process of acceptance.

Who should know? We feel this should be handled on 'a need to know' basis. Obviously school and class teachers must know, as they should not be faced with an unexpected seizure. We even encourage the parents to educate the teacher on first aid measures and some even keep the rectal DZ at school. Neighbours, family members and friends where the child spends substantial time must also be informed. We feel that as the accident rate in epilepsy is quite low (probably epileptics and their parents are reflexly more careful), it is better to supervise activities like swimming, cycling etc, rather than impose strict restrictions. Girls should stay away from kitchen stoves. The patient should not feel deprived. Downplaying the parents' anxieties and avoiding overprotection is also beneficial, as this leads to secondary anxiety and overdependence in the patient. Toddlers with drop attacks should wear cycle helmets to prevent injury. This supervision should continue for at least a year after the seizures are in remission.

Discontinuation of therapy

In epidemiological studies approximately 70-80% of patients enter long term remission. From developing countries data on untreated patients also suggests that at least 50% enter long-term remission. Hence it appears that the majority of patients will lose their epileptic tendency regardless of treatment. AED therapy is probably only symptomatic, preventing recurrent clinical seizures and having little or no effect on the natural history of epilepsy. If the epileptic tendency spontaneously resolves, AED therapy will not be needed and should be discontinued. This helps not only as the patient is spared the myriad adverse effects, but also as the patient and families feel a sense of relief that they are past the disease.

Several studies have addressed the risk of relapse after discontinuation to try and establish a predictive model that might help both patient and doctor to decide whether the risk is worth taking.

The **risk of relapse** ranges from between 20-40% in most studies and this risk is maximum in the first year after discontinuation. About 75-80% of the risk is in the first year and this is almost completed by the end of the fourth year suggesting that almost all patients who cross the four year mark will probably not have a recurrence and can be considered 'cured' of their disease. The median risk at 1 year is about 25% and by the second year about 29%. Several factors have been studied to decide which are most predictive. These will be discussed in some detail.

Age at onset

Clearly onset in early infancy and childhood as well as adolescence confers a higher risk of relapse as opposed to onset in childhood. The risk is almost 1.8 times in adolescent onset. The risk in early onset cases may be partly explained by the increased incidence of handicaps in this group (see below).

The risk with adolescent onset may be partly explained by the high incidence of juvenile myoclonic epilepsy (JME), a syndrome known to have significant chance of relapse after AED discontinuation.

Remote symptomatic seizures are those that are symptomatic of brain injury sustained sometime in the past. Clearly the risk is increased about one and a half times in these children, especially those with mental retardation of a severe degree. Cerebral palsy does confer some risk though this is much lower.

An **abnormal EEG** at discharge probably increases risk of relapse as well; exceptions are the benign partial epilepsies where there is little correlation of an abnormal EEG and clinical seizure occurrence. Focal slowing on the EEG and epileptiform activity are probably important risk factors.

Electroclinical syndromes if diagnosed, sometimes help, as studies have shown that BECTS always remits, JME rarely remits while BEOPS and absence epilepsy remit 75-80% of the time. The problem is that syndromes are diagnosed in less than half the children.

Type of seizure does not really help as similar seizure types can occur in and malignant epileptic syndromes.

Severity of epilepsy i.e. a longer period of active epilepsy, higher number of seizures prior to stopping AEDs, etc probably confer an additional risk though this has not been studied in a systematic manner. Status epilepticus is probably not a major risk factor.

Other equivocal risk factors include breakthrough seizures during fever in children. Family history does not seem to be a major risk factor; neither does a previously failed attempt at discontinuation, suggesting that one may try this process more than once.

Even those who are seizure free on AEDs have a 20% risk of relapse suggesting that this is part of the natural history of epilepsy which AEDs do not apparently influence.

Generally the longer you are seizure free the higher chance of remission. The **minimum seizure free period** would be about two years, though studies with 1 year and 5 years of seizure freedom have shown similar rates of relapse. These years of seizure freedom probably are not important in themselves and these figures probably reflect on the substrate of the particular epilepsy syndrome.

There have been studies to try and correlate the number of risk factors with the risk of relapse and have found that with no risk factor, relapse rates are as low as 12%, with one risk factor this rises to 46% and with two factors to 71%. These figures are similar for cryptogenic and remote symptomatic seizure disorders.

Finally the patient or family must understand all these risks and they should be encouraged to participate in the decision making process. It is always a good idea to try discontinuation before driving is learnt and before the child becomes totally independent and unsupervised. The risk of injury and status epilepticus, though low, is obviously more of a problem in an unsupervised teenager who keeps late hours, misses sleep and may drink alcohol.

For one year cycling on the road unsupervised activities like swimming, cooking etc should be avoided, as the maximum risk of relapse is during this period.

Tapering of drugs over 6-8 weeks is adequate and long drawn out tapering periods do not decrease the risk of seizures, withdrawal seizures are a problem more with PB, PM, BZDs and VGB. If a patient does relapse most will need a reinstatement of treatment though one could wait if an obvious precipitating factor was involved.

In summary, the average risk of relapse after discontinuation of AEDs after a two-year seizure free period is about 30%. This risk is higher if the age at onset was in infancy or adolescence, in those with remote symptomatic seizures and in those with abnormal EEGs at time of discontinuation. Certain electroclinical syndromes also determine prognosis of relapse. Severity of epilepsy, duration of active epilepsy, difficulties in achieving control and breakthrough seizures with fever, are probably risk factors as well. A full discussion with the family about the risks and benefits of discontinuation is very important as the child and parents should feel part of the decision making and must understand that they may need AEDs again. Short tapering over 2

months is adequate. The biggest advantage of discontinuation is the feeling of well being which occurs as the child and the family feels that they are rid of the disease.

This review of the salient points of management of epilepsy is far from complete. A complete list of references and suggesting reading is with the author and available on request.