

RESEARCH ARTICLE

Drug utilization pattern of antiepileptic drugs in a tertiary care teaching rural hospital

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ABSTRACT

Background: Antiepileptic drugs (AEDs) are also commonly used therapy for other conditions like prophylaxis for a manic-depressive disorder, to relieve neuralgic pain and for many more conditions apart from epilepsy. Data suggest that 45% of AEDs prescriptions were for conditions other than epilepsy. All of these uses are off-label except for some AEDs approved for limited indications. **Aims and Objective:** To study the AEDs utilization pattern in a tertiary care teaching rural hospital in India. **Materials and Methods:** Patients who prescribed AEDs by treating physician from the various outpatient departments of a tertiary care hospital were enrolled in the study irrespective of their diagnosis. Their demographic data, clinical profile and drug use related details were obtained from the case files and history and analyzed. **Results:** Out of total 160 patients enrolled, the majority were male 103 (64.4%), in the age group of 18-65 years (123, 76.9%), and from neuromedicine 149 (93.1%) department. 81 (50.63%), 45 (28.12%), and 10 (6.25%) were diagnosed as epilepsy, pain, and psychomotor disorders, respectively, and remaining patients having a dual indication for AEDs prescription. Partial epilepsy (45, 47.87%) was the most common type and cryptogenic (44, 46.80%) was most common aetiological factor among epileptic patients. Average number of AEDs prescribed per patient was 1.331. 113 (70.6%) patients were managed by monotherapy. Most frequently prescribed AEDs were pregabalin (20.19%) followed by phenytoin (16.90%). Conventional AEDs (78.95%) were prescribed more frequently than newer AEDs (21.05%) for epilepsy; while newer AEDs (68.10%) were frequently prescribed in patients suffering from non-epileptic condition. 52% of drugs were prescribed by generic name. No fixed dose combinations of AEDs were prescribed throughout this study period. **Conclusions:** The use of AEDs not limited to epilepsy only. AEDs were prescribed more frequently in neuropathic pain and psychiatric disorders other than epilepsy. AEDs are usually prescribed as monotherapy and by generic name and not as fixed dose combination. Awareness about off-label use of AEDs is essential for its appropriate use.


KEY WORDS: Drug Utilization Study; Antiepileptic Drugs; Non-epileptic Uses

INTRODUCTION

Epilepsy is a common, chronic neurological disorder which requires long-term management and imposes a large burden

on health-care systems. Treatment with antiepileptic drugs (AEDs) is the most common choice for epilepsy management. Pharmacological treatment available for management of epileptic patients is AEDs. Therapy for these patients is only symptomatic with the available drugs. The drugs are effective neither for prophylaxis nor for cure.^[1,2]

AEDs are also commonly used therapy for other conditions like prophylaxis for a manic-depressive disorder,^[3] to relieve neuralgic pain, and for many more conditions apart from epilepsy. Data suggest that 45% of AEDs prescriptions were for conditions other than epilepsy.^[4] All of these uses

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are off-label except for some AEDs approved for limited indications, i.e., gabapentin and pregabalin for post-herpetic neuralgia, benzodiazepines as sedatives-hypnotics and antianxiety, pregabalin for fibromyalgia, diabetic neuropathy, topiramate for prophylaxis of migraine headache.^[5]

To assess the prescribing pattern of AEDs in various diseases (both epilepsy and non-epileptic conditions) is important to know expanded utilization of these AEDs in various conditions and co-relate with available literature. There are limited studies from India which describe utilization pattern of AEDs in all conditions.

Taking into consideration of above points, this study was planned to study the various facets of AEDs prescribing in Shree Krishna Hospital, a tertiary care teaching rural hospital attached to Pramukhswami Medical College, Karamsad, Gujarat.

MATERIALS AND METHODS

A prospective observational study spread over 1 year and 7 months duration was undertaken from February 2010 to October 2011, in Shree Krishna Hospital, a tertiary care teaching rural hospital attached to Pramukhswami Medical College, Karamsad, Gujarat, India. The protocol was approved by the Institutional Human Research Ethics Committee of the Institute. All the patients were explained clearly about the nature and purpose of the study in the language they understood, and written informed consent was obtained before enrolling them for the study. For the pediatric patients, written informed consent was obtained from the parents.

Sample Size

All the patients visited to outpatient department (OPD) of Neuromedicine, Neurosurgery, and Paediatric Department of the Shree Krishna Hospital in the study duration and who receive AEDs as the treatment from irrespective of diagnosis, age or sex were included in the study.

Collection of Data

Data of recruited patients were collected from the respective department and from patient case sheet, and discharge card to complete filling of case record form. In this hospital, the

specialty OPD is conducted by neurophysician, neurosurgeon and pediatric epilepsy clinic by the pediatrician on the specific day of the week and month in later case (Monday, Wednesday, Friday of each week – neurosurgery and neuromedicine; every alternate Thursday – pediatrics epilepsy clinics). The researcher had allotted special time of 9 am-1 pm of every special OPD day to visit these departments. All patients taking treatment in these clinics were eligible for inclusion in this study. Hence, all patients who visited these OPD were explained in prior about the purpose and nature of study in the language they can understand and written informed consent was obtained before enrolling them into study. The patients who gave informed written consent were enrolled.

Format of Analysis

Patient details

Age and sex wise analysis; departments: Three groups, i.e., pediatrics, neuromedicine, neurosurgery; diagnosis: Three groups, i.e., epilepsy, neuropathy, and psychomotor disorder (again categorized in subgroups).

Analysis of AEDs

Total number of AEDs prescribed per patient; average number of AEDs prescribed per patient; AEDs prescribed by generic name or brand name or both; prescription pattern of AEDs according to their diagnosis in category and subcategory.

RESULTS

Data of total 160 patients were collected from OPD of Neuromedicine, Neurosurgery, and Paediatrics of Shree Krishna Hospital.

The mean age of the patients having epilepsy was 37.41 with a range of 1-79 years. Age distribution of the patients who were taking AEDs for pain disorders and psychomotor disorders were <18 years (02, 0), 18-65 years (46, 24), >65 years (14, 04), respectively. The mean age of patients who had pain disorders and psychomotor disorders were 49.85 and 50.82 years, respectively. Mean age of male and female patients was 43.76 and 42.67 years, respectively. Another information on demographic data is presented in Table 1.

Table 1: Demographic data: Age, sex and department wise distribution of patients

Age (years)	Department									Total		
	Medicine			Surgery			Paediatrics			M	F	Total (%)
	M	F	Total (%)	M	F	Total (%)	M	F	Total (%)			
<18	6	2	8 (5.0)	1	0	1 (0.7)	5	0	5 (3.1)	12	2	14 (8.8)
18-65	69	49	118 (73.8)	4	1	5 (3.1)	0	0	0	73	50	123 (76.8)
>65	18	5	23 (14.4)	0	0	0	0	0	0	18	5	23 (14.4)
Total	93	56	149 (93.1)	5	1	6 (3.8)	5	0	5 (3.1)	103 (64.4)	57 (35.6)	160 (100)

A total 184 diseases had been observed in 160 patients who were enrolled in this study. This discrepancy is because one patient might suffer from more than one disease at a time (Table 2). The patients who were diagnosed epilepsy, classified according to classification given by ILAE in 2010 (Table 3). Total 62 patients diagnosed as pain disorders with 81 total conditions with dominancy of migraine headache (12 patients), diabetic neuropathy (10 patients), and radiculopathy (9 patients).

The frequency of prescribing of AEDs of various groups was 213 among 160 patients included in this study. Hence, average number of AEDs prescribed per patient was counted as 1.331 (213/160). All AEDs were prescribed by oral route. The dosage forms were either capsule, tablet or syrup. On initiation of therapy with new AEDs, all the AEDs were started at very low dose and then increased over 10-15 days to the maintenance dose. The opposite way was applied for stoppage of drugs; i.e. when physician wanted to stop any drug, whenever there was adverse event or failure of therapy, the de-escalation was also done over 10-15 days.

Table 2: Distribution of the patients according to diseases in which AEDs were indicated

Diseases	Number of patients (%)
Epilepsy alone	81 (50.63)
Pain disorders alone	45 (28.12)
Psychomotor disorder alone	10 (6.25)
Pain disorders with psychomotor disease	11 (6.88)
Psychomotor disorder with seizure	07 (4.38)
Epilepsy with pain disorders	6 (3.75)
Total	160 (100)

AED: Antiepileptic drugs

Table 3: Classification and distribution of patients having epilepsy (N=94)

Types of epilepsy	Number of patients (%)
Generalized seizure	
GTCS	28 (29.78)
Generalized tonic seizure	01 (1.07)
Generalized myoclonic seizure	08 (8.51)
Total	37 (39.36)
Partial seizure	
Simple partial seizure	04 (4.25)
CPS without generalization	16 (17.02)
CPS with generalization	20 (21.27)
Total	45 (47.87)
GTCS/CPS with generalization	05 (5.32)
Prophylaxis of seizures	12 (12.77)

CPS: Complex partial seizures, GTCS: Generalized tonic-clonic seizures

Out of 213 AEDs prescribed, 111 (52%) drugs were prescribed by generic name, 78 (37%) and 24 (11%) drugs were prescribed by brand name or both by generic and brand name. As 213 AEDs had been prescribed in 160 patients, many patients were prescribed more than one drug at a time. 113 (70.6%) patients were prescribed monotherapy, where 41 (25.6%) and 6 (3.8%) patients were prescribed dual and triple therapy, respectively. No fixed dose combinations of AEDs were prescribed throughout this study period.

Phenytoin sodium and pregabalin were most commonly prescribed AED in epilepsy and pain disorders, respectively. The most common drugs prescribed for generalized epilepsy were valproate followed by phenytoin. The most common AEDs prescribed were oxcarbazepine, phenytoin in the patients having partial epilepsy and prophylaxis of epilepsy, respectively. Conventional AEDs (78.95%) were prescribed more frequently than newer AEDs (21.05%) for epilepsy. Total 78 and 38 AEDs were prescribed for pain disorders and psychomotor disorder. The most common drug prescribed for both the conditions was pregabalin. Newer AEDs (68.10%) were most commonly prescribed in patients suffering from non-epileptic condition than conventional AEDs (31.90%). Overall, 120 (56.34%) and 93 (43.66%) AEDs prescriptions were of older generation and newer generation, respectively (Table 4).

DISCUSSION

The treatment with AEDs is the most common choice for epilepsy management. AEDs are also commonly used therapy for other conditions like prophylaxis for a manic-depressive disorder, to relieve neuralgic pain and for many more conditions apart from epilepsy. All of these uses are off-label except for some AEDs approved for limited indications.

A total of 160 patients were enrolled in this study who were prescribed AEDs, out of this majority (76.9%) of the patients were from age group 18-65 years irrespective of diagnosis. This finding is matched with Arulkumaran et al. study conducted in Coimbatore with 48% of patients being middle age between 31 and 60 years.^[6] In the subgroup of epileptic patients, 77.7% were from 18 to 65 years of age. This finding suggests a lack of peak at extremes of age for epilepsy. This may be because of relative young and middle age of study population. However, it contradicts the western studies with a higher prevalence of epilepsy in extremes of age.^[7-9]

In this study, a number of male patients was higher than female patients. The same pattern was seen in Arulkumaran et al. study conducted in Coimbatore, Pal et al. study conducted in Cuttack, and Pal et al. study in Chandigarh, India.^[10,11] All these studies are hospital based. However,

Table 4: Prescription pattern of AED in different diseases

Drugs	Diseases						Total
	Epilepsy	Pain disorders	Psycho-motor disorders	Epilepsy with pain disorders	Epilepsy with psycho-motor disorders	Pain disorders with psycho-motor disorders	
Pregabalin	01	26	08	0	0	08	43
Phenytoin	31	0	0	02	03	0	36
Oxcarbazepine	16	09	02	01	01	0	29
Carbamazepine	12	07	0	02	01	0	22
Clonazepam	09	03	0	0	06	04	22
Valproate	18	01	0	0	02	0	21
Clobazepam	13	0	0	01	01	0	15
Topiramate	01	06	0	0	0	02	09
Levetiracetam	06	0	0	01	0	0	07
Phenobarbital	04	0	0	0	0	0	04
Gabapentin	0	03	0	0	0	0	03
Lamotrigine	01	0	0	0	0	0	01
Divalproate	0	01	0	0	0	0	01
Total	112	56	10	07	14	14	213

Sridharan study (2003) and Bharucha study in India stated that there was no difference in prevalence of epilepsy in both sexes in rural area.^[12,13] The difference may be because of our study is hospital based; Sridharan study and Bharucha study were population based. Moran et al. in the UK stated that the prevalence of epilepsy was same in both sexes.^[14] Similar study in Dutch by Lammers et al. showed equal distribution in both sexes.^[15]

In our study, the majority of the patients were from neuromedicine department which suggests that being a tertiary care hospital we have special clinic conducted as neuromedicine and neurosurgery, most of the patients referred to speciality clinic or higher number of patient visits OPD of neuromedicine. There was less number of patients from pediatric department because frequency of pediatric epilepsy clinic was less (once in 15 days) than neurosurgery and neuromedicine clinic (trice in a week).

About 51.09% and 48.91% patients were prescribed AEDs for epileptic and non-epileptic indication, respectively, in our study. The similar finding was observed by Arulkumaran et al. study in Coimbatore.^[6] In 2003, neurologists in the US reported that 45% of their AEDs prescriptions were for conditions other than epilepsy, with a migraine and neuropathic pain commanding the bulk of them.^[4] There is rising trend of prescribing AEDs for pain and mood disorders.^[16,17] These findings reveal that frequency of use of AEDs in non-epileptic conditions is same that of the epileptic use.

Partial seizures were the most common type followed by generalized epilepsy in our study. Other studies conducted in various parts of India suggest that generalized seizure was the most common type of epilepsy.^[6,11,18] In a review

done by Shridharan, it was found that partial seizures were more common than generalized seizures.^[12] The most common type of pain disorders was migraine followed by diabetic neuropathy and radiculopathy in our study for which AEDs were prescribed. For psychomotor disorders mood disorders including anxiety, dysthymia and depression were the most common indication. A similar finding was seen in Arulkumaran et al. study in Coimbatore.^[6]

Average number of AEDs prescribed was 1.331 per patient in our study. The results of Mathur study in Hyderabad, Arulkumaran et al. study in Coimbatore, India confirmed our finding.^[6,18] The similar finding was seen in Moran et al. study in the UK, Hanssens et al. study in Oman, Chen et al. study in Taiwan.^[14,19,20] We are not able to distinguish average number of AEDs prescribed per patients between epileptic and non-epileptic conditions because many patients were having overlapping diseases.

In our study, all patients were prescribed AEDs by the oral route of administration. Dose escalation was of each drug was done over 10-15 days in our study, is advisable as the incidence of dose-related adverse effects associated with AEDs is often a function of the rapidity of dose escalation.^[21] Slow dose escalation have some advantages, e.g. with most AEDs, adaption (tolerance) to adverse central nervous and sometimes gastrointestinal side effects occurs slowly after initiation of treatment, and immediate prescription of full maintenance dosages causes tolerability problems; some patients can be optimally controlled even at doses below the initial target maintenance doses; it may allow identification of the lowest dose regimen at which patient can respond. Unfortunately, for many AEDs, starting dose and guidelines for dose escalation are poorly defined in literature.^[22]

It was found in our study that majority (52%) of the AEDs were prescribed by generic names, followed by 37% and 11% of the AEDs which were prescribed by brand name and by both generic and brand name, respectively. In study institute, a revised formulary based on essential drugs was implemented in 1998 and was updated regularly. There is full scope for institutional physicians to prescribe by generic names. It is also important to prescribe by generic names, particularly in a hospital attached to a medical college where medical students are taught medicines by generic name and generic prescribing is emphasized. Importance of sticking to brand name is also important for some of the AEDs with narrow therapeutic index because change from one brand to generic drug might not be therapeutically equivalent to branded drug, which could put patients at risk of breakthrough seizures or other adverse events.^[23,24]

We have found that 70.6% patients were prescribed monotherapy of AEDs. Arulkumaran *et al.* study in Coimbatore, India revealed that about 76.87% patients were managed with monotherapy.^[6] The monotherapy rate 79-82% was found by Tsiropoulos *et al.* study in Denmark which also includes patients having non-epileptic conditions.^[17] The difference may be because of some of our study population were having >1 conditions for which AEDs were prescribed, overlapping indications might increase the number of AEDs per patients or as the study conducted in tertiary care center and treatment resistant cases were referred to our study site might cause more number of patients had treatment resistant diseases our study population. In the literature also stat that monotherapy by AEDs is preferred because 70% patients with epilepsy are managed by monotherapy and chances of drug-drug interactions are increased with polytherapy as most of AEDs are hepatic microsomal enzyme inhibitors/inducers and also they have narrow therapeutic index.^[25,26]

Overall pregabalin was the most common AED prescribed, followed by phenytoin in our study. Hsieh *et al.* study conducted in Taiwan revealed that carbamazepine and valproic acid were the most common AEDs used and among the newer generation of AEDs, gabapentin was the most frequently used.^[6] These findings differ with our finding; the reason may be the higher prevalence of non-epileptic conditions in our study than another study.

Overall, most frequently prescribed AEDs were phenytoin followed by valproate, oxcarbazepine, and carbamazepine/clonazepam. Mathur *et al.* study in Hyderabad showed similar finding.^[18] Different finding seen in Arulkumaran *et al.* in Coimbatore, India as valproic acid was commonest AED prescribed followed by carbamazepine, phenytoin, and oxcarbazepine.^[6] Similar study by Pal *et al.* in Cuttack, India showed that valproic acid was most common AED prescribed followed by phenytoin and carbamazepine.^[10] Hanssens *et al.* study in Oman also reveal that Sodium valproate was the most frequently prescribed AED, followed by

carbamazepine, phenytoin, and lamotrigine.^[19] It was found that carbamazepine was most frequently prescribed AED, followed by phenytoin, valproate and clonazepam for epilepsy by Chen *et al.* study in Taiwan.^[20]

The dissimilarity is seen in utilization pattern of various AEDs in both Indian studies and also in studies conducted out of India. This may be because of the prevalence of different types of epilepsy. Pregabalin was most common AED prescribed for both conditions. Oxcarbazepine was the second most commonly prescribed AED for neuropathy, clonazepam for psychomotor disorders. Arulkumaran *et al.* study in Coimbatore showed that oxcarbazepine followed by gabapentin were commonly prescribed AEDs for non-epileptic condition.^[6] It was found that newer AED like gabapentin was commonly prescribed for pain disorders by Hsieh *et al.* study in Taiwan.^[16] In 2002, gabapentin was approved by FDA for post-herpetic neuralgia.^[27] Pregabalin is recently approved by FDA for neuropathic pain and some motor disorders, i.e. restless leg syndrome. It was also approved for generalized anxiety disorders (2006), fibromyalgia (2007), diabetic neuropathic pain (2004) and post-herpetic neuralgia (2004).^[28,29] Pregabalin has better pharmacokinetic profile and similar adverse event profile to gabapentin and is equally efficacious for treatment of pain disorders.^[30] The different pattern of prescribing may be due to different types of disease prevalent in our study population for which AEDs were prescribed than that of other studies; different classification of disease conditions: We classified as two main categories as pain disorders and psychomotor disorders.

It was seen in our study that conventional AEDs were commonly prescribed for epileptic conditions; newer AEDs frequently prescribed for non-epileptic conditions. Hsieh *et al.* study Taiwan stated that newer AEDs were used primarily to treat pain disorders and the primary class of drugs used to treat epileptic disorders was conventional AEDs.^[16] It was found in Arulkumaran *et al.* study in Coimbatore that older AEDs were the most frequently used (77.72%) when compared with newer AEDs for epilepsy.^[6] So our result is consistent with other studies.

CONCLUSION

The use of AEDs not limited to epilepsy only. AEDs were prescribed more frequently in neuropathic pain and psychiatric disorders other than epilepsy. AEDs are usually prescribed as monotherapy and by generic name and not as fixed dose combination. Multiple factors influence the selection and acceptance of AEDs by physicians and patients, including age, gender of the patient, the weighing of efficacy against potential ADRs, epilepsy syndromes and type, co-morbid conditions, recommendations from peers, experience with AEDs treatment, and the system of health care prevailing in

a particular area. Awareness about off-label use of ADEs is essential for its appropriate use.

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