

NI Feature: The Quest

COMMENTARY

Access this article online
Quick Response Code:

Website: www.neurologyindia.com
DOI: 10.4103/neuroindia.NI_1070_16

Recent advances in Epilepsy Research in India

Aparna B Dixit¹, Jyotirmoy Banerjee¹, P Sarat Chandra², Manjari Tripathi³

Abstract:

There are more than 10 million persons with epilepsy (PWE) in India. Despite availability of antiepileptic drugs (AEDs), there is a large treatment gap varying from 50 to 70% among PWE. For treatable epilepsy, this gap can be attributed to poor education, poverty, cultural beliefs, stigma, and poor healthcare infrastructure; whereas for chronic epilepsy, this gap can be attributed to lack of proper diagnosis and treatment. To prevent, treat, and cure epilepsy, researchers worldwide have made exciting advances across all areas of epilepsy research. Studies carried out in India have also shown substantial progress; however, most of them are focused on the epidemiological aspects of epilepsy, genetic associations, identification, and validation of new AEDs in animal models of epilepsy. Very few studies are reported on understanding the process of epileptogenesis, a dynamic process by which neurons begin to display abnormal firing patterns that cause epileptic seizures. Animal epilepsy models can be used for in depth studies; however, studies conducted on resected brain tissues from epilepsy patients are clinically relevant. Finally, more funding support from government and collaborations among basic research institutes, medical institutes, as well as industries is required to raise the standards of epilepsy research in India. This review focuses on the evaluation of the current status of epilepsy research in India and the need to identify potential anti-epileptogenic interventions.

Key Words:

Antiepileptic drugs, biomarkers, epilepsy, epileptogenesis

Key Messages:

In India, substantial progress has been made on the epidemiological aspects of epilepsy, genetic associations, identification, and validation of new antiepileptic drugs; however, research focusing on understanding of the process of epileptogenesis to identify new drug targets is still in its infancy and demands more attention.

Epilepsy is one of the most common neurological diseases causing significant medical and social morbidity. Epilepsy is characterized by recurrent, usually unprovoked, epileptic seizures, as well as by the cognitive, psychosocial, and social consequences of this condition.^[1,2] The disturbances of neuronal activity that occur during seizures may result in strange sensations, emotions, and behaviors. They may also sometimes cause convulsions, abnormal movements, and loss of consciousness.^[3] There are 50 million people living with epilepsy worldwide, and most of them reside in developing countries. It is estimated that there are more than 10 million persons with epilepsy (PWE) in India. Its prevalence is approximately 1% of our population and is higher in the rural (1.9%) compared with the urban population (0.6%). The burden of epilepsy, as estimated using the

disability-adjusted life years (DALYs), accounts for 1% of the total burden of disease in the world. This does not take into account the morbidity caused by social stigma and isolation, which PWE in our country face; this in turn leads to escalation of the disease burden.^[4] The disorders affect both male and female subjects and can develop at any age. Despite advances in epilepsy treatment, a large treatment gap exists in India, which can be attributed to the lack of knowledge of antiepileptic drugs (AEDs), poverty, cultural beliefs, stigma, poor health care infrastructure, and shortage of trained professionals. The annual economic burden of epilepsy in India is 88.2% of the gross national product (GNP) per capita and 0.5% of the GNP.^[5]

On the basis of etiology, epilepsy can be divided into three major categories: Idiopathic, symptomatic, and cryptogenic. Idiopathic epilepsies are generally thought to arise from

This is an open access article distributed under the terms of the Creative Commons Attribution-NonCommercial-ShareAlike 3.0 License, which allows others to remix, tweak, and build upon the work non-commercially, as long as the author is credited and the new creations are licensed under the identical terms.

For reprints contact: reprints@medknow.com

¹Center of Excellence for Epilepsy, A joint NBRC-AIIMS Collaboration, NBRC, Manesar, ²Department of Neurosurgery, ³Department of Neurology, AIIMS, New Delhi, India

Address for correspondence:

Prof. Manjari Tripathi, Department of Neurology, AIIMS, New Delhi - 110 029, India.
E-mail: mtipathiaiims@gmail.com

How to cite this article: Dixit AB, Banerjee J, Chandra PS, Tripathi M. Recent advances in Epilepsy Research in India. *Neurol India* 2017;65:S83-92.

genetic abnormalities; symptomatic epilepsies arise from the effects of an epileptic lesion, which could be focal, such as a tumor, or a defect in metabolism; cryptogenic epilepsies involve a presumptive lesion that is difficult to uncover during evaluation.^[6] The symptoms vary considerably from one person to another. In some cases, people experience a type of seizure complex called status epilepticus. These are defined as seizures that last for more than 5 minutes or seizures that recur without recovery of consciousness. Prolonged status epilepticus can damage the brain and may be life-threatening.^[7] Infectious diseases play an important role in the development of seizures and on the long-term burden causing both new-onset epilepsy and status epilepticus. It is estimated that nearly 2–3 lakh patients may die due to epilepsy if they remain untreated.^[7]

Despite the availability of a range of AEDs, approximately three-quarters of the individuals diagnosed with epilepsy continue to experience seizures; such epilepsy is referred to as pharmacoresistant epilepsy (PRE).^[8] A small proportion of the PRE patients undergo therapeutic resection of the epileptogenic zone (EZ). Accurate localization of the EZ is an important issue in epilepsy surgery because EZ is not discrete and focal, rather the epileptogenic networks can spread ictal activity to different regions of the brain. To decipher the molecular-clinical mechanisms underlying epilepsy, including PRE, it is necessary to understand the dynamic process of epileptogenesis.^[9] Brain insults such as traumatic brain injury (TBI), ischemic stroke, intracerebral hemorrhage, infections, tumors, cortical dysplasia, several neurodegenerative diseases, and prolonged acute symptomatic seizures such as complex febrile seizures or status epilepticus^[10] can induce “epileptogenesis,” a process by which normal brain tissue is transformed into tissue capable of generating spontaneous recurrent seizures. Epileptogenesis is a dynamic process and can recruit distantly connected areas in a cascade of spreading activity from the central epileptogenic focus outward through both normal and abnormal brain tissues to different parts of the brain.^[11] Thus, the process of epileptogenesis itself may lead to the development of pharmacoresistant epilepsy. Numerous reports on epileptogenic process have been published in recent years to understand the different stages involved in the process. A study reported that a potential epileptogenic insult leads to prolonged high rates of nonlinear dynamical regimes of intermittency type as the hallmark of epileptogenesis.^[12] Another study reported antiepileptogenic repair of excitatory and inhibitory synaptic connectivity after neocortical trauma.^[13] Studies show the common mechanisms underlying epileptogenesis and the comorbidities of epilepsy.^[14] Several studies at molecular level have identified antiepileptogenic targets. mTOR pathway inhibition has been proposed as a new therapeutic strategy in epilepsy and epileptogenesis.^[15] Regulation of the cell surface expression of chloride transporters have been associated with epileptogenesis.^[16] Synaptic vesicle glycoprotein 2A (SV2A) have been shown to regulate kindling epileptogenesis via GABAergic neurotransmission.^[17] Recently, LAU-0901 was identified as an antiepileptogenic drug which antagonises platelet-activating factor receptor (PAF-r), mitigating dysfunctional epileptic neuronal circuits and dysmorphic dendritic spines.^[18] Many groups are focusing on the development of better model systems to understand the process of epileptogenesis. A refined model of acquired epilepsy for the identification and validation of biomarkers of

epileptogenesis have been developed in rats.^[19] A recent study used multimodality imaging to assess the blood–brain barrier impairment during epileptogenesis.^[20] Early recognition and intervention in the epileptogenic process could prevent the development of chronic epilepsy/PRE in patients with epileptic seizures. Many studies in various aspects of epilepsy including PRE have been reported from different parts of India; however, most of them have examined the association of genetic variants, efficacy of already existing AEDs, or identification of new AEDs. Very few studies have focussed on understanding the process of epileptogenesis, identifying the patients at risk for chronic epilepsy, and finding new treatment options to prevent chronic epilepsy in these patients. In this review, we have provided an overview of the recent advances in different areas of epilepsy research in India. We have also proposed that more studies should be conducted on the valuable human brain tissues to identify new drug targets with antiepileptic or disease modifying effects.

Research Progress in Epilepsy

Indian Epilepsy Association (IEA) affiliated to International Bureau of Epilepsy (IBE), and Indian Epilepsy Society (IES) affiliated to International League Against Epilepsy (ILAE), are the two major epilepsy societies in India. IEA and IES consist of medical doctors and professionals from the fields of epilepsy. The role of IEA and IES is to form a task force to liaise with traffic authorities, public health officials, epidemiologists, and importantly, sister organizations, such as the Indian Academy of Paediatrics and Indian Medical Association, with the aim of preventing epilepsy. There are four medical institutes in India, All India Institute of Medical Sciences (AIIMS), New Delhi, National Institute of Mental Health and neurosciences (NIMHANS), Bengaluru, Sree Chitra Tirunal Institute for Medical Sciences and Technology (SCTMIST), Thiruvananthapuram, and Christian Medical College (CMC), Vellore, that are extensively involved in clinical as well as basic epilepsy research.

Research progress in the causes of epilepsy

Several studies have reported the existence of various forms of epilepsy associated with different causes in India, including symptomatic epilepsy, idiopathic epilepsy, partial generalized seizures, and the unclassified type of epilepsy.^[21] Many case control studies in India have found febrile seizures, head injury, developmental delay, as well as family history of epilepsy, birth by complicated delivery, and neonatal seizures to be significant risk factors.^[21]

Role of infections

The central nervous system (CNS) infections are a major cause for acute symptomatic epilepsy. Seizures are not uncommon in patients with human immunodeficiency virus (HIV) infection, tuberculous meningitis, rabies, Japanese B encephalitis, and malaria. Neurocysticercosis (NCC) is the most severe form of cysticercosis in which cysts develop in the CNS. Most of the recent research is focused on NCC-associated epilepsy. It was estimated that in 2011, human NCC-associated active epilepsy caused an annual median loss of Rupees 12.03 billion with losses of Rupees 9.78 billion from north India and Rupees 2.22 billion from south India. The results indicate that human NCC causes significant health and economic impact in India.^[22]

Role of genetic variants

Large number of studies published in recent years in India have focussed on the identification of the association of genetic variants with epilepsy. Past research work has shown an association of hot water epilepsy (HWE) with family history, and two loci for HWE at chromosomes 10q21.3-q22.3^[23] and 4q24-q28^[24] were identified. Exome sequencing suggested *EAT3* or *SLC1A1* gene, a glutamate transporter gene, as the causative gene. Studies have shown association of *KCNQ3* and *hSKCa3* genes, absence of *GABRA1* Ala 322Asp mutation, association of *KCNQ3* gene in juvenile myoclonic epilepsy and polymorphisms in *BRD2*, and *LGI4* as risk factors for juvenile myoclonic epilepsy.^[22] *Reelin (RELN)*, located on human chromosome 7q22, is considered to be a potential candidate gene for childhood epilepsy. In a study conducted in West Bengal, India, 63 patients with childhood-onset epilepsy and 103 healthy controls were recruited. Case-control analysis revealed significant over-representation of G/C and G/C + C/C genotypes, and C allele of exon 22 G/C marker (rs362691) in cases compared to controls.^[25] Recently toll-like receptor-4 polymorphisms and serum matrix metalloproteinase-9 were identified in newly diagnosed patients with calcified NCC and seizures.^[26] In our recent report, we did not find mutations in *GABRG2* receptor gene as a major factor in the pathogenesis of mesial temporal lobe epilepsy (TLE) in the Indian population.^[27] Samanta *et al.*, reported epilepsy with *PCDH19* mutation that was masquerading as benign partial epilepsy in infancy.^[28] A recent study shows the genetic association of *KCNJ10* rs1130183 with epilepsy; and, the computational analysis of the deleterious nonsynonymous single nucleotide polymorphisms (SNPs) of *KCNJ10* gene also showed association with seizure susceptibility.^[29] Gupta *et al.*, studied the association of 1q44 microdeletion in hemiconvulsion-hemiplegia-epilepsy (HHE) syndrome and reported that HHE may be a chance co-occurrence.^[30] Another study revealed that pyridoxine-dependent epilepsy is associated with antiquitin deficiency mutation in the *ALDH7A1* gene.^[31] Srikumar *et al.*, explored the structural insights on human laforin mutation K87A in Lafora disease, and identified that the flexibility of K87A mutated laforin structure, with replacement of acidic amino acid to aliphatic amino acid in the functional carbohydrate binding module (CBM) domain, have more impact in abolishing glycogen binding that favors Lafora disease.^[32] Dubey *et al.*, identified and characterized novel splice variants of the human *EPM2A* gene mutated in Lafora progressive myoclonus epilepsy. They identified three novel *EPM2A* splice variants with the potential to code for five distinct proteins in alternate reading frames and suggested that alternative splicing could possibly be one of the mechanisms by which *EPM2A* may regulate the cellular functions of the proteins it codes for.^[33] Ring chromosome 20 [r(20)] manifests as a refractory epilepsy syndrome with complex partial seizures (CPS), nocturnal frontal lobe seizures, and nonconvulsive status epilepticus (NCSE) in a majority of cases.^[34]

A meta-analysis by Kukreti *et al.*, indirectly suggests a possible role of the *ABCC2* transporter at the blood-brain barrier in altered drug response in people with epilepsy.^[35] This study warranted further studies in different ethnic groups to investigate the effects of the *ABCC2* haplotypic variants and perform stratified analysis on the basis of different phenotypic

covariates. In another study, the same group reported genetic contribution of *CYP1A1* variant on treatment outcome in epilepsy patients and indicated that rs2606345 influences drug response in women with epilepsy by lowering *CYP1A1* expression.^[36]

Pharmacoresistant epilepsy

Patients are said to have PRE if they failed two or more AEDs used in their appropriate, adequate dosage, combinations, and in appropriate indications after an adequate duration of treatment (not more than 2 years) in adult patients (16 years and above). In pediatric patients, diagnosis of PRE should be made much earlier (sometime even within weeks of onset of seizures), particularly if they present with epileptic encephalopathy, infantile spasms, catastrophic onset of epilepsy, seizure frequency of >1 month, and disabling seizures. Our earlier reports indicate that, in north India in the intractable group, 83% of patients had partial seizures, and 7% had generalized onset. The significant predictors of intractability are radiological evidence of structural cerebral abnormality, nonresponse to first AED, delayed milestones, high initial seizure frequency of more than one per month, partial seizure type, age of onset before 14 years, and febrile convulsions. The most common radiological features in the intractable group are known epileptogenic structural abnormalities such as mesial temporal sclerosis, dysembryoplastic neuroepithelial tumor, and perinatal hypoxic ischemic brain injuries.^[37]

Research progress in the diagnosis of epilepsy

The diagnosis and management of PWE are based on the accurate historical description of the ictal event. An accurate description helps in correctly classifying the seizure type and epilepsy syndrome. It also guides the physician in starting the appropriate AED for the PWE. In patients with drug-resistant epilepsy, the description of semiology also helps in the lateralization and localization of the possible ictal onset zone. The gold standard for determining semiology is the video electroencephalogram (EEG) recording, and several studies have focused on the accuracy of investigations such as EEG, ictal single-photon emission positron computed tomography (SPECT), and positron emission tomography (PET). We recently systematically evaluated the accuracy of home videos in assessing the semiological signs in PWE. India has the second largest percentage of mobile phone users, and this valuable tool had never before been evaluated for assessing PWE (http://en.wikipedia.org/wiki/List_of_countries_by_number_of_mobile_phones_in_use).^[38] The results of our study show that the widespread availability of mobile phones, even in the rural areas of the country, can be harnessed to capture seizures and classify epilepsy accurately. This will have long-term implications for patient management as well as for clinical research of PWE in India. In one of our cross-sectional studies, we have assessed the impact of clinical epilepsy severity and pretreatment hypsarrhythmia severity on epilepsy and cognitive outcomes in treated children with West syndrome. We have reported that the Kramer Global Score ≤ 8 and Early Childhood Epilepsy Severity Score (E-Chess) ≤ 9 in the past 1 year were associated with a favourable epilepsy outcome but not with the neurodevelopmental or motor outcome.^[39]

Recently Mahale *et al.*, reported that predictive factors for acute seizures are altered mental status (GCS <8), focal deficits, hemorrhagic infarct, involvement of frontal lobe, and superior sagittal sinus with high D-dimer levels.^[40] Datta *et al.*, performed multiparametric magnetic resonance imaging (MRI) studies of hippocampus and amygdalae in temporal lobe epilepsy (TLE) and suggested that rapidly measurable single-slice parameters (Hippocampal angle [HA], parahippocampal angle [PHA], medial distance ratio [MDR]) can readily delineate TLE in a time-constrained clinical setting, which contrasts with customary three-dimensional hippocampal volumetry that requires many slice computation.^[41] We have published a screening tool to identify surgical candidates with drug refractory epilepsy in resource-limited settings. Using the best available evidence, we have developed a decision-making tool which can provide a comprehensive quick guide for determining candidacy for epilepsy surgery evaluations in resource-limited settings.^[37]

Research Progress in the Treatment of Epilepsy

New drug treatment

Synthetic drugs

Ongoing basic research efforts throughout the world, including India, continue to identify targets for therapy development. Most studies focus on the role of either gamma-aminobutyric acid (GABA), a key neurotransmitter that inhibits activity in the CNS; or, the blocking of the activity of the excitatory neurotransmitter, glutamate. As epilepsies involve so many different underlying mechanisms, a single therapy will not be beneficial for all; tailored approaches are needed for the management of specific syndromes. Gupta *et al.*, studied the effect of the selective cyclooxygenase-2 (COX-2) inhibitor etoricoxib on seizures, oxidative stress, and learning and memory, and reported that the anticonvulsant activity of the COX-2 inhibitor etoricoxib in pentylenetetrazole-kindled rats is associated with memory impairment.^[42] To elucidate the anticonvulsant effect of piperine and its mechanisms of action using *in-silico*, *in-vivo*, and *in-vitro* techniques, Mishra *et al.*, used the parameterizer and analysis software system [PASS] to determine its possible activity and mechanisms.^[43] The latency for development of convulsions and mortality rate was recorded in different experimental mouse models of epilepsy with various doses of piperine. They evaluated the effect of piperine on Na(+), and Ca(2+) channels using the whole cell patch clamp technique. This study revealed that piperine decreased mortality in the maximum electroshock seizure (MES) model, delayed the onset of tonic-clonic convulsions on administration of pentylenetetrazole (PTZ), reduced associated mortality, and delayed the onset of tonic-clonic seizures. Finally, they proposed the Na(+) channel antagonist activity as a contributor to the complex anticonvulsant mechanisms of piperine. Another group evaluated the effect of bezafibrate as an anti-kindling agent in preventing the development of PTZ-induced seizures and suggested its potential for therapeutic applications in TLE.^[44] Talampanel was shown to be protective in kainic acid-induced neonatal status epilepticus model.^[45] Recently, N-[4-(4-(alkyl/aryl/heteroaryl)-piperazin-1-yl)-phenyl]-carbamic acid ethyl ester derivatives were designed, synthesized, and pharmacologically evaluated as novel anticonvulsant agents. Studies based on *in-silico* analysis reported computer-aided

identification of sodium channel blockers in the clinical treatment of epilepsy and ligand-based drug design of new heterocyclic imines of GABA analogues in the discovery of new GABA-AT inhibitors.^[46,47]

Ayurvedic and botanical drugs

Almost 60 different herbs mentioned in Ayurveda literature have been studied for their antiepileptic activity. *Asparagus racemosus* root extract were shown to have ameliorative effect against pentylenetetrazol-induced kindling and associated depression and memory deficit.^[48] Aloe vera leaf extract were anticonvulsive in acute and chronic models of epilepsy in mice.^[49] Pahuja *et al.*, reported effects of *Anacyclus pyrethrum* on pentylenetetrazole-induced kindling, spatial memory, oxidative stress, and rhokinase II expression in mice. Aqueous extract of *Anethumgraveolens* leaves was shown to be effective in reducing the seizures induced by pentylenetetrazole in mice.^[50,51] Ethnomedicinal plants have been used for treating epilepsy by indigenous communities of the sub-Himalayan region of Uttarakhand.^[52] Anticonvulsant activity was found in the fraction isolated from the ethanolic extract of heartwood of *Cedrusdeodara*.^[53] *Ficus religiosa* L. figs are shown to be potential herbal adjuvants to phenytoin for improved management of epilepsy and associated behavioral comorbidities.^[54] *Glycyrrhizaglabra* root extract showed anticonvulsant action and amelioration of oxidative stress in pentylenetetrazole-induced seizure in albino rats.^[55] *Marsileaquadrifolia* Linn showed antiepileptic properties in maximal electroshock and pentylenetetrazole-induced rat models of epilepsy.^[56,57] Black seed oil showed promising clinical outcome as adjuvant therapy in intractable epilepsies.^[58] *Trichosanthesstricuspidata* modulated oxidative toxicity in brain hippocampus against pilocarpine-induced status epilepticus in mice.^[59] Anticonvulsant activity of ethanol extracts of *Vetiveriazizanioides* roots and *Zingiberofficinale* rhizomes extracts were reported in experimental mice.^[60,61] Curcumin was shown to be effective against pentylenetetrazol-induced seizure threshold in mice with the possible involvement of adenosine A1 receptors, and is antiepileptogenic in kainate-induced model of TLE; protective against lithium-pilocarpine induced status epilepticus, cognitive dysfunction, and oxidative stress in young rats; ameliorative against seizure severity, depression – like behavior, learning, and memory deficit in post-pentylenetetrazole-kindled mice.^[62-67] Curcumin supplementation improves mitochondrial and behavioral deficits in experimental model of chronic epilepsy.^[68] *Withania somnifera* and withanolide A. were shown to have ameliorating effects on impaired motor learning attributed to altered AMPA receptor function in the cerebellum of rats with TLE.^[69] Naveen *et al.*, performed psychiatric analysis to show the positive effects of Yoga on epilepsy.^[70]

Optimising already existing treatments

With the aim of evaluating the effects of reducing the number of AEDs administered to patients with drug-refractory epilepsy (PRE) during their admission and documenting any change in seizure frequency in the subsequent follow-up, our group conducted a study on a total of 962 patients with PRE. Our study proved that optimization or reduction of the number of AEDs in patients with PRE leads to a reduction or to no change in seizure frequency with a significant decrease in adverse effects.^[71] The study of Suresh *et al.*, compared the efficacy and

safety of levetiracetam (LEV) and carbamazepine (CBZ) in partial epilepsy, and reported that LEV monotherapy and CBZ monotherapy demonstrated similar efficacy for the treatment of partial epilepsy and were well tolerated.^[72] A systematic review and meta-analysis study to evaluate the efficacy and safety of AEDs in patients with active convulsive seizures when no intravenous access is available suggested that, when intravenous access is not available, nonintravenous routes of administration of benzodiazepines should be considered for the control of acute seizures in children/adults.^[73]

Surgical management of epilepsy

Nearly one-third patients with newly diagnosed epilepsy on long-term follow-up will have their seizures unsatisfactorily controlled by treatment with available AEDs. Surgery remains an effective option for PRE. The types of surgery could be curative (resective surgeries: amygdalohippocampectomy, lesionectomy, and multilobar resections; functional surgeries: hemispherotomy) and palliative (multiple subpial transaction, corpus callosotomy, and vagal nerve stimulation). Epilepsy surgery in indicated cases has a success range of 50–86% in achieving seizure freedom compared with <5% success rate with AEDs in PRE.^[37] Researchers continue to refine the surgical techniques to make them less invasive and to prevent cognitive and other neurological deficits that can result from surgery. In India, the three major comprehensive epilepsy surgery centers with advanced imaging tools such as magnetic resonance imaging (MRI), single photon emission computed tomography (SPECT), positron emission tomography (PET), and magnetoencephalography (MEG), as well as a multidisciplinary team of neurologists, neurosurgeons, neuroradiologists, electrophysiologists, psychologists, and psychiatrists operate at the All India Institute of Medical Sciences (AIIMS), New Delhi, NIMHANS, Bangalore, Christian Medical College (CMC) in Vellore, and Sree Chitra Tirunal Institute for Medical Sciences and Technology (SCTMIST), Thiruvananthapuram. Almost in the last two decades, these four centers have undertaken over 4000 epilepsy surgeries, out of which more than 2000 epilepsy surgeries were performed in AIIMS, New Delhi. The success of any epilepsy surgery program depends on the early identification of potential surgical candidates. Our group is extensively involved in research to refine surgery protocols. We have reported that the decision making for epilepsy surgery needs a multidisciplinary approach in which different investigators involved with the program work in conjunction to create an integrated picture of epileptogenesis and its impact on the patient and caregivers. Knowing when not to operate, because of the need for further investigations, is as important as selecting which patient may benefit from surgery in a resource-limited setting.^[37,74] Recently, we have shown that administering a structured questionnaire in the native language of patients by trained personnel leads to better localisation and lateralisation and may help to arrive at a hypothesis about the epileptogenic zone (EZ).^[75] In a pilot study, we have shown that intraoperative coregistration of MRI, PET, and electrocorticographic data for neocortical lesional epilepsies may improve the localization of the epileptogenic focus.^[76] Previously we have also shown that concordance between the non-invasive investigations, ictal SPECT [iSPECT] and fludeoxy glucose PET [FDG-PET] is an important predictive factor for surgical outcome in extra-temporal epilepsy.^[77] We have also reported that delineation of ictal-onset zone (IOZ) by

ictal-magnetoencephalography (ictal-MEG) helped to convert drug resistant epilepsy (DRE) patients unsuitable for surgery or planned for phase II monitoring into candidates suitable for surgery, even ECoG-guided resections, and resulted in favourable outcomes in those who were operated.^[78] We have described two novel techniques that utilize an endoscope for performing a hemispherotomy and corpus callosotomy.^[79,80] We have also described our experience with the use of an endoscope for hypothalamic hamartomas.^[81] In addition, we have also described for the first time a combination of corpus callosotomy combined with commissurotomy for better control of seizures in patients with Lennox-Gastaut syndrome (LGS) with severe-to-profound mental retardation.^[82] The utilization of the endoscope for all the three approaches has led to the coining the term “endoscopic epilepsy surgery” to denote the emergence of a new subspecialty of epilepsy surgery. Complete corpus callosotomy combined with anterior, hippocampal, and posterior commissurotomy performed in patients with severe drop attacks and nonlocalizing epilepsy has been demonstrated to be safe and efficacious in LGS. Drop attacks ceased completely in all patients, and there was a significant improvement in all other seizure types (90% reduction in 66% of cases). This was also accompanied with a significant improvement in cognition. We would also be hesitant at this stage to perform this procedure in patients with well-preserved cognitive status. Future studies, recruiting larger number of patients, especially those involving comparing this procedure with performance of only a corpus callosotomy, may be helpful in further establishing its role. Ictal subtraction SPECT and interictal FDG-PET were reported as noninvasive functional tools that can provide important information in addition to MRI and video EEG.^[83] Because this combination is based on different mechanisms of action, the combined information may be more useful. The presence of concordance between intraoperative SPECT and PET may be useful in predicting a better long-term postsurgical outcome for extratemporal epilepsies compared with temporal epilepsies. Diffusion tensor imaging tractography (DTIT) was proposed to be a novel technique to delineate Meyer’s loop (ML) and play an important role in planning surgical resection in TLE as well as in predicting the postoperative visual performance and disability.^[84] We have shown that intraoperative MRI (iMRI) increases the extent of resection, mainly in lesional epilepsy surgeries, with good seizure outcomes, but it was not found to be very beneficial in prototype mesial temporal sclerosis surgeries and disconnection surgeries.^[85] We have reported surgery for medically intractable epilepsy caused by post-infectious etiologies.^[86] We have performed a retrospective study of 129 children who underwent epilepsy surgeries and assessed their quality of life.^[87] This study, the largest reported from India, has demonstrated satisfactory results of epilepsy surgery in children. Our group has reported that removal of lesions over the eloquent cortex (which is a special surgical challenge because it can produce deficits) can be better optimized by the combined use of multimodal neuronavigation (fMRI and tractography) and cortical stimulation under awake conditions.^[88] We have also compared the effects of different anesthetic techniques on electrocorticography in patients undergoing epilepsy surgery and found that optimal electrocorticography recordings were possible with the use of either isoflurane or propofol. Addition of nitrous oxide to either of the anesthetic regimens suppressed the ECoG score.^[89]

Research progress in assessing the role of education in the treatment of epilepsy

Our recent study is one of the very few studies which have proven the efficacy of educational programs responsible for drug adherence in a population cohort with minimal educational background. This study paves the way to conduct a larger community-based study with a longer follow-up and more rigorous protocols for self-care management to assess the efficacy of health education in outcomes of drug adherence and self-care in PWE. Including these strategies will result in a holistic management of PWE, irrespective of their educational status.^[90] A recent study by Kolar *et al.*, reports that the school-based health education programs for epilepsy awareness among school children are very important to bring changes in their attitude, behaviour, and practices.^[91] Even among the primary healthcare doctors, overutilization of EEG, improper prescription of AEDs, and inadequate skills in the management of AED-resistant epilepsies have been reported.^[92]

Research progress in reducing the comorbidities associated with epilepsy

Comorbidities or co-occurring psychiatric, neurodevelopmental, and sleep disorders are relatively common in individuals with epilepsy. In adults, depression and anxiety disorders are the two most frequent psychiatric diagnoses. Attention deficit hyperactivity disorder and anxiety frequently affect children with epilepsy. People with neurodevelopmental disabilities, such as autism spectrum disorder, attention deficit disorder, and learning disabilities, are known to be at higher risk for epilepsy. Seizures, despite being relatively brief in time, leave a dramatic impact not only on the quality of life of those who are living with them but also on those who witness them.^[93] Various functional magnetic resonance imaging (fMRI) language tasks (lexical reading, semantic decision, and semantic-syntactic processing) can cover important language components and guide surgeons for preservation of important functional brain areas during surgery. This will also reduce the development of comorbidities in these patients. Using fMRI as a tool, we have shown that impairment of memory, language, and executive function is common among patients with drug refractory epilepsy.^[94] The most prevalent impairment is in executive function. There is no significant difference in the degree, prevalence, or selectivity of impairment in either of the three domains, between the TLE versus ETLE groups. Srivastava *et al.*, reported major depression and mixed anxiety depression as the most common neuropsychiatric manifestations in patients of NCC.^[95] In a population-based study, epilepsy was found in 23.7% of the children with intellectual disability,^[96] which was associated with a lower intelligent quotient score. Clinical studies revealed a higher frequency of psychiatric comorbidity in children with longer duration of seizures, increased frequency of seizures, poor compliance with medications, and especially, anticonvulsant polytherapy.^[97,98] Another study on women with epilepsy suggested that they are vulnerable to poor child rearing practices even after intervention.^[99] These comorbid conditions have the potential to alter the pharmacodynamics and pharmacokinetics of AEDs, or the AEDs and seizure itself can lead to the development of comorbidities. Hence, more basic research investigations are needed to explore these associations.

Research progress in understanding the process of epileptogenesis

Very few investigators in India are trying to understand the process of epileptogenesis to identify biomarkers to develop antiepileptogenic treatment. Previous studies in rats have shown that downregulation of 5HT_{2C} receptors as well as NMDA R1 expression in pilocarpine induced epilepsy in rats.^[100] The above mentioned studies were largely focused on the risk factors and genetic susceptibility to the disease. Kumar *et al.*, observed high levels of plasma apoE in TLE patients.^[101] The study was limited to a single protein, and further studies are required to identify novel biomarkers for TLE. Array-based profiling studies have shown implication of aberrant gene expression patterns in epileptogenesis. Venugopal *et al.*, identified a set of genes that were differentially expressed in the surgically resected tissue from seizure zones when compared with the nonseizure zones in cases of intractable medial temporal lobe epilepsy (MTLE) due to medial temporal lobe sclerosis (MTS) using DNA microarrays.^[102] We have performed transcriptome analysis of hippocampal tissues resected from patients with MTLE-hippocampal sclerosis (HS) using RNAseq approach. Differential gene expression analysis of the RNAseq data revealed 56 significantly regulated genes in MTLE patients. Gene cluster analysis identified three important hubs of genes mostly linked to neuroinflammation and innate immunity, synaptic transmission, and neuronal network modulation, which are supportive of the intrinsic severity hypothesis of pharmacoresistance. This study identified various genes such as *FN1* which are central in our analysis, *NEUROD6*, *RELN*, *TGF β R2*, *NLRP1*, *SCRT1*, *CSNK2B*, *SCN1B*, *CABP1*, *KIF5A*, and antisense RNAs such as *AQP4-AS1* and *KIRREL3-AS2* as providing important insights into understanding the pathophysiology or genomic basis of drug refractory epilepsy due to MTS.^[103] In another study, we delineated the contribution of glutamatergic tone under resting conditions to hyperexcitability in patients with MTLE.^[104] Resected cortical samples were obtained from patients with MTLE. In these samples, spontaneous excitatory postsynaptic currents (EPSCs), sensitive to N-methyl-D-aspartate (NMDA) receptor antagonist R-2-amino-5-phosphonopentanoate [APV] (50 μ M) and α -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor [AMPA] receptor antagonist 6-cyano-7-nitroquinoxaline-2,3-dione [CNQX] (10 μ M) were recorded from pyramidal neurons at -70 mV. We observed that the frequency of EPSCs was higher in slices obtained from patients with MTLE compared to those from nonepileptic controls. We also examined spontaneous fast current transients (CTs) recorded from these pyramidal neurons under cell-attached configuration. The frequency of CTs increased in the absence of extracellular Mg²⁺ in brain slice preparations and were completely blocked by APV. We found that the frequency of CTs in pyramidal neurons is higher in case of MTLE samples compared to nonepileptic controls. This study suggests that enhanced endogenous activity of NMDA receptor contributes to hyperexcitability in slice preparations obtained from patients with MTLE. Sanjay *et al.*, reported that impaired dendritic inhibition leads to epileptic activity in a computer model of CA3 region of the hippocampus, suggesting that greater synaptic plasticity occurring in the entire network because of increase in the reception of external excitatory inputs (caused by impaired dendritic inhibition) makes the network more susceptible to generation of epileptic activity.^[105]

Future Research

As summarized in Table 1, studies carried out in India are mostly focused on the epidemiological aspects of epilepsy, genetic associations, or on identifying and validating new AEDs in animal models of epilepsy. Chronic epilepsies such as PRE lack effective therapies because of our lack of understanding of the cellular and molecular mechanisms that lead to aberrant neuronal network formations during the course of epileptogenesis. Many research groups across the world have examined the epileptogenic process to understand the different stages in this process. In animals, acquired epilepsy is studied most commonly with kindling models, status epilepticus models, and traumatic brain injury models. A recent study in animal model reported LAU-0901 as an AED, which limits kindling epileptogenesis and induces neuroprotection by antagonising PAF-r. This study suggested that PAF-r activation after brain injury is a key contributor to dysfunctional neuronal circuitry in epileptogenesis and may contribute to limbic seizures.^[20] In a recent paper, we reviewed various possible explored as well as unexplored epileptogenic markers that may also have the potential to serve as potential diagnostic/prognostic biomarkers of PRE.^[106] As none of the animal models for epilepsy could replicate the etiopathological conditions in humans, it is important to perform such studies in human brain tissues to conceptualize its role in epileptogenesis in humans.^[106] The well-defined resected brain tissue from focal epilepsy patients undergoing surgery are valuable and are ideal model systems for not only understanding the process of epileptogenesis but also for the development of novel biomarkers.^[106] Potential molecular biomarkers of epileptogenesis, including markers of inflammation, synaptic alterations, and neurodegeneration, may also have the potential for localizing the EZ. Identification of different steps in epileptogenesis will have benefits in clinical practice pertaining to either correct diagnosis or treatment. It may also help in the identification of patients who are at risk to develop chronic and sometimes refractory epilepsy. Early recognition and intervention could prevent chronic epilepsy in patients with epileptic seizures.

Conclusion

There is a need to increase the quality of epilepsy research in India to understand the underlying biology of epilepsy which will further aid in devising new treatments and cure for chronic epilepsies. National and international collaborations and support from funding agencies are needed to conduct quality research in India. Studies should focus on the use of underutilized resected brain tissues from focal epilepsy patients undergoing surgery to understand the process of epileptogenesis. Understanding the process of epileptogenesis may identify markers for early recognition and interventions for epilepsy.

Acknowledgement

This work mentioned in the article is supported by the grants Centre of Excellence for Epilepsy, a collaborative project between National Brain Research Centre, Manesar and All India Institute of Medical Sciences, New Delhi, Grant: BT/01/COE/09/08 and BT/Bio-CARe/07/9816/2013-2014 funded by Department of Biotechnology, Ministry of Science and technology, Govt. of India.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

References

1. Chang BS, Lowenstein DH. Epilepsy. *N Engl J Med* 2003;349:1257-66.
2. Engel JJ, Pedley TA. *Epilepsy: A Comprehensive Textbook*. Philadelphia: Lippincott Williams & Wilkins; 2008.
3. Giourou E, Stavropoulou-Deli A, Giannakopoulou A, Kostopoulos GK, Koutroumanidis M. Introduction to Epilepsy and Related Brain Disorders. In: Voros NS, Antonopolous CP (editors.) *Cyberphysical Systems for Epilepsy and Related Brain Disorders*. Switzerland; Springer International Publishing 2015; p. 11-38.
4. Tripathi M, Jain DC, Devi MG, Jain S, Saxena V, Chandra PS, *et al.* Need for a national epilepsy control program. *Ann Indian Acad Neurol* 2012;15:89-93.
5. Thomas SV, Sarma PS, Alexander M, Pandit L, Shekhar L, Trivedi C, *et al.* Economic burden of epilepsy in india. *Epilepsia* 2001;42:1052-60.
6. Shorvon SD. The causes of epilepsy: Changing concepts of etiology of epilepsy over the past 150 years. *Epilepsia* 2011;52:1033-44.
7. Lawson T, Yeager S. Status epilepticus in adults: A review of diagnosis and treatment. *Crit Care Nurs* 2016;36:62.
8. Dixit AB, Banerjee J, Tripathi M, Chandra PS. Presurgical epileptogenic network analysis: A way to enhance epilepsy surgery outcome. *Neurol India* 2015;63:743-50.
9. Dixit AB, Banerjee J, Tripathi M, Chandra PS, Banerjee J. molecular biomarkers in drug-resistant epilepsy: Facts and possibilities. *Int J Surg* 2015;36(Pt B):486-91.
10. Banerjee PN, Filippi D, Allen Hauser W. The descriptive epidemiology of epilepsy- A review. *Epilepsy Res* 2009; 85:31-45.
11. Braizer MA. Electrical seizure discharge within the human brain: The problem of spread. In: *Epilepsy, Its Phenomena in Man*. New York: Academic Press; 1973.
12. Rizzi M, Weissberg I, Milikovsky DZ, Friedman A. Following a potential epileptogenic insult, prolonged high rates of nonlinear dynamical regimes of intermittency type is the hallmark of epileptogenesis. *Sci Rep* 2016;6:31129.
13. Prince DA, Gu F, Parada I. Antiepileptogenic repair of excitatory and inhibitory synaptic connectivity after neocortical trauma. *Prog Brain Res* 2016;226:209-27.
14. Mazarati A, Sankar R. Common mechanisms underlying epileptogenesis and the comorbidities of epilepsy. *Cold Spring Harb Perspect Med* 2016;6.
15. Citraro R, Leo A, Constanti A, Russo E, De Sarro G. mTOR pathway inhibition as a new therapeutic strategy in epilepsy and epileptogenesis. *Pharmacol Res* 2016;107:333-43.
16. González MI. Regulation of the cell surface expression of chloride transporters during epileptogenesis. *Neurosci Lett* 2016;628:213-8.
17. Tokudome K, Okumura T, Shimizu S, Mashimo T, Takizawa A, Serikawa T, *et al.* Synaptic vesicle glycoprotein 2A (SV2A) regulates kindling epileptogenesis via GABAergic neurotransmission. *Sci Rep* 2016;6:27420.
18. Musto AE, Rosencrans RF, Walker CP, Bhattacharjee S, Raulji CM, Belayev L, *et al.* Dysfunctional epileptic neuronal circuits and dysmorphic dendritic spines are mitigated by platelet-activating factor receptor antagonism. *Sci Rep* 2016;6:30298.
19. Brandt C, Rankovic V, Töllner K, Klee R, Bröer S, Löscher W.

- Refinement of a model of acquired epilepsy for identification and validation of biomarkers of epileptogenesis in rats. *Epilepsy Behav* 2016;61:120-31.
20. Breuer H, Meier M, Schneefeld S, Härtig W, Wittneben A, Märkel M, *et al.* Multimodality imaging of blood-brain barrier impairment during epileptogenesis. *J Cereb Blood Flow Metab* 2016 pii: 0271678X16659672.
21. Santhosh NS, Sinha S, Satishchandra P. Epilepsy: Indian perspective. *Ann Indian Acad Neurol* 2014;17(Suppl 1):S3-11.
22. Singh BB, Khatkar MS, Gill JP, Dhand NK. Estimation of the health and economic burden of neurocysticercosis in India. *Acta Trop* 2017;165:161-9.
23. Ratnapriya R, Satishchandra P, Kumar SD, Gadre G, Reddy R, Anand A. A locus for autosomal dominant reflex epilepsy precipitated by hot water maps at chromosome 10q21.3-q22. *Hum Genet* 2009;125:541-9.
24. Ratnapriya R, Satishchandra P, Dilip S, Gadre G, Anand A. Familial autosomal dominant reflex epilepsy triggered by hot water maps to 4q24-q28. *Hum Genet* 2009;126:677-83.
25. Dutta S, Gangopadhyay PK, Sinha S, Chatterjee A, Ghosh S, Rajamma U. An association analysis of reelin gene (RELN) polymorphisms with childhood epilepsy in eastern Indian population from West Bengal. *Cell Mol Neurobiol* 2011;31:45-56.
26. Lachuriya G, Garg RK, Jain A, Malhotra HS, Singh AK, Jain B, *et al.* Toll-like receptor-4 polymorphisms and serum matrix metalloproteinase-9 in newly diagnosed patients with calcified neurocysticercosis and seizures. *Medicine* 2016;95:e3288.
27. Dixit AB, Ansari A, Banerjee J, Tripathi M, Chandra PS. Mutations in GABRG2 receptor gene are not a major factor in the pathogenesis of mesial temporal Lobe epilepsy in Indian population. *Ann Indian Acad Neurol* 2016;19:236-41.
28. Samanta D. Epilepsy with PCDH19 mutation masquerading as benign partial epilepsy in infancy. *Neurol India* 2016;64:327-8.
29. Phani NM, Acharya S, Xavy S, Bhaskaranand N, Bhat MK, Jain A, *et al.* Genetic association of KCNJ10 rs1130183 with seizure susceptibility and computational analysis of deleterious non-synonymous SNPs of KCNJ10 gene. *Gene* 2014;536:247-53.
30. Gupta R, Agarwal M, Boqqula VR, Phadke RV, Phadke SR. Hemiconvulsion-hemiplegia-epilepsy syndrome with 1q44 microdeletion: Causal or chance association. *Am J Med Genet A* 2014;164A:186-9.
31. Jagadeesh S, Suresh B, Murugan V, Suresh S, Salomans GS, Struys EA, *et al.* Pyridoxine-dependent epilepsy owing to antiquitin deficiency-mutation in the ALDH7A1 gene. *Paediatr Int Child Health* 2013;33:113-5.
32. Srikumar PS, Rohini K, Rajesh PK. Molecular dynamics simulations and principal component analysis on human laforin mutation W32G and W32G/K87A. *Protein J* 2014;33:289-95.
33. Dubey D, Parihar R, Ganesh S. Identification and characterization of novel splice variants of the human EPM2A gene mutated in Lafora progressive myoclonus epilepsy. *Genomics* 2012;99:36-43.
34. Radhakrishnan A, Menon RN, Hariharan S, Radhakrishnan K. The evolving electroclinical syndrome of "epilepsy with ring chromosome 20". *Seizure* 2012;21:92-7.
35. Grover S, Kukreti R. A systematic review and meta-analysis of the role of ABCC2 variants on drug response in patients with epilepsy. *Epilepsia* 2013;54:936-45.
36. Talwar P, Kanojia N, Mahendru S, Baghel R, Grover S, Arora G, *et al.* Genetic contribution of CYP1A1 variant on treatment outcome in epilepsy patients: A functional and interethnic perspective. *Pharmacogenomics J* 2015; DOI: 10.1038/tpj.2016.1
37. Chandra PS, Tripathi M. Epilepsy surgery: Recommendations for India. *Ann Indian Acad Neurol* 2010;13:87-93.
38. Dash D, Sharma A, Yuvraj K, Renjith A, Mehta S, Vasantha PM, *et al.* Can home video facilitate diagnosis of epilepsy type in a developing country? *Epilepsy Res* 2016;125:19-23.
39. Sehgal R, Gulati S, Sapra S, Tripathi M, Pandey RM, Kabra M. Prognostic utility of clinical epilepsy severity score versus pretreatment hypsarrhythmia scoring in children with West syndrome. *Clin EEG Neurosci.* (2016) pii: 1550059416662425.
40. Mahale R, Mehta A, John AA, Buddaraju K, Shankar AK, Javali M, *et al.* Acute seizures in cerebral venous sinus thrombosis: What predicts it? *Epilepsy Res* 2016;123:1-5.
41. Datta S, Sarkar S, Chakraborty S, Mulpuru SK, Basu S, Tiwary BK, *et al.* MRI characterization of temporal lobe epilepsy using rapidly measurable spatial indices with hemisphere asymmetries and gender features. *Neuroradiology* 2015;57:873-86.
42. Katyal J, Kumar H, Gupta YK. Anticonvulsant activity of the cyclooxygenase-2 (COX-2) inhibitor etoricoxib in pentylenetetrazole-kindled rats is associated with memory impairment. *Epilepsy Behav* 2015;44:98-103.
43. Mishra A, Punia JK, Bladen C, Zamponi GW, Goel RK. Anticonvulsant mechanisms of piperine, a piperidine alkaloid. *Channels* 2015;9:317-23.
44. Saha L, Bhandari S, Bhatia A, Banerjee D, Chakrabarti A. Anti-kindling effect of bezafibrate, a peroxisome proliferator-activated receptors alpha agonist, in pentylenetetrazole induced kindling seizure model. *J Epilepsy Res* 2014;4:45-54.
45. Dhir A, Chavda V. Pre- and post-exposure talampanel (GYKI 53773) against kainic acid seizures in neonatal rats. *Pharmacol Rep* 2016;68:190-5.
46. Kumari S, Mishra CB, Tiwari M. Design, synthesis and pharmacological evaluation of N-[4-(4-(alkyl/aryl/heteroaryl)-piperazin-1-yl)-phenyl]-carbamic acid ethyl ester derivatives as novel anticonvulsant agents. *Bioorg Med Chem Lett* 2015;25:1092-9.
47. Mathew B, Mathew GE, Suresh J, Usman D, Shiva Subramanyan PN, Safna KF. Ligand based drug design of new heterocyclic imines of GABA analogues: A molecular docking approach for the discovery of new GABA-AT inhibitors. *Cent Nerv Syst Agents Med Chem* 2016 [PMID: 26725889].
48. Pahwa P, Goel RK. Ameliorative effect of Asparagus racemosus root extract against pentylenetetrazol-induced kindling and associated depression and memory deficit. *Epilepsy Behav* 2016;57(Pt A):196-201.
49. Rathor N, Arora T, Manocha S, Patil AN, Mediratta PK, Sharma KK. Anticonvulsant activity of Aloe vera leaf extract in acute and chronic models of epilepsy in mice. *J Pharm Pharmacol* 2014;66:477-85.
50. Arash A, Mohammad MZ, Jamal MS, Mohammad TA, Azam A. Effects of the aqueous extract of Anethum graveolens leaves on seizure induced by pentylenetetrazole in mice. *Malays J Med Sci* 2013;20:23-30.
51. Rostampour M, Ghaffari A, Salehi P, Saadat F. Effects of hydro-alcoholic extract of Anethum graveolens seed on pentylenetetrazol-induced seizure in adult male mice. *Basic Clin Neurosci* 2014;5:199-204.
52. Sharma J, Gairola S, Gaur RD, Painuli RM, Siddiqi TO. Ethnomedicinal plants used for treating epilepsy by indigenous communities of sub-Himalayan region of Uttarakhand, India. *J Ethnopharmacol* 2013;150:353-70.
53. Dhayabaran D, Florance EJ, Nandakumar K, Shanmugarathinam A, Puratchikody A. Anticonvulsant activity of fraction isolated from ethanolic extract of heartwood of Cedrus deodara. *J Nat Med* 2014;68:310-5.
54. Singh P, Singh D, Goel RK. Ficus religiosa L. figs — a potential herbal adjuvant to phenytoin for improved management of

- epilepsy and associated behavioral comorbidities. *Epilepsy Behav* 2014;44:171-8.
55. Chowdhury B, Bhattamisra SK, Das MC. Anti-convulsant action and amelioration of oxidative stress by Glycyrrhiza glabra root extract in pentylenetetrazole-induced seizure in albino rats. *Indian J Pharmacol* 2013;45:40-3.
56. Sahu S, Dutta G, Mandal N, Goswami AR, Ghosh T. Anticonvulsant effect of *Marsilea quadrifolia* Linn. on pentylenetetrazole induced seizure: A behavioral and EEG study in rats. *J Ethnopharmacol* 2012;141:537-41.
57. Snehunsu A, Mukunda N, Satish Kumar MC, Sadhana N, Naduvil NS, Vijay KK, *et al.* Evaluation of anti-epileptic property of *Marsilea quadrifolia* Linn. in maximal electroshock and pentylenetetrazole-induced rat models of epilepsy. *Brain Inj* 2013;27:1707-14.
58. Shawki M, El WL, Shatla R, El-Saeed G, Ibrahim S, Badary O. The clinical outcome of adjuvant therapy with black seed oil on intractable paediatric seizures: A pilot study. *Epileptic Disord* 2013;15:295-301.
59. Smilin Bell AG, Sivasudha T, Suganya M, Rameshkumar A, Jayadevi R. *Trichosanthes tricuspidata* modulates oxidative toxicity in brain hippocampus against pilocarpine induced status epilepticus in mice. *Neurochem Res* 2013;38:1715-25.
60. Gupta R, Sharma KK, Afzal M, Damanhoury ZA, Ali B, Kaur R, *et al.* Anticonvulsant activity of ethanol extracts of *Vetiveria zizanioides* roots in experimental mice. *Pharm Biol* 2013;51:1521-4.
61. Hosseini A, Mirazi N. Acute administration of ginger (*Zingiber officinale* rhizomes) extract on timed intravenous pentylenetetrazol infusion seizure model in mice. *Epilepsy Res* 2014;108:411-9.
62. Agarwal NB, Jain S, Agarwal NK, Mediratta MK, Sharma KK. Modulation of pentylenetetrazole-induced kindling and oxidative stress by curcumin in mice. *Phytomedicine* 2011;18:756-9.
63. Akula KK, Kulkarni SK. Effect of curcumin against pentylenetetrazol-induced seizure threshold in mice: Possible involvement of adenosine A1 receptors. *Phytother Res* 2014;28:714-21.
64. Kiasalari Z, Roghani M, Khalili M, Rahmati B, Baluchnejadmojarad T. Antiepileptogenic effect of curcumin on kainate-induced model of temporal lobe epilepsy. *Pharm Biol* 2013;51:1572-8.
65. Sharma V, Nehru B, Munshi A, Jyothy A. Antioxidant potential of curcumin against oxidative insult induced by pentylenetetrazol in epileptic rats. *Methods Find Exp Clin Pharmacol* 2010;32:227-32.
66. Choudhary KM, Mishra A, Poroikov VV, Goel RK. Ameliorative effect of Curcumin on seizure severity, depression like behavior, learning and memory deficit in post-pentylenetetrazole-kindled mice. *Eur J Pharmacol* 2013;704:33-40.
67. Agarwal NB, Jain S, Nagpal D, Agarwal NK, Mediratta PK, Sharma KK. Liposomal formulation of curcumin attenuates seizures in different experimental models of epilepsy in mice. *Fundam Clin Pharmacol* 2013;27:169-72.
68. Kaur H, Bal A, Sandhir R. Curcumin supplementation improves mitochondrial and behavioral deficits in experimental model of chronic epilepsy. *Pharmacol Biochem Behav* 2014;125:55-64.
69. Soman S, Anju TR, Jayanarayanan S, Antony S, Paulose CS. Impaired motor learning attributed to altered AMPA receptor function in the cerebellum of rats with temporal lobe epilepsy: Ameliorating effects of *Withania somnifera* and withanolide A. *Epilepsy Behav* 2013;27:484-91.
70. Naveen GH, Sinha S, Girish N, Taly A B, Varambally S, Gangadhar B N. Yoga and epilepsy: What do patients perceive?. *Indian J Psychiatry* 2013;55(Suppl S3):390-3.
71. Dash D, Aggarwal V, Joshi R, Padma MV, Tripathi M. Effect of reduction of antiepileptic drugs in patients with drug-refractory epilepsy. *Seizure* 2015;27:25-9.
72. Suresh SH, Chakraborty A, Virupakshaiah A, Kumar N. Efficacy and safety of levetiracetam and carbamazepine as monotherapy in partial seizures. *Epilepsy Res Treat* 2015;2015:415082.
73. Jain P, Sharma S, Dua T, Barbui C, Das RR, Aneja S. Efficacy and safety of anti-epileptic drugs in patients with active convulsive seizures when no IV access is available: Systematic review and meta-analysis. *Epilepsy Res* 2016;122:47-55.
74. Tripathi M, Ray S, Chandra PS. Presurgical evaluation for drug refractory epilepsy. *Int J Surg* 2016; 405-410.
75. Chaudhari RM, Ramanujam B, Appukuttan R, Sharma A, Kunwar Y, Tejaniya G, *et al.* Utility of a questionnaire tool (QUARAS) for localizing and lateralizing seizures in the epilepsy monitoring unit (EMU). *Clin Neurol Neurosurg* 2017; 153:64-66.
76. Malhotra V, Chandra SP, Dash D, Garg A, Tripathi M, Bal CS, *et al.* A screening tool to identify surgical candidates with drug refractory epilepsy in a resource limited settings. *Epilepsy Res* 2016;121:14-20.
77. Chandra PS, Vaghania G, Bal CS, Tripathi M, Kuruwale N, Arora A, *et al.* Role of concordance between ictal-subtracted SPECT and PET in predicting long-term outcomes after epilepsy surgery. *Epilepsy Res* 2014;108:1782-9.
78. Ramanujam B, Bharti K, Viswanathan V, Garg A, Tripathi M, Bal CS, *et al.* Seizure: Can ictal-MEG obviate the need for phase II monitoring in people with drug-refractory epilepsy? A prospective observational study. *Seizure* 2016;45:17-23.
79. Chandra PS, Kurwale N, Garg A, Dwivedi R, Malviya S, Tripathi M. Endoscopy-assisted interhemispheric transcallosal hemispherotomy: Preliminary description of a novel technique. *Neurosurgery* 2015;76:485-94.
80. Chandra SP, Tripathi M. Endoscopic epilepsy surgery: Emergence of a new procedure. *Neurol India* 2015;63:571-82.
81. Chandra SP, Kurwale NS, Chibber SS, Banerji J, Dwivedi R, Garg A, *et al.* Endoscopic-Assisted (Through a Mini Craniotomy) Corpus Callosotomy Combined With Anterior, Hippocampal, and Posterior Commissurotomy in Lennox-Gastaut Syndrome: A Pilot Study to Establish Its Safety and Efficacy. *Neurosurgery* 2016;78:743-51.
82. Newale S, Bachani DS. Demographic characteristics of epilepsy patients and antiepileptic drug utilization in adult patients: Results of a cross-sectional survey. *Neurol India* 2016;64:1180-6.
83. Sunhee K, James MM. SPECT Imaging of epilepsy: An overview and comparison with F-18 FDG PET. *Int J Mol Imaging* 2011;813028:9.
84. James JS, Radhakrishnan A, Thomas B, Madhusoodanan M, Kesavadas C, Abraham M, *et al.* Diffusion tensor imaging tractography of Meyer's loop in planning resective surgery for drug-resistant temporal lobe epilepsy. *Epilepsy Res* 2015;110:95-104.
85. Chandra SP, Chouksey P, Arora A, Garg A, Sarkar C, Bal C, *et al.* Impact of intraoperative MRI on outcomes in epilepsy surgery: Preliminary experience of two years. *Br J Neurosurg* 2015;29:380-5.
86. Chandra PS, Bal C, Garg A, Gaikwad S, Prasad K, Sharma BS, *et al.* Surgery for medically intractable epilepsy due to postinfectious etiologies. *Epilepsia* 2010;51:1097-100.
87. Dagar A, Chandra PS, Chaudhary K, Avnish C, Bal CS, Gaikwad S, *et al.* Epilepsy surgery in a pediatric population: A retrospective study of 129 children from a tertiary care hospital in a developing country along with assessment of quality of life. *Pediatr Neurosurg* 2011;47:186-93.
88. Kumar A, Chandra PS, Sharma BS, Garg A, Rath GK, Bithal PK, *et al.* The role of neuronavigation-guided functional MRI and diffusion tensor tractography along with cortical stimulation in patients with eloquent cortex lesions. *Br J Neurosurg* 2014;28:226-33.
89. Bindra A, Chouhan RS, Prabhakar H, Chandra PS, Tripathi M.

- Perioperative anesthetic implications of epilepsy surgery: A retrospective analysis. *J Anesth* 2015;29:229-34.
90. Dash D, Sebastian TM, Agarwal M, Tripathi M. Impact of health education on drug adherence and self care in people with epilepsy with low education. *Epilepsy Behav* 2015;10:213-17.
 91. Kolar Sridara MM, Govindappa L, Sinha S. Outcome of a school-based health education program for epilepsy awareness among schoolchildren. *Epilepsy Behav* 2016;57(Pt A):77-81.
 92. Amudhan S, Gururaj G, Satishchandra P. Epilepsy in India II: Impact, burden, and need for a multisectoral public health response. *Ann Indian Acad Neurol* 2015;18:369-81.
 93. England MJ, Liverman CT, Schultz AM, Strawbridge LM. (editors). Committee on the Public Health Dimensions of the Epilepsies; Board on Health Sciences Policy; Institute of Medicine. *Epilepsy Across the Spectrum: Promoting Health and Understanding*. The National Academies Press (US), March 20, 2012. The National Academies Collection: Reports funded by National Institutes of Health.
 94. Chaudhary K, Kumaran SS, Manjari Tripathi. Mapping of cognitive functions in chronic intractable epilepsy: Role of fMRI. *Indian J Radiol Imaging*. 2014;24:51-6.
 95. Srivastava S1, Chadda RK, Bala K, Majumdar P. A study of neuropsychiatric manifestations in patients of neurocysticercosis. *Indian J Psychiatry*. 2013;55:264-7.
 96. Lakhan R. The coexistence of psychiatric disorders and intellectual disability in children aged 3-18 years in the barwani district, India. *ISRN Psychiatry* 2013;2013:875873.
 97. Amruth G, Praveen-Kumar S, Nataraju B, Kasturi P. Study of psychiatric comorbidities in epilepsy by using the Mini International Neuropsychiatric Interview. *Epilepsy Behav* 2014;33:94-100.
 98. Choudhary A, Gulati S, Sagar R, Kabra M, Sapra S. Behavioral comorbidity in children and adolescents with epilepsy. *J Clin Neurosci* 2014;21:1337-40.
 99. Saramma PP, Sarma PS, Thomas SV. Effect of a self-instructional module on the child rearing knowledge and practice of women with epilepsy. *Seizure* 2014;23:424-8.
 100. Krishnakumar A, Nandhu MS, Paulose CS. Upregulation of 5-HT2C receptors in hippocampus of pilocarpine-induced epileptic rats: Antagonism by Bacopa monnieri. *Epilepsy Behav* 2009;16:225-30.
 101. Kumar A, Tripathi M, Pandey RM, Ramakrishnan L, Srinivas M, Luthra K. Apolipoprotein E in temporal lobe epilepsy: A case-control study. *Dis Markers* 2006;22:335-42.
 102. Venugopal AK, Ghantasala S, Kumar S, Mahadevan A, Dhevi L, Selvan N, *et al.* Transcriptomic profiling of medial temporal lobe epilepsy. *J Proteomics Bioinform* 2012;5:1000210.
 103. Dixit AB, Banerjee J, Srivastava A, Tripathi M, Sarkar C, Kakkar A, *et al.* RNA-Seq analysis of hippocampal tissues reveals novel candidate genes for drug refractory epilepsy in patients with MTLE-HS. *Genomics* 2016;107:178-88.
 104. Banerjee J, Dixit AB, Tripathi M, Chandra PS. Enhanced endogenous activation of NMDA receptors in pyramidal neurons of cortical samples obtained from patients with mesial temporal lobe epilepsy: A mechanism of hyper excitation. *Epilepsy Res* 2015;117:11-6.
 105. Sanjay M, Neymotin SA, Krothapalli SB. Impaired dendritic inhibition leads to epileptic activity in a computer model of CA3. *Hippocampus* 2015;25:1336-50.
 106. Dixit AB, Tripathi M, Chandra PS, Banerjee J. Molecular biomarkers in drug-resistant epilepsy: Facts and possibilities. *Int J Surg* 2016;36(Pt B):483-91.

