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Research Article

COST VARIATION STUDY OF ANTIEPILEPTIC DRUGS AVAILABLE IN INDIA

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ABSTRACT

Objective: To list the available dosage forms in different strengths of various antiepileptic drugs marketed in India. To calculate percentage cost variation of individual formulation of drug manufactured by different companies. To evaluate percentage cost variation of drug due to different dosage forms and formulation of the same drug by cost/defined daily dose (DDD) method and to identify less costlier antiepileptic.

Methods: Cost of a particular drug being manufactured by different companies, in the same strength and dosage forms was obtained from "Current Index of Medical Specialties" 2015 and "Indian Drug Review" September 2015. The difference in the maximum and minimum price of the same drug manufactured by different pharmaceutical companies and the percentage cost variation was calculated. The price was measured in Indian rupess (cost/DDD units). The percentage cost variation of drug due to different formulations was also calculated using minimum and maximum cost/DDD. The cost of each drug were also estimated as mean cost per DDD considering different formulation cost.

Results: The prices of total 11 drugs available in 12 different dosage forms and 65 formulations were reviewed. Except Zonisamide, all drugs (for 31 different formulations) showed more than 100% cost variation. Levetiracetam (conventional 250 mg tablet) showed a maximum of 1034.09% and carbamazepine (dispersible 100 mg tablet) showed minimum cost variation of 2.09%. Levetiracetam formulations showed high (3125.74%), and Topiramate formulations showed less (11.7%) variation in cost to achieve same DDD. The topiramate was expensive, and phenobarbital was cheaper based on cost/DDD only.

Conclusion: There was a high-cost variation of antiepileptic drugs. It shows need for conducting pharmacoeconomic analysis. The prescribers and patient should be educated about drug prices. The government has to change the pricing policy of medicine.

Keywords: Antiepileptics, Cost/defined daily dose, Cost variation.

INTRODUCTION

The Indian pharmaceutical market has over 20,000 medicine formulations [1]. These drugs are mainly sold under brand names and generic branded names [2,3]. Availability of same drug under different dosage forms with different brands creates a lot of problems for the physicians in choosing the less costlier drug for individual patients [4]. Individual drugs will be having great cost variation in the market which may directly influence the compliance and group of people not accessing health care [5-7]. This implies the need for cost analysis of available formulations of drugs in the practice of medicine to identify needs to reduce cost for selecting less costlier alternatives in prescribing. Optimizing the cost of therapy helps to promote the rational use of drugs [1].

Epilepsy is the most common neurological condition worldwide with an Indian prevalence of 572.8/100,000 population/year, affecting people of all ages [8]. Around 50 million people worldwide have epilepsy and may require treatment for years [9]. Around 90% of the people with epilepsy in developing countries are not receiving appropriate treatments and related to patients' ability to pay and that of availability of drugs [10,11]. To treat different types of epilepsy, there exists different antiepileptics under different brands and formulations with large variation in cost here in India. Cost variation profile of drugs give insight at unnecessary cost burden. Reducing cost measures are important. Keeping these things in mind, we conducted studies with the objective (a) to list the available dosage forms in different strengths of various antiepileptic drugs marketed in India. (b) to calculate % cost variation of individual formulation of drug manufactured by different companies. (c) To evaluate % cost variation of drug due to different dosage forms and formulation of the same drug by cost/defined daily dose (DDD) method and to identify less costlier antiepileptic drug. Cost per DDD units, is a cost measure as recommended by the World Health Organization for analysis of drug use [12]. DDD represents assumed average maintenance dose per day for a drug used for its main indication in adults [12,13]. Cost/DDD can provide a fixed unit of measurement independent of the dosage form (e.g. Tablet strength) enabling the researcher to assess trends in drug consumption and to perform comparisons [14]. Here mean Cost/DDD method is used to identify less and expensive formulations and also to calculate average cost of individual drug.

The rationale of this study is that by observing the cost variation and identifying less costlier antiepileptic formulation; it helps in rational prescribing. The prescriber and patient become aware about the cost and avaibility of different formulations of antiepileptics in market. This study also provide a method how to select less costlier drugs formulations in formulary.

METHODS

Current Index of Medical Specialities (CIMS) 2015 and Indian Drug Review (IDR) September 2015 drug manuals was used to identify the price (in Indian rupees) of various brands of antiepileptic drugs. Minimum and maximum price were noted. Price was measured in cost/DDD unit for comparison purpose. Cost/DDD of each formulation was calculated as minimum cost/DDD and maximum cost/DDD and mean cost/DDD. DDD was identified by the World Health Organization Collaborating Center for Drug Statistics Methodology-Anatomic Therapeutic Classification/DDD Index 2015. Price of a particular drug (single drug) in the same strength, number and dosage forms being manufactured by different companies was compared to price variation. The following formula was used to analyse the cost variation.

% Cost variation of due to brands=(Price of most expensive brand– Price of least expensive brand)/(Price of least expensive brand)×100

% Cost variation of drug due to formulation =(Mean cost per DDD of most expensive formulation of same drug– mean cost per DDD of least expensive formulationof same drug)/(mean cost per DDD of least expensive formulation of same drug)×100

Cost per DDD of drug=(average of mean cost per DDD of different formulation of same drug)

Drugs available in fixed dose combination and also the drugs manufactured by only one company or being manufactured by different companies however, in different strengths were excluded. Microsoft excel 2007 was used for analysis of results.

RESULTS AND DISCUSSIONS

Availability of anti-epileptic drugs

The availability of dosage forms and their formulation under different dosage levels are listed in Table 1. Drugs like tiagabine, ethosuximide, primidone, (available in only one brand in India), vigabatrin, (available in fixed dose combinations) were excluded from our study. Thus a total of 11 drugs were reviewed which were available in 12 different dosage forms and 65 different formulations with different brands. Oxcarbamaxepine was being manufactured largly under 65 companies and Zonisamide under only 5 companies.We observed most drug formulations were available in tablets (chewable, dispersible, conventional, enteric coated, controlled, etc.) (73.84%) followed by injection (9.23%), liquids (syrup and oral solution) (9.23%,) and capsules (7.69%) dosage forms. We observed that at most sodium valproate was available in 6 dosage forms and in 12 different formulations. The knowledge of these readily available dosage forms and formulation provides information to select the appropriate drug dosage form in practise. We noted that when there is availability of different dosage forms of same drug in the market; cost variation of that drug due to dosage forms alone is possible.

Cost variation analysis

Here we have described the % cost variation under following two heads.

Cost variation due to different brands

Except zonisamide, all drugs (for 31 different formulations) showed more than 100% price variation (ranging from 101.31% to 1034.09%) due to different brands. On the other hand utilization pattern of these

Table 1: Available dosage forms and formulations of different antiepileptic drugs

ATC code (DDD)	Name of drug	Dosage form	Dosage strength/ formulation	No. of companies reviewed	Formulation code
N03AF01 (100 mg)	Carbamazepine	Controlled release	200		F1
		Controlled release	300	45	F2
		Controlled release	400		F3
		Conventional release	100		F4
		Conventional release	200		F5
		Conventional release	400		F6
		Dispersible	100		F7
		Chewable tablet	100		F8
		Syrup	100 mg/100 ml		F9
N03AX09 (300 mg)	Lamotrigine	Conventional	25	17	F10
		Conventional	50		F11
		Conventional	100		F12
		Modified release	50		F13
		Modified release	100		F14
		Modified release	200		F15
		Dispersible tab	25		F16
		Dispersible tab	50		F17
		Dispersible tab	100		F18
N03AX15 (200 mg)	Zonisamide	Capsule	25	5	F19
		Capsule	50		F20
		Capsule	100		F21
N03AG01 (1500 mg)	Sodium valproate	extended release	200	35	F22
		Extended release	250		F23
		Extended release	500		F24
		Extended release	750		F25
		Extended release	1000		F26
		Enteric coated	200		F27
		Enteric coated	300		F28
		Enteric coated	500		F29
		Syrup	200 mg*5 ml*100 ml		F30
		Oral solution	250 mg*5 ml*100 ml		F31
		Injection	100 mg*1 ml*5 ml		F32
		Controlled release	200		F33
		Controlled release	300		F34
		Controlled release	500		F35
N03AX11 (300 mg)	Topiramate	Conventional	25	16	F36
		Conventional	50		F37
		Conventional	100		F38
N03AB02 (300 mg)	Phenytoin	Conventional	50	34	F39
		Conventional	100		F40
		Conventional	150		F41
		Conventional	200		F42
		Conventional	300		F43
		Injection	50 mg 2 ml		F44

Contd...

Table 1: Contd...

ATC code (DDD)	Name of drug	Dosage form	Dosage strength/ formulation	No. of companies reviewed	Formulation code
		Injection	50 mg*1 ml*2 ml		F45
		Capsule	100mg		F46
		Extended release	300		F47
N03AA02 (100 mg)	Phenobarbital	Conventional tablets	30	47	F48
		Conventional tablets	60		F49
		Injection	200 mg*1 ml*1 ml		F50
N03AF02 (1000 mg)	0xcarbazepine	Conventional	450	65	F51
		Conventional	150		F52
		Conventional	300		F53
		Conventional	600		F54
		Conventional	900		F55
N03AX14 (1500 mg)	Levetiracitam	Conventional	250	26	F56
		Conventional	500		F57
		Oral syrup	100 mg*1 ml*100 ml		F58
		Oral solution	100 mg*1 ml*100 ml		F59
		Infusion	500 mg*5 ml*5 ml		F60
		Injection	100 mg*1 ml*5 ml		F61
N03AX18 (300 mg)	Lacosamide	Conventional	50	7	F62
		Conventional	100		F63
S01EC01 (750 mg)	Acetazolamide	Conventional	250	23	F64
		Capsule	250		F65

DDD: Defined daily dose

drugs e.g. phenytoin, levetiracetam, carbamazepine, oxcarbamazepine, sodium valproate, phenobarbital is increasing in India [15-17]. This shows that there is a high chance of cost variation in prescribing of antiepileptic drugs and unnecessary cost burden. Levetiracetam (conventional 250 mg tablet) accounts for maximum cost variation of 1034.09% while one formulation of carbamazepine (dispersible 100 mg tablet) accounts for minimum cost variation of 2.09% in our study. This showed us that more emphasis has to be given to select brands of levetiracetam during prescribing or selection in formulary. The % cost variation profile of all drugs under different formulation was as listed in Table 2. The high cost variation in antiepileptic drugs at marketplace is not new. Gupta et al. in 2011 had also observed more than 100% variation in the cost of selected anti-epileptics. We reviewed more antiepileptic drug formulations in comparison. They observed significant variations in tablet phenytoin 100 mg (136.8%); tablet carbamazepine 200 mg (70.08%) and tablet valproic acid 200 mg (55.32%). Our results is compliant to these results of high variation which is increasing now. They also found that the newer anti-epileptic drugs like gabapentin, clobazam, levetiracetam, were having lot of variations in their brands of same strength in comparison to older first line antiepileptic drugs like phenytoin, phenobarbitone, carbamazepine and valproic acid [18].We have also found these drugs were highly varied compared to older antiepileptics. Nowadays, new brands are being added by companies and are owing to greater variation in these drugs. Another antipsychotic cost variation study (2014) also found cost variation having above 100% in most of antipsychotics [4]. These are indeed unacceptable situation for the patient. The data regarding cost burden from cost variation are lacking in India. In the United States brand name drugs are often dispensed when less costly generic alternatives are available, (cost variation in prescribing) resulting in an estimated $8.8 billion in excess expenditure per year [19]. The careful appraisal of cost variation is thus necessary to optimize the drug cost and savings. The costly brand of same generic drug is scientifically proved to be in no way superior to its economically cheaper counterpart. Thus, least costlier generic drugs can be selected for the formulary system in the hospital. For EU healthcare system; outcomes generated by generic drug prescribing is 25 billion pound savings each year [20].

Cost variation of different dosage forms (and their formulation) of same drug

Since DDD is independent with dosage form and price, average Cost/ DDD can be used to compare the cost of different formulation. Giwa

Table 2: % Cost variation in brand name of drugs manufactured by different companies

Formulations	Minimum cost/ DDD (Indian rupees)	Maximum cost/ DDD (Indian rupees)	% cost variation in brands
Carbamazepine			
F1	6.79	11.75	73.0486
F2	6.08	12.24	101.3158
F3	6.36	11.4375	79.83491
F4	6.18	17.5	183.1715
F5	5.58	11.25	101.6129
F6	6.1925	10.3125	66.5321
F7	8.6	8.78	2.093023
F8	7.77	9.64	24.06692
F9	14.7	40.1	172.7891
Lamotrigine			
F10	33.41	60	79.58695
F11	30.942	54	74.52007
F12	23.4	45	92.30769
F13	39	51.6	32.30769
F14	36	47.4	31.66667
F15	37.935	42.15	11.11111
F16	24	60	150
F17	22.5	50	122.2222
F18	19.875	47.1	136.9811
Zonisamide			
F19	25.6	30.72	20
F20	22.392	23.6	5.394784
F21	17.558	21	19.6036
Sodium valproate			
F22	15	27	80
F23	24	33	37.5
F24	13.5	29.25	116.6667
F25	19.846	21.6	8.838053
F26	17.4	25.5	46.55172
F27	14.2	36	153.5211
F28	12.95	35	170.2703
F29	11.97	28.5	138.0952
F30	1.125	3.3375	196.6667
F31	1.425	3.57	150.5263
F32	8.49	10.5	23.67491
F33	18	28.5	58.33333
F34	17	28	64.70588
F35	18	28.8	60

Contd...

Table 2: Contd....

Formulations	Minimum cost/ DDD (Indian rupees)	Maximum cost/ DDD (Indian rupees)	% cost variation in brands
Topiramate			
F36	22.8	70.8	210.5263
F37	21.6	83.01	284.3056
F38	23.55	71.4	203.1847
Phenytoin			
F39	4.2	6	42.85714
F40	3.15	12	280.9524
F41	1.34	3.47	158.9552
F42	3.5415	3.9	10.12283
F43	0.98	3.15	221.4286
F44	6.12	9	47.05882
F45	3.3	3.9	18.18182
F46	0.648	5.79	793.5185
F47	5.6	5.8	3.571429
Phenobarbital			
F48	1.6167	6.846667	323.4964
F49	1.1	4.671667	324.697
F50	0.64	1.2355	93.04688
Oxcarbazepine			
F51	21.493	26.66667	24.0714
F52	17.593	39.33333	123.5738
F53	14.667	31.43333	114.3133
F54	15	26.78333	78.55556
F55	22.22	23.86111	7.385739
Levetiracitam			
F56	26.4	299.4	1034.091
F57	22.5	56.7	152
F58	4.44	5.664	27.56757
F59	4.35	5.925	36.2069
F60	16.35	59.7	265.1376
F61	16.2	44.1	172.2222
Lacosamide			
F62	27	60	122.2222
F63	23.4	24	2.564103
Acetazolamide			
F64	2.07	20.97	913.0435
F65	2.07	12.84	520.2899

DDD: Defined daily dose

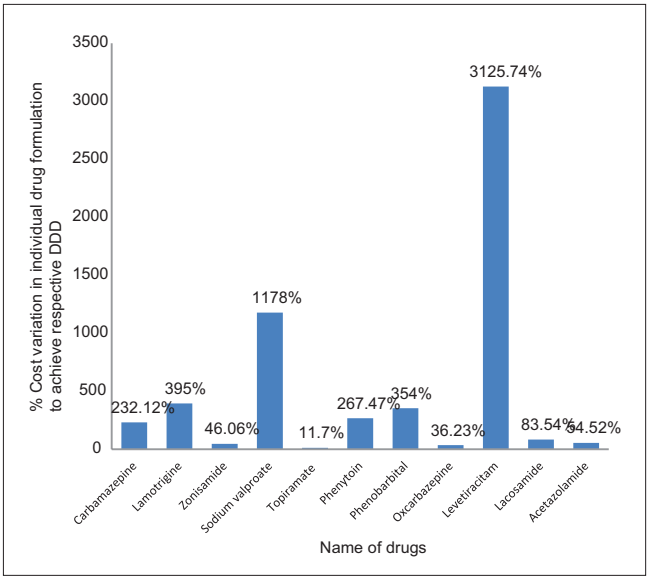

Fig. 1: % Cost variation in individual drug formulation to achieve respective defined daily dose

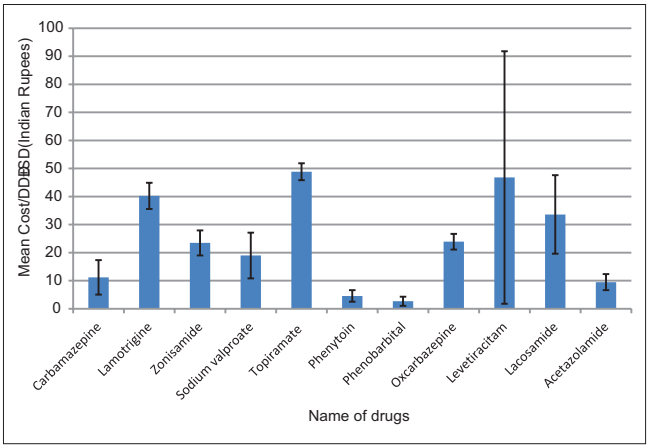

Fig. 2: Mean cost/defined daily dose±standard deviation (Indian Rupees) of different antiepileptic drugs

et al. (2014) had conducted cost minimisation study for antidiabetics utilisation in Nigeria using mean cost/DDD comparison method [21]. We have not found reference with such methods conducted in the Indian set up so far.

For a drug, different formulations were available with different cost. However the cost to achieve same DDD varies between two or more formulations. In this respect we have analysed the cost variation of drug in formulations. The drug with high cost variation in formulation has to be carefully selected in formulary or in prescribing. Based on the results of antiepileptics, levetiracetam formulations have high (3125.74%) and topiramate formulations have less (11.7%) variation of cost to achieve their respective DDD. Among 6 different formulations of levetiracetam, some can contain extra high cost. F58 anf F59 (liquid preparations) formulations were cheaper than other formulations and to be selected. Does an extra increase in cost/DDD of each formulation is worth or not, is to be evaluated to draw conclusion about least costlier formulation of every drug. For an instant there exist 9 different formulations of carbamazepine (cost variation, 232.12%) where syrup formulation has a higher cost than a tablet formulation. This may be obvious that syrup is having high bioavaibility and allows easy titration of dose than tablets and has better preference for certain patient groups and increasing compliance. At other side, tablets will be the cheapest option. In case of Acetazolamide capsule 150 mg is readily cheaper than 150mg tablet. All these findings showed that least costly formulation can be selected with careful appraisal of cost. Most critically drug formulation with high cost variation (>100%) has to be closely appraised before adding to formulary viz. Levetiracetam, carbamazepine, lamotrigine, valproate, phenobarbital, phenytoin (Fig. 1).

We had also calculated mean cost/DDD±SD of each drug to identify less costlier antiepileptic drugs based on the cost data. We found that topiramate was expensive (Rs 48.86±3) and Phenobarbital was cheaper (Rs 2.68±1.65) drug among 11 different antiepileptics based on cost/DDD only. Both these drugs can be used in the treatment of partial seizures (newly diagnosed, refractory monotherapy. Refractory adjunct regimens) [22]. It showed that high gap to treat the same indication. The cost profile of drugs were as illustrated in Fig 2. Acetazolamide based on these results it showed that newer generation antiepileptics like levetiracetam, topiramate, lamotrigine zonisamide, lacosamide were more expensive than older antiepileptics like phenytoin, carbamazepine, phenobarbital etc. levetiracetam had variable price with high cost deviation.

The reason for the high price variation in India is the pricing policy for the medicines. The prices of all medicines not under price control have been left to the market forces. The maximum allowable post manufacturing expense (MAPE) permitted for medicines under price control is 100% and ceiling prices have been fixed for these. For the other medicines, there is no restriction on the MAPE, resulting in large

and variable prices [23]. The variation in prices of the same medicine but sold under different brands is therefore large. A consequence of high variation in cost may decrease in patient compliance [6]. Apart from that it is increasing direct medical cost, hospital pharmacy budget, and unnecessary cost mobilization from patient, provider and societal perspective respectively. To decrease such cost containment, the role of government in changing pharmaceutical pricing policy is very important. Generic drug products are often cheaper than branded products and selection of less costlier generic drug is possible [24]. Formulary selection of generic drugs by cost minimization principles is necessary. We have shown that Cost/DDD will become useful tool to compare the price of different dosage forms and formulations of same drug while selecting formulary. It has been observed that doctors have suboptimal awareness of drug cost [25]. This situation can be improved by giving greater emphasis during medical training program of doctors [26]. A mention of the drug cost is also required in medical literature and drug advertisement. The patient also has to be educated to be aware of high variation in cost.

The results of this study demonstrate large cost variation existing of antiepileptics in India. However, this profile will be changing from time to time. The selected dosage form and formulations of antiepileptic drugs which were manufactured till research date by different companies were only reviewed.

CONCLUSION

There are lot of dosage forms available for antiepileptic drugs. The wide gap of variation in cost of antiepileptic drug is due to different brands and dosage forms and formulation. There is urgent need to reduce such unnecessary cost variation by change in drug pricing policy from government authorities. The prescribers and patient should be educated about high cost variation in drugs. Pharmacist can also help to reduce cost in hospital settings by formulary selection of less costlier generic drugs conducting cost variation analysis.

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