Pharmacophore

ISSN-2229-5402

Journal home page: http://www.pharmacophorejournal.com

MIGRAINE, OVERVIEW, DISEASE BURDEN, PREVENTIVE THERAPY; GABAPENTIN AND PREGABALIN

Noura Mohammedrashed Alharby[1*], Yara Refaat Alharbi[2], Hanan Obaidallah Al Rehaily[1], Mohammad Abdulrahman Bakhsh[3], Ibraheem Abdulrahman Wedhaya[4], Fawaz Falah Alhejaili[5], Azuaf Ahmad M Ghabban[6]

1. *Consultant family medicine, Public health administration, Saudi Arabia*
2. *General Practitioner, Armed forces hospital - Dahran, Saudi Arabia*
3. *General Practitioner, King Abdulaziz Hospital, Saudi Arabia*
4. *General Dentist, Andalusia Hospital, Jeddah, Saudi Arabia*
5. *General Practitioner, Compliance manager in health affairs in Jeddah, Saudi Arabia*
6. *General Practitioner, Al Mahgar PHCC, Saudi Arabia.*

ARTICLE INFO

Received:
03 Jan 2020
Received in revised form:
21 Feb 2020
Accepted:
23 Feb 2020
Available online:
28 Feb 2020

Keywords: Migraine, Gabapentin, Pregabalin, diagnosis and management

ABSTRACT.

Background: Migraine is a chronic debilitating neurological disease that can interfere with a patient's quality of life and disturb daily routine chores. Migraine preventive therapy is crucial as acute treatment. Patients who suffer from frequent attacks with or without aura are a candidate for migraine prophylaxis. **Objective**: We aim to provide an overview of migraine and the role of gabapentin and pregabalin in migraine preventive therapy. **Methodology**: We searched in the PubMed database for relevant articles using the following Mesh terms: "Migraine," "Migraine preventive therapy," "Gabapentin," and "Pregabalin." **Conclusion**: Both gabapentin and pregabalin have antinociceptive properties. They worked by modulating the Calcium channel to enhance and increase the synthesis of GABA in the brain. Some data showed an excellent response to these drugs in terms of decrease migraine attack severity and frequency. Yet, the mechanism behind these effects is not clearly understood, and more randomized clinical trials are needed to establish their exact efficacy and safety on migraine prevention.".

To Cite This Article: Noura Mohammedrashed Alharby, Yara Refaat Alharbi, Hanan Obaidallah Al Rehaily, Mohammad Abdulrahman Bakhsh, Ibraheem Abdulrahman Wedhaya, Fawaz Falah Alhejaili and *et al.*, (2020), "Migraine, Overview, Disease Burden, Preventive Therapy; Gabapentin and Pregabalin", ***Pharmacophore, 11(1),*** *153-158.*

Introduction, Prevalence, and Disease Burden

Migraine is a chronic disorder characterized by episodic attacks, which is differentiated according to the attack frequency into two main subtypes; Episodic and Chronic Migraine (CM), previously called transformed migraine [1, 2]. While episodic migraine is described by attacks that occur less than 15 days monthly, chronic migraine is defined as headache attacks on at least 15 days monthly [1]. Chronic migraine patients represent the most serious and disabled subclass of the migraine spectrum [2]. By definition, chronic migraine is a typical episode of headache that affects the patient on at least 15 days per month for three months or more; additionally, only eight of these headache episodes per month need to meet the diagnostic criteria for migraine [2]. While most patients have episodic headaches, some of them suffer from increasing headache frequency with time, until the attacks occur almost daily [3]. Many patients with chronic migraines will have headaches day as a migraine attack associated with nausea or photophobia [2]. Notably, if a patient meets the diagnostic criteria for chronic migraine, other types of headaches are excluded [2]. Appropriate management of these patients is often complicated, and represent a challenging situation for primary health physicians [2, 4-7]. The prevalence of chronic migraine is at least 1% to 2% of the general community [1, 2].

The incidence of CM has not been studied yet; however, the American Migraine Prevalence and Prevention (AMPP) has reported that patients with episodic migraine in the United States population have a 2% incidence of chronic migraine in a subsequent year [1]. In Germany's prospective study, the incidence of CM was 14% [1]. The prevalence varies based on age and gender; nonetheless, the prevalence is considerably similar among preadolescent males and females at approximately 5% [8]. The prevalence peaked at around 20% in females during the third and fourth decades of life, with an identical peak

Corresponding Author: Noura Mohammedrashed Alharby; Consultant Family Medicine, Public Health Administration, Saudi Arabia. Email: Nouraalharbi597@gmail.com

of 10% for males [8]. With age increasing, the prevalence starts to decrease for both sexes by the seventh decade, reaching 5% in males and 5% to 10% in females [8]. Migraine is a chronic debilitating and incurable disease; to clarify, almost one out of five CM patients experience occupational incapacity secondary to migraine [8, 9]. As the prevalence peak is reported in early middle age, migraine leads to significant morbidity and productivity disturbance and influences not only the individual but also their families [8]. CM can impact the person's ability to perform routine duties, build and maintain functional family, social, and community relations [1]. Therefore, CM patients have been recognized as one of the segments suffering most from headache [1]. Episodic migraine can transform into CM at around the rate of 3% per year in the general population and 14% per year among patients following a specialty clinic [3].

Migraine is characterized by prominent headache, with a wide variety of other associated symptoms that occur before, during, and after the attack of headache [8]. The most common associated symptoms include nausea, vomiting, and sensitivity to sensory stimuli [8]. The migraine's headache is ordinarily unilateral, gradual, throbbing in nature, and can be worsened by daily routine activities, light, voices, and smells [8]. Within hours to days before the headache attack, most patients report feeling fatigued, anorexic, or food cravings, restlessness, and mood changes [8]. Aura, which has been reported in approximately 30% of migraine experience, occurs sporadically and does not typically involve most migraine attacks [8]. Classically, migraine aura consists of visual phenomena that arise and cease 5 to 20 minutes before the migraine attack [8]. Spots of blurry or grayed vision that block visual input (scotoma), flashes of light, or an arch with "zig-zag" lines have been reported as a visual aura [8]. Less commonly, the aura can represent a deficit in sensory, motor, and language function and may imitate manifestations of transient ischemic attacks or strokes [8]. Aura is typically last for 5 to 20 minutes, but maybe up to 60 minutes; also, the aura may overlap with headache onset [8]. Although most CM patients have a history of migraine without aura attacks, some may have a history primarily of migraine with aura [2].

Pathophysiology:

The pathogenesis of migraine symptoms is believed to result from vascular and neurological events befalling predominantly in the cranial meninges' arteries [9]. Two main theories dominate the etiology and the pathogenesis of migraine headaches [9]. The vascular theory, which Thomas Willis introduced in the 19th century, suggested that the pain is caused by vasodilatation of the cerebral meningeal arteries [9]. This theory led to the use of vasoconstrictive properties to acutely terminate a migraine attack [9]. The neuronal theory suggested that the vascular events during migraines are explained by neuronal network dysfunction, leading to the activation of the neurogenic inflammatory process [9]. Two assumptions have been driven from this theory; however, both still a matter of controversy [9]. The first one is the involvement of the trigeminal nerve system in pain generation through its innervation of the meningeal blood vessels [9]. The second suggested that the phenomenon of cortical spreading depression may be the trigger of the pain; besides, cortical spreading depression is presumed to be an intense wave developing across the cerebral cortex, causing interruption of the ionic gradient (Ca^{+2}, Na^{+}, K^{+}) and followed by suppression of the neural activity [9]. Some expert opinion argues that the cortical spreading depression is the etiology of aura's neurological symptoms only [9]. Based on animal studies and functional imaging studies in humans, the aura is a feature of intense cortical neuronal discharge followed by cortical depression that initiates in the posterior occipital lobe; therefore, the visual aura is a predominant symptom [8].

Discussion

Diagnosis

Migraine is usually diagnosed clinically, and physical examination should be performed to rule out high intracranial pressure [8]. Laboratory and neuroimaging are used to help excluding secondary disorders that lead to migrainous pain [8]. The secondary cause of headache varies from benign (caffeine withdrawal) to potentially severe (cerebral vasospasm, tumors, hemorrhagic stroke) [8]. Hence, understanding the patient's symptoms, medical history, and risk factors is crucial to diagnose migraine [8]. The International Headache Society Classification has been reported that CM can be diagnosed accurately if the patient has headaches on at least 15 days per month with at least eight of these days showing migraine features, and if the headache duration is at least four hours per day [2] The Classification Committee of the International Headache Society has produced a straightforward and guidance diagnostic criteria of CM, which are shown in Table 1 [2]. The patient must have at least five previous migraine episodes as a crucial feature of the diagnostic criteria; consequently, careful questioning for the previous migraine attacks and the associated symptoms, onset, and duration [2] Another essential feature of the diagnostic criteria is the fast response to triptan treatment early during the attack; nevertheless, this attack of headache is considered migrainous even if it does not manifest all migraine clinical features [2].

Table 1. diagnostic criteria for migraine with and without aura[2]

Migraine with Aura	**Migraine without Aura**
At least five attacks with: • 4-72 hour duration • At least two of: unilateral location	At least two attacks with: • Aura with visual, sensory, and/or language symptoms, each completely reversible • At least two of:

pulsating pain moderate or severe intensity aggravation by or causing avoidance of physical activity during the attack. • At least one of: nausea and/or vomiting • No other apparent causes	1. At least one aura symptom spreads gradually over > 5 minutes and/or two or more symptoms occur in succession. 2. Individual aura symptoms last 5-10 minutes. 3. At least one aura symptom is unilateral 4. The aura is accompanied, or followed within 60 minutes, by headache. • Not better accounted for by another diagnosis

Approach for Management

The management of CM requires pharmacological and non-pharmacological interventions; additionally, appropriate management of CM must consider the patient's comorbidities, preferences and needs, migraine features, frequency, severity, and the impact on the quality of life [8]. The first step in migraine management is to identify and manage the triggers such as sleep deprivation, alcohol, hunger or dehydration, and prolonged exposure to a strong stimulus (light, sounds, strong scents), as well as to identify the possibility for medication overuse headache (MOH) [8]. Interestingly, certain foods such as chocolate, aged cheeses, red wine, monosodium glutamate, and aspartate; however, this topic is not supported by scientific researches and is an area of debate [8].

Since migraine is an unpredictable condition, patients may become free of symptoms for a specific time and vice versa; consequently, CM patients may require treatment adjustments over time [8]. Pharmacological interventions include treatment for acute attack or prophylactic, and the role of acute treatment is to quickly cease the migraine symptoms [8]. While preventive medications require several weeks or longer to begin the effect, it cannot substitute for acute drugs and vice versa [8]. This literature review will focus on the preventive measures of CM, and acute treatment and non-pharmacological treatment are beyond this review's scope.

Preventive Treatment

The pharmacological prophylactic treatment is used if the patient has recurrent attacks of migraine [10]. Many pharmacological options are available, including those approved by the Food and Drug Administration (FDA) [10], including anti-epileptic drugs, antidepressants, beta-blockers, calcium channel blockers, serotonin antagonists, botulinum neurotoxins, NSAIDs, and others [11]. Nevertheless, these drugs are associated with low adherence rates, and CM patients have less than 30% adherence rate after six months of therapy initiation [10]. In the United States, around 40% of migraine patients, almost 12 million people are candidates for prophylactic therapy, but only one fifth (19.6%) receives migraine-specific preventive treatment [12]. The goal of migraine preventive therapy is to reduce the severity and frequency of migraine attacks and make the attack more responsive to acute treatment; hence, improving the quality of life for those patients [13]. US, Canadian, and European guidelines have established the indications for prophylactic migraine therapy; these indications are summarized in Table. 2 [11].

The impact of prophylactic migraine therapy has been demonstrated by Silberstein and colleagues [11]. They found that, during the second six months of initiation preventive therapy, migraine diagnosis-related office and other outpatient visits decreased by 51.1%, emergency diagnosis of migraine attack decreased 81.8%, CT scans decreased 75%, MRIs decreased 88.2%, and various migraine drugs dispensation decreased 14.1% [11]. Preventive therapy can be preemptive, short term, or maintenance [11]. Preemptive therapy is usually used when a known trigger exists, such as exercise or sexual activity; consequently, the patient must be instructed to administer the prophylactic medication before the trigger [11]. Short-term prevention is preferred if the patient is undergoing a time-limited exposure to a provoking factor, such as menstruation or high attitude [11]. Maintenance preventive therapy is used when the patient needs continuous treatment [11].

Table 2. Indications for Prophylactic Migraine Treatment [11]

• Recurrent migraine attacks significantly interfere with a patient's quality of life and daily routine despite trigger management, appropriate use of acute medications, and lifestyle modification strategies.
• Frequent headaches (four or more attacks per month or eight or more headaches days per month).
• Failure of, contraindication to, overuse of, or troublesome side effects from acute medications.
• Patient preference, that is, the desire to have as few acute attacks as possible.
• Presence of certain migraine conditions: hemiplegic migraine (now called migraine with brainstem aura); frequent, prolonged, or uncomfortable aura symptoms; or migrainous infarction.

Gabapentin

Gabapentin was introduced in the United States in 1994 as an anticonvulsant therapy, and it has an antinociceptive (analgesic) effect as well [13]. Recently, gabapentin has been frequently used in neuropathic pain treatment, such as diabetic neuropathy, postherpetic neuralgia, and trigeminal neuralgia [13]. The mechanism of action is not entirely understood, but it though that it modulates the α2δ subunit of Ca^{+2} channels to enhance and increase the concentration and presumably the synthesis rate of GABA in the brain [13, 14]. The pervasion of α2δ-1 Ca^{+2} channels in the brain and spinal cord likely related

to gabapentin's benefit in seizure, pain, and many other disorders [15]. It may also decrease the release of inflammatory neuropeptides that influence headache pain, such as substance P and calcitonin gene-related peptide (CGRP) [15]. Besides, gabapentin may reduce the release of excitatory neurotransmitters, such as glutamate [15].

Gabapentin was approved by the U.S FDA on December 30, 1993, to treat partial seizure as adjuvant therapy, with and without secondary generalization, in patients above the age of 12 years [14, 16]. It is an amino acid with a similar structure to the inhibitory neurotransmitters GABA; however, its antiepileptic effect does not seem to be associated with any direct impact on the GABAergic system [16]. Besides, it has been effectively used in bipolar disorder, peripheral neuropathy, diabetic neuropathy, complex regional pain syndrome, trigeminal neuralgia, a periodic limb movement disorder of sleep, migraine headaches, and drug and alcohol withdrawal syndrome [12]. The commonly reported side effects include somnolence (20%), dizziness (18%), ataxia (13%), and fatigue (11%) [12]. Gabapentin has no particular risk of fetal malformations, although it was found to be related to low birth weight and preterm birth [14].

One double-blind, randomized placebo-controlled study on the preventive effect of gabapentin 1200mg/day in 63 patients with migraines over three months was directed [12]. The study showed a statistically significant reduction in the number of attacks, and the intensity of migraines in patients who received gabapentin [12]. Gabapentin was tolerated well with few adverse effects [12]. Mathew et al. concluded that gabapentin was effective and fully tolerated in migraine's preventive treatment [17]. Further, a double-blind, multicenter placebo-controlled trial was using a baseline of four weeks followed by an eight weeks double-blind treatment phase with a dose of 2400 mg per day concluded a statistically significant number of patients with at least a 50% reduction in the four weeks migraine rate and the number of days per four weeks period with an attack of migraine [14]. Another trial of three months of gabapentin 1200mg/day has decreased migraine's intensity and frequency [14]. Furthermore, gabapentin is commonly prescribed as prophylactic therapy for non-migrainous headache [14]. A meta-analysis of certain studies showed little evidence that gabapentin, in any dose, is effective in prophylactic migraine therapy [18]. Importantly, dose-comparison found that gabapentin 2000 mg/day is no more efficient than 1200 mg/day [18].

Gabapentin withdrawal symptoms

It is unadvisable for abrupt discontinuation of gabapentin due to the risk of withdrawal symptoms, and these symptoms are similar to alcohol or benzodiazepine withdrawal [19, 20]. Due to the augmented effect of gabapentin on the GABA, the same neurotransmitter augmented by alcohol and benzodiazepines, it is judiciously used to treat alcohol withdrawal symptoms [19]. Gabapentin withdrawal symptoms include irritability, agitation, anxiety, tachycardia, tremor, diaphoresis, myalgia, and gastrointestinal upset [19, 20]. Further, one patient report flu-like symptoms with gabapentin withdrawal, and it was the first reported association between gabapentin withdrawal and flu-like symptoms [20].

Pregabalin

Pregabalin is broadly used to treat neuropathic pain, partial seizure, spinal cord damage, and was approved by the FDA in 2007 for fibromyalgia treatment [21, 22]. Pregabalin has believed to bind the α2δ subunit of the voltage-gated Ca^{+2} channel, resulting in channel blockade and reduces the Ca^{+2} influx at neuron terminal and consequently decrease the synaptic release of several excitatory neurotransmitters such as glutamate, noradrenaline, and substance P [22, 23]. Yet, unlike gabapentin, pregabalin was not shown to bind to $GABA_B$ receptors [23]. The mechanism of action of pregabalin is consistent with the theory of glutaminergic mechanism in migraine pathophysiology; to clarify, plasma and cerebrospinal fluid glutamate levels were found to be high and that levels have been significantly reduced after administering pregabalin preventive therapy for migraine [21]. Generally, pregabalin has no serious adverse effects and is considered a safe drug with good patient tolerance [22, 24]. Common adverse effects include nausea, dizziness, dry mouth, and body weight increase [24]. Calandre et al. reported that pregabalin is tolerated well, but 33.3% of patients exhibited dose-dependent side effects, particularly after dosage adjustment [22].

In an open-label study, pregabalin showed to be associated with moderate but clinically significant improvement in attack frequency, pain severity, intake of NSAIDs, and triptan use in patients with refractory CM [21]. Notably, there was a reduction in migraine-associated disability as measured by the HIT-6 scores [21]. An observational study concluded that after one and three months of using pregabalin, there was a significant reduction in mean days with headache per month [22]. Almost one-quarter of the study sample has a response rate equal to or more than 50% regarding decreasing numbers of daily headaches per month [22]. Also, pregabalin was tested to relieve migraine-associated allodynia that is present in 65.1% of the sample population and related to the patient gender (female) [24]. Among the 41 CM patients who received pregabalin preventive therapy, three patients (7.3%) had symptoms relieved completely; additionally, medication was moderately effective, mildly effective, or ineffective for 12 patients (29.3%), 20 patients (48.8%), and six patients (14.6%) respectively [24]. The MIDAS and HIT-6 scores were significantly reduced after treatment [24]. Anti-epileptic drugs such as gabapentin and pregabalin may have better preventive results in the elderly population than other therapeutic options due to few side effects on the cardiovascular system and mood disorders such as anxiety and depression, which are relatively common in the elderly [22].

Conclusion

Migraine is a chronic neurological disorder manifested by episodic attacks of headache associated with nausea, vomiting, photophobia, phonophobia, and aura. It is more prevalent in females, with an overall prevalence of 1% to 2% of the general population. Migraine can significantly impair patients' quality of life, including performing routine daily activities, build and maintain family, social, and community relationships. Migraine preventive therapy aims to reduce the frequency and severity of headache attacks, increase attack response to acute treatment, and improve overall life quality. Anti-epileptic drugs, especially gabapentin and pregabalin, have shown some promising prophylactic effect for chronic migraines. Moreover, with the few adverse effects, it seems suitable for older patients due to their safety profile on the cardiovascular system and elderly mood disorders. These studies have some limitations, but it can signify the positive impact of gabapentin and pregabalin and, to some extent, justify their use in CM preventive therapy. Therefore, a randomized-double-blind clinical trial is strongly recommended to establish these drugs' efficacy and safety in migraine preventive treatment.

References

1. Manack AN, Buse DC, Lipton RB. Chronic migraine: epidemiology and disease burden. Curr Pain Headache Rep. 2011 Feb;15(1):70-8. doi: 10.1007/s11916-010-0157-z. PMID: 21063918.
2. Becker WJ. The Diagnosis and Management of Chronic Migraine in Primary Care. Headache. 2017 Oct;57(9):1471-1481. doi: 10.1111/head.13089. Epub 2017 May 26. PMID: 28548676.
3. D'Amico D. Pharmacological prophylaxis of chronic migraine: a review of double-blind placebo-controlled trials. Neurol Sci. 2010 Jun;31 Suppl 1:S23-8. doi: 10.1007/s10072-010-0268-7. PMID: 20464578.
4. Shakeri H, Rahmanian V, Shakeri M, Mansoorian E. Study Of Anti-Hbs Antibody Titer And Associated Factors Among Healthcare Staff Vaccinated Against Hepatitis B More Than Ten Years In Hospitals Of Jahrom In 2016. Pharmacophore. 2018;9(1):156-61.
5. Sundus A, Ismail NE, Gnanasan S. Exploration of healthcare practitioner's perception regarding pharmacist's role in cancer palliative care, Malaysia. Pharmacophore. 2018;9(4):1-7.
6. Antony VC, Azeem K. Health-Related Quality of Life among Saudi Undergraduate Students with Different Categories of Body Mass Index. Int. j. pharm. res. Allied sci. 2019;8(2):15-21.
7. Zhytnik T, Yermak H, Moskalyova L, Podplota S, Fedorova O, Liapunova V. Socio-Psychological Aspects of HIV Infection Prevention among First-Year University Students as a Health-Saving Factor. Int. j. pharm. res. Allied sci. 2020;9(1):1-8.
8. Kahriman A, Zhu S. Migraine and Tension-Type Headache. Semin Neurol. 2018 Dec;38(6):608-618. doi: 10.1055/s-0038-1673683. Epub 2018 Dec 6. PMID: 30522135.
9. Bagnato F, Good J. The Use of Antiepileptics in Migraine Prophylaxis. Headache. 2016 Mar;56(3):603-15. doi: 10.1111/head.12781. Epub 2016 Mar 3. PMID: 26935348.
10. Turner DP, Golding AN, Houle TT. Using a graphical risk tool to examine willingness to take migraine prophylactic medications. Pain. 2016 Oct;157(10):2226-2234. doi: 10.1097/j.pain.0000000000000630. PMID: 27820159; PMCID: PMC5433431.
11. Silberstein SD. Preventive Migraine Treatment. Continuum (Minneap Minn). 2015 Aug;21(4 Headache):973-89. doi: 10.1212/CON.0000000000000199. PMID: 26252585; PMCID: PMC4640499.
12. Zain S, Khan M, Alam R, Zafar I, Ahmed S. Comparison of efficacy and safety of topiramate with gabapentin in migraine prophylaxis: randomized open-label control trial. J Pak Med Assoc. 2013 Jan;63(1):3-7. PMID: 23865122.
13. Mathew NT, Rapoport A, Saper J, Magnus L, Klapper J, Ramadan N, Stacey B, Tepper S. Efficacy of gabapentin in migraine prophylaxis. Headache. 2001 Feb;41(2):119-28. doi: 10.1046/j.1526-4610.2001.111006119.x. PMID: 11251695.
14. Marmura MJ, Kumpinsky AS. Refining the Benefit/Risk Profile of Anti-Epileptic Drugs in Headache Disorders. CNS Drugs. 2018 Aug;32(8):735-746. doi: 10.1007/s40263-018-0555-z. PMID: 30073584.
15. Perloff MD, Berlin RK, Gillette M, Petersile MJ, Kurowski D. Gabapentin in Headache Disorders: What Is the Evidence? Pain Med. 2016 Jan;17(1):162-71. doi: 10.1111/pme.12931. PMID: 26398728.
16. Mack A. Examination of the evidence for off-label use of gabapentin. J Manag Care Pharm. 2003 Nov-Dec;9(6):559-68. doi: 10.18553/jmcp.2003.9.6.559. PMID: 14664664.
17. Schoonman GG, Wiendels NJ, Ferrari MD. Gabapentin in migraine prophylaxis: is it effective and well-tolerated? Headache. 2002 Mar;42(3):235. doi: 10.1046/j.1526-4610.2002.02060.x. PMID: 11903552.
18. Linde M, Mulleners WM, Chronicle EP, McCrory DC. Gabapentin or pregabalin for the prophylaxis of episodic migraine in adults. Cochrane Database Syst Rev. 2013 Jun 24;2013(6): CD010609. doi: 10.1002/14651858.CD010609. PMID: 23797675; PMCID: PMC6599858.
19. Norton JW. Gabapentin withdrawal syndrome. Clin Neuropharmacol. 2001 Jul-Aug;24(4):245-6. doi: 10.1097/00002826-200107000-00011. PMID: 11479399.
20. Tran KT, Hranicky D, Lark T, Jacob Nj. Gabapentin withdrawal syndrome in the presence of a taper. Bipolar Disord. 2005 Jun;7(3):302-4. doi: 10.1111/j.1399-5618.2005.00200.x. PMID: 15898970.

21. Calandre EP, Garcia-Leiva JM, Rico-Villademoros F, Vilchez JS, Rodriguez-Lopez CM. Pregabalin in the treatment of chronic migraine: an open-label study. Clin Neuropharmacol. 2010 Jan-Feb;33(1):35-9. doi: 10.1097/WNF.0b013e3181bf1dbe. PMID: 19935409.
22. Pizzolato R, Villani V, Prosperini L, Ciuffoli A, Sette G. Efficacy and tolerability of pregabalin as preventive treatment for migraine: a 3-month follow-up study. J Headache Pain. 2011 Oct;12(5):521-5. doi: 10.1007/s10194-011-0338-0. Epub 2011 Apr 9. PMID: 21479703; PMCID: PMC3173619.
23. Puppe A, Limmroth V. GABAergic drugs for the treatment of migraine. CNS Neurol Disord Drug Targets. 2007 Aug;6(4):247-50. doi: 10.2174/187152707781387305. PMID: 17691980.
24. Zhang N, Chen CF, Yu FY. Effects of pregabalin on central sensitization in patients with migraine. Int J Clin Pharmacol Ther. 2015 Apr;53(4):277-83. doi: 10.5414/CP202205. PMID: 25669613.