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## Current Concepts and Future Perspectives in Cost-Effectiveness Analysis of Antiepileptic Drugs: A Review



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### ABSTRACT

Cost-effectiveness analysis plays an important role in selecting proper AEDs (Anti Epileptic Drugs) as most of the epileptic conditions requires a chronic treatment. This review focus on the cost-effectiveness analysis of AED's and co-morbidities in the epileptic population. Current studies on incremental cost-effectiveness ratio suggest that newer AED's have high efficacy with low or optimal cost. On the shreds of evidence emphasized on cost-effectiveness ratio and co-morbidities, the current epileptic treatment is done with a proper selection of AED's appropriate for epileptic conditions. The co-morbidities have an important role in the burden of epilepsy. The incidence of adverse drug reaction is seen more with older AED's than the newer ones.



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## INTRODUCTION

Pharmacoeconomics can be defined as the branch of economics that practices cost-benefit, cost-effectiveness, cost minimization, cost of illness and cost of utility analysis to compare pharmaceuticals products and treatment strategies. The purpose of all pharmacoeconomic studies is to make the excellent discretion within defined parameters<sup>1</sup>.

The outcomes in pharmacoeconomics include lower cost: better outcome; higher cost: better outcome, lower cost: poorer outcome; higher cost: poorer outcome<sup>1</sup>.

In economic evaluations, the selection of the appropriate comparator is one of the most critical factors in estimating the cost-effectiveness of a medical technology, and both cost of care and health gain, have to be analyzed. In the case of recent pharmaceuticals, the comparator can be the current gold standard therapy, if the new medicine competes with the most widely used first-line technology<sup>2</sup>.

The primary measure of interest for the economic analysis was the incremental cost-effectiveness ratio (ICER)<sup>3</sup>. Cost-effectiveness analysis is the comparison of cost per standardized unit of effectiveness for two or more interventions, which gives varying kind of outcomes<sup>1</sup>. In CEA, the incremental cost effects are expressed in non-monetary units (eg: years of life saved, quality of life, reduction of disease severity)<sup>4</sup>. In the literature and especially in drug, therapy CEA is the most applied form of economic studies. It allows comparisons to be made between two equivalent areas of medicine with similar outcomes and is one of the best tools for decision-makers can use, to assess and potentially improve the performance of their health systems. It indicates which interventions provide the highest "value for money" and helps them choose the interventions and programmes which maximize health for the available resources<sup>5,6</sup>.

CEA requires information on:

- The extent to which current and potential interventions improve population health, i.e., effectiveness.
- The resources required to implement the interventions, i.e., costs<sup>6</sup>

Methods of evaluating socioeconomic relationships have evolved over many years, and a number of specific approaches have been developed. Among the techniques available, cost-

effectiveness analysis (CEA) has emerged as the most widely used and accepted method. Yet, despite considerable effort by the analytical community to refine this technique into one more useful for making health policy decisions, much debate and confusion still persist among analysts, readers, and policy-makers concerning methods standards and the overall usefulness of CEA in resource allocation decision making<sup>7</sup>. Over the years, use of the term CEA has broadened to describe methods for relating the cost and outcome of a specified activity. CEA has taken on an increasingly larger role in health care policy debates as rising medical expenditures force society to confront the broad issue of value received for money expended<sup>7, 8</sup>.

For drugs, CEA is used to make national as well as institutional formulary decisions. Clinicians are now using CEA to evaluate particular medical interventions. In CEA, consequences are expressed in natural health units (e.g., years added onto life expectancy); in CUA, consequences are expressed in patient preference measures combining length and quality of life (eg, quality-adjusted life year [QALY]); and in CBA, all consequences are expressed in monetary terms<sup>9</sup>.

Epilepsy is the second most common neurological disease affecting almost 50 million people worldwide<sup>10</sup>. According to ILAE 2017 (International League Against Epilepsy), epilepsy is a disease of the brain defined by any of the following conditions: a) At least two unprovoked (or reflex) seizure and a probability of further seizure similar to the general recurrence risk (at least 60%) after two unprovoked seizures, occurring over the next ten years. b) Diagnosis of an epilepsy syndrome<sup>11</sup>.

The epilepsy is associated with the high burden of co-morbidities, like depression, anxiety, dementia, migraine, heart diseases, peptic ulcers, and arthritis, eight times more than in general population. Currently, the relevance of epilepsy is increasing because they affect epilepsy prognosis and quality of life<sup>12</sup>.

The etiology of epilepsy is a major determinant of clinical course and prognosis, the etiology of epilepsy is divided into four categories: idiopathic, symptomatic, provoked, and cryptogenic<sup>13</sup>.

About 70 million people have epilepsy worldwide and nearly 90% of them are found in developing regions and having a median prevalence of 1.54% for rural and 1.03% for urban

areas. With a prevalence of 1%, more than 12 million peoples with epilepsy present in India<sup>10</sup>.

The treatment of epilepsy is with anti-epileptic drugs AED's and by epileptics high incidence of mood and behavioral issues, including depression, anxiety, and irritability. In the treatment of epilepsy, adverse effects of AED's and psychological symptoms are of particular importance because they can negatively affect the quality of life<sup>14</sup>. Individuals with epilepsy have a variety of treatment options. Medications are the first options and mainstay of treatment for most people. AED's treat the symptoms, not the underlying disease. Medications to treat seizures are usually called antiepileptic drugs or AED's<sup>15</sup>. The ultimate goal of treatment helps the person become seizure free without side effects of medications or other treatments. There are many available AED's, with the majority of older AED's metabolized by the liver. These 'older' AED's are thought of as the 1<sup>st</sup> generation of seizure medications. They tend to have more side effects, including cognitive and sedating effects, many of which may worsen in relation to dose<sup>16</sup>. There are 1<sup>st</sup> (older) and 2<sup>nd</sup> (newer) generation (includes those have been approved since the early 1990's) AED's used to treat epilepsy. 1<sup>st</sup> generation AEDs includes bromides, phenobarbital, phenytoin, primidone, ethosuximide, carbamazepine, clonazepam, Valproate and 2<sup>nd</sup> generation includes felbamate, gabapentin, lamotrigine, topiramate, levetiracetam, oxcarbazepine, zonisamide, pregabalin, lacosamide, rufinamide, ACTH, clobazam, ezogabine of the newer AED's, now called 2<sup>nd</sup> generation drugs, the efficacy is at least equal to the older agents and they appear to be safer and better tolerated by patients. The occurrences of adverse drug reactions are more in 1<sup>st</sup> generation than in 2<sup>nd</sup><sup>17</sup>.

The annual economic burden of epilepsy in India is 88.2% of GNP (Gross National Product) per capita and 0.5% of the GNP<sup>18</sup>. In addition to the epidemiologic and social burden of epilepsy, epilepsy also carries a substantial financial burden. Epilepsy results in a significant economic cost in terms of treatment lost productivity and increased health care utilization<sup>19</sup>. Estimates suggest that some countries spend as much as one percent of their total national health care expenditure on epilepsy care and treatment<sup>20</sup>.

As per GBD (Global burden of disease) analysis for 2010, epilepsy accounted for 0.7% of the global burden or more than 17 million DALYs and nearly 90% of these were reported from low and middle-income countries (LMICs)<sup>10</sup>. According to GBD 2010 analysis, the prevalence of epilepsy varied from 2 to 10 per 1,000 population in southeast Asia region and

more than half of the total DALYs due to epilepsy were accounted from India<sup>10,22</sup>. This huge burden from India is probably because of the large population, lower income and education, socio-cultural prejudices, inadequate resources, competing infections and non-communicable disease, and the low importance given to public health aspects of epilepsy.

### **Methods of Assessment of Cost and Effectiveness in Economic Analysis**

Cost-effectiveness analysis is a method for assessing the gains in health relative to the cost of different health interventions and it involves dividing the cost of an intervention into monetary units by the expected health gain measured in natural units such as a number of lives saved. The cost of the treatment is calculated by direct and indirect cost for epileptic patients. The incremental cost-effectiveness ratio (ICER) is calculated as the additional cost divided by the additional health gain. The incremental cost-effectiveness is the additional cost of extending a particular intervention divided by the additional health gain that would result<sup>23</sup>.

Goyal et al., states that in developing countries, the economy plays a very important role in managing the burden of epilepsy by the routine availability of low-cost antiepileptic drugs (AEDs). In the study, the cost-effectiveness calculated as the ratio of cost of treatment and improvement in the quality of life with every combination<sup>24,25</sup>.

The effectiveness can be achieved by measurement of outcome that is health benefits across therapies are measured in natural units and synthesis of cost and benefits by cost per life year gained, cost per patient cured, cost per life saved etc<sup>5</sup>.

### **Cost-Effectiveness Analysis of Antiepileptic Drugs**

Chisholm et al., reported that low-cost AEDs as the first line intervention strategy for reducing the global burden of epilepsy. The most effective strategy for reducing the burden of epilepsy in developing region is the use of phenobarbitone or phenytoin<sup>25</sup>.

Carbamazepine and Valproic acid produce (average) cost-effectiveness ratio in the range of 1\$ 1,100-3,000 which are more expensive and reported that by scaling-up the routine availability of low-cost AED's, significant proportion of the current burden of epilepsy can be avoided<sup>25,26,20</sup>.

Goyal et al., states that in a one-year observational study, the patients on monotherapy had a quality of life than on poly-therapy in the patients of generalized tonic-clonic (GTCSs) and partial seizure, the disadvantage of the combination of AED's, is additive neurotoxic side effects. Cost analysis of dual therapy in epilepsy with valproic acid+lamotrigine, valproic acid+clonazepam, oxcarbazepine+clobazam and phenobarbitone+phenytoin concluded that phenytoin and phenobarbitone is a more cost-effective combination therapy and older drugs are equally efficacious as compared to newer in controlling seizure frequency and improving the quality of life, but are more cost effective<sup>24</sup>.

Pennington et al. reported that mainly, due to the cost of providing appropriate accommodation and living support along with appropriate activities for people with intellectual disability, cost of health and social services of supporting people with epilepsy and intellectual disability are high and epilepsy-related health care cost is a small portion of overall costs<sup>27</sup>.

Haroon et al., states epilepsy is slightly more prevalent in the male gender in India and Denmark, and a 1:1 male: female ratio has been reported in Srilanka<sup>28,29</sup>. Even for those not responding to conventional AED's, newer AED's, provides clinicians with the wider choice to achieve therapeutic efficacy<sup>28</sup>. The main reason for introducing a newer AED's is the persistence in seizure activity<sup>28,30</sup>.

Several other studies show a higher percentage of patients were prescribed monotherapy (70-96%) in India, Srilanka, and Nigeria. Even though there is no evidence from randomized controlled (RC) studies, that shows polytherapy is superior to monotherapy in achieving seizure control. The study indicates that increasing usage trends of newer AED's, Clinically, increase polytherapy with a significant escalation in the cost of therapy<sup>28</sup>.

Wilby et al. reported that for the treatment of newly diagnosed patients experiencing either partial or generalized seizure, the older mono-therapies appeared to be cost-effective when compared with newer AED's. However, in the case of patients who have experienced adverse events with older AED's who have failed to respond to the older drugs or where such drugs are contraindicated, the newer AED's, used as monotherapy may cost effective<sup>31</sup>.

Jost et al., states that the main sources of AED's were private pharmacies in Madagascar, and the financial burden for people with epilepsy was still important in the capital of Madagascar.

Sodium valproate remains the most expensive drug although it remains the most available instead of phenobarbital<sup>32</sup>.

### **Co-morbidities of Epilepsy**

A co-morbid condition (or co-morbidity) is one that occurs during the course of an index disease (eg. Epilepsy). 50% adults with active epilepsy have at least one co-morbid medical disorder.

Gimenez et al., states that high percentages of patients with epilepsy have co-morbidity and is a precise factor when selecting the suitable AED's. The co-morbidities included are psychiatric disorders, cardiovascular disease, lung diseases, kidney disease, metabolic disorders, infection, and consists of subcategories. The treatment of these patients with anti-epileptics, the clinician should take special consideration of potential side effects and interactions with other medication in patients with co-morbidities<sup>33,34,35</sup>.

Keezer et al. reported that co-morbidities of epilepsy indicate an important burden for people with epilepsy. Some conditions, such as depression and migraine, negatively affect seizure outcome and quality of life. And the study also gives a measure of co-morbidity is by epilepsy specific co-morbidity index (ESI)<sup>12,36,37</sup>.

Chisholm et al. reported that co-morbidity is a further (unmeasured) factor that can increase the cost of treatment without corresponding health improvements<sup>25</sup>.

### **FUTURE PERSPECTIVE**

The cost-effective analysis had to involve more direct comparison of newer Vs newer and of newer Vs older AED's, within clinical trials, taking into account of different treatment within monotherapy and adjunctive therapy. One example of such a trial is the SANAD (Standard And New Antiepileptic Drugs) trial which is on the way<sup>25</sup>.

### **CONCLUSION**

In conclusion, it was found that epilepsy-related health care cost is the small fraction of overall cost. Several newer AED's, have now been introduced with the aim of increasing the efficacy and reducing side effects. Epilepsy is associated with not only seizures but also a variety of serious co-morbidities, as other complication increases the expenditure will also



increase. The cost due to adverse events is higher with older AED's than newer drugs. The newer AED's, are having high cost than that of older AED's. Ultimately, the burden of epilepsy for the patients, in terms of severely reduced quality of life, and for the custodians, in terms of cost would be best addressed and reduced by achieving optimal control of seizure with anti-epileptic treatment. While selecting a drug for epileptic patients both cost and effectiveness should be the criteria for the patients without other complication.

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