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Epilepsy and Depression, Comorbidity Problems of Treatment Tactics

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Abstract

Objective: Despite the availability of literary data on the treatment of comorbidity of epilepsy and depression, their therapy has not been fully resolved. However, epilepsy and depression are often combined.

Materials and Methods: The aim of the study was development therapy in the comorbidity of epilepsy and depression in adults. The study included 100 patients with epilepsy. The severity of depression was studied by using the Hamilton scale, ICD-10 and DSM-5 criterions. Patients were observed at the Mental Health Center of the Ministry of Health of the Republic of Azerbaijan from January 2018 to January 2020 for 24 months. Patients took standard antiepileptic drugs (depakin-chrono 1000 mg/day, lamotrigine 150 mg/day, levitracetam 3000 mg/day) and antidepressant drug-citalopram was taken 10 mg twice a day, in the morning and in the evening.

Results: Depression of varying severity was detected in 70% of the examined patients 10 cases of mild, 40 moderate and 20 case of severe depression without psychotic symptoms.

Conclusion: The combination of anticonvulsants with antidepressants Citalopram 10 mg in morning and evening (per os) reduces the frequency of seizures and reduces the severity of depression. The study of comorbidity of epilepsy and depression is of great theoretical and practical importance. First, it will contribute to the early detection of depression. Second, prevent suicides. Third, it will help reduce refractory epilepsy. Finally, improve their quality of life for patients with epilepsy.

Keywords: Epilepsy; Depression; Comorbidity; Treatment

Introduction

Around 400 BC, Hippocrates observed that "melancholy usually becomes epileptics and epileptics become melancholic" [1]. Recurrent seizures are associated with a number of harmful effects. Seizure-related deaths can account for up to 40% of all deaths in patients with chronic epilepsy. The rate of sudden death, which accounts for 7-17% of deaths among patients with epilepsy, is estimated to be 27 times higher in patients with seizures than those who do not have seizures [2].

The incidence of epilepsy in the European countries and the United States is about 40-70 cases per 100,000 population, while in developing countries the incidence is much higher. It is interesting that the incidence of epilepsy in men, especially in old and senile age, is higher than that of women [3].

Some authors indicates that depression deserves special attention due to its high frequency (10-30% of patients) and the risk of suicide occurring among epileptic patients is much more frequent than the average among population [4,5].

Further, the author believes that in addition to changes in the mood as a result of primary epileptic brain dysfunction, negative social stigmatization plays an important role in the development of depression, which leads to restrictions on education, occupation, social contacts, spending of free time.

According to various authors, depressive disorder in epilepsy occurs from 22% to 58% of patients [6].

In addition, the relationship between epilepsy and depression in the literature, the treatment of combined pathology, molecular basis etc. [7,8].

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Materials and Methods

In accordance with the Helsinki Declaration of the World Medical Association "Recommendations for doctors engaged in biomedical research involving people", adopted by the 18th World Medical Assembly (Finland, 1964, revised in Japan in 1975, Italy-1983, Hong Kong-1989, the South African Republic-1996, Edinburgh-2000); The Constitution of the Republic of Azerbaijan, the Law "On Psychiatric Assistance" (adopted on 12.06.2001, with amendments and additions-11.11.2011, Decisions of the Cabinet of Ministers of the Republic of Azerbaijan No. 83, dated April 30, 2010 "On Approval of the Rules for Conducting Scientific, Preclinical and Clinical studies of medicines "are established:

1. The conditions of the conducted researches corresponded to the generally accepted norms of morality, the requirements of ethical and legal norms, as well as the rights, interests and personal dignity of the participants of the studies were observed;

2. Conducted research is adequate to the topic of research work;

3. There is no risk for the subject of research;

4. Participants in the study were informed about the goals, methods, expected benefits of the study and associated with risk and inconvenience in the study;

5. The subject's informed consent about participation in the research was received;

The decision of the Ethical Committee at the Azerbaijan Psychiatric Association on the article of NA. Aliev, ZN. Aliev "Epilepsy and depression, treatment tactics" submitted for publication in psychiatric journals: in connection with compliance with its legislative requirements and regulatory documents is to approve the article by NA. Aliyev, ZN. Aliev "Epilepsy and depression, treatment tactics".

Epilepsy is one of the most common neuropsychiatric diseases. In the adapted version of the ICD-10 revision (put in place by order No. 170 of the Ministry of Health of the Russian Federation of May 27, 1997) in class VI, diseases of the nervous system-disorders related to epilepsy are provided for only 15 headings (G40 Epilepsy-G40.0-G40.9; G41 Epileptic status-G41.0-G41.9). In class V, mental and behavioral disorders associated with epilepsy are treated in a 17 rubric. In other words, the number of mental and behavioral disorders associated with epilepsy is greater than that of neurological. Therefore, we consider it expedient to consider epilepsy as a neuropsychic disorder.

Patients were observed at the Mental Health Center of the Ministry of Health of the Republic of Azerbaijan from January 2018 to January 2020 for 24 months. Patients took standard antiepileptic drugs (depakin-chrono 1000 mg/day, lamotrigine 150 mg/day, levitracetam 3000 mg/day) Antidepressant drug-citalopram was taken 10 mg twice a day, in the morning and in the evening.

We examined 70 patients with G40.3 Generalized idiopathic epilepsy and 30 patients G 40.0 Focal epilepsy (Total=100). Patients were examined in the interictal period.

Clinical characteristics of enrolled patients was shown in the Table 1.

Results

Results of this study were presented in the Table 2.

As can be seen from Table 2, Depression of varying severity was detected in 70% of the examined patients 10 cases of mild, 40 moderate and 20 case of severe depression without psychotic symptoms. Depression in generalized idiopathic epilepsy about 2.5 times more common than in focal epilepsy. In comparison with the general population, patients with epilepsy comorbid depression have more than twice as much depression as women.

Table 1: Clinical characteristics of enrolled patients.

Indicators	Quantity
Number of patients	100
Sex, men/women	50/50
The average age (18-45)	31,0±4,0 years
The duration of the disease	10,0±2,2 years
Non-working	70
Disabled persons	30
Frequency of epilepsy attacks	Often
G40.3 Generalized idiopathic epilepsy	70 (70 %)
G 40.0 Focal epilepsy	30 (30 %)
ICD-10; DSM- 5 296.21 and The Hamilton scale:	
Norm 0-7	30(30%)
Depression of varying severity:	70 (70%)
Mild depression ICD-10; DSM- 5 296.21 (8–16 points)	10 (5%)
Moderate severe depression ICD-10; F32.0; DSM- 5; 296.22 (17–23 ponts)	40 (20%)
Severe depression without psychotic symptoms ICD-10; F32.2; DSM- 5; 296.23 (over 24 ponts)	20 (10%)
Epilepsy type and Depression	
Depression in Generalized idiopathic epilepsy G40.	50 (62%)
Depression in Focal epilepsy G 40.0	20 (38%)

Table 2: Indicators beginning and end of the study.

Indicators	Beginning of the study	End of the study
ICD-10; DSM- 5 296.21 and The Hamilton scale [9]		
Norm 0-7	30(30%)	-
Depression of varying severity:	70 (70%)	normal
Mild depression ICD-10; DSM- 5 296.21 (8–16 points)	10 (5%)	normal
Moderate severe depression ICD-10; F32.0; DSM- 5; 296.22 (17–23 points)	40 (20%)	10 patients of mild depression*
Severe depression without psychotic symptoms ICD-10; F32.2;; DSM- 5; 296.23 (over 24 points)	20 (10%)	-
Frequency of seizures:		
Remission	-	50
Rare	-	20
Average Frequency	-	3
Frequent	100	7

* Wilcoxon's test is W=80; *P*=0.022 (the changes are statistically significant).

Discussion

From literature it is known that among people with epilepsy, depression is extremely common and is associated with intense personal suffering and a sharp decline in the quality of life [10]. According to other systematic review, 23.1% of people with epilepsy suffer from depression during the past year, compared with 6.6% in the general population [11,12]. The lifetime prevalence of depression is estimated to be 30-35% among people with epilepsy, compared with 16.2% in the general population [13,14].

The results study of Swinkels et al., [15] shows a higher prevalence of mood and anxiety disorders in patients with epilepsy, compared with the general population. They found that the subgroup of temporal lobe epilepsy patients, in particular, suffer from these disorders. But they cannot exclude that some methodological short-comings in their design may have obscured more pronounced differences between the TLE and extra-TLE subgroups.

Depression can be diagnosed in: 1) from 20% to 30% of patients with recurrent seizures; 2) from 6% to 9% of patients in remission; 3) from 50% to 55% of patients attending hospital epilepsy clinics [16]. Men with epilepsy have a higher risk of developing depression, while in the general population; depression is more common in women [17].

According some literature data the prevalence of depression occurs 5 times more often in patients with controlled seizures and 10 times in patients with uncontrolled. It is not known whether depression in these patients can be considered primarily as part of the primary pathology of the central nervous system or as a clear response to an epileptic disorder with all the difficulties of daily coping [18].

In TLE affective disorders are important comorbidities, primarily due to suicidal potential in all its forms, including gestures, thoughts, or successful attempts, which range from 10% to 15% in patients *versus* 1-1.5% in the general population [19].

It is known that depression affects the results of seizure treatment. There is a high comorbidity between depression and seizures. Depression rates are higher in patients with epilepsy than in the general population (1% to 3% of men, 2% to 9% of women) [20]. Depression can be diagnosed in: 1) from 20% to 30% of patients with recurrent seizures; 2) from 6% to 9% of patients in remission; 3) from 50% to 55% of patients attending hospital epilepsy clinics [16]. Men with epilepsy have a higher risk of developing depression, while in the general population; depression is more common in women [17].

Table 3: Antidepressant and Risk of seizures (%).

Antidepressant	Risk of seizures (%)
High risk (not indicated for epilepsy patients)	
Bupropion <450 mg	0.4
450 to	0.6
600 mg	to 2.19
Clomipramine	0.5 to 1.66
Maprotiline	0.4 to 15.6
Intermediate risk	
Tricyclics	0.1 to 4
Amitriptyline	0.4 to 0.5
Imipramine	0.6 to 0.9
Low risk	
Citalopram	<0.1
Fluoxetine	<0.1 to 0.2
Fluvoxamine	0.2
Paroxetine	0.1
Sertraline	< 0.1
Trazodone	< 0.1
Venlafaxine	0.1 to 0.2
Mirtazapine	< 0.1
Duloxetine	0.2

The relationship between the development of depressive disorders and the side effects of the use of a number of antiepileptic drugs is described. Long-term use of phenobarbital and other barbiturates most often leads to amnestic-intellectual decline, depression and even suicidal readiness in patients with epilepsy, which has been shown by both Russian and foreign researchers [21,22]. According to some authors, the appointment of antiepileptic drugs with GABAergic properties (vigabatrin and tiagabine, as well as gabapentin) is fraught with sedation and more often causes depression. Topiramate has a thymoleptic effect, but at the same time, it can cause anxiety, irritability and anxiety, and in some cases (mainly with rapid titration or starting from high doses)-psychosis [23,24]. In this regard, the

purpose of this communication is to determine.

Treatment for epilepsy is not limited to achieving a seizure-free state. It should also include the management of common psychiatric and neurological comorbidities affecting an average of 30 to 50% of patients with epilepsy, which have a significant impact on their lives at various levels. Mood and anxiety disorders are the most common comorbid mental disorders, while stroke and migraine are among the most common neurological comorbidities. Primary mood disorders have a bidirectional relationship with these two neurological disorders. In addition, depression and migraine were associated with more severe epilepsy, while depression was associated with more severe stroke and migraine. And so, the treatment of epilepsy cannot be limited to achieving cessation of seizures, it must include the simultaneous treatment of concomitant neurological and psychiatric disorders [25].

The typology of affective disorders in epilepsy is proposed, including preictal, ictal, interictal and postictal states. Various variants of affective states (depressive, dysphoric, manic) in epilepsy are considered. Depending on the severity of depressive symptoms, mild, moderate and severe depression in epilepsy was identified. The article presents clinical observations of patients with epilepsy, which show the effectiveness of anticonvulsants in relation to affective disorders [26].

A number of authors attribute psychosocial factors (life problems, financial difficulties, difficulties in adaptation at work) to the main reasons for the development of depression in patients with epilepsy. The low level of physical activity of patients with epilepsy can be considered as a risk factor for the development of depression and anxiety [27]. It has been shown that the risk of developing epilepsy in a patient with depression is 4-7 times higher than in the population, and a history of suicide attempt increases the risk of developing epilepsy 5 times [28]. The available evidence, therefore, confirms the presence of common biological mechanisms of development of depression and epilepsy [29].

Depression is one of the most common diseases in epileptic patients, affecting 1 in 4 patients and is associated with psychological and neurobiological causes. The common neurobiological mechanisms of epilepsy and depression, and depression, have a complex one-way relationship that suggests that some epileptic syndromes may be a premorbid symptom. Sertraline and cytitalopram may be considered first-line treatment for moderate to severe depression, although psychological treatment should always be offered in mild to moderate degree [30].

The question may arise, why we used the antidepressant citalopram. The fact is that citalopram has the lowest risk of seizures. This is visible from Table 3.

Antidepressants' seizure potential in any patient according to McConnell H, Duncan D [31] and Barry JJ [32].

One of the mechanisms explaining the comorbidity of epilepsy with depression is the theory of Post RM [33] about kindlingю Kindling, in the classical sense, involves the gradual increase in sensitivity to the intermediate repetition of the same sub-electrical stimulation over time, with the amygdala being the most studied region. This is associated with repetitive sub-excitation stimulation: threshold reduction after electrical discharge; prolongation and spread of blood pressure; Progression of the seizure phase ending in full-scale tonic-clonic convulsions of the forelegs with ascent and descent; and from evolutionary stimuli to spontaneous seizures. This evolving process is immediately accompanied by changes in the spatiotemporal expression of early genes (IEG), neurotrophic factors, and Late-action Genes (LEG), as well as a related change in the efficacy model of various pharmacological interventions. Because pulse memorization is a paradigmatic behavioral manifestation, some pharmacological seizures are caused by local anesthesia, such as cocaine and lidocaine, and some epileptic syndromes are most likely homologously modeled with fomentation. However, since non-epileptiform syndromes, such as recurrent episodes of affective disorder and some pain syndromes, contain heterogeneous elements of evolution similar to sedation, some of the principles involved in the burning process may be related to the understanding and treatment of these syndromes. For example, it is possible to try to distinguish between secondary and adaptive genes involved in the initial pathological processes of the evolution of the syndrome. This differentiation can have a significant impact on the development of therapeutic approaches to suppress or enhance these changes, respectively. In these cases, the results obtained from the fomenting model are necessarily indirect and limited, because different neuroanatomical and biochemical processes are likely to affect the development of each neuropsychiatric syndrome. Given these well-known limitations of non-homologous models, recurrence may provide information on the longitudinal course, progression, and treatment of some neuropsychiatric syndromes that can then be tested directly in the clinically [33].

Thus, depending on the state of awakening of the neuron, different clinical manifestations occur: kindling, convulsions, affective disorders, hallucinations, pain syndrome and other neurological, psychopathological symptoms. In other words, it can be concluded that epilepsies, pain syndromes, and affective disorders have common kindling-like mechanisms.

The limitation of our work: 1) a small number of patients; 2) a short time observation.

Thus, for a group of examined patients with epilepsy in more than half of cases, depression is characterized to a certain degree of severity. The study of comorbidity of epilepsy and depression is of great theoretical and practical importance. First, it will contribute to the early detection of depression. Second, prevent suicides. Third, it will help reduce refractory epilepsy. Finally, improve their quality of life for patients with epilepsy.

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Conflict of Interest Statement

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be

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References

1. Hippocrates volume II. 1923.
2. WHO. Neurological Disorders: Public Health Challenge. 2010.
3. Wolf P. Praxisbuch Epilepsien. Diagnostik, Behandlung, Rehabilitation. Kohlhammer. 2003.
4. Kanner AM. Depression and epilepsy: a new perspective on two closely related disorders. Epilepsy Curr. 2006; 6: 141-146.
5. Kanner AM. Epilepsy and mood disorders. Epilepsia. 2007; 9: 20-22.
6. Kanner AM. Depression in epilepsy: a complex relation with unexpected consequences. Curr Opin Neurol. 2008; 21: 190-194.
7. Mula M, Schmitz B, Sander JW. The pharmacological treatment of depression in adults with epilepsy. Expert Opin Pharmacother. 2008; 9: 3159-3168.
8. Aliyev NA, Aliyev ZN, Aliyeva SE. Selective neuronal potassium channel opener (SNEPCO) flupirtine in treatment-resistant epilepsy comorbid depression in adults. Ment Health Addict Res. 2018; 3: 4-5.
9. Zimmerman M, Martinez JH, Young D, Chelminski I, Dalrymple K. Severity classification on the Hamilton Depression Rating Scale. J Affect Disord. 2013; 150: 384-388.
10. Gilliam F, Hecimovic H, Sheline Y. Psychiatric comorbidity, health, and function in epilepsy. Epilepsy Behav. 2003; 4: 26-30.
11. Fiest KM, Dykeman J, Patten SB, Wiebe S, Kaplan GG, Maxwell CJ, et al. Depression in epilepsy a systematic review and meta-analysis. Neurology. 2013; 80: 590-599.
12. Kupfer DJ, Frank E, Phillips ML. Major depressive disorder: new clinical, neurobiological, and treatment perspectives. Lancet. 2012; 379: 1045-1055.
13. Victoroff JI, Benson F, Grafton ST, Engel J Jr, Mazziotta JC. Depression in complex partial seizures. Electroencephalography and cerebral metabolic correlates. Arch Neurol. 1994; 51: 155-163.
14. Kanner AM, Schachter SC, Barry JJ, Hersdorffer DC, Mula M, Bruce MT, et al. Depression and epilepsy: epidemiologic and neurobiologic perspectives that may explain their high comorbid occurrence. Epilepsy Behav. 2012; 24: 156-168.
15. Swinkels WAM, Kuyk J, de Graaf EH, van Dyck R, Spinhoven P. Prevalence of Psychopathology in Dutch Epilepsy Inpatients: A Comparative Study. Epilepsy Behav. 2001; 2: 441-447.
16. Jackson MJ, Turkington D. Depression and anxiety in epilepsy. J Neurol Neurosurg Psychiatry. 2005; 76: 45-47.
17. Gaitatzis A, Trimble MR, Sander JW. The psychiatric comorbidity of epilepsy. Acta Neurol Scand. 2004; 110: 207-220.
18. Harden CL, Goldstein MA. Mood disorders in patients with epilepsy: epidemiology and management. CNS Drugs. 2002; 16: 291-302.
19. Jones JE, Hermann BP, Woodard JL, Barry JJ, Gilliam F, Kanner AM, et al. Screening for major depression in epilepsy with common self-report depression inventories. Epilepsia. 2005; 46: 731-735.
20. Gilliam FG. Diagnosis and treatment of mood disorders in persons with epilepsy. Curr Opin Neurol. 2005; 18: 129-133.
21. Mazarati A, Siddarth P, Baldwin RA, Shin D, Caplan R, Sankar R. Depression after status epilepticus: behavioural and biochemical deficits and effects of fluoxetine. Brain. 2008; 131: 2071-2078.
22. Mehndiratta P, Sajatovic M. Treatments for patients with comorbid epilepsy and depres- sion: a systematic literature review. Epilepsy Behav. 2013; 28: 36-40.
23. Koh S, Magid R, Chung H, Stine CD, Wilson DN. Depressive behavior and selective down-regu- lation of serotonin receptor expression after early-life seizures: reversal by environmental enrichment. Epilepsy Behav. 2007; 10: 26-31.
24. Woif P. Praxisbuch Epilepsien. Diagnostik, Behandlung, Rehabilitation. Kohlhammer. 2003.
25. Kanner AM, Ramses Ribot R, Mazarati A. Bidirectional relations among common psychiatric and neurologic comorbidities and epilepsy: Do they have an impact on the course of the seizure disorder? Epilepsia Open. 2018; 3: 210-219.
26. Usyukina MV. Phenomenology and therapy of affective disorders in epilepsia. Meditsinskiy Sovet. 2018; 1: 64-69.
27. De Lima C, de Lira CA, Arida RM, Andersen ML, Matos G, de Figueiredo Ferreira Guilhoto LM, et al. Association between leisure time, physical activity, and mood disorder levels in individuals with epilepsy. Epilepsy Behav. 2013; 28: 47-51.
28. Kimiskidis VK, Triantafyllou NI, Kararizou E, Gatzonis SS, Fountoulakis KN, Siatouni A, et al. Depression and anxiety in epilepsy: the associ- ation with demographic and seizure-related variables. Ann Gen Psychiatry. 2007; 6: 28.
29. Ribot R, Ouyang B, Kanner AM. The impact of anti- depressants on seizure frequency and depressive and anxietydisorders of patients with epilepsy: Is it worth investigating? Epilepsy Behav. 2017; 70: 5-9.
30. Mula M. Epilepsy and depression: An update. Arch Med Health Sci. 2019; 7; 104-111.
31. McConnell HW, Snyder PJ. Psychiatric comorbidity in epilepsy: basic mechanisms, diagnosis, and treatment. American Psychiatric Publishing. 1998.
32. Barry JJ. The recognition and management of mood disorders as a comorbidity of epilepsy. Epilepsia. 2003; 44: 30-40.
33. Post RM. Do the epilepsies, pain syndromes, and affective disorders share common kindling-like mechanisms? Epilepsy Res. 2002; 50: 203-219.