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Cognition and Memory Impairment Among Patients of Epilepsy in Pakistan-The Role of Conventional and Newer Anti-Epileptics

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Abstract

Objective: The present study was designed to evaluate the effects of antiepileptic drugs on cognition and psychomotor functions among patients of epilepsy in twin cities of Pakistan.

Method: A descriptive cross-sectional study design was used. A pre-validated data collection tool i.e. Mini Mental State Examination (MMSE) questionnaire, which is a practical method for grading the cognitive state of patients was distributed to a sample of 382 epileptic patients. After data collection the data was cleaned, coded and statistically analyzed using SPSS version 21.

Results: Out of 382 respondents, 60.5% (n = 231) had normal cognition level, 27.7% (n = 106) had mild decline in cognition level, 10.5% (n = 40) had moderate cognitive impairment and only 1.3% (n = 5) had severe cognitive impairment. Of the total respondents, 27.7 % (n = 106) were prescribed with valporic acid and among them 61.9 % (n = 65) were having questionably significant cognitive impairment, 23.8 % (n = 25) were having mild impairments, 10.4 % (n = 10.4) were having moderate impairments and 4.6 % (n = 5) were suffering from severe cognitive impairment.

Conclusion: The results of the present study concluded questionably significant cognitive impairment that requires further psychometric testing among epileptic patients in Pakistan.

Introduction

Epilepsy could be complex due to other neurological co morbidities including cognitive impairment, psychiatric disorders like anxiety and depression and social problems. These co-morbidities arise because of recurrent seizures, medication adverse effects and adverse social reaction towards epilepsy i.e. stigma [1]. With the advancements in the field of medicine, there has been increasing interest in the optimization of medication therapy that requires careful selection of appropriate drug, with minimal side effect profile and in the right dose that meets individual patient requirements. Assessment of cognitive adverse impact of anticonvulsive medications started in early 1970s probably due to wide range of available drug treatments during that period [2]. Impairment in cognitive abilities like problems of memory and concentration was observed in up to 48% of patients with convulsive disorder, taking single anticonvulsive medication. Generally, it is indicated that the newer anti-convulsive drugs have more safe cognitive profile as compared to the conventional ones [3]. Antiepileptic drugs are the mainstay treatment of epilepsy. Optimum treatment with antiepileptic drugs could result in seizure control in up to 70 % of epilepsy patients [4]. Despite of these benefits associated with the use of anti-epileptic drugs adverse effects accompanied by antiepileptic drugs use are leading cause of treatment failure. The adverse effects leads to discontinuation of medication regimen in approximation of 25% of the epileptic patients and poor patient compliance with medication therapy [5].

Antiepileptic drugs also produce psychiatric side effects in about 15-20% of patients, leading to higher risk of suicidal thoughts and behavioral imbalance [5]. first-generation anticonvulsive drugs especially benzodiazepines and

carbamazepine has been reported responsible for causing coordination disturbances including tremors, body imbalance, sedation and vertigo. According to a meta-analysis of eight newer anticonvulsive drugs, coordination difficulties are associated with the use of all in comparison to placebo [6]. Topiramate belonging from newer antiepileptic drugs seems to be responsible for causing difficulties in attention and dysfunction of verbal abilities [5]. Adverse effects of different antiepileptic agents on cognition and psychomotor functions impose additional burden on individuals with epilepsy. In the past few decades, these effects were studied worldwide for the better understanding of different factors associated with increased psychosocial burden, but it is still neglected in Pakistan. Therefore, the present study was designed to evaluate the effects of antiepileptic drugs on cognition and psychomotor functions among patients of epilepsy in twin cities of Pakistan.

Method

A descriptive cross-sectional study design was used to evaluate the effects of anti-epileptic drugs on cognition and psychomotor functions among patients of epilepsy in twin cities i.e. Islamabad (Federal Capital) and Rawalpindi (Twin City) of Pakistan. Study sites for this research included public and private tertiary health care facilities and neurology clinics located in twin cities of Pakistan. Study respondents included in the study were: epileptic patients above 16 years of age, both genders and persons who could easily read and write. Any patient having co morbidity or taking drug that can affect or induce seizures were excluded from the study. Calculation of sample size was performed by Raosoft® sample size calculator to determine the size of sample representing the study population. The calculated sample size was 382 to achieve 95% confidence interval and 5% margin of error. As no National data of epileptic patients is available for the country, so convenient sampling technique was used for the study and all the respondents that were available at the time of data collection and willing to participate in the study were selected.

A pre-validated data collection tool i.e. Mini Mental State Examination (MMSE) questionnaire, which is a practical method for grading the cognitive state of patients was used. Written permission was obtained from the respective organization for using the tool. Mini Mental State Examination (MMSE) is a brief clinical test of mental status that consists of total of eleven questions. The MMSE begins with a graded assessment of orientation to place and time; this is followed by testing two aspects of memory. The first is the immediate recall for three objects presented orally, followed by a serial sevens task which is interposed to assess attention, concentration, and calculation, and also to prevent the individual from rehearsing the three objects previously learned. The final section surveys aphasia by testing functions of naming, repetition, understanding a three-stage command, reading, writing and copying a drawing.

The MMSE can be easily administered by trained health care professional. The person administering the MMSE is required to be receptive about patient embarrassment if patient was unable to answer these questions. Respondents were informed that this is another way of determining how the treatment is affecting their cognitive abilities. Total score of MMSE is 30. A score range of 0-10 indicates severe cognitive impairment, 11-20 score range indicates moderate cognitive impairment, 21-25 indicates mild cognitive impairment while a score of 26-30 shows cognitive impairment of questionable significance. MMSE was self-administered by principal investigator after obtaining written/verbal consent from the respondents. The questionnaire was collected back on the same day to avoid any study biasness. After data collection the data was cleaned, coded and statistically analyzed using SPSS version 21. Descriptive statistics comprising of frequency and percentages were calculated. Chi-Square test ($p \geq 0.05$) was used to find association among different variables.

Results

Most of epileptic patients were from age group of 16-20 i.e. 37.1% (n=142). Out of 382 respondents, 59.4% (n=227) were males while 40.57% (n=155) were females. The qualification level of the respondents was: Primary 30.62% (n = 117), Matric 25.1% (n= 96), Intermediate 21.9% (n =84), Bachelors 15.7% (n = 60) and Master 6.54% (n = 25). Family history for epilepsy was positive in 28.5% (n=109) of respondents while negative in 71.2% (n=272). Regarding their medication therapy patients on polytherapy were 57.3 % (n= 219), while 42.7% (n=163) were on monotherapy. Of the total respondents, 18.3% (n=70) of epileptic patients had undergone through psychotherapy. Most of the patients, 55.2% (n=212) have not felt disease related stigmatization (Table 1).Out of 382 respondents, 60.5% (n = 231) had normal cognition level, 27.7% (n = 106) had mild decline in cognition level, 10.5% (n = 40) had moderate cognitive impairment and only 1.3% (n = 5) had severe cognitive impairment (Table 2).

Table 1: Demographic Characteristics of Epileptic Patients in Pakistan.

Indicators	n (%)	
Age	16 - 20	142 (37.1)
	21-30	103 (26.96)
	30-40	77 (20.15)
	40-50	38 (9.9)
	>50	22 (5.7)

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Gender	Male	227 (59.4)
	Female	155 (40.57)
Marital Status	Married	175 (45.8)
	Unmarried	207 (54.1)
Qualification	Primary	117 (30.62)
	Matric	96 (25.1)
	Intermediate	84 (21.9)
	Bachelor	60 (15.7)
	Masters	25 (6.54)
Current Income	10,000 - 20,000	121(31.6)
	21,000 - 35,000	156(40.83)
	36,000 - 50,000	66(17.3)
	>50,000	38(9.9)
Residence Setting	Rural	156 (40.8)
	Urban	226 (59.2)
Sector Of treatment	Public	159 (41.6)
	Private	223 (58.4)
Family History	Positive	109 (28.5)
	Negative	272 (71.2)
Medication Therapy	Monotherapy	167 (43.7)
	Polytherapy	215 (56.3)
Psychotherapy	Yes	70 (18.3)
	No	311 (81.4)
Stigmatization	Yes	169 (44.2)
	No	212 (55.2)
Any Other Mental Disorder	Anxiety	59 (15.4)
	Depression	18 (4.7)

Table 2: Interpretation of MMSE among patients of Epilepsy in Pakistan.

Interpretation	n (%)
Severe (0-10)	5 (1.3)
Moderate (11-20)	40 (10.5)
Mild (21-25)	106 (27.7)
Questionably significant (26-30)	231 (60.5)

Out of 382 respondents, 27.7 % (n = 106) were being prescribed with valporic acid and among them 61.9 % (n = 65) were having questionably significant cognitive impairment, 23.8 % (n = 25) were having mild impairments, 10.4 % (n = 10.4) were having moderate impairments and 4.6 % (n = 5) were suffering from severe cognitive impairment. On the other hand out of 6 % (n = 23) patients on carbamazepine monotherapy, 73.9 % (n = 17) were having questionably significant impairment, 13 % (n = 3) had mild impairment in cognition and 17.3 % (n = 4) had moderate cognitive impairment. Out of 9 % (n = 38) patients on levetiracetam monotherapy, 78.9 % (n = 30) were having impairment of questionably significant nature, 13 % (n = 5) had mild impairment in cognition while 7.8 % (n = 3) had moderate impairment (Table 3). Significant association for cognitive impairment and demographic variables such as age (p = 0.003), qualification (p = 0.001) and medication therapy (p = 0.023) was observed. Hence, age, qualification and type of medication therapy might be significant factors that can contribute towards cognitive impairment among epileptic patients (Table 4).

Table 3: Interpretation of MMSE according to most Prescribed Monotherapy Antiepileptic Drugs among Epileptic Patients.

Drug Used	Questionably Significant26-30 n (%)	Mild 21-25 n (%)	Moderate 11-20 n (%)	Severe 0-10 n (%)
Valporic Acid	65 (61.9)	25 (23.8)	11 (10.4)	5 (4.6)

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Carbamazepine	17 (73.9)	3 (13)	4 (17.3)	0
Levetiracetam	30 (78.9)	5 (13)	3 (7.8)	0

Table 4: Interpretation of MMSE score among Epileptic Patients according to Different Demographic Characteristics.

Indicators		Severe (0-10) n (%)	Moderate (11-20) n (%)	Mild (21-25) n (%)	Questionably significant (26-30) n (%)	P value
Age	16-20 Y	5 (3.52)	14 (9.85)	36 (25.35)	87 (61.26)	0.003
	20-30 Y	0	6 (5.82)	31 (30)	66 (64)	
	30-40 Y	0	8 (10.38)	16 (20.77)	53 (68.8)	
	40-50 Y	0	5 (13.1)	14 (36.8)	19 (50)	
	>50	0	7 (31.8)	9 (40.9)	6 (27.2)	
Gender	Male	3 (1.32)	24 (10.57)	59 (25.99)	141 (62.11)	0.832
	Female	2 (1.2)	16 (10.32)	47 (30.32)	90 (58.06)	
Qualification	Primary	4 (3.41)	23 (19.65)	42 (35.89)	48 (41.02)	0.001
	Matric	1 (1.04)	10 (10.41)	30 (31.25)	55 (57.29)	
	Intermediate	0	6 (6.97)	18 (21.42)	60 (71.42)	
	Bachelor	0	1 (1.66)	12 (24)	47 (94)	
	Masters	0	0	4 (16)	21 (84)	
Current Income	<10,000-20,000	1 (0.82)	9 (7.43)	34 (29.09)	77 (63.66)	0.482
	21,000-35000	3 (1.92)	20 (12.8)	49 (31.41)	84 (53.84)	
	36,000-50,000	0	9 (13.63)	14 (22.22)	43 (65.15)	
	>50,000	1 (2.56)	2 (5.12)	9 (23.07)	27 (69.23)	
Medication Therapy	Monotherapy	4 (2.39)	20 (11.97)	34 (20.35)	110 (65.86)	0.023
	Polytherapy	1 (0.46)	20 (9.30)	72 (33.48)	122 (56.74)	

Discussion

Neuropsychological impairment is an important co-morbidity of chronic epilepsy involving various factors that include epilepsy factors i.e. aetiology, age of disease onset, type of seizure and its severity, duration of epileptic discharge, use of antiepileptic medications etc [7]. Such disruptions can lead to inability of an individual to perform on psychosocial level precipitating problems like school failure, unemployment, development of psychiatric complications and social isolation [8]. The results of present study reported cognitive impairment among epileptic patients which was questionably significant requiring further psychometric measurement. Most of the respondents of the study were in the age group of 16-20 years and males. Similar findings were reported from other studies [9, 10].

In many developing countries, epilepsy is not considered as a neurological disease rather perceived to be caused by supernatural forces or possession by evil spirits [11]. These beliefs surrounding epilepsy, pose epileptic patients towards the feeling of being stigmatized and discrimination that contribute towards additional distress to person with epileptic disorder than the seizures themselves [12].The results of present study showed that majority of the respondents have not felt disease related stigma. These findings are in accordance with another study conducted in Pakistan also reporting that epileptic patients do not appear to be highly stigmatized [13]. Epilepsy is associated with psychiatric complications, memory dysfunction, cognitive abilities and personality. All these factors hinder with relations and work performance of epileptic patients. The results of the present study also reported presence of anxiety as common co-morbidity among epileptic patients. According to World Health Organization depression and anxiety are frequent co-morbidities in 50 % of the epileptic patients [14].

Antiepileptic drugs (AED) treatment being the mainstay of treating epilepsy aims at controlling seizures without inducing side effects. All antiepileptic drugs have potential to cause central nervous system dysfunction and other side effects. Side effects are also crucial factors in determination of patient willingness to take drug for long term duration [8]. Classic and new generation antiepileptic drugs have potential to cause mixed effects on cognition and behavior [15]. Use of single agent whenever possible can be employed to reduce harmful effect on cognition. The present study showed that more patients taking polytherapy scored mild cognitive impairment on MMSE scale as compared to percentage of patients on monotherapy. These findings are in line with study which showed that polytherapy contributes more adverse effects in cognition and behaviour as compared to monotherapy [15]. Valporic acid is widely used antiepileptic drug, known to be effective in various seizures types, bipolar disorder, migraine and neuropathic pain.

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The results of the present study revealed that among patients on valporic acid therapy, attention appears to be impaired with 10% of patients on valporic acid therapy. These findings are in line with other studies which have reported evidence of attention impairment by the use of valporic acid [16,17]. Carbamazepine is most effective against partial seizures with or without secondary generalization. Many adverse effects on cognition and psychomotor functions are associated with carbamazepine [18]. In the current study patients on carbamazepine therapy scored low on memory domains of MMSE as compared to valporic acid. These results are in accordance with another study which reported that memory profile of carbamazepine was observed worse as compared to valporic acid [3]. Levetiracetam belonging from newer class of antiepileptic agents have more favorable cognitive profile [19-22]. In the current study, patients on levetiracetam therapy have higher score on MMSE scale. These findings are in accordance with another study conducted in US for determination of levetiracetam impact on cognitive status of elderly patients, which reported improved score of mini mental state examination [23]. Another study conducted for the determination of cognitive and neuropsychological functions reported improvement in mean score of MMSE in patients taking levetiracetam therapy [24].

Conclusion

The results of the present study concluded questionably significant cognitive impairment that require further psychometric testing among epileptic patients in Pakistan. Anxiety was observed commonly among epilepsy patients and epileptic patients do not appear to be highly stigmatized. Valporic acid was most commonly prescribed agent for the treatment of epilepsy. Attention and memory appeared to be most commonly affected domains among epileptic patients on valporic acid and carbamazepine therapy while patients on levetiracetam therapy reported better scores on measures of attention and cognition. Hence, monotherapy should be used whenever possible and staying within the therapeutic window for antiepileptic drug blood levels with adherence to recommended drug dose and titration rate can help to minimize adverse effects of antiepileptic drugs on cognitive impairment.

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