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Dr. Bindu Menon

Greetings from the Editorial team!

We bring in the next issue of the EI newsletter as the monsoon welcomes us. In this issue we have for you a few focused articles that are anticipated to contribute to epilepsy care and wish to thank respective authors for the same. Dr. Rupa, has presented an over view and has discussed precipitating factors as well as the treatment options for febrile seizures one of the common types that affects children exclusively during fever. Dr. Rohit Joshi, has presented yet another spectrum of epilepsy seen in children with cerebral palsy [CP]. A link between heightened risk for epilepsy in children with CP was first recognized by Freud more than 100 years ago.

We successfully continue with the newly added section on drug corner where Dr. Rajni Rathore gives us a status on use of second generation AED - Perampanel, a non-competitive AMPA receptor antagonist. The technological advancement is an ongoing process with epilepsy being no exception, and in this regard Drug Resistant Epilepsy [DRE] continues to remain a dilemma for treating clinician. Dr. Chanda Kulkarni has briefly outlined on a novel implantable device for delivery of anti-epileptic drugs, which may give a new hope in the treatment of patients with DRE.



Dr. Sita Jayalakshmi

To continue with the treatment aspects, Ms. Shanmukhi has touched upon importance of managing psychosocial aspects as a part of comprehensive epilepsy care. She reminds us on how the magnitude of burden and stigma associated with epilepsy could be sometimes much more distressing to patients than the disorder itself!

Do we really know how the patients feel about their illness? In this regard we encourage our readers to collect patient experience stories, which will go a long way towards motivating patients to cope with epilepsy. The editorial team will also appreciate receiving contributions involving scientific writings to amplify information in the field of epilepsy for our readers.

The notice and nomination forms for the election of - President-Elect, Secretary-General, Treasurer and 5 Executive Committee Members are enclosed with this issue of Newsletter. The last date for filing nominations is November 15, 2017 and for withdrawal November 30, 2017.

This issue should arrive in your inbox just when you're preparing to meet deadlines to participate in a wide range of conferences coming up in the last quarter of 2017. Please note the announcements on upcoming national and international level conferences on the last page.

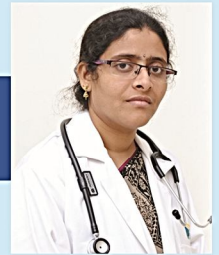
Lastly, we congratulate Dr. Satish Chandra, for the prestigious award that he has received from the government of Karnataka and wish him more success in the years to come.

We wish our readers good reading and learning.



Dr. Chanda Kulkarni

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FEBRILE SEIZURES :

Febrile seizure is a convulsive event, exclusively occurring in childhood. The international league against Epilepsy (ILAE) defines FS as “A seizure in association with a febrile illness in the absence of a CNS infection or acute electrolyte imbalance in children older than 1 month of age without prior afebrile seizures”.

BURDEN OF PROBLEM :

Febrile seizures are most common type of seizures affecting 2% to 14% of children. However they are the most benign type of all seizures occurring in childhood. The peak incidence is between 18 to 22 months of age. Incidence of febrile seizures is about 2% & 5 % in US and Western Europe, 6 % to 9% in Japan and 14% in India.

PRECIPITATING FACTORS FOR FEBRILE SEIZURES :

Three important precipitating factors for febrile seizures are :

- 1) body temperature
- 2) extra cranial infections
- 3) genetic Factors.

Seizures are usually precipitated when body temperature rises above 38°C rectally. Usually occurs during the first 24 hours of febrile illness. But in some cases seizures occur before the onset of fever. Extracranial infections like URI, Otitis media, gastroenteritis, pneumonia, UTI. Sometimes febrile seizures may occur after pertussis and measles vaccination. Genetic factors play an important role in precipitating febrile seizures. It has polygenic inheritance. Most commonly inherited as autosomal dominant inheritance. The background prevalence risk of febrile seizures rises from 1 in 30 to 1 in 5 where one sibling is affected and 1 in 3 if both parents and a previous child had febrile seizures.

Genetic epilepsies with febrile seizures plus (GEFS+) is a familial epilepsy syndrome with a wide range of fever related epilepsies described as febrile seizures plus.

CLASSIFICATION OF FEBRILE SEIZURES :

Conventionally febrile seizures have been classified as simple or complex based on duration, recurrence and presence of focal features.

SIMPLE FEBRILE SEIZURES	COMPLEX FEBRILE SEIZURES
Constitutes 80-85%	Constitute 15-20%
Generalized tonic –clonic motor activity	Focal seizures manifestations.
Seizure activity lasts for < 15 min with rapid return of consciousness	Prolonged seizure activity exceeding 15 min.
Seizure does not recur more than once within 24 hours	Recurrs for more than once within 24 hours
No postictal neurological abnormalities	Postictal neurological abnormalities may be present
Normal CNS child.	Child with cerebral palsy.
No EEG abnormalities	EEG abnormalities may be seen.
No Anti-epileptic drugs required.	Anti-epileptic drugs are usually required.

HOW TO DIFFERENTIATE FEBRILE SEIZURES FROM CNS INFECTIONS ?

A major concern in any febrile child with a seizure is the possibility of CNS infection incidence of meningitis in children with febrile seizures is about 2% to 5%.

Clinical features suggestive of CNS infection are

- 1) History of irritability, decreased feeding or lethargy.
- 2) Complex febrile seizures.
- 3) Any physical signs of meningitis or encephalitis (bulging fontanelle, neck stiffness, photophobia, focal neurological signs)
- 4) Prolonged postictal altered consciousness or neurological deficit (> 1 hr)
- 5) Incomplete immunization in children aged 6-18 months against Hemophilus influenza and streptococcus pneumoniae.

American Academy of pediatrics (AAP) suggest Lumbar puncture for infants less than 12 months and strongly recommends for infants between 12 to 18 months of age because of vague symptomatology of meningoencephalitis.

INDICATIONS FOR LP IN CHILDREN WITH FEBRILE SEIZURES

- 1) Seizures on arrival to the emergency room.
- 2) Focal seizure.
- 3) Febrile status.
- 4) Suspicious findings on physical and neurological examination.
- 5) First complex febrile seizure.
- 6) Prolonged lethargy or any altered level of consciousness after the seizure.

WHAT OTHER INVESTIGATIONS ARE NEEDED ?

No routine laboratory investigations like CBC, blood glucose or electrolytes, serum calcium levels are needed in a child with simple febrile seizures. Investigations to rule out the source of infection may be done if necessary.

Neuroimaging (CT scan Brain or MRI Brain) are not indicated in simple febrile seizures. MRI Brain is indicated in prolonged febrile seizures.

Electroencephalogram of febrile seizures or epilepsy even if the result is abnormal. Thus an EEG isography (EEG) has a limited value in the workup of FS. EEG would not predict the future recurrence of febrile seizures or epilepsy even if the result is abnormal. Thus an EEG is indicated it is delayed until or repeated after > 2 week have passed. EEG should therefore generally be restricted to special cases in

which epilepsy is highly suspected and it should be used to delineate the type of epilepsy rather than to predict its occurrence.

TREATMENT OF FEBRILE SEIZURES IN ITS ACUTE PHASE :

Febrile seizures are usually benign and self-limiting attacks (often lasting less than 10 min) and protective measures are merely required. Protect the child from injury during the seizure. Do not restrain the child or put anything in the mouth. Check the airway & place the child in the recovery position when the seizure stops. Explain that the child may be sleepy for up to an hour. Acute medications such as rectal diazepam (0.5 mg/kg) or buccal (0.4-0.5 mg/kg) or intranasal (0.2 mg/kg) midazolam administration are effective in stopping ongoing seizures. Parents should be advised to seek a medical advice if seizures last for more than 5 min.

INTERMITTENT THERAPY FOR FEBRILE SEIZURES :

Intermittent use of antipyretics such as ibuprofen or acetaminophen at the onset of fever does not prevent the recurrence of seizures but makes the child feel comfortable. Intermittent use of oral diazepam (clobazam) is proved to be effective to prevent the recurrence of seizure but AAP does not recommend it because of potential adverse effects because many cases of recurrent febrile seizures occur before the recognition of fever.

CONTINUOUS ANTICONVULSANT THERAPY FOR FEBRILE SEIZURES :

Anticonvulsants like phenobarbital and valproate have been proven effective in preventing recurrent febrile seizures in children who are at risk of developing epilepsy in the later life. But taking into consideration about the benign nature of febrile seizures long-term anticonvulsants are advised in children with febrile seizures below 12 months of age and who had multiple febrile seizures.

RISK FACTORS FOR RECURRENT FEBRILE SEIZURES:

Definite risk factors are family history of febrile seizures, age < 18 months, peak temperature, duration of fever.

RISK FACTORS FOR SUBSEQUENT EPILEPSY IN CHILDREN WITH FEBRILE SEIZURES :

Definite risk factor.

- 1) Neuro developmental abnormality
- 2) Complex febrile seizures
- 3) Family H/o epilepsy
- 4) Duration of Fever

Possible risk factor : 1) > 1 complex Feature.

PROGNOSIS AND OUTCOME :

Children with recurrent simple febrile seizure are not at risk of developing decline in IQ, learning abilities or neurocognitive abnormalities. Risk of developing epilepsy in children with H/o febrile seizures is also a concern. Risk or mortality is very less in simple febrile seizures unless the child has a febrile status.

REFERENCES:

1. Nelson text book of pediatrics 19th edition
2. Neurology research international volume 2015, article Id849341
3. Febrile seizures: risks, evaluation, prognosis ILAE-2015
4. American academy of pediatrics, subcommittee on febrile seizures neurodiagnostic evaluation-pediatrics 2011;127

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Cerebral palsy is the most common cause of physical disability in early childhood. Epilepsy is known to have a high association with cerebral palsy. All types of epileptic seizures can be seen in patients with cerebral palsy. Complex partial and secondary generalized ones are the most frequent seizure types. In persons with cerebral palsy and mental retardation, the diagnosis of epilepsy presents unique difficulties. Generally they are not able to describe the epileptic events themselves, parents are not able to describe them well and persons trained in epilepsy witness the events only rarely. Some syndromes, such as Infantile spasms, West and Lennox-Gastaut syndrome, are particularly frequent. Children with cerebral palsy are rarely free of epilepsy. It has been observed that epileptic seizures in children with cerebral palsy tend to have an earlier onset; they often appear in children with cerebral palsy and learning difficulties; they are more severe in patients with a more severe degree of cerebral palsy.

Epidemiology

In the general childhood population, the prevalence of epilepsy is between 3 and 6 per 1000. Overall, epilepsy occurs in between 15 to 55% of children and adults with CP. If learning disability coexists, the risk to children with CP is much higher, rising to 71%. Epilepsy is more common in some forms of CP than others. Although Paine found children with tetra- or triplegic CP to be among the least likely to have epilepsy, but most of the authors showed at least 50%, and up to 94% to be affected. In hemiplegic CP, at least one-third, and up to a half in some series, have continuing seizures. With spastic or ataxic diplegia, the risk is somewhat lower at 16 to 27%. With the exception of reports from Germany and Sweden, that show much higher frequencies, epilepsy is noted to complicate dystonic/dyskinetic CP in about one-quarter of cases; and seems to be only rarely associated with pure ataxic CP. Thus, those cerebral palsies with possibly the more cortical pathologies seem most likely to be complicated by epilepsy.

Predisposing factors

The increased risk of epilepsy in CP is believed to be linked to genetic and perinatal factors. First-degree relatives of children with CP and seizures have been reported to have an increased incidence of seizures. Among the perinatal factors, structural and developmental defects of the brain, chromosomal defects, intrauterine infections and hypoxic ischemic brain injuries are the more obvious causes that may result in seizures. Brain imaging may provide a clue regarding the timing and nature of the brain insult in these children.

Diagnosis of epilepsy in CP – a challenge !

It becomes very challenging in a clinical setting to elicit seizure history from the carers of the patient. They often give a poor history of seizure, mainly because they are unaware of different types and presentations of seizure activities. Parental social background, education and underlying psychiatric illness also contribute to the problem of eliciting a good history. In my practice, I am often forced to ask direct questions to the carers while taking the history and sometimes to imitate various seizure types!

Classification of the type of epilepsy is often difficult in children with CP for many reasons; firstly the partial onset prior to generalization may not be apparent or witnessed; impairment of consciousness during

ictal period may be difficult to detect in a child with severe handicaps; lastly, the differentiation between myoclonic, brief tonic and atonic seizures could be difficult without ictal EEG or video EEG.

Imaging may both identify underlying causes of neurological problems and provide information about the feasibility and practicalities of surgical treatment. MRI is the method of choice for structural lesions. A wide range of developmental and acquired lesions may be identified. Particularly for genetic and prognostic reasons, it is important that the underlying lesion is defined as completely as possible. However, the presence of an anatomical change does not necessarily mean that the precise source of epileptic seizures has been identified. Ictal SPECT can identify localized epileptogenesis within areas of cortical dysplasia. Coordination of the findings on MRS with other forms of imaging might have the potential for further identifying relevant smaller lesions within larger areas of abnormal brain. Functional MRI (fMRI) can identify focal changes, even when seizures are not clinically evident. Co-registration of functional and structural imaging can further localize lesions in the minority for whom surgery is being considered.

Epileptic seizures can take many forms. They may be difficult to distinguish from other involuntary movements, particularly in dystonic/dyskinetic or ataxic CP. In addition, children with CP may have breath-holding spells, reflex anoxic attacks, vaso-vagal syncope, and other types of non-epileptic paroxysmal disorders. Therefore it is important to consider all possible causes of sudden alterations of movement and/or consciousness before concluding that an attack is epileptic. Most difficulties arise in distinguishing tonic, atonic, and myoclonic seizures from dyskinesia, and stereotyped movement patterns sometimes seen in children with severe learning disabilities. Although an individual child may have several sorts of epileptic seizures, the pattern of each type of seizure tends to be the same each time it occurs. Video recordings of characteristic attacks can be helpful even if movement artefacts make the EEG difficult to interpret. There are also problems with taking the EEG findings in isolation: children with CP may have changes comparable with those seen in epilepsy even if no clinical seizures have occurred.

Why good seizure control is important ?

In studies on children with epilepsy and CP, the proportion of hemiplegic children with 'focal and epileptic manifestations' on EEG was higher in those without than those with clinically evident attacks: once again emphasizing the need to be cautious in interpretation of the recordings. Eighty-three percent of children with CP and epilepsy, not further defined, had interictal background abnormalities. However, the EEG findings have much wider implications than the possible diagnosis of epilepsy. Abnormal EEGs in children without CP have been correlated with poor cognitive or behavioural functioning. Continuous spike-wave activity during sleep causes abnormal cerebral glucose metabolism and loss of cognitive function: clearly it should be avoided if possible. Children with CP have high risks of learning difficulties: interictal seizure discharges may compound these.

Treatment

In most children, epilepsy will be treated with antiepileptic drugs (AEDs), but dietary therapy or surgical intervention could be relevant for some. Once seizures start in association with CP, they are likely to recur, so there is little rationale for delaying treatment, particularly if epileptic discharges are seen on the EEG. The seizure type and, if definable, the epileptic syndrome are the most important guides to the choice of treatment. With the exception of infantile spasms/West syndrome, **Sodium valproate** is a good first choice for the epilepsies which are likely to present after the neonatal period. For neonates, **Phenobarbitone** still has an

important role. Before prescribing sodium valproate for a young child with disabilities, it is essential to consider whether the child could have a metabolic disorder, especially one involving the urea cycle or carnitine metabolism or hyperglycinemia, which might be precipitated by this drug. **Carbamazepine** is useful in partial seizures. Phenytoin is difficult to use because of its saturation kinetics, and it is poorly absorbed if given orally in close association with milk or formula feeds. Lamotrigine is a good choice for treatment of epilepsies with tonic, atonic, myoclonic, or absence seizures (with the exception of severe myoclonic epilepsy in infants), but its role in symptomatic partial and generalized seizures is less convincing. Gabapentin, while possibly not as effective as some other AEDs, has a very good adverse-event profile. **Topiramate** has a good record of control of partial seizures, and with lamotrigine can prevent atonic seizures, but side-effects tend to limit its usefulness. Lethargy, anorexia, and weight loss are common and would be particularly undesirable in those with CP. Nevertheless, when tolerated, topiramate is a highly effective AED. The place of **vigabatrin** for partial seizures has been severely compromised by the recognition that up to 50% of those treated will develop concentric visual field defects. However, when partial seizures are resistant to all other drugs, vigabatrin continues to be recommended. For most people with CP, the recommendations for visual field assessments before and during treatment are impractical, but it is certainly important to consider that the CP might be additionally complicated by poor vision, and to be very cautious about the use of vigabatrin in these circumstances. Currently, information on tiagabine, remacemide, and stiripentol in CP is too limited for comment. However, stiripentol can be effective in severe myoclonic epilepsy in infancy, which may very rarely complicate CP.

The medical treatment of West syndrome deserves special comment. Before the availability of vigabatrin, adrenocorticotrophic hormones, or steroids were usually given, but their side-effects, and the temporary nature of the administration were disadvantages. Vigabatrin has been shown to be at least as efficacious, and to be associated with positive benefits on cognition and behaviour, at least in the context of tuberous sclerosis. Thus, despite the concerns about visual fields, it remains first choice therapy for West syndrome, given the proviso that considerable thought should be given to its use in those with known visual problems. Other alternatives in West syndrome are: high dose sodium valproate, lamotrigine, benzodiazepines, topiramate, and pyridoxine. These may be given singly or in various combinations. Some AEDs can make some seizures worse. In particular, carbamazepine and vigabatrin are contraindicated in myoclonic and absence seizures; and gabapentin can precipitate myoclonia. Drugs other than AEDs given to patients with CP may provoke seizures: the most important is baclofen, particularly if given in high dosage. The **ketogenic diet** is experiencing new popularity. If used, it is essential that it is supervised by a competent dietician. The diet tends to be unpalatable, can make the recipient feel ill, and can be associated with hypoglycaemia which may be sufficiently severe to be fatal. Only the most motivated of carers are likely to persist with administration of this diet, but it can be helpful when AEDs fail. **Vagal nerve stimulator** has also been found effective in certain cases.

Often polytherapy is required to control seizure. Non-convulsive status is a recognized problem which often goes unattended. A short course of steroid is sometimes effective when others have failed in such condition.

The earlier onset of seizures, coupled with the need for more prolonged antiepileptic drug therapy and the use of polytherapy will pose a significant burden on these children with CP and seizures. In spite of adequate drug therapy, poor seizure control, defined as daily or weekly recurrences in spite of adequate serum levels of appropriately used drugs is frequently seen. In particular, children with Spastic Quadraplegia more often needed polytherapy, require 3 or more anticonvulsants and despite which some had refractory seizures. This may be due to the more extensive brain pathology seen on brain imaging in this group of children.

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‘Polymer Implants’ – A New Hope for Treating Drug Resistant Epilepsy [DRE]!

Epilepsy affects 1% of world’s population and there are estimated 10 million people with epilepsy [PWE] in India. Epilepsy is one of the most common neurological disorders often requiring long term treatment with anti-epileptic drugs [AEDs]. In 1990 only half a dozen drugs were available for treatment now called as older AEDs or First generation AEDs. During the last decade more than 15 newer drugs have been released by US-FDA and are categorized under newer AEDs [Second and Third generation AEDs].

Need for new AEDs was based on the fact that, older drugs are known to effectively suppress seizures in majority of the patients, but are frequently associated with a wide range of side/adverse effects, drug-drug interactions, need for their therapeutic drug level monitoring and problems associated with medication adherence. It is reported that around 20-40% patients have medically refractory drug resistant epilepsy [DRE].

Several drug/non-drug related factors are reported to contribute in development of DRE such as - inadequate dosage, patient non-compliance, wrong choice of AED, alteration in drug targets rendering them ineffective, misdiagnosis and people with severe forms of epilepsy with frequent seizures. Failure of AEDs to reach their target site of action is one of the drug related factors responsible for medically refractory epilepsy. A series of articles by Patrick Kwan, as the Theme Editor, for ‘advanced drug delivery reviews’ including the dedicated theme issue focused on ‘anti epileptic drug delivery’ reports on the involvement of various pharmacological properties of AEDs contributing to DRE like – absorption, distribution, metabolism and excretion. The author also emphasizes on novel systems for delivery of AEDs primarily targeted to include bypassing intestinal metabolism and delivering more predictable doses. [Preface, by **Larry Baum**, as Theme Editor] [1]

Anderson and Saneto have explored evidence for using intravenous, intramuscular, intranasal, and rectal route of administration of AEDs in emergency treatment of convulsive status epilepticus [SE] when oral route of administration of AEDs is not feasible. In addition rapid absorption of AEDs by non-oral routes like buccal

of administration of AEDs is not feasible. In addition rapid absorption of AEDs by non-oral routes like buccal and sublingual particularly in cooperative patients has been reported to be effective. An auto-injector containing 10 mg DIAZEPAM is available for administration by intramuscular [IM] route in US military for treatment of SE and severe recurrent seizures.

Further, a recent ‘transporter’ hypothesis proposed for drug resistance indicates that efflux drug transporter proteins are over-expressed at the blood-brain barrier in patients with DRE, thus preventing adequate concentration of AEDs at the seizure focus. Such transporter proteins involved in the brain that are most studied include – P-glycoprotein (P-gp or ABCB1), multidrug resistance-associated proteins (MRPs) and breast-cancer resistance protein (BCRP or ABCG2). Hence, inhibition of P-gp, down regulation of P-gp expression, inhibition of epilepsy related up-regulation P-gp and use of drug delivery systems that can bypass the blood brain barrier are possible strategies that are proposed to overcome the transporter mediated drug resistance. The examples of alternate delivery systems that are currently under investigation are polymer implants (Poly (lactic-co-glycolic acid) loaded with AEDs inserted into the seizure focus. This is one of the emerging techniques reported to gradually release AED over extended period. Advantage of such implants would be escape of drugs from proteins as this mode of drug delivery bypasses the gut and the blood brain barrier; thereby improving drug availability to achieve optimal concentrations at the site of action and reduced side effects.

In summary authors say while oral route is the most frequent, the intramuscular, intravenous, and rectal routes of administration of AEDs are used in emergencies or when patient is unable to swallow. The buccal and sublingual routes are used rarely.

Therefore, the recent work is focused to overcome AED resistance, using biodegradable polymer brain Implants thereby bypassing their metabolism. This route is under evaluation for targeted and controlled AED delivery which may soon bring in new hope for patients with DRE.

Reference :

1. **Larry Baum [Theme Editor]** Preface - Advanced Drug Delivery Reviews 64 (2012) 885–886.

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Persons with epilepsy (PWE) most often have associated psychological, psychiatric and social issues. In fact, a high number of PWE have depressive illness and psychosis. They also have negative social skills and impaired coping mechanisms. Unemployment and higher anxiety states are more frequent for women with epilepsy as compared to men with epilepsy. Women with epilepsy also have more difficulty finding life partners and have higher rate of divorce compared with males. Women with epilepsy rarely use constructive coping methods, and thus have poor psychosocial status and adjustment within the family and society.

Epilepsy affects 50 million people worldwide. Early signs in childhood may be cognitive delay, speech difficulties, language difficulties or learning disabilities. With increasing age, PWE commonly have multiple psychological, psychiatric and social problems due to their illness (1) and also due to medication. PWE frequently have poor knowledge of epilepsy; and therefore are more prone to having low self-esteem, feel stigmatised by the society and develop social maladjustment. These issues may be due to attitude and perception of the society.

Twenty-five percent of adults with epilepsy describe social stigma as a result of epilepsy. Adults with epilepsy fear rejection from their peers and from other people. Adolescents with epilepsy report more depression, anhedonia, social anxiety and obsessive symptoms than patients in general population of same age group. They have low self-esteem; often associated with higher seizure frequency. There are significant negative attitudes in the adolescent public globally worldwide, resulting in loneliness and social avoidance in school. Moreover, employability of adolescents with epilepsy is influenced by the frequency and severity of seizures, age at onset, interseizure psychosocial disabilities including self-esteem, personality, and problem-solving style and social discrimination. (2)

One study reported that social skills are inversely proportionate to depression and negative social skills are inversely associated with anxiety. (3) Important predictors of good outcome are good quality of life at the beginning and few side effects of therapy. Significant predictors of poor outcome were poor health perception and presence of depression. Different types of epilepsy can present with different types of psychiatric disorders. Patients who suffer from juvenile myoclonic epilepsy tend to have anxiety and mood disorders. (3) Patients with mesial temporal sclerosis more commonly have psychotic disorders. (3)

Among adults with epilepsy, worsening anxiety is more frequent for women with epilepsy and more mood disorders and social problems in comparison to male patients. Women with epilepsy have more comorbidities. Female patients with epilepsy have more difficulty finding life partners compared with male patients. In a study in India, female patients with epilepsy in India between 15-40 years old had little quality of life. (2) Female patients have more difficulty finding life partners and have higher rate of divorce compared with males. Women with epilepsy rarely use constructive coping methods and they use less problem solving techniques. (2) As a result there is poor psychosocial status and adjustment within the family and society. Epilepsy and the anticonvulsant therapy have effect on female reproductive function such as menstruation and fertility. In another recent study in India, 38.4% of 375 women with epilepsy had infertility. (4) The most common causes of infertility were treatment with numerous antiepileptic drugs, older age, and lower education. (4)

Management of psychosocial problems in PWE includes adequate counseling therapy. Social support through support groups, is beneficial to improve social integration. These groups can provide resources for the patient in helping them communicate with the society.

Psychosocial interventions are important for PWE. Psychosocial interventions are useful to increase self-mastery and promote positive adjustment to a diagnosis, which therefore will improve the patients' quality of life. Educational intervention can lead to improvement in knowledge of illness and attitude to the disease with statistical significance. To assist people with epilepsy, treating neurologists/physicians should be aware of social resources and social welfare systems that are available for the patients.

References

- [1] Maree L Hackett, Nicholas S Glozier, Alexandra L Martiniuk, Stephen Jan, Craig S Anderson. Sydney epilepsy incidence study to measure illness consequences: the SESIMIC observational epilepsy study protocol. BMC Neurol. 2011; 11: 3.
- [2] Gopinath M, Sarma PS, Thomas SV. Gender-specific psychosocial outcome for women with epilepsy. Epilepsy Behav. 2011 Jan;20(1):44-7.
- [3] Ma TM, Hou WK, Hung A, Lee TM. Personality traits and social behaviors predict the psychological adjustment of Chinese people with epilepsy. Seizure. 2010 Oct;19(8):493-500.
- [4] Sapna Cheravallloor Sukumaran, P. Sankara Sarma, Sanjeev V. Thomas. Polytherapy increases the risk of infertility in women with epilepsy. Neurology. 2010;75:1351-1355.

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PERAMPANEL CURRENT STATUS

Perampanel is a first-in-class selective noncompetitive AMPA receptor antagonist shown to be effective as adjunctive treatment for partial-onset seizures. Perampanel— 2-(2-oxo-1-phenyl-5-pyridin-2-yl-1,2 dihydropyridin-3-yl) benzonitrile hydrate (4:3) or benzonitrile, 2-(1',6'-dihydro-6'-oxo-1'-phenyl[2,3'-bipyridin]-5'-yl)—was discovered and developed by Eisai Laboratories. In July 2012, perampanel was granted market authorization by the European Commission as an adjunctive treatment for partial onset seizures with or without secondarily generalized seizures in patients with epilepsy who are aged 12 years and older. [1] In India, CDSCO approved Perampanel on 02.12.2016 for the adjunctive treatment of partial-onset seizures with or without secondarily generalized seizures in patients with epilepsy aged 12 years and older.

PHARMACOLOGY AND PHARMACOKINETICS

Perampanel is an orally active, non-competitive, and selective alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) glutamate receptor antagonist. Perampanel is a structurally distinct non-competitive AMPA receptor antagonist which inhibits AMPA-induced increase in intracellular Ca^{2+} and selectively blocks AMPA receptor-mediated synaptic transmission, thus reducing neuronal excitation to exert anti-epileptic activity. This antagonistic action prevents AMPA receptor activation by glutamate and results in the inhibition of neuronal excitation, repetitive neuronal firing, and the stabilization of hyper-excited neural membranes. Perampanel inhibits AMPA-induced increase in intracellular Ca^{2+} and selectively blocks AMPA receptor-mediated synaptic transmission, thus reducing neuronal excitation. It also acts at the N-methyl-D-aspartate (NMDA) and the kainate receptors in the excitatory postsynaptic membranes of the neurons, though the principal ionotropic glutamatergic receptor activity involves AMPA. [2]

Perampanel is rapidly absorbed after oral administration and almost completely absorbed, with peak plasma concentrations reaching at 15 minutes to 2 hours after oral dosing. Food slows the rate of absorption but does not affect the extent of absorption. There is a negligible first-pass metabolism, and it is slowly eliminated with a steady-state plasma concentration apparent after 2 weeks. The elimination half-life is long, estimated around 70 hours, allowing a once-daily regimen. [2, 3] It is primarily eliminated by hepatic oxidative metabolism via oxidation and sequential glucuronidation. Perampanel is 95% bound to plasma proteins and is extensively metabolized. About 70% of the dose is excreted in the feces whereas less than 2% is excreted

unchanged in the urine. Perampanel is oxidized into a dihydrodiol metabolite and an N-acetyl cysteine conjugate by CYP3A4 and CYP3A5 and is then excreted as glucuronidated metabolites; about 50% of perampanel is excreted unchanged. It does not function as an enzyme inducer or inhibitor.

Carbamazepine, phenytoin, and oxcarbazepine may induce perampanel metabolism, and higher perampanel doses may be required. It also decreases levonorgestrel concentrations and patients may require additional nonhormonal forms of contraception while taking perampanel.

ADVERSE REACTION AND DRUG INTERACTION

Most common adverse events were CNS-related symptoms dizziness, drowsiness, blurred vision, imbalance, somnolence, vertigo, aggression and anger, loss of coordination, irritability and slurred speech. These symptoms are more common at higher doses. Other Special adverse events reported are unexplained falling, particularly in the elderly and psychiatric symptoms. Perampanel labeling includes a warning for possible psychiatric symptoms: aggression, hostility, unusual changes in mood, personality, or behavior, and other behavioral symptoms such as homicidal ideation and threats. Development of rashes is rare. Perampanel is liable to be abused; very high doses produced euphoria with responses similar to ketamine, although subjects liked it less and had experienced it more negatively than ketamine; it produces dissociative effects similar to ketamine. Perampanel has a black box warning noting that some people taking the drug have undergone serious psychiatric and behavioral changes.

DOSAGE AND ADMINISTRATION

Perampanel is commercially available in round, biconvex, film-coated tablets. Tablet strengths include 2, 4, 6, 8, 10, and 12 mg formulations. Maximum frequency for dosage increases is every 2 weeks starting at 2 mg/day. There are no adequate and well-controlled studies in pregnant women, and perampanel is rated as Category C. Patients older than 12 years of age may be dosed as adults. In dose-ranging studies, 2-12 mg of active drug per day has been evaluated. A minimal effective dose of 4 mg and a plateau in efficacy is observed at 8 mg daily. Doses of 4-12 mg/day are reported to be well tolerated both once and twice daily.

PATIENT PERSPECTIVE

Perampanel is a new type of anti epileptic drug with an encouraging clinical profile based upon a design that inhibits excitatory amino acids that are linked to epileptic seizure generation and spread.[4] Unique theoretical concerns for perampanel include behavioral and psychiatric side effects because of the drug's mechanism of action (similar to phencyclidine). The use of perampanel should be monitored to assess patients for temporal signs of anger; aggression; unfavorable changes in mood, personality or behavior; and

other behavioral symptoms, including the emergence of suicidal thoughts or gestures. Perampanel should be reduced if this occurs; if symptoms are severe or are worsening, then it should be discontinued immediately. Withdrawing the drug is reported to produce no unexpected withdrawal-like symptoms, though abrupt discontinuation may increase seizure frequency. Patients need be advised not to drive or operate machinery until sufficient experience on perampanel has been attained, especially when co administered with other central nervous system (CNS) depressant medications, including alcohol. In the absence of co administered enzyme-inducing antiepileptic drugs, the recommended initial starting dose is 2 mg orally at bedtime (4 mg with enzyme-inducing antiepileptic drugs). This may be increased by 2 mg/day every week to a total of 4 to 8 mg/day. The maximum recommended daily dose is 12 mg at bedtime. Laboratory testing, changes in vital signs, and altered cardiac function noted on EKG

parameters have not been observed; therefore, seizure control is indicative of efficacy and routine serologic monitoring is not required. The FDA has recommended that perampanel be classified as a scheduled drug with a potential for abuse or addiction. Side effects include irritability, aggression, anger, anxiety, paranoia, euphoric mood, and agitation. Serious or life-threatening psychiatric and behavioral adverse reactions have been reported in patients taking perampanel. [5]

CURRENT CLINICAL RECOMMENDATIONS

Clinical recommendations are based on literature review and on the clinical expertise of the panel members. The main pros and cons of the use of perampanel in paediatric epilepsies are summarized in Table 1

Main advantages and disadvantages for the use of perampanel in childhood epilepsies

ADVANTAGES	DISADVANTAGES
Proved effectiveness in partial onset and primarily generalized seizures	Possible interaction with enzyme inducing AEDs
Favourable cognitive profile	Possible psychiatric adverse events
Single daily administration	-
Overall good risk/benefit ratio	-

According to the clinical experience of the panel members, the rate and severity of adverse events, including psychiatric symptoms, can be decreased by starting at low doses, and titrating slowly. Furthermore, slow titration could also allow an assessment of clinical efficacy of perampanel at low dosages. The risk of some adverse events, such as dizziness, is lower taking perampanel at bedtime. The favorable cognitive profile,

ease of use of the titration scheme and once-daily formulation offer advantage over other AEDs and make this drug particularly suitable for adolescent population.[6]

CONCLUSION

Perampanel is the first AMPA-receptor antagonist marketed for the treatment of partial onset seizures with or without secondary generalization. Its efficacy in clinical trials is similar to that of AEDs approved for use in the past decade. The proportion of patients rendered seizure-free in the clinical trials was about 7%, which is also in line with data from drug trials of other AEDs. Thus, perampanel does not appear to confer significantly better seizure control than other AEDs available in the US and EU. Perampanel is considered a safe drug with an acceptable tolerability profile. The most common side effects are well-known to physicians using AEDs, and include the usual suspects such as dizziness, somnolence, headache, and fatigue. Anxiety and irritability may be seen in some patients taking perampanel, but there was no evidence of increased risk for suicidality, psychosis, or major depression. With this efficacy and side-effect profile, perampanel promises to be a useful drug for treating patients with epilepsy.

REFERENCES

1. Zaccara G, Giovannelli F, Cincotta M, Iudice A. AMPA receptor inhibitors for the treatment of epilepsy: The role of perampanel. *Expert Rev Neurother* 2013;13:647-55.
2. Ceolin L, Bortolotto ZA, Bannister N, Collingridge GL, Lodge D, Volianskis A. A novel anti-epileptic agent, perampanel, selectively inhibits AMPA receptor-mediated synaptic transmission in the hippocampus. *Neurochem Int* 2012;61:517-22.
3. Templeton D, Ferry J. Pharmacokinetics of perampanel, a highly selective AMPA-type glutamate receptor antagonist. *Epilepsia* 2009;50:98-9.
4. Rogawski MA, Hanada T. Preclinical pharmacology of perampanel, a selective non-competitive AMPA receptor antagonist. *Acta Neurol Scand Suppl* 2013:19-24.
5. Shih JJ, Tatum WO, Rudzinski LA. New drug classes for the treatment of partial onset epilepsy: Focus on perampanel. *Ther Clin Risk Manag* 2013;9:285-93.
6. Paola De Liso, Romina Moavero, Giangennaro Coppola. Current role of perampanel in pediatric epilepsy. De Liso et al. *Italian Journal of Pediatrics* 2017; DOI 10.1186/s13052-017-0368-6.

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Well-done and heartiest congratulations to Dr. Satish! on be-half of all the members of Indian Epilepsy Association [IEA] and Indian Epilepsy Society [IES].





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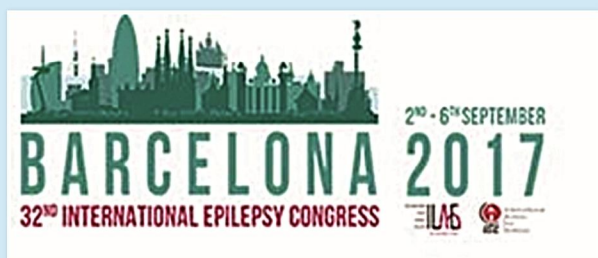
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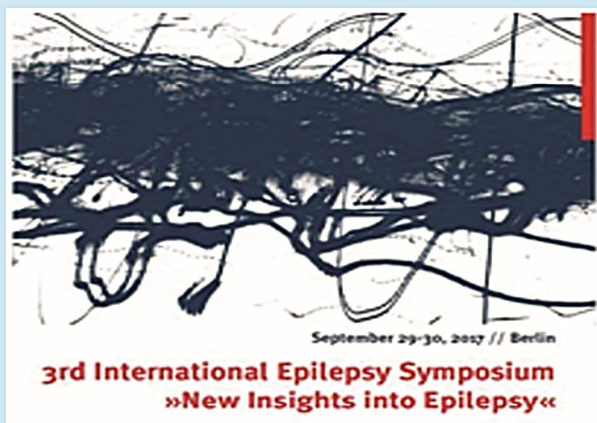


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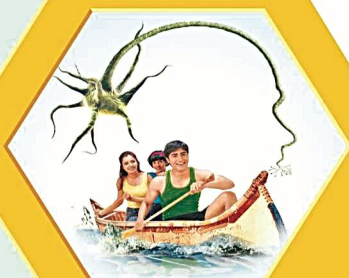


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