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RESEARCH ARTICLE

Lamotrigine in the Prophylaxis of Migraine: Comparison of Effectiveness in Migraine with and without Aura in Patients with Depression and Anxiety Symptoms

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ABSTRACT

Objective: Managing treatment of migraine attacks, especially migraine attacks with aura may be challenging. Both frequent attacks and drugs used for treatment may lead to some unwanted side effects which affect individuals' life quality badly. This study aimed to investigate effectiveness of lamotrigine (LTG), an antiepileptic agent and mood stabilizer which has low side effects, that blocks sodium channels, in patients with migraine with aura (MwA) and migraine without aura (MwoA) who have mild-to-moderate depressive and anxious symptoms.

Materials and Methods: A prospective, open-label, cross-sectional, and long-term dose titration study was designed. A slow dose-escalation was introduced for LTG: 25 mg/daily for 2 weeks, 50 mg/daily for 2 weeks, and if needed dose increased, not exceeding 200 mg/daily. Dose tapering was planned for after the regular use of 6 months. Ethics Committee approval was obtained and written and verbal consent forms were acquired from participants.

Results: The study comprised 128 migraineurs; 78 of them had MwA and 50 of them had MwoA. Mean age of all participants 36.1+9.64 years. In both groups; number of days with headache ($p<0.001$) and migraine attacks ($p<0.001$), visual analog scale scores ($p<0.001$), and MIDAS scores ($p<0.001$) significantly reduced after treatment. Migraine attack frequency was significantly lower in MwA than MwoA after treatment ($p=0.008$).

Conclusion: LTG should be considered as an alternative in prophylaxis of MwA as well as MwoA, especially in treating patients with depressive and anxious complaints and who have tolerance problems to side effects. Randomized, double-blind, and placebo-controlled large-scale studies are needed to prove efficacy of LTG.

Keywords: Lamotrigine, migraine, migraine with aura, prophylaxis of migraine

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INTRODUCTION

Migraine is a paroxysmal neurological disease that is characterized by moderate or severe recurrent headache attacks with accompanying symptoms such as nausea-vomiting and/or phonophobia-photophobia-osmophobia. Although it varies between geographical regions (9–35%), the 1-year prevalence of migraine worldwide is around 15% and is 2–3 times more common in women.[1,2] The migraine prevalence studies performed on the Turkish population have reported it to be 16.7%.[3]

Migraine headache is often difficult to cope with, which is among the most common reasons for applying to neurology outpatient clinics.[4] Even, it may be really challenging to diagnose a migraine attack. Sometimes, various temporary neurological findings (visual, sensory, speech and/or language, motor, brainstem, and retinal) called aura are seen in 15–30% of migraineurs, and these symptoms may cause patients to get panic and apply to the emergency room and undergo a series of additional tests.[5,6] On the other hand, it has been shown

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that the risk of ischemic stroke and cardiovascular heart disease is higher, particularly among patients with migraine with aura (MwA).[7,8] Therefore, managing the MwA, especially those with long-lasting aura attacks, is of utmost importance.

Only acute attack treatment is recommended for infrequent and relatively not long-lasting attacks, but this might be exceptional for patients with MwA. Migraine patients often need prophylactic treatment because migraine attacks affect the functionality and quality of life of individuals. Since the pathophysiology of migraine has still not been fully elucidated and has a complex nature, agents with various action mechanisms are used in a wide range of prophylaxis.[9] The first-line medical treatments with proven effectiveness in prophylaxis are tricyclic antidepressants, beta-blockers, calcium channel blockers, and antiseizure drugs such as topiramate and valproic acid. However, the side effects of these conventional drugs often cause problems. In recent years, interventional methods such as anti-CGRP agents, botulinum toxin-A, and peripheral nerve blockade have started to be considered among the treatment options for migraine treatment.[10] Nonetheless, it is necessary to think multi-dimensionally when deciding on prophylaxis. Comorbidities, gender, age, previous drug experience, and the socioeconomic status of the patients should also be considered.

Lamotrigine (LTG) is an antiseizure agent whose primary action mechanism is blocking sodium channels. Experimental studies have demonstrated that the blockade of sodium channels indirectly inhibits neuronal glutamate release and, therefore, can prevent cortical spreading depression (CSD), which has been suggested in the pathophysiology of migraine.[11,12]

LTG is not a first-line treatment agent in migraine prophylaxis. On the other hand, the effectiveness of LTG is shown in various studies and case reports for migraine prophylaxis, especially for MwA.[13–18]

Randomized-controlled studies on the use of LTG in MwA and migraine without aura (MwoA) are very limited.[17,19] Based on our clinical observations and literature, the present study aimed to investigate the effectiveness of LTG in patients with MwA and MwoA who previously used at least two first-line agents for migraine prophylaxis in sufficient duration and dose and who could not get a complete response or could not continue treatment due to side effects.

MATERIALS and METHODS

Selection of Cases

The patients included in the study were selected among those who were admitted to the neurology outpatient clinic of Istanbul Mehmet Akif Ersoy Thoracic and Cardiovascular Surgery Training and Research Hospital, between January 2014 and December 2017, and who were followed up with a definitive diagnosis of migraine for the past 2 years according to the current International Classification of Headache (ICHD)-3 beta (2013)[20] criteria at the time of the study. The patients' medical records were reviewed before our data analysis, and it was ensured that the patients included in the study also met the current diagnostic criteria of ICHD-3 (2018).[2]

Inclusion and exclusion criteria

Inclusion criteria were: (i) A definite diagnosis of MwoA according to the ICHD-3 for at least 2 years; (ii) a definite diagnosis of MwA according to the ICHD-3 for at least 2 years; iii) aged >18 and <60 years; iv) at least three attacks of MwoA or at least two attacks of long-lasting (>24 h) migrane without aura in the past 3 months (v) at least one typical migraine aura with headache or without headache per month in the past 3 months (vi) patients with normal cranial magnetic resonance imaging (MRI); (vii) patients with normal parameters in blood tests given in the past 3 months; (viii) patients with mild to moderate depression and anxiety symptoms; ix) patients with the previous failure of at least two prophylactic agents.

Exclusion criteria were: (i) Other preventive migraine treatments in the past 3 months before being included in the study; (ii) any other comorbid medical condition (e.g., pregnancy and cardiac, hepatic, renal, psychiatric, and other neurological diseases).

Ethics Committee approval (dated: April 04, 2013-decision no: 1) was obtained for this study and written and verbal consent forms were acquired from all participants per the Declaration of Helsinki.

Study Design

A prospective, open-label, cross-sectional, and long-term dose titration study was designed. Admission to LTG therapy was based on the neurologist's clinical judgment, considering possible sensitivities to medications, previous ineffective preventive treatments, and patient preferences. All patients completed the headache diary, Beck anxiety (BAI), and Beck depression (BDI) inventories for the past 3 months before starting treatment. Data collection was based on patients' self-reports and on headache diaries. Psychiatric consultation was requested for patients with high BDI (>30) and BAI (>26) scores and those with suspected psychiatric illness in their history. Patients who were not approved by the psychiatrist were excluded from the study.

Dose regimen, titration, and evaluation

A slow dose-escalation was introduced for LTG: 25 mg/daily for 2 weeks, 50 mg/daily for 2 weeks, and if needed dose

was increased, not exceeding 200 mg/daily. The patients were seen at regular visits throughout the study, and dose adjustments were made according to the frequency of their attacks. Dose tapering was planned for after the regular use of 6 months, and if the headaches increased the same dose was continued. All patients were followed for a period of at least 12 months after starting treatment.

Endpoint results were evaluated at the end of 1 year, including evaluation for the past 3 months: pre- to post-treatment change of monthly frequency of auras, migraine attacks, and days with headache, Visual analog scale (VAS), and MIDAS scores within and between two groups. Dropouts and type and frequency of side effects were reported.

At the end of the follow-up period; (i) if the patient reported a reduction of at least 50% of migraine attacks; that patient defined as a "responder" (ii) if the patient reported no migraine attacks; that patient defined as "optimal responder".

Statistical Analysis

Statistical Program for the Social Sciences (SPSS) Windows version 22.0 package program (IBM Corp., Armonk, New York, USA) was used for analysis. As descriptive statistics, mean±standard deviation values were presented for numerical variables and number and % values for categorical variables. The Shapiro–Wilk test was used for the conformity of the data to the normal distribution. Independent t-test was used to compare normally distributed quantitative data. Mann–Whitney U test was used for continuous variables. Wilcoxon-Rank test was used for comparison of before and after treatment quantitative data that did not fit the normal distribution. Categorical data were compared with the Pearson Chi-square test. The statistical significance limit was accepted as $p<0.05$.

RESULTS

Demographical and Clinical Data

Three hundred and fifty migraine patients were eligible to participate in the study among those who admitted to the neurology outpatient clinic consecutively during the study period. Among those who had severely high BDI and anxiety scores and who needed additional psychiatric treatment as a result of psychiatry consultation were excluded before the treatment initiation (n=200). One hundred and fifty patients were recruited in the study, but 12 patients due to skin rush and 10 patients who did not want to continue the study due to side effects dropped out at the first 2 weeks of the treatment initiation.

As a result, 128 patients included in this study: 78 (60.9%) of them had MwA and 50 (39.1%) of them had MwoA. Among 78 patients with MwA, 70 (89.8%) of them had visual auras and 6 (7.7%) of them had sensory auras and two of them had language auras (2.5%).The mean age of 128 patients included in the study was 36.1 ± 9.64 years. One hundred and nine (93%) patients were female and 9 patients (7%) were male.

There was no significant difference between the MwA and MwoA groups regarding age, migraine onset age, age groups, and gender distribution. There was no significant difference between two groups in terms of pre-treatment BDI and BAI scores (Table 1). The previous prophylaxis treatments of patients are given in Table 2.

The dose of LTG was increased up to 100 mg/daily in 55.5 % (n=60) of the patients, 150 mg/daily in 27% (n=29), and up to 200 mg/daily in 17.6% (n=19). Observed side effects were given in Table 3.

There was no difference between MwoA and MWA groups in terms of VAS (p=0.108) and MIDAS (p=0.946) scores and frequency of days with headaches (p=0.850) and migraine attacks (p=0.349) per month in pre-treatment evaluation. The number of days with migraine attacks was significantly lower in MwA than MwoA (p=0.008) after the treatment with LTG (Table 4). Treatment responder rates (<50% reduction in migraine attack frequency) were significantly high in MwA compared to MwoA. Auras disappeared in 30.8% and significantly reduced (<50% of aura attacks) in 38.4% and not changed in 30.8% in patients with MwA (Table 5).

In both groups; number of days with headache and migraine attacks, VAS scores, and MIDAS scores significantly reduced after the treatment (Table 4).

DISCUSSION

The present study determined that LTG significantly reduced the number of days with headache, migraine attack frequency, pain severity, and migraine disability scores in both MwA and MwoA. However, the frequency of migraine attacks was significantly reduced in MwA compared to MwoA, and treatment responder rates were significantly higher in MwA. In addition, the aura frequency was significantly reduced in patients with MwA. The majority of patients (87%) responded to LTG daily doses between 100 and 150 mg No severe side effects related to LTG use were seen (Table 3).

LTG is thought to be efficient in treating migraine patients with aura since it inhibits the CSD.[12] Its effect on migraine patients without aura, as well as preventing the CSD may have been due to the blocking other presynaptic potassium

Table 1. Demographic and clinical data

	MwoA 39.1% (n=50)		MwA 60.9% (n=78)		p
	n	%	n	%	
Age (mean+SD) (min-max)	37.4±9.37 (18–56)		35.3±9.77 (19–56)		0.224[a]
Age groups (years)					
(18–25)	6	12	15	19.2	0.115[b]
(26–35)	9	18	24	30.8	
(36–45)	26	52	25	32.1	
(46–56)	9	18	14	17.9	
Gender					
Female	46		73		0.739[b]
Male	4		5		
Age of disease onset (mean SD) (years)	24.8±6.32 (15–39)		24.3±5.39 (16–38)		0.808[c]
Disease duration (mean±SD) (years)	12.6±7.81 (2–30)		10.9±7.89 (2–30)		0.211[c]
BDI score	19.1±5.09 (3–28)		21.4±5.12 (10–29)		0.17[c]
BAI score	17.3±7.35 (0–28)		19.2±4.8 (4–28)		0.224[c]

[a]: Independent t test, [b]: Pearson Chi-square test; [c]: Mann–Whitney U test. MwoA: Migraine without aura; MwA: Migraine with aura; SD: Standard deviation; BDI: Beck depression inventory; BAI: Beck anxiety inventory

Table 2. Previous prophylaxis agents used by patients

Previous prophylaxis agents	n	%
Antidepressants±Beta-blockers	38	29.7
Antidepressants±Ca-channel blockers	15	11.7
Antiepileptics±Beta blockers	16	12.5
Antiepileptics± Ca-channel blockers	19	14.8
Antidepressants±Antiepileptics	10	7.8
Antidepressants±Antiepileptics±Ca-channel blockers	5	3.9
Beta-blockers±Ca-channel blockers	6	4.6
Antidepressants±Beta-blockers±Ca-channel blockers	11	8.6
Antiepileptics±Beta-blockers±Ca-channel blockers	8	6.3
Total	128	100

Table 3. Temporary side effects reported after LTG initiation

	LTG (n=150) %
Nausea/vomiting[a]	18
Dizziness[a]	10
Skin rush[b]	8
Diarrhea[a]	9
Difficulty in sleeping[a]	15
Somnolance[a]	10

[a]: Ten of the patients who had one or two of these side effects dropped out within two weeks of the study; [b]: These patients (n=12) dropped out within two weeks of the study. LTD: Lamotrigine

and calcium channels, 5-hydroxytryptamine (5-HT1) and 5-HT3 receptors in the central nervous system, or by affecting nitric oxide synthesis.[21–24] All of these possible mechanisms are also closely related to migraine pathophysiology.[25] Furthermore, although CSD is considered the main pathophysiological mechanism causing migraine aura, it remains unclear whether CSD is the initiator of a migraine attack or epiphenomenon. Moreover, there is strong preclinical evidence that activation of the trigeminovascular system, which triggers the onset of migraine pain, can be induced by CSD while the majority of migraineurs still experience migraine attacks without aura.[10,26] Supporting this context, it has been suggested that CSD may lead to symptoms that are not typically classified as auras.[27,28]

Table 4. Comparison of pretreatment and posttreatment within groups

	Pre-treatment		Post-treatment		p
	n	%	n	%	
MwoA					
Number of days with headache per month	13.4±4.08 (7–25)		5.24±3.34 (2–17)		<0.001[a]
Number of days with migraine attack per month	4.74±2.07 (2–12)		2.2±1.16 (1–6)		<0.001[a]
VAS score	7.28 ±2.51 (1–10)		2.74 ±1.61 (1–7)		<0.001[a]
MIDAS score					
Grade 1		0	36	72	<0.001[b]
Grade 2	15	30	10	20	
Grade 3	20	40	4	8	
Grade 4	15	30		0	
MwA					
Number of days with headache per month	13.76±4.82 (7–27)		4.83±2.64 (2–16)		<0.001[a]
Number of days with migraine attack per month	4.32±1.72 (2–10)		1.7±0.79 (1–4)		<0.001[a]
Number of days with aura per month	3±1.38 (1–6)		0.94±0.78 (0–3)		<0.001[a]
VAS score	6.7±2.32 (3–10)		2.24±1.42 (1–8)		<0.001[a]
MIDAS score					
Grade 1		0	61	78.2	<0.001[b]
Grade 2	24	30.7	14	17.9	
Grade 3	29	37.2	3	3.8	
Grade 4	25	32.1		0	

[a]: Wilcoxon rank test; [b]: Pearson Chi-square test. MwoA: Migraine without aura; MIDAS: Migraine Disability Assessment; MwA: Migraine with aura; VAS: Visual Analog Scale

Table 5. Responder rates between groups

	MwA (n=78)		MwoA (n=50)		p
	n	%	n	%	
Optimal responder (aura)	24/78	30.8	–	–	
Responder (aura)	30/78	38.4	–	–	
Non Responder (aura)	24/78	30.8	–	–	
Responder (migraine attack frequency)	70/78	90.9	34/50	68	**0.002[a]**
Non-responder (migraine attack frequency)	7/78	9.1	16/50	32	

[a]:Pearson Chi-square test. MwA: Migraine with aura; MwoA: Migraine without aura

The literature has some controversies on the effectiveness of LTG, but in recent years, the data supporting the therapeutic effect of LTG are getting larger.[12,17] Steiner et al.[29] reported that LTG was not superior to placebo in the prophylaxis of migraine attacks in their study, which included a small number of migraineurs with and without aura. In contrast, following this study, it was reported that LTG reduces the frequency of migraine attacks with aura.[13,15] On the other hand, in yet another small-scale and short-term study, LTG was not found superior to low-dose topiramate or placebo. However, it was underlined that although it was not statistically significant when compared with the placebo group, LTG reduced the frequency of headaches, and also photophobia and dizziness accompanying migraine pain were significantly reduced compared to the placebo.[30] Another very recent study in MwA reported that LTG is as effective as topiramate and better tolerated in terms of side effects. The authors of this study mentioned that using at least 6 months of treatment has better endpoints than 3 months.[17] In the previous studies mentioned above, the number of patients with MwA and MwoA is low, and the duration of usage is short (<3 months). The relatively higher number of patients with MwoA and MwA and the long-term use of LTG in our study may have led to better results.

The present study excluded those patients with severe depression. However, mild-to-moderate depression and anxiety symptoms were accompanied by a significant proportion of our patients. It is necessary to underline that it was not easy to find patients without depression and/or anxiety symptoms in our patient population. Various studies demonstrated a bidirectional relationship between migraine, depression, and anxiety disorders that they have common pathophysiological mechanisms and that the presence of one increases the risk of developing the other.[31–34] It is well-known that LTG reduces symptoms of depression and anxiety and is a good mood stabilizer.[35,36] LTG may have broken the vicious cycle of depression-anxiety-migraine, and therefore, we might have obtained better results in reducing migraine attack frequency, VAS, and MIDAS scores compared to other studies. However, unfortunately, we could not reveal the relief of depressive and anxious symptoms with an objective scale after the treatment.

Limitations of the Study

This study had some limitations. Although the lack of a placebo group was the most significant limitation, we thought that it would be unethical to use a placebo for at least 6 months when it is considered that all patients had a failure of previous treatments and the majority had frequent and intensive headaches. Another limitation was that we could not compare the duration of aura and headache attacks before and after the treatment.

We preferred to use a drug that patients had not tried before, with fewer side-effect profiles. We investigated the effectiveness of LTG in MwoA and MwA, which had been previously conducted in low-scale and limited numbers. LTG significantly reduced the number of days with headache, migraine attack frequency, pain severity, and migraine disability scores in both MwA and MwoA groups. The rate of patients who responded well to the treatment was higher in MwA, as expected.

CONCLUSION

LTG is promising and should be considered as an alternative in the prophylaxis of MwoA as well as MWA, especially in treating patients with depressive and anxious complaints and who have tolerance problems to side effects of other first-line drugs. To monitor treatment response, starting LTG with a gradual escalation and using effective doses for at least 6 months should be considered. Randomized, double-blind, and placebo-controlled large-scale studies are undoubtedly needed to prove the efficacy of LTG.

Disclosures

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Ethics Committee Approval: The study was approved by the Şişli Etfal Training and Research Hospital Clinical Research Ethics Committee (No: 1, Date: 04/04/2013).

Informed Consent: Written informed consent was obtained from all patients.

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REFERENCES

1. Ashina M, Katsarava Z, Do TP, Buse DC, Pozo-Rosich P, Özge A, et al. Migraine: epidemiology and systems of care. Lancet 2021;397:1485–95.
2. Headache Classification Committee of the International Headache Society (IHS) The International Classification of Headache Disorders, 3rd edition. Cephalalgia 2018;38:1–211. [CrossRef]

3. Baykan B, Ertas M, Karlı N, Uluduz D, Uygunoglu U, Ekizoglu E, et al. Migraine incidence in 5 years: A population-based prospective longitudinal study in Turkey. J Headache Pain 2015;16:103. [CrossRef]
4. Atalar AÇ, Bozkurt M, Çalişkan Z, Vo P, Ertaş M, Baykan B. Living with burden of migraine: The analysis of "My Migraine Voice" survey results in Turkey. Noro Psikiyatr Ars 2019;58:115–20. [CrossRef]
5. Lucas C. Migraine with aura. Rev Neurol (Paris) 2021;177:779–84.
6. Foroozan R, Cutrer FM. Transient neurologic dysfunction in migraine. Neurol Clin 2019;37:673–94. [CrossRef]
7. Lai J, Dilli E. Migraine aura: Updates in pathophysiology and management. Curr Neurol Neurosci Rep 2020;20:17. [CrossRef]
8. Adelborg K, Szépligeti SK, Holland-Bill L, Ehrenstein V, Horváth-Puhó E, Henderson VW, et al. Migraine and risk of cardiovascular diseases: Danish population based matched cohort study. BMJ 2018;360:k96. [CrossRef]
9. Grazzi L. Migraine and prophylaxis. Neurol Sci 2020;41(Suppl 2):383–4.
10. Dodick DW. A phase-by-phase review of migraine pathophysiology. Headache 2018;58(Suppl 1):4–16. [CrossRef]
11. Bogdanov VB, Multon S, Chauvel V, Bogdanova OV, Prodanov D, Makarchuk MY, et al. Migraine preventive drugs differentially affect cortical spreading depression in rat. Neurobiol Dis 2011;41:430–5. [CrossRef]
12. Buch D, Chabriat H. Lamotrigine in the prevention of migraine with aura: A narrative review. Headache 2019;59:1187–97. [CrossRef]
13. Lampl C, Buzath A, Klinger D, Neumann K. Lamotrigine in the prophylactic treatment of migraine aura--a pilot study. Cephalalgia 1999;19:58–63. [CrossRef]
14. Lampl C, Katsarava Z, Diener HC, Limmroth V. Lamotrigine reduces migraine aura and migraine attacks in patients with migraine with aura. J Neurol Neurosurg Psychiatry 2005;76:1730–2. [CrossRef]
15. D'Andrea G, Granella F, Cadaldini M, Manzoni GC. Effectiveness of lamotrigine in the prophylaxis of migraine with aura: An open pilot study. Cephalalgia 1999;19:64–6. [CrossRef]
16. Rampello L, Alvano A, Chiechio S, Malaguarnera M, Raffaele R, Vecchio I, et al. Evaluation of the prophylactic efficacy of amitriptyline and citalopram, alone or in combination, in patients with comorbidity of depression, migraine, and tension-type headache. Neuropsychobiology 2004;50:322–8. [CrossRef]
17. Smeralda CL, Gigli GL, Janes F, Valente M. May lamotrigine be an alternative to topiramate in the prevention of migraine with aura? Results of a retrospective study. BMJ Neurol Open 2020;2:e000059. [CrossRef]
18. Cologno D, d'Onofrio F, Castriota O, Petretta V, Casucci G, Russo A, et al. Basilar-type migraine patients responsive to lamotrigine: A 5-year follow-up. Neurol Sci 2013;34(Suppl 1):S165–6. [CrossRef]
19. Banzi R, Cusi C, Randazzo C, Sterzi R, Tedesco D, Moja L. Selective serotonin reuptake inhibitors (SSRIs) and serotonin-norepinephrine reuptake inhibitors (SNRIs) for the prevention of migraine in adults. Cochrane Database Syst Rev 2015;4:CD002919. [CrossRef]
20. Headache Classification Committee of the International Headache Society (IHS). The International Classification of Headache Disorders, 3rd edition (beta version). Cephalalgia 2013;33:629–808. [CrossRef]
21. Kang D, Kim GT, Kim EJ, La JH, Lee JS, Lee ES, et al. Lamotrigine inhibits TRESK regulated by G-protein coupled receptor agonists. Biochem Biophys Res Commun 2008;367:609–15. [CrossRef]
22. Dibué-Adjei M, Kamp MA, Alpdogan S, Tevoufouet EE, Neiss WF, Hescheler J, et al. Cav2.3 (R-Type) calcium channels are critical for mediating anticonvulsive and neuroprotective properties of lamotrigine in vivo. Cell Physiol Biochem 2017;44:935–47. [CrossRef]
23. Bourin M, Masse F, Hascoët M. Evidence for the activity of lamotrigine at 5-HT(1A) receptors in the mouse forced swimming test. J Psychiatry Neurosci 2005;30:275–82.
24. Kim KJ, Jeun SH, Sung KW. Lamotrigine, an antiepileptic drug, inhibits 5-HT3 receptor currents in NCB-20 neuroblastoma cells. Korean J Physiol Pharmacol 2017;21:169–77. [CrossRef]
25. Sardo P, Ferraro G. Modulatory effects of nitric oxide-active drugs on the anticonvulsant activity of lamotrigine in an experimental model of partial complex epilepsy in the rat. BMC Neurosci 2007;8:47. [CrossRef]
26. Bolay H, Vuralli D, Goadsby PJ. Aura and head pain: Relationship and gaps in the translational models. J Headache Pain 2019;20:94. [CrossRef]
27. Charles A, Hansen JM. Migraine aura: New ideas about cause, classification, and clinical significance. Curr Opin Neurol 2015;28:255–60.
28. Hadjikhani N, Vincent M. Neuroimaging clues of migraine aura. J Headache Pain 2019;20:32. [CrossRef]
29. Steiner TJ, Findley LJ, Yuen AW. Lamotrigine versus placebo in the prophylaxis of migraine with and without aura. Cephalalgia 1997;17:109–12.
30. Gupta P, Singh S, Goyal V, Shukla G, Behari M. Low-dose topiramate versus lamotrigine in migraine prophylaxis (the Lotolamp study). Headache 2007;47:402–12.
31. Haythornthwaite JA. Migraine headaches and psychopathology: Future directions. J Psychiatr Res 1993;27:183–6. [CrossRef]
32. Zwart JA, Dyb G, Hagen K, Ødegård KJ, Dahl AA, Bovim G, et al. Depression and anxiety disorders associated with headache frequency. The Nord-Trøndelag Health Study. Eur J Neurol 2003;10:147–52. [CrossRef]
33. Ligthart L, Hottenga JJ, Lewis CM, Farmer AE, Craig IW, Breen G, et al. Genetic risk score analysis indicates migraine with and without comorbid depression are genetically different disorders. Hum Genet 2014;133:173–86. [CrossRef]
34. Yang Y, Zhao H, Heath AC, Madden PA, Martin NG, Nyholt DR. Shared genetic factors underlie migraine and depression. Twin Res Hum Genet 2016;19:341–50. [CrossRef]
35. Naguy A, Al-Enezi N. Lamotrigine uses in psychiatric practice. Am J Ther 2019;26:e96–102. [CrossRef]
36. Zavodnick AD, Ali R. Lamotrigine in the treatment of unipolar depression with and without comorbidities: A literature review. Psychiatr Q 2012;83:371–83. [CrossRef]