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THE BURDEN OF EPILEPSY AND IMPACT OF ANTI-EPILEPTIC MEDICATIONS ON COGNITION AND PSYCHOMOTOR FUNCTIONING: A LITERATURE REVIEW

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ABSTRACT

Introduction: Adverse effects associated with the use of antiepileptic agents are one of the leading cause of treatment failure in people with epilepsy. Potential of antiepileptic agents to adversely impact cognition and behavior is of serious concern as these are major therapeutic modalities for seizure control. The literature review aims to identify and review the burden of disease, barriers to effective management, medication trends of epilepsy and impact of anti-epileptic drugs on cognition and psychomotor functioning worldwide. Material and Methodology: A total of 55 studies were retrieved from databases related to epilepsy and psychomotor function. The studies were categorized on the basis of their country of publishing into developed countries, developing countries, and Pakistan. Results: The results of the review concluded that there is a need to monitor cognitive impairment in epilepsy patients on anti-epileptic therapy. Patients using older anti-epileptics such as benzodiazepines and carbamazepine reported higher cognition deficits whereas those using newer agents such as levetiracetam therapy appeared to have better cognition. Conclusion: There is a need to initiate educational campaigns and training of health professionals and volunteers about epilepsy, its management and early detection of cognitive disabilities among patients on antiepileptic drug therapy.

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INTRODUCTION

Epilepsy is a common neurological disorder worldwide, characterized by recurring episodes of involuntary body movements involving part of the body (partial) or the entire body (generalized), and sometimes accompanied by loss of consciousness and control of bowel or bladder function [1]. Worldwide 50 million people currently living with epilepsy and approximately 80% of the total disease burden lies in developing world. The approximated percentage of the people having epilepsy in a specified time is between 4 and 10 out of 1000 people, while in some countries it might be much higher. Pakistan has a prevalence rate of 9.98 out of 1,000 population, with higher prevalence among age group younger than 30 years and in rural population [1]. Antiepileptic drugs are among the most commonly prescribed centrally active agents. Treatment with these agents aims at seizures control without induction of adverse effects. All antiepileptic agents possess possibility of causing impairment in brain functions. Adverse effects associated with the use of antiepileptic agents are one of the leading cause of treatment failure in people with epilepsy and contributing towards negative impact on patient adherence also preclude attainment of fully affective doses.

Potential of antiepileptic agents to adversely impact cognition and behaviour is of serious concern as these are major therapeutic modalities for seizure control. Assessment of cognitive impact of antiepileptic drugs is an important aspect in the epilepsy management and optimization of epilepsy care [2]. Patients treated with multiple antiepileptic drugs are at increased risk of cognitive deficits. Sometimes these drugs have adverse effects on memory, thinking and learning ability are more debilitating for the individual patient than the seizure themselves [3]. People with epilepsy report significant impact of disease on family dysfunction, reduced social and leisure opportunities and increased level of psychiatric co morbidities. Hence, adverse effects of different antiepileptic agents on cognition and psychomotor functions impose additional burden on individuals with epilepsy [4].

The evaluation of cognitive complications caused by antiepileptic drug use is important for better management of epilepsy and improved patient health related quality of life. In the past few decades, these effects have been studied worldwide for the better understanding of different factors associated with increased psychosocial burden in epilepsy, but it is still neglected by healthcare professionals.

Objective

The main objective is to identify and review the burden of disease, barriers to effective management, medication trends of epilepsy and impact of anti-epileptic drugs on cognition and psychomotor functioning worldwide.

Methodology

The electronic databases PubMed, Google Scholar, and Science Direct, were searched for articles published from 2000 to 2018. The search terms used with each database were epilepsy, psychomotor function, anti-epileptics and cognition. Full-text papers, as well as abstracts, were retrieved and included in review. A total of 55 studies were retrieved from databases related to epilepsy and psychomotor function. The studies were categorized on the basis of their country of publishing into developed countries, developing countries, and Pakistan. 35 studies from developed countries, 15 from developing countries, and 5 studies from Pakistan were included in this review (Table 1). Quantitative cross-sectional surveys, as well as qualitative studies, were also included in this study.

Table 1 Details of Countries and Number of Included Studies.

Regions	Number of studies included	Countries
Developed countries	35	USA, Australia, UK, Japan, Germany, Belgium, Switzerland, Sweden, Canada, Denmark, Greece, Spain, Italy, Finland, Ireland, Netherlands
Developing countries	15	Turkey, China, South Africa, Ghana, Malaysia, India, Taiwan, Iran, Qatar, Eritrea, Jordan
Pakistan	5	

RESULTS AND DISCUSSION

Overview of Burden of Disease, Medication Trends and Barriers to Management of Epilepsy in Developed Countries

Epilepsy being one of the oldest condition known to mankind, is still the most common neurological condition that affect people of all ages. Worldwide 50 million people are estimated to have a diagnosis of epilepsy and majority of epileptic patient proportion found in under developed world [5]. This geographic variation in the epilepsy incidence is likely to be associated with genetic and environmental differences yet causality has not been fully explained [6]. Incidence of epilepsy among developed countries is 50/100,000/year. Age-specific incidence rates have changed, with reduction in younger age groups and an increase among persons of age above 60 [6]. This may be the result of adoption of healthier lifestyles by the expecting mothers, improved prenatal care and improved immunization strategies. All these factors contributed towards reduction of neuronal defects as caused by birth hypoxia and reduction of central nervous system viral infections [6]. According to a study, in the USA epilepsy is the fourth most common neurological condition after migraine , stroke and Alzheimer's disease and it is estimated that each year 150,000 new cases are diagnosed [7]. According to a review article, it is estimated that approximately 6 of 1000 Europeans have active epilepsy [8]. The prevalence of epilepsy in Australia is 7.5 per 1000 [8]. According to a review study conducted by NIH, prevalence of epilepsy seems to be higher in males than females as reported by various studies. However, absolute difference in gender-specific prevalence is minimal [9].

A study conducted in Brazil reports the prevalence of active epilepsy to be higher in those with lower socioeconomic status (7.5 per 1000) as compared to prevalence in affluent group (1.6 per 1000) [9]. A prevalence study conducted in USA suggests high prevalence of epilepsy among African-American race [9].

Barriers to Effective Epilepsy Control in Developed Countries

Although prognosis for seizure control is good and over 70% patients enter remission yet the impact of epilepsy goes beyond the seizures [6]. Challenges faced by epileptic patients include access to high-quality health care, problems in schools, uncertainty about social and employment situations, limitations on driving and dealing with stigma and common public misunderstandings [10]. Hence epilepsy impose high burden upon individual, family and society [10]. Epileptic patients have high morbidity, including bodily injuries because of falling, emotional disturbances, having high risk of premature death. Other brain dysfunctions include verbal disabilities, delayed cognitive abilities (De Boer et al., 2008).

Epilepsy is a stigmatizing condition. Stigma can be perceived stigma or enacted stigma. Perceived stigma refers to individuals perception of being stigmatised, whereas enacted refers to actual event of being stigmatised. In developed countries, there is significant evidence for the perceived and little evidence for enacted stigma [11]. There is evidence of violation of rights of people with epilepsy in developed countries as well [4]. In the United Kingdom 36% of epileptic patients were unable to avail insurance. Patients with convulsive disorders have been treated with damaging behaviour in many domains of life over many centuries as once stated that ‘‘The history of epilepsy can be summarised as 4000 years of ignorance, superstition and stigma, followed by 100 years of knowledge, superstition and stigma” [4].

Treatment Trends for Epilepsy in Developed Countries

Antiepileptic drugs (AEDs) are among the most frequently prescribed centrally active agents [12]. Non-pharmacological epilepsy management options are surgery and vagus nerve stimulation in few selected individuals [13]. Primary goals of treatment with anti-epileptic drugs are the achievement of complete seizure freedom ideally in the absence of adverse events. Optimal treatment with antiepileptic drug can stop seizures in up to 70% of patients with epilepsy but in remaining patients remission is elusive [13]. Currently the best pharmacotherapy option for treatment of epilepsy is monotherapy, and it is mandatory when starting treatment with antiepileptic drugs. Appropriate drug for the specific type of seizure and seizure syndrome having low adverse event profile and expected best efficacy should be selected at appropriate dose and slowly titrating to achieve optimum response [13]. Use of single antiepileptic agent is usually sufficient in most patients with newly diagnosed epilepsy and chances of success of monotherapy are maximum. Even after the failure of first drug at maximum tolerated dose, a trial of second monotherapy may also prove to be effective in considerable minority of patients [14]. Despite of the poor image of polypharmacy, monotherapy fails in significant proportion of patients, necessitating the trial of polypharmacy with anticonvulsants. Approximately 39% of non-responders were helped by the addition of second anti-epileptic drug with 17% becoming seizure free [14]. Adverse effects associated with antiepileptic drugs are leading cause of treatment failure among patients of epilepsy [15]. Older agents like benzodiazepines, phenytoin, carbamazepine are associated with sedative effects and coordination disturbances like vertigo, ataxia, gait difficulties, unsteadiness however these may also be caused by newer agents. According to a meta-analysis of eight newer anticonvulsive drugs, coordination difficulties are associated with the use of all in comparison to placebo [16]. Antiepileptic drugs also produce psychiatric side effects in about 15-20% of patients, leading to higher risk of suicidal thoughts and behavioural imbalance [15]. According to a review study, long-term use of anti-epileptic drugs causes abnormalities of bone, also leading to sexual dysfunction and other reproductive organs [17]. Antiepileptic drugs are also associated with the risk of development of teratogenic effects [15]. According to a prospective study conducted in UK, risk is higher with valporate and phenobarbital [18]. According to a report published by American Academy of Neurology and American Epilepsy Society risk of congenital malformation with valporate is higher as compared to carbamazepine and possibly comparable to phenytoin and Lamotrigine [19]. Antiepileptic drugs being enzyme inducer and enzyme inhibitors increase the risk of adverse drugs interactions, that are more common when polytherapy is used [15].

Cognitive and Psychomotor Effects of Antiepileptic Medications

Interest in the determination of cognitive adverse effects of antiepileptic started in 1970s. From January 1970 up to December 1998 , 1357 articles on the cognitive effects of antiepileptic drugs were published in peer-reviewed journal [20]. Classic and new generation anticonvulsive agents can cause both positive and negative effect on cognition and behaviour. Characterizing the medicine effect can be complex because of different disease factors and societal factors that contribute cognitive outcomes among epileptic patients [21]. Classic anticonvulsive agents have been studied in more detail as compared to newer AEDs.

(a) Effects of Barbiturates and Benzodiazepines on Cognition and Psychomotor Functions

Barbiturates and Benzodiazepines appear to produce most damaging effects on cognitive abilities and leads to reduced awakening and deteriorating multiple domains of cognition [21]. Phenobarbital can decrease IQ in children by 10 points, this reduction in score can be significant in some children While in adults too it appears to provoke adverse impact on cognition more than phenytoin and carbamazepine and [22]. Clobazam belonging from benzodiazepines class, possess strong anticonvulsant properties and anxiolytic properties as well. It was approved in 1974 as a treatment for anxiety and as adjunctive treatment of epilepsy [23]. It is very effective and well tolerated antiepileptic medication with minimal side effects that may include including; excessive sedation, ataxia , irritability and behavioural change [24]. A cross-sectional community based study in Netherland reported that commonly reported complaints were memory deterioration (21%), fatigue (20%), tiredness (19%) and attention problems (16%) [25]. Literature supports the fact that all the classic anticonvulsive medications can cause slowing of psychomotor speed [22].

(b) Effect of Valproic Acid on Cognition and Psychomotor Functions

Valproic acid is widely used antiepileptic drug , known to be effective in various seizure types such as absence, myoclonic, generalized tonic-clonic seizures, it also possess effectiveness in status epilepticus. Valproic acid is also used for the treatment of bipolar disorder, migraine and neuropathic pain [26]. Many studies have reported that valproic acid exerts little negative impacts on cognitive functions. An open label, randomized study for the evaluation of changes in attention in epileptic patients after 3-month of treatment with topiramate or valproic acid reported no increase in reaction time, however there is modest data of attention impairment by utilization of valproic acid [27]. Another cross-sectional study for the evaluation of neuropsychatric profile of patients taking valproic acid or topiramate reported that patients taking valproic acid have better profile of attention, verbal skills and short term memory as compared to patients on topiramate therapy [28]. Another double blind, placebo controlled randomised study conducted for the evaluation of differential cognitive and behavioural effects of topiramate and valporate reported that cognitive problems for valproic acid include memory impairment in 17% patients, speech abnormalities in 7% patients, attention problem in 10 % of patients [29]. A clinical trial conducted in United States for the neuropsychological effects of lamotrigine, ethosuximide and valproic acid in children reported that attention problems with valproic acid were more as compared to ethosuximide or lamotrigine [30].

(c) Effects of Carbamazepine on Cognition and Psychomotor Functions

Carbamazepine is a tricyclic compound that is most effective against partial seizures with or without secondary generalization. It is an anticonvulsant and mood-stabilizing drug and used mainly in the management of epilepsy, bi-polar disorder, schizophrenia, attention-deficit hyperactivity disorder and post-traumatic stress disorder. It may exacerbate juvenile myoclonic epilepsy and may also worsen absence seizures[31]. Many cognitive and psychomotor effects are linked to carbamazepine. A comparative study for evaluation of neuropsychological effects of carbamazepine versus valproic acid reported cognitive adverse effects of carbamazepine including excessive sedation, disturbances of concentration and visual motor coordination and psychomotor slowing**.** Patients taking valproic acid had lower scores of total aggression and verbal aggression [32]. Children being treated with carbamazepine had performance poor than children being treated with valproic acid, particularly on domains of memory [22]. According to a randomized , double-blind placebo-controlled study conducted in Norway for the assessment of discontinuation of antiepileptic drugs monotherapy particularly carbamazepine and valproic acid on measures of attention, reaction time and speed of information processing reports that discontinuing the anticonvulsive medicine, performance improved in tests that require complex cognitive process [33]. A multicenter, open-label, randomized study conducted in Korea compared monotherapy of lamotrigine and carbamazepine in newly diagnosed or untreated patients with partial epilepsy for the comparison of long-term cognitive and behavioral effects of carbamazepine versus lamotrigine reported that cognitive profile of lamotrigine is better than carbamazepine, however carbamazepine has more favorable behavioral effects then lamotrigine [34]. An open label , non-interventional surveillance study conducted in Germany for the evaluation of cognitive outcomes of patients taking levetiracetam or carbamazepine monotherapy suggests mild but superior cognitive profile of levetiracetam as compared to carbamazepine [35]. Another study conducted in Netherland to investigate cognition among patients of chronic partial epilepsy on carbamazepine monotherapy reported no impairment in selective attention, memory or executive function tests however speed of information processing was slower [36].

(d) Cognitive and Psychomotor Effects of Newer Antiepileptic Drugs

Information regarding newer antiepileptic medications is incomplete, although initial results of comparison of these agents in comparison with placebo produced promising results however few direct comparisons with older agents have been made. Newer antiepileptic agents include gabapentin, lamotrigine, topiramate, levetiracetam and vigabatrine [21].

(e) Effects of Topiramate on Cognition and Psychomotor Functions

Topiramate being an effective antiepileptic drug have wide range of activity. Its use is more common in different childhood epilepsy syndromes, including Lennox Gastaut syndrome [22]. Greatest concerns surrounds topiramate because of its cognitive adverse effects while considering newer antiepileptic agents [37]. A randomized clinical trial for the evaluation of topiramate effects on cognition in comparison to valporate reported that topiramate is associated with cognitive impairment particularly it affects verbal fluency, memory and attention [38]. Similar findings i.e. topiramate can induce clinically significant cognitive decline are reported by a retrospective study conducted in UK [39]. In a double blind, randomized study conducted in USA for evaluation of efficacy and tolerability of topiramate as monotherapy, most general neurobehavioral negative effects reported included attentiontional problems, and memory difficulty [40]. A drug audit conducted in Netherland for determining the retention time i.e. time zone between when treatment was initiated up to the treatment discontinuation up to 2 years , of three most commonly used antiepileptic agents including topiramate, lamotrigine and levetiracetam concluded that almost half of patients on topiramate discontinued treatment because of the drug's negative impact on cognitive abilities [41]. Another open label, 1 -year follow up study conducted for evaluating effects of topiramate therapy in epileptic patients on cognition reported impairment in cognitive function i.e. language skills, attention and memory improved after discontinuation of therapy [42] . Similar findings were reported by two other studies , one retrospective study carried out for the evaluation of cognitive effects of topiramate [39]. And the second study was open label, for evaluation of improvement in neuropsychological functions after withdrawal of topiramate in epilepsy patients [43]. A study conducted in adult patients with partial seizures for measuring cognitive effects of topiramate versus lamotrigine reported that lamotrigine had significantly less impact than topiramate on measures of cognition when used as adjunctive therapy for partial seizures [44]. An open label, comparative study of topiramate and oxcarbazepine conducted in Korea found worse performance of digit span and verbal fluency for topiramate [45].

(f) Effects of Oxcarbazepine on Cognition and Psychomotor Functions

Oxcarbazepine is a keto homologue of carbamazepine, having different metabolic profile. A multicentre, open-label, randomized study conducted in seven European countries to investigate the effect of oxcarbazepine against standard antiepileptic drug therapy (carbamazepine and valproate) on cognitive function in children and adolescents with newly diagnosed partial seizures reported little evidence of cognitive adverse effect by the use of oxcarbazepine over 6 months period [46]. In another clinical study conducted on 70 patients, for the evaluation of cognitive performance of oxcarbazepine monotherapy reported no worsening in cognitive domains, and there is mild evidence of enhancement in some patients [47]. Another open label trial conducted for the evaluation of cognitive performance of oxcarbazepine have indicated no worsening in learning abilities, memory or concentration in patients treated with oxcarbazepine [48]. A double blind, comparative randomized study compared oxcarbazepine to phenytoin, observed no differential effect on cognition between oxcarbazepine and phenytoin [49].

(g) Effects of Lamotrigine on Cognition and Psychomotor Functions

Lamotrigine was introduced first in Europe in 1991 and then in USA in 1994 [50]. It is effective and well tolerated in both elders and children. Existing data suggest that the cognitive impairments that are commonly associated with the use of antiepileptic drug therapy are uncommon in patients who receive lamotrigine as monotherapy, and when it is used as an add-on therapy, it does not exacerbate any preexisting cognitive problem, while in some cases it appear to improve cognition [51]. Another retrospective study conducted in Netherland for evaluation of long-term clinical experience with Lamotrigine indicated little evidence of cognitive impairment associated with use of Lamotrigine. Some, even felt being more energetic [52]. A double-blind, placebo-controlled, crossover study in children found that there were no cognitive adverse effects on performance measures of concentration, language skills, short-term memory and working memory [53].

(h) Effects of Levetiracetam on Cognition and Psychomotor Functions

Levetiracetam belongs from class of newer antiepileptic agents that is structurally different from other antiepileptic drugs. It is effective for reducing partial seizures among epileptic patients , both as adjunctive and as monotherapy. It has favourable pharmacokinetic profile with good bioavailability, linear pharmacokinetics, limited protein binding, lack of hepatic metabolism and rapid achievement of steady state concentration. Preclinical data suggests that levetiracetam may lack significant negative impact on cognitive measures [54]. These findings were supported by an open label study conducted to verify whether patients with partial epilepsy on levetiracetam therapy as add-on treatment show any improvement of cognitive function reported noteworthy improvements in concentration and verbal fluency with levetiracetam [55]. Similarly in another study it is reported that patients on levetiracetam therapy showed enhanced psychomotor speed, attention and memory [35]. Another open label study conducted on 39 child patients for the evaluation of safety profile of levetiracetam in children reported improvement in cognition i.e. improvement of concentration and alertness in some patients unrelated to seizure control [56]. An open-label , prospective , uncontrolled , phase 4 levetiracetam study conducted in US for the determination of its safety, efficacy and its impact on cognitive status of elderly patients that are diagnosed with Alzheimers disease or other cognitive impairment using mini mental state examination (MMSE) reported improved score and cognitive functioning by the use of levetiracetam [57]. Similar findings were reported by another prospective, multi-centre, open-label study to investigate the efficacy of levetiracetam and determine its effects on cognitive and neuropsychological function using MMSE reported improvement of mean score of mini mental state examination [58]. Similarly another comparative study for evaluation of comparative effects of topiramate and levetiracetam on cognition observed no change of cognitive performance after dose titration of levetiracetam however there was worsening of cognitive domains of cognitive speed and verbal fluency among topiramate group [59].

(i) Effects of Gabapentin on Cognition and Psychomotor Functions

Gabapentin is a novel antiepileptic medication, originally developed as gaba amino butyric acid mimetic compound to treat spasticity and has been shown to have potent anticonvulsant activity [60]. According to a randomised, double-blind study of gabapentin and carbamazepine conducted in USA for evaluation of neuropsychological and behavioural effects of gabapentin and carbamazepine in healthy volunteers reported slowing of EEG by the prolonged use of gabapentin and carbamazepine [61]. According to a study carried out in UK it was reported that gabapentin was most likely to be associated with treatment failure due to inadequate seizure control and carbamazepine the least likely. Lamotrigine was clinically better than carbamazepine in terms of cost and effect [62].

(j) Effects of Pregabalin on Cognition and Psychomotor Functions

Pregabalin is structural analogue of gaba-amino butyric acid but is functionally not related to it. It is currently used for epilepsy, neuropathic pain and generalized anxiety disorder. In the clinical trials of pregabalin, it has been shown to be highly effective and well tolerated as adjunctive therapy for partial seizures with or without secondary generalization [63] . According to an open label, comparative study conducted to examine short-term impact of pregabalin versus levetiracetam reported no significant difference between two drugs for different cognitive domains [64]. A double blind , placebo controlled study conducted to establish the efficacy, safety, and tolerability of pregabalin as adjunctive treatment in patients with partial seizures reported that it is well tolerated in patients with partial seizures [65]. A prospective, open label add-on trial conducted to determine efficacy of pregabalin reported few cognitive adverse effects that may include dizziness, behavioral change and somnolence [66].

Overview of Burden of Disease, Medication Trends and Barriers to Management of Epilepsy in Developing Countries

Epilepsy being common serious brain disorder affecting 50 million people worldwide and among them 40 million people are currently living in developing countries. Incidence of epilepsy in developing countries may be as high as 190 / 100,000 people while the reported prevalence rate is 5 to 10 per 1000 people. Because of rapidly increasing populations in these countries, epilepsy pose a significant health and socioeconomic burden that require urgent attention [67]. According to a survey study conducted in Saudi Arabia to determine prevalence of epilepsy and other convulsive disorders and cause of epilepsies in Saudi Arabian population reported that prevalence rate of epilepsy in Saudi Arabia was 6.54 per 1000 population [68]. Prevalence study conducted in rural Honduras reported that prevalence in Honduras is 23.3 per 1000 population and partial seizures were common [69]. In Africa reported incidence of acute seizures in young children to be in excess of 1000 per 100,000 per year [70].

Barriers to Effective Epilepsy Control in Developing Countries

In developing countries multiple factors like perinatal medical problems, malnourished mothers and home deliveries by untrained birth attendants and neonatal exposure to multiple central nervous system infections along with the trends of inter-family marriages contribute towards the risk of developing epilepsy among newborns [5].

Epilepsy is a worldwide trouble that affect all races, age groups, social strata's and regions that contribute enormous physical, social, emotional and financial burden on persons, families because of misinterpretation stigmatization of epilepsy patients and fear. These problems are universal but particularly more common in developing countries. Out of total 50 million epileptic patients, 85% live in developing countries and about three quarter of them receive no treatment or diagnosis [67]. Epilepsy "treatment Gap" as defined by International League against Epilepsy(ILAE) is " the difference between the number of people with active epilepsy and the number whose seizures are being appropriately treated in a given population at a given point in time, expressed as a percentage" [71]. In Sub-Saharan Africa, approximately 65 to 95% are not receiving anticonvulsants , and this percentage is highest in rural areas [72]. The percentage of treatment gap in India is 75% , in Ethiopia is 98% , in Philippines is 85% while in Sudan is 60% [73]. Some of the reasons behind this high treatment gap may include poor understanding of disease, stigmatization, cultural beliefs, insufficient availability and supply of antiepileptic drugs, scarcity of trained medical personals , poor infrastructure , and lack of prioritization in national health policies [71].

In many developing countries, epilepsy is not considered as a neurological disorder rather perceived as caused by supernatural forces or possession by evil spirits [71]. This misunderstanding and the resulting social stigmatization and discrimination contribute towards more suffering to person with epilepsy than the seizures themselves [74]. According to a survey study conducted in India to ascertain prevalence of epilepsy, quantifying knowledge and determination of attitude and practice towards epilepsy among people of the state of Kerala reported that the attitudes towards epilepsy were far more negative as compared to developed countries despite of comparable literacy rate. Nearly one third respondents also believed that epileptic patients could not have happy married and sexual life [74]. Similar findings are reported by another survey study conducted in Malaysia on public awareness, attitude and knowledge towards epilepsy reported that the respondents were familiar with epilepsy, but respondents maintained negative attitude towards the people with epilepsy [75]. According to a survey study conducted in Zambia to determine knowledge, behaviour and practices of Zambian clerics with respect to epilepsy reported that like other African countries, epilepsy is a stigmatizing condition in Zambia, familiarity with the condition is not associated with more tolerance towards it, tolerance towards the condition is limited even among the clerics having family member with the disease [76]. Another survey study conducted in Zambia to predict factors responsible for felt stigma, reported that felt stigma was less among patients who were able to conceal their condition from community and was greater among patients who believe that their condition is contagious or who reside in communities where contagion beliefs were common [77]. Literature review study conducted in Africa for the determination of mortality associated with epilepsy reported that proportion of deaths associated with epilepsy may be much higher in comparison to other parts of the globe [78]. Seizures can affect neurocognitive function , particularly in case of seizures that are complex , repetitive or prolonged. A study conducted in China to investigate long-term outcome of cognitive and attention functions reported that complex febrile seizures were associated with cognitive function impairment [79]. A review study from Africa reported that behavioural and emotional problems were common in 26% of children suffering from acute symptomatic seizures[70].

Effects of Antiepileptic Drugs on Cognition and Psychomotor Functions in Developing Countries

Epilepsy, being a neurological condition if treated properly then approximately 70% of those with disease can lead fruitful and satisfying lives, with freedom from seizures [71]. Most often prescribed antiepileptic drugs in developing countries are phenobarbitone and phenobarbital. These are cheapest and prescribed in 65-85% of treated epilepsy patients [71]. Regarding the adverse effects linked with the use of anticonvulsive drugs, data from developing countries is limited.

Overview of Burden of Disease, Medication Trends and Barriers to Management of Epilepsy in Pakistan

The epilepsy prevalence in Pakistan is estimated to be 9.99 per 1000 population .Higher prevalence is find out in people of age younger than 30 years and in rural population and prevalence reduced slightly in ages between 40 and 59. Epilepsy considered to be idiopathic in 21 to 76% of cases. Treatment gap is high with 27% of those with disease living in urban areas and only 1.9% of people living in rural areas being treated with antiepileptic drugs [80]. A descriptive study of five hundred epileptic patients conducted in Lahore, mean age of patients observed was 17.7± 9.87 years, with 58% males and 42% females. Family history was positive in 60% of cases and 46.9% had history of febrile convulsions. Most commonly reported seizures were Generalized tonic-clonic seizures (43%) followed by partial seizures (24%) of patients. Among the people with epilepsy, 13% patients had depression and 10.1% were mentally retarded [81]. A population-based, cross-cultural comparative study of epilepsy reported crude prevalence rate of epilepsy in Pakistan to be 9.98 per 1000 of population while in 7.0 per 1000 in Turkey. In both the countries prevalence was twice in rural areas than in urban areas . In Pakistan mean age of onset of epilepsy was 13.3years while 12.9 years in Turkey [82] .

Barriers to effective Epilepsy Control in Pakistan

Many researches regarding psychosocial and behavioural impact of epilepsy had been conducted in developed world but limited data is available for the developing countries. An epidemiological study conducted in Karachi, indicated that in Pakistan degree of stigmatization faced by epileptic people do not appear to be high, however there seems to be minor relationship between disease and educational potential along with grades of children with epilepsy, performing of everyday tasks and possibility of marriage and having children. People with epilepsy having highest education were avoided less often, faced fewer problems, and were more frequently married as compared to people with less education. Most people with epilepsy assumed that their illness had physical basis while 3% thought it to be caused by some paranormal causes such as curse, sin , bad spirit and poverty . Majorly patients were taking allopathic medicines while some were also being treated with traditional healers [83]. A cross-sectional study conducted in slum area of Karachi concluded that, lack of public awareness towards epilepsy is a significant reason to high occurrence of negative attitude .Increased familiarity with the disease is linked with positive attitude towards disease [84]. A cross-sectional study conducted in various schools of Karachi for the assessment of knowledge, attitude, practice towards epileptic child and their ability to help a convulsing child revealed that epileptic child being an educationally vulnerable group need additional support of educational staff. The study also observed that majority of teachers thought that epileptic child's academic achievement is hampered by the disease stigma and that special schools are preferred for such children. However it was encouraging to know that majority of teachers were in opinion that epileptic children should be engaged in outdoor activities like other children and that mass education programmes should be arranged to increase awareness among community.

Epilepsy is associated with psychological distress and psychiatric co morbidity i.e. depression and anxiety , that may be caused by seizure activity, poor seizure control, use of anticonvulsant medications, adjustment difficulties, feelings of helplessness and loss of control over one's life .Unpredictability limits mobility, hinders work and education and may lead towards psychological disorders [85]. A study conducted in Pakistan for assessment of psychological distress among patients of epilepsy reported high prevalence of psychological distress(70%), people with uncontrolled epilepsy were more affected in comparison to people having controlled epilepsy [85].

Treatment Trends for Epilepsy in Pakistan

There are about sixteen classic and newer antiepileptic agents registered for use in Pakistan. A drug utilization review of antiepileptic drugs carried out in three tertiary care teaching hospitals in Karachi reported that despite the availability of newer antiepileptic agents, older agents still dominated in pharmacotherapy of epileptic seizures. Among epileptic patients valproic acid has highest utilization rate (16.8%) followed by diazepam and phenytoin. Among non-epileptic patients gabapentin was prescribed most frequently followed by pregabalin in Pakistan [86] .

Anticonvulsants are one of the commonest causes of drug-related cutaneous adverse reactions and carbamazepine being the most notorious drug (25-33) associated with Stevens Johnson Syndrome among Asians, while in Caucasians frequency is low (5-6%). Over-all estimated risk is 1.5 to 6.2 per 10,000 new users , mostly occurring within two months of anticonvulsants usage [87]. A case was reported of a Pakistani girl of 10 years old with generalized tonic-clonic seizure, being prescribed carbamazepine. After one month of the commencement of carbamazepine therapy acute onset of fever , skin rash and sore throat were reported [87]. Another case study of Steven-Johnson syndrome caused by the use of Lamotrigine, is reported in 56 years old lady having prolonged history of depression and anxiety from last 20 years. Because of poor control of depression symptoms lamotrigine was added to her medications. Her anxiety and depression symptoms showed significant improvement but she was diagnosed with Stevens-Johnson syndrome associated with use of lamotrigine hence lamotrigine was stopped [88].

CONCLUSION

The results of the review concluded that there is a need to monitor cognitive impairment in epilepsy patients on anti-epileptic therapy. The review concluded that attention and memory were most affected domains of cognition among patients of epilepsy. Patients using older anti-epileptics such as benzodiazepines and carbamazepine reported higher cognition deficits whereas those using newer agents such as levetiracetam therapy appeared to have better cognition. There is a need to initiate educational campaigns and training of health professionals and volunteers about epilepsy, its management and early detection of cognitive disabilities among patients on antiepileptic drug therapy. Long-term Longitudinal studies are required to establish the impact of disease related and drug related factors on cognition.

Abbreviations

AED-Anti-Epileptic Drugs

Authors' Statements

Competing Interests

The authors declare no conflict of interest.

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