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EPILEPSY AND ERECTILE DYSFUNCTION: CORRELATIONS AND EFFECTS OF ANTIEPILEPTIC DRUGS

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ABSTRACT. The association between erectile dysfunction (ED) and epilepsy, was never clearly defined, even tough was often described. In this study we try to demonstrate that antiepileptic medication causes an increased prevalence of ED, and that alcohol, depression and the type of medication used chronically have an important role in ED of epileptic patients**.** In 66 male patients (42.91 ± 5.585 years), diagnosed with epilepsy ED was assessed using the International Index of erectile function, short version (IIEF5). A complete medical history, medication use, alcohol consumption, associated comorbidities, the annual number of seizures were recorded. A general physical examination was done to rule out other diseases. The data obtained were compared with those of a control group, consisting of 30 people aged 40-65 years (52.27 ± 8.35). Analyzing the IIEF5 scores of the 2 groups we observed that 53 patients from the group 1 (80.30%) had some degree of ED (IIEF5 values lower than 22), and 9 patients (30%) of the 30 from control group. Among patients with carbamazepine use 16 reported ED, 12 of those with the use of valproate, 10 of those with usage of levetiracetam, 9 of those with usage of phenytoin, and 3 patients with usage of oxcarbazepine and lamotrigine. The results that were obtained in this study showed that there is a correlation between prevalence of ED and antiepileptics drugs used chronically in patients with epilepsy. Given that ED had a prevalence of more then 90% in patients who used carbamazepine, phenytoin, valproic acid and levetiracetam we conclude that these antiepileptics with enzyme inducing hepatic potential causes ED by increasing the metabolism of sexual hormones.
KEYWORDS erectile dysfunction, IIEF5, epilepsy, lamotrigine, oxcarbazepine

INTRODUCTION

The association between erectile dysfunction (ED) and epilepsy, was never clearly defined, even tough was often described. In male patients with epilepsy has been demonstrated an increased risk of ED, for up to about 60%, compared to 3-9% in the general population [1]. There are many sexual disorders described as having a direct link with epilepsy, the most important being low sexual desire, reduced potency and impaired sexual performance. However, in some recent studies was demonstrated that epilepsy can interfere withphysiological dysfunctions and the sexual desire is not affected at all [2,3]. The most common sexual dysfunction, which has been described in patients with epilepsy is hiposexuality, defined as an overall reduction in sexual interest and sexual activity.

The exact location of the epileptic discharge which can cause ED, was also long-debated in previous studies. It is assumed that patients with temporal lobe epilepsy (TLE) are more prone to sexual dysfunction and hypogonadism, given that TLE is more common in males [4,5]. Also, recent studies have indicated that there is a higher prevalence of ED in patients with focal seizures of TLE compared with patients with primary generalized epilepsy [6].

A correlation between ED and the severity or frequency of episodes of seizures is demonstrated by the fact that there is an increased incidence of erectile dysfunction in times of post-seizure stress or during periods of increased frequency of seizures [7], compared to patients with long periods without seizures, indicating that the treatment for epilepsy can determine an improvement in sexual function.

Epileptic seizures have close correlation with changes in the autonomic nervous system function. During generalized tonic-clonic seizures, these changes are considered to be non-specific, while epileptic discharges in partial seizures are considered to be discrete and specific. The epileptic discharges from temporal lobe region are transmitted through hypothalamic pathways, determining the alteration of normal secretion gonadotropin hormones and ot the basal levels of dopamine, which results in hyperprolactinemia and hypogonadism [8].

There are numerous studies that have shown that antiepileptic drugs significantly alter serum levels of sex hormones and the feedback mechanism of the hypothalamic-pituitary-gonadal pathways, with an important role in ED. The impact of its role in erectile dysfunction, compared with the psychosocial problems and the effects of epileptiform discharge is much less

clear. Also, antiepileptics with liver enzyme induction potential can increase the metabolism of sex hormones.

In this study we try to demonstrate that antiepileptic medication causes an increased prevalence of ED, and that alcohol, depression and the type of medication used chronically have an important role in ED of epileptic patients.

MATERIALS AND METHODS

In this study were included 66 male patients (group 1) 32-56 years (42.91 ± 5.585), diagnosed with epilepsy at the Clinical Department of Neurology County Hospital Emergency Arad between February 2014 January 2016. ED was assessed using the International Index of erectile function, short version (IIEF5). The data obtained were compared with those of a control group, consisting of 30 people aged 40-65 years (52.27 ± 8.35).

This study was conducted with the approval of the Ethics Committee of the Arad County Emergency Hospital in agreement with the Declaration of Helsinki (1989) World Medical Association and the approval of the Ethics Committee of the Western University "Vasile Goldis". All patients included in the study, and those in the control group, received a consent form.

In the epilepsy patients included in the study was taken a complete medical history, and were recorded medication use, alcohol consumption, associated comorbidities, the annual number of seizures. A general physical examination was done to rule out other diseases. The patients and those from the control group who used phosphodiesterase-5 inhibitors (PDE5) were excluded from the study. All patients had a computed tomography (CT 520 Series General Electric Optima SYS) to exclude the organic epileptic causes.

In order to assess ED was used the International Index of Erectile Function, the short version (IIFE5) consisting of 5 questions, each question with a score between 0 and 5 points, with a maximum score of 25 points. ED can be classified, in terms of the IIFE5 questionnaire as: without erectile dysfunction (between 22 and 25 points; grade 1), mild (between 17 and 21 points; grade 2), mild to moderate (between 12 and 16 points; grade 3), moderate (between 8 and 11 points; grade 4) and severe (between 1 and 7 points; grade 5).

The state of depression of patients was assessed using the Hamilton Depression Scale (HAM-D questionnaire), a questionnaire composed of 17 questions, each question with a score between 0 and 4 points, resulting in a score between 0-50 points [7]. According to HAM-D questionnaire, depression can be classified as: between 0-7 points normally, between 8-13 points mild depression, moderate depression between 14-18 points, 19-22 points severe depression and very severe depression over 23 points.

The persons from the control group completed the IIEF5 and HAM-D questionnaire depending on erectile function and depression status at the time of evaluation.

Statistical analysis

The IBM SPSS Statistics software for Windows, version 20.0 was used for statistical analysis. Data obtained were tested for normal distribution using the Shapiro-Wilk test, using an average of the values plus / minus a standard deviation (SD) for normally distributed data, and median for data without normal distribution. For comparisons between groups, t test was used for unpaired samples for data with normal distribution, Mann-Whitney U test for data without normal distribution, and Chi-square test for variables. Correlations between HAM-D score, IIEF5 scores, medication use and alcohol consumption were calculated using the Spearman's d correlation test for data without normal distribution, and Pearson correlation test for data with normal distribution, and considered significant for values of p less than 0.05.

RESULTS

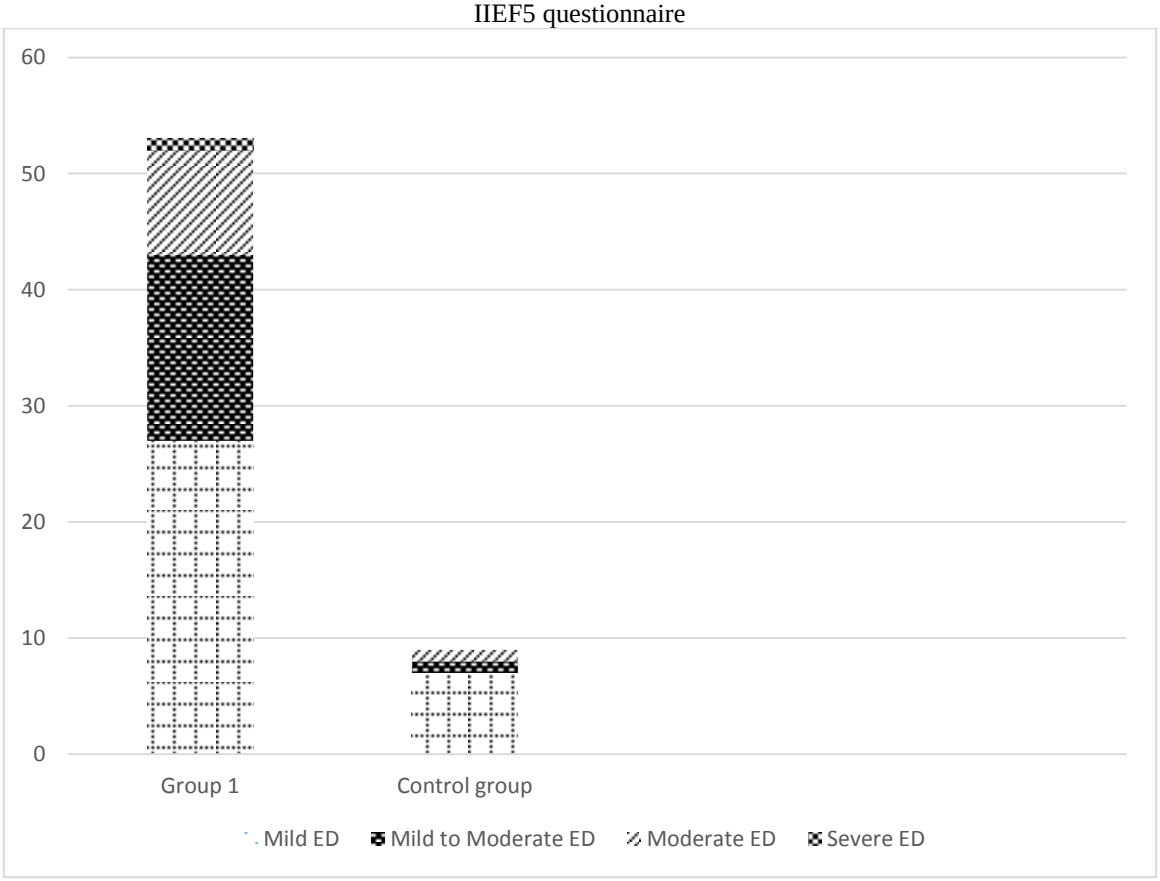
1.Prevalence and severity of erectile dysfunction

Analyzing the IIEF5 scores of the 2 groups we observed that 53 patients from the group 1 (80.30%) had some degree of ED (IIEF5 values lower than 22), and 9 patients (30%) of the 30 from control group. Using Tukey's Hinges test, it was observed that the values of IIEF5 of the group 1 [median 17.5; Q1-Q3 quartiles range (IQR) 15-21] were lower than the control group (median 22.5 IIEF5; IQR 21-24; $p < 0.001$). So for, 27 of the 66 patients with epilepsy (40.91%) and 7 (23.33%) in the control group had a mild ED, mild to moderate ED was reported in 16 patients from the study group (24.24%) and at 1 patient from the control group (3.33%). The moderate ED was reported at 9 patients from the group 1 (13.64%) and at 1 patient in the control group (3.33%), severe ED was reported at 1 patient in the group with epilepsy (1.52%) and to none from the control group. (Table I, Fig. 1)

Table 1. The percentage and the degree of erectile dysfunction in 66 patients with epilepsy and those 30 patients in the control group

	Group 1	**Control group**	**p* values**
No. of patients	**66**	**30**	
Age			
Mean±SD	42.91±5.585	52.27±8.346	<0.001
Median(Q1-Q3)	42 (39-45)	52 (45-60)	
IIEF5			
Mean±DS	17.24±4.427	21.83±3.312	<0.001
Median (Q1-Q3)	17.5 (15-21)	22.5 (21-24)	
Pacients with ED			
No (%)	53 (80.30%)	9 (30%)	<0.001
Severity of ED (Nr (%))			
Mild	27 (40.91%)	7 (23.33%)	0.095
Mild to moderate	16 (24.24%)	1 (3.33%)	0.018*
Moderate	9 (13.64%)	1 (3.33%)	0.165*
Severe	1 (1.52%)	0	>0.999*

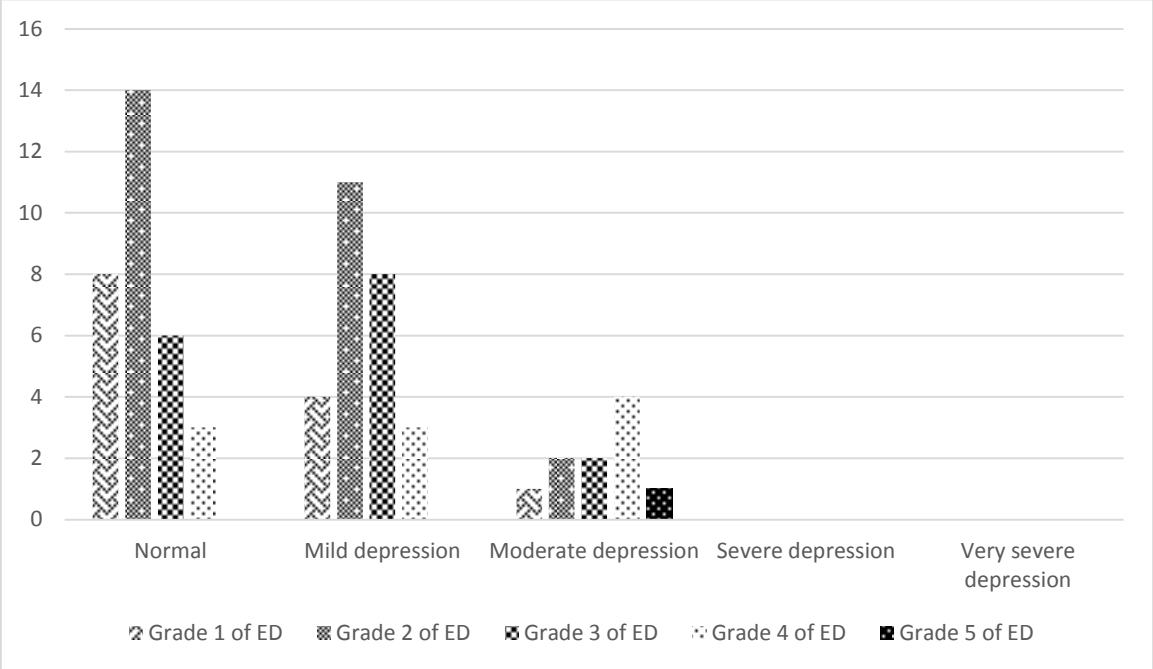
Figure 1. The ED distribution for the 66 patients with epilepsy and 30 patients in the control group, according to the IIEF5 questionnaire



2. Association between erectile dysfunction and depression

In terms of depression, no patients from the two groups had a Hamilton score greater than 23, which indicates a very severe depression. Severe Depression was reported in 1 patient (3.33%) fromt the control. Moderate depression has been reported at 10 patients from the group with epilepsy (15.15%) and at 3 patients (10%) of the control group, and mild depression has been reported at 25 patients (37.87%) from group 1 and 7 patients (23.33%) in the control group. In the group of patients with epilepsy, from the 10 patients with moderate depression one pacient reported severe ED, 4 patients reported moderate ED and 2 patients had mild and mild to moderate ED. Of the 25 patients with mild depression 2 patients had moderate ED , 8 patients had mild to moderate ED and 11 patients had mild ED. Of the 31 patients without depression 3 patients had moderate ED, 6 had mild to moderate ED and 14 patients have reported mild ED. (Fig2)

Figure 2. Repartition of ED based on depression



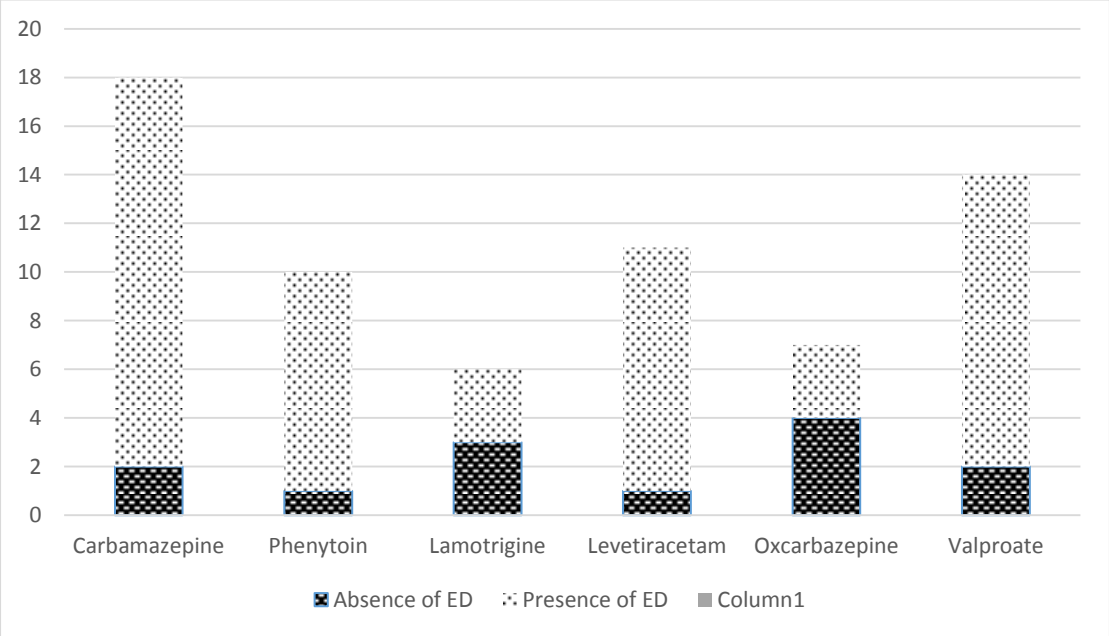
3. Association between erectile dysfunction and alcohol consumption

In terms of alcohol consumption it was found that 35 patients (53.03%) of 66 with epilepsy had consumed alcohol and 31 patients (46,97%) were without chronic alcohol consumption antecedents. In patients with chronically consume alcohol 31 reported some degree of erectile dysfunction, and 22 patients from those without alcohol consumption.

4. Association between erectile dysfunction and antiepileptic medication

At the epileptic patients after a complete anamnesis was found that 18 patients (27.27%) use as antiepileptic medication carbamazepine (CBZ), 10 patients (15.15%) use phenytoin (PHT), 11 patients (16.66%) use levetiracetam (LVT), 14 patients (21.21%) use valproate (VAL), 7 patients (10.60) use oxcarbazepine (OXC) and 6 patients (9.09%) using lamotrigine (LMT). Among patients with carbamazepine use 16 reported ED, 12 of those with the use of valproate, 10 of those with usage of levetiracetam, 9 of those with usage of phenytoin, and 3 patients with usage of oxcarbazepine and lamotrigine. (Fig 3)

Figure 3. ED prevalanece based on the antiepileptic medication use



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DISCUSSION

In patients with epilepsy in the pathogenesis of erectile dysfunction can be considered numerous etiologies. It is very likely that the epilepsy, antiepileptic drugs, and also the psychosocial factors play an important role in the ED. So the initial evaluation of any patient with epilepsy who have erectile dysfunction should include a psychological screening, a complete analysis of of depression and anxiety, a history of sexual function and the couple relationship and also complete history of antiepileptic medication usage. Also a special importance have the level of serum free testosterone, estradiol and prolactin.

In a recent study it was shown that phenytoin, phenobarbital and testosterone are hydroxylated by a common hepatic system, called system of microsomal enzymes, which increase the metabolism and clearance of free testosterone and also lowering the level of serum free testosterone [9] . The urine low concentration of 17-ketosteroide have also been reported in patients treated with antiepileptic drugs and an increase in circulating levels of sex hormone binding globuline [10,11].Despite the normal regulatory testicular function and normal pituitary function, increased hepatic synthesis and secretion of sex hormone binding globulin, the concentration of total serum testosterone were elevated but the concentration serum of free testosterone was much lower [12,13,14].

Analysis of data obtained shown that there is a close correlation between presence of ED and medication use. Antiepileptics with hepatic enzyme induction potential (carbamazepine, phenytoin) increase the metabolism of sex steroids, and the valproic acid is an enzymatic inhibitor that can increases the serum levels of free androgens. Certain antiepileptics can have cognitive side effects, some of which can induce anxiety and depressive disorders, thereby facilitating ED through these psychiatric adverse reactions.

In the current study, 53 patients (94.64%) of 66 had some degree of ED, so we can state that antiepileptic medication adversely affect the sexual function. There are still notable differences by the fact that the patients using carbamazepine, valproate, phenytoin and levetiracetam the prevalence of EDexceeds 90%, but the patients who used oxcarbazepine and lamotrigine the prevalence stands at around 50%.

The alcohol consumption does not appear to directly influence the prevalence of patients with epilepsy, given that just over 50% of patients with epilepsy and alcohol consumption had ED. Alcohol on the other hand is a risk factor for producing an epileptic seizure, and thus indirectly may influence sexual activity of epileptic patients.

Depression is a frequent pathology in patients with epilepsy, and certainly contributes to impaired sexual activity in these patients. In our study 35 patients (53.03%) had mild or moderate depression, of whom one patient reported severe ED, 6 patients experienced moderate ED, 10 patients had mild to moderate ED, and 13 patients reported mild ED.

Based on data obtained in this study we performed a multiple logistic regression. The multiple logistic regression, which try to estimate erectile dysfunction in patients with epilepsy (which gives us real diagnosticof the patient to have or not have ED, which is a variation of binary form presence / absence of disease) was based on independent predictor variables: age, HAM-D score, medication use and alcohol consumption. The multiple logistic regression is considered only in epileptic patients (patients in group 1), using a sequential method of testing the significance of independent variables for the model, namely the method based on Forward Wald statistic test. The final model is obtained in 3 steps. Details of SPSS model can be found in the following tables:

Case Processing Summary

UnweightedCases[a]		N	Percent
Selected Cases	Included in Analysis	66	100.0
	Missing Cases	0	.0
	Total	66	100.0
Unselected Cases		0	.0
Total		66	100.0

a. If weight is in effect, see classification table for the total number of cases.

Dependent Variable Encoding

Original Value	Internal Value
Absenta DE	0
Prezenta DE	1

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Categorical Variables Codings

		Frequency	Parameter coding (1)
Alchol	NO	31	1.000
	YES	35	.000
Medication_PHT	Other medication	56	1.000
	Phenytoin	10	.000
Medication_LMT	Other medication	60	1.000
	Lamotrigine	6	.000
Medication_LVT	Other medication	55	1.000
	Levetiracetam	11	.000
Medication_OXC	Other medication	59	1.000
	Oxcarbazepine	7	.000
Medication_VPT	Other medication	52	1.000
	Valproate	14	.000
Medication_CBZ	Other medication	48	1.000
	Carbamazepine	18	.000

Omnibus Tests of Model Coefficients

		Chi-square	df	Sig.
Step 1	Step	5.537	1	.019
	Block	5.537	1	.019
	Model	5.537	1	.019
Step 2	Step	4.643	1	.031
	Block	10.180	2	.006
	Model	10.180	2	.006
Step 3	Step	6.188	1	.013
	Block	16.369	3	.001
	Model	16.369	3	.001

Model Summary

Step	-2 Log likelihood	Cox & Snell R Square	Nagelkerke R Square
1	59.958[a]	.080	.128
2	55.314[b]	.143	.227
3	49.126[c]	.220	.349

a. Estimation terminated at iteration number 4 because parameter estimates changed by less than .001.
b. Estimation terminated at iteration number 5 because parameter estimates changed by less than .001.
c. Estimation terminated at iteration number 6 because parameter estimates changed by less than .001.

Classification Table[a]

	Observed		Predicted		
			ED presence		Percentage Correct
			ED absence	ED presence	
Step 1	ED presence	ED abscence	4	9	30.8
		ED presence	3	50	94.3
	Overall Percentage				81.8
Step 2	ED presence	ED absence	4	9	30.8
		ED presence	3	50	94.3
	Overall Percentage				81.8
Step 3	ED presence	ED absence	5	8	38.5
		ED presence	3	50	94.3
	Overall Percentage				83.3

a. The cut value is .500

Variables in the Equation

		B	S.E.	Wald	df	Sig.	Exp(B)	95% C.I.for EXP(B)	
								Lower	Upper
Step 1[a]	Medication_OXC(1)	2.002	.845	5.613	1	.018	7.407	1.413	38.828
	Constant	-.288	.764	.142	1	.706	.750		
Step 2[b]	Medication_LMT(1)	2.058	.924	4.958	1	.026	7.833	1.280	47.956
	Medication_OXC(1)	2.346	.878	7.136	1	.008	10.444	1.868	58.402
	Constant	-2.346	1.199	3.828	1	.050	.096		
	Pacient Age	.207	.095	4.798	1	.028	1.231	1.022	1.482
Step 3[c]	Medication_LMT(1)	2.260	.989	5.227	1	.022	9.586	1.381	66.556
	Medication_OXC(1)	2.328	.924	6.350	1	.012	10.258	1.678	62.726
	Constant	-11.007	4.315	6.507	1	.011	.000		

a. Variable(s) entered on step 1: Medicatie_OXC.
b. Variable(s) entered on step 2: Medicatie_LMT.
c. Variable(s) entered on step 3: Varsta_Pacient.

The final significantly model obtained (p = 0.001) by which we determine whether a patient has or not ED using significant predictors is characterized in the table below (results in the table below are the essential results in the tables above, tables provided by software SPSS 20). Note that the model significant predictors are patient age and medication. For the final formula will take in consideration specially the new generation antiepileptic medication, lamotrigine and oxcarbazepine.

Variable	**Coeficient (B)**	**Standard Error (SE)**	**Wald statistic**	**Grade of freedom**	**p-value**	**Exp (B)**	**95% IC pentru Exp (B)**
Patient Age	0.207	0.095	4.798	1	0.028	1.231	1.022– 1.482
LMT medication	2.260	0.989	5.227	1	0.022	9.586	1.381 – 66.556
OXC medication	2.328	0.924	6.350	1	0.012	10.258	1.678 – 62.726
Constant	-11.007	4.315	6.507	1	0.011	<0.001	

The interpretation of the variables in the regression equation obtained for the diagnostic of ED for a patient with epilepsy (patients like those in group 1) is :

- Age of the patient: an increase with a unit value of age value (assuming other variables remain constant), the chance of the patient to have ED is increased by a factor of Exp (0.207) = 1.231 (thus the chances of having ED are 1,231 bigger). For an increase with k years of the age value, the odds ratio increases and has the value Exp (k * B). Thus, for k = 10 (value up 10 years of age) the chance to have ED increase with Exp (10 * 0.207) = exp (2.07) = 7.925.
- Medication LMT: Presence of LMT mediccation (assuming other variables remain constant) increases the chance of the patient to have ED with a factor of Exp (2.260) = 9.586 (chances of ED are 9.586 higher for patients taking LMT medication compare to a patient not taking LMT medication).
- Medication OXC: Presence of OXC mediccation (assuming other variables remain constant) increases the chance of the patient to have ED with a factor of Exp (2.328) = 10.258 (chances of ED are 10.258 higher for patients taking OXC medication compare to a patient not taking OXC medication).

The logistic regression equation obtained is: Logit (DE) = -11.007 + 0.207 * (patient age) + 2.260 * (LMT medication) + 2.328 * (OXC medication)

How can we use this equation? We can predict the likelihood of ED for a patient for wich we know the age and whether or not use LMT medication, respectively OXC medication. For example, if we consider a patient with epilepsy (patients like those from group 1) 43 years old, medication LMT = 0 (did not use LMT) and medication OXC = 1 (Use of OXC) we obtained: Logit (DE) = -11.007 + 0.207 + 2.328 * 43 = 0.222. We transform this value in probability: Prob = exp (0,222) / (1 + exp (0,222)) = 0.5552. Therefore, the probability that a patient 43 years old, medication LMT = 0 (did not use LMT) and medication OXC = 1 (use) to be diagnosed with ED is 55.52%.

CONCLUSIONS

The results that were obtained in this study showed that there is a correlation between prevalence of ED and antiepileptics drugs used chronically in patients with epilepsy. Given that ED had a prevalence of more then 90% in patients who used carbamazepine, phenytoin, valproic acid and levetiracetam we conclude

that these antiepileptics with enzyme inducing hepatic potential causes ED by increasing the metabolism of sexual hormones.

In order to demonstrate this aspect would require a study in which included wil analyse the serum level of sex hormones at admission and after 6 months from the chronic use of each type of antiepileptic drug.

On the other hand, in patients taking antiepileptic of new generation, such as lamotrigine and oxcarbazepine, there was a prevalence of ED at about 50%, suggesting that these antiepileptics could influence less the erectile function compared with classic antiepileptics. This approach requires, however, a study in which at patients with classic antiepileptics classic would be introduceg a medication from new generation, and watched while if there is a significant change in sexual activity after such replacement.

Currently, the most studied antiepileptic drug is oxcarbazepine, with positive effect on the classic antiepileptic drug-induced ED, but it is possible that lamotrigine have a similar effect. It is worth mentioning that these new generation drugs have certain limitations depending on the type of epilepsy. But regardless of etiology was proven that in patients with epilepsy the ED can be successfully treated using 5 phosphodiesterase inhibitors, without any negative impact on the frequency or on the seizures onset.

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Compliance with ethical standards

Conflict of interest None