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ORIGINAL ARTICLE

Antiepileptic Drugs and Mental Health Status of Patients with Epilepsy

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ABSTRACT

Many patients with epilepsy suffer also from coexisting psychological problems. These mental co-morbidities have a significant impact on quality of life of patients with epilepsy. Recent studies have shown that although antiepileptic drugs (AEDs) treat epilepsy, they may increase risk of mental disorders in these patients. Due to the lack of adequate research in this area, we assessed psychiatric disorders in patients with idiopathic tonic-clonic seizure who were treated with antiepileptic drugs. This descriptive-cross-sectional research was conducted on 170 patients with tonic-clonic seizure using the SCL-90-R questionnaire and the results were analyzed by descriptive statistics, T test and chi-square test. The prevalence of psychiatric disorders in patients was 38.8%. All antiepileptic drugs were associated with different kind of mental disorders but there wasn't any relationship between mental disorders and any type of antiepileptic drug except psychosis that was significantly lower in sodium valproate consumers ($p \leq 0.001$). Our findings show that a subgroup of epileptic patients is generally prone to develop mental disorders during antiepileptic therapy, despite different pharmacological properties of the AEDs. Negative psychotropic effects of AEDs should be considered in treatment of patients with epilepsy.

Keywords: *Mental disorder, Antiepileptic drugs, Epilepsy*

Epilepsy is a chronic cerebral disease with various etiologies and clinical features. Some cases have not a certain cause, which are known as idiopathic tonic-clonic seizure [1]. Studies show that 26 to 35 percent of patients with this complication suffer from mental disorders [2-3]. These disorders have a broad spectrum which includes issues such as depression, anxiety, psychosis, agoraphobia, *etc* [4,5]. Several factors may cause mental disorders in patients with epilepsy [6,7]. It is imperative to evaluate psychological effects of antiepileptic drugs [8]. Recent studies have shown that although these drugs treat epilepsy, they may increase risk of mental disorders in these patients [9-11]. These effects not only reduce patients' quality of life but also increase life-threatening situations such as suicides [12,13]. The results presented in literature regarding this issue are different. For example, studies conducted in USA showed that mood and Attention deficit hyperactivity disorder (ADHD) disorders in people who use epileptic drugs are higher [14], while studies conducted in UK showed that these drugs increase incidence of anxiety and sleep disorders in patients with epilepsy [15]. Another study in Croatia also showed that some antiepileptic drugs including lamotrigine are associated with increase in psychosis cases [16]. It seems that psychological effects are not limited to certain antiepileptic drugs [11,16,17]. Given the lack of parallel data in literature and importance of performing regional studies due to differences in patterns of psychiatric disorders in different areas [18], this study aimed to determine prevalence of psychiatric disorders in terms of types of drugs used in patients with idiopathic tonic-clonic epilepsy in Iran.

Table 1. Frequency of mental disorders in patients.

Scale	Frequency (%)	Mean	Standard deviation
Somatization	70 (41.2)	0.99	0.75
Obsessive-compulsive	84 (49.4)	1.04	0.74
Interpersonal sensitivity	79 (46.5)	1.03	0.79
Depression	81 (47.6)	1.02	0.77
Anxiety	73 (42.9)	1.01	0.85
Hostility	63 (37.1)	0.88	0.79
Phobia	54 (38.1)	0.73	0.66
Paranoid ideation	77 (45.3)	0.96	0.79
Psychosis	53 (31.2)	0.73	0.67
Others	77 (45.3)	0.97	0.67
Total(GSI)	66 (38.8)	0.94	0.66

PATIENTS AND METHODS

This descriptive and cross-sectional study was performed through simple sampling of 170 patients with idiopathic tonic-clonic seizure. The population, who were diagnosed to have idiopathic tonic-clonic seizure by neurologists, was consisted of direct referrals to Shafa Hospital or referrals from private offices of Kerman city. The diagnosis was confirmed through physical findings and history (no aura, no focal signs ...), as well as normal laboratory findings, and MRI and CT brain scans. In addition, the patients had no abnormal focal findings in EEG. Patients who seized after head trauma and patients with mental retardation (IQ below 70) were excluded from this study. Patients who had another disease or have been taking drugs other than antiepileptic medicines (especially psychiatric drugs) and patients abusing alcohol and drug were also excluded from the study. Regiments of all patients were the same; otherwise they were excluded from the study. A questionnaire was completed for each patient about demographic factors and their medications. Participation in the study was voluntary and the research was approved by the Ethics Committee of Kerman University. Sample size was determined as 170 subjects with a 5% alpha and 10% beta errors. The Symptom Checklist-90-Revised (SCL-90-R) questionnaire, which reliability and validity was confirmed in Iran, was used to assess psychiatric disorders [19]. This test consists of 90 questions which examine 9 major psychiatric disorders. These aspects include: anxiety, hostility, depression, interpersonal sensitivity, somatization, obsessive-compulsive, phobic anxiety and paranoid ideation. There are seven additional questions in the questionnaire which was not included in any of the nine dimensions of the above categories, while they are clinically important and can help to total indicators of the test. Scoring of this 90 questions questionnaire includes five degrees (none, little, some, much, very much) in which none rates zero and very much rates 4. To determine the prevalence of each mental disorder, a cut of point equal to 2.5 or greater was used and mean scores of 2.5 or more in each dimension was considered as morbid state. The test was interpreted using the Global Severity Index (GSI). In this index, the cut of point is 1.3 [19]. Ethical approval for this study was obtained from the Health Research Ethics Board of Kerman University of Medical Sciences. To analyze the data and to determine the prevalence of psychiatric disorders, SPSS-17 statistical software and descriptive statistics (mean, frequency percent, and standard deviation), and *t*-test and chi-square test were used. In this study, $p \leq 0.05$ was considered statistically significant.

RESULTS

In the present research, 170 patients were evaluated whose age range was 15 to 60 years. About 43.5% of patients were male and the others were Female. The mean age was 230 ± 30.40 years. The mean duration of suffering from epilepsy and the mean age of onset were 9.6 ± 8.69 and 14.4 ± 10 years, respectively. The prevalence of psychiatric disorders in patients was 38.8% . Valproate sodium, carbamazepine, topiramate, lamotrigine and phenobarbital were the most prevalent drugs that were used by patients respectively. About 70.6% of patients were under monothrapy and the others were under polythrapy.

The prevalence of psychiatric disorders in epileptic patients was 38.8%. (Table 1). All antiepileptic drugs were associated with different kind of mental disorders but there was not any relationship between type of antiepileptic drug and mental disorders. The only exception was psychosis that was significantly lower in sodium valproate consumers (Table 2).

DISCUSSION

The prevalence of psychiatric disorders in epileptic patients was 38.8%. This finding was as same as other

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Table 2. Frequency of mental disorders according to kind of antiepileptic drugs.

Mental disorder	Drugs																*p* value
	Valproate				Carbamazepine				Lamotrigine				Topiramate				
	yes		no		yes		no		yes		no		yes		no		
	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%	
Somatization	19	38	31	62	18	38.2	29	61.8	8	50	8	50	7	41.2	10	58.8	0.813
Obsessive-compulsive	23	46	27	54	26	55.3	21	44.7	8	50	8	50	11	64.7	6	35.3	0.708
Interpersonal sensitivity	22	44	28	56	27	57.4	20	42.6	9	56.2	7	43.8	10	58.5	7	41.2	0.527
Depression	23	46	27	54	22	46.8	25	53.2	7	43.7	9	56.3	10	58.8	7	41.2	0.815
Anxiety	18	36	32	64	20	42.5	27	57.5	11	68.7	6	31.3	10	58.8	7	41.2	0.123
Hostility	17	34	33	66	20	42.5	27	57.5	8	50	8	50	7	41.2	10	58.8	0.631
Phobia	13	26	37	74	19	40.4	28	59.6	7	43.7	9	56.3	5	29.4	12	70.6	0.295
Paranoid ideation	19	38	31	62	23	48.9	24	51.5	7	43.7	9	56.3	9	53	8	47	0.686
Psychosis	11	22	39	78	16	34	31	66	5	31.2	11	68.8	6	35.2	11	64.8	0.001

countries such as Norway, Spain, and Canada [20-22]. The studies in the United States of America also show high rates of mental disorders in more than thirty percent of patients [23,24]. The only strong research methodology in Iran was performed in Tehran in 2001 by Mohammadi et al. which reported the same frequency, although all types of epilepsy have been evaluated in this study [18]. However, the prevalence has been reported 17% [25] to 44% [26] in some studies. Our findings showed that all antiepileptic drugs were associated with different kind of mental disorders but there was not any relationship between type of antiepileptic drug and mental disorders. The only exception was psychosis that was significantly lower in sodium valproate consumers. Our findings are as same as the results of studies in UK as these studies showed that all antiepileptic drugs can cause rage, anxiety, mood disorders symptoms and psychosis in patients with epilepsy, although psychosis incidents were the same in all patients using antiepileptic drugs in these studies, i.e. incidence of psychosis was not higher in case of using any certain antiepileptic drug in these patients [15]. A study conducted in Germany showed that anti-epileptic drugs are associated with psychological symptoms similar as our study; however, lamotrigine is associated with higher incidences of psychosis [27]. Report presented from Croatia also confirmed this finding [16]. Moreover, studies performed in Italia which results were the same as our studies, showed that all drugs are associated with risk of mental disorders; however, topiramate consumption was associated with an increase in psychiatric disorders [11]. Meanwhile, mood disorders were at the top of these disorders [12] which was seen in 10% of people who used topiramate [28] but with a lower degree of psychosis states [16]. Moreover, results of this study showed incidence of psychological effects when patients used carbamazepine and sodium valproate. Studies performed in other countries showed incidence of depression in 1% of people who used sodium valproate and carbamazepine [28]. Furthermore, incidence of suicide has been reported in consumers of valproate and carbamazepine [29-31]. Although all drugs were not investigated in these researches, other studies showed that these disorders are not particularly specified to a particular drug, i.e. consuming a certain drug would not result in these orders. For example, increased social phobia and other forms of anxiety disorders are reported when patients use gabapentin [32], or depression is associated with using phenobarbital [33]. This also holds true for newer drugs including zonisamide, vigabatrin, Tiagabine, levetiracetam and felbamate [28]. Some differences between results of various studies are obviously caused by variety of methodologies, differences between target population, and type of assessment test [34]. Fortunately, some evidence suggests that stopping these drugs would result in return of symptoms [35]; however, sometimes intensity of mental disorders in consumers of anti-epileptic drugs is so high that some revision should definitely be taken into in consumption of these drugs. For example, phenobarbital treatment, as the first drug treatment for epilepsy, is excluded in many countries due to high prevalence of behavioral disorders, particularly in children [34].

The exact cause of psychotic symptoms in people who use anti-epileptic drugs is still unclear [36] .Based on mechanisms of antiepileptic drugs, it can be said that many of these drugs have different functional effects on various neurotransmitter system. Thus, psychologist may prescribe these drugs for treatment of a variety of psychological diseases due to functional complication of them [15,29,37]. Published results indicated effect of these drugs on neurotransmitters like serotonin, norepinephrine glutamate, and gamma aminobutyric acid (GABA) [38,39]. For example, studies showed that most drugs which affect GABA system may cause depression (such as Phenobarbital and topiramate) and drugs associated with suicide affect serotonin [29]. It seems that part of psychological symptoms is associated with endocrine or metabolic disorders which are themselves induced by seizure [40]. Other factors such as reduced folate, drug interactions, and existence of structural brain lesions also contribute to psychological symptoms [28]. Meanwhile, psychological symptoms highly affect person if there were any background of mental disorder in his family. Moreover, it is highly prevalent in patients with some forms of epilepsy such as temporal lobe epilepsy or any background of this

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disease in their family [29]. Also, social issues such as marriage and work limitations should be considered too [40]. It should be noted that adverse psychiatric effects of antiepileptic drugs should be distinguished from psychological effects of epilepsy itself. In this regard, psychology consultation should be taken into account [30].

Patterns of drug use in our study were similar to other studies which were performed in other countries including United States [14]. This indicates that patterns of drug use in this study were selected based on scientific data. The limitation of our study was sample size, so that we had considered only some of the antiepileptic drugs in our study. Furthermore, some of the drugs lack statistical values due to low consumption and should be investigated further with complementary tests. Moreover, all antiepileptic drugs were not evaluated in this study because all our patients had primary tonic-clonic seizures and some of the medications are not used to control seizures in this form of epilepsy. In general, given the high prevalence of epilepsy and excessive consumption of antiepileptic drugs and high prevalence of psychiatric disorders in patients with epilepsy, it seems that a general view of psychological effects of these drugs is necessary for all doctors because considering capabilities of these drugs in causing psychological effects as well as prescription of drugs with lower psychological effects may reduce a part of psychological disorders of these patients and improve their quality of life.

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