A COMPLETE REVIEW OF MIGRAINE

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ABSTRACT

Migraine characterized by recurrent headaches present with aura or without aura. Various treatment modalities ranging from 5-hydroxytryptamine 1B/1D agonists, non-steroidal anti-inflammatory drugs to steroids are available for acute treatment of migraine. Prophylaxis for chronic migrainous cases is usually with β blockers, calcium channel blockers, and antiepileptics. Even many nutraceutical preparations are helpful in migraine including riboflavin, vitamin b12. This review focuses on the newer agents available for treatment of migraine with some insight into their clinical trials.

Keywords: Headache, Nutraceutical, Prophylaxis, Triptans, Cortical spreading depression.

INTRODUCTION

The word “migraine” is from the Greek ἡμικρανία (hemikrania), “pain on one side of the head,” from ἡμι- (hemi-), “half,” and κρανίον (kranion), “skull.” The disorder may also be described as a vascular headache associated with changes in the size of arteries within and outside the brain [1]. It is usually accompanied by a plethora of comorbidities influencing its clinical expression and complicating its treatment and is a chronic and debilitating neurological disorder. It is polygenetic with high susceptibility to epigenetic factors affecting millions of people worldwide. This is mainly because of changes in hormonal levels. 15% of people suffer from migraine worldwide with 1.4-2.2% suffering from chronic migraine [2,3]. Global data show prevalence of migraine increasing during adolescence with peaks in midlife and the prevalence declining rapidly after 50 years. Migraine presents as headache, visual, auditory, olfactory, and cutaneous stimuli hypersensitivity along with nausea and vomiting [4]. Both environmental and genetic factors play a role in development of migraine with more than two-thirds cases having familial history [5]. Boys are more affected than girls before puberty compared to women more affected than men as age increases [6].

SIGNS AND SYMPTOMS

Migraines are self-limiting usually presenting as recurrent severe headache. It is associated with autonomic symptoms. It presents with aura in 15-30% and without aura in the rest [7]. Migraine varies from person to person with respect to severity of pain, duration of attack, and its frequency. A migraine lasting longer than 72 hrs is termed status migrainosus. Different phases of migraine include the prodrome, aura, pain, and postdrome. The prodromal phase occurs 4-72 hours before the headache in 60% of patients, the aura usually precedes headache in 15-20%, severe headache occurs in the pain phase, and postdromal phase usually follows the attack of migraine [8].

THE PATHOPHYSIOLOGY OF MIGRAINE

The best solutions to medical conditions come only from understanding the pathophysiology of the disease state. As per Wolff’s vascular theory, vascular constriction leading to hyperperfusion of cortex later followed by vascular dilation was put forward as the main pathophysiological mechanism. Currently, neurovascular hypothesis involving the trigeminovascular system is considered. Other hypothesis includes mutations of neuronal calcium channels leading to hypersensitivity resulting in migraine attacks. It is also postulated that increased dopaminergic activity in thalamus/hypothalamus causing modulation in central pain pathways also plays a role in migraine attacks. Other mechanisms put forward include cortical spreading depression (CSD), release of vasoactive peptides like substance P, calcitonin gene-related peptide (CGRP), from trigeminal neurons, nitric oxide (NO), serotonin, excess activation of N-methyl-D-aspartate receptor (NMDA) receptors without modulation by brain stem pain centers due to dysfunction of these centers, over activity of excitatory neurotransmitters such as aspartate, and glutamate causing neuronal excitability, and finally, neurogenic inflammation plays an important role in migraine attack development [9-12].

TREATMENT OF MIGRAINE

It can be divided into treatment of acute attacks and treatment of chronic migraine. As per the United States Consortium (2000) recommended guidelines [13] for treatment of acute migraine include pharmacological and non-pharmacological modalities as shown in Table 1.

Specific treatment

Triptans

Triptans are selective agonists at 5-hydroxytryptamine 1B (5-HT1B) and 1D. Mechanism of action includes intracranial vessel vasoconstriction (5-HT1B), peripheral neuronal inhibition (5-HT1D), and presynaptic dorsal horn stimulation (5-HT1D) producing second-order brain stem neuronal inhibition. Triptans influence the function of 5-HT1F receptors and enhance descending inhibitory pain pathways. Triptans reduce pain severity in 2 hrs per randomized controlled trials (RCTs). Oral formulations are usually preferred over other formulations, but 6 mg subcutaneous injection of sumatriptan appears to be the most efficacious. As per the current evidence, all oral formulations have equal efficacy except for frovatriptan which is less efficacious but has longer duration action. Parenteral preparations are more useful than oral preparations, but the choice of medications depends on clinician as well as the patient. Triptans are the first-line drugs used in acute treatment of moderate-to-severe migraine with best pain relief occurring if it is taken within 30 minutes of attack, and a second dose is usually recommended after 2-4 hrs of initial dose. It is best used in combination with antiepileptics and non-steroidal anti-inflammatory drugs (NSAID’s). Adverse effects include serotonin syndrome when used in combination with selective serotonin reuptake inhibitors and it should be used with caution in patients having ischemic heart disease [14-22]. Characteristics of triptans are summarized in Table 2.

Ergot and derivatives

Ergots act on multiple receptors including 5HT, and this accounts for robust side effect profile. It is used in acute management of migraine. Side effect includes nausea as well as due to severe vasoconstriction. It
is contraindicated in patients with vascular disease, hepatic problems, renal dysfunction, and in hypertensives. It is avoided in pregnancy. Dihydroergotamine (DHE) is the only preparation available and is used both parentally as well as intranasally. Repeated administration of DHE is very effective in refractory cases as well as status migraine. It is very safe and effective, but it requires hospital administration [23-25].

**Non-specific treatment**

**NSAIDs**

Good quality evidence supports the use of NSAID’s alone or in combination with specific agents. NSAID’s in combination with antiemetics are comparable to oral triptans. Recently, powdered preparation of diclofenac sodium is approved for treatment of acute attack. Intravenous (IV) ketorolac can be used for emergency management of migraine. NSAID’s needs to be used with caution in patients with renal toxicity [26-29]. Characterized of different NSAID’s are summarized in Table 3.

**Neuroleptics/antiemetics**

Dopamine d2 receptors antagonists can be used alone or in combination to treat headache as well as to treat nausea. It is mostly used in emergency settings and is available in oral, parenteral, and suppository forms but concerns over extrapyramidal side effects, tardive dyskinesia, and lack of familiarity in their effect on migraine attacks restricts their use to a great extent [30-33]. Characteristics of antiemetics are summarized in Table 4.

**Corticosteroids**

Steroids are suggested for acute treatment as well as for status migranosus [34]. It acts by reducing the neurogenic inflammation and reduction of vasogenic edema and also plays important role in central serotonergic pathways [35]. One study showed addition of dexamethasone 4 mg per oral to triptans plus NSAID reduces recurrence and is well tolerated in patients with frequent attacks [36,37].

**Opioids**

It is the most prescribed drug for acute and rescue therapy in migraine in America. Recent studies have discouraged the use of opioids mainly because it decreases gray matter, increases CGRP release, releases pro-inflammatory peptides, and also causes glutamate receptor activation. It also results in degmalanization of mast cells and causes vasodilation. Side effects are also high and result in overuse headache and disease progression [38,39].

**NEWER AGENTS**

**CGRP antagonists**

Based on migraine pathology theories, trigeminal ganglion activation causes activation of nociceptive neurons which leads to subsequent release of CGRP. Increased CGRP levels cause plasma protein extrusion, vasodilation, and mast cell degranulation ultimately leading to neurogenic inflammation. Drugs which antagonize CGRP include olcegepant, telcagepant, MK-3207, and BI-44370TA [40]. Prevents binding of endogenous CGRP on its receptors and suppresses the stimulation of CGRP on trigeminal ganglion neurons. It inhibits CSD. They lack vasoconstrictive effect. Olcegepant is as effective as oral triptans with less cardiovascular side effects such as blood pressure increase and tachycardia. However, one major limitation is IV dosing. Telcagepant was initially claimed to be as potent as rizatriptan causing pain relief in 2 hrs and also sustained pain relief at 2.4 hrs and relief of migraine-associated symptoms with overall good tolerability profile, but later, the Phase 2 trial was terminated claiming the drug showed increase in liver transaminases [40].

**Lasmiditan**

It is 5-HT1F Receptor agonist. In experiment model, it blocks neurogenic inflammation, decreases c-Fos expression, and lacks vasoconstriction.

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### Table 1: Treatment of acute migraine attacks

| Specific treatment | Triptans | Ergot and its derivatives | Non-specific treatment | Antiemetics | NSAIDs and non-narcotic analgesics | Narcotics – Opiate analgesics |
|--------------------|----------|---------------------------|-----------------------|-------------|----------------------------------|-------------------------------|
| Group 1: Fast acting | Sumatriptan | 3 | 200 mg oral | 40 mg intranasal | 12 mg subcutaneous | Prochlorperazine, Ondansetron |
| Rizatriptan | 2-3 | 30 mg (if on propranolol) | | | | |
| Almotriptan | 3-4 | 25 mg | | | | |
| Zolmitriptan | 3 | Two tablets or 10 mg maximum oral daily dose. Two sprays or 10 mg intranasal | 80 mg | | | |
| Eribitran | 4 | | | | | |
| Group 2: Slow acting triptans | Frovatriptan | 26 | 7.5 mg | | | |
| Naratriptan | 6 | 5 mg | | | | |

### Table 2: Triptan characteristics

| Drugs | Half-life (hrs) | Maximum daily dose |
|-------|---------------|--------------------|
| Aspirin | Tablet/oral solution | 650-1000 mg |
| Ketorolac | Tablet | 10 mg |
| Ketoprofen | Capsule | 50-75 mg |
| Ketoprofen-extended release | Capsule | 200 mg |
| Diclofenac potassium | Tablet/powder | 50 mg |
| Meclofenamate | Capsule | 50 mg, 100 mg |
| Ibuprofen | Capsule, tablet, oral suspension | 400-1 mg |
| Etorodolac | Tablet/capsule | 200-500 mg |
| Naproxen | Tablet | 120-550 mg |
| Naproxen-controlled release | Tablet | 750-850 mg max |

### Table 3: NSAID’s characteristics

| Drugs | Formulation | Dose used |
|-------|-------------|-----------|
| Aspirin | Tablet/oral solution | 650-1000 mg |
| Ketorolac | Tablet | 10 mg |
| Ketoprofen | Capsule | 50-75 mg |
| Ketoprofen-extended release | Capsule | 200 mg |
| Diclofenac potassium | Tablet/powder | 50 mg |
| Meclofenamate | Capsule | 50 mg, 100 mg |
| Ibuprofen | Capsule, tablet, oral suspension | 400-1 mg |
| Etorodolac | Tablet/capsule | 200-500 mg |
| Naproxen | Tablet | 120-550 mg |
| Naproxen-controlled release | Tablet | 750-850 mg max |

### Table 4: Antiemetics characteristics

| Drug | Formulation | Dose of migraine |
|------|-------------|------------------|
| Prochlorperazine | Tablet, suppository | 5-10 mg |
| Metoclopramide | Tablet | 25 mg |
| Chlorpromazine | Tablet | 10 mg |
| Promethazine | Tablet | 25-50 mg |
| Ondansetron | Tablet, oral disintegrating tablet | 4 mg |

Main postulated mechanisms include inhibition of protein leakage, blockage of secondary trigeminal neuronal activation, and inhibition of neuropeptide release like glutamate. Double-blind placebo controlled parallel group study in 512 patients: Oral form and dose of 50, 100, 200, and 400 mg in moderate-to-severe migraine proved that is as effective as sumatriptan without causing vasodension, but major drawback is major central nervous system (CNS) side effects. Studies also show
high improvement in headache response in 2 hrs but also show high 24-h headache recurrence rate [41].

Tezampanel
- Competitive antagonist of the α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) and kainate receptor (subtype GluR) of the ionotropic glutamate receptor family. Randomized triple-blind parallel group double dummy, multicenter trial showed that 1.2 mg/kg tezampanel had (69%) headache response rate when compared to 6 mg/kg x c sumatriptan which had a response rate of 86%. Effective and well tolerated in migraine. It can be used only through IV route dasolampanel is an orally bioavailable analog of tezampanel. Both the drugs were never marketed [42].
- Other newer agents are summarized in Table 5.

Prophylaxis
It is indicated when a patient meets the following criteria [43]:
- 2 or more attacks/month
- Recurring migraines – significantly interfere with daily activity
- Contraindication/failure/overuse-acute therapies
- Overwhelming costs of acute therapies
- Uncommon migraine conditions – hemiplegic, basilar migraine.

Beta-blockers
Various beta-blockers used are summarized in Table 6. The mechanisms by which they act include inhibition of central beta receptors antagonize 5-HT1A and 5-HT1B receptors thereby reducing neuronal excitability. Inhibits NO production by blocking inducible NO synthase and inhibits excitatory activity of glutamate thereby reducing neuronal activity. They also inhibit kainate-induced currents (synergistic with NMDA blockers) and reduce neuronal activity and also have additional membrane stabilizing action [44,45].

Carvedilol - Novel B-blocker in migraine
In an open-label trial of 76 patients, a dose of 3.125-6.25 mg twice a week was used and was found that 60% of patients had 50% reduction in monthly migraine attack frequency and severity, but in 26% patients, there was a lack of efficacy with the drug [46].

Calcium channel blockers
Inhibits calcium entry and prevents intoxication of cells exposed to cerebral hypoxia due to CSD [47]. Various drugs used are summarized in Table 7. Other possible mechanisms include inhibition of 5-HT release, inhibition of neurovascular inflammation, and CSD.

ANTIEPILEPTICS
Divalproex sodium
It is a combination of valproic acid and sodium valproate. It is used at a dose of 500-1500 mg/day. Mechanisms include prolongation of sodium channel inactivation, suppression of calcium-mediated T current, inhibit gamma-aminobutyric acid (GABA) transaminase.
headache and refractory to other preventive therapies were given a dose of 100-600 mg every 3rd day. Results showed 65% of patients reduction in frequency of migraine attacks [53].

**Antidepressants**

Possible mechanisms include reuptake inhibition of serotonin and noradrenaline, α-adrenergic and NMDA – receptor antagonism, sodium and calcium channel blocking action, and potassium channel activation. Increase in GABA receptor action and opioid receptor binding/-opioid-mediated effect are other minor actions. Reduces inflammation by decreasing the synthesis of prostaglandin E2 and decreasing the level of tumor necrosis factor α. Various drugs are summarized in Table 8. Venlafaxine is used at a dose of 75-225 mg. A double-blind placebo controlled trial showed venlafaxine better than placebo. Start with 37.5 mg extended release tablet, week followed by 75 mg for another week, then 150 mg extended release in the morning [54].

**DRUGS ACTING ON RENIN ANGIOTENSIN SYSTEM**

Renin angiotensin system plays a role in neurogenic inflammation and causes increased susceptibility to oxidative stress. It also causes endothelial dysfunction and neuromodulation in nociception. Lisinopril alters sympathetic activity and inhibits free radical activation. It also increases prostacyclin synthesis and blocks the degradation of bradykinin, substance P, and encephalin. In a double-blind placebo controlled crossover study, patients aged 19-59 years with migraine were treated with 20 mg lisinopril for 11 weeks. 21% of patients showed 50% reduction in migraine attacks [55]. In a comparative study of candesartan versus propranolol for migraine prophylaxis, 72-43% patients showed >50% reduction in migraine and it was equally efficacious to propranolol [56].

**Onabotulinum toxin**

FDA approved drug for prophylaxis of migraine at a dose of 100 IU. It is used in a chronic headache.

Moreover, it is injected in craniofacial muscles usually the temporalis. It inhibits neurogenic inflammation by inhibiting the release of noiceptive mediators such as glutamate, substance P, and CGRP from peripheral terminals of efferent nerves. The analgesic action of on a botulinum toxin is central yet to be proved. It is is effective after three hours of injection and the action lasts for seven days. Novel delivery routes such as topical/subcutaneous applications are under research [57].

**H₂ agonists**

Used to limit the excessive inflammatory response through H₂ receptor activation. Drugs include Ne-methyl histamine and investigational drug SCH 50971. Phase III double-blind placebo controlled trial for 12 weeks in 60 patients with dose of 1-3 mg twice a week caused reduction in headache frequency, intensity, and duration in 80% of patients. Decreases in the use of analgesics was also noted [58].

**Tonabersat**

Preclinical studies show inhibition of CSD. It inhibits neurogenic inflammation and also inhibits the gap junctional intercellular communication between neurons and satellite glial cells. Various randomized double-blind parallel group placebo controlled multicenter studies for acute migraine were tried. Conflicting reports of headache relief at 2/4 hrs and reasons unfound. In one study with 40 mg on 39 patients, it was found to be effective for migraine with aura when compared to without aura, reinforcing its inhibitory effect on CSD [59].

**NUTRACEUTICALS IN MIGRAINE**

**Magnesium**

Multiple studies show migraine is associated with low levels of magnesium. Magnesium causes influx of calcium into neurons causing glutamate release into neurons causing neuronal activation.

Onset and propagation of CSD are delayed and decreases. It also causes change in neurotransmitter secretion and intensifies the secretion of substance P. Used in patients with aura and perimenstrual migraine. Used at a dose of 1 g IV and 300-600 mg orally of chelated magnesium (taurate, glycinate, and oxide). Magnesium + L-carnitine are a newer preparation available [60].

**Coenzyme Q 10 (CoQ)**

It promotes electron transfer from Complex I and Complex II to cytochrome C and helps in adenosine triphosphate (ATP) production. Protects mitochondria from free radical damage. Study of 1478 migraine patients from 3 to 22 years of age showed low levels of CoQ in 33% of patients. Randomized control trial of 42 patients receiving 100 mg TID for 3 months found it superior to placebo and 48% of patients has >50% reduction in migraine attacks [61].

**Riboflavin**

It is a co-factor in the Krebs cycle. Abnormal phosphorylation of adenosine diphosphate to ATP is prevented with riboflavin. Randomized control trial with 400 mg riboflavin taken daily for 3 months was superior to placebo for reduction of migraine frequency [62]. Randomized control trial with 400 mg of riboflavin + feverfew + low dose magnesium was comparable to a 25 mg of active riboflavin. Greater than 40% of patients showed 50% reduction in migraine attacks [63].

**Vitamin B12**

It helps in conversion of homocysteine to methionine. Studies show vitamin B12 deficiency that causes increase levels of urine methylmalonic acid levels in patients and worsens migraine. Possible mechanism of vitamin B12 in migraine includes its excitatory role in the CNS by acting on NMDA receptors. It also plays a significant role in initiation, duration, and progression of migraine and activation of trigeminovascular system [64].

**Feverfew**

It sold as capsules of dried leaves of the weed plant Tanacetum parthenium. Animal models show feverfew acts by inhibition of nitroglycerine-induced Fos expression and inhibition of nuclear factor kappa-B. Open-label trial with T. parthenium (300 mg) + Salix alba (white willow) for 12 weeks showed decrease in pain intensity and duration of migraine randomized double-blind placebo controlled trial (riboflavin 400 mg + magnesium 300 mg + feverfew 100 mg) for 3 months, positive results were seen. Recently two trials with purified stable extract of feverfew and MIG99 showed very low clinical effects with various complications and was ineffective in the treatment of migraine [65].

**Petasites (butterbur root)**

*Petasites hybridus* is a very poisonous plant, and detoxified root extract is safe. Mechanisms include inhibition of the synthesis of leukotrienes. It also decreases the intracellular concentration of calcium and used in the prophylaxis of migraine in children. A small study of 100 mg/day and larger study of 150 mg/day versus placebo have shown efficacy [66].

**CONCLUSION**

With many newer agents now under clinical trials as well as in use, physicians should be aware of these drugs and their side effects, so they can use these agents for treating recurrent and chronic cases of migraine. Furthermore, further well-designed clinical trials are needed to prove the efficacy of these agents in treatment of migraine. Hence, further research is needed to find out the safest and effective treatment for a chronic migraine, further designing of proper animal models for
studying migraine, to identify newer drug targets and how to prevent the migraine at the patient level from acute attack going in for chronic attack.

REFERENCES

1. Timothy SY, Mava Y, Bashir HJ, Bwala AY. Impact of weather conditions on migraine in north eastern Nigeria. Int J Pharm Sci 2011;3(3):133-6.
2. Vos T, Flaxman AD, Naghavi M, Lozano R, Michaud C, Ezzati M, et al. Years lived with disability (YLDs) for 1160 sequelae of 289 diseases and injuries 1990-2010: A systematic analysis for the global burden of disease study 2010. Lancet 2012;380(9859):2163-96.
3. Natoli JL, Manack A, Dean B, Butler Q, Turkel CC, Stovner L, et al. Global prevalence of chronic migraine: A systematic review. Cephalalgia 2010;30(5):599-609.
4. Abeer AK, Gihan SL. Flash dissolving sublingual almotriptan malate lyotabs for management of migraine. Int J Pharm Sci 2017;9(1):125-31.
5. Headache Classification Subcommittee of the International Headache Society. The International Classification of Headache Disorders: 2nd ed. Cephalalgia 2004;24 Suppl 1:9-160.
6. Lay CL, Broner SW. Migraine in women. Neurol Clin 2009;27(2):503-11.
7. Gilmore B, Michael T. Treatment of acute migraine headache. Am Fam Physician 2011;83(3):271-80.
8. Aminoff MJ, Simon RP, Greenberg DA, Michael J. Clinical Neurology. ed. New York, NY: Lange Medical Books/McGraw-Hill; 2009. p. 85-8.
9. Gasparini CF, Sutherland HG, Griffiths LR. Studies on the pathophysiology and genetic basis of migraine. Curr Genomics 2013;14(5):300-15.
10. Sarrouilhe D, Dejean C, Mesnil M. Involvement of gap junction channels in the pathophysiology of migraine with aura. Front Physiol 2014;5:78.
11. Kaiser EA, Russo AF. CGRP and migraine: Could PACAP play a role too? Neuropeptides 2013;47(6):451-61.
12. Calra AA, Elliott D. Acute migraine: Current treatment and emerging therapies. Ther Clin Risk Manag 2007;3(3):449-59.
13. Loder E. Triptan therapy in migraine. N Engl J Med 2010;363(1):63-70.
14. Fox AW. Onset of effect of 5-HT1B/1D agonists in migraine. Headache 2008;48(6):914-20.
15. Lipton RB, Stewart WF, Stone AM, Láinez MJ, Sawyer JP; Disability in Strategies of Care Study group. Stratified care versus step care therapies. Ther Clin Risk Manag 2007;3(3):449-59.
16. Ferrari MD, Goadsby PJ, Roon KI, Lipton RB. Triptans (serotonin, 5-HT1B/1D agonists) in migraine prophylaxis-a five-year review. Headache 2004;44(5):538-45.
17. Ahn AH, Basbaum AI. Where do triptans act in the treatment of migraine? Pain 2005;115(1-2):1.
18. Cady RK. Treating an acute attack of migraine. Headache 1989;29(7):425-7.
19. Hocherman S. Antidepressants and triptans: A comparison of efficacy and side-effect profiles. Psychopharmacology (Berl) 2005;179(12):207-17.
20. Elovitz MA. Zonisamide in the treatment of headache disorders. Asian J Pharm Clin Res, Vol 10, Issue 10, 2017, 57-62.
21. Kruskal JC. Zonisamide in the treatment of headache disorders. Asian J Pharm Clin Res, Vol 10, Issue 10, 2017, 57-62.
22. Kirthi V, Derry S, Moore RA, McQuay HJ. Aspirin with or without an antiemetic for acute migraine headaches in adults. Cochrane Database Syst Rev 2010;10:CD008039.
23. Quiring JN, Gardner B, Traina F, Vancampen K, Quinter MG, et al. An overview of the preclinical aspects of topiramate in the treatment of migraine patients. Curr Pain Headache Rep 2004;8(3):178-84.
24. Kaniecki RG. Migraine prevention with Carvedilol: A prospective, open-label trial. Headache 2003;43:589.
25. Petrobion D. Calcium channels and calcineurinopathies of the central nervous system. Mol Neurobrol 2002;25(1):31-50.
26. Solomon GD. Verapamil in migraine prophylaxis-a five-year review. Headache 1989;29(7):425-7.
27. Freitag FG, Collins SD, Carlson HA, Goldstein J, Saper J, Silberstein S, et al. A randomized trial of divalproex sodium extended-release tablets in migraine prophylaxis. Neurology 2002;58(11):1652-9.
28. Shank RP, Gardocki JF, Streeter AJ, Maryanoff BE. An overview of the clinical and preclinical aspects of trimethadione in the treatment of headache disorders. Cephalalgia 2001;21:374-5.
29. Ozylacın SN, Talu GK, Kızıltan E, Yuceal B, Ertas M, Disci R. The efficacy and safety of verapamil in the prophylaxis of migraine. Headache 2005;45(2):144-52.
30. Schneider H, Stone DM, Gebel G, Sand S, Tovin G. Prophylactic
treatment of migraine with angiotensin converting enzyme inhibitor (lisinopril): Randomised, placebo controlled, crossover study. BMJ 2001;322(7277):19-22.

56. Bender WI. ACE inhibitors for prophylaxis of migraine headaches. Headache J Head Face Pain 1995;35(8):470-1.

57. Ashkenazi A, Silberstein SD. Botulinum toxin and other new approaches to migraine therapy. Annu Rev Med 2004;55:505-18.

58. Millán-Guerrero RO, Pineda-Lucatero AG, Hernández-Benjamin T, Tene CE, Pacheco MF. N-methylhistamine safety and efficacy in migraine prophylaxis: Phase I and phase II studies. Headache J Head Face Pain 2003;43(4):389-94.

59. Hauge AW, Asghar MS, Schytz HW, Christensen K, Olesen J. Effects of tonabersat on migraine with aura: A randomised, double-blind, placebo-controlled crossover study. Lancet Neurol 2009;8(8):718-23.

60. Peikert A, Wilimzig C, Köhne-Volland R. Prophylaxis of migraine with oral magnesium: Results from a prospective, multi-center, placebo-controlled and double-blind randomized study. Cephalalgia 1996;16(4):257-63.

61. Sándor PS, Di Clemente L, Coppola G, Saenger U, Fumal A, Magis D, et al. Efficacy of coenzyme Q10 in migraine prophylaxis: A randomized controlled trial. Neurology 2005;64(4):713-5.

62. Schoenen J, Jacquy J, Lenaerts M. Effectiveness of high-dose riboflavin in migraine prophylaxis. A randomized controlled trial. Neurology 1998;50(2):466-70.

63. Maizels M, Blumenfeld A, Burchette R. A combination of riboflavin, magnesium, and feverfew for migraine prophylaxis: A randomized trial. Headache 2004;44(9):885-90.

64. Bianchi A, Salomone S, Caraci F, Pizza V, Bernardini R, D’Amato CC. Role of magnesium, coenzyme Q10, riboflavin, and vitamin B12 in migraine prophylaxis. Vitam Horm 2004;69:297-312.

65. Pittler MH, Ernst E. Feverfew for preventing migraine. Cochrane Database Syst Rev 2004;1:CD002286.

66. Lipton RB, Góbel H, Einhäuserl KM, Wilks K, Mauskop A. Petasites hybridus root (butterbur) is an effective preventive treatment for migraine. Neurology 2004;63(12):2240-4.

67. Giffin NJ, Kowacs F, Libsi V, Williams P, Goadsby PJ, Kaube H. Effect of the adenosine A1 receptor agonist GR79236 on trigeminal nociception with blink reflex recordings in healthy human subjects. Cephalalgia 2003;23(7):287-92.

68. Lassen LH, Ashina M, Christiansen I, Ulrich V, Grover R, Donaldson J, et al. Nitric oxide synthase inhibition: A new principle in the treatment of migraine attacks. Cephalalgia 1998;18(1):27-32.

69. Tfelt-Hansen P. Site of effect of LY2951742 for migraine prophylaxis. Lancet Neurol 2015;14(1):31-2.

70. Chabi A, Zhang Y, Jackson S, Cady R, Lines C, Herring WJ, et al. Randomized controlled trial of the orexin receptor antagonist filorexant for migraine prophylaxis. Cephalalgia 2015;35(5):379-88.

71. Meents JE, Neeb L, Reuter U. TRPV1 in migraine pathophysiology. Trends Mol Med 2010;16(4):153-9.

72. Vogler B, Rapoport AM, Tepper SJ, Sheffell F, Bigal ME. Role of melatonin in the pathophysiology of migraine: Implications for treatment. CNS Drugs 2006;20(5):343-50.

73. Magni G, Ceruti S. P2Y purinergic receptors: New targets for analgesic and antimigraine drugs. Biochem Pharmacol 2013;85(4):466-77.