ISSN: 2320 - 4230

Journal of Drug Discovery and Therapeutics 1 (7) 2013, 69-75

RESEARCH ARTICLE

PRESCRIBING PATTERNS OF ANTI-EPILEPTIC DRUG IN DIFFERENT AGE GROUP IN INDIA

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Received 28 June 2013; Revised 07 July 2013; Accepted 10 July 2013

ABSTRACT

For improving overall care in epileptic patients, careful evaluation of pharmacotherapy, seizure control, quality of life and cost effectiveness are helpful but such data are relatively meagre from developing countries. The present study was undertaken to audit and describes the antiepileptic drugs (AEDs) utilization patterns in different Hospitals. More research studies are required in this area due to lack of well-defined studies in India to conclude which is the most frequent class of epilepsy seen with the AED's used. We retrieved prescription data from patient profile forms and medical record department. We documented essential data in a Patient Profile Form, specifically designed for our study. A total of 100 patients data were recorded in the study. In our study we found that percentage of men suffering from epilepsy was 63 % and percentage of females was 37%. The overall aim in treating epilepsy (therapy) should be complete control of seizures, without causing any untoward reaction due to the medication.

KEYWORDS: Antiepileptic drug, Prescribing pattern, Prescription list

INTRODUCTION:

An epileptic seizure is a transient paroxysm of uncontrolled discharges in neurons and a medical condition with recurrent, unprovoked seizures.[1] It is a chronic disorder characterized by recurrent seizures[2] and second most common chronic neurological condition seen by neurologists. Though monotherapy is usually recommended in epilepsy but polytherapy is often required for patients with multiple seizure types or refractory disease.[3] Epilepsy can be treated effectively in approximately 60% of patients who become seizure free with the first or second line antiepileptic drug (AED) that they are prescribed.[4] The drawback of polypharmacy is higher incidence of adverse effects, drug interactions and added costs.[5] More than a century ago, ***John Hughlings Jackson*** the father of modern concepts of epilepsy proposed that seizures is developed by occasional, sudden, excessive, rapid and local discharges of "gray matter". The coming of the electroencephalogram (EEG) in the 1930s permitted the recording of electrical activity from the scalp of humans with epilepsy and demonstrated that the epilepsies are disorders of neuronal excitability.[6] The important role of synapses in mediating communication among neurons in the mammalian brain suggested that defective synaptic function might lead to a seizure. The general approach to treatment involves the identification of goals, assessment, development of a care plan, and a follow-up evaluation with quality of life. During the assessment phase, it is critical to establish an accurate diagnosis of the seizure type and classification.[7] The diagnosis of epilepsy is essentially clinical, based on an eyewitness account of the seizure. Neurological examination and investigations may be normal between attacks. Sometimes patients may not be aware of the nature of attacks and seizures occurring at night may go unnoticed and hence may not be reported. The choice of the most appropriate drug treatment for a patient with seizures depends upon the accurate classification of the seizures and the type of epilepsy or epileptic syndromes. Over 80% of epileptic patients can achieve a significant reduction in seizure frequency with monotherapy (one drug) alone. The risk of significant adverse effects and drug interaction increases when polytheraphy (more than one drug) is used.[8] The ultimate goal of treatment for epilepsy is no seizure and no side effects with an optimal quality of life. The best quality of life is associated with a seizure free state.[9]

A large number of drugs are currently available for the treatment of epilepsy. Conventional drugs like phenytoin, carbamazepine, valproic acid and ethosuximide are commonly used as first line drugs. They are relatively less expensive than the newer antiepileptic drugs like gabapentin, lamotrigine, vigabatrin, topiramate, tiagabine and zonisamide. They have lesser adverse effects and have a few drug interactions.[10-11]

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DIFFERENT TYPE OF SEIZURES:

Epileptic seizures have been classified variously:

1. Partial seizures- Beginning focally in a cortical site, formally known as focal seizure, distortion of hearing and seen, feel jerky movement. It involved only one portion of the brain. The accounts of partial seizure types are roughly 60% of all epilepsies. These are two types.

a. Simple partial seizure- A *simple* partial seizure is associated with preservation of consciousness i.e. normal consciousness. Lasting is ½-1 min. Convulsion are confined to a group of muscle or localized sensory disturbance depending on the area of cortex involved in the seizure.

b. Complex partial seizure- Formally known as temporal lobe epilepsy or psychomotor epilepsy. A *complex* partial seizure is associated with impairment of consciousness. The majority of complex partial seizures originate from the temporal lobe. During the seizure, patient appears dazed and confused behavior, purposeless movements such as- walking, mumbling, head turning, pulling of clothing may be observed and emotional changes lasting 1-2 min.

c. Simple partial or Complex partial seizures secondarily generalized- The partial seizure occur first and evolves into generalized tonic-clonic seizures with loss of consciousness.

2. Generalized seizures- Seizure that involves both hemispheres widely from the outset (Commission on Classification and Terminology, 1981). The generalized epilepsies have account for approximately 40% of all epilepsies. These are three types.

a. Absence seizure (minor epilepsy, petit mal)- Prevalent in children, lasts about ½ min or 15-30 sec. momentary loss of consciousness, patient apparently freezes and stares in one direction, eye may roll upward. No muscular component or little bilateral jerking. They occur in children and disappear by adolescence. It is not preceded by aura.

b. Tonic-clonic seizure (major epilepsy, grand mal) - It is most common. Lasts 1-2 min. The usual sequence is aura, cry, unconsciousness, tonic spasm of all body muscle, clonic jerking followed by prolonged sleep and depression of all CNS function.

c. Myoclonic seizure- shock-like momentary contraction of muscle of a limb or the whole body.

EPIDEMIOLOGICAL DATA:

Epilepsy is a common neurological disorder affecting almost 50 million people worldwide.[12] Approximately, 85% of people affected with epilepsy live in developing countries.[13] About 20% of all epileptics on earth inherent in India.[14] Accurately 60% of all epilepsies are idiopathic or cryptogenic.[15] It is estimated that there are 55, 00,000 persons with epilepsy in India, 20, 00,000 in USA and 3, 00,000 in UK[16-17]. A recent study reported that the problem is nearly two and half times higher in rural areas as compared to urban areas, where they are not receiving any treatment.[18] The annual economic burden of epilepsy in India is 88.2%.[19]

ETIOLOGY:

Seizures occur because a group of cortical neurons discharge abnormally in synchrony. The etiology of epilepsy is often Idiopathic. Anything that disrupts the normal homeostasis of neurons and their stability can trigger hyper excitability and seizures. The etiology commonly consists of a lesion in some part of the cortex, such as a tumor, developmental malformation, damage due to trauma or stroke, etc. Such lesions often are clear on brain magnetic resonance imaging (MRI), and toxic accounted for less than 1% of all causes.[20] Alternatively, the etiology may be genetic. Reduction of inhibitory synaptic activity or enhancement of excitatory synaptic activity might be expected to trigger a seizure.[21] Seizures are thought to arise from the cerebral cortex and not from other central nervous system (CNS) structures such as the thalamus, brainstem, or cerebellum. There are thousands of medical conditions that can cause epilepsy from genetic mutations to traumatic brain injury.

WHO RESPONSE:

World Health Organization (WHO), International League Against Epilepsy (ILAE) and the International Bureau for Epilepsy (IBE) are carrying out a global campus, 'Out of the Shadows' to provide better information and raise awareness about epilepsy.[22] Drug use/usage/utilization evaluation (DUE) was defined by World Health Organization (WHO) in 1977 and it was as originally known as drug utilization review (DUR) in the 1980's.[23]

SUDDEN UNEXPECTED DEATH IN EPILEPSY:

Most often, people with epilepsy recover perfectly after a seizure. A very small number of people may be dying. If a person with epilepsy dies unexpectedly and no clear cause of death can be found, it is called sudden unexpected death in epilepsy (SUDEP). Sometimes, it is called sudden unexplained death in epilepsy. There is no way of predicting who will be affected by SUDEP. But the single most important risk factor is uncontrolled generalized tonic-clonic seizures.

MATERIALS AND METHODS:

We visited to hospital and consulted doctors. With the help of them we talk to many patients and ask many questions from them regarding their health and disease. We found that patient suffering from epilepsy have

problem of generally loss their consciousness and violent convulsion with permanent headache. A thorough survey and prospective study of 100 epileptic patients was undertaken to study the prescribing pattern of AEDs from different cities hospitals in Delhi, NCR region and Lucknow in India. The study included 100 epileptic patients among whom majority of male (63 patients) was more in the comparison with females (37 patients) (Fig-1).

Majority of the patients 35 were in the age group of 40-50 years, followed by 30 patients of 29-39 years and 19 patients were in both age group of 18-28 years and 51-64 years. About 16 patients were in the age group of 65 years and above. Our data shows that most of the patients were from the age group of 40-50 years and majority of the recruit patients were male.(Fig-2) Generalized Tonic-Clonic Seizures (GTCS) was found to be more prevalent 62 patients out of which 39 were males and 23 were female, followed by Simple Partial Seizures (SPS) 11 patients, 07 were males and 04 were females. Total numbers of Myoclonic Seizures (MS) were 08 patients out of which 06 males and 02 female. Generalized Clonic Seizures (GCS) 09 patients out of which 03 was male and 06 female. In Complex Partial Seizures (CPS) 05 patients, 04 were male and 01 was female. Generalized Tonic Seizures (GTS) of 03 patients, there were only male patients. In Atonic Seizures (AS) a total of 02 patients, of which 01 male and 01 female. (Fig-3)

DRUG THERAPY:

Anti-epileptic drugs (AEDs) are the medications used in the treatment of epilepsy. Monotherapy was the usual dictum, but polytherapy were needed for patients with multiple seizure types or refractory disease.[24-25] Hence we have made an attempt to study the prescribing pattern of AEDs in the treatment of different types of epilepsy. The drug have prescribed in a different manner i.e. the usage of sodium valproate accounts for 42 patients of which 30 were male patients and 12 were female patients, followed by phenytoin 16 patients of which 10 were males and 06 were females. Phenobarbitone usage was 27 patients, of whom 17 were male patients and 10 were females. Carbamazepine usage was 10 patients of which, 6 were males and 04 were females. 05 of Lamotrigine, 05 patients were males and we did not have any female patients recorded (Fig-4). Sodium Valproate was the most widely prescribed anti-epileptic drug in hospitals. It was the first choice for patients with generalized seizures and used to prevent nearly all other major seizures as well. Choosing the right AED for you will depend on your epilepsy syndrome, age, gender, and many other individual factors such as drug and food interaction. Taking a single drug is preferable in most cases of epilepsy. If the drug of choice doesn't control your seizures or if unwanted side effects occur, then a second drug may be tried and the first is usually withdrawn. Only when seizures are resistant to single drug therapy should a combination of drugs is necessary.[Table-1]

DRUG & FOOD INTERACTION WITH AEDs:

It is essential to remember that, several food and medicine have unpredictable effects on seizure control. Uses of AEDs with food or other medication can cause an increased or decreased the seizure occurrence. There are several AEDs that interact with food and medicine [Table-2] and can obtain without a prescription i.e. OTC drug. Many prescription medications that have not been included in this table can also interact with antiepileptic medicines.

RESULTS:

A total of 100 patient files were studied. 63% patients were male and 37% patients were female. Occurrence of epilepsy was more in 40-50 years of age. We have found to be Sodium valproate is the most prescribed drug in this therapy and it is the most common drug used in India.

Figure 1: Graphical representation of the distribution of 100 epileptic patients based on the gender.

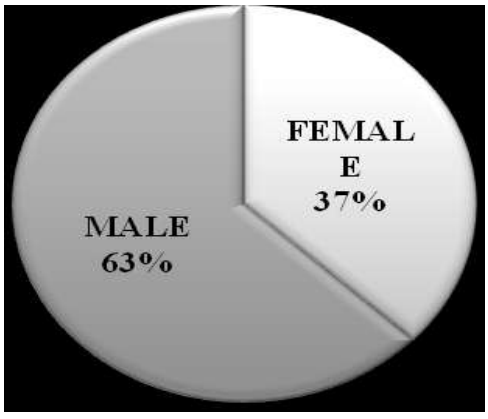

Figure 2: Graphical representation of distribution of age group with number of patients.

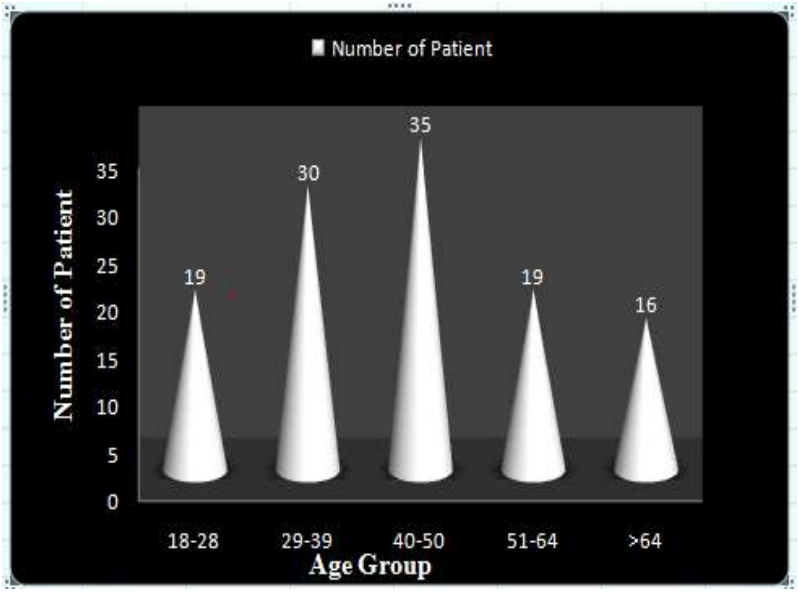

Figure 3: Graphical representation of distribution of types of seizures among both the genders

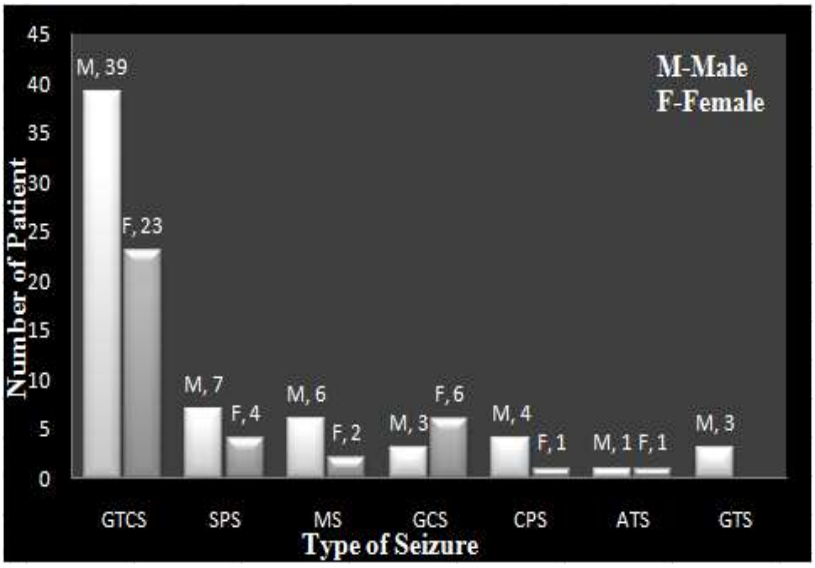

Figure 4: Graphical representation of prescribing pattern of AEDs among both genders

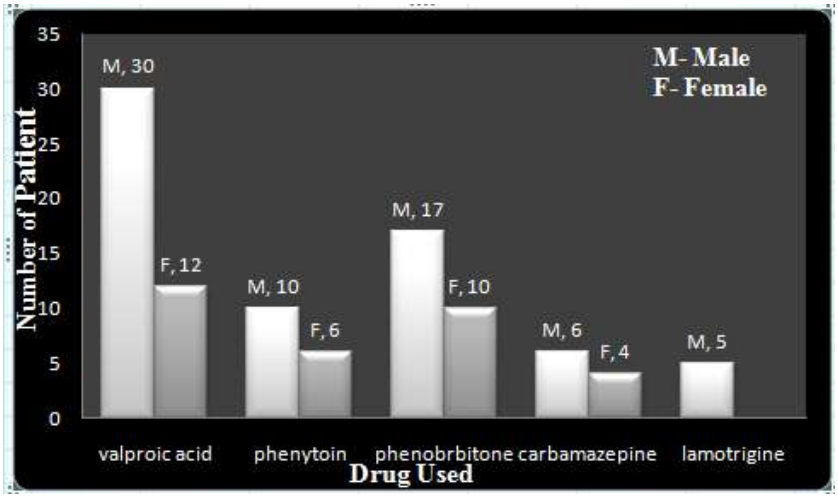

Table 1: Type of seizure and drug prescribed based on prescription analysis:

Sr. No.	Patient Age	Sex	Diagnosis	Medication
1.	43	M	Generalized tonoc-clonic seizure	Tab Valproate (400mg) TDS
2.	40	M	Partial seizure	Tab Valproate 400mg TDS & Tab Calcium 500mg IOD
3.	20	M	Generalized clonic seizure	Tab Valproate (400mg) TDS
4.	18	M	Seizure disorder	Tab FS FA 10mg IOD Tab Valproate (400mg) TDS Tab Calcium 500mg Volinigel
5.	32	F	Seizure disorder	Inj Eptoin 500mg in 100 ml Tab Tegritol 200mg BD Tab Axn gold 10mg BD
6.	38	F	Seizure disorder	Tab Mezetol 200mg TDS Tab Valproate 400mg TDS
7.	42	M	Seizure disorder	Solfoton 60mg TDS Tab Valproate 400 mg
8.	60	M	Seizure disorder	Lamictal 25mg BDS Neurontin 300mg BDS
9.	50	F	Seizure disored	Valproate 400mg TDS Tab Calcium 500mg IOD

Table 2: Interaction of AEDs with other medication

Sr. No.	AEDs	OTC, Vitamins & Herbal Drug	Effect On Epilepsy	REASON
1.	Phenytoin	Antacids (Al, Mg) Alcohol Chlorpheniramine Aspirin Theophylline Shankhapushipi	Decreases Decreases Increase Decreases/ Increase Decreases Decreases	Interfere with absorption Interfere with absorption Not known Displacement of phenytoin from plasma protein Interfere with absorption Lowered plasma phenytoin levels
2.	Carbamazepine	Terfenadine Grapefruit Asthma Medication (Theophylline only)	Increase Increase Decrease	Displacement of drug from plasma protein Increase the bioavailability Induce metabolism of carbamazepine
3.	Sodium valproate	Antacids (Al, Mg) Aspirin	Decrease Increase	Delayed absorption Inhibit the clearance
4.	Phenobarbitone	Alcohol	Increase	Inhibition of hepatic microsomal enzyme
5.	Diazepam	Alcohol Smoking tobacco Grapefruit	Increase Decreases Increase	Inhibition of hepatic microsomal enzyme Enhance the elimination Increase the bioavailability
6.	Gabapentin	Antacids	Decreases	Decrease the bioavailability
7.	Primidone	Alcohol	Increase	Inhibition of microsomal enzyme

DISCUSSION:

Now drug utilization studies (DUS) involving prescribing pattern and economic aspects in epileptic patients has been evoked. This is mainly due to an increased usage of newer AEDs that have increases the market value and costs of epilepsy treatment. However, more valuable and cost effective drug was available behind this Doctor's prescribed useless and economical drug. The present study aims to look at this aspect on Indian epileptic patients. About 100 epileptic patients were studied during a period of several months at the different hospitals in Delhi, NCR region and Lucknow. We found a higher percentage of male epileptics (63%) as compared with females (37%) [Fig-1]. Epilepsy occurring in men more than female has been reported in India. The reasons behind gender differences are not clear but it suppose that estrogen has a seizure activating effect, whereas progesterone exerts a seizure protective effect. Estrogen has an inhibitory effect on GABA receptors, potentiates excitatory glutaminergic activity, and can promote the development of seizure. Progesterone has the opposite effect and appears to potentiate GABA receptor activity and reduce neuronal discharge rate. Maximum patients included in the study were between the age groups of 40-50 years followed by 29-39 years. A higher percentage of patients were found to have generalized tonic-clonic seizures followed by Simple Partial Seizures, Myoclonic Seizures, Generalized Clonic Seizures, Complex Partial Seizures, Generalized Tonic Seizures and Atonic Seizures. In recent years, the number of drugs approved for epilepsy has been doubled. Newer AEDs provides clinicians with a wider choice to help patients achieve therapeutic efficacy even for those not responding to a conventional AED. The main reason for introducing a newer AED is the persistence of seizure activity. We found that a higher percentage of patients prescribed only monotherapy. Our observations are in contrast to several other studies where a higher percentage of patients were prescribed monotherapy (70-96%) in India. The wide use of polytherapy is a concern particularly, since there is no evidence from randomized controlled studies that shows polytherapy is superior to monotherapy in achieving seizure control. Sodium valproate was found to be the most commonly prescribed conventional AED than after phenytoin, Phenobarbitone and other drug came in work. A newer AEDs lamotrigine cover 5%. Although use of phenytoin has declined due to more side effects as compared with either carbamazepine or sodium valproate, we still found phenytoin use in 30% of prescriptions. This is because of higher efficacy of phenytoin in controlling epileptic seizures. In USA, phenytoin continuous to be the most commonly used AED. The second and third most commonly prescribed newer drugs were levetiracetam and lamotrigine respectively. Among the AED combinations, most frequently used combination was sodium valproate + clobazam followed by carbamazepine + clobazam. It is difficult to arrive at any conclusion regarding the efficacy of drug. In spite of > 50% reduction in seizures was observed in patients who were prescribed sodium valproate. To conclude, our study indicates an increasing trend toward usage of sodium valproate. However, our study was limited to hospital with limited number of patients and was designed for limited duration of time.

ACKNOWLEDGEMENT:

We wish to thank all the doctor's and staff of different hospitals in Delhi, NCR region and Lucknow for their kind cooperation in issuing the medical reports. We also extend our sincere gratitude to all the faculty of members of pharmacy department for his valuable guidance. We extend our heartfelt thankfulness to the director of Sunder Deep Pharmacy College for timely support to complete this work and my colleagues.

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