Psychiatric Squele of Sodium Valproate Versus Carbamazipine in Patients with Primary Generalized Epilepsy

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Abstract

Background: psychiatric and behavioral side effects are common in patients with epilepsy and it may represent an intrinsic feature of the disease itself or a side effect of the antiepileptic use. Our aim in the present study is to assess the psychiatric side effects of Sodium Valproate and Carbamazipine .as these drugs are the most commonly used antiepileptic drugs in Iraq.

Methods: 80 patients with primary generalized epilepsy on Carbamazipine and 50 patients on Sodium Valproate were enrolled in the present study; all the patients were assessed for any psychological disturbances using semi-structural interview based on the tenth edition of the international classification of the diseases(ICD 10) adopted by WHO.

Results: thirty percent of patients taking Sodium Valproate and (9%) of patients taking Carbamazipine were found to have depression while (16%) of patients taking Sodium Valproate and (20%) of patients taking Carbamazipine were found to have anxiety. There were no reported psychosis, suicidal attempts, cognitive deficit and mania in both groups of patients in the present study.

Discussion: Carbamazipine is associated with lower rates of psychological side effects than Sodium Valproate; this result may be related to mood stabilization effects of Carbamazipine.

Conclusion: Carbamazipine is preferred to Sodium Valproate when the efficacy of both drugs is comparable.

Key words: antiepileptic drugs, Sodium valproate, Carbamazipine, depression, anxiety, psychiatric side effects.

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Introduction

It has been known for longer time that antiepileptic drugs influence the mental state [1] Psychiatric and behavioral side effects are common in patients with epilepsy taking the antiepileptic drugs [2]. A particular antiepileptic drug may influence one particular aspect of behavior positively and another drug influences negatively the same particular behavioral aspect [3]. Antiepileptic drug like Phenobarbitone is proved to have negative adverse psychological effects, other antiepileptic drugs like Sodium Valproate and Carbamazipine showed less negative adverse psychological effects. Suppression of seizure at the expense of deterioration in the psychological state of the patients is not necessarily appropriate clinically and can provoke a great burden on the patients [4]. prior to the nineteenth's century, epilepsy was considered as a form of demonic possession [5]. Earlier of the last century reports declared some kind of inverse relation ship between epilepsy and Psychiatric disorders [6]. According to this postulation Von Medina introduced the electroconvulsive therapy (ECT) for treatment of Psychiatric disorders like depression and schizophrenia [7]. The discovery of antiepileptic drugs in the mid nineteenth's century had revolutionized the treatment of epilepsy.

Sodium Valproate and Carbamazipine are the most commonly used antiepileptic drugs in Iraq.

Our objective of this study is to determine the presence of any psychiatric and behavioral side effects and also to compare negative adverse psychological effects of Sodium Valproate in comparison with those of Carbamazipine

Methods

Two groups of patients Included in the present study the first comprised 130 patients with generalized epilepsy on antiepileptic treatment; 80 patients of them were on Carbamazipine (55 males and 25 females) , their ages were between 20-65 years, the other 50 patients were on Sodium Valproate (35 males and 15 females) ,their ages were between 18 -65 years. The second enrolled group was used as a control group and included 50 patients with generalized epilepsy before commencement of antiepileptic treatment including 30 males and 20 females, their ages was between 15 and 68 years.

Each patient was examined at Al-kindi hospital consultation clinic between June 2005 and June 2007. The enrolled patient should have normal blood picture, normal brain CT scan and generalized non focal Electroencephalographic (EEG) changes.

Detailed history of the convulsive attack was taken from the other family members and also they were inquired about symptoms of anxiety like fear , irritability , restlessness , sensitivity to noise , dry mouth , epigastric discomfort , excessive wind , frequent bowel motions , chest discomfort , palpitation , muscle tension , frequent urination and sleep disturbances , also inquired about other psychological aspects before and after the epileptic disease onset and before and after the start of the antiepileptic drugs; any patients with history of psychological abnormality before the epileptic disease onset were excluded from this study.

The patient then examined thoroughly neurologically and after that a detailed psychiatric assessment was done using a semi-structural interview based on the tenth edition of the international classification of diseases (ICD10) that was adopted by world health organization (WHO) (8).

The patient who showed any positive finding on the semistructred interview was subjected to the application of the international classification of diseases (ICD10) diagnostic criteria in that area to determine the psychiatric feature amounts to a disorder or represents only a symptom of depression or general anxiety disorder (GAD) according to the international classification of diseases (ICD10) diagnostic criteria (see **Table -1** and 2 respectively)

(Table-1)

Symptoms needed to meet criteria for depressive episode in thinternational classification of diseases (ICD10) diagnostic criteria

A--	
1- Depressed mood. 2- Loss of interest and enjoyment. 3- reduced energy and decreased activity	
B--	
1-Reduced concentration 2-Reduced self esteem and confidence. 3- Ideas of guilt and unworthiness 4-pessimistic thought 5- Ideas of self harm 6-Disturbed sleep 7-diminished appetite	
Mild depressive episode	: At least 2 from (A)& 2 from (B).
Moderate depressive episode	: At least 2 from (A)& 3 from (B).
Sever depressive episode	: At least 3 from (A)& 4 from (B).

(Table-2)

Symptoms needed to meet criteria of generalized anxiety disorder (GAD) in the international classification of diseases (ICD10) diagnostic criteria

A--psychological arousal	
1-worry and apprehension	4-feeling of loss of control
2-feeling tense	5- irritability
3- difficulty in concentration	6-sleep disorder
B—Muscle tension	
1-tension headache	3- tremor
2-inability to relax	4-aching muscle
C—autonomic arousal	
1-Dizziness	4-palpitation
2-Sweeting	5-tackypnea
3-palpitation	6-dry mouth and ---etc

Patient should have primary anxiety symptoms most days for continuous few weeks at least and usually for few months

Results

Depressive and anxiety disorders were found in 22(17%) and 24(30%) respectively out of the 130 patients of our sample after commencement of antiepileptic drugs; while these disorders were found in 3 (6%) and 6 (12%) out of 50 patients respectively before starting drug therapy. On other hand depression and anxiety symptoms were found in 33 (25%) and 31(24%) patients out of the total sample after commencement of the antiepileptic drug, while these symptoms were found in 8 (16%) and in 5(10%) patient out of 50 respectively before starting therapy. (See **Table- 3**).

(Table-3)

Psychiatric problems prior to and after the starting antiepileptictreatment.

	Depressive disorder	Depressive symptoms	Anxiety disorder	Anxiety symptoms	normal	total
Before therapy	3/ 50(6%)	8/ 50 (16%)	6/50 (12%)	5/ 50 (10%)	28/50(56 %%)	50/50
After therapy	22 /130(17%)	33/130 (25%)	24/130 (18%)	31/130 (24%)	20/130(15 %)	130/130

30.907
DF = 5, P-Value = 0.001

There was significant differences between depressive disorder and anxiety disorder before and after antiepileptic drugs, these disorders were higher after commencement of the treatment (P-value =0.001)(see table 3).

Depressive disorder was found in 15 out of 50 (30%) patients on Sodium Valproate and in 7 out of 80 patients (9%) on Carbamazepine; depression symptoms rate are shown in table (4).

(Table-4)

Depressive symptoms and depressive disorder in patients on Sodium Valproate and on Carbamazepine 9 out of 15(60%) patients on Sodium Valproate had mild depressive disorder and the remaining 6 patients had moderate depressive disorder, no severe case were recorded; all 7 depressed patients on Carbamazepine had mild depressive disorders.

	Depressive disorder	Depressive symptoms	total
Patients on Sodium valproate	15 / 50[30%]	13/ 50[26%]	28/50
Patients on Carbamazepine	7 /80 [9%]	20/80 [25%]	27/80
	X2= 6.790 DF = 1, P-Value = 0.009	X2= 0.010 DF = 1, P-Value = 0.922	

X2= 0.187 DF = 2, P-Value = 0.911

12 out of the 15 patients on Sodium Valproate were above age of 40 years while 5 of the 7 patients on Carbamazepine were above age of 40 years (see table 5).

(Table -5)

Age distribution in patients with depressive disorders

	Below 40 year	Above 40 year	Total
Patients on Sodium Valproate	3	12	15
patients on Carbamazepine	2	5	7
Total		5	

X2= 0.200 DF = 1, P-Value = 0.655

10 patients with depressive disorder on Sodium Valproate were males and 5 were females; while 4 of the 7 on Carbamazepine were males and 3 were females (see **Table- 6**).

(Table-6)
Sex distribution in patients with depressive disorders.

	male	female	total
Patients on Sodium Valproate	10 (66%)	5(33%)	15
patients on Carbamazepine	4 (57%)	3(43%)	7

On applying the semi-structured interview on patients on both antiepileptic drugs in the present study, (31) patients were found to have symptoms of anxiety. On applying the tenth international classification of the disease criteria (ICD 10) of the general anxiety disorder (GAD), only (24) patients was satisfied the general anxiety disorder (GAD) disease criteria **(**see **Table- 7).**

(Table-7)
Anxiety symptoms and disorder in patients on Sodium Valproate and on Carbamazepine.

	Anxiety Disorder	Anxiety Symptoms
Patients on Sodium Valproate	8/50(16%)	19/50(42%)
patients on Carbamazepine	16/80(20%)	12/80(12.5%)
Total	24/130(18%) X2= 0.227 DF = 2, P-Value = 0.893	31/130(24%) X2= 5.327 DF = 2, P-Value = 0.070

(7 out of the 9) patients having anxiety disorder on Sodium Valproate were above age of 40 years while 9 of the 15 patients on Carbamazepine were above age of 40 years (see **Table -8**).

(Table-8)
Age distribution in patients with anxiety disorders

	Below 40 years	Above 40 years	Total
Patients on Sodium Valproate	2	7	9
patients on Carbamazepine	6	9	15
total	8	16	24

X2= 0.800 DF = 4, P-Value = 0.938

7 patients with anxiety disorder on Sodium Valproate were males and 2 were females; while 10 of the 15 patients on Carbamazepine were males (see Table 9).

Table -9)
Sex distribution in patients with anxiety disorders.

	Male	Female	Total
Patients on Sodium Valproate	7 (77%)	2(23%)	9
	10(66%)	5 (34%)	15

Co morbid agoraphobia was seen in 1 patient out of 16 (6%) with generalized anxiety disorder taking Carbamazepine and in one patient out of 8(12%) with generalized anxiety disorder taking patient out of 15 (6%) with depressive disorder on Sodium Valproate.

Increased sleeping period day and night were seen in 60 out of 80 (75%) of patients on Sodium Valproate, and in 1 patient out of 7(14%) with depressive disorder on Carbamazepine, and in 1

Carbamazepine and in 10 out of 50(20%) of patients on Sodium Valproate.

Discussion

Treatment of epileptic patients by antiepileptic drugs carries beneficial effects on control of the seizure recurrences and harmful side effects of the drugs especially psychiatric and behavioral one [9] .

The present study showed statistically a highly significant difference in the development of psychiatric abnormalities (depressive disorder and symptoms and anxiety symptoms and disorder) in patients with generalized epilepsy before and after commencement of both Sodium Valproate and Carbamazepine antiepileptic drugs with significant higher incidence after start of the antiepileptic drugs (P=0.001) .

The study showed a significant difference in incidence of depressive disorders between treatment with Sodium Valproate (30%) and Carbamazepine(9%)antiepileptic drugs with higher rate of depression in patients taking Sodium Valproate (P=0.009) ; this difference is correlated to the structural similarity of Carbamazepine with the tricyclic antidepressant medication resulting in property of antidepressant effect for this antiepileptic drug [10] , also this drug proved to have depressant effect on limbic kindled function [11] . The rate of depressive disorder in patients on Carbamazepine is in approximate to the result of Brent etal who found (10%) of their patients on Carbamazepine were depressed [12]. And in consistence with Robertson etal result who found 11% of their patients on Carbamazepine were depressed [13]. All the above studies were used different scaling systems for categorizing depressive disorder and in spite of that the results almost similar to each other [12,13]. More sever depressive disorder was found in patient on Sodium Valproate than those on Carbamazepine and this milder and low rate of depression in patients on Carbamazepine are related to the antidepressant and tranquilizer effect of Carbamazepine in comparison to Sodium Valproate[10] .

The present study showed no significant differences between both groups of patients (who were on Carbamazepine and on Sodium Valproate) in having depressive symptoms, anxiety disorder and anxiety symptoms, these results may be explained by multiple social , economic , epilepsy psychopathology and many other factors and not merely to the use of antiepileptic drugs .

The age distribution of patients on Carbamazepine and on Sodium Valproate who developed anxiety and depressive disorders is consistent with clinical facts that the depressive disorder is more prevalent with advancing age while anxiety is started at younger age [14].

The present study showed more male affected by anxiety disorder and depressive disorders in patients on Carbamazepine and on Sodium Valproate this is not consistent with the general fact of relative female preponderance [15]. This

gender controversy is explained by more incidence of generalized epilepsy in males [(1)] , also this lower rate of females prevalence is related to the limited use of Sodium Valproate(which is correlated to higher psychiatric side effects in the present study) in females because of the well known side effects of the drug during women reproductive life [(9).]

The present study showed more frequent presence of agoraphobia in approximately equal rates in both groups of patients and this is due to presence of the psychopathology of epileptic illness in addition to physical and psychological side effects of the drugs.

The present study showed high rates of hypersomnia in both groups of patients and this is due to narcotic effects of those drugs which carry strong narcotic effects [(9).]

There are no reported cases of psychosis, mania, or suicidal attempts in the present study, these results were in accordance to Wolf who found a very low percentage (0.5%) in patients on Sodium Valproate; he explained those results on the base of forced normalization phenomena which means development of psychosis in patients with after strict control of their epilepsy [(14).]

Conclusions

1. There is high association between antiepileptic drugs and psychological disorders.
2. Carbamazepine is associated with lower rates of psychological side effects than Sodium Valproate, so we recommend using Carbamazepine in epileptic patients with psychiatric problems.

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