Prescription pattern of antiepileptic drugs in a tertiary care center of India

Rupa Joshi¹, Manjari Tripathi², Pooja Gupta¹, Sheffali Gulati³, Yogendra Kumar Gupta*¹

Abstract:
OBJECTIVES: The present study aimed to determine the pattern of prescription of antiepileptic drugs (AEDs) in a cohort of patients with epilepsy (PWE) attending a tertiary care center of North India.
MATERIALS AND METHODS: Demographic variables including age, gender, age at onset, type and frequency of seizures, and prescription of all AEDs (dose and duration) were noted. Descriptive analysis of the use of AEDs was done, and their different combinations were studied.
RESULTS: A total of 1187 prescriptions were evaluated. Demography showed 65.7% of males; mean age of 21.9 years (range: 2–77 years), generalized seizures (53%), and focal seizures (47%). Only 21.8% of the patients were seizure free with no seizure in 1 year of treatment. The five most frequently prescribed AEDs out of 12 AEDs were sodium valproate (VPA) (49.6%), clobazam (CLB) (39.3%), levetiracetam (LEV) (28.4%), carbamazepine (CBZ) (27.3%), and phenytoin (PHT) (26.5%). Monotherapy was effective in 36.6% of the patients. Sodium VPA (39.4%), PHT (25.6%), and CBZ (20.1%) were commonly used as monotherapy. Polytherapy was required in 63.4% of the patients, and most commonly prescribed combinations were PHT + CLB (n = 53), sodium VPA + CLB (n = 62), CBZ + CLB (n = 45), PHT + sodium VPA + CLB (n = 28), and CBZ + sodium VPA + CLB (n = 31).
CONCLUSIONS: Polytherapy is a very common practice in our tertiary care center. Sodium VPA, a highly prescribed AED, results in good control of generalized seizures, whereas focal seizures are well controlled by CBZ alone as well as in combination. The present study highlights the commonly prescribed combinations of AEDs resulting in control of different types of seizures.
Keywords: Adverse effects, monotherapy, polytherapy, seizures

Introduction
Despite the current availability of more than 20 different antiepileptic drugs (AEDs), almost 30% of the patients with epilepsy (PWE) do not retain seizure freedom on pharmacological treatments.[1] Pharmaco-epidemiological studies have documented a budding trend in AED use, especially in refractory patients.[2] Although some PWE may respond to resective surgery,[3] in majority of the patients, the recognition of a suitable AED regimen is the limiting factor. They should extensively reduce seizure frequency and minimize the risk of adverse effects.[4] Monotherapy is desirable and polytherapy is advocated when a PWE does not respond to the first AED.

Variations in selection of AEDs in PWE occur among developed and developing countries. The availability of newer AEDs has changed the prescription pattern for different types of seizures and the guidelines for the management of epilepsy in India. The constant evolution in drug development makes it exigent for physicians to maintain a trail of the diverse signals of AEDs with particular patient characteristics. It is increasingly difficult to make appropriate treatment choices with respect to an individual PWE, despite

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the existence of well-known guidelines by renowned neurological associations such as the International League Against Epilepsy (ILAE) and the American Academy of Neurology and the American Epilepsy Society. Evidence exists in support of preferential treatment choices in patient groups, especially extremes of ages and women of childbearing age. The direct applicability of these in the Indian setting may not be true due to factors such as higher cost of newer AEDs and lack of medical insurance. Nonetheless, various newer AEDs such as LEV, oxcarbazepine, zonisamide, topiramate, and lacosamide are presently available in a developing country like India, but data for their use are lacking in the Indian population.

The present study offers a unique opportunity to analyze and compare the prescribing pattern of AEDs in terms of their efficacy with respect to different types of seizures, age groups, and gender. This, in turn, would result in enhancement of public health and safety with respect to the usage of AEDs, which will be a pertinent and imperative issue for prescribers, health authorities, and policymakers.

Materials and Methods

Patients

PWE were recruited consecutively from the epilepsy clinic from October 4, 2010, to September 26, 2013. Enrollment criteria included patients of any age, of either gender and on any AED at a stable dose for at least 3 months at the time of evaluation. Patients with any other comorbid condition, such as hypertension, metabolic syndrome, and renal disorder, which predated epilepsy were excluded from the study. The study was started after approval from the Institutional Ethics Committee, and all patients had given informed consent before participating. The study was conducted as per the guidelines of Indian Good Clinical Practice (GCP) as harmonized with ICH-GCP guidelines. The treatment protocol of the patients remained unaffected by participation in the study. Enrolled patients were prescribed the following AEDs:

Older AEDs were phenobarbital, phenytoin (PHT), carbamazepine (CBZ), clobazam (CLB), clonazepam (CLZ), sodium valproate (VPA), a combination of two or more than two older AEDs, or a combination of one or more older and newer AEDs.

Newer AEDs were levetiracetam (LEV), oxcarbazepine (OXC), lamotrigine (LTG), topiramate (TPM), zonisamide (ZNS), lacosamide (LCM), or any combination of these.

The particulars of the participants collected at the time of their enrollment comprised baseline demographics, type(s) of seizures, and characteristics of the disease as per ILAE, information of the existing treatment regimens (dose and duration), and any other medications prescribed concurrently. In addition, the acquisition cost of defined daily dose of the most frequently prescribed brand of each AED (older and newer) during the study was noted. All data were recorded on hard case report forms and then subsequently entered in the electronic media, allowing cross-checking at any time.

Objectives

The primary objective of the present study was to compare the prescription pattern of AEDs in terms of their efficacy (control of seizures) with respect to different types of seizures.

The secondary objectives were to analyze (1) seizures outcome in two different groups; good (seizure free with no seizure in previous 6 months) and poor (varying from at least one seizure in 6 months to daily seizures); (2) commonly used combination of AEDs eliciting seizure freedom; (3) prescription pattern of AEDs in children and adults; (4) gender-wise distribution of AEDs; and (5) cost analysis of AEDs.

Statistical analysis

The study data were analyzed using descriptive statistics. The Chi-square test was used for the frequency of AED prescription between the different groups. Assessed variables were gender, age, age at onset of seizures, type of seizures, frequency of seizures, use of older and newer AEDs, monotherapy and polytherapy, etc., Odds ratios and their 95% confidence intervals were used to compute the predictive value of a variable.

Results

Demographic analysis

A total of 1187 consecutive patients including both men (780, 65.7%) and women (407, 34.3%) were enrolled in the study, and their demography is reported in Table 1. The mean age of the patients was 21.9 years (range, 2 years to 77 years). Majority of the enrolled patients were from the age of 11–30 years (62.4%). Only 20% of the patients were between the ages of 31–60 years. The patients younger than 10 years and older than 60 years were 16.6% and 1%, respectively [Figure 1a].

The mean age at the onset of seizures in the present study was 13.5 and ranged from 1 month to 75 years. Majority of the patients (947, 79.8%) had their first seizure in younger age, i.e., below the age of 20 years, and 0.5% of the patients had their first seizure in older age (above 60 years). The detailed pattern of age at onset of seizures is shown in Figure 1b.
Prevalence of antiepileptic drug treatment regimens

About one-third of the patients (36.6%) were being managed on a single AED treatment regimen, and the remaining 63.4% of the patients were on polytherapy of AEDs. Polytherapy included a combination of AEDs varying from two to six AEDs. VPA, PHT, CBZ, and LEV were the most regularly prescribed AEDs in monotherapy regimens. Among polytherapy (753), 387 patients were on a combination of two AEDs and 268 were on a combination of three AEDs, whereas 89 patients were on a combination of four AEDs. Combinations of five and six AEDs were prescribed in 7 and 2 patients, respectively.

Gender-wise utilization of antiepileptic drugs

Gender differences exist in the use of different AEDs, as presented in Figure 2. The prescription of PHT and VPA was significantly higher in males, whereas CBZ, LEV, and CLZ were higher in females. Although the use of newer AEDs such as OXC, ZNS, and TPM was higher in females, it did not show a statistically significant difference from males.

Utilization of antiepileptic drugs in children and adults

Patients were divided into children (≤18 years) and adults (>18 years). The prescription of VPA and LTG was significantly higher in children, whereas PHT was higher in adults. The distribution of CBZ, LEV, ZNS, TPM, OXC, and CLB did not differ significantly between the age groups [Figure 3].

Utilization of antiepileptic drugs in specific seizure types

The seizures were broadly classified into two types as per new criteria of classification of seizures (Berg et al., 2010): generalized and focal seizures. No significant difference was found in the prevalence of both types of seizures in the present study, i.e., generalized seizures (629, 53%) and focal seizures (558, 47%). Within seizure type, there was a difference in utilization pattern of AEDs. In generalized seizures, the prescription of VPA and CLZ was significantly higher, whereas CLB, CBZ, OXC, and LCM were higher in focal seizures. Other AEDs such as LEV, PHT, LTG, TPM, ZNS, and PHB were almost equally prescribed in both generalized and focal seizures [Figure 4].

Combination of antiepileptic drugs prescribed to patients with different types of epilepsy resulting in good control of seizures
A higher proportion of patients achieved good seizure control (57.2%) compared to patients with poor control of seizures (42.8%). More patients were seizure free on VPA and LEV in generalized seizures as compared to focal seizures, whereas CBZ, OXC, and CLB elicited good control of focal seizures. Polytherapy with VPA resulted in well control of generalized seizures, whereas a combination of PHT with LEV and CLB had better control of focal seizures. CBZ was only prescribed in focal seizures in combination with CLB, LEV as well as VPA. A combination of VPA with LEV, CLB, and CLZ was most commonly prescribed in generalized seizures, whereas VPA with LTG resulted in better control of focal seizures [Figure 5].

Cost of commonly prescribed antiepileptic drugs
Among the older AEDs, the cost of sodium VPA was higher as compared to other older AEDs. On the other hand, the cost of LEV was highest among newer as well as older AEDs, followed by TPM and ZNS [Table 2].

Discussion
The availability of numerous antiepileptic drugs (AEDs) have drastically improved the seizure control in patients with epilepsy. Nevertheless, further innovative research is required to substantiate the outward enhancement in tolerability presented by various newer AEDs.[4]

The documentation of the most and least commonly used AEDs can be obtained from the studies involving epidemiological data analysis. The least frequently used AEDs include the drugs which freshly entered the market that have restricted acquaintance to patients or older drugs which were substituted by more efficacious and tolerable AEDs.

Most of the surveys on the utilization of AEDs in the Indian population were performed in the earlier years.
and these mentioned mainly the older AEDs and therefore do not reflect the scenario of prescription patterns of newer AEDs such as ZNS, LEV, and LCM. Among previous studies conducted in India, many have been based on epidemiological data of AED consumption in specific setting of patients from a particular region, either from a state of South or east India, with a limited sample size. In the present study, a total of 1187 patients coming from different areas of the country were enrolled from a tertiary care center.

The present study observed maximum PWE in the age group of 10–30 years. This is in comparison to a U-shaped incidence of age distribution usually found in economically developed countries.[11,12] In almost 50% of the patients, the onset of seizures occurred at their early age (within 10 years). The brain, at a younger age, is at a higher risk of developing seizures, and early childhood epilepsies are known to be complex in their etiology and management. It depends on physiological immaturities in ion homeostasis, various developmental characteristics, and severity of early-onset epilepsy.[13]

The higher use of PHT and VPA in males rather than females is a well-known fact due to their teratogenic potential,[14] whereas CBZ, LEV, and CLZ were found to be safe in females[15] and thus significantly higher prescription of them in the present study. In children, the significantly higher prescription of VPA and LTG in the present study can be explained due to their efficacy in children with epilepsy[16] and vice versa for PHT and other AEDs.

Among the distribution of AED treatment regimens, polytherapy was found to be a significant finding as around two-third of the patients were prescribed a combination of two or more AEDs. The patients referred from primary and secondary care centers to our study center were tried with older AEDs to control their seizures. Most of the regimens with a combination of two or more AEDs were in accordance with the guidelines for epilepsy treatments. The extensive use of polytherapy in the present study is contradictory to many other studies conducted in India as well as other Asian countries[17,18] where the incidence of usage of monotherapy is still higher than polytherapy. This can be a result of data collection from a large tertiary care center in the present study or preference for newer AEDs, which were mostly approved as an adjunctive treatment only. The higher frequency of the use of sodium VPA in the present study is contradictory to various other studies where other drugs such as PHT and CBZ were used.[17,19]

Epilepsy and seizure types were noted to be vital for deciding the treatment. The present findings about seizure types suggest that both generalized and focal seizures were equally distributed, whereas this difference of distribution is found to be significant in Western countries where the occurrence of focal seizures was more prominent than generalized seizures. There was no significant difference in the prevalence of both types of seizures in PWE. However, this difference of distribution is found to be significant in Western countries where the occurrence of focal seizures was more prominent than generalized seizures.[20] The finding of our study is concordant with other studies from Asian countries.[11,19]

Being a broad-spectrum AED, VPA was the most frequently prescribed AED in our study for patients with generalized seizures as well as focal seizures. The AEDs which were commonly prescribed in generalized epilepsy included LEV > LTG > CLZ > TPM > PHB. The most frequently prescribed AEDs in focal seizures were CBZ > OXC > TPM > CLB > PHT and ZNS [Figure 2], in concordance with their use in the management of focal seizures. However, TPM and CLB have also shown efficacy in few cases of generalized epilepsy.[14,8,21]

Most of the combinations were least frequently used either in one or two patients (data not shown) in accordance with the fact that AED treatment is very individual. The frequency of the most commonly used combination of two, three, and more than three AEDs in different seizure types resulted in good seizure control, as mentioned in Figure 5. In the treatment of focal seizures, only CBZ and OXC were used as monotherapy in the present study.[22] Moreover, LTG also resulted in seizure control only when prescribed with VPA in focal seizures.[23] Indeed, a risk of rash may arise due to inhibition of metabolism of LTG by VPA, except LTG was added at a low dose and then gradually increased.[24]

The finding of higher prescription of CBZ and CLB resulting in freedom from focal seizures is in concordance with the study by Arya and Glauser, 2013,[25] The type of seizures played a prominent role in selection of treatment regimens among older as well as newer AEDs. Hence, reporting of prescription pattern of AEDs should also emphasize on standardized prevalence rates of specific AEDs.

Drug acquisition cost affects prescribing pattern of AEDs. In the present study, the cost of defined daily dose of the most commonly prescribed brand of both older and newer AEDs was noted. The defined daily dose of a drug DDD is the assumed average maintenance daily dose for its primary indication (WHO, 2013).[26] Sodium VPA, the most frequently prescribed AED in our study, was also the costliest among older AEDs.
Among newer AEDs, LEV was the costliest and also most frequently prescribed. It was observed that the newer AEDs were generally more expensive as compared to the older AEDs. The data of the present study are in concordance with the finding of another study which compared the cost of different brands of AEDs and found the newer AEDs as much costlier in comparison to older AEDs.[27] The analysis of the cost of the defined daily doses of individual AEDs can further help the government policies and regulations for controlling the cost of the most effective and frequently prescribed AEDs.

However, the pace of the use of newer AEDs has robustly improved. Certainly, in our setup, the use of older AEDs was almost double than the newer AEDs and VPA appeared to be the most frequently prescribed AED. LEV was most commonly used among newer AEDs. On the contrary, a very few patients were prescribed with monotherapy of other newer AEDs, such as OXC and TPM, whereas a study in Italy showed gabapentin as the most commonly used newer AED and OXC and LEV as the least used AEDs.[28]

**Conclusions**

The present study highlights the pattern of the use of older and newer AEDs resulting in good seizure control in different types of epilepsy. Among newer AEDs, LEV and OXC were used both as monotherapy and polytherapy, whereas all other newer AEDs were mostly prescribed as an add-on therapy. Prescription patterns are consistent with existing evidences regarding the continuum of efficacy of individual newer and older AEDs in different seizure types.

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**Conflicts of interest**

There are no conflicts of interest.

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