A STUDY ON DRUG USE EVALUATION OF ANTI-EPILEPTICS AT A MULTISPECIALTY TERTIARY CARE TEACHING HOSPITAL.

K.S.G. ArulKumaran,* S.Palanisamy, A.Rajasekaran
KMCH College of Pharmacy, Coimbatore-48
E-mail: yesmiarul@yahoo.com

ABSTRACT: A prospective observational study was conducted at a multi-disciplinary, super-specialty corporate hospital. The total study population was 268, in the group of patients suffering from generalized tonic-clonic seizures, sodium valproate was the most frequently prescribed AED (Anti-Epileptic Drugs), followed by carbamazepine and phenytoin. In generalized tonic seizures, sodium valproate was commonly prescribed followed by carbamazepine, topiramate, oxcarbazepine and clobazam. In generalized clonic seizures, sodium valproate and phenytoin were commonly used AEDs followed by lamotrigine and clonazepam. In absence seizures and atonic seizures, sodium valproate was the only used AED. In myoclonic seizures, sodium valproate was the most frequently prescribed AED, followed by clobazam. In the group of patients with simple partial seizures, carbamazepine was the most frequently prescribed AED, followed by phenytoin and oxcarbazepine. In complex partial seizures, carbamazepine was used followed by sodium valproate, lamotrigine and topiramate. In secondary generalized seizures, phenytoin, oxcarbazepine and clobazam were the most frequently used AEDs.

Key Words: Drug Use Evaluation, Anti-Epileptic Drugs, AED, Epilepsy, Drug Utilization

INTRODUCTION
Epilepsy is a chronic disorder characterized by recurrent seizures¹. Epilepsy is the second most common chronic neurological condition seen by neurologists. It is estimated that there are 55,00,000 persons with epilepsy in India, 20,00,000 in USA and 3,00,000 in UK². Approximately 60% of all epilepsies are idiopathic or cryptogenic. Almost any type of brain pathology can cause seizures/epilepsy. The etiology of seizure is multifactorial in any given individual and it best thought of as an interaction between genetically determined seizures thresholds, underlying predisposing pathologies or metabolic derangements and acute precipitating factors³. There are factors such as head injury and infection for which a clear and substantial risk for epilepsy has been established and a direct causal relationship could be assumed⁴.

The general approach to treatment involves the identification of goals, assessment, development of a care plan, and a follow-up evaluation. During the assessment phase, it is critical to establish an accurate diagnosis of the seizure type and classification⁵. 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; seizures occurring at night may go unnoticed and hence may not be reported. Patients with infrequent or mild seizures may not receive ongoing medical care and so may be missed in epidemiological surveys. Patients may also tend to deny a history of epilepsy in view of the stigma attached to it or feign epilepsy⁶. It is recommended that the guidelines established by the ILAE (International League Against Epilepsy) commission of epidemiology and prognosis be followed in epidemiologic studies of epilepsy⁷.

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. The aim of therapy is to minimize the recurrence of the seizures and the adverse drugs. Over 80% of epileptic patients can achieve a significant reduction in seizure frequency with one drug alone. The risks of significant adverse effects and drug interaction increase when more than one drug is used. 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.

Drug utilization was defined by World Health Organization (WHO) in 1977 as “the marketing, distribution, prescription, and use of drugs in a society, with special emphasis on the resulting medical, social and economic consequences”. Drug use/usage/utilization evaluation (DUE) was originally known as drug utilization review (DUR) in the 1970’s and early 1980’s. The terms drug utilization review (DUR) and drug use evaluation (DUE) is interchangeable.

Study of the epidemiology of epilepsy is of immense value in understanding the causes, outcome and prevention of epilepsy. It is also useful in planning proper services for persons with epilepsy and improving their quality of life. There is an urgent need for studies regarding incidence of epilepsy, prevalence of epilepsy syndromes, risk factors, and pharmacotherapy data from developing countries such as India. In many societies, epilepsy is still considered a curse of God and people do not seek help from the doctor. The treatment gap may be narrowed by better identification of persons suffering from epilepsy, better delivery of treatment and education of public.

The main objectives of the study were To describe the drug utilization pattern of anti-epileptic drugs (AEDs), To get an insight into the type and etiology of various forms of epileptic seizures, To review drug use and/or prescribing patterns, To study the effects (beneficial and adverse) of antiepileptic drugs, To promote appropriate drug use through patient counseling and other intervention, Provision of results for the clinicians, so as to aid in selecting appropriate antiepileptics and Publication of the report in the journals to serve as information to the health care professionals.

**METHODOLOGY**

**Study Design:** Prospective observational study

**Study Setting:** The study was conducted at a multi-disciplinary, super-specialty corporate hospital for a period of 8 months from July 2008 to February 2009

**Inclusion/ exclusion criteria:** The study population was limited to those who were continuously eligible for the outpatient and inpatient during the entire study period. Patients were identified through pharmacy drug prescriptions and the identification was for all inpatients and outpatients. By hospital policy all drugs are prescribed for a maximum period of 3 months. Consequently, all patients presented at least twice during the study period.

**Drugs used:** Following drugs were available and used in the hospital at the time of data collection.

- Phenytoin - Dilantin, Epitol, Eptoin.
- Carbamazepine - Tegritol, Zeptol, Carbatol, Mazetol, Manocarb, Zen retard.
- Sodium valproate - Encorate chrono, Epilex chrono, Valparin chrono.
- Lamotrigine - Lamitor-DT, Lametec.
- Gabapentin - Gabantin, Gaepalept.
- Topiramate - Topamac, Topaz.
- Fosphenytoin - Fosolin.
- Oxcarbazepine - Oleptal, Oxetal, Oxetol, Trioptal.
- Clonazepam - Epitril, Petril, Lonazep, Rivotril, Naze.
- Phenytoin - Dilantin, Epsolin, Eptoin.
- Sodium valproate - Encorate chrono, Epilex chrono, Valparin chrono.
- Carbamazepine - Tegritol, Zeptol, Carbatol, Mazetol, Manocarb, Zen retard.
- Sodium valproate - Encorate chrono, Epilex chrono, Valparin chrono.
- Lamotrigine - Lamitor-DT, Lametec.
- Gabapentin - Gabantin, Gaepalept.
- Topiramate - Topamac, Topaz.
- Fosphenytoin - Fosolin.
- Oxcarbazepine - Oleptal, Oxetal, Oxetol, Trioptal.
- Clonazepam - Epitril, Petril, Lonazep, Rivotril, Naze.
- Phenytoin - Dilantin, Epsolin, Eptoin.
- Sodium valproate - Encorate chrono, Epilex chrono, Valparin chrono.

**RESULTS**

268 patients were included in the Prospective observational study in which 31% (84) were inpatients and 69% (184) were outpatients. With respect to the admission status the large majority of the patients were outpatients. The demographic data revealed that number of male and female patients were 63% (170) and 37% (98) respectively. The age ranged from 02 - 82 yrs with 48% (129) of patients being middle age between 31 and 60. 6% (16) of patients were newly diagnosed cases of epileptic seizures. All follow-up patients had an established (clinical, neurophysiological and/or neuroradiological) diagnosis of epileptic and non-epileptic problems. 50% (134) patients were consulted because of a seizure and the remaining 50% (134) were because of non-epileptic related problems.

**Classification and etiology of epileptic seizures**

Cryptogenic epilepsy was the most common cause of epileptic seizures, followed by idiopathic, trauma/head injury, infection and systemic disease, metabolic disorder and toxic accounted for less than 1% of all causes. The etiologies of epileptic seizures are summarized in table 1.

Generalized tonic-clonic seizures accounted for almost 55.22%, followed by simple partial seizure (16.42%), complex partial seizures (8.21%), generalized tonic seizures (7.46%), myoclonic seizures (5.22%), secondary generalized seizures (2.99%), absence seizures (2.24%), and generalized clonic seizures (1.49%). Atonic seizures less commonly accounted for 0.75%. The classifications of epileptic seizures are summarized in Table 2.

**Pharmaco-epidemiologic data**

**AED utilization pattern:** A total of 346 AEDs were prescribed over the study period, corresponding to an average of 1.29 AED per patient. The overall utilization pattern of AEDs is summarized in Table 3. In this study population 76.87% (206) were prescribed an
AED in monotherapy and 17.54% (47) needed dual therapy. Polytherapy (≥ 3 AEDs) was used only in 5.22% (14) of patients. A combination of four AEDs was found in 0.37% (1) of patients.

AEDs for the treatment of epileptic seizures are summarized in table 4. In this epileptic population 60.45% (81) were prescribed an AED in monotherapy and 29.10% (39) needed dual therapy. Polytherapy was used only in 9.70% (13) of patients. Four AEDs in 0.75% (1) patient.

In the group of patients with partial seizures, 41.67% (15) were treated with monotherapy, 41.67% (15) with a combination of two drugs and 16.66% (6) with polytherapy. In the group of patients suffering from generalized seizures 67.35% (66) were treated with monotherapy and 24.49% (24) with a combination of two drugs and 7.14% (7) with a combination of three drugs and 1.02% (1) with four drugs.

**AED use profile**

Independent of the AED use profile (both monotherapy and combination therapy), sodium valproate (23.27%) was the most frequently prescribed AEDs, followed by carbamazepine (22.77%), phenytoin (16.83%), oxcarbazepine (11.39%), clobazam (9.40%), lamotrigine (5.94%), topiramate (4.46%), clonazepam (2.97%), and phenobarbitalone (2.48%). Gabapentin was less commonly accounted for 0.49% of patients. The use profile of antiepileptics for the treatment of different types of epileptic seizures is summarized in table 5.

In the group of patients with partial seizures, 30.15% were treated with carbamazepine, 15.87% were treated with phenytoin and 14.28% with oxcarbazepine. In the group of patients suffering from generalized seizures, 28.78% were treated with sodium valproate followed by 19.42% carbamazepine and phenytoin.

In the group of patients suffering from generalized tonic-clonic seizures, sodium valproate was the most frequently prescribed AED, followed by carbamazepine and phenytoin. In generalized tonic seizures, sodium valproate was commonly prescribed followed by carbamazepine, topiramate, oxcarbazepine and clobazam. In generalized clonic seizures, sodium valproate and phenytoin were commonly used AEDs followed by lamotrigine and clonazepam. In absence seizures and atonic seizures, sodium valproate was the only used AED. In myoclonic seizures, sodium valproate was the most frequently prescribed AED, followed by clobazam.

In the group of patients with simple partial seizures, carbamazepine was the most frequently prescribed AED, followed by phenytoin and oxcarbazepine. In complex partial seizures, carbamazepine was used followed by sodium valproate, lamotrigine and topiramate. In secondary generalized seizures, phenytoin, oxcarbazepine and clobazam were the most frequently used AEDs.

Comparing the prescribing pattern of AEDs, it was found that older AEDs were the most frequently used (77.72%) when compared with newer AEDs (22.28%).

**Beneficial effect:**

The goal of therapy is complete seizure control without unacceptable side effects.

**Definition of control:**

a. Good control is characterized by an absence of seizure activity since prior visit.
b. Fair control is characterized by one seizure since last visit.
c. Poor control is characterized by more than one seizure since last visit.

From the data, it was found that 67.91% (91) patients were in good control, 14.18% (19) patients were in fair control and 17.91% (24) patients were in poor control.

**Non-epileptic problems:**

In this non-epileptic study population, 93.28% (125) AEDs were prescribed as monotherapy and 5.97% (8) needed dual therapy. Polytherapy was used in 0.75% (1) patient.

In the group of patients with non-epileptic problems, 71.64% (96) of patients were treated for neuropathic pain, 10.45% (14) were treated for traumatic brain injury, 8.21% (11) for migraine, 5.22% (7) were treated for trigeminal neuralgia and 4.48% (6) for mood disorders.

Oxcarbazepine 48.61% (70) was found to be the most frequently prescribed AED for non-epileptic problems followed by Gabapentin 16.67% (24), phenytoin 15.28% (22), clobazam and clonazepam 4.86% (7), carbamazepine 3.47% (5), topiramate 2.78% (4), and sodium valproate 2.08%, phenobarbitalone 1.39% (2).

**Therapeutic drug monitoring of anti-epileptic drugs:**

During the study period therapeutic drug monitoring (TDM) was performed on only two patients. Relative to the number of patients treated for epilepsy, with sodium valproate followed by carbamazepine were only monitored.

**Tolerability:**

Sixteen patients were reported because of ADRs related to his anti-epileptic therapy: phenytoin was involved in seven ADRs (rash, urticaria, ataxia, Steven Johnson syndrome, gingival hypertrophy). Carbamazepine (rash, maculo papular rash), and oxcarbazepine (hyponatremia, osteoporosis, rash), was reported in four patients. Sodium valproate was involved in one ADRs (rash).

**DISCUSSION**

Unlike the subjects included in other pharmacoepidemiological studies, our study population was characterized by its middle age. Almost 48% of the patients were between 31 and 60. In our study, the lack of a peak in the elderly was probably because of the relative young and middle age of our study population. Generalized tonic clonic seizures followed by simple partial seizures were the most common type of epileptic seizures encountered in our study. The key to treating epilepsy is correct diagnosis of the seizure type and,
when possible, the type of epilepsy. Most patients with epilepsy respond to one of the first-line AEDs; second-line agents may be useful in patients who do not respond to one or a combination of the first-line agents. The selection of antiepileptic drugs (AEDs) is increasingly more complex as new agents become available. The best AED therapy is dependent on optimal seizure control and absence of unacceptable side effects. In our study, sodium valproate was the first-line drug prescribed in generalized seizures, followed by carbamazepine and phenytoin. Carbamazepine and sodium valproate were the AEDs of choice for the treatment of partial seizures. In this study group, sodium valproate was most commonly prescribed for the treatment of GTCS, GTS, GCS, absence, atonic and myoclonic seizures. In our study carbamazepine was the first line drug prescribed in SPS and CPS, although phenytoin was used sporadically. Increasing evidence suggests that valproic acid is a good alternative when carbamazepine and phenytoin fail.

Monotherapy was the therapy of choice in the majority of patients with partial or generalized seizures. Polytherapy offers no advantage over monotherapy. It increases the potential for drug-drug interactions, results in failure to evaluate the individual drugs, can increase the risk of chronic toxicity (including neurocognitive problems, may affect compliance and is associated with a higher cost of medication and the necessity for TDM). Despite this, polytherapy may be the only way of achieving improved seizure control in only 10% of patients with epilepsy.

Considering all types of generalized seizures sodium valproate was the most frequently prescribed AED, followed by carbamazepine. In partial seizure carbamazepine followed by phenytoin were the most frequently prescribed AEDs. A first line AED should be one, such as valproic acid, with a broad spectrum of activity that is easily managed by clinicians who may not have special expertise in the recognition of differing seizure types and epileptic syndromes.

68% of the study sample has achieved good control of epilepsy. Our study shows that most epileptics can be effectively managed with the conventional AEDs. Patients in good control need not be seen more frequently than every four to six months if they had no seizures for a six-month period. Patients whose seizure control is fair or poor should be assessed for medication adherence and other exacerbating factors. Physicians should consider placing patients on directly observed therapy (DOT) when serum levels are low and patient experience seizures.

1.5% of the study population was subjected to monitoring of AED serum levels. Sodium valproate and carbamazepine were monitored for the purpose of drug interactions and compliance.

As the ADR data were retrieved from patient medical records, it is very likely that ADR reporting was under estimated. Most accurate data could have been obtained by questioning the patient directly.

The standard AEDs such as carbamazepine, phenytoin and sodium valproate have been shown to have equivalent efficacy in the management of epileptic seizures. A more favorable pharmacokinetic profile is observed in the majority of the newer AEDs in contraposition to the classic agents. Good absorption linear kinetics and low drug-drug interaction potential make these drugs easier to use.

Newer AEDs, used as monotherapy, may be cost-effective for the treatment of patients who have experienced adverse events with older AEDs who have failed to respond to the other drugs, or where such drugs are contraindicated. In our study the limited prescribing of new generation AEDs indicated that these drugs are still relatively under used.

Oxcarbazepine was found to be the most frequently prescribed AED for non-epileptic problems, followed by gabapentin. Newer anticonvulsants such as oxcarbazepine may offer improved tolerability and fewer drug-drug interactions compared to older drugs like carbamazepine.

**CONCLUSION**

Unlike other studies, generalized seizures were most prominent, probably explaining the unique drug utilization profile. Monotherapy was most frequently used in all types of epileptic seizures. The selection of the AEDs corresponds well with the known efficacy profile for specific epileptic seizure types. The most commonly prescribed AED as sodium valproate, followed by carbamazepine, phenytoin for epilepsy. Oxcarbazepine, phenytoin was prescribed for non-epileptic problems. Most epileptics can be effectively managed with the conventional oral AEDs.

<table>
<thead>
<tr>
<th>S.No</th>
<th>Etiology</th>
<th>No of patients</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Idiopathic</td>
<td>6</td>
<td>4.48</td>
</tr>
<tr>
<td>2</td>
<td>Cryptogenic</td>
<td>111</td>
<td>82.83</td>
</tr>
<tr>
<td>3</td>
<td>Trauma/head injury</td>
<td>5</td>
<td>3.73</td>
</tr>
<tr>
<td>4</td>
<td>Infection</td>
<td>5</td>
<td>3.73</td>
</tr>
<tr>
<td>5</td>
<td>Systemic disease</td>
<td>5</td>
<td>3.73</td>
</tr>
<tr>
<td>6</td>
<td>Metabolic disorder</td>
<td>1</td>
<td>0.75</td>
</tr>
<tr>
<td>7</td>
<td>Toxic</td>
<td>1</td>
<td>0.75</td>
</tr>
</tbody>
</table>
Table 2. Classification of epileptic seizures. (N=134)

<table>
<thead>
<tr>
<th>S. No</th>
<th>Classification of seizures</th>
<th>No of patients</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>GTCS</td>
<td>74</td>
<td>55.22</td>
</tr>
<tr>
<td>2.</td>
<td>GTS</td>
<td>10</td>
<td>7.46</td>
</tr>
<tr>
<td>3.</td>
<td>GCS</td>
<td>02</td>
<td>1.49</td>
</tr>
<tr>
<td>4.</td>
<td>Absence seizures</td>
<td>03</td>
<td>2.24</td>
</tr>
<tr>
<td>5.</td>
<td>Myoclonic seizures</td>
<td>07</td>
<td>5.22</td>
</tr>
<tr>
<td>6.</td>
<td>Atonic seizures</td>
<td>01</td>
<td>0.75</td>
</tr>
<tr>
<td>7.</td>
<td>SPS</td>
<td>22</td>
<td>16.42</td>
</tr>
<tr>
<td>8.</td>
<td>CPS</td>
<td>11</td>
<td>8.21</td>
</tr>
<tr>
<td>9.</td>
<td>SGS</td>
<td>04</td>
<td>2.99</td>
</tr>
</tbody>
</table>

Table 3. Overall AEDs utilization (N=268)

<table>
<thead>
<tr>
<th>S. No</th>
<th>AED therapy</th>
<th>No of patients</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>Monotherapy</td>
<td>206</td>
<td>76.87</td>
</tr>
<tr>
<td>2.</td>
<td>Dual therapy</td>
<td>47</td>
<td>17.54</td>
</tr>
<tr>
<td>3.</td>
<td>Three drugs</td>
<td>14</td>
<td>5.22</td>
</tr>
<tr>
<td>4.</td>
<td>Four drugs</td>
<td>1</td>
<td>0.37</td>
</tr>
</tbody>
</table>

Table 4. AEDs for the treatment of epileptic seizures. (N=134)

<table>
<thead>
<tr>
<th>S.No</th>
<th>AED Therapy</th>
<th>No of patients</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Partial seizures</td>
<td>Generalized seizures.</td>
</tr>
<tr>
<td>1.</td>
<td>Monotherapy</td>
<td>41.67% (15)</td>
<td>67.35% (66)</td>
</tr>
<tr>
<td>2.</td>
<td>Dual therapy</td>
<td>41.67% (15)</td>
<td>24.49% (24)</td>
</tr>
<tr>
<td>3.</td>
<td>Three drugs</td>
<td>16.66% (6)</td>
<td>7.14% (7)</td>
</tr>
<tr>
<td>4.</td>
<td>Four drugs</td>
<td>0% (0)</td>
<td>1.02% (1)</td>
</tr>
</tbody>
</table>
Table 5. AED use profile as a function of the type of epileptic seizure. (N=202)

<table>
<thead>
<tr>
<th>S.No</th>
<th>Antiepileptic drug</th>
<th>Generalized seizures (No of drugs)</th>
<th>Partial seizures(No of drugs)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>GCT</td>
<td>GS</td>
</tr>
<tr>
<td>1.</td>
<td>Sodium Valproate</td>
<td>27</td>
<td>3</td>
</tr>
<tr>
<td>2.</td>
<td>Carbamazepine</td>
<td>24</td>
<td>2</td>
</tr>
<tr>
<td>3.</td>
<td>Phenytoin</td>
<td>21</td>
<td>1</td>
</tr>
<tr>
<td>4.</td>
<td>Lamotrigine</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td>5.</td>
<td>Clonazepam</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>6.</td>
<td>Phenobarbionate</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>7.</td>
<td>Topiramate</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>8.</td>
<td>Oxcarbazepine</td>
<td>12</td>
<td>2</td>
</tr>
<tr>
<td>9.</td>
<td>Clobazam</td>
<td>9</td>
<td>2</td>
</tr>
<tr>
<td>10.</td>
<td>Gabapentin</td>
<td>1</td>
<td></td>
</tr>
</tbody>
</table>

REFERENCES
6) Sridharan, R., Radhakrishnan, K., Ashok, PP. & Mousa, ME. Epilepsia 1986;27:60-65


*****