Full Length Research Paper

DRUG UTILIZATION PATTERN OF ANTIEPILEPTIC DRUGS AND DIRECT AND INDIRECT COST ESTIMATION IN THE TREATMENT OF EPILEPSY AT TERTIARY CARE HOSPITAL

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Abstract

Purpose: Prescription pattern may have changed with advent of newer antiepileptic drugs. Cost of management remains the important reason responsible for treatment gap. Current study was done observe prescription pattern and cost of epilepsy management to the patients.

Methods: A prospective observational questionnaire based cross sectional survey was conducted in neurology OPD for 12 months. A demographic profile and prescription data of AEDs for past 1 year were collected from diagnosed cases of GTC, CPS and SPS for at least 1 year of treatment. WHO indicators were used for analyzing current prescriptions and direct and indirect cost of treatment for past 1 year was analyzed.

Results: A total of 275 AEDs were prescribed to 138 patients. GTC was most common condition with 43.47%. Average no. of AEDs prescribed per encounter was 1.99 with 52% of newer AEDs. Phenytoin was commonly prescribed (24%) for GTC and SPS with secondary generalization. Valproate was commonly prescribed for CPS while carbamazepine for SPS. Average consultation time was app. 15 minutes. App. 98% of patients had correct knowledge of drug dosage. An average total cost borne by patients was Rs. 14589 per year which constitutes to 53% of per capita income.

Conclusion: Older antiepileptic drugs are still commonly prescribed drugs. High prescription of brand names and prescription of drugs outside of hospital formulary as only limited drugs are available on schedule list, may be the reason for cost burden to epileptic patients.

Keywords: Indirect cost, Drug utilization, Antepileptics, WHO indicators.

INTRODUCTION

Epilepsy describes a condition in which a person has recurrent seizures due to a chronic, underlying process. It refers to a clinical phenomenon rather than a single disease unit, since there are numerous forms and causes of epilepsy. (Longo *et al.,* 2012) It is the most common neurological condition worldwide with Indian prevalence of 572.8/100,000 population/year. (Banerjee *et al.,* 2010) This figures shows rising trends as treatment gaps for active epilepsy exceeded 75% in most low-income countries. (Ana-Claire Meyer *et al.,* 2010) The main aim of management of epilepsy is to achieve complete control of seizure attacks. A large number of drugs are currently available for the treatment of epilepsy. Older/conventional drugs like phenytoin, carbamazepine, valproic acid and phenobarbitone are commonly used as first line drugs. They are relatively less expensive than the newer

anti-epileptics but have serious side effect. Drugs like levetiracetam, gabapentin, lamotrigine, vigabatrin, topiramate, lacosamide and zonisamide are the newer ones and currently used as add-on or alternative therapy. A couple of studies have shown that, older antiepileptic drug like phenytoin and sodium valproateare predominantly used as first line therapy. (Shobhana *et al.,* 2010; ArulKumaran *et al.,* 2009) One of the reasons for increasing trends in treatment gap is cost of treatment of epilepsy in developing countries. Economic assessments of the national burden of epilepsy have been conducted in a number of high income countries (Beran *et al.,* 1995; Gessner *et al.,* 1993; Cockerell *et al.,* 1994) and more recently in India (Thomas *et al.,* 2001), and have clearly demonstrated the significant economic implications the disorder has in terms of health care service needs, premature mortality, and lost work productivity. For example, the Indian study calculated that the total cost per case of these

consequences of epilepsy amounted to US $344(Rs 13755/- in Indian Rupees) per year (equivalent to 88% of average income per capita). (Thomas *et al.,* 2001) This study would shed light on prescription pattern of antiepileptic drugs in tertiary care hospital. The prescriptions pattern may have changed due to availability of newer anti-epileptic drugs which are less toxic, equally efficacious than older anti-epileptic drugs. Cost of epilepsy had been estimated in several developed countries, but there were few studies which mentioned the direct and indirect cost estimation due to epilepsy. Cost estimates are very important in health care planning and delivery of services. Keeping all these factors in mind it was decided to conduct current study with objective to study the utilization pattern of anti-epileptic drugs (AEDs) in Generalized tonic-clonic seizures, simple partial seizure, complex partial seizure which are commonly encountered type of epilepsy according to WHO/INRUD indicators and also to estimate the direct and some of the indirect costs of epilepsy, thus emphasizing total financial burden of epilepsy to the patient.

MATERIALS AND METHODS

The study was conducted after obtaining permission from the Institutional Ethics Committee. A prospective observational questionnaire based cross sectional survey conducted in collaboration with Dept. of Neurology of Seth Gordhandas Sunderdas Medical College & King Edward VII Memorial Hospital, Mumbai. A total of 138 patients were included in the study over duration of 12 months. Diagnosed cases of epilepsy (GTC, SPS and CPS) for at least 1 year between the age of 18-65yrs of either sex were included while patients with major neurologic disabilities such as mental retardation, aphasia, or motor deficits, patient with secondary epilepsy were excluded. Patients diagnosed as epilepsy by neurologist, satisfying inclusion/ exclusion criteria were included in the study. Before interviewing the patient written informed consent was taken. The drug prescription given by neurologist was noted down.

Details such as demographic, past medical consultations before approaching the current service, details of treatment of epilepsy in the last 1 year and until the date, the cost of medical consultation, anti-epileptic drugs (AEDs), travels, and lost working days, the number of outpatient visits and hospitalizations during the past 12 months for investigations and treatment of seizure or its complications (such as injuries, AED toxicity) were ascertained. All investigations with their frequency for epilepsy during the past 12 months as well as until the time of evaluation were separately collected.

Costs were calculated as direct costs of illness were grouped as those related to Diagnosis, cost of medicines, medical consultations, hospitalization, travel indirect costs included, costs of lost working days due to seizures or visits to hospitals. Each hospital visit was considered as loss of 1 working day to the patient as well as to the accompanying person. The cost related to the loss of wages for the attendant who accompanied the patient to the clinic was also included in the indirect cost. *Data analysis:* Data was analyzed using descriptive statistics for drug utilization pattern using WHO/INRUD indicators. Financial burden was expressed as direct and indirect cost.

RESULTS

The study spanned around 12 months and enrolled 138 patients. The age of the volunteers expressed as mean±S.D. was 31.72±19.01. 81 volunteers were males while remaining 57 were females. Most of the patients (app.90%) belong to upper/upper lower and middle/lower middle class of socioeconomic profile using modified Kuppuswamy scale. The average per capita income for study participants for last 1 year was Rs. 27630. The type of epilepsy encountered in our study with their frequency is mentioned in Figure No.1
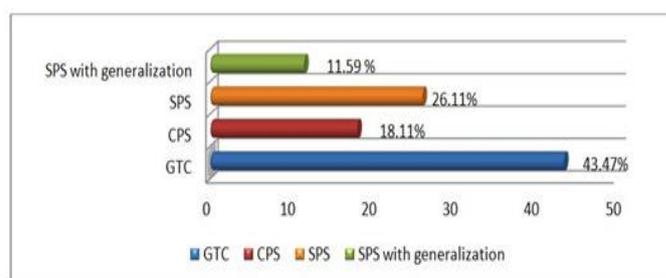

Figure 1. Percentage distribution of type of epilepsy

Drug Utilization

The prescriptions observed were complete in terms of mentioning the dosage form, dose, frequency of administration and the duration of treatment. A total 275 antiepileptic drugs were prescribed to 138 patients. Out of which phenytoin was the most commonly prescribed drugs with the frequency of 66 (24%) followed by valproate with the frequency of 45 (16.36%). The least prescribed drug was gabapentin with the frequency of 6 (2.18%). The detail analysis of prescription pattern is mentioned in Table 1.

Table 1. Drug utilization pattern of Antiepileptic drugs

AEDs	Frequency	Percentage
Phenytion	66	24%
Sodium valproate	45	16.36%
Levetiracetam	41	14.9%
Clobazam	25	9.09%
Carbamazepine	22	8%
Lamotrigine	21	8%
Divalproex	11	4%
Zonisamide	11	4%
Clonazepam	10	3.63%
Oxcarbazepine	6	2.18%
Gabapentin	6	2.18%
Total	275	

Table 2. Antiepileptic drugs with average duration and frequency of TDM

Drugs	Avg. duration (months)	Avg. frequency of TDM
Phenytoin	12	2.07
Valproate	7.9	1.51
Levetiracetam	7.1	0
Clobazam	6.3	0
Carbamazepine	5.6	1.3
Lamotrigine	5.3	0.4
Divalproex	4.8	0
Zonisamide	4.6	0
Clonazepam	3.9	0
Gabapentin	3.1	0
Oxcarbazepine	2.3	0

48.36% were older antiepileptic drugs while remaining were newer. 38.4% of the patients were prescribed monotherapy, while two AEDs were prescribed to 31.15% patients. 25.36% and 7.24% patients were prescribed three and four AEDs respectively. During last 1 year of medical management of epilepsy, 108 patients had therapeutic drug monitoring while remaining 30 patients did not require therapeutic drug monitoring. Out of 108 patients 72 patients were monitored once while 28 patients were monitored twice. 8 patients were monitored thrice or more in past 1 year. Phenytoin was given for average duration of 12 months with average frequency of therapeutic drug monitoring (TDM) was 2.07 being the highest while gabapentin was prescribed for average duration of 3.1 months with average frequency of TDM was none being the lowest as mentioned in Table 2.

WHO/INRUD indicators

Average number antiepileptic drugs prescribed was 1.99. Furthermore 8.72 % of drugs were prescribed by generic name. 44.72% drugs were prescribed by from hospital formulary list. The average cost per prescription for antiepileptic drugs was Rs. 147.02. Detail analysis of patient and facility WHO/INRUD indicators are depicted in Table No. 3. The copy of essential drug list or formulary was present at hospital formulary.

Table 3. WHO/INRUD indicators

Prescription indicators	
Average no. of drug prescribed per encounter	3.1
Average no. of AEDs prescribed per encounter	1.99
average cost per prescription for antiepileptic drugs	Rs 147.02
Percentage of drugs prescribed by generic name	8.72%
Percentage of drugs prescribed from hospital formulary	44.72%
Patient Indicator	
Average consultation time	15 minutes 34 seconds
Percentage of drugs actually dispensed	30.9%
Patient's knowledge of correct dosage	97.1%

Cost analysis

The average annual costs borne by epileptic patient came to be Rs. 14589.1 which was divided into direct cost (Rs 10227.7) and indirect cost (Rs 4361.4). The details of cost segregation into various cost heading are represented in Table 4. While segregating of annual costs on the basis of treatment groups, it was found that older drugs cost less (Rs 1027.7) than newer drugs (Rs 3858.3) while patients receiving older drugs spent more money on investigations as compared to patients receiving newer drugs. The details are mentioned in Table 5.

Table 4. Cost segregation into various cost heading

Cost Head	Mean	S.D.	Minimum	Maximum
Drugs (in Rs)	4998.2	2682.66	0	9742.5
Investigations (in Rs)	4886.08	3345.93	50	8950
Travel/Registration (in Rs)	343.48	205.52	60	750
Direct (A+B+C) (in Rs)	10227.76	4202.2	1377.8	17311.34
Indirect (in Rs)	4361.42	3940.33	667	20000
Total (D+E) (in Rs)	14589.18	6869.18	2877.8	27572.5

Table 5. Segregation of annual costs on the basis of treatment groups

	Older AEDs (N=133)	Newer AEDs (N=142)
Cost (in Rs)	1027.76	3858.32
Investigations (in Rs)	2852.6	2145.6
Total (in Rs)	3880.36	6003.92

DISCUSSION

Our study highlighted that, phenytoin was the most commonly prescribed drug (24%) followed by valproate (16.36%). Similar results were obtained by Mathur *et al.* 2010. (Shobhana *et al.,* 2010) Recently published studies (2002-2013) mention that sodium valproate was the most commonly drug prescribed followed by phenytoin or other drugs. (ArulKumaran *et al.,* 2009; Hanssens *et al.,* 2002; Pathak *et al.,* 2013; Murthy *et al.,* 2012; Malerba *et al.,* 2011; Landmark *et al.,* 2011) An Indian study by Thomas SV *et al* 2001 mentioned that carbamazepine was prescribed most commonly. (Thomas *et al.,* 2001) The reason for discrepancies in prescription pattern varies according to the availability, affordability, place of practice, type of epilepsy and preference of treating neurologist. Phenytoin is broad spectrum antiepileptic most commonly used for partial onset seizure as well as generalised clonic tonic seizures. Being cheap, it is also widely available, which enhances its use in our set up of tertiary care hospital. We found almost equal use of newer (52%) as well as older (48%) antiepileptic's drugs. This is in contrast to studies performed in India highlighted limited use of newer antiepileptics drugs. (ArulKumaran *et al.,* 2009; Guidelines for the management of epilepsy in India, 2013) Studies performed in abroad (Norway) mentioned equal[14] or high uses of newer antiepileptics. (Malerba *et al.,* 2011)

The discovery of newer antiepileptic drugs has not altered the basic principles of the medical therapy of epilepsy, but it has considerably increased treatment choice. So far, no studies have shown that the newer drugs have superior anticonvulsant efficacy than conventional agents. However, the newer drugs have a more favourable side effect profile, which may stand for a significant advantage in the treatment of a chronic disorder. In our study we found that 38 % of the patients were on monotherapy, 30% were on dual therapy and remaining patients were on polytherapy i.e. > 3 or more drugs (32%). These result are not in conjuncture with other studies(Shobhana *et al.,* 2010; ArulKumaran *et al.,* 2009; Murthy *et al.,* 2012; Malerba *et al.,* 2011) which found that most of the patients (≥50%) were prescribed single drug. Guidelines mention that medical management of newly diagnosed epileptic patients should start with monotherapy. (Guidelines for the management of epilepsy in India *et al.,* 2013) Polytherapy should be considered when failure of two attempts of monotherapy. Patients included in our study were old patients on antiepileptic drugs for at least 1 year.

Also most of the patients attending our epilepsy OPD belong to category of refractory epilepsy as this being tertiary referred centre which explains the high prescription of polytherapy in our set up. Our study mentioned that during last 1 year of medical management of epilepsy, 108 patients had therapeutic drug monitoring while remaining 30 patients did not undergo therapeutic drug monitoring.

Out of 108 patients 72 patients were monitored once while 28 patients were monitored twice. 8 patients were monitored thrice or more in past 1 year. A study performed by Hassen *et al*., mentioned that TDM was performed 156 times for 108 patients that correlate with our findings. (Hasan *et al.,* 2010) In this study one patient was monitored four times, two patients were monitored three times and 14 patients were monitored two times. Another study performed by Thomas SV *et al*., stated that only 1 patient was monitored out of 285 patients. (Thomas *et al.,* 2001) The therapeutic drug monitoring was performed for phenytoin, valproate, carbamazepine and lamotrigine. Out of which phenytoin was most commonly monitored drugs because the average duration of treatment with phenytoin was on an average 12months. As against lamotrigine was least monitored drugs because average duration of treatment was on an average 5.3 months**.** (Table 2) A study performed by Shakya *et al*., mentioned that the same drugs were monitored in study except carbamazepine was most commonly monitored drug. (Shakya *et al.,* 2008) As per the GEMIND (Guidelines for Epilepsy Management in India) routine monitoring of AED blood levels is not recommended and should be done only when clinically indicated. Indications for TDM monitoring are,

- Detection of AED non-compliance in case of uncontrolled seizures.
- Documenting suspected AED toxicity.
- Adjustment of AED dose while managing drug interactions.
- Specific clinical conditions (e.g. status epilepticus, liver or renal disease and pregnancy).

The reason for TDM monitoring at our set up could be either any one of them. Our study revealed that 100% of the prescriptions were complete in the terms of describing the dose, route of administration, frequency and duration of treatment. This implies that basic principles of rational use of medicines are being followed at our institute. A recently published study by Zakharo S *et al*., mentioned that most frequent medication errors appeared using drugs affecting the nervous system (psycholeptics and antiepileptics). (Zakharov *et al.,* 2012) The prescription errors occurred mainly due to omission of dose, route of administration and frequency of administration. For example an order for Celebrex, a cyclooxgenase-2 inhibitor used for arthritis, might be entered as Cerebryx, an antiepileptic drug, with vastly different consequences to the patient. (Rosen, 2004) The completeness of prescriptions in our study comes as a welcome finding in a tertiary care hospital where neurologist have to cater an enormous patient load. This further highlighted the fact that little effort by prescribers can go a long way in the propagation of correct prescription practice.

Polypharmacy literally means 'many drugs'. It is defined differently by different researchers and guidelines. The most common definition is use of five or more drugs at the same time in the same patient. (Werder *et al.,* 2003) The average number of AEDs drug prescribed was 1.99, so polypharmacy was not evident at our setting. The concurrent use of multiple drugs leads to increased chances of drug interactions and adverse drug reactions. So the current practice in our hospital show compliance to rational prescribing guidelines.

Percentage of AEDs prescribed by generic name was low (8.72%) as compared to WHO recommendation of 100%. None of the published studies on antiepileptic drugs utilization mentioned this issue. A tertiary care hospital like ours in India mostly caters to patients from the low socioeconomic strata. Hence, generic prescribing will substantially reduce the cost of drugs for the patients and subsequently improve compliance. Having said that, the absence of bioequivalence records among generic forms and the relatively broad criteria for bioequivalence with the branded drug allow differences in drug exposure to arise that may be clinically relevant and necessitate monitoring of plasma levels when switching formulations to avoid loss of seizure control or emergence of side effects. Management of these issues carries a significant cost, which should be weighed carefully against the cost savings acquired when purchasing the drug. (Krämer *et al.,* 2007) Only 44.72% were prescribed from the hospital drug schedule. The hospital schedule list contains only older drugs on schedule explain the high prescription of drugs outside hospital schedule list as almost 50% of the drugs are newer which are not on list. Our study emphasize that average consultation per patient was 15 minutes and 34 seconds. None of the published studies on epilepsy emphasized the current fact. Enough consultation time need to be given to epileptic patients as patients require long term therapy with good compliance as well as epilepsy associated psychiatric problem. Association of British Neurologists mentioned that the average consultation time for new patients was 30-60 minutes while for follow up patients it can vary upto 15-30 minutes. (Association of British Neurologists, 2006) Considering the patients load at the tertiary care hospital, it would be very difficult to provide sufficient time for each of the patients.

In comparison to average consultation time provided by Association of British Neurologists, our neurologist provided sufficient time for each patient. Our study emphasizes that approximately 97% patients have knowledge of correct dosage. It measures the effectiveness of the information given to patients on the dosage schedule of the drug they receive. Goldstein *et al* and Dawkins *et al* reported that more than one-quarter of epilepsy patients gave incorrect information concerning their AED regimens. (Goldstein *et al.,* 1997; Dawkins *et al.,* 1993) The disparity may largely be due to patient sampling. Dawkins' patients were identified from general practices, whereas our study included patients who had received long-term treatment from epilepsy experts. In addition, our study population consisted mostly of patients with good seizure control and who complied optimally with their AED regimens. None of the previously published study highlighted this fact. Essential medicines are those that satisfy the priority health care needs of the majority of the population.

The primary purpose of National List of Essential Medicines (NLEM) is to promote rational use of medicines considering the three important aspects i.e. cost, safety and efficacy. A copy of such essential drug list or schedule was present at hospital formulary. As mentioned earlier 44.72% of drugs are prescribed from hospital formulary which formulates 85 drugs out of 275 were prescribed from hospital formulary. Only 3 antiepileptic drugs were present at hospital formulary namely phenytoin, valproate and carbamazepine out of which

phenytoin was commonly prescribed and dispended from hospital formulary. Our study focused that an average cost per prescription was approximately Rs. 147. None of the currently published studies on utilization pattern of antiepileptic drugs shed upon this issue. This cost excludes the cost of drugs which were provided by hospital formulary. If not a single drug was available at hospital formulary then average cost per prescription for AEDs would be Rs 225.27. It emphasize that the beneficiaries gained by patients when maximum number of drugs prescribed from hospital formulary. This fact has utmost importance as most of the patients attending tertiary care hospital OPD belong to lower socioeconomic class. Our study focussed that average annual costs borne by epileptic patient came to be Rs. 14589.1. On splitting this cost direct cost was Rs 10228 and indirect cost was Rs 4361. On further splitting of direct cost, it was found that investigation (Rs 4998.2) contributed to maximum expenditure followed by drugs (Rs 4886.08) then to travel (Rs 343.48). Patients had to pay only Rs. 10 for OPD paper. No consultation and hospitalisation charges were taken from patients. An Indian study performed by Krishan A *et al*., 2004 mentioned that annual treatment cost for patients attending the hospital was U.S.$11,470 which is very high in comparison to our study. But this study also included cost in emergency and inpatient management which was not calculated in our study. (Krishnan *et al.,* 2004) Another Indian study Thomas *et al.,* 2001 mentioned that annual cost of epilepsy per patient was INR 13,755. In contrast to our study the direct cost was INR 3,725 (USD, 93), and the indirect cost was INR 10,031 (USD, 251). (Thomas *et al.,* 2001) A systematic review published on Cost of epilepsy in 2008 by Strzelczyk A *et al.,* mentioned that annual direct cost ranged between $ 40 to $ 4748. While indirect cost ranged between 12 to 85%. (Strzelczyk *et al.,* 2008)

Another European study conducted by Hammer *et al*., focussed that indirect costs were higher than direct cost which contrasted our study result. However author also mentioned that medications contributed higher to direct cost which simulate with our result. (Hamer *et al.,* 2006) An American study mentioned that Ivanova JI *et al*., 2010 mentioned that epilepsy related direct cost was $ 3,290 which only included patients with partial seizures. (Ivanova *et al.,* 2010) A recent European study conducted by Pato A 2013 focussed that mean total direct medical costs were 1,010.4 €, with the drugs being the most significant item which simulated with our study. (Pato-pato, 2013) On segregating the cost based upon treatment received, it has been found that patients receiving newer had to spend more money (Rs. 6003.92) as compared to patients receiving older drugs (Rs.3880.36). This cost includes medication as well as investigation cost. The reason is patients on older drugs spent less money for purchasing medications while other groups had to spend more money on medications. Another important finding is cost of investigation for patients receiving older drugs were higher (Rs. 2852.6) as compared to patients receiving newer drugs (Rs. 2145.6).

No doubt, newer antiepileptic drugs are costly medication, significantly increases direct cost of epilepsy management. Older drugs have very narrow therapeutic index; need to be monitored for longer duration of time. Also, older drugs are known to have unfavourable adverse effect profile as compared to newer drugs. Hence to avoid to development of

side effect and also for optimum seizure frequent TDM is required for older drugs. Such issues are less frequent with newer drugs. Since both the drugs are equally effective in controlling seizure duration and frequency; patients had to spend more money for monitoring older drug therapy as compared to newer drugs. That might the reason for high cost of investigation for patients receiving older drugs as compared to patients receiving newer drugs. But another angle to this issue is in spite of less requirement of TDM, the difference between cost was not so high (Table 5), hence newer AEDs have higher investigational cost which contradict above mentioned statement. It has been found that the average annual per capita income was Rs 27,630. And the annual costs borne by epileptic patient came to be Rs. 14589, which means that 52.80% of per capita income spent on epilepsy management per year. Considering the India as developing country and most of the patients attending OPD at tertiary hospital belongs to lower socioeconomic data, these figures should raise alarm in the mind of policy makers.

Conclusion

Thus through our study it was concluded that principles of prescription were compliant with the prescription indicators mentioned by WHO/INRUD except that very less drugs were prescribed by generic name, but because of lack of bioequivalent data, many guidelines allows brand prescribing for antiepileptic drugs. Older antiepileptic drugs were still commonly prescribed drugs as compared to newer drugs. As more than 50% of drugs were newer, by increasing availability of newer drugs at hospital formulary would definitely attenuate economic burden of epilepsy management.

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