

# Improving the treatment of migraine and epilepsy comorbidity

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**Abstract.** The article is aimed to determine the specific features of common neurological diseases, migraine and epilepsy comorbidity, correct selection of drugs and increasing the effectiveness of treatment in cases where migraine and epilepsy are comorbid. A total of 60 (100%) patients were recruited during the study. 30 of them (the main group) were diagnosed with migraine and epilepsy and were prescribed lamotrigine, and 30 patients (the control group) were diagnosed with migraine and epilepsy and were prescribed convulex. The clinical course of migraine, the level of cognitive disorders, the quality of life of patients, and the level of limitation of daily work were studied in patients of both groups.

## 1 Introduction

Migraine is a common disorder, occurring in 17.1% of women and 5.6% of men [1]. Migraine is one of the most disabling diseases [2]. According to WHO data, migraine ranks sixth among specific causes of disability and first among neurological causes [3]. The occurrence of other comorbid diseases along with migraine causes its transition to a chronic type [4], further reduces the quality of life, and increases the medical and economic damage [5, 6]. Migraine has many comorbidity diseases [7]. The one of them is epilepsy. Migraine and epilepsy are molecular and pathophysiologically related comorbid disorders [8]. At the same time, several scientific works have been done on the fact that migraine and epilepsy are genetically related diseases [9, 10]. In particular, the mutation of genes has been identified, which causing the comorbidity of hemiplegic migraine and epilepsy [11].

An imbalance between excitatory (glutamate) and inhibitory (GABA) is considered to be a primary importance in the development of epilepsy and migraine. And, the effectiveness of anticonvulsant drugs in the preventive treatment of migraine can be another proof of the relationship between these two diseases [12]. At the same time, antiepileptic drugs, in particular valproate and topiramate, have been found to be highly effective in the prevention of migraine [13]. These drugs have been shown to reduce migraine headache attacks by 45%. At the same time, research has been done on the effectiveness of other anticonvulsant drugs, such as, gabapentin, carbamazepine and lamotrigine. Lamotrigine has been shown to be particularly effective in migraine with aura. Until now, the mechanism of effect of anticonvulsant drugs on migraine has not been fully clarified. Several mechanisms of action of each drug are hypothesized. Valproate, topiramate, and gabapentin act through

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nociceptive modulation of GABA and/or glutamatergic transmission. These anticonvulsants enhance GABA inhibition. Valproate and gabapentin affect the metabolism of GABA, preventing its conversion to succinate. Topiramate enhances GABA inhibition, has an excitatory effect on GABA<sub>A</sub>-receptors. At the same time, topiramate directly affects glutamate receptors, reducing their activity. Valproate, gabapentin and topiramate reduce the activity of sodium ion channels. These drugs modulate calcium ion channels. Valproate blocks T-type calcium ion channels; Topiramate inhibits L-type calcium ion channels. In summary, anticonvulsants exert their therapeutic effects by influencing ion channels and biochemical modulation of neuronal excitability.

But there are some conflicting opinions about the effectiveness of anticonvulsant drugs in the prevention of migraine. For example, there are scientific studies on the low effectiveness of gabapentin in the prevention of migraine. Levetiracetam and lamotrigine have conflicting results on the effectiveness of migraine prevention [14].

It is very important to choose the right anticonvulsant drugs in cases where migraine and epilepsy occur together. Because these drugs have many side effects. One of the most common side effects is cognitive impairment. Migraine and epilepsy are both chronic neurological disorders and both cause cognitive impairment (3).

In cases where these two diseases coexist, cognitive impairment becomes more evident [15]. In the treatment of migraine and epilepsy, treatment often focuses on treating the underlying disease and ignores cognitive impairment. Therefore, we evaluated the effect of antiepileptic drugs on the course of two diseases and on cognitive impairment.

Purpose: to improve the treatment of comorbid migraine and epilepsy.

## 2 Methods

The study was conducted in the Tashkent city, in patients who received treatment in the period from 2020 to 2023 years at the consultative polyclinic department of the Tashkent Medical Academy. All examined patients voluntarily agreed to participate in the study.

Patients included in the study were selected using the following criteria.

1. Patients are 18-55 years old.
2. Patients with migraine and epilepsy (grand mal).

Exclusion criteria of patients included in the study:

3. Pregnant and lactating women
4. Patients with concomitant severe somatic diseases
5. Patients with diseases such as mental illness, alcoholism, drug addiction, etc
6. Patients with organic diseases of the brain

A total of 60 patients were involved in the study. During the study, the diagnosis of migraine was based on the 2013 diagnostic criteria of the International Headache Society (ICHD-3).

Patients were divided into groups according to the difference in treatment:

1. 30 patients diagnosed with migraine and epilepsy and receiving lamotrigine (main group)
2. 30 patients diagnosed with migraine and epilepsy who received convulex (comparison group).

All patients in both groups were prescribed NSAIDs, tranquilizers for the treatment of migraine. Patients in the main 1<sup>st</sup> group were prescribed lamotrigine for the treatment of epilepsy and preventive treatment of migraine, and patients in 2<sup>nd</sup> group were prescribed the convulex. Patients were re-examined after 3 and 6 months.

The diagnostic complex consists of the following:

- 1) clinical, neurological examinations
- 2) brain MRI or MSCT
- 3) VAS scale to assess headache intensity

- 4) MIDAS scale to assess limitation of daily work activities
- 5) QVM scale to assess quality of life in patients
- 6) the MMSE scale was used to determine cognitive impairment

### 3 Standardized instruments

The VAS (The visual analog scale for pain) scale was used to assess the intensity of headache in patients. The scale consists of a 10 cm (100 mm) horizontal line, with the left edge indicating no pain and the right edge indicating "excruciating pain." The patient is asked to mark the line according to the level of pain. Answers are measured from the beginning of the left side using a ruler (mm). The minimum score is 0 (mm) and the maximum score is 100 (mm).

QVM questionnaire was used to assess patients' quality of life. The questionnaire consists of a set of 20 questions and assesses the quality of life in terms of functional, psychological, social and medical aspects. One of five types of answers to the questions is chosen. The answers will look like this:

- It didn't get worse
- It got a little heavier
- Moderately aggravated
- Significantly aggravated
- He became very heavy

The results are evaluated by calculating the total number of points. A minimum score of 0 indicates the worst quality of life impairment, and a maximum score of 100 indicates the best quality of life. In the analysis of the results, information is obtained about "how difficult the patient's life has been during the last 3 months". The QVM questionnaire also provides information on the extent to how much migraine attacks affect daily work activities and the extent of work limitation. The questionnaire covers all aspects of daily work activities, including sleep, nutrition, sex life, migraine triggers.

The MIDAS (Migraine Disability Assessment questionnaire) scale was used to assess daily and work performance in patients.

The MIDAS scale consists of a total of 7 questions, of which 5 questions focus on the loss of time or productivity, as well as determining the level of limitation in activities at work, school or family, and in social life. The result of the MIDAS scale is 0 points (no disadaptation), up to 270 points (loss of full functioning). Using the MIDAS scale, it is possible to determine 4 levels of limitation of daily and work activities in migraine. The results are evaluated according to:

- I. 0-5 points (very little limitation of daily work activities)
- II. 6–10 points (minimal limitation of daily activities)
- III. 11–20 points (significant limitation of daily activities)
- IV.  $\geq 21$  points (severe limitation of daily activities)

Cognitive impairment in patients was determined using the MMSE scale. The result is evaluated by scoring the answers in each section. The highest score is 30 points, and the cognitive status is considered normal. The lower score, the higher the cognitive impairment. The results can be evaluated according to:

- 29-30 points – no cognitive impairment
- 28 points – mild cognitive impairment
- 25–27 points – moderate cognitive impairment
- 20-24 points – mild dementia
- 10–19 points – moderate dementia
- <10 points – severe dementia

## 4 Statistical analysis

Statistical analysis was performed using GraphPad Prism 7 software for Mac. Information collected; the database was created using Microsoft Excel for Mac. Descriptive data are presented as means, standard deviations (SD), and percentages. The statistical cut-off \* $p < 0.05$ , \*\* $p < 0.01$  and \*\*\* $p < 0.001$  are considered statistically significant.

## 5 Result

The age and gender distribution of the patients included in the study was determined through a questionnaire. According to the statistical results of the study, the distribution of patients in both groups with comorbid migraine and epilepsy by gender was dominated by women, and there was no statistically significant difference in age:

Group 1 (30 people): 18 (60%) were women, 12 were men (40%), the average age was  $31.5 \pm 3.7$  years.

Group 2 (30 people): 20 (66.7%) were women, 10 were men (33.3%), the average age was  $28.4 \pm 5.2$  years.

The distribution of patients in the study groups by gender and age is given in table 1.

**Table 1.** Demographic characteristics of the patients included in the study.

Groups	1 <sup>st</sup> group (n=30)	2 <sup>nd</sup> group (n=30)
Gender and age		
Women n (%)	18 (60%)	12 (40%)
Men n (%)	20 (66.7%)	10 (33.3%)
Average age	$31.5 \pm 3.7$	$28.4 \pm 5.2$

## 6 Preliminary inspection

### 6.1 Assessment of headache level in patients

In patients the level of headache was assessed using the VAS scale. Patients were examined twice: an initial examination and a re-examination after 3 months. According to the results obtained in the initial examination, it was found that both groups of patients (30 people) had mostly strong and moderate headaches. In patients of group 1, it was  $8.7 \pm 2.6$  points on the VAS scale. In patients of the 2nd group, this indicator was  $9.3 \pm 1.5$  points. No statistically significant difference was observed ( $p > 0.05$ ). Table 2 shows the results of comparison of the VAS scale of headache level in the patients of the study groups.

In the re-examination, the results of the VAS scale revealed a decrease in the level of headache in both groups of patients. Average headache level in patients in the main group was  $1.96 \pm 2.75$  points, in the comparison group it was  $2.3 \pm 2.5$  points. There was no statistically significant difference in headache reduction between patients receiving Convulex and lamotrigine (Table 3).

**Table 2.** Comparative results of headache levels in patients.

VAS Scale	1 <sup>st</sup> group (n=30)	2 <sup>nd</sup> group (n=30)
No pain	-	-
Mild headache	1 (3,3%)	2 (6,7%)
Moderate headache	19 (63,4%)	21 (70%)
Severe headache	10 (33,3%)	7 (23,3%)

**Table 3.** Comparative analysis of pretreatment and posttreatment headache scores in study groups.

	Before treatment		Re-examination (After 3 months)		P indicator
	Group 1	Group 2	Group 1	Group 2	
VAS scale (average score)	8.7±2.6	9.3±1.5	1.96±2.75	2.3±2.5	p>0.05

## 6.2 Assessment of quality of life

We assessed the quality of life of patients in the research groups using the QVM questionnaire. According to the results of the questionnaire, a low quality of life indicator was found in both groups of patients at the initial examination. The average score of the QVM questionnaire in the main group of patients was 57.7±13.3 points. In the second group of patients, this index was equal to 61.2 ± 10.4 points. After 6 months, when the patients were re-examined, it was found that the quality of life was improved in both groups compared to the initial examination. According to the QVM questionnaire, it was 93.5±9.2 points in patients receiving lamotrigine in group 1, and 71.7±8.6 points in patients receiving convulex in group 2. Based on these results, we can conclude that the quality of life index of patients in the main group improved statistically significantly more than patients in the comparison group (p < 0.05).

The results of the comparison of the quality of life in the study groups at the initial and re-examination are given in Table 4.

**Table 4.** Comparative results of quality of life.

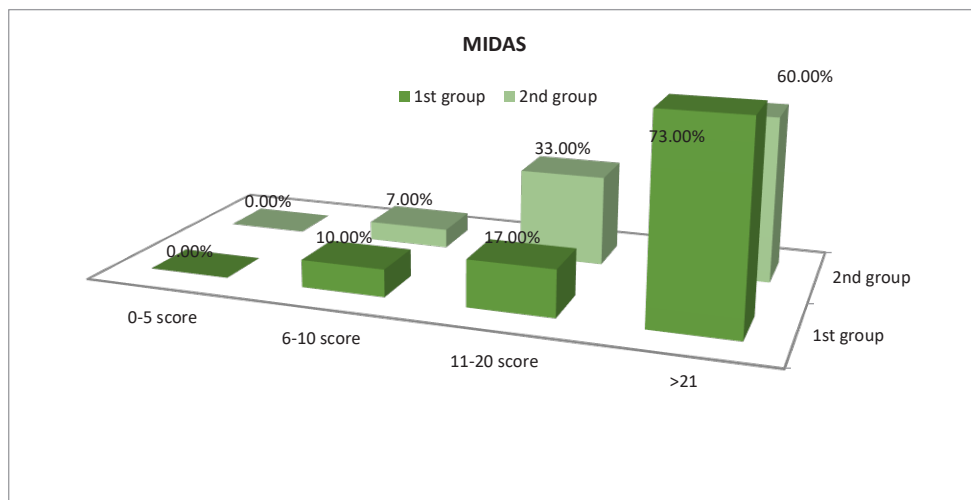
QVM questionnaire (average score)	1 <sup>st</sup> group (n=30)	2 <sup>nd</sup> group (n=30)
Preliminary examination	57.7±13.3	61.2± 10.4
Re-examination	93.5±9.2*	71.7±8.6

Note: reliability index, (p<0.05).

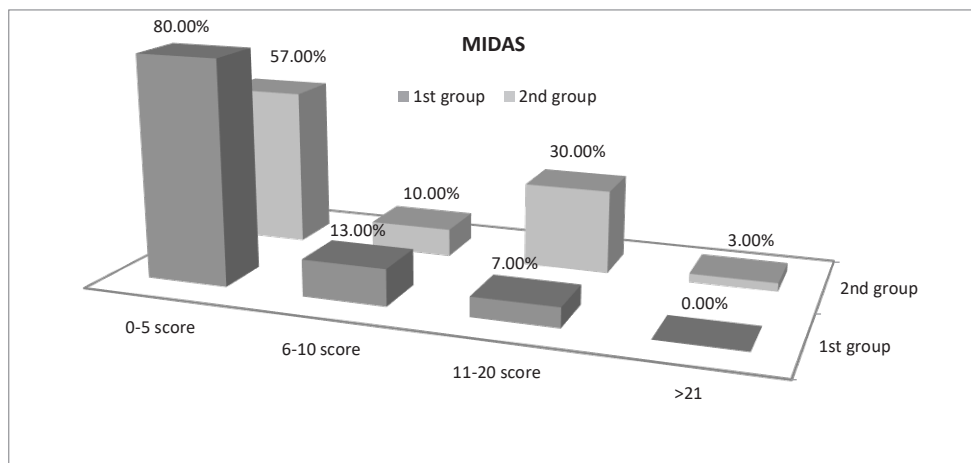
## 6.3 Results of assessment of limitation of daily activities

We assessed the limitation of daily activities using the MIDAS scale. At the initial examination, the average score on the MIDAS scale was 35.6±9.72 in patients who received lamotrigine in the main group (30 people), that is, it was found that patients had a strong limitation of daily work activities. The mean score in the control group (30 patients) who received convulex was almost the same as in the main group and was 39.3±11.5. At the initial examination, severe and moderate limitation of daily activities was noted more in

both groups of patients. In the re-examination, it was found that both groups of patients had a significant improvement in their daily functioning. In the review according to the MIDAS scale, it was found that the patients in the main group had a statistically significant higher degree of greenness of the daily activities compared to the patients in the comparison group ( $p < 0.05$ ). This indicator was  $6.5 \pm 5.3$  points in patients of the 1st group,  $13.2 \pm 8.6$  points in the patients of the 2nd group. Comparative results of limitation of daily work activities in patients of study groups are presented in Figures 1 and 2.



**Fig. 1.** Comparative results of the level of limitation of daily work activities in patients in the study groups at the initial examination.



**Fig. 2.** Comparative results of the level of limitation of daily work activities in patients in research groups in a review.

As shown in the figure above, in cases where migraine and epilepsy coexist, lamotrigine was found to lead to a statistically significant improvement in daily functioning ( $p < 0.05$ ).

### 6.4 Assessment of cognitive impairment in patients

We assessed cognitive impairment in patients using the MMSE scale. According to the obtained results, in the initial examination, both groups of patients had different levels of cognitive impairment. According to the MMSE scale, it was  $23.1 \pm 4.6$  points in 1st group and  $24.4 \pm 3.7$  points in 2nd group patients. After 6 months, the patients were re-examined and the cognitive status of the patients was evaluated. At follow-up, the majority of lamotrigine-treated patients in group 1 had no cognitive impairment and averaged  $29.2 \pm 1.6$  points on the MMSE scale. In group 2 patients receiving convulex, cognitive impairment remained, with an average MMSE score of  $23.6 \pm 2.3$  at re-examination. During the study, the comparative level of cognitive impairment at baseline and follow-up is given in Table 5.

**Table 5.** Assessment of cognitive impairment at baseline.

MMSE scale (average score)	1 <sup>st</sup> group (n=30)	2 <sup>nd</sup> group (n=30)
Preliminary examination	$23.1 \pm 4.6$ *	$24.4 \pm 3.7$
Re-examination	$29.2 \pm 1.6$	$23.6 \pm 2.3$

The results of our study showed that lamotrigine administration to patients with comorbid migraine and epilepsy reduces cognitive impairment. At the same time, it causes a statistically significant improvement in quality of life and daily functioning ( $p < 0.05$ ).

## 7 Discussion

The results of our study showed that in cases of comorbid migraine and epilepsy, lamotrigine drug recommendation was effective in the prevention of migraine and treatment of epilepsy, as well as in the treatment of cognitive disorders in patients ( $p < 0.05$ ). Convulex also showed high effectiveness in the prevention of migraines and in the treatment of epilepsy. But there was no effect on the treatment of cognitive disorders.

Many scientific studies have been conducted on the effectiveness of anti-epileptic drugs in the prevention of migraine.

In 2016, Spritzer SD and a number of scientists conducted a scientific study on the effectiveness of anticonvulsant drug – topiramate in the comorbidity of migraine and epilepsy. According to the results of this research, the high effectiveness of topiramate in the treatment of epilepsy and prevention of migraine was determined (17).

At the same time, Linde M and several scientists meta-analyzed the scientific studies conducted on the effectiveness of topiramate in the prevention of migraine, and noted that a dose of 100 mg (day) of topiramate is effective in migraine prevention (9).

In 2020 Smeralda CL and a number of scientists conducted research, it was found that lamotrigine is as effective as topiramate in the prevention of migraine, especially this drug is highly effective in migraine with aura (17).

## 8 Conclusion

According to the results of our study, lamotrigine treatment in patients with comorbid migraine and epilepsy significantly reduces cognitive impairment along with treatment of

seizure syndrome and reduction of headache attacks. Statistically significant improvements in quality of life and daily functioning are observed after lamotrigine administration. Therefore, we recommend prescribing lamotrigine to improve the effectiveness of migraine prevention, epilepsy and cognitive impairment treatment.

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