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Review Article

Optimizing epilepsy treatment in children, adults and elderly: clinical perspectives

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ABSTRACT

Epilepsy is a common neurological condition among all age groups. Its diagnosis depends on clinical history and is supported by investigations like electroencephalograph and magnetic resonance imaging. In children, febrile seizures and juvenile myoclonic seizures are common. In adults and elderly, epilepsy could be new onset or present since childhood. Several antiseizure medications (ASMs) are available for treatment of epilepsy. Each of these drugs has different advantages as well as limitations. Several factors including patient related factors (e. g. age, comorbidities, and gender), seizure characteristics and epilepsy type, and drug related factors (namely, pharmacokinetics, pharmacodynamics, efficacy, side effects, and risk of drug-drug interactions) are considered while selecting drug therapy. There are concerns related to teratogenicity due to pharmacotherapy in females of child-bearing potential. Elderly patients also need special considerations while selecting an appropriate treatment option for epilepsy. Advisory board meetings with a group of expert neurologists were conducted at eight cities across India to gain clinical insights on management of epilepsy in different age groups. Consensus was supported by relevant literature obtained from PubMed and Google scholar using the keywords 'epilepsy', 'diagnosis', 'children', 'adults', 'elderly', and 'management'. According to the experts, choice of appropriate ASM is driven by patient- and drug-related factors and seizure characteristics. In India, valproate remains a commonly prescribed agent except in females of childbearing age. Levetiracetam is preferred because of its safety profile whereas clobazam is an effective initial add-on therapy. Newer drugs are largely useful as adjuvants.

Keywords: Drug therapy, Epilepsy, Optimization, Risk benefit ratio

INTRODUCTION

Epilepsy is a common neurological disorder impacting people across all age groups. According to the international league against epilepsy (ILAE), it is defined as disease of the brain having any one of these: >2 unprovoked (or reflex) seizures occurring >24 hours apart; one unprovoked (or reflex) seizure and a probability of further seizures similar to the general recurrence risk (at least 60%) after two unprovoked seizures, occurring over the next 10 years; or diagnosis of an epilepsy syndrome.[1]

According to the new classification by the ILAE, based on the semiology, seizures are classified as focal or generalized onset or unknown onset.[2] Over 70 million people across the world are affected with epilepsy, with a high risk of bimodal distribution in infants and elderly.[3] India contributes about one sixth to the total population with epilepsy. The overall ranges for prevalence and incidence of epilepsy in India are 3.0-11.9 per 1,000 and 0.2-0.6 per 1,000 population per year, respectively. The reported rates of types of epilepsy differ based on the study settings. Hospital-based studies suggest prevalence of

focal onset epilepsy between 57% and 80%, and community-based studies suggest generalized onset seizures between 54.5% and 79%. Among generalized onset seizure types, tonic-clonic seizures are the most common.[4]

The causes of epilepsy could be idiopathic, cryptogenic, or symptomatic. In symptomatic cases, cause of epilepsy is identifiable, whereas idiopathic cases have a genetic cause. Cryptogenic (probably symptomatic) cases have no known cause for epilepsy. Presentation, severity, etiologies and hence treatment of epilepsy can differ among patients.[5]

Diagnosis of epilepsy depends on clinical history and is supported by investigations such as electroencephalography (EEG) and magnetic response imaging (MRI). Once diagnosed, understanding seizure type or syndrome is important for selection of optimal treatment and for better outcomes. The goals of treatment with antiseizure medications (ASMs) include seizure freedom or reduction in frequency of seizures without risk of adverse events, and treatment helps patients maintain usual daily activity.[6]

Several pharmacological, surgical, immunological, and dietary options are available for the treatment of epilepsy.[5] Despite availability of many drugs, treatment gap is an important challenge in epilepsy management.[7] In India, treatment gap ranges from 22% in urban areas to 99% in rural areas.[8] Availability and access to healthcare and poor diagnostics contribute to the treatment gap in epilepsy.

Over last three decades, there has been significant increase in the number of ASMs available for the treatment of epilepsy. Although newer agents do not have better efficacy as compared to older drugs, they have other advantages, such as fewer adverse events and different mechanisms of action making it possible to have synergic combinations. Furthermore, newer agents have lesser or no risk of pharmacokinetic interactions.[9]

With the availability of many drugs, it is important for clinicians to be familiar with the options in the armamentarium. A specific drug is selected considering patient-related factors, drug-related factors, and seizure characteristics. Patient-related factors include age, gender, race, and comorbidities (e.g. headache and mood disorder).[10] The risk of seizure recurrence and risk-benefit ratio are also considered when initiating an ASM.[6,10] Most new drugs are initially approved as adjuvant therapy because of limited/no data on efficacy when used as monotherapy in newly diagnosed cases. Limited clinical evidence is available on the current practices on the diagnosis and management of epilepsy in different patient groups in India. The objective of this article was to present expert views on the management of epilepsy in Indian patients of different age groups.

Eight advisory board meetings with expert neurologists were conducted at eight locations across India to understand clinical insights regarding the management of epilepsy in different age groups. The selected experts brainstormed on the current treatment of epilepsy in India, and experts' opinions were compiled into a consensus document that was furthers substantiated by relevant literature evidence obtained from PubMed and Google Scholar using the keywords 'epilepsy', 'diagnosis', 'children', 'adults', 'elderly', and 'management'.

EPILEPSY IN CHILDREN

Epilepsy in children can be different from that seen in adults. These differences may be related to types of seizure and epilepsy syndrome.[11] Clinicians should take a comprehensive and neurologically focused history and conduct thorough clinical examination. This is important for both diagnosis and management of epilepsy in children.[8] The objectives of treatment of epilepsy in children include providing freedom from seizures without adverse events and helping patients achieve overall function similar to their age-specific population.[11] Three important types of seizures in children, namely, febrile seizures, juvenile myoclonic epilepsy, and absence epilepsy are discussed below.

Febrile seizures

Febrile seizures are the most common types of seizure in children between 6 months and 5 years of age; they affect about 3% of children in this age group.[12] Some experts suggest an upper limit of up to 6 years for the occurrence of febrile seizures.[13] Febrile seizures are also the most common type of convulsive disorder in children. These seizures are associated with fever but without presence of intracranial infection or other causes of seizures such as hypoglycemia or acute electrolyte disturbance.[13]

Febrile seizures can be simple or complex.[14] Most patients have simple febrile seizures, which are generalized, generally lasting less than 15 minutes. Simple febrile seizures are generalized tonic-clonic seizures without focal features. They resolve spontaneously and do not recur within 24 hours. Complex febrile seizures differ from simple seizures in terms of frequency, type, and duration and usually occur multiple times in 24 hours. They are focal in nature, last longer than 10 minutes, and are associated with post-ictal complications.[12,13] These seizures may need antiepileptic drugs for stopping the attack.[13]

Obtaining medical history from the parents provides important clues for the diagnosis of febrile seizures. History should be taken regarding type and duration of seizure, recent infection, prior episodes of seizures, family history, and use of medications, including antibiotics. Evaluation should be done to identify the cause of fever.[13]

Neurological investigations such as neuroimaging [computed tomography (CT) and magnetic resonance imaging (MRI)] and electroencephalogram are not

required if the child has simple febrile seizures. Lumbar puncture is done in patients with signs suggestive of meningeal or central nervous system infection.[12] If abscess is seen on MRI, lumbar puncture should be avoided.[13] Simple febrile seizure is associated with excellent prognosis, but risk of epilepsy is more in children with complex febrile seizures, multiple seizures, seizure occurrence after the age of 3 years, family history of epilepsy and those with focal seizures.[12,15] Other risk factors for epilepsy in children with febrile seizures include neurological abnormality, history of developmental delay, preterm birth, and abnormal findings on EEG.[15,16] Intracranial infections should be ruled out in children with complex febrile seizures.[13] Other differential diagnosis of febrile illness include rigors, syncope, delirium, and breath-holding spells.[13]

Management of febrile seizures includes providing symptomatic control of seizures and identification and treatment of cause of fever.[13] In children with febrile seizures, long-term treatment with ASM is not required. In most cases, prognosis of condition is excellent. However, some children may develop long-term problems. Seizures in children cause severe anxiety and panic reactions in parents; hence, clinicians should counsel and reassure parents about the benign nature of febrile seizures. Useful medications in the management of febrile seizures include antipyretics and benzodiazepines.[12] Antipyretic agents help reduce temperature but do not have a role in prevention of seizures.[12,17] Benzodiazepines i.e. rectal diazepam and buccal or nasal midazolam are useful for aborting the seizure attack.[12] Clobazam is another useful medication for intermittent therapy in children with febrile seizures.[18] Overall, febrile seizures recur in about 30% cases.[19] Continuous use of ASM for prevention of febrile seizures is not recommended.[17]

Up to 10% of patients with mesial temporal lobe epilepsy have a history of febrile seizures.[18] In such cases, ASM is useful in providing effective seizure control. Refractory cases of mesial temporal lobe epilepsy may need surgical treatment.[18]

Juvenile myoclonic epilepsy

Juvenile myoclonic epilepsy (JME) is a common type of genetic generalized epilepsy.

Seizures generally occur in the early morning after waking up or after taking a nap. Overall, it accounts for 3%-12% of adult epilepsy cases.[20] Most commonly, patients with JME have bilateral myoclonia without loss of consciousness. Most patients also present with generalized tonic-clonic seizures and some (~20-21%) have absence seizures.[21,22] JME starts at around pubertal age. Seizures are triggered by sleep deprivation and sudden arousal.[23] Alcohol is also an important trigger for the onset of seizures in patients with JME. In patients with JME, non-pharmacological as well as pharmacological treatments play an important role. Patients should be advised to have adequate sleep, maintain sleep-wake pattern, and avoid excessive consumption of alcohol. Patients with known history of photosensitivity should avoid triggering visual stimuli.[24] While selecting pharmacological treatment, efficacy as well as risk of adverse events with an ASM should be considered. Moreover, pharmacological therapy should be carefully selected in patients with JME because some drugs may aggravate seizures. For example, phenytoin and carbamazepine have been reported to aggravate myoclonic and absence seizures in patients with JME. Therefore, these two drugs are avoided in JME.[24]

Valproate is effective in JME for controlling myoclonic, absence, and generalized tonic-clonic seizures.[20] In male patients with JME, sodium valproate is the first drug of choice.[24] A retrospective study with 103 patients reported that low-dose valproate ($\leq$1000 mg/day) provides similar results of seizure freedom as high-dose valproate. Therefore, authors suggested to use low doses of valproate as initial treatment. Females contributed 54.4% to this study population.[20] In female patients, lamotrigine is preferred because of concerns related to teratogenicity, major congenital malformations, weight gain, and polycystic ovary syndrome with valproate. Data from a preliminary study suggests levetiracetam as a first line ASM during pregnancy.[25] In patients not responding to monotherapy, valproate plus small doses of lamotrigine can be effective. In patients with contraindications for use of valproate, levetiracetam may be combined with lamotrigine. Withdrawal of treatment is associated with recurrence of seizures; hence, patients with JME usually need to take continuous treatment.[24] Levetiracetam can be useful in its treatment, but psychiatric side-effects observed in 13.3% adult patients[26] is one of the limitations for the use of levetiracetam.[27]

Absence epilepsy

Childhood absence epilepsy is a common epilepsy syndrome in children. It is estimated that in children with epilepsy, approximately 10% of seizures are typical absence seizures.[28] This syndrome is characterized by specific seizure semiology.[29] These are generalized seizures with stoppage of activity for short period.[19] According to clinical characteristics and EEG, absence seizures may be typical, atypical, or with specific features. According to syndrome classification, it may be childhood absence epilepsy or juvenile absence epilepsy.[30]

Absence seizures may occur alone or may occur in children with other epileptic syndromes. Patients with absence seizures have impaired quality of life.[28] Genetic factors are considered as important cause for the occurrence of absence seizures.[28] Careful clinical history, physical examination, prolonged hyperventilation, and EEG are important in diagnosing absence seizures.[29] EEG shows generalized 3-Hz spike-and-wave pattern.[19]

The condition may be associated with significant cognitive and psychiatric comorbidities. Recognition and treatment

of these comorbidities should also be considered. The ASMs useful in the treatment of absence seizure include ethosuximide, valproate, and lamotrigine.[19,28,29] Amongst these, ethosuximide and valproate are common preferences for treatment of absence seizures.[29] Rare adverse events with use of ethosuximide include aplastic anemia, dermatological reactions, and kidney and liver impairment.[28]

Valproate has broad spectrum of efficacy, but is associated with more adverse events than ethosuximide whereas lamotrigine is less effective.[29,31] Lamotrigine can also cause serious dermatological reactions.[28] Carbamazepine, oxacarbazepine, phenytoin, and phernobarbital should be avoided in patients with absence seizures as these drugs may cause worsening of the condition. Similarly, tiagabine and vigabatrin should also be avoided in these patients.[29]

Overall, although several pharmacological options are available for the management of epilepsy in children, most seizures can be treated by oral valproic acid.[32] In addition to drug therapy, behavioral therapy can also play a significant role. Clinicians should counsel and educate parents on emergency care in seizures.

Unmet needs in the treatment of epilepsy in children

One of the important concerns for the use of ASMs is their effect on cognition-related parameters such as attention and speed of processing. Similarly, many children with epilepsy may also have cognition-related problems. It is difficult to examine the actual effects on cognition. Moreover, there is limited evidence from randomized controlled trials in this regard.[33] Differentiating effects on cognition due to disease versus drug is also difficult.

More research related to genetic predisposition, epilepsy syndromes, and refractory epilepsy is required. Despite the availability of several medicines, medication failure is still a challenge.[34] Better understanding on maximizing available resources and precision medicine for children with epilepsy is another unmet need.

EPILEPSY IN ADULTS

Epilepsy in adult patients is an important public health related concern due to burden of the problem and impact on the family and society. Generalized seizures are more common than focal seizures in adults.[35] Treatment considerations in adult patients differ from that in children and elderly.

Different factors including age, gender, seizure type, and comorbidities such as headache, migraine, and other pathologies are important while choosing the right treatment. Patients' on-going medications are also reviewed carefully. Medication should have documented efficacy and should not cause clinically important drug-drug-interactions so that better patient compliance can be achieved. Patient adherence and compliance are also important. It is important to check history of injury or any other insult that has potential to affect treatment. Individualized treatment approach by identification of the cause and seizures type is important to optimize treatment.

Many old and new ASMs are available for the treatment of epilepsy. Table 1 summarizes the choice of treatment based on epilepsy type.[36]

Table 1: ASMs recommended by type of epilepsy.

Type of seizures	ASM
Generalized onset seizures	Sodium valproate, lamotrigine, levetiracetam, topiramate
Refractory generalized onset seizures	Adjuvant treatment levetiracetam, perampanel
Focal onset seizures	Carbamazepine, gabapentin, lamotrigine, levetiracetam, oxcarbazepine, topiramate, sodium valproate, zonisamide
Focal onset refractory seizures	Adjuvant treatment Eslicarbazepine acetate, lacosamide, perampanel, pregabalin

ASM: Antiseizure medication

Sodium valproate is the first-line therapy for treatment of generalized onset seizures including tonic-clonic seizures, atypical absence seizures, and myoclonic and atonic seizures as well as focal onset seizures (Table 2).[6]

Table 2: First-line treatment options based on epilepsy subtype.

Type of seizures	First-line therapy
Tonic clonic seizures	Sodium valproate, lamotrigine, levetiracetam, topiramate
Absence seizures	Ethosuximide, sodium valproate
Atypical absence, myoclonic, atonic seizures	Sodium valproate, lamotrigine, topiramate

Despite the availability of several options, sodium valproate remains the gold standard and best antiepileptic drug for the treatment of idiopathic generalized and unclassified epilepsies in adult male patients.[37] A few studies have reported benefits of using low-dose valproate (<1000 mg/day) in idiopathic generalized epilepsy.

A study (n=54) reported control of generalized tonic-clonic seizures, JME, and juvenile absence epilepsy in 92.9%, 78.3% and 29.5% of patients, respectively. Sodium valproate also helps reduce the incidence of adverse events.[38] Because of its efficacy in migraine prophylaxis and bipolar disorder, it can be useful in patients with epilepsy having these comorbidities.[39] It is also useful in refractory generalized epilepsies. The side-effect profile of

valproate needs to be considered while using this drug in patients with epilepsy.

EPILEPSY IN WOMEN OF CHILDBEARING AGE

There are some concerns while selecting an ASM in women especially those in the child-bearing age group. With current understanding from prospective registries and meta-analyses, the risk of major congenital malformations from different ASMs and the same ASM at different dosages is known.[40,41]

The European Registry of Antiepileptic Drugs and Pregnancy with data from 42 countries compared risks associated with 8 ASMs.[42] The prevalence of major congenital malformations for valproate, phenobarbital, phenytoin, carbamazepine, and topiramate was 10.3%, 6.5%, 6.4%, 5.5%, and 3.9%, respectively. For oxcarbazepine, lamotrigine, and levetiracetam, the prevalence rate was 3.0%, 2.9%, and 2.8%, respectively.[42] Thus, according to the available evidence, sodium valproate is associated with highest risk of major congenital malformations. Low rates of major congenital malformation were seen with lamotrigine, levetiracetam, and oxcarbazepine.[40]

The risk of these malformations with sodium valproate is also dose-dependent.[40,41] Valproate at ≤650 mg/day is associated with higher risk of major congenital malformations than levetiracetam at 250-4000 mg/day.[41] Other agents such as phenobarbital, phenytoin, carbamazepine, and lamotrigine also have dose-dependent risk.[40] In adolescent females with generalized epilepsy, levetiracetam and lamotrigine may be appropriate options. If the patients have behavioral side effects with levetiracetam and lamotrigine is not suitable, then sodium valproate may be prescribed with caution. Sodium valproate should not be given if a female is planning pregnancy. Lacosamide and clobazam are good options for add-on therapy. In case of focal epilepsy, the choice of treatment can be carbamazepine, levetiracetam, or phenytoin.

EPILEPSY IN ELDERLY

Epilepsy is the third most common type of brain disease in elderly people after stroke and dementia. In most elderly patients, seizures are of focal type.[43] Epilepsy in them may be new onset or continuation from adulthood. A study reported focal onset seizures in 61.3% patients.[44] Although rare, generalized epilepsy can be seen in elderly people. Epileptic seizures may be missed in this population and/or misdiagnosed. Underlying disease of brain can cause epilepsy in elderly, which also is an important prognostic factor. Cerebrovascular disease and degenerative disease of central nervous system are important causes of epileptic seizures in elderly people. In some patients, cause may not be identified.[43] Comorbidities such as diabetes and hypertension are common in these patients.[44] Due to increased rates and age related changes such as reduced renal and liver functions, elderly patients need special attention during epilepsy management.[45] Other clinically important concerns that need to be considered include altered pharmacokinetics and risk of adverse drug reactions.[45] Electrolyte imbalance can be associated with seizures in the elderly.[46] Moreover, due to comorbidities many elderly patients may be receiving other treatments that increase the risk of drug interactions with ASMs.[45] Considering these problems, clinicians should select a drug with less adverse effects including cognition-related side effects and minimal risk of drug interactions.[45] Carbamazepine, lamotrigine, gabapentin, and sodium valproate are effective ASMs in elderly patients.[43] In a retrospective study, levetiracetam (50.4%) and phenytoin (31.1%) were the two most commonly used medications in elderly patients.[44] Reported retention rates, an important indicator of overall combined measure of effectiveness and tolerability for lamotrigine, carbamazepine, and gabapentin are 20% to 73%, 36% to 67%, and 49%, respectively.[43]

Carbamazepine has a relatively low therapeutic index and is associated with a risk of skin rashes. Moreover, it is an enzyme inducer, posing risk of drug interactions.[45] Higher dose of carbamazepine may be associated with more adverse events.[43] Hyponatremia is a known problem with the use of carbamazepine. Moreover, association between human leukocyte antigen (HLA)-B*1502 allele and serious skin reactions is included as box warning in the label of carbamazepine by the United States Food and Drug Administration.[47] Lamotrigine is also associated with risk of skin rashes. Slow and complex titration is another limitation with lamotrigine. Limitations with gabapentin include limited efficacy, need of multiple-daily dosing and renal clearance.[45] Gabapentin is associated with lower retention rate than carbamazepine and lamotrigine.[43] Sodium valproate is a good alternative in elderly patients due to several advantages including clinical experience of many years, efficacy in different seizure types including focal seizures, availability in several formulations, and ease of titration.[43,45] Drugs with longer half-life and extended release formulations allowing once daily dosage can help improve adherence and compliance to treatment.[45]

In this regard, sodium valproate chrono preparations are useful. The limitations for use of valproate include risk of adverse events such as weight gain, encephalopathy, and tremors.[45] Risk of parkinsonism is another concern for use of valproate in the elderly.[43] Levetiracetam does not have risk of clinically important drug interactions. It is not metabolized in the liver and has a favorable tolerability profile.[43,48] These advantages make it an attractive option for use in elderly patients with epilepsy.[43] Psychiatric adverse events and dose adjustment in patients with renal impairment should be considered while using levetiracetam.[45] A narrow therapeutic index and risk of drug-drug interactions are limitations for use of phenytoin in elderly patients.[48] Oxcarbazepine is also associated with risk of pronounced hyponatremia in elderly patients.[48]

Zonisamide and topiramate are associated with cognitive adverse events, renal stone, and weight reduction.[45] Clobazam is a useful adjuvant agent for treatment of refractory epilepsy. Clobazam has linear pharmacokinetics. Other pharmacokinetic advantages of clobazam include high bioavailability and minimal drug interactions with other ASMs. It has both antiepileptic and anxiolytic action.[49] Lacosamide is another useful adjuvant agent for treatment of epilepsy in the elderly.[50] Dizziness and arrhythmia are limitations for use of lacosamide.[45]

Elderly people may need low doses of ASMs to control the seizures.[44] Drugs which are excreted via renal system need dosage adjustment in elderly patients having impaired kidney function. Examples of these agents include levetiracetam, topiramate, pregabalin, gabapentin, ethosuximide, and vigabatrin.

UNMET NEEDS IN THE TREATMENT

Although several ASMs are available today, there is no significant difference in the efficacy with different monotherapies. Clinicians are still awaiting drugs with better efficacy as monotherapy. More research on prediction of patients for refractory epilepsy and alternative treatment options for refractory epilepsy is required. Similarly, there is a need for research on precision medicine in epilepsy. New antiepileptic drugs including brivaracetam and perampanel have become available for use as an adjuvant therapy in patients with focal epilepsy. However, further research on efficacy and safety of these drugs in Indian patients is required. Moreover, efforts for improving treatment gap still need to be strengthened. Lastly, coordinated efforts between pharmaceutical industry, healthcare providers, patients and their caregivers, and government will be essential to eliminate stigma associated with epilepsy and improve the outcomes of treatment.

CONCLUSION

Epilepsy is an important neurological condition across all age groups. Over the last thirty years, there has been significant progress in the availability of ASMs for the treatment of epilepsy. Clinicians should select the appropriate treatment option based on patient-related factors (e.g. age, gender, race, and comorbidities), drug-related factors (e.g. bioavailability, metabolism, excretion, risk of drug interactions, half-life, adverse effect profile, and dosage frequency), and seizure characteristics (i.e. type of seizure and seizure syndrome). Although several options are available today, valproate still remains one of the most commonly prescribed ASMs due to confidence in usage with long experience and broad-spectrum efficacy in all age groups. An important concern for its use is for females in the child-bearing age group. Levetiracetam is another popular agent because of its well tolerated safety profile. Most of the newer ASMs are useful as adjuvant treatments in patients with uncontrolled epilepsy. Clobazam is an effective initial add-on therapy, and it also offers benefit of anxiolysis.

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