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# IDENTIFICATION, EVALUATION AND ANALYSIS OF DRPs IN PATIENTS WITH SEIZURE DISORDERS IN A TERTIARY CARE TEACHING HOSPITAL

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**ABSTRACT**

The primary objective of the study was the identification, evaluation and analysis of Drug Related Problems (DRPs). This study identifies Adverse Drug Reactions (ADRs) and categorizes drug-drug interactions based on their severity. A prospective observational study was conducted in a tertiary care teaching hospital for a period of 6 months. All inpatients in Medicine, Pediatric, Intensive Care Unit (ICU) and emergency wards with clinical diagnosis of seizure irrespective of age, sex and presence of concurrent diseases were included in the study. Out of 100 patients enrolled, most commonly found etiology was fever, followed by epilepsy. Generalised Tonic Clonic Seizure (GTCS) was found to be the major seizure type. Out of 184 drugs, Hydantoin was the most prescribed class of drug, i.e. 31.52%. The most common drug prescribed was Phenytoin 29.35%. Out of total 190 drug-drug interactions, 9 (4.74%) were major, 111 (58.42%) were moderate and 70 (36.84%) were minor. 59 (59%) prescriptions follows the standard guideline. A total of 17 ADRs were identified. The present study has attempted to reveal the drug related problems in seizure disorder. Even though, majority prescriptions follows standard guideline; a large margin does not. Out of the 17 ADRs found, 11 were due to Phenytoin and 6 were due to Sodium Valproate. Hence, this study has vital role in the treatment of seizure.

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## INTRODUCTION

A seizure is a paroxysmal event due to abnormal excessive or synchronous neuronal activity in the brain. Depending on the distribution of discharges, this abnormal activity can have various manifestations, ranging from dramatic convulsive activity to experimental phenomena not readily discernible by an observer.[1] It is estimated that approximately 15% of people with strokes will eventually develop epileptic seizures. Vascular malformations and cerebral aneurysms may also cause symptomatic epilepsy, whether or not hemorrhage has occurred.[2]

The fundamental principle is that seizures may be either focal or generalized.

**Focal Seizure or Partial Seizure - Focal seizure can be sub-classified into**

- Simple Partial Seizure: Discharge remains localized and consciousness is fully preserved.
- Complex Partial Seizure: Seizure progresses with loss of consciousness.
- Secondary Generalized Seizure: Convulsive seizure occurs with loss of consciousness.[3]

**Generalized seizure:** Generalized seizures are thought to arise at some point in the brain but immediately and rapidly engage neuronal networks in both cerebral hemispheres.[1]

- Absence Seizure - Typical absence seizures are characterized by sudden, brief lapses of consciousness without loss of postural control.[1]
- Tonic Clonic Seizure - The initial phase of the seizure is usually tonic contraction of muscles throughout the body. Respirations are impaired, secretions pool in the oropharynx, and cyanosis develops. Bladder or bowel incontinence may occur at this point.[1]
- Atonic Seizure - Atonic seizures are characterized by sudden loss of postural muscle tone lasting 1–2 seconds.[1]
- Myoclonic Seizure - Myoclonus is a sudden and brief muscle contraction that may involve one part of the body or the entire body.[1]

**Anti-epileptic drugs are those drugs used to prevent the seizures or epilepsy. They are classified as follows:**

1. Barbiturate: Phenobarbitone, Pentobarbitone
2. Deoxybarbiturate: Primidone
3. Hydantoin: Phenytoin, Fosphenytoin
4. Iminostilbene: Carbamazepine, Oxcarbamazepine
5. Succinimide: Ethosuximide
6. Aliphatic Carboxylic Acid: Valproic Acid
7. Benzodiazepines: Clonazepam, Diazepam, Clobazam
8. Phenyltriazine: Lamotrigine
9. Cyclic GABA analogue: Gabapentin
10. Newer Drugs: Levetiracetam, Tiagabin, Topiramate, Vigabatrin [4]

Control of seizures can be achieved through medication adherence. More than half of epilepsy patients have poor seizure control due to non adherence to medication. In addition, non adherent patients were also more likely to be hospitalized.[5]

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".[6]

DRP is defined as 'an event or circumstance involving drug therapy that actually or potentially interferes with desired health outcomes. An actual problem has resulted in clinical manifestations like adverse drug reaction or therapy failure due to incorrect dosage.[7]

## MATERIALS AND METHODS

A prospective observational study was conducted in the inpatients having seizure disorders in Medicine, Pediatric, ICU and Emergency ward with irrespective of age, sex presence of concurrent diseases in a tertiary care teaching hospital of Davangere for a period of 6months**.** The demographic details, clinical diagnosis, seizure type, lab investigations, drug, dose, frequency, dosage of Anti-Epileptic Drugs (AEDs) were recorded. All prescriptions will be assessed for DRPs such as ADRs, Drug-Drug Interaction etc.

### Ethical issues

The ethical clearance for the study was obtained from Institutional ethical committee of Bapuji Pharmacy College, Davangere.

### Study procedure

The study was carried out by regular visits to various in-patient departments and case sheets of 100 patients were collected. The relevant data collected from case sheets were properly documented in a separate data collection form. The obtained data were then identified, evaluated and analyzed based on gender, age group, known case of epilepsy, etiology, type of seizure, route of administration, class of AEDs, AEDs prescribed, type of AEDs prescribed, type of therapy, comparison of prescription against standard guideline, drug-drug interaction based on severity, drug-drug interactions with AEDs, distribution of suspected ADRs.

**RESULTS**

A total of 100 prescriptions were collected, out of which 63 (63%) were males and 37 (37%) were females.

**Table 1: Distribution based on AEDs Prescribed.**

| AEDs | Number (n=184) | Percentage (%) |
|---|---|---|
| Phenytoin | 54 | 29.35 |
| Levetiracetam | 37 | 20.12 |
| Valproic acid | 30 | 16.30 |
| Clobazam | 21 | 11.42 |
| Lorazepam | 12 | 6.52 |
| Midazolam | 10 | 5.43 |
| Clonazepam | 5 | 2.72 |
| Fosphenytoin | 4 | 2.17 |
| Carbamazepine | 3 | 1.63 |
| Oxcarbazepine | 3 | 1.63 |
| Phenobarbitone | 2 | 1.09 |
| Alprazolam | 1 | 0.54 |
| Diazepam | 1 | 0.54 |
| Topiramate | 1 | 0.54 |

A total of 184 AEDs were prescribed, Hydantoin 58 (31.52%) was the frequently prescribed class followed by Benzodiazepines 50 (27.17%), Newer drugs 38 (20.66%), Aliphatic Carboxylic Acid 30 (16.30%), Iminostilbene 6 (3.26%), Barbiturates 2 (1.09%). Out of the 184 AEDs prescribed the frequently prescribed drug was Phenytoin 54 (29.35%), followed by Levetiracetam 37 (20.12%), Valproic acid 30 (16.30%), Clobazam 21 (11.42%), Lorazepam 12 (6.52%), Midazolam 10 (5.43%), Clonazepam 5 (2.72%), Fosphenytoin 4 (2.17%), Carbamazepine 3 (1.63%), Oxcarbamazepine 3 (1.63%), Phenobarbitone 2 (1.09%), Alprazolam 1 (0.54%), Diazepam 1 (0.54%) and Topiramate 1 (0.54%). [Table 1]

**Table 2: Comparison of prescription against Standard Guidelines.**

| Following standard guidelines | Number (n=100) | Percentage (%) |
|---|---|---|
| Yes | 59 | 59 |
| No | 41 | 41 |

59 (59%) of prescription were in accordance with the standard guidelines. [Table 2].

**Table 3: Distribution of Drug-Drug Interactions based on severity.**

| Drug–Drug Interaction classification | Number (n=190) | Percentage (%) |
|---|---|---|
| Major | 9 | 4.74 |
| Moderate | 111 | 58.42 |
| Minor | 70 | 36.84 |

There were a total of 190 drug interactions. They were categorized into three based on severity. Major 9 (4.74%), Moderate 111 (58.42%) and Minor 70 (36.84%). [Table 3].

**Table 4: Distribution of drug-drug interactions with AEDs.**

| Interactions | Major (n=5) | Percentage (%) | Moderate (n=94) | Percentage (%) |
|---|---|---|---|---|
| AED + AED | 1 | 20 | 39 | 41.49 |
| AED + OTHERS | 4 | 80 | 55 | 58.51 |

There were 99 drug interaction involving AEDs, out of which 5 were major and 94 were moderate interaction .In the 5 major drug interactions there were only one interaction involving both AEDs (Diazepam + Phenytoin). Remaining 4 major interactions involved an AED + other drug (Fosphenytoin + Nifedipine, Fosphenytoin + Ondansetron, Dopamine + Phenytoin, Cilastatin, Imipenam + Valproic Acid). There were 94 moderate interactions in which AED + AED (39) and AED + other (55). [Table 4]

**Table 5: Distribution of Suspected ADRs.**

| Drug | ADRs | Number (n=17) |
|---|---|---|
| Phenytoin | Anemia | 5 |
| | Rashes | 4 |
| | Gum hypertrophy | 1 |
| | Thrombocytopenia | 1 |
| Sodium Valproate | Anemia | 3 |
| | Thrombocytopenia | 2 |
| | Alopecia | 1 |

Among 100 patients suspected ADRs were 17. Majority of the ADR were due to Phenytoin (rashes 4, gum hypertrophy 1, anemia 5, thrombocytopenia 1) followed by Sodium Valproate (anemia 3, thrombocytopenia 2, alopecia 1). [Table 5]

**DISCUSSION**

Our study was conducted in a tertiary care teaching hospital. A total of 100 patients were enrolled and were categorised based on gender, age, known case of epilepsy or not, etiology, type of seizure and categorised AEDs based on their class and type. We also categorized the type of therapy, adherence of the prescription to standard guideline, based on drug-drug interaction, suspected ADRs.

Unlike subjects included in other studies, our study population was characterised by pediatric patients. Among the 100 patients, majority of the patients come under the age group of 1-10 years and the least number of patients was from the age group of 31-40 years. This was in contrast to the study done by Juny Sebastian et al in which 29.8% patients were from the age group of 11- 20 years and only 3.4% were from the age group of above 60 years.[8] This shows a higher prevalence of seizure disorders in the age group of 1-10. According to the literatures, the incidence of epilepsy has a bimodal distribution with a peak in the first decade and a second peak in the elderly.[2,9,10] Our study also shows more prevalence of seizure in males i.e. 63% male patients and 37% female patients which was similar to the study conducted by Juny Sebastian et al, males were 61.3% and females were 38.7%.Out of 100 patients, 42% of patients were known case of epilepsy who were admitted to the hospital with a recurrent episode of seizures and remaining 58% of patients were newly diagnosed with seizures.[8]

In our study GTCs (63%) was the most occurred type of seizure which is similar to the study conducted by K.S.G Arulkumaran et al.[11] But second most occurred type of seizure was a febrile seizure (19%) which is in contrast to the study conducted by Wakjira Rishe et al.[6] This is because our study enrolled more number of paediatric patients who were prone to febrile seizures. Generalized tonic-clonic seizures accounted for almost 63%, followed by febrile seizure 19%, tonic seizure 9%, focal seizure 6%, myoclonic seizure 2%, pseudo seizure 1%. Regarding various etiologies of seizure our study noted that 32(32%) of patients had fever, followed by epilepsy 30%. The other cause were head injury 9(9%), meningoencephalitis9 (9%), Cerebrovascular accident6 (6%), cerebral palsy3 (3%), meningitis3 (3%), Chronic kidney disease2 (2%), idiopathic 1 (1%), hypocalcaemia 1 (1%), Rheumatoid heart disease 1 (1%), trigeminal neuralgia 1 (1%) and others 2(2%).

AEDs are the drug of choice for treatment of seizure which needs a close monitoring due to the higher incidence of DRPs, ADRs and interactions. Our study also reveals that still conventional drugs are used more frequently than newer drugs which is similar to study conducted by Manisha Naithani et al.[12] It was also observed that AEDs were mostly prescribed by IV route followed by oral ie, IV 114(54.03%), Oral 97(45.97%). Mostly IV route is preferred over oral route to get an easy and fast control over seizure episodes.

Majority of DUE studies emphasize that, monotherapy was the therapy of choice in the majority of patients with partial or generalized seizures. Poly-therapy offers no advantage over monotherapy. In our study most of the patient received monotherapy followed by dual therapy i.e. 55% patient received monotherapy and 20% received dual therapy Similar to a study conducted by Wakjira Rishe et al Monotherapy was received by patients 78.6% and dual therapy by 21.4% of patients.[7]

In our study, a total of 184 AEDs are prescribed, out of which 31.52% of patients received AEDs of the class Hydantoins followed by Benzodiazepines (27.17%), Newer Drugs (20.66%). Barbiturates were the least prescribed class. It was interesting to note that out of the 184 AEDs prescribed, Phenytoin was most frequently prescribed AED ie, 29.35% followed by Levetiracetam 20.12% and Valproic acid of 16.30%. The highly used AED among the study population was Phenytoin (41.7%) patients and Valproic acid (41.%), both were mainly used for generalized seizures. The reason for high use of Phenytoin was lower cost and ease of availability. A study conducted by Juny Sebastian et al has a similar drug use profile i.e., Phenytoin was frequently prescribed drug,[8] but this was in contrast to the study conducted by Wakjira Rishe et al because Phenobarbitone 92.8% was the most commonly prescribed AED followed by Phenytoin 3.8%, Carbamazepine 1.7% and Sodium valproate 1.4%.[7]

The treatment of seizure depends on the type of seizure and the ultimate goal of treatment for epilepsy is no seizure and no side effects with an optimal quality of life. In our study it was noted that 59(59%) of prescriptions followed standard guideline. In our study, about 190 drug interactions were identified and were categorized as major 9(4.74%), moderate 111(58.42%), minor 70 (36.84%). Out of this we observed that there was 1 major interaction involving AED + AED and 39 moderate interaction involving AED + AED. We also observed that there were4 major and 55 moderate drug interactions involving AED + other drugs. Out of the 190 drug interactions, above 50% of interactions involved AEDs.

The adverse effects data were retrieved from patient medical records and by questioning the patient directly. From our study, we were able to identify 17 suspected ADRs. Majority of the ADR were due to Phenytoin (rashes 4, gum hypertrophy 1, anemia 5, thrombocytopenia 1) followed by Sodium Valproate (anemia3, thrombocytopenia 2, alopecia 1). Many literatures evidences suggest that Phenytoin causes ADR's like rashes, gum hypertrophy, anemia, thrombocytopenia and Sodium valproate causes ADR's like anemia, thrombocytopenia, alopecia.

## CONCLUSION

To conclude, this study provides insight about the seizure occurrence, the AED drug prescription and drug related problems in seizure disorder. The finding of our study concluded that drug-drug interactions, ADRs are quite common in the prescription of seizure disorder. Even though majority of the prescription follows standard guidelines (59%), a large margin of prescription does not follow (41%). The uses of newer AEDs (20.65%) have been improved in the present times but still conventional AEDs (79.35%) are most frequently prescribed. GTCS were the most prominent seizure encountered. Monotherapy was most commonly used in all type epileptic seizure.

The primary objective of this study was to identify DRPs. The study reveals that DRPs are common in antiepileptic drug prescriptions in seizure disorders. We had suspected 17 ADRs and 190 drug-drug interactions. Majority of the ADR were due to Phenytoin ie, skin rashes was seen in 4 patients, gum hypertrophy in 1 patient, anemia was suspected in 5 patients, thrombocytopenia in 1 patient. Remaining ADRs were suspected with Sodium Valproate ie, anemia in 3 patients, thrombocytopenia in 2, alopecia in 1 patient. In our study, about 190 drug interactions has been found out and are categorized as major 9(4.74%), moderate 111(58.42%), minor 70(36.84%). Out of this we observed, one AED + AED major interaction and 39 AED + AED moderate interactions. Also 4 major and 55 moderate AED + Other drug-drug interactions were noted.

This shows a significant incidence of drug-drug interactions and ADR occurrence in prescribing pattern of AEDs in seizure disorder. Therefore it is important to closely monitor and identify the drug related problems that are related to AEDs, thus to improve the quality of treatment.

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