Chapter

Therapeutic Management: When and What

Theodoros Mavridis, Marianthi Breza, Christina I. Deligianni and Dimos D. Mitsikostas

Abstract

Migraine is a widespread brain disease that is classified as the second most disabling condition and has the third highest prevalence of all medical conditions. Despite its non-emergent or life-threatening nature, migraine can progress to chronic type, a subform associated with significant morbidity and drug overuse. In the management of migraine, it is important therefore to introduce early prophylactic treatment in order to limit migraine chronification. In this chapter, we will go through all the treatment options, both acute and preventive, pharmaceutical and non-pharmaceutical following this flowchart: 1. Introduction; 2. General principles; 2.1 Symptomatic therapy; 2.2 Prophylactic management; 3. Pharmaceutical therapies; 3.1 Symptomatic; 3.1.1 Disease-specific; 3.1.2 No disease-specific; 3.2 Prophylactic; 3.2.1 Disease-specific; 3.2.2 No disease-specific; 3.3 Non-Pharmaceutical therapies; 3.4 Neuromodulation; 3.4.1 Invasive; 3.4.5 Non-invasive; 3.5 Nutrient (nutraceuticals); 3.6 Dietary interventions; 3.7 Acupuncture; 3.8 Physical therapy; 5. Patient centricity and patient education.

Keywords: therapy, pharmaceutical therapy, non-pharmaceutical therapy, symptomatic treatment, prophylactic treatment, devices, cognitive behavioral therapy, physical therapy, acupuncture, nutrient, nutraceuticals, dietary interventions, patient centricity, patient

1. Introduction

The last decade heralded a new era in migraine therapeutics, with the emergence of novel targeted therapies. Recent advances in the field of migraine research have resulted to newly available acute and preventive treatment options, including gepants (calcitonin gene-related peptide (CGRP)-receptor antagonists), anti-CGRP/R monoclonal antibodies (mAbs), and ditans (5-HT_{1F} receptor agonists). Several advances were also achieved in non-pharmaceutical therapeutics, with the advent of devices for vagus nerve stimulation (VNS), external trigeminal nerve stimulation (eTNS), and transcranial magnetic stimulation (TMS) [1]. This chapter provides a comprehensive overview of available therapeutic approaches in migraine (pharmaceutical and non-pharmaceutical), summarizing both acute and prophylactic options.

The therapeutic management of migraine is multidisciplinary, including both pharmaceutical and non-pharmaceutical approaches. The choice of pharmaceutical treatment should be individualized, taking into consideration the characteristics of the migraine attack, the patients' comorbidities, and treatment preferences [2, 3].

The symptomatic migraine treatment aims to rapidly relief headache, restore function, and prevent recurrence. To date, simple analgesics, nonsteroidal anti-inflammatory drugs (NSAIDs), and triptans are the most widely prescribed medications for acute migraine [1]. Triptans (selective serotonin 5-$HT_{1B/1D}$ receptor agonists) have shown to inhibit the release of calcitonin gene-related peptide (CGRP) and were first approved for acute migraine therapy in the early 1990s [4]. However, these drugs are not efficient in all patients and might have vasoconstrictive properties that could be a contraindication [1], leaving room for new, disease-specific symptomatic treatments. The development of two novel classes of drugs, gepants (CGRP receptor antagonists) and ditans (serotonin 5-HT1F receptor agonists), for the symptomatic treatment of acute migraine allows management of patients that do not tolerate or respond to the above agents [1].

Every year about 3% of patients convert from episodic to chronic migraine (≥15 headache days per month, of which ≥8 migraine days) [1]. It is important therefore to introduce early prophylactic treatment in order to limit migraine chronification. The calcitonin gene-related peptide (CGRP) antagonists were approved in 2018 and represent the first class of novel targeted medications specifically designed and approved for migraine prevention. The newly approved monoclonal antibodies against the ligand CGRP or its receptor (anti-CGRP/R mAbs) are fremanezumab, erenumab, and galcanezumab, while eptinezumab is waiting for approval in 2020 [5]. Ubrogepant, lasmiditan, and rimegepant are emerging acute migraine therapies that are also waiting to be added to the arsenal of current migraine management [6].

The use of non-pharmaceutical approaches is recommended as adjunct therapy or as alternative to the first-line pharmaceutical treatment [7, 8]. Complementary interventions are used to minimize the overuse of acute pain medication or adverse effects (AEs) and as alternative when preventive pharmaceutical therapy fails or is contraindicated. Non-pharmaceutical strategies suggested include approved devices for migraine, cognitive behavioral therapies, physical therapy, improving quality of sleep, acupuncture, and dietary solutions [9–11].

Overall, novel therapies signify a paradigm shift in migraine management and not only bring new hope to patients suffering for migraine but also change the clinician's approach to the treatment of migraine [1]. While migraine therapy is currently undergoing tremendous development, unmet needs of patients remain, which, if addressed, have the potential to further enhance available treatment options and improve the quality of life of migraineurs. Identification of predictive biomarkers for responders and nonresponders to therapies, and elucidation of underlying migraine pathophysiology are still lacking, and are essential for the development of novel therapeutic targets and individualized migraine prevention.

2. General principles

To date, there is no cure for migraine, but migraine can be successfully treated in many cases.

Therefore, education of patients is of great significance. This could be achieved by thoroughly explaining patients' disorder, purpose, and means of management. Patient information leaflets on migraine and management are available from the Headache Federations (Lifting The Burden) [12]. Prior to treatment and during follow-up assessments, patients should be monitored and evaluated using recommended assessment tools: the HALT-30 Index that assesses burden in terms of lost productive time, the Migraine Disability Assessment Test (MIDAS), the Headache

Impact Test (HIT-6), which evaluates the headache impact and severity, and the Headache Under-Response to Treatment Questionnaire (HURT), which evaluates efficacy and ensures that the optimal treatment has been reached [12–18]. A calendar is recommended to be used by the patients with migraine, in order to monitor acute medication or overuse [12].

Regarding triggers and predisposing factors, modification of lifestyle, where applicable, is recommended. However, triggers are not always avoidable. Over the years, the significance of trigger factors in migraine has been overemphasized [2, 12].

Management of migraine in special populations (pregnant women, children, nonresponders, and elderly with comorbidities) should be carried out only by headache specialists [12].

The purpose of pharmacotherapy of primary headache is mostly to control symptoms in order to minimize the impact of the disorder on each individual patient's life and lifestyle. For treatment to be effective, first, it is crucial that the correct diagnosis has been made. Then, the choice of therapy requires an individual approach, as each patient is unique. Severity and frequency of attacks, disability causing, other symptoms, time to peak, patient preferences, comorbidities, drug interactions, side effects, and prior therapies that failed should be all taken into consideration [2].

Acute treatment should be taken as early as possible in the headache phase to abort an attack. Prophylactic treatment is administered periodically in order to reduce the frequency and severity of migraine attacks. Often a combination of acute and prophylactic treatment is needed [2].

Pharmaceutical treatment for acute attacks is used almost by all patients with migraine. Prophylactic treatment should be recommended in nonresponders to acute treatment or not well-controlled patients, whose quality of life is impaired by migraine [12].

The following recommendations are highlighted from the Headache Consortiums and Federations Management principles, as the main clinical recommendations that should be prioritized in pharmaceutical treatment.

2.1 Symptomatic therapy

When migraine attacks are not severe or disabling for less than 4 days per month, only symptomatic therapy is considered [2]. It is important to know when to treat a migraine attack and which therapy and route of administration are preferred, especially in patients experiencing nausea and vomiting. Generally, patients are advised to receive the abortive treatment as early as possible in the attack to reduce the intensity and duration of migraine as well as the accompanying features. In case of an inadequate response, it can be repeated after two hours (same or other treatment). There is a restriction on the duration of usage of symptomatic treatment due to the probability of developing medication overuse headache (MOH). Thus, taking into account the criteria of ICHD-III [19], intake of symptomatic treatment should not exceed 10 days per month for ergotamine, triptans, or combinations of drugs, or 15 days per month for NSAIDs, paracetamol, and aspirin.

Non-opioid analgesics (eg. NSAIDs, aspirin and paracetamol, or combinations with caffeine) with the addition of antiemetics (if needed), are the first-line treatment for mild to moderate attacks. Analgesics should be administered early in the attack and in adequate dosage, and during the aura phase for the case of migraine with aura. When vomiting is present, rectal forms of analgesics and use of antiemetics might be suggested. It is noted that paracetamol (1 g) on its own has lower efficacy and it should not be considered as first-line treatment alone. Opioids are thought to be ineffective and potentially addictive; thus, they should be avoided [12].

Triptans are recommended as first-line treatment for patients with moderate-severe migraine attacks, or where analgesics failed. Triptans are more effective when administered while headache is mild, but their use during aura is controversial for safety reasons. Combination therapy using triptans and NSAIDs should also be considered when triptans alone are not efficient to control migraine attacks. Subcutaneously injected sumatriptan (6 mg) should be considered when every other symptomatic treatment has failed, as a rescue medication. Triptans are associated with recurrence of migraine attack within 48 hours in up to 40% of patients that responded and with moderate consistency of efficacy across the attacks. Triptans should be avoided in uncontrolled hypertension, coronary heart disease, cerebrovascular disease or peripheral vascular disease, multiple risk factors for coronary or cerebrovascular disease. Finally, the use of triptans in the elderly should be with great caution due to comorbidities, preferably by headache specialists [12]. There are many strategies from stratified treatment to individual/tailored approach [20]. We suggest that a tailored approach is better as many subgroups of migraineurs exist and many patients exhibit adverse event in one or more therapies [12, 21]. All pharmaceutical symptomatic treatment is summarized in **Table 1**.

Type	Drugs	Action mechanism	Indications	Route of administration	Adverse Events	Recommendation level	Federation Approvals
Disease Specific	Ergots Dihydroergotamine Ergotamine	Activation of 5-HT1B/D receptors located on intracranial blood vessels Affinity for dopamine and noradrenaline receptors	Acute	 IV, IM, SC, Intranasal Oral, Rectal	Nausea Vomiting Paraesthesia Ergotism	Low to Moderate	FDA/EMA approved
	Triptans Sumatriptan Zolmitriptan Naratriptan Rizatriptan Almotriptan Eletriptan Frovatriptan	5-HT1B/1D receptor agonists Induce vasoconstriction Inhibit pain pathways Reduce input to the trigeminal nucleus caudalis	Acute	 Oral, Nasal, Rectal, SC Oral, Nasal Oral Oral Oral Oral Oral	Chest symptoms Nausea Distal Paraesthesia Fatigue	High	FDA/EMA approved
	Ditans Lasmiditan	5-HT1F receptor agonist	Acute	Oral	Dizziness Somnolence Fatigue Nausea	High	FDA approved
	Gepants Ubrogepant Rimegepant	Calcitonin gene-related peptide (CGRP) receptor antagonists	Acute	 Oral Oral	Somnolence Dry mouth Nausea	High	FDA approved
No Disease Specific	NSAIDs ASA Ibuprofen Naproxen Diclofenac Tolfenamic Dexketoprofen Acetaminiphen	Non-selective inhibitors of the cyclooxygenase (COX) enzymes (COX-1/2 isoenzymes)	Acute (Naproxen both as acute and preventive)	Oral, IM, IV, Rectal	Peptic ulceration and bleeds Hemorrhagic cerebrovascular accidents Renal impairment	High	FDA/EMA approved
	Antiemetics Metoclopramide Domperidone	Muscarinic activity D2 receptor antagonist 5-HT4 receptor agonist 5-HT3 receptor antagonist Peripherally selective dopamine D2 and D3 receptor antagonist	Acute	 Oral, IM, IV, Rectal Oral, Rectal	Higher risk of QT prolongation Acute dystonic reactions, Akathisia Mild sedation	Moderate	FDA/EMA approved

Table 1.
Pharmaceutical acute treatment in migraine management.

Type	Drugs	Action mechanism	Indications	Route of administration	Adverse Events	Recommendation level	Federation Approvals
Disease Specific	Anti-CGRP/RmAbs	Monoclonal antibodies	Preventive		Injection site pain/erythema	High	
	Erenumab	Against CGRP receptor		SC	Upper respiratory infection		FDA/EMA approved
	Fremanezumab	Against CGRP ligand		SC	Urinary infection		FDA/EMA approved
	Galcanezumab	Against CGRP ligand		SC	Fatigue Nausea/ Vomiting		FDA/EMA approved
	Eptinezumab	Against CGRP ligand		IV	Joint/back pain Abdominal pain Dysmenorrhea Dry mouth Constipation		FDA/EMA approval pending
No Disease Specific	Anticonvulsants		Preventive				FDA/EMA approved
	Topiramate	Action on (1) voltage-gated sodium channels (2) high-voltage-activated calcium channels (3) GABA-A receptors (4) AMPA/kainate receptors (5) carbonic anhydrase isoenzymes.		Oral	Paresthesia Numbness Fatigue Anorexia/ Weight loss Memory/ Concentration difficulties Renal calculi	High	
	Valproate	Blockade of voltage-gated sodium channels Increases brain levels of gamma-aminobutyric acid (GABA)		Oral IV	Nausea Somnolence Dizziness Weight gain Hair loss Spina bifida	Moderate	
	Beta-blockers	β1/β2 receptor antagonists	Preventive	Oral	Nausea Diarrhea		FDA/EMA approved
	Metoprolol				Fatigue Dizziness	High	
	Propranolol				Bronchospasm Exacerbation of Raynaud's syndrome	High	
	Atenolol				Bradycardia Hypotension Heart block	Low/ Moderate	
	Nadolol				Sexual/ Erectile dysfunction	Low/ Moderate	
	Timolol				Alteration of glucose/lipid metabolism	Low/ Moderate	
	Bisoprolol						
	Calcium Channel Blockers (CCBs)		Preventive				
	Flunarizine	Selective calcium entry blocker with calmodulin binding properties and histamine H1 blocking activity		Oral	Weight gain Daytime sedation Stomach complaints Dry mouth	High	EMA approved
	Verapamil	Blocks voltage-dependent calcium channels		Oral	Constipation Dizziness Nausea Low blood pressure Headache	Low	FDA/EMA approved
	Angiotensin II Receptor Blockers (ARBs)		Preventive	Oral	Back pain Dizziness Flu-like symptoms Sore throat Nasal congestion	High	
	Candesartan	Selectively blocking the binding of angiotensin II to the AT1 receptor					EMA approved
	Angiotensin Converting Enzyme (ACE) Inhibitors		Preventive	Oral	Headache Dizziness Cough Difficulty swallowing/ breathing Anaphylaxis Hyperkalemia Fatigue Diarrhea	Low	FDA/EMA approved
	Lisinopril	Inhibits angiotensin-converting enzyme (ACE) antagonist					
	Antidepressants		Preventive				
	Venlafaxine	Serotonin-norepinephrine reuptake inhibitor		Oral	Fatigue Constipation Dizziness Insomnia Nausea Headache Dry mouth Sexual/ Erectile dysfunction	Low	FDA/EMA approved
	Amitriptyline	Tricyclic antidepressant		Oral	Sedation Dry mouth Urinary retention Constipation Weight gain Blurred vision Tachycardia	Low	FDA/EMA approved
	OnabotulinumtoxinA	Interruption of signal transmission by the nerve cells to the muscles	Preventive	IM	Neck pain Muscular weakness Eyelid ptosis Injection pain	High	FDA/EMA approved

Table 2.
Pharmaceutical preventive treatment in migraine management.

2.2 Prophylactic management

Preventive treatment of migraine attacks is recommended when attacks are severe or frequent (more than 4 days per month) or there are contraindications, adverse effects, failure, or inadequate response of proper use of acute medication. The aim is to reduce frequency, duration, and severity of attacks and conversely increase the effect of acute treatment. The most important in preventive treatment of migraine is to know when to start the treatment and to manage and monitor the migraine patient, so that the disease does not switch from episodic to chronic, a subform associated with significant morbidity and drug overuse [22] and/or complicate with medication overuse headache (MOH). Today, we have both pharmaceutical and non-pharmaceutical (devices, nutrients, etc.) treatment options in our arsenal.

Prophylactic pharmaceutical treatment include no disease-specific agents, such as beta-adrenergic blockers without partial agonism (atenolol, bisoprolol, metoprolol, and propranolol), calcium channel antagonists (flunarizine), antidepressants (amitriptyline), anticonvulsants (topiramate, sodium valproate), and botulinum toxin for the case of chronic migraine exclusively, and disease-specific pharmaceutical regiments, namely the newly introduced CGRP monoclonal antibodies (erenumab, fremanezumab, and galcanezumab) [12].

Drugs that appear ineffective should be discontinued only after 2–3 months at minimum, in order to achieve and observe efficacy. Failure of one drug does not predict failure of others in a different class. Tapered withdrawal may be considered after 6 months of good control, and should be considered no later than after 1 year [12]. To increase adherence, it is recommended to start with a low dose and slowly increase the dosage to the preferable one.

The anti-CGRP/R monoclonal antibodies have demonstrated good efficacy and excellent tolerability in phase II and III clinical trials with only injection site reactions to be the most common treatment-related adverse events [22].

The available treatments have different efficacy and adverse events/contradictions, and each option must be individualized and tailored in the patient's profile and needs. All pharmaceutical prophylactic treatment is summarized in **Table 2**.

3. Pharmaceutical therapies

As previously stated, the pharmaceutical treatment of migraine is divided into symptomatic/acute (to stop the migraine crisis and alleviate the concomitant symptoms, e.g., nausea, vomiting) and preventive/prophylactic (to reduce the frequency, intensity, and severity of the attacks). Drugs from both categories are further divided into substances that have been designed specifically for migraine and to drugs that are used primarily for the treatment of other diseases (non-specific).

3.1 Symptomatic

3.1.1 Disease-specific

3.1.1.1 Ergots

Ergotamine and dihydroergotamine are the two main drugs of this category, and they exert their action via activating 5-HT1B/D receptors located on intracranial blood vessels. They also have affinity for dopamine and noradrenaline receptors [2]. Evidence shows that dihydroergotamine is more effective than ergotamine.

Nowadays, there are some preparations of ergotamine and dihydroergotamine alone or in combinations (usually with antiemetics or caffeine) [23, 24]. Ergots can also induce medication overuse headache (MOH) with very low doses and their use must be limited to less than 10 days per month. Contraindications are coronary artery disease due to the constriction of the coronal vessels [25], arterial hypertension, and cerebrovascular diseases. Due to their impact on the vascular system, they should not be used in combination with other vasoconstrictor drugs. Other contraindications include Raynaud disease, renal or hepatic failure, pregnancy, and lactation.

3.1.1.2 Dihydroergotamine (DHE)

It is available for oral, intravenous (IV), intramuscular (IM), subcutaneous (SC), and intranasal use, whereas the latter route of administration is less reliable and nasal irritation is a common adverse effect [26]. However, its availability varies across countries significantly. The combination of DHE with antiemetics (where the preparation is available) seems to be effective for the treatment of acute migraine. Intravenous formulation of DHE is very effective and well-tolerated for the treatment of migraine [27]. It is proposed as an acute management of chronic migraine in the primary care to the subgroup of patients who do not respond to NSAID-triptan combinations (1 mg of subcutaneous or intramuscular dihydroergotamine) [26]. Nevertheless, two points must be taken into account: (i) DHE route of administration is mostly parenteral, and self-administration is difficult and takes time for the patient to learn. (ii) It is not clear if the addition of an antiemetic (metoclopramide) in the preparation is responsible for the efficacy of DHE (unknown if there is an additive action) [24]. Doses vary depending on the route of administration, i.e., 1 mg SC, 2 mg intranasal, and 2.5 mg *per os*.

3.1.1.3 Ergotamine

Ergotamine is an ergopeptine and the second migraine drug of the ergot family. The most common combination launched in the market is ergotamine tartare + caffeine. Ergotamine has been in clinical practice over 70 years, but there is no common ground for the use of this agent. There are many trials in the literature, which attempts to validate the efficacy of ergotamine. It is recommended for the treatment of acute headache, only in patients with prolonged attacks (>48 hours) or in whom headache recurrence is a substantial issue [28]. This recommendation is in accordance with the European Federation of Neurological Societies' (EFNS) guidelines [20]. EFNS also stated that status migrainosus can be treated by dihydroergotamine (low level of evidence). In many clinical trials [29–32], ergot derivatives showed lower efficacy than triptans and more adverse events (AE). Therefore, these substances should be dealt with caution [2]. Major AEs are nausea, vomiting, and should be avoided in patients who report these common associated symptoms of migraine, or later than >2 hours after the onset of migraine when the gastric stasis has already occurred. Other AEs are paraesthesia, and ergotism (due to long-term use or ergot derivatives).

3.1.1.4 Triptans

Triptans are 5-HT1B/1D receptor agonists and very effective for the acute management of migraine. They are specific to treat migraine as they act at the pathophysiology of migraine, inducing vasoconstriction, inhibiting pain pathways, and reducing the input to the trigeminal nucleus caudalis. There are many available

triptans, i.e., sumatriptan, naratriptan, zolmitriptan, rizatriptan, almotriptan, eletriptan, and frovatriptan. With the exception of sumatriptan (oral, subcutaneous, and intranasal) and zolmitriptan (oral and intranasal), the other triptans are for oral use only. Generally, triptans are recommended for moderate to severe attacks and there is good evidence (level A) that combining a NSAID with a triptan will prevent from migraine recurrence [2, 12, 20, 21]. The choice of triptan is and should be individualized. Triptans have different pharmacokinetic and pharmacodynamic profile. Subcutaneous sumatriptan (6 mg) is more effective than oral sumatriptan and is preferred when associated symptoms, such as nausea and vomiting, occur. Intranasal spray has fewer side effects than intramuscular sumatriptan (discomfort, nasal irritation, and unpleasant taste). Comparative studies show that eletriptan has the highest efficacy with short-term and sustained effect. The above conclusion is consistent in many studies. Rizatriptan and zolmitriptan are thought to come in second and third place, respectively, in terms of efficacy, although further analysis shows that sumatriptan, rizatriptan, almotriptan, and zolmitriptan are very similar regarding clinical outcome. Naratriptan and frovatriptan have less but longer efficacy than sumatriptan and are relatively safer than other triptans. Naratriptan, frovatriptan, and almotriptan are also preferred for symptomatic treatment in patients that migraine attack recurs after successful treatment (pain free and most bothersome symptom free in 2 hours posttreatment) [2, 12, 20, 21, 24, 33–36]. Triptans can be given in combination with NSAIDs and the effect is considered to be additive. The most common and well-documented combination is that of sumatriptan with naproxen and is the one indicated for migraine attacks that do not respond to oral high efficacy triptans (e.g., eletriptan 40 or 80 mg, or rizatriptan 10 mg) [21]. Another combination that showed effectiveness in acute treatment is frovatriptan with dexketoprofen. Generally, triptans are safe and effective. Due to the vasoconstrictive action, triptan should be avoided to migraineurs with uncontrolled arterial hypertension, cardiovascular and/or cerebrovascular disease, and peripheral vascular disease. Systematical reviews and cohort studies showed that there is not any correlation between the use of triptans and higher cardiovascular risk, however [37, 38]. Nonetheless, the use of triptans is not recommended in high-risk patients. Finally, as with ergots, the use of triptans should be limited to 10 days per month to avoid medication overuse headache [2, 19–21].

3.1.1.5 Ditans

Ditans are a relatively new and different class of specific acute migraine management. The first and only approved by the Food and Drug Administration (FDA) until now is lasmiditan, a selective 5-HT1F receptor agonist, which shows minimal to zero vasoconstrictor activity in contrast to triptans. It is a suitable candidate for migraineurs where triptans are contraindicated or not well tolerated. Lasmiditan is given orally (starting dose of 50 mg and subsequently increase up to 200 mg if there is no benefit). Because lasmiditan penetrates the blood-brain barrier; it presents common AEs from the central nervous system (CNS, dizziness, somnolence, fatigue, and nausea) that restricts its use to those who drive or operate heavy machinery [39–42].

3.1.1.6 Gepants

The study of CGRP and its implication to the pathophysiology of migraine has led to discovery of a new class of drugs that are CGRP receptor antagonists. Gepants are suitable for treatment of acute migraine in patients who do not tolerate the triptans or when triptans are contraindicated. The first attempts for the manufacture of

these type of drugs led to a dead end, as many of the trials were terminated due to hepatotoxicity. Now, we have two gepants that received FDA approval, ubrogepant (2019) and rimegepant (2020) for the treatment of acute migraine in adult patients. However, more clinical trials and real-world evidence are needed to prove their efficacy and tolerability [43].

3.1.2 No disease-specific

3.1.2.1 Nonsteroidal anti-inflammatory drugs

The most well-studied drugs of this category include acetylsalicylic acid (ASA) (aspirin 900–1000 mg), ibuprofen (200–800 mg), naproxen (275–825 mg), diclofenac (50–100 mg), tolfenamic acid (200 mg), and dexketoprofen (50 mg) [44–51]. The difference in dosage depends on the available formulation for each country and the proposed guidelines of each Headache Society [2, 12, 20, 21, 24]. The use of NSAID should be as soon as possible to achieve maximal effect and to preempt the gastric stasis. If the migraineur does experiences nausea or vomiting, parenteral formulations (suppository, intramuscular, and intravenous) of the above drugs should be given with combination of a prokinetic (see below Prokinetics) [12]. For moderate to severe attacks, combinations of NSAID with triptans are recommended. All NSAIDs have more or less (depends on the COX-2 selectivity) the same adverse events including GI bleeds, peptic ulceration, hemorrhagic cerebrovascular accidents, and renal impairment. They should not be given in patients with uncontrolled hypertension or history of peptic ulcer. In case of peptic ulcer, they can be prescribed for a small period of time together with protein pump inhibitors (PPIs).

3.1.2.2 Acetaminophen

Acetaminophen (paracetamol 1000 mg) is a NSAID with different mechanism of action. It is effective in some patients although it has weaker recommendation than NSAIDs for the management of acute headache [12]. On the other hand, the combination of paracetamol with ASA and caffeine is more effective than single drugs and is recommended for the treatment of mild to moderate severity attacks [20, 21, 52–54].

3.1.2.3 Antiemetics/Prokinetics

Many antiemetics (metoclopramide, domperidone, chlorpromazine, prochlorperazine, droperidol, ondansetron, and granisetron) have been studied for the treatment of acute migraine, both as monotherapy as well as adjuvants. The main action as prokinetics is via their dopamine receptor antagonism. Many of them show anti-migrainous action. With the exception of metoclopramide and domperidone, the other antiemetics have a higher risk of QT prolongation and higher rates of acute dystonic reactions, akathisia (extrapyramidal action) and mild sedation, and besides their efficacy (even some of them over triptans) [55–59], they are not recommended for the treatment of migraine. On the other hand, metoclopramide is a mild analgesic when given orally and more efficient when given intravenously. Despite monotherapy with antiemetics is not recommended, adjuvant therapy [45], especially when associative symptoms like nausea or vomiting are present, or latter in the course of migraine (gastric stasis has already occurred), is strongly suggested. The usual dose is for domperidone 10 mg (supportive evidence of efficacy is for 20 mg) up to three times per day or 30 mg (by suppository up to twice per day) and for metoclopramide 10 mg (up to three times per day). Metoclopramide

20 mg is recommended for adults and adolescents, whereas domperidone 10 mg for children due to the possible side effects (dyskinesia, akathisia) [12, 20].

3.1.2.4 Other drugs

Other drugs with low level of evidence that are found to be effective in the acute treatment of migraine attacks are intravenous valproate (dose up to 800 mg) [60–62], adjunctive therapy with parenteral dexamethasone (intramuscular or intravenous) for treatment of acute migraine and status migrainosus [20, 21, 63, 64], and a combination of paracetamol with intravenous tramadol [65].

3.2 Prophylactic medications

3.2.1 Disease-specific

3.2.1.1 Anti-calcitonin-gene-related peptide/receptor monoclonal antibodies (anti-CGRP/R mAbs)

All four anti-CGRP/R mAbs share several pharmacokinetic advantages over small anti-CGRP/R molecules (e.g., greater target specificity and prolonged half-life, making them suitable for monthly administration to prevent migraine). Three of these macromolecules target the CGRP ligand (fremanezumab, galcanezumab, and eptinezumab), while a fourth (erenumab) targets the CGRP receptor [66–68]. They require parenteral administration and have a preferential peripheral site of action, since only 0.1–0.5% of the mAb cross the blood–brain barrier due to their large size (molecular weight around 150 kDa) [66, 69–72]. All four mAbs have shown particular effectiveness for the prevention of both episodic and chronic migraine [71, 72]. Besides the initial skepticism regarding their safety and their potential cardiovascular effect (due to preclinical data that came from studying and blocking CGRP,66) and liver toxicity that emerged after the initial failure of gepants, no safety flags occurred during the large program of their development and all four anti-CGRP/R mAbs have shown similar tolerability and safety in Phase II and III trials. The most common AEs, which were reported during clinical trials, are injection site pain, erythema, respiratory infection, nasopharyngitis, sinusitis, influenza, urinary infection, fatigue, nausea, vomiting, joint pain, back pain, headache, abdominal pain, dysmenorrhea, and dry mouth. Real-world evidence revealed constipation as one of the common adverse effects (not in clinical reporting). Anti-CGRP/R mAbs should be avoided in pregnant and nursing women, as well as in patients with psychiatric, pulmonary, and cardiovascular medical history, until more data are available. Regarding their efficacy, there is not much evidence or head-to-head clinical trials to support the superiority of one drug against the other. Due to their mechanism of action, pharmacokinetics, clinical effect, and cost, Headache societies have formulated practical guides on the proper use of anti-CGRP/R mAbs [5, 12, 21].

3.2.1.2 Erenumab

Erenumab is the first drug of the anti-CGRP/R category and the only until now that prevents native CGRP ligand binding to the CGRP receptor. It is an IgG2 antibody and the only fully human anti-CGRP/R mAb. At 70 mg, the estimated elimination half-life of erenumab is 21 days, supporting monthly subcutaneous dosing and, thus, betterment in patient compliance [73–75]. It is recommended for both

episodic and chronic migraine, as well as the treatment of MOH [76]. There are two formulations of erenumab (70 and 140 mg) with almost similar efficacy, and there is a suggestion of starting with the lower dose and increase if there is little efficacy [77]. A review of 3 randomized trials and their extensions suggested that erenumab 140 mg monthly might be preferred over the 70 mg monthly dose in patients with EM or CM and prior preventive treatment failures (>2) [77]. It is administered subcutaneously (SC) once per month, thus achieving better adherence among migraine patients compared to oral daily medications.

3.2.1.3 Fremanezumab

Fremanezumab is a fully humanized IgG2 mAb that potently and selectively binds to both α and β isoforms of CGRP [78]. It is effective for the prevention of episodic and chronic migraine. It is administered SC and has one formulation of 225 mg, which can be administered either once per month, or three consecutive doses (total of 675 mg) every 3 months. Both dosage options have shown similar efficacy and adverse events [79].

3.2.1.4 Galcanezumab

Galcanezumab is a humanized IgG4 mAb with a long half-life (~28 days) that binds to both α- and β-CGRP isoforms with approximately equal affinity [80]. Again, several trials have proven its efficacy for the preventive treatment of migraine [81–83]. As the other two aforementioned mAbs, galcanezumab is subcutaneously administered. The suggested starting dose is 240 mg (2 consecutive doses of 120 mg formulation) as a starting dose and then 120 mg subcutaneously every month [84].

3.2.1.5 Eptinezumab

Eptinezumab is the last anti-CGRP/R mAb discovered till now. It is a humanized IgG1 antibody that potently and selectively binds to both α and β forms of human CGRP [85]. The plasma half-life of eptinezumab after an intravenous infusion of 1000 mg is 31 days. There are two clinical trials (PROMISE-1 and PROMISE-2) that support its efficacy in episodic and chronic migraine prevention [86, 87]. Eptinezumab is the only intravenously anti-CGRP/R mAb and the recommended dose is 100 mg over 30 minutes every 3 months. It is not yet approved by the FDA or EMA (under development).

3.2.2 No disease-specific

Several drug classes, originally developed for other diseases (e.g., epilepsy, hypertension), have shown efficacy for the preventive treatment of migraine. Repurposed drugs may lack the disease-specific mechanism of action and have several adverse effects and contraindication, but show comparable efficacy to CGRP mAbs and are less expensive. As with the use of disease-specific treatments, when using nonspecific drugs, our main goal is individualizing our choice, taking into account the clinical characteristics, medical history, and comorbidities of the patient (e.g., sex, weight, anxiety/depression, hypertension, endocrinological disorders, pregnancy, etc.). The main categories are anticonvulsants, antihypertensive and antidepressant drugs, and other agents (e.g., onabotulinumtoxinA, butterbur, coenzyme Q10, NSAIDs, and others).

3.2.2.1 Anticonvulsants

3.2.2.1.1 Topiramate

Topiramate is one of the most studied drugs for the prevention of migraine, with several clinical studies, systematical reviews, and meta-analysis, showing its efficacy for both episodic and (fewer evidence) chronic migraine [26, 88–93]. Usual dosage ranges between 25 and 100 mg daily (in two divided doses) and there is suggestion, with the risk of more adverse events, of increasing the total dose up to 200 mg daily when the effect is suboptimal [2, 12, 20, 21, 26]. Main AEs of topiramate are paresthesia/numbness (results in intolerance), fatigue, anorexia/weight loss, memory and concentration difficulties, and renal calculi (uncommon but serious adverse effect). It is contraindicated in pregnant women as it increases the risk of facial clefts and lowers birth weight. Due to the weight loss, topiramate is recommended to obese migraine patients [89, 90, 94].

3.2.2.1.2 Valproate

Whereas valproate is indicated for the preventive treatment of episodic migraine, its side effects (nausea, somnolence, dizziness, weight gain, and hair loss) and the contraindication to women in childbearing age and pregnancy (teratogenic) have limited its use. Usual doses range between 500 and 1800 mg per day and there is limited evidence of intravenous administration of valproate in status migrainosus [2, 12, 20, 21, 95].

3.2.2.2 Other anticonvulsants

Other anticonvulsants, such as gabapentin, have not proven their efficacy for prevention of episodic migraine and therefore are not recommended [96, 97] .

3.2.2.2.1 Antihypertensive

The two major categories of antihypertensive drugs that show migraine preventive effect are beta-blockers and calcium channel blockers. Most of the evidence emerged from studies regarding hypertension reported fewer headaches in the intervention group vs. the placebo group [98].

3.2.2.3 Beta-blockers

Beta-blockers that are available in almost every country and are recommended from almost all Headache Societies for the preventive treatment of episodic migraine are metoprolol (50–200 mg daily) and propranolol (40–240 mg daily). Other beta-blockers with fewer studies are atenolol (25–100 mg daily), nadolol (20–240 mg daily), timolol (10–30 mg daily), and bisoprolol (5–10 mg daily). Beta-blockers are recommended in hypertensive patients who are under 60 years old or nonsmokers [94, 99, 100]. Due to their mechanism of action and their dosage that is proven to be efficacious for migraine prevention, are not well tolerated and are contraindicated in patients with bradycardia, low blood pressure, cardiac conduction blocks, asthma, depression, and Raynaud phenomenon [2, 12, 20, 21, 101].

3.2.2.4 Calcium channel blockers

The only drug of this category with good level of evidence is flunarizine, a non-specific calcium channel blocker, with calmodulin binding properties and histamine

H1 blocking activity. Recommended dose ranges between 5 and 10 mg daily and is prescribed to hypertensive patients older than 60 or smokers, as well as to patients with Raynaud syndrome. The most common AEs are weight gain, daytime sedation, stomach complaints, and dry mouth, and while there are reports of depression and extrapyramidal symptoms, there is no confirmation [102]. Verapamil is another calcium channel blocker with migraine preventive properties, but it has conflicting supporting data and many Headache Societies do not accept its use for episodic migraine [2, 12, 20, 21, 103].

3.2.3 Angiotensin receptor blockers (ARBs)/angiotensin converting enzyme (ACE) inhibitors

There is also data supporting the use of ACE inhibitors and ARBs as preventive migraine treatments. Candesartan, a specific ARB, has shown positive results in small-scale crossover studies and is used for migraine prophylaxis (16–32 mg) [104, 105]. The most common AEs include back pain, dizziness, flu-like symptoms, sore throat, and nasal congestion. Similarly, a small-scale double-blind cross-over study, found lisinopril (ACE inhibitor) to be effective in episodic migraine [106]. The above data are not universally approved [2, 12, 20, 21].

3.2.3.1 Antidepressants

Antidepressants are recommended as a second-line drugs with level B documentation [20]. The two drugs of this category are amitriptyline and venlafaxine. Among the two amitriptyline, a tricyclic antidepressant has been studied the most [103]. The usual dose ranges between 10 and 150 mg. Its sedative properties have limited its use and it is suggested only at bedtime and especially to those who suffer from insomnia. It also has a place as a second choice drug for chronic migraine [26]. Except sedation, amitriptyline's AEs include dry mouth, urinary retention, constipation, weight gain, blurred vision, and tachycardia. Venlafaxine, a serotonin-norepinephrine reuptake inhibitor, has a weaker recommendation as migraine prophylaxis and is preferred to those who suffer from depression and/or anxiety and those who have also tension-type headaches (TTH). The usual dose ranges between 37.5 and 150 mg daily [2, 12, 20, 21, 94].

3.2.4 Other drugs

3.2.4.1 OnabotulinumtoxinA

Whereas many randomized trials did not prove onabotulinumtoxinA's efficacy for treating episodic migraine (EM) and it is not recommended [107–109], data extracted from chronic migraine (CM) trials recommend onabotulinumtoxinA as an effective and well-tolerated treatment. OnabotulinumtoxinA has a good level of documentation (Level A), and there is specific protocol regarding its use (PREEMPT protocol), monitoring of the patients, and evaluating their response. It should be administered according to the PREEMPT injection protocol, i.e., injecting 155 U–195 U to 31–39 sites every 12 weeks. The most common reported AEs are neck pain, muscular weakness, eyelid ptosis, and injection-site pain, and the sub-analysis of the PREEMPT studies found that adverse events decreased over time [26, 110–112]. Its use in CM with MOH is debatable after a recent trial that showed no superiority against acute withdrawal alone [113].

3.3 Non-pharmaceutical therapies

Like the pharmaceutical, the non-pharmaceutical treatments—neuromodulation devices in particular—gain even more ground in the treatment of migraine.

A set of variables arrange this alternative so far, therapeutic approach. First, the pathophysiology of migraine refers to a multidisciplinary spectrum of mechanisms; second, the disease is among the most disabling medical conditions requiring application of all available treatment options; third, the existing medicinal selections (symptomatic or preventative) are related with poor adherence due to safety and poor response rates ; and finally, there is an international movement encouraging non-pharmaceutical interventions in medicine, including the community mitigation strategies. Patients' preferences rate the non-pharmaceutical interventions for migraine highly [3]. All these factors create large space for non-pharmaceutical treatment options in migraine, which can be used alone or as adjunct therapy to pharmacological agents minimizing unnecessary drug exposure. There is good evidence for neuromodulation and biobehavioral therapies, including cognitive behavioral therapy (CBT), biofeedback, and relaxation training. Less evidence suggests physical therapy, sleep management, acupuncture, and dietary modifications.

3.4 Neuromodulation

Neuromodulation approaches for migraine treatment includes invasive and noninvasive ones. Both procedures act by stimulating the nervous system centrally or peripherally, leading to pain relief, either acutely or preventively. They are constantly gaining space in the treatment of migraine and are addressed either to refractory patients or to patients who do not want medical treatment. All neuromodulation devices are summarized in **Table 3**.

3.4.1 Invasive

There are three invasive neurostimulation methods investigated for migraine and available, yet in very limited use because of the high cost of the device, the surgical implementation needed, and the lack of good evidence of efficacy. In addition, their accessibility and reimbursement vary by country significantly. Thus, they are recommended for patients with refractory forms of CM only. The most common AEs include migration of the leads, infection, and paraesthesias [7].

3.4.2 Invasive occipital nerve stimulation (iONS)

Invasive occipital nerve stimulation (iONS) has been used to treat refractory CM cases. The exact mechanism of the neuromodulation effect in CNS remains unclear. From three randomized, sham-controlled studies [114–116], only one showed a significant improvement of migraines in the treated group comparing to sham group or the medication treated group [115]. Electrodes must be implanted subcutaneously above the great occipital nerve (GON), which present great anatomical variability among individuals [117]. The leads are implanted bilaterally, while a small generator is implanted subaxillary. The AEs include lead migration, paraesthesias, infections, and battery depletion, but safety data look better than the other invasive procedures [116].

3.4.3 Vagal nerve stimulation (VNS)

Vagal nerve stimulation (VNS) is already applied in patients with refractory epilepsy. The stimulation of vagal afferents decreases the activity of the nociceptive neurons of the spinothalamic and spinoreticular tract, which, in their turn, inhibit the nociceptive transmission in spinal and trigeminal nucleus complex, leading to

Type	Device	Action mechanism	Indications	Route of administration	Adverse Events	Recommendation Level	Federation approvals
Non-Invasive	Supraorbital nerve Stimulation (eTNS)	Regulates peripheral and central pathways of migraine	Acute and Preventive treatment of migraine	Forehead transcutaneously 20 min daily in prevention/60 mins on attack	Allodynia Paresthesia (Minor)	Moderate	FDA approved CE marked
	Transcranial Magnetic Stimulation (TMS)				Lightheadedness Tingling Tinnitus		
	sTMS	Attenuates the evoked firing rate of thalamocortical projection neurons	Acute Preventive MwA or MwoA	Over Occipital cortex		Moderate	FDA approved
	rTMS	Interrupts the brain hyperactivity associated with migraine	Acute and Preventive EM, CM	Over Occipital cortex		Low	-
	Non-invasive Vagus Nerve Stimulation (nVNS)	Antinociceptive on trigeminal nucleus complex nVNS inhibits CSD	Acute	On neck (on route of vagus nerve)	Neck twitching Change in voice Erythema at the site	Moderate	FDA approved CE marked
	Remote electrical Neuromodulation (REN)	Modulate cephalic pain processing, via endogenous analgesic mechanisms	Acute	Applied on the lateral upper arm	Transient sensation of mild warmth Redness/ Numbness of arm/hand		FDA approved
Invasive	Transcranial Direct Current Stimulation (tDCS)	Modulates cortical hyperexcitability	Prevention of EM /CM	Leads applied over visual cortex	Headache Pain Disturbed vision Fatigue	Low	-
	Percutaneous Mastoid Stimulation	May control CSD	Prevention of EM	Leads placed on ear mastoid, over the skin	None	Low	-
	Invasive Occipital Nerve Stimulation (iONS)	Unclear	Prevention of Refractory CM	Implanted subcutaneously implanted leads above GON	Lead migration Paraesthesia Infections Battery depletion	Low	-
	Invasive Vagal nerve stimulation (iVNS)	Inhibits the nociceptive transmission in spinal and trigeminal nucleus complex	Prevention of Refractory CM	Implanted leads over the Vagal nerve	Infection Muscle cramps Local pain Battery depletion	Low	-
	High Cervical Spinal Cord Stimulation		Prevention Refractory CM	Implanted leads	Lead migration Infections	Low	-

Table 3.
Neuromodulation in migraine management.

cephalic pain control. There is data from case series with refractory CM only showing that patients with implanted VNS (iVNS) reached more than 50% reduction in headache frequency and severity [118, 119]. The scarce clinical experience in this field make iVNS not a common treatment option, for the time being, since it is an invasive procedure with adverse effects (infection, muscle cramps, local pain, and battery depletion), though the clinical experience in the field of epilepsy shows to be safe.

3.4.4 High cervical spinal cord stimulation

This invasive procedure trialed in open label studies in patients suffering from CM and showed a significant reduction in headache frequency and intensity in treated patients, but further investigation is required [120, 121].

3.4.5 Noninvasive

Noninvasive neuromodulation devices provide a safe and well-tolerated therapeutical option in symptomatic and prophylactic treatment of migraine alone or in combination with pharmaceutical treatment. Their evidence of efficacy is moderate to good and almost equivalent to that of drug treatments, while their safety profile may outperform them. There are accessibility, reimbursement, and price issues, however.

3.4.6 Supraorbital nerve stimulation

This is a peripheral noninvasive nerve stimulation or an external trigeminal nerve stimulation device which initiates transcutaneously a mild electric current via leads that are placed on the forehead, stimulating supraorbital and supratrochlear nerves. There is evidence of dysregulated central and peripheral pathways in migraine and evidence that external trigeminal nerve stimulation may normalize function of these pathways [122]. Sham-controlled studies showed that 1-hour stimulation with this device reliefs headache pain during a migraine attack significantly [123], while daily 20-minute treatment decreases the monthly migraine days in patients suffering from EM [124]. The device is FDA approved and CE marked as preventive and acute therapy in migraine. Only mild AES are reported and despite some concerns related to the methodology followed in the preventive trial, its efficacy seems comparable to pharmaceutical preventive treatments [122, 125].

3.4.7 Transcranial magnetic stimulation (TMS)

TMS is a well-established and safe procedure already applied in other neurological diseases, modulating the excitability of cortical neurons dependently on the frequency of the stimulus. Thus, only the single-pulse stimulation (sTMS) and the repetitive-pulse stimulation (rTMS) are used to treat migraine.

sTMS is proved to inhibit both mechanical and chemically-induced cortical spreading depression in animals [126]. In addition, sTMS attenuates the evoked firing rate of third-order thalamocortical projection neurons, indicating the probable neuromodulatory effect in migraine [126]. Overall, sTMS interrupts the brain hyperactivity associated with migraine. sTMS devices are portable and patient-controlled and are applied over the occipital cortex in patients with either migraine with aura (MwA) or migraine without aura (MwoA) for acute or preventive treatment. One sham-controlled study showed that sTMS caused higher rates in 2-hour pain relief posttreatment than the sham group in patients with MwA [127]. Open-label studies have shown an efficacy either in acute or preventive treatment in MwA or MwoA [128–131]. The most common AEs recorded in the trials were lightheadedness (3.7%), tingling (3.2%), and tinnitus (3.2%) [131]. The device is FDA approved for acute and preventive treatment of migraine for people aged more than 12 years.

rTMS and especially high frequency rTMS seem to have a positive effect in the prevention of both EM and CM. Treatment with rTMS caused a significant decrease of monthly headache days over sham-treated patients, for both cases of CM [132] and EM [133], but another sham-controlled study did not confirm the results in CM, probably because of a large effect size [134]. Overall, the majority of rTMS studies reported reductions in headache frequency, duration, intensity, abortive medication use, depression, and functional impairment, with no significant adverse events [135]. Further investigation is needed, however.

3.4.8 Noninvasive vagus nerve stimulation (nVNS)

As in iNVS, the nVNS results in an ascending antinociceptive on trigeminal nucleus complex. In addition, nVNS inhibits cortical spreading depression in rats [136]. In migraineurs, the device is applied on the neck, and it produces an electrical stimulus of adjustable intensity, and therefore, stimulates transcutaneously the cervical part of vagus nerve. The evidence of efficacy in symptomatic treatment of migraine is good [8]. One sham-controlled, class 1 study has showed its efficacy in acute treatment of migraine [137], whereas its efficacy in migraine prevention remains debatable [138–140]. It is used in acute treatment of migraine with consisted results similar to the use of NSAIDs or triptans [141]. In a small-size open-label study, nVNS showed promising results as mini-prophylactic treatment of the menstrual migraine [142]. Reported AEs are neck twitching, change in voice, and redness at the site of stimulation. It is generally well tolerated by the patients, however. The portable nVNS device has received FDA approval and is CE marketed for the symptomatic treatment of migraine.

3.4.9 Remote electrical neuromodulation (REN)

Not only cranial nerves but also peripheral somatic nerve stimulation may also modulate cephalic pain processing, via descending endogenous analgesic mechanisms (conditioned pain modulation). There is evidence that the stimulation of upper arm peripheral nerves (median and musculocutaneous) controls cephalic pain [143]. A noninvasive, portable, and wireless device, applied on the lateral upper arm between the bellies of deltoid and triceps muscles, delivers electrical stimuli that alleviate migraine pain [144]. The device has been tested for acute migraine treatment in one randomized, sham-controlled study showing superiority over sham stimulation in achieving pain relief and freedom and relief of most bothering symptoms without significant AEs [145]. Notably, the treatment efficacy is comparable with this of the current use pharmaceutical ones [146]. Its use is contraindicated to patients with other active implantable medical devices and it is FDA approved for the symptomatic treatment of migraine.

3.4.10 Transcranial direct current stimulation (tDCS)

There is some evidence suggesting that tDCS modulates cortical hyperexcitability and therefore it serves as a preventive treatment for CM and EM. The small-size, sham-controlled studies based on both rationales of anodal stimulation (excitatory) and cathodal (inhibitory) on visual cortex mostly have shown positive effect—with limitations—on reduction in monthly migraine days, headache frequency, pain duration, and severity. Contradictions include previous stroke or epilepsy and comorbidity with psychiatric disorders, among others. This procedure is under investigation currently [147–150].

3.4.11 Percutaneous mastoid stimulation

There is evidence suggesting that the stimulation of fastigial nucleus displays neuroprotective, in particular the stimulation of fastigial nucleus elicits long-lasting suppression of periinfarction depolarizing waves and protect rats against cerebral ischemia [151]. Because cortical spreading depression shares characteristics with periinfarction depolarizing waves, it was speculated that this stimulation of this nucleus may be useful in migraine prevention [152]. The new device for this purpose has electrodes that are placed on the bilateral ear mastoid over the skin.

After few open label studies, one sham-controlled showed a significant reduction in migraine days and response rate vs. sham group in patients suffering from EM, without AEs [152]. The device is under development and further studies are needed.

3.5 Nutrient (nutraceuticals)

Nutraceuticals have been defined as, "a food (or part of a food) that provide medical or health benefits, including the prevention and/or treatment of a disease" [153]. There is an increasingly and demanding use of them by sufferers of chronic diseases including migraine [154], for which there is evidence supporting cerebral energy deficiency [155]. Nutraceuticals may cover this metabolic gap in brain, but the equality of data is low to moderate, however.

3.5.1 Riboflavin

Riboflavin (vitamin B2) is an essential component and precursor of riboflavin 5-phosphate, and modulates the electron transport chain, contributing in energy production in mitochondria. There is evidence indicating that oxygen metabolism is impaired in migraineurs' mitochondria resulting in energy insufficiency [155]. Results from placebo-controlled studies showed efficacy in reducing the frequency of headache days in adult migraineurs [156], but not children [157], or when administered as component in compliment [158]. According to available evidence, riboflavin could be suggested as preventive treatment in adults with EM in a daily dose of 400 mg [20, 159, 160].

3.5.2 Coenzyme Q10

Coenzyme Q10 has a similar action with riboflavin. In placebo-controlled studies, CoQ10 reduced the monthly headache days in adults with EM [161] but its efficacy in children and adolescents remains unclear [115]. There is Level C recommendation for its use as prophylactic treatment in EM [20, 160], and strong recommendation from the Canadian Headache Society (CHS) [159] in a dosage of 100 mg TID.

3.5.3 Magnesium

Magnesium deficiency may increase migraine susceptibility. Oral magnesium has been studied in migraine prophylaxis largely [162], as the intravenous $MgSO_4$ for the symptomatic treatment of migraine [163]. Oral magnesium is suggested for migraine prophylaxis with level B or C of evidence [20, 160], in a daily dose of 600 mg. A later meta-analysis downgraded the level of evidence, however [162]. Adverse events with magnesium are soft stool, diarrhea, and flushing. For the symptomatic treatment of migraine, intravenous $MgSO_4$ has failed to show beneficial effect in terms of reduction of pain and rescue medications, while several adverse effects reported questioning the clinical relevance of this symptomatic treatment [163].

3.5.4 Petasites hybridus or Butterbur

Petasites is a herbal extract, with moderate to good evidence of efficacy in migraine prevention [164, 165]. However, there are safety issues related with liver toxicity [166]. Yet, it is recommended as a second-choice treatment for the prevention of migraine [20, 167].

3.5.5 Tanacetum parthenium *(Feverfew)*

Feverfew is a medicinal plant that has been investigated for the migraine prophylaxis with controversial results. A recent review presents some positive findings in comparison to previous ones [168, 169]. Not major AEs are reported (usually mouth ulcers and gastrointestinal complaints). CHS does not recommend the use of Feverfew for migraine prevention; AAN/AHS recommends it as probably effective (level B) and EFNS as possibly effective (level C).

3.5.6 Ginkgolide-B

Ginkgolide-B is an extract from *Ginkgo biloba* tree that has shown efficacy in the prevention of migraine in a small-size, open label study [170], without any other confirmation.

3.5.7 Omega-3 polyunsaturated fatty acids (OPFAs)

The exact mechanism of OPFAs in migraine is unknown. One placebo-controlled study showed no significant difference between active and placebo group in reduction of migraine days [171].

3.6 Dietary interventions

Different types of dietary interventions have been suggested and studied in migraine prevention such as weight loss diet, low fat diets, ketogenic diets, and elimination diets, being the most popular and well-studied ones, and there are reports for several others. Because of the high comorbidity of headache with obesity, weight loss diet is a promising approach linked through inflammatory mediators that are released from adipose tissue. Nevertheless, it does not come out that weight loss or change in dietary intake may attenuate migraine frequency [172].

3.7 Acupuncture

Unrelated to placebo effect, a proportion of patients respond to acupuncture treatment in practice. From recently reviews, acupuncture shows at least not inferior efficacy in the prevention of migraine comparing to conventional prophylactic treatment at a 3-month follow-up vs. placebo, although there is lot of discussion about the high proportion of placebo effect in this procedure (no significant difference between verum acupuncture vs. sham acupuncture groups) [173, 174]. Only minor gastrointestinal AEs are reported. Despite the debatable mechanism of action and the methodological shortcomings of the relative research, the evidence suggests its use in migraine prevention, representing a therapeutic option for those patients who do not prefer medicinal treatments or display nocebo behaviors, which are very prevalent among migraineurs [11]. High recurrence rates after 6-month follow-up have been reported, however [174].

3.8 Physical therapy

The use of physical activity in alleviating the burden of migraine is unclear and data are missing. A cross-sectional study showed that physically active respondents had lower odds of migraine than moderately active respondents [175]. Physical treatment may have an effect, however, several musculoskeletal dysfunctions, in particular neck pain and vestibular symptoms have been reported to coexist with

migraine [176, 177]. Thus, physical interventions may improve clinical outcomes when combined with pharmacotherapy. These include manual treatment of trigger points and stretching of the sternocleidomastoid and upper trapezius muscles, among other techniques (e.g., relaxation and aerobic exercise). Although physical therapy is recommended [178], the evidence of efficacy is very limited, and the documentation is rather empirical. A meta-analysis of controlled trials found that physical therapy techniques reduced the duration of migraine attacks but had no effect on pain intensity and attack frequency [179]. Thus, further investigation is needed.

4. Cognitive behavioral therapies

Though it is generally believed that biofeedback, relaxation training, and CBT improve migraine treatment outcomes either alone, or more often, in combination with medications, the evidence is poor. In one randomized trial among young patients (10–17 years old) suffering from chronic migraine, the use of CBT (10 sessions) plus amitriptyline resulted in greater reductions in days with headache and migraine-related disability compared with the use of headache education plus amitriptyline [180]. A recent meta-analysis found that 54% of individuals with migraine reported at least 50% reduction in migraine frequency after psychological therapy, vs. 24% of controls [181]. Because CBT differs substantially from traditional psychotherapy, it focuses on here and now and it is typically time limited; this therapeutic option may help practitioners in migraine management, in pediatric populations in particular [182].

5. Patient centricity and patient education

Migraine is a heterogeneous disease with a spectrum of clinical manifestations varying between individuals. The choice of therapy requires an individual approach, as each patient is unique. Severity and frequency of attacks, disability causing, other symptoms, time to peak, patient preferences, comorbidities, drug interactions, side effects, and prior therapies that failed should be all taken into consideration [2]. Before proposing any therapeutic approach, local availability and accessibility to medications should also be considered. Patient preferences and needs of each individual are essential to achieve treatment adherence and patient-reported satisfaction. Fast-acting drugs are generally preferred from patients with migraine during acute attacks [183]. Effectiveness of drugs seems to be the most important issue regarding prophylactic treatment, followed by time to effect and adverse events [184]. Although patient centricity has been established in the last years, it is not yet a standard practice to include patients at all appropriate levels of decision-making processes that are related to their health and well-being. Patient education is also of great significance to ensure treatment adherence. This could be achieved by thoroughly explaining patients' disorder, purpose, and means of management. Ineffective clinician-patient communication is a major reason for patient treatment nonadherence. Patients thus should be counseled in advance on the potential benefits of the proposed therapy as well as on the treatment-related adverse effects that may appear. In conclusion, clinicians should always individualize their treatment strategy to the specific needs of each migraine sufferer, with multidisciplinary approaches, usually both pharmaceutical and non-pharmaceutical. Patients should be encouraged to take an active role in their own therapy [21]. Due to the heterogeneity of migraine, developers of guidelines should engage

patients and patients' organizations to identify and ensure that patient preferences and values are taken into account. Patient engagement should be a major part of migraine care decision-making, avoiding a population level "one-size-fits-all" solution.

Author details

Theodoros Mavridis[1*], Marianthi Breza[1], Christina I. Deligianni[1,2] and Dimos D. Mitsikostas[1]

1 1st Department of Neurology, Eginition Hospital, Medical School, National and Kapodistrian University of Athens, Athens, Greece

2 Neurology Department, Athens Naval Hospital, Athens, Greece

*Address all correspondence to: mavridismdr@gmail.com

References

[1] Terwindt GM. Emerging treatments for headache: Advances in 2019. The Lancet Neurology. 2020;**19**(1):7-8

[2] Mitsikostas DD, Paemeleire K. Pharmacological Management of Headaches. Springer; 2016. pp. 19-28

[3] Mitsikostas DD, Belesioti I, Arvaniti C, Mitropoulou E, Deligianni C, Kasioti E, et al. Patients' preferences for headache acute and preventive treatment. The Journal of Headache and Pain. 2017;**18**(1):102

[4] Tfelt-Hansen P, De Vries P, Saxena PR. Triptans in migraine. Drugs. 2000;**60**(6):1259-1287

[5] Sacco S, Bendtsen L, Ashina M, Reuter U, Terwindt G, Mitsikostas D-D, et al. European headache federation guideline on the use of monoclonal antibodies acting on the calcitonin gene related peptide or its receptor for migraine prevention. The Journal of Headache and Pain. 2019;**20**(1):6

[6] Green MW, Cowan R, Freitag FG. Chronic Headache: A Comprehensive Guide to Evaluation and Management. Springer; 2018. pp. 37-63

[7] Martelletti P, Jensen RH, Antal A, Arcioni R, Brighina F, de Tommaso M, et al. Neuromodulation of chronic headaches: Position statement from the European Headache Federation. The Journal of Headache and Pain. 2013;**14**(1):86

[8] Reuter U, McClure C, Liebler E, Pozo-Rosich P. Non-invasive neuromodulation for migraine and cluster headache: A systematic review of clinical trials. Journal of Neurology, Neurosurgery, and Psychiatry. 2019;**90**(7):796-804

[9] Rehman T, Ahmad S, Fatima Q. Effects of dietary supplementations and herbs on migraine—A systematic review. 2019;**16**(3):20180143

[10] Lee HJ, Lee JH, Cho EY, Kim SM, Yoon S. Efficacy of psychological treatment for headache disorder: A systematic review and meta-analysis. The Journal of Headache and Pain. 2019;**20**(1):17

[11] Mitsikostas DD. Nocebo in headache. Current Opinion in Neurology. 2016;**29**(3):331-336

[12] Steiner TJ, Jensen R, Katsarava Z, Linde M, MacGregor EA, Osipova V, et al. Aids to management of headache disorders in primary care (2nd edition). The Journal of Headache and Pain. 2019;**20**(1):57

[13] Steiner TJ, Lipton RB, Al Jumah M, Al-Khathami A, Allena M, Andrée C, et al. The headache-attributed lost time (HALT) indices: Measures of burden for clinical management and population-based research. The Journal of Headache and Pain. 2018;**19**(1):12

[14] Steiner TJ, Buse DC, Al Jumah M, Westergaard ML, Jensen RH, Reed ML, et al. The headache under-response to treatment (HURT) questionnaire, an outcome measure to guide follow-up in primary care: Development, psychometric evaluation and assessment of utility. The Journal of Headache and Pain. 2018;**19**(1):15

[15] Westergaard ML, Steiner TJ, MacGregor EA, Antonaci F, Tassorelli C, Buse DC, et al. The headache under-response to treatment (HURT) questionnaire: Assessment of utility in headache specialist care. The Journal of Headache and Pain. 2013;**33**(4):245-255

[16] Buse DC, Sollars CM, Steiner TJ, Jensen RH, Al Jumah MA, Lipton RB. Why HURT? A review of clinical

instruments for headache management. Current Pain and Headache Reports. 2012;**16**(3):237-254

[17] Bigal ME, Rapoport AM, Lipton RB, Tepper SJ, Sheftell FD. Assessment of migraine disability using the migraine disability assessment (MIDAS) questionnaire: A comparison of chronic migraine with episodic migraine. Headache. 2003;**43**(4):336-342

[18] Lipton RB, Stewart WF, Sawyer J, Edmeads JG. Clinical utility of an instrument assessing migraine disability: The migraine disability assessment (MIDAS) questionnaire. Headache. 2001;**41**(9):854-861

[19] Headache Classification Committee of the International Headache Society (IHS). The International Classification of Headache Disorders. Vol. 38(1), 3rd ed. 2018. pp. 1-211

[20] Evers S, Áfra J, Frese A, Goadsby PJ, Linde M, May A, et al. EFNS guideline on the drug treatment of migraine—Revised report of an EFNS task force. European Journal of Neurology. 2009;**16**(9):968-981

[21] Kouremenos E, Arvaniti C, Constantinidis TS, Giannouli E, Fakas N, Kalamatas T, et al. Consensus of the Hellenic Headache Society on the diagnosis and treatment of migraine. The Journal of Headache and Pain. 2019;**20**(1):113

[22] Agostoni EC, Barbanti P, Calabresi P, Colombo B, Cortelli P, Frediani F, et al. Current and emerging evidence-based treatment options in chronic migraine: A narrative review. The Journal of Headache and Pain. 2019;**20**(1):92

[23] Capobianco DJ, Cheshire WP, Campbell JK. An overview of the diagnosis and pharmacologie treatment of migraine. Mayo Clinic Proceedings. 1996;**71**(11):1055-1066

[24] Jonathan HS. Acute treatment of migraine in adults. In: Post T, ed. UpToDate. Waltham, MA: UpToDate; 2020 [Accessed: 13 April 2020]

[25] MaassenVanDenBrink A, Reekers M, Bax WA, Ferrari MD, Saxena PR. Coronary side-effect potential of current and prospective antimigraine drugs. Circulation. 1998;**98**(1):25-30

[26] Becker WJ. The diagnosis and management of chronic migraine in primary care. Headache. 2017;**57**(9):1471-1481

[27] Nagy AJ, Gandhi S, Bhola R, Goadsby PJ. Intravenous dihydroergotamine for inpatient management of refractory primary headaches. Neurology. 2011;**77**(20):1827-1832

[28] Tfelt-Hansen P, Saxena PR, Dahlöf C, Pascual J, Láinez M, Henry P, et al. Ergotamine in the acute treatment of migraine: A review and European consensus. Brain. 2000;**123**(1):9-18

[29] Randomized A. Double-blind comparison of sumatriptan and cafergot in the acute treatment of migraine. European Neurology. 1991;**31**(5):314-322

[30] Christie S, Göbel H, Mateos V, Allen C, Vrijens F, Shivaprakash M. Crossover comparison of efficacy and preference for rizatriptan 10 mg versus ergotamine/caffeine in migraine. European Neurology. 2003;**49**(1):20-29

[31] Diener HC, Jansen JP, Reches A, Pascual J, Pitei D, Steiner TJ. Efficacy, tolerability and safety of oral eletriptan and ergotamine plus caffeine (Cafergot®) in the acute treatment of migraine: A multicentre, randomised, double-blind, placebo-controlled comparison. European Neurology. 2002;**47**(2):99-107

[32] Láinez MJA, Galván J, Heras J, Vila C. Crossover, double-blind clinical trial comparing almotriptan and ergotamine plus caffeine for acute migraine therapy. European Journal of Neurology. 2007;**14**(3):269-275

[33] Thorlund K, Mills EJ, Wu P, Ramos E, Chatterjee A, Druyts E, et al. Comparative efficacy of triptans for the abortive treatment of migraine: A multiple treatment comparison meta-analysis. Cephalalgia. 2014;**34**(4):258-267

[34] Dahlöf C. Infrequent or non-response to oral sumatriptan does not predict response to other triptans—Review of four trials. Cephalagia. 2006;**26**(2):98-106

[35] Ferrari MD, Roon KI, Lipton RB, Goadsby PJ. Oral triptans (serotonin 5-$HT_{1B/1D}$ agonists) in acute migraine treatment: A meta-analysis of 53 trials. The Lancet. 2001;**358**(9294):1668-1675

[36] Johnston MM, Rapoport AM. Triptans for the management of migraine. Drugs. 2010;**70**(12):1505-1518

[37] Roberto G, Raschi E, Piccinni C, Conti V, Vignatelli L, D'Alessandro R, et al. Adverse cardiovascular events associated with triptans and ergotamines for treatment of migraine: Systematic review of observational studies. Cephalalgia: An International Journal of Headache. 2014;**35**(2):118-131

[38] Hall GC, Brown MM, Mo J, MacRae KD. Triptans in migraine: The risks of stroke, cardiovascular disease, and death in practice. Neurology. 2004;**62**(4):563-568

[39] Goadsby PJ, Wietecha LA, Dennehy EB, Kuca B, Case MG, Aurora SK, et al. Phase 3 randomized, placebo-controlled, double-blind study of lasmiditan for acute treatment of migraine. Brain. 2019;**142**(7):1894-1904

[40] Oswald JC, Schuster NM. Lasmiditan for the treatment of acute migraine: A review and potential role in clinical practice. Journal of Pain Research. 2018;**11**:2221-2227

[41] Kuca B, Silberstein SD, Wietecha L, Berg PH, Dozier G, Lipton RB. Lasmiditan is an effective acute treatment for migraine. A phase 3 randomized study. Neurology. 2018;**91**(24):e2222-e2232

[42] Tepper SJ, Krege JH, Lombard L, Asafu-Adjei JK, Dowsett SA, Raskin J, et al. Characterization of dizziness after lasmiditan usage: Findings from the SAMURAI and SPARTAN acute migraine treatment randomized trials. Headache. 2019;**59**(7):1052-1062

[43] Moreno-Ajona D, Pérez-Rodríguez A, Goadsby PJ. Gepants, calcitonin-gene-related peptide receptor antagonists: What could be their role in migraine treatment? Current Opinion in Neurology. 2020;**33**(3):309-315

[44] Marmura MJ, Silberstein SD, Schwedt TJ. The acute treatment of migraine in adults: The American Headache Society evidence assessment of migraine pharmacotherapies. Headache. 2015;**55**(1):3-20

[45] Kirthi V, Derry S, Moore RA. Aspirin with or without an antiemetic for acute migraine headaches in adults. Cochrane Database of Systematic Reviews. 2013;**4**:Cd008041

[46] Biglione B, Gitin A, Gorelick PB, Hennekens C. Aspirin in the treatment and prevention of migraine headaches: Possible additional clinical options for primary healthcare providers. The American Journal of Medicine. 2020;**133**(4):412-416

[47] Rabbie R, Derry S, Moore RA. Ibuprofen with or without an antiemetic for acute migraine headaches in adults.

Cochrane Database Systematic Reviews. 2013;**4**:Cd008039

[48] Law S, Derry S, Moore RA. Naproxen with or without an antiemetic for acute migraine headaches in adults. Cochrane Database Systematic Reviews. 2013;**10**:Cd009455

[49] Derry S, Rabbie R, Moore RA. Diclofenac with or without an antiemetic for acute migraine headaches in adults. Cochrane Database Systematic Reviews. 2013;**4**:Cd008783

[50] Myllylä VV, Havanka H, Herrala L, Kangasniemi P, Rautakorpi I, Turkka J, et al. Tolfenamic acid rapid release versus sumatriptan in the acute treatment of migraine: Comparable effect in a double-blind, randomized, controlled, parallel-group study. Headache. 1998;**38**(3):201-207

[51] Gungor F, Akyol KC, Kesapli M, Celik A, Karaca A, Bozdemir MN, et al. Intravenous dexketoprofen vs placebo for migraine attack in the emergency department: A randomized, placebo-controlled trial. Cephalalgia: An International Journal of Headache. 2016;**36**(2):179-184

[52] Lipton RB, Stewart WF, Ryan RE Jr, Saper J, Silberstein S, Sheftell F. Efficacy and safety of acetaminophen, aspirin, and caffeine in alleviating migraine headache pain: Three double-blind, randomized, placebo-controlled trials. Archives of Neurology. 1998;**55**(2):210-217

[53] Diener H, Pfaffenrath V, Pageler L, Peil H, Aicher B. The fixed combination of acetylsalicylic acid, paracetamol and caffeine is more effective than single substances and dual combination for the treatment of headache: A multicentre, randomized, double-blind, single-dose, placebo-controlled parallel group study. Cephalalgia: An International Journal of Headache. 2005;**25**(10):776-787

[54] Goldstein J, Silberstein SD, Saper JR, Ryan RE Jr, Lipton RB. Acetaminophen, aspirin, and caffeine in combination versus ibuprofen for acute migraine: Results from a multicenter, double-blind, randomized, parallel-group, single-dose, placebo-controlled study. Headache. 2006;**46**(3):444-453

[55] Orr SL, Aubé M, Becker WJ, Davenport WJ, Dilli E, Dodick D, et al. Canadian Headache Society systematic review and recommendations on the treatment of migraine pain in emergency settings. Cephalalgia: An International Journal of Headache. 2015;**35**(3):271-284

[56] BET 1: Metoclopramide or prochlorperazine for headache in acute migraine? Emergency Medicine Journal. 2013;**30**(7):595-596

[57] Friedman BW, Irizarry E, Solorzano C, Latev A, Rosa K, Zias E, et al. Randomized study of IV prochlorperazine plus diphenhydramine vs IV hydromorphone for migraine. Neurology. 2017;**89**(20):2075-2082

[58] Kostic MA, Gutierrez FJ, Rieg TS, Moore TS, Gendron RT. A prospective, randomized trial of intravenous prochlorperazine versus subcutaneous sumatriptan in acute migraine therapy in the emergency department. Annals of Emergency Medicine. 2010;**56**(1):1-6

[59] Bigal ME, Bordini CA, Speciali JG. Intravenous chlorpromazine in the Emergency Department treatment of migraines: A randomized controlled trial. Journal of Emergency Medicine. 2002;**23**(2):141-148

[60] Mazaheri S, Poorolajal J, Hosseinzadeh A, Fazlian MM. Effect of intravenous sodium valproate vs dexamethasone on acute migraine headache: A double blind randomized clinical trial. PLoS One. 2015;**10**(3):e0120229

[61] Edwards KR, Norton J, Behnke M. Comparison of intravenous valproate versus intramuscular dihydroergotamine and metoclopramide for acute treatment of migraine headache. 2001;**41**(10):976-980

[62] Leniger T, Pageler L, Stude P, Diener HC, Limmroth V. Comparison of intravenous valproate with intravenous lysine-acetylsalicylic acid in acute migraine attacks. Headache. 2005;**45**(1):42-46

[63] Colman I, Friedman BW, Brown MD, Innes GD, Grafstein E, Roberts TE, et al. Parenteral dexamethasone for acute severe migraine headache: Meta-analysis of randomised controlled trials for preventing recurrence. BMJ. 2008;**336**(7657):1359-1361

[64] Singh A, Alter HJ, Zaia B. Does the addition of dexamethasone to standard therapy for acute migraine headache decrease the incidence of recurrent headache for patients treated in the emergency department? A meta-analysis and systematic review of the literature. Annals of Emergency Medicine. 2008;**15**(12):1223-1233

[65] Silberstein SD, Freitag FG, Rozen TD, Kudrow DB, Hewitt DJ, Jordan DM, et al. Tramadol/acetaminophen for the treatment of acute migraine pain: Findings of a randomized, placebo-controlled trial. Headache. 2005;**45**(10):1317-1327

[66] Giamberardino MA, Affaitati G, Costantini R, Cipollone F, Martelletti P. Calcitonin gene-related peptide receptor as a novel target for the management of people with episodic migraine: Current evidence and safety profile of erenumab. Journal of Pain Research. 2017;**10**(0):2751-2760

[67] Wrobel Goldberg S, Silberstein SD. Targeting CGRP: A new era for migraine treatment. CNS Drugs. 2015;**29**(6):443-452

[68] Bigal ME, Walter S, Bronson M, Alibhoy A, Escandon R. Cardiovascular and hemodynamic parameters in women following prolonged CGRP inhibition using LBR-101, a monoclonal antibody against CGRP. Cephalalgia: An International Journal of Headache. 2014;**34**(12):968-976

[69] Edvinsson L. CGRP receptor antagonists and antibodies against CGRP and its receptor in migraine treatment. British Journal of Clinical Pharmacology. 2015;**80**(2):193-199

[70] Edvinsson L. The journey to establish CGRP as a migraine target: A retrospective view. Headache. 2015;**55**(9):1249-1255

[71] Martelletti P. Erenumab is effective in reducing migraine frequency and improving physical functioning. BMJ Evidence-Based Medicine. 2018;24(2):76

[72] Edvinsson L, Haanes KA, Warfvinge K, Krause DN. CGRP as the target of new migraine therapies—Successful translation from bench to clinic. Nature Reviews. Neurology. 2018;**14**(6):338-350

[73] Vu T, Ma P, Chen J, Hoon J, Van Hecken A, Yan L, et al. Characterizing the relationship between AMG 334 concentration and capsaicin-induced increase in dermal blood flow in healthy subjects and migraine patients using pharmacokinetic-pharmacodynamic modeling. Headache. 2015;**55**(0):175-176

[74] Sun H, Dodick DW, Silberstein S, Goadsby PJ, Reuter U, Ashina M, et al. Safety and efficacy of AMG 334 for prevention of episodic migraine: A randomised, double-blind, placebo-controlled, phase 2 trial. The Lancet Neurology. 2016;**15**(4):382-390

[75] de Hoon J, Van Hecken A, Vandermeulen C, Yan L, Smith B, Chen JS, et al. Phase I, randomized, double-blind, placebo-controlled, single-dose, and multiple-dose studies of erenumab in healthy subjects and patients with migraine. Clinical pharmacology and therapeutics. 2018;**103**(5):815-825

[76] Goadsby PJ, Reuter U, Hallstrom Y, Broessner G, Bonner JH, Zhang F, et al. A controlled trial of erenumab for episodic migraine. The New England Journal of Medicine. 2017;**377**(22):2123-2132

[77] Ornello R, Tiseo C, Frattale I, Perrotta G, Marini C, Pistoia F, et al. The appropriate dosing of erenumab for migraine prevention after multiple preventive treatment failures: A critical appraisal. The Journal of Headache and Pain. 2019;**20**(1):99

[78] Bigal ME, Escandon R, Bronson M, Walter S, Sudworth M, Huggins JP, et al. Safety and tolerability of LBR-101, a humanized monoclonal antibody that blocks the binding of CGRP to its receptor: Results of the Phase 1 program. Cephalalgia: An International Journal of Headache. 2014;**34**(7):483-492

[79] Dodick DW, Silberstein SD, Bigal ME, Yeung PP, Goadsby PJ, Blankenbiller T, et al. Effect of fremanezumab compared with placebo for prevention of episodic migraine: A randomized clinical trial. JAMA. 2018;**319**(19):1999-2008

[80] Vermeersch S, Benschop RJ, Van Hecken A, Monteith D, Wroblewski VJ, Grayzel D, et al. Translational pharmacodynamics of calcitonin gene-related peptide monoclonal antibody LY2951742 in a capsaicin-induced dermal blood flow model. Journal of Pharmacology and Experimental Therapeutics. 2015;**354**(3):350-357

[81] Stauffer VL, Dodick DW, Zhang Q, Carter JN, Ailani J, Conley RR. Evaluation of galcanezumab for the prevention of episodic migraine: The EVOLVE-1 randomized clinical trial. JAMA Neurology. 2018;**75**(9):1080-1088

[82] Skljarevski V, Oakes TM, Zhang Q, Ferguson MB, Martinez J, Camporeale A, et al. Effect of different doses of galcanezumab vs placebo for episodic migraine prevention: A randomized clinical trial. JAMA Neurology. 2018;**75**(2):187-193

[83] Skljarevski V, Matharu M, Millen BA, Ossipov MH, Kim BK, Yang JY. Efficacy and safety of galcanezumab for the prevention of episodic migraine: Results of the EVOLVE-2 Phase 3 randomized controlled clinical trial. Cephalalgia: An International Journal of Headache. 2018;**38**(8):1442-1454

[84] Gklinos P, Mitsikostas DD. Galcanezumab in migraine prevention: A systematic review and meta-analysis of randomized controlled trials. Therapeutic Advances in Neurological Disorders. 2020;**13**:1756286420918088

[85] Dodick DW, Goadsby PJ, Silberstein SD, Lipton RB, Olesen J, Ashina M, et al. Safety and efficacy of ALD403, an antibody to calcitonin gene-related peptide, for the prevention of frequent episodic migraine: A randomised, double-blind, placebo-controlled, exploratory phase 2 trial. The Lancet Neurology. 2014;**13**(11):1100-1107

[86] Ashina M, Saper J, Cady R, Schaeffler BA, Biondi DM, Hirman J, et al. Eptinezumab in episodic migraine: A randomized, double-blind, placebo-controlled study (PROMISE-1). Cephalalgia: An International Journal of Headache. 2020;**40**(3):241-254

[87] Kudrow D, Lipton R, Silberstein S, Cady R, Schaeffler B, Biondi D, et al.

Eptinezumab for prevention of chronic migraine: Results of 2 infusions in the phase 3 PROMISE-2 (prevention of migraine via intravenous eptinezumab safety and efficacy–2) trial (P2.10-006). Neurology. 2019;**92**(15 Supplement) P2.10-006

[88] Shamliyan TA, Choi J-Y, Ramakrishnan R, Miller JB, Wang S-Y, Taylor FR, et al. Preventive pharmacologic treatments for episodic migraine in adults. Journal of General Internal Medicine. 2013;**28**(9):1225-1237

[89] Brandes JL, Saper JR, Diamond M, Couch JR, Lewis DW, Schmitt J, et al. Topiramate for migraine prevention: A randomized controlled trial. JAMA. 2004;**291**(8):965-973

[90] Silberstein SD, Neto W, Schmitt J, Jacobs D, Group ftM-S. Topiramate in migraine prevention: Results of a large controlled trial. Archives of Neurology. 2004;**61**(4):490-495

[91] Diener H-C, Bussone G, Oene JV, Lahaye M, Schwalen S, Goadsby P. Topiramate reduces headache days in chronic migraine: A randomized, double-blind, placebo-controlled study. Cephalalgia: An International Journal of Headache. 2007;**27**(7):814-823

[92] Diener H-C, Agosti R, Allais G, Bergmans P, Bussone G, Davies B, et al. Cessation versus continuation of 6-month migraine preventive therapy with topiramate (PROMPT): A randomised, double-blind, placebo-controlled trial. The Lancet Neurology. 2007;**6**(12):1054-1062

[93] Linde M, Mulleners WM, Chronicle EP, McCrory DC. Topiramate for the prophylaxis of episodic migraine in adults. Cochrane Database of Systematic Reviews. 2013;**6**

[94] Jonathan HS. Preventive treatment of migraine in adults. In: Post T, editor. UpToDate. Waltham, MA: UpToDate; 2020 [Accessed: 13 April 2020]

[95] Linde M, Mulleners WM, Chronicle EP, McCrory DC. Valproate (valproic acid or sodium valproate or a combination of the two) for the prophylaxis of episodic migraine in adults. Cochrane Database of Systematic Reviews. 2013;**6**:CD010611

[96] Linde M, Mulleners WM, Chronicle EP, McCrory DC. Gabapentin or pregabalin for the prophylaxis of episodic migraine in adults. Cochrane Database of Systematic Reviews. 2013;**6**:CD010609

[97] Mulleners WM, McCrory DC, Linde M. Antiepileptics in migraine prophylaxis: An updated Cochrane review. Cephalalgia. 2015;**35**(1):51-62

[98] Law M, Morris JK, Jordan R, Wald N. Headaches and the treatment of blood pressure. Circulation. 2005;**112**(15):2301-2306

[99] Larochelle P, Tobe SW, Lacourcière Y. β-Blockers in hypertension: Studies and meta-analyses over the years. Canadian Journal of Cardiology. 2014;**30**(5):S16-S22

[100] Schumann S-A, Hickner J. When not to use beta-blockers in seniors with hypertension. The Journal of family practice. 2008;**57**(1):18-21

[101] Jackson JL, Kuriyama A, Kuwatsuka Y, Nickoloff S, Storch D, Jackson W, et al. Beta-blockers for the prevention of headache in adults, a systematic review and meta-analysis. PLoS One. 2019;**14**(3):e0212785

[102] Stubberud A, Flaaen NM, McCrory DC, Pedersen SA, Linde M. Flunarizine as prophylaxis for episodic migraine: A systematic review with meta-analysis. Pain. 2019;**160**(4):762-772

[103] Pringsheim T, Davenport WJ, Becker WJ. Prophylaxis of migraine headache. Canadian

Medical Association Journal. 2010;**182**(7):E269-E276

[104] Tronvik E, Stovner LJ, Helde G, Sand T, Bovim G. Prophylactic treatment of migraine with an angiotensin II receptor blocker: A randomized controlled trial. JAMA. 2003;**289**(1):65-69

[105] Stovner LJ, Linde M, Gravdahl GB, Tronvik E, Aamodt AH, Sand T, et al. A comparative study of candesartan versus propranolol for migraine prophylaxis: A randomised, triple-blind, placebo-controlled, double cross-over study. Cephalalgia: An International Journal of Headache. 2014;**34**(7):523-532

[106] Schrader H, Stovner LJ, Helde G, Sand T, Bovim G. Prophylactic treatment of migraine with angiotensin converting enzyme inhibitor (lisinopril): Randomised, placebo controlled, crossover study. British Medical Journal. 2001;**322**(7277):19

[107] Evers S, Vollmer-Haase J, Schwaag S, Rahmann A, Husstedt I-W, Frese A. Botulinum toxin A in the prophylactic treatment of migraine—A randomized, double-blind, placebo-controlled study. Cephalalgia: An International Journal of Headache. 2004;**24**(10):838-843

[108] Elkind AH, O'Carroll P, Blumenfeld A, DeGryse R, Dimitrova R. A series of three sequential, randomized, controlled studies of repeated treatments with botulinum toxin type A for migraine prophylaxis. The Journal of Pain. 2006;**7**(10):688-696

[109] Silberstein S, Mathew N, Saper J, Jenkins S, Group ftBMCR. Botulinum toxin type A as a migraine preventive treatment. Headache. 2000;**40**(6):445-450

[110] Aurora SK, Dodick DW, Diener H-C, DeGryse RE, Turkel CC, Lipton RB, et al. OnabotulinumtoxinA for chronic migraine: Efficacy, safety, and tolerability in patients who received all five treatment cycles in the PREEMPT clinical program. Acta Neurologica Scandinavica. 2014;**129**(1):61-70

[111] Diener H-C, Dodick DW, Turkel CC, Demos G, DeGryse RE, Earl NL, et al. Pooled analysis of the safety and tolerability of onabotulinumtoxinA in the treatment of chronic migraine. European Journal of Neurology. 2014;**21**(6):851-859

[112] Bendtsen L, Sacco S, Ashina M, Mitsikostas D, Ahmed F, Pozo-Rosich P, et al. Guideline on the use of onabotulinumtoxinA in chronic migraine: A consensus statement from the European Headache Federation. The Journal of Headache and Pain. 2018;**19**(1):91

[113] Pijpers JA, Kies DA, Louter MA, van Zwet EW, Ferrari MD, Terwindt GM. Acute withdrawal and botulinum toxin A in chronic migraine with medication overuse: A double-blind randomized controlled trial. Brain. 2019;**142**(5):1203-1214

[114] Lipton R, Goadsby P, Cady R, Aurora S, Grosberg B, Freitag F, et al. PRISM study: occipital nerve stimulation for treatment-refractory migraine: PO47. Cephalalgia: An International Journal of Headache. 2009;**29**:30

[115] Saper JR, Dodick DW, Silberstein SD, McCarville S, Sun M, Goadsby PJ. Occipital nerve stimulation for the treatment of intractable chronic migraine headache: ONSTIM feasibility study. Cephalalgia: An International Journal of Headache. 2011;**31**(3):271-285

[116] Silberstein SD, Dodick DW, Saper J, Huh B, Slavin KV, Sharan A, et al. Safety and efficacy of peripheral nerve stimulation of the occipital nerves for the management of chronic

migraine: Results from a randomized, multicenter, double-blinded, controlled study. Cephalalgia: An International Journal of Headache. 2012;**32**(16):1165-1179

[117] Natsis K, Baraliakos X, Appell HJ, Tsikaras P, Gigis I, Koebke J. The course of the greater occipital nerve in the suboccipital region: A proposal for setting landmarks for local anesthesia in patients with occipital neuralgia. Clinical Anatomy. 2006;**19**(4):332-336

[118] Hord ED, Evans MS, Mueed S, Adamolekun B, Naritoku DK. The effect of vagus nerve stimulation on migraines. The Journal of Pain. 2003;**4**(9):530-534

[119] Lenaerts M, Oommen K, Couch J, Skaggs V. Can vagus nerve stimulation help migraine? Cephalalgia: An International Journal of Headache. 2008;**28**(4):392-395

[120] De Agostino R, Federspiel B, Cesnulis E, Sandor PS. High-cervical spinal cord stimulation for medically intractable chronic migraine. Neuromodulation. 2015;**18**(4):289-296

[121] Arcioni R, Palmisani S, Mercieri M, Vano V, Tigano S, Smith T, et al. Cervical 10 kHz spinal cord stimulation in the management of chronic, medically refractory migraine: A prospective, open-label, exploratory study. European Journal of Pain. 2016;**20**(1):70-78

[122] Lauritsen CG, Silberstein SD. Rationale for electrical parameter determination in external trigeminal nerve stimulation (eTNS) for migraine: A narrative review. Cephalalgia: An International Journal of Headache. 2019;**39**(6):750-760

[123] Chou DE, Shnayderman Yugrakh M, Winegarner D, Rowe V, Kuruvilla D, Schoenen J. Acute migraine therapy with external trigeminal neurostimulation (ACME): A randomized controlled trial. Cephalalgia: An International Journal of Headache. 2019;**39**(1):3-14

[124] Schoenen J, Vandersmissen B, Jeangette S, Herroelen L, Vandenheede M, Gérard P, et al. Migraine prevention with a supraorbital transcutaneous stimulator. A randomized controlled trial. Neurology. 2013;**80**(8):697-704

[125] Mitsikostas DD, Rapoport AM. New players in the preventive treatment of migraine. BMC Medicine. 2015;**13**(1):279

[126] Andreou AP, Holland PR, Akerman S, Summ O, Fredrick J, Goadsby PJ. Transcranial magnetic stimulation and potential cortical and trigeminothalamic mechanisms in migraine. Brain. 2016;**139**(7):2002-2014

[127] Lipton RB, Dodick DW, Silberstein SD, Saper JR, Aurora SK, Pearlman SH, et al. Single-pulse transcranial magnetic stimulation for acute treatment of migraine with aura: A randomised, double-blind, parallel-group, sham-controlled trial. The Lancet Neurology. 2010;**9**(4):373-380

[128] Clarke BM, Upton ARM, Kamath MV, Al-Harbi T, Castellanos CM. Transcranial magnetic stimulation for migraine: clinical effects. The Journal of Headache and Pain. 2006;**7**(5):341-346

[129] Bhola R, Kinsella E, Giffin N, Lipscombe S, Ahmed F, Weatherall M, et al. Single-pulse transcranial magnetic stimulation (sTMS) for the acute treatment of migraine: Evaluation of outcome data for the UK post market pilot program. The Journal of Headache and Pain. 2015;**16**(1):51

[130] Irwin SL, Qubty W, Allen IE, Patniyot I, Goadsby PJ, Gelfand AA. Transcranial magnetic stimulation for migraine prevention in adolescents: A pilot open-label study. Headache. 2018;**58**(5):724-731

[131] Starling AJ, Tepper SJ, Marmura MJ, Shamim EA, Robbins MS, Hindiyeh N, et al. A multicenter, prospective, single arm, open label, observational study of sTMS for migraine prevention (ESPOUSE Study). Cephalalgia: An International Journal of Headache. 2018;**38**(6):1038-1048

[132] Brighina F, Piazza A, Vitello G, Aloisio A, Palermo A, Daniele O, et al. rTMS of the prefrontal cortex in the treatment of chronic migraine: A pilot study. Journal of the Neurological Sciences. 2004;**227**(1):67-71

[133] Misra UK, Kalita J, Bhoi SK. High-rate repetitive transcranial magnetic stimulation in migraine prophylaxis: A randomized, placebo-controlled study. Journal of Neurology. 2013;**260**(11):2793-2801

[134] Conforto AB, Amaro E, Gonçalves AL, Mercante JP, Guendler VZ, Ferreira JR, et al. Randomized, proof-of-principle clinical trial of active transcranial magnetic stimulation in chronic migraine. Cephalalgia: An International Journal of Headache. 2014;**34**(6):464-472

[135] Stilling JM, Monchi O, Amoozegar F, Debert CT. Transcranial magnetic and direct current stimulation (TMS/tDCS) for the treatment of headache: A systematic review. Headache. 2019;**59**(3):339-357

[136] Morais A, Liu TT, Qin T, Sadhegian H, Ay I, Yagmur D, et al. Vagus nerve stimulation inhibits cortical spreading depression exclusively through central mechanisms. Pain. 2020;161(7):1661-1669

[137] Tassorelli C, Grazzi L, de Tommaso M, Pierangeli G, Martelletti P, Rainero I, et al. Noninvasive vagus nerve stimulation as acute therapy for migraine. The randomized PRESTO study. Neurology. 2018;**91**(4):e364-e373

[138] Silberstein SD, Calhoun AH, Lipton RB, Grosberg BM, Cady RK, Dorlas S, et al. Chronic migraine headache prevention with noninvasive vagus nerve stimulation. The EVENT study. 2016;**87**(5):529-538

[139] Diener H-C, Charles A, Goadsby PJ, Holle D. New therapeutic approaches for the prevention and treatment of migraine. The Lancet Neurology. 2015;**14**(10):1010-1022

[140] Diener H-C, Goadsby PJ, Ashina M, Al-Karagholi MA-M, Sinclair A, Mitsikostas D, et al. Non-invasive vagus nerve stimulation (nVNS) for the preventive treatment of episodic migraine: The multicentre, double-blind, randomised, sham-controlled PREMIUM trial. 2019;**39**(12):1475-1487

[141] Martelletti P, Barbanti P, Grazzi L, Pierangeli G, Rainero I, Geppetti P, et al. Consistent effects of non-invasive vagus nerve stimulation (nVNS) for the acute treatment of migraine: Additional findings from the randomized, sham-controlled, double-blind PRESTO trial. The Journal of Headache and Pain. 2018;**19**(1):101

[142] Grazzi L, Egeo G, Calhoun AH, McClure CK, Liebler E, Barbanti P. Non-invasive vagus nerve stimulation (nVNS) as mini-prophylaxis for menstrual/menstrually related migraine: An open-label study. The Journal of Headache and Pain. 2016;**17**(1):91

[143] Nir RR, Yarnitsky D. Conditioned pain modulation. Current Opinion

in Supportive and Palliative Care. 2015;**9**(2):131-137

[144] Yarnitsky D, Volokh L, Ironi A, Weller B, Shor M, Shifrin A, et al. Nonpainful remote electrical stimulation alleviates episodic migraine pain. Neurology. 2017;**88**(13):1250-1255

[145] Yarnitsky D, Dodick DW, Grosberg BM, Burstein R, Ironi A, Harris D, et al. Remote electrical neuromodulation (REN) relieves acute migraine: A randomized, double-blind, placebo-controlled, multicenter trial. Headache. 2019;**59**(8):1240-1252

[146] Rapoport AM, Bonner JH, Lin T, Harris D, Gruper Y, Ironi A, et al. Remote electrical neuromodulation (REN) in the acute treatment of migraine: A comparison with usual care and acute migraine medications. The Journal of Headache and Pain. 2019;**20**(1):83

[147] DaSilva AF, Mendonca ME, Zaghi S, Lopes M, DosSantos MF, Spierings EL, et al. tDCS-induced analgesia and electrical fields in pain-related neural networks in chronic migraine. Headache. 2012;**52**(8):1283-1295

[148] Antal A, Kriener N, Lang N, Boros K, Paulus W. Cathodal transcranial direct current stimulation of the visual cortex in the prophylactic treatment of migraine. Cephalalgia. 2011;**31**(7):820-828

[149] Przeklasa-Muszyńska A, Kocot-Kępska M, Dobrogowski J, Wiatr M, Mika J. Transcranial direct current stimulation (tDCS) and its influence on analgesics effectiveness in patients suffering from migraine headache. Pharmacological Reports. 2017;**69**(4):714-721

[150] Auvichayapat P, Janyacharoen T, Rotenberg A, Tiamkao S, Krisanaprakornkit T, Sinawat S, et al. Migraine prophylaxis by anodal transcranial direct current stimulation, a randomized, placebo-controlled trial. Journal of the Medical Association of Thailand. 2012;**95**(8):1003-1012

[151] Reis DJ, Kobylarz K, Yamamoto S, Golanov EV. Brief electrical stimulation of cerebellar fastigial nucleus conditions long-lasting salvage from focal cerebral ischemia: Conditioned central neurogenic neuroprotection. Brain Research. 1998;**780**(1):161-165

[152] Juan Y, Shu O, Jinhe L, Na Y, Yushuang D, Weiwei D, et al. Migraine prevention with percutaneous mastoid electrical stimulator: A randomized double-blind controlled trial. Cephalalgia. 2017;**37**(13):1248-1256

[153] Brower V. Nutraceuticals: Poised for a healthy slice of the healthcare market? Nature Biotechnology. 1998;**16**(8):728-731

[154] Orr SL. Diet and nutraceutical interventions for headache management: A review of the evidence. Cephalalgia. 2016;**36**(12):1112-1133

[155] Gross EC, Lisicki M, Fischer D, Sándor PS, Schoenen J. The metabolic face of migraine—From pathophysiology to treatment. Nature Reviews. Neurology. 2019;**15**(11):627-643

[156] Schoenen J, Jacquy J, Lenaerts M. Effectiveness of high-dose riboflavin in migraine prophylaxis A randomized controlled trial. Neurology. 1998;**50**(2):466-470

[157] MacLennan SC, Wade FM, Forrest KML, Ratanayake PD, Fagan E, Antony J. High-dose riboflavin for migraine prophylaxis in children: A double-blind, randomized, placebo-controlled trial. Journal of Child Neurology. 2008;**23**(11):1300-1304

[158] Gaul C, Diener H-C, Danesch U, on behalf of the Migravent® Study G. Improvement of migraine symptoms with a proprietary supplement containing riboflavin, magnesium and Q10: A randomized, placebo-controlled, double-blind, multicenter trial. The Journal of Headache and Pain. 2015;**16**(1):32

[159] Pringsheim T, Davenport W, Mackie G, Worthington I, Aube M, Christie SN, et al. Canadian Headache Society guideline for migraine prophylaxis. Canadian Journal of Neurological Sciences. 2012;**39** (2 Suppl 2):S1-S59

[160] Silberstein SD, Holland S, Freitag F, Dodick DW, Argoff C, Ashman E. Evidence-based guideline update: Pharmacologic treatment for episodic migraine prevention in adults. Report of the Quality Standards Subcommittee of the American Academy of Neurology and the American Headache Society. Neurology. 2012;**78**(17):1337-1345

[161] 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. 2005;**64**(4):713-715

[162] Teigen L, Boes CJ. An evidence-based review of oral magnesium supplementation in the preventive treatment of migraine. 2015;**35**(10):912-922

[163] Choi H, Parmar N. The use of intravenous magnesium sulphate for acute migraine: Meta-analysis of randomized controlled trials. European Journal of Emergency Medicine. 2014;**21**(1):2-9

[164] Agosti R, Duke RK, Chrubasik JE, Chrubasik S. Effectiveness of petasites hybridus preparations in the prophylaxis of migraine: A systematic review. Phytomedicine. 2006;**13**(9):743-746

[165] Prieto JMJBTT. Update on the efficacy and safety of Petadolex®, a butterbur extract for migraine prophylaxis. 2014;**4**:1-9

[166] Rajapakse T, Pringsheim T. Nutraceuticals in migraine: A summary of existing guidelines for use. Botanics: Targets and Therapy. 2016;**56**(4):808-816

[167] Holland S, Silberstein SD, Freitag F, Dodick DW, Argoff C, Ashman E. Evidence-based guideline update: NSAIDs and other complementary treatments for episodic migraine prevention in adults: [RETIRED]. Report of the Quality Standards Subcommittee of the American Academy of Neurology and the American Headache Society. 2012;**78**(17):1346-1353

[168] Pittler MH, Ernst E. Feverfew for preventing migraine. Cochrane Database of Systematic Reviews. 2004;**1**:CD002286

[169] Wider B, Pittler MH, Ernst E. Feverfew for preventing migraine. Cochrane Database of Systematic Reviews. 2015;**4**:CD002286

[170] Usai S, Grazzi L, Bussone G. Gingkolide B as migraine preventive treatment in young age: Results at 1-year follow-up. Neurological Sciences. 2011;**32**(1):197-199

[171] Pradalier A, Bakouche P, Baudesson G, Delage A, Cornaille-Lafage G, Launay J, et al. Failure of omega-3 polyunsaturated fatty acids in prevention of migraine: A double-blind study versus placebo. Neurological Sciences : Official Journal of the Italian Neurological Society and of the Italian

Society of Clinical Neurophysiology. 2001;**21**(8):818-822

[172] Evans WE, Raynor HA, Howie W, Lipton RB, Thomas GJ, Wing RR, et al. Associations between lifestyle intervention-related changes in dietary targets and migraine headaches among women in the Women's Health and Migraine (WHAM) randomized controlled trial. Cephalalgia. 2020;**6**(2):119-125

[173] Trinh KV, Diep D, Chen KJQ. Systematic review of episodic migraine prophylaxis: Efficacy of conventional treatments used in comparisons with acupuncture. Medical Acupuncture. 2019;**31**(2):85-97

[174] Linde K, Allais G, Brinkhaus B, Fei Y, Mehring M, Vertosick EA, et al. Acupuncture for the prevention of episodic migraine. Cochrane Database of Systematic Reviews. 2016;**6**:CD001218

[175] Hammond NG, Colman I. The role of positive health behaviors in the relationship between early life stress and migraine. Headache. 2020;60(6):1111-1123

[176] Lampl C, Rudolph M, Deligianni CI, Mitsikostas DD. Neck pain in episodic migraine: Premonitory symptom or part of the attack? The Journal of Headache and Pain. 2015;**16**(1):80

[177] Ashina S, Bendtsen L, Lyngberg AC, Lipton RB, Hajiyeva N, Jensen R. Prevalence of neck pain in migraine and tension-type headache: A population study. The Journal of Headache and Pain. 2015;**35**(3):211-219

[178] Kropp P, Meyer B, Meyer W, Dresler T. An update on behavioral treatments in migraine—Current knowledge and future options. Expert Review of Neurotherapeutics. 2017;**17**(11):1059-1068

[179] Luedtke K, Allers A, Schulte LH, May A. Efficacy of interventions used by physiotherapists for patients with headache and migraine—Systematic review and meta-analysis. 2016;**36**(5):474-492

[180] Powers SW, Kashikar-Zuck SM, Allen JR, LeCates SL, Slater SK, Zafar M, et al. Cognitive behavioral therapy plus amitriptyline for chronic migraine in children and adolescents: A randomized clinical trial. JAMA. 2013;**310**(24):2622-2630

[181] Sharpe L, Dudeney J, Williams A, Nicholas M, McPhee I, Baillie A, et al. Psychological therapies for the prevention of migraine in adults. Cochrane Database of Systematic Reviews. 2019;**7**:CD012295

[182] Pérez-Muñoz A, Buse DC, Andrasik F. Behavioral interventions for migraine. Neurologic Clinics. 2019;**37**(4):789-813

[183] Smelt AFH, Louter MA, Kies DA, Blom JW, Terwindt GM, van der Heijden GJMG, et al. What do patients consider to be the most important outcomes for effectiveness studies on migraine treatment? Results of a Delphi study. PLoS One. 2014;**9**(6):e98933

[184] Peres MFP, Silberstein S, Moreira F, Corchs F, Vieira DS, Abraham N, et al. Patients' preference for migraine preventive therapy. PLos One. 2007;**47**(4):540-545