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Review Article

A review on cost effective analysis of antiepileptic drugs

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Abstract: 80% of the epilepsy patients were resides in developing countries. 12 million patients with epilepsy were in India that is One-sixth of the global burden is due to epilepsy. Those diseases were treated properly there is a greater reduction in seizure and people may leads to proper life, if untreated that may become a large increase in burden. Drugs are the main treatment for epilepsy. As compared with conventional AEDs newer drugs are much expensive some newer drugs were 10 to 20 times costlier than older drugs. if those expensive drugs reduce the seizure events, improves the quality of life and with lesser ADRs then the benefit justify the higher cost of the drug. The epilepsy burden can be reduced mainly by giving epilepsy care at low cost, given the lack of expertise in the management of epilepsy in poor areas.

Keywords: Antiepileptic drug, Cost, Epilepsy.

Introduction

Epilepsy is the most common neurological disorder which may affects the quality of life and also may poses a health as well as economic burden. 70 million people in the world affected by epilepsy[1,2]. Globally, nearly 2.4 million people are diagnosed with epilepsy each year. In comparing with high income countries there can two times higher the number of new cases in low and middle-income countries. From a general population at a given time there is 4 and 10 per 1000 having active epilepsy (i.e. continuing seizure with the need for treatment), and in some low and middle-income countries the proportion is much higher as 7 and 14 per 1000 people[3].

Most of the people with epilepsy reside in developing countries, 10 million people are having epilepsy in India, most of them do not receive appropriate medication for their condition and make a large treatment gap, this may due to lack of knowledge of AEDs, poverty, cultural beliefs, stigma, poor health infrastructure and shortage of trained professionals. Infectious disease plays an important role in seizures and long-term burden causing new-onset epilepsy and status epilepticus. Tremendous changes can be made in India by proper education and appropriate health care services. Epilepsy was estimated to account for 0.5% of the global burden of disease[3-6]. The prevalence of epilepsy in India is about 1%, the prevalence is higher in rural compared to urban population, In the Bangalore Urban Rural Nero-epidemiological Survey a prevalence rate of 8.8 in 1000 people was observed, with the rate in rural communities being twice than that of urban areas[7,8]. In United States, epilepsy patients younger than 14 years of age are about 300,000 and more. More than 500,000 are older than 65. The incidence rate of epilepsy may increase in childhood and it may be decreasing order in adult life second high rate in the age greater than 65 years[9].1.5 million women were affected with epilepsy in united states[10]. The prevalence of epilepsy was higher in the Saharan Africa[11]. 200,000 new cases are diagnosed each year of this 45000 patients are children younger than 15 years, males are much more affected than the females African-Americans are affected higher than that of Caucasians[12].

Drugs are the main treatment for epilepsy, 60-90% of epilepsy can be controlled by the proper selection and use of antiepileptic drugs[13]. In the 20th century the standard AEDs such as phenytoin, Phenobarbital, primidone, valproic acid, Carbamazepine, and ethosuximide are combined for the better effect but later in 1970's several studies showed that monotherapy was equally efficacious, less toxic and more tolerable than polytherapy[14]. The second-generation AEDs felbamate, Gabapentin, lamotrigine, topiramate, tiagabin, levitriacetam, pregabalin are available the advantage of most newer AEDs including more safe profile, fewer side effects and less drug interactions these second-generation drugs are also safer to monotherapy[15].

Most of the AEDs are cheap, the volume of prescription, duration of treatment is high enough for the poor people. About 50% of the patient become seizure free and may lead to normal life seizure can be controlled in majority with Monotherapy[16,17]. Drug side effect play an important role the selection of drugs, quality of life and compliance in patients. There is high

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prevalence of cutaneous reaction in patients less than 5 years. Commonly occurring side effects for AEDs are memory problem, fatigue, tremors, osteoporosis, depression, drowsiness, dizziness, weight change. AEDs may be causing the stevens-johnson syndrome (5-10%), which is a life-threatening side effect, most commonly using drug phenytoin may be causing hypersensitivity and drug eruption, phenobarbitone may causing various skin reaction that may self-limited after drug discontinuation. The newer drug lamotrigine may cause rash, lymphadenopathy and drug eruptions[13]. These may have elevated the health care cost of patient many studies show that the side effects of AEDs are also a reason for economic burden of epilepsy. The newer AEDs are more expensive than the older once the cost of lamotrigine for initial treatment was 20 times than that of the phenytoin if a patient taking a new AED is able to return to work and has advantage in terms of causing fewer ADR or improve seizure control, then the benefit justify the high cost of the drug[13].

ADRs can be arises due to inappropriate medication use and is a great risk for the elderly due to increased susceptibility for this may result of age related pharmacokinetic and pharmacodynamic changes, co-morbidities and multiple drug use. ADRs may increase the annual cost of the disease due to increased hospitalization, prolongation of hospital stay, additional clinical investigation in more severe cases[18]. Pharmacoeconomics is a branch of economics that measures and compares the cost, risk and benefit of programs, services or therapies and determines which alternative produces the best health outcome[16]. There are many pharmacoeconomic methods they are Cost minimization, cost benefit, cost effectiveness, cost utility analysis. Outcome may be positive or negative[19].

Scope

12 million patients with epilepsy were reside in India of 70 million in the world that is, one-sixth of the global burden. In developing countries more than 80% of the individuals having epilepsy and disease were untreated; if there getting the proper medication those could live normal life. The patients without taking treatment greatly increases burden. Many traditional AEDs are considered to have a narrow therapeutic index so slight variation in drug absorption could result in significant negative health outcome, that could be a greater risk. Newer AEDs are more expensive than the older drugs, if a drug may produce fewer side effects or improving seizure control, then the benefit may justify the higher cost of the drug. The choice of drug is important as, patient whose epilepsy response to a particular AED are likely to continue to be treated with that drug for many years, as drug changes can be associated with deterioration in seizure control and side effects.

Methodology

A systematic literature search was performed using the databases Academic Search Complete, EMBASE, MEDLINE, MEDSCAPE, MICROMEDEX, LEXICOMB. Health economic evaluation of AEDs, mainly focused the economic evaluation and comparison of two AEDs for epilepsy treatment. Many studies were initially identified and 30 were finally included. Information regarding AEDs studies, cost effectiveness, incidence rate was extracted from each study. Then the included studies were summarized and a quality assessment was performed over a period of 3 months.

Results and Discussion

Epilepsy can be occurring in any age groups both male and female, but more frequently in infant, adolescence, old age. More than 50 million 0f the people are having epilepsy worldwide of this 80% were resides in developing countries. In countries like India if those diseases were treated properly there must be a great reduction in those conditions, if untreated there must be large increase in the burden[20]. Treatment gap is the percentage of people with untreated epilepsy, it is ranges from 22% in India. 90% of treatment gap seen in village areas. In a study at Kolkata, India a study on epilepsy over 5 years 476 participants having active epilepsy over 100,802 participants. The age-adjusted prevalence rate was 4.71 per 1000. The incidence rate was 38.3 per 100,000 and the mortality rate of epilepsy was 2.4. the overall year of life lost (YLL) were 755 per 100,000 general population and overall year of lives lived with disability(YLD) ranges from14.45-31 per 100,00 general populations, both YLL and YLD value were higher in males than in females[21].

In India prevalence of epilepsy was 5 per 1000 the prevalence of India as compared with other developed countries are comparable. Prevalence is 5 in 100 and incidence rate of 50 in 100,000, and the prevalence in urban or semi-urban area is 5.11 and in 5.77. the prevalence of men is 5.88 in case of rural men it is 5.39; urban men it is 6.52. then the prevalence of female 5.51 in case of rural women it is 4.83; urban women it is 6.54. The prevalence of epilepsy in Pakistan was found to be 10 per 1000 and the epilepsy in rural is 35.5% and urban is 60%. The prevalence of Pakistan is much higher than that of India. The overall relevance of china is 3.5 per 1000 the prevalence of rural is 3.17% and in urban is about 2.34%.the prevalence of epilepsy in Bangladesh is about 10-12 per 1000 people. The prevalence of epilepsy in Iran is 7.87 per 1000 people it is higher than the prevalence of India and lower than the prevalence of Pakistan. The age adjusted prevalence of North America is 5 in 1000 and 7.1 in North America. The prevalence of Argentina is 3.7 per 1000 people. The prevalence of

epilepsy varies from 2.2-58 per 1000 in African region. The prevalence study from Asia was from 1.5 per 1000 in Japan to 10 per 1000 in Pakistan[22-24].

Generally, in most of the studies the prevalence is same in adult people it may increase after the age of 50 in developed countries. The epilepsy in adult and childhood are primary in nature others are secondary. The prevalence of male is high in India than the female. The other Asian countries such as China, Turkey, and Saudi-Arabia the prevalence is high in males. In Pakistan, there is the prevalence of female is higher. The prevalence is higher in male than female in North, Central and South America[25-28].

There are many co morbidities for the epilepsy. There are additional burden of stigma and societal attitudes may lead to anxiety and depression. The prevalence of psychiatric co morbidities of epilepsy was about 5.9-55%. The risk factors including catastrophic childhood epilepsy syndrome, anti-epileptic drug polypharmacy, abnormalities in the brain morphology and early age of seizure onset. The premature mortality with epilepsy is due to epilepsy causative factors such as tumors, cerebrovascular diseases or may be related to seizures, status epilepticus or due to co morbid depression leading to suicide. The neurological co morbidities are migraine, cognitive impairment including multifactorial causes such as underlying structural brain damage and MRI volumetric anomalies, seizure duration and its increased frequency, effects of AEDs. Some of the AED cause fetal abnormalities in mother with epilepsy. Cognitive, psychiatric, behavioral, and psychosocial problems occur in all types of epilepsy that gives a huge burden for the patients and also caretakers[29].

Epilepsy is easily preventable and treatable condition it is a major health problem due to high stigma, wide socioeconomic inequity, large treatment gap, and poor epilepsy healthcare delivery system in India, thus the psychosocial and economic impact of epilepsy become more crucial while addressing the problem of epilepsy. There must require well-trained professionals were needed for the prevention, improved care, and rehabilitation of patient with epilepsy in India for reducing the treatment gap. Epilepsy imposes a substantial economic burden to the epilepsy patients. The cost involved in the epilepsy care can be grouped into direct, indirect and intangible costs. Cost due to pretreatment help seeking, cost of treating co morbid condition, cost of side effect of AEDs and their management are the part of direct cost. Intangible and indirect costs are not always included in most of the studies. Thus the actual economic burden due to epilepsy is expected to be much higher than the available information. The estimated annual economic burden of epilepsy in India was found to be 88.2%. The direct cost is 27.1% and indirect cost is 72.9%, in most studies from India shows that indirect cost exceeded the direct cost. In recent study shows 85% of the total cost is indirect cost lack of continuity in treatment due to indirect cost burden. In another research cost of drug, investigation, and inpatient care as a major component of direct cost. And the direct treatment cost is 30%, travelling 6% and productivity loss is 64%. The costs of AEDs become an important factor to the economic burden of epilepsy in India. The cost due to AEDs depending on the factors such as type of therapy, type of drug, type of healthcare and their duration. The maximum annual drug cost for minimum for phenobarbitone and in case of newer AEDs such as lamotrigine, levitriacetam and lacosamide are having higher cost as compared to other AEDs among the newer AEDs clobazam had the lowest cost. The cost of treatment of epilepsy caused by neurocysticercosis was much higher because of the additional cost for the extra drug[30,31]. The treatment cost also influencing the drug adherence. When cost of the drug was reduced by the government, high travel charge emerged as a major contributor of direct cost. This highlights the critical role of accessibility affordability of healthcare, further determined by urban-rural disparity among the population that used public sector in the absence of universal health assurance program. There were estimated that 1 million people in India having refractory epilepsy and half of it needs surgery but only less than 500 surgeries were undertaken and there must be a high surgical treatment gap and huge healthcare burden, 80% of healthcare cost in epilepsy are accounted by the patient with drug-resistant epilepsy[20].

There are many new AEDs were marketed in recent decade, quality of life must become the central focus of epilepsy treatment. In socioeconomic evaluation, costs are the resources expended to obtain a desired state of health the resource expenditures incurred for the prevention, diagnosis, treatment of a particular disease included under cost. The newer AEDs are more expensive that is the direct medical cost, the indirect cost to the society through lost productivity or premature death is many times more than the direct cost. There are more advantages for the newer AEDs than the conventional using drugs such as tolerability, safety, and ease of administration and better control of seizure, improvement in the quality of life. The high initial cost of pre-surgical evaluation and epilepsy surgery may offset by gains in increased number of quality adjusted life years. a multicenter study involving one center each from 8 states of India was carried out recently, and carried out some of the direct cost of epilepsy care in India. Patient included all age groups, about 6% of them never taking any AED, polytherapy reduced from 48-22% patient after referral to an advanced

epilepsy Centre. Nearly 70% of them take one EEG, 36% had one or more scan and only 8.5% had one MRI scan. The direct cost of treatment was over Rs.5000/-. The mean loss of working day were 58 days. The cost of loss of work may Rs.6000/-. The out of pocket expenditure for epilepsy in Kerala is approximately Rs.46700/-. The newer AEDs having more advantages over conventional AEDs those drugs are economically more effective[32,33,34].

The quality of life was almost comparable for the most AEDs on all the parameters of QULIE-10 comparing older drugs with newer AEDs did not reveal a significant difference. The newer AEDs must be weighed against their cost. They determine Response Ratio(RR) to analyze efficacy of AED, RR was calculated for 12 patients as only these were found to have the baseline seizures at the initiation of therapy and were prescribed add-on newer AEDs. The value shows at least 50% or more reduction in seizures when observed after 12 weeks and result shows >50% reduction in seizure was observed in 4 out of 12 patients who were prescribed add-on newer AEDS. The majority of patient attending the clinic was aged between 11-30 years. Most of the patients were males. Monotherapy with AEDs are more than that of dual therapy and polytherapy were very rare in this study. Carbamazepine was most frequently prescribed AED. The cheapest drugs used in Bangladesh were phenobarbitone and phenytoin, the cost of Carbamazepine and valproic acid were slightly higher which shown in table no: 1. PHT cause ADR such as gum hypertrophy and CNS manifestations, But CBZ shows serious side effects such as anemia and skin rashes. VPA and PHB experience weight gain \was shown in table no: 2. In this study adjustment of drug dose or withdrawal due to ADR caused by the AEDs[35-37].

Table 1. Cost of AEDs

AED	Mean maintenance dose (mg/day)	Cost per unit mg/tab (Taka[1])	Annual cost (Taka)	Annual cost (International Dollar[2])
CBZ	400	200 (3.5)	2556	196.12
VPA	600	200 (3)	3285	252.06
PHB	60	30 (1.5)	1096	84.10
PHT	300	100 (2)	2190	168.06
TOP	50	25 (10)	7300	560.24
LTG	100	50 (12)	8760	672.28

Table 2. Adverse drug reactions (ADR) with AED monotherapy

Sample	Type of reaction	AED			
		N		(%)	
		CBZ	VPA	PHB	PHT
		67 (11.6%)	46 (25.7%)	16 (23.5%)	11 (64%)
Blood	Anaemia, pancytopenia	15	1	0	0
Skin	Rash, urticaria, photosensitivity, SJS	11	0	0	0
Mouth	Gum hypertrophy/hyperplasia, ulcer	0	0	0	7
GIT	Nausea, vomiting	23	4	7	0
Liver	Hepatitis	14	3	1	0
CNS	Drowsiness, ataxia, vertigo	1	0	0	2

The health related QoL in all 4 groups (valproic acid+lamotrigine, valproic acid+ clonazepam, oxcarbazepine+clobazam, phenobarbitone+ phenytoin) improves with the decrease in seizure frequency and a negative relationship between seizure frequency and QoL. The combination of valproic acid+lamotrigine has synergistic effect, single bedtime dose for better drug compliance, but having the disadvantage as high cost and increased reports of cutaneous reactions. Clonazepam or lamotrigine with valproic acid are effective combination in once a day schedule for the patient with primary generalized epilepsy with poor control on valproic acid mono-therapy[38,39,40,41,42]. This study shows that phenytoin and phenobarbitone is a more cost effective option therapy than other combination.

The low prize traditional AEDs may cause many life-threatening side effects the low prize make the traditional AED attractive first choice, the seeming tolerance profiles of the new medications and the decreased need for hematologic monitoring may consider for the selection of AEDs. Older drug phenytoin may cause lymphadenopathy, lymphoma also drug-drug interactions. Carbamazepine a boxed warning emphasizes that aplastic anemia and agranulocytosis, liver damage and CNS side effects. Phenobarbital is limiting its usefulness in children behavioral problems and cognitive deficit are more commonly seen. Valproic acid emphasizes that hepatic failure and children having metabolic disorders and organic brain disease. Interactions with other AEDs are common. Newer AEDs also showing adverse effects such as felbamate shows acute liver failure, children with aplastic anemia were reported. Gabapentin shows primarily CNS symptoms in children including somnolence, headache and dizziness. Lamotrigine shows rashes, many observed in children, CNS side effects. Levitriacetam may adversely affect on CNS. Somnolence, ataxia, headache and psychiatric complications. This study said that almost all the AEDs shows side effects[43-45].

Desipramine was more effective and less expensive than Gabapentin and pregabalin under all the condition. Gabapentin was more effective than pregabalin but at an incremental cost of 216,000 dollar/ QALY. Below 140 dollar/month. Gabapentin become more cost effective than

pregabalin at a threshold OF 50,000 dollar/QALY, and below 115 dollar/month Gabapentin dominated pregabalin. Desipramine appears to be more effective than Gabapentin or pregabalin for the treatment of epilepsy. After its price fall, Gabapentin will be more cost-effective than pregabalin[46,47].

Conclusion

It can be concluded that newer AEDs are mostly free of major ADRs and lesser drug interactions, there use were lesser because of their high cost in the poor countries. Other than the cost factors the use of these drugs may reduce the prevalence and treatment gap in countries like India this may also increases the quality of life of the patient with epilepsy the patients with surgically treatable epilepsy should undergo surgery early as possible for the better outcome there must be proper education about the treatment of epilepsy by the healthcare providers for the better understanding of patient with epilepsy in lower and lower middle income countries the epilepsy burden can be reduced mainly by giving epilepsy care at low cost, given the lack of expertise in management of epilepsy in poor areas, suggest neurologists and psychiatrists should combine and give services for the management of epilepsy in poor areas.

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