Advances in Medicine and Engineering Interdisciplinary Research, 2024, Volume 2, Issue 3
DOI: 10.32629/ameir.v2i3.2602
ISSN Online: 2972-3825
ISSN Print: 2972-3833

Migraine - A Challenge for the General Practitioner

María Loreto Cid[1, 2*]

1. Neurologist - Pain Specialist, Head of the Pain Unit, Military Hospital, Santiago, Chile.
2. Headache GDT-SONEPSYN Coordinator
*Corresponding author. Email address: marialoretocid@gmail.com

Abstract: Headache is always a challenge for the physician because it is one of the most frequent reasons for consultation in outpatient pathology. We know that the first challenge is to make the differential diagnosis between the primary headaches (like migraine and tensional type headache), and secondary headaches. However, primary headaches account for almost 90% of consultations, and within these, migraine has currently become one of the greatest challenges for medicine, due to the great deterioration in the patient's quality of life and the associated family, social and labor costs.

Key words: migraine; headache; analgesics; chronic migraine; preventive

1. Introduction

Headache is one of the most frequent causes of consultation in medicine [1]. To better understand and organize it, the International Headache Society (IHS), has tried to organize it in the "International Classification of Headaches (ICHD)", the latest version (ICHD-3) of which was published in 2018 [2]. Consider:

-Primary headaches: In which the headache is not only a symptom, but a disease in itself and does not correspond to an underlying structural pathology. There are four categories: migraine, tension headache, trigemino-autonomic headaches and other primary headaches.

-Secondary headaches: In these headaches, the pain is secondary to another cause, which may be systemic (associated with sinusitis, systemic fever, intoxication, cervical or dental pathology, etc.) or neurological (meningitis, tumors, subarachnoid hemorrhage).

There are a number of warning signs or "red flags" [3] that help us to suspect a secondary cause [4], especially those of neurological origin, which may have a more ominous prognosis (Table 1) and require early management.

Table 1. Red flags

-Recent onset headache (less than 6 months).	-Progressive headache.
-Headache in patient older than 50 years.	-Headache and fever.
-Change in headache character.	-Headache and convulsions.
-Sudden and severe headache (thunderclap headache).	-Headache and alteration of the neurological examination.
-Headache in patients with a history of neoplasia, recent ECT or HIV/AIDS.	

However, the greatest number of consultations corresponds to primary headaches, and within these, migraine is the most frequent, due to the disability caused by each crisis, which leads patients to seek treatment.

2. What is Migraine?

Migraine is a highly disabling neurological disease with a chronic course, characterized by episodes of pain, affecting approximately 12% of the population. This condition typically affects the young population and can begin in childhood, increasing in frequency during adolescence. It becomes more frequent in the female sex (2:1), with a peak incidence between 20 and 40 years of age.

Although it is not a pathology associated with mortality, it is currently considered one of the diseases that causes the most "disability years" globally, especially in the age group of 20 to 50 years old [5, 6], which is generally the most productive age where labor costs (absenteeism, low pain productivity), medical and emergency counseling, medication, examinations, and family and social costs are high [7]. If well managed, this disease is usually preventable. However, in many cases, it is underdiagnosed and undertreated.

Its characteristic is semi chronic local headache, mostly retro-orbital headache, usually pulsatile, accompanied by nausea, vomiting, and/or photophobia. It is also often allergic to sound and odor. Its intensity is moderate or severe, and the crisis may last from 4 to 72 hours (Table 2) [2]. However, typical symptoms usually do not appear, and the headache may be brand new or oppressive. But migraine has some characteristics, such as severity, the presence of nausea and photophobia, and worsening with exercise, which helps us guide differential diagnosis, especially tension headache.

Table 2. Diagnostic criteria for migraine according to the International Classification of Headache (ICHD-III).

A. At least five crises that meet criteria B-D.
B. Headache episodes of 4-72 hrs duration (untreated or unsuccessfully treated).
C. Headache has at least two of the following four features: ■ Unilateral location. ■ Pulsatile character. ■ Pain of moderate or severe intensity. ■ Worsens interferes with or makes it difficult to perform usual physical activities (walking or climbing stairs).
D. At least one of the following symptoms during the headache. ■ Nausea and/or vomiting. ■ Photophobia and phonophobia.
E. Not attributable to another ICHD-III diagnosis.

The onset of pain may be preceded by an initial phase or prodrome, where the patient describes increased irritability, insomnia, cravings, or sensitivity to light and noise. According to the IHS classification, this definition corresponds to a "migraine without aura" (ICHD-3) [2]. When headache is accompanied by neurological symptoms or "premonitory", it is called "migraine with premonitory", which may be of visual, sensory, or linguistic type, usually occurring 5 to 60 minutes before the onset of the pain, but may be accompanied or present after the onset [2]. In some cases, only the halo appears without pain (equivalent to migraine). About 20% of migraine sufferers have premonitory symptoms.

Migraine can also be classified into episodic migraine (less than 14 crises per month) and chronic migraine (more than 15 crises per month) based on the number of crises per month, as we will see, which is of great significance in evaluating and managing migraines.

3. Why do Migraines Occur?

The pathophysiology of migraine is complex and still under study. The new theory [8, 9] assumes the existence of control centers at the brainstem (periaqueductal gray matter, thalamic sites) and hypothalamic levels, where external or environmental factors that cause steady-state changes (Table 3) can regulate or trigger crises by activating these centers or "pacemakers". This in turn activates the trigeminal nerve through the "trigeminal vascular system", in which the trigeminal nerve afferent pathway and its connection with the meningeal blood vessels play an important role. Vasodilation and neurogenic inflammation occur in the meningeal blood vessels, releasing various vasoactive peptides that ultimately cause pain, such as substance P, especially calcitonin gene-related peptide (CGRP) and vasodilator peptide. Research has shown that its release is significantly increased during migraine crises [10], which is a hallmark of more specific new drug research in recent years. Current research indicates that the genetic basis of migraine is manifested by changes in the calcium channel subtype (Canalopathia) [8].

Table 3. Migraine triggering factors

-Stress and anxious symptoms	-Alcohol and tobacco use
-Changes in sleep schedules	-Dehydration and excessive heat
-Fasting periods	-Intense odors, such as perfumes or air fresheners.
-Certain foods such as chocolate, ripe cheeses, Chinese cuisine, sausages, peanuts, tomatoes, consumed in excess.	-Hormonal changes (menstrual period)

4. How is Migraine Studied?

Since there is no structural damage, there are no tests to confirm it, and its suspicion is based on its clinical picture. For this reason, other secondary headaches should always be ruled out [4]. Therefore, in the first evaluation of a patient, neuroimaging, brain CT with contrast or brain MRI should be requested, the latter is of choice if available [11]. This is especially true if there is a change in the character of the pain or other red flags [12, 13]. Depending on the degree of suspicion, laboratory tests may be requested, such as blood count, biochemical profile, thyroid tests, etc [11]. Other studies, such as lumbar puncture, may be requested to rule out infectious conditions such as meningitis or encephalitis [11], usually in the context of an emergency department or hospitalized patient evaluation. The usefulness of electroencephalogram for the study of patients with headache in general has not been demonstrated, except if it is associated with compromised consciousness or in children.

5. How is Migraine Managed?

Migraine management currently requires multidisciplinary support, especially when it is high frequency or chronic, considering multiple pharmacological and non-pharmacological aspects, which must go hand in hand, in all patients.

There are three main areas of management to consider:

(1) Management of comorbidities.

(2) Non-pharmacological management.

(3) Pharmacological management: acute and preventive.

5.1 Management of comorbidities

There are associated pathologies that can worsen the course of a headache, such as mood disorders (depression, generalized anxiety syndrome) [14], temporomandibular dysfunction, fibromyalgia, sleep disorders (obstructive apneas for example), obesity, among others [15]. Therefore, the presence of comorbidities in migraine patients should always be

investigated and considered within the overall management of the patient. It is currently known that migraine patients also have a higher frequency of classic cardiovascular risk factors such as hypertension, dyslipidemia and diabetes mellitus [16].

5.2. Non-pharmacological management

It is essential to initiate treatment and should consider:

- Patient education, to understand their disease and how to manage it.
- Management of external triggers (mentioned in Table 3). It is of great value for the patient to recognize which of these triggers affect him/her, and to generally favor a good stress management, adequate sleep and eating schedules, adequate fluid intake and moderating consumption of trigger foods, for example [17].
- Encourage healthy lifestyles and regular exercise [17].
- Psychologist support, relaxation therapies and cognitive behavioral techniques can be very helpful in patients and should be recommended [17].
- It is very important to educate the patient about the use (and abuse) of analgesics in the first consultation, in order to prevent headache due to analgesic abuse.
- The use of "headache calendars" by the patient, to record frequency of episodes, intensity, use of analgesics, etc, is very useful in the follow-up of therapy.
- Within complementary medicine, acupuncture has shown effectiveness in some patients [18].

5.3 Pharmacological management

It considers acute management of the crisis and preventive or prophylactic management.

5.3.1 Acute management: Aims to control the seizure, recover patient's functionality, be pain-free after 2 hours, and have no recurrence within 24 hrs [19].

1) Non-migraine-specific analgesic drugs:

-Paracetamol: recommended for mild to moderate attacks [19, 20].

-Nonsteroidal anti-inflammatory drugs Nonsteroidal anti-inflammatory drugs (NSAIDs): very effective. Good evidence for ibuprofen, naproxen and ketorolac [19-22].

-Opioids: have not demonstrated greater effectiveness than the previous ones [22] and present more severe adverse effects (nausea, vomiting, somnolence), greater frequency of pain recurrence, increased risk of headache due to analgesic abuse [23] and addiction. Therefore, its indication should be restricted only to patients who cannot use other analgesics [24, 25].

2) Specific analgesic drugs:

-Ergotamines: their efficacy is moderate [21] in migraine attacks and they tend to quickly cause headache due to analgesic abuse [5], so they should be used with caution. Due to their vasoconstrictor effect, they should be avoided in patients with severe hypertension or heart disease. They are contraindicated in pregnancy and lactation [26].

-Triptans: treatment of choice for moderate and severe seizures [19-22]. They are HT-1 1B/1D serotonergic receptor agonists, whose action is through vasoconstriction of leptomeningeal vessels, inhibition of neurogenic inflammation and on some neurons of the trigeminal vascular complex [26]. There are 7 types, but currently in Chile we have only three: naratriptan, frovatriptan and eletriptan. Their use is not recommended in patients with coronary heart disease or severe hypertension. Caution should be exercised with adverse effects such as drowsiness or a feeling of chest tightness, especially in the more potent ones (eletriptan and sumatriptan).

We can also count on: prokinetics (metoclopramide or domperidone) for nausea management [27], and sublingual analgesic formulations or suppositories for vomiting.

-Use the indicated drug at the onset of pain.

-Prefer the use of a drug with adequate potency for the level of pain [19]. It is not always necessary to escalate in each crisis from mild analgesics to more potent ones. The patient can directly take a more potent one if the pain is severe, thus avoiding the use of more drugs than necessary and that are not effective.

-Education on the maximum number of analgesics to use in the month, if a patient is requiring a greater amount than recommended, it is time for medical control to reevaluate the therapy.

5.3.2 Preventive or prophylactic therapy: its objective is to reduce the number of seizures per month, their duration and intensity, and to improve quality of life. Unfortunately, studies show that only one-third of patients who require preventive therapy are receiving it [28].

We indicate preventive therapy when [29]:

-There are 4 or more crises per month.

-The crises are severe or very difficult to manage.

-There is a poor response to analgesics.

How to use preventive therapy [29]:

-Gradual start and titration until effective doses are reached.

-Maintain for at least 3-6 months, however, the maximum time of use depends on each patient.

-Remember that the onset of action can be between 3-4 weeks, so the patient should be educated about this latency and also about its potential adverse effects.

-It is very important to manage expectations with migraine therapies, since there are no "curative" treatments, but there are good schemes that can substantially improve the quality of life.

We currently have drugs with a very good level of evidence [30, 31], such as:

-Tricyclic antidepressants: Amtriptyline has the best evidence in its class [30-32], in low doses (12.5-25 mg), but important side effects such as somnolence, weight gain and orthostasis. It is of choice in patients with depressive symptoms or insomnia.

-Beta blockers: Propanol (40-160 mg), Nadolol (5-10 mg), and Metoprolol (25-50 mg) [30-31]. Their side effects, such as weight gain and depressive symptoms, should be considered and avoided in patients with diabetes (which may mask hypoglycemia) and asthma. I prefer new selective beta blockers such as metoprolol. The choice for young patients or HTA patients.

-Calcium channel blockers: Flunarizine at doses of 5 to 10 mg/day. [20, 32]. Avoid their prolonged use in older adults due to the risk of extrapramidal symptoms, and also consider that they can cause weight gain and depression.

-Anticonvulsants: Valproic acid and sodium divalproate with good response [30-31]. They should not be used in women of childbearing age due to risk of teratogenicity. Other adverse effects include weight gain and altered liver tests. Topiramate (25-100 mg) has been shown to be very effective in episodic and chronic migraine [30, 34], but it has adverse effects that can be significant, so its use by specialists is recommended. Drowsiness, paresthesia and visual disturbances should be warned when initiating therapy with this drug, and should be avoided in patients with a history of nephrolithiasis.

Second line and with less evidence we have: gabapentin [35], candesartan [29-30], venlafaxine [29], riboflavin (vitamin B6) [29] and oral magnesium [29]. The choice of preventive treatment will ultimately depend on the individual patient, the adverse effects of each drug, concomitant pathologies and other drugs in use.

Chronic migraine: according to the current IHS classification (ICHD-3), chronic migraine is defined as more than 15 painful days per month for more than 3 months, of which 8 episodes must have typical migraine characteristics [5]. Its prevalence is close to 2% [36]. It is currently considered a separate entity in the classification of migraine [5], because it has been shown to cause greater disability and impairment of quality of life [37], and its management can be more complex. There are certain risk factors in the evolution of a headache that can lead it to become chronic [38], such as:

- Obesity.
- Sleep disturbances (insomnia, obstructive sleep apnea syndrome).
- Untreated mood disorders or stressful life events.
- Associated chronic pain syndromes (such as fibromyalgia or temporomandibular dysfunction).
- Previous high frequency of headache attacks.
- Excessive use of caffeine and analgesic drugs.

Most of these factors are modifiable, so the physician's work to prevent an episodic migraine from becoming chronic is very important. Treatment of chronic migraine, therefore, is initiated by correcting risk factors that may favor it becoming chronic [38].

The drugs that have shown the greatest utility in preventive treatment for chronic migraine [38-40] are:

- Topiramate: effective in chronic migraine and in patients with drug abuse headache [41].
- Botulinum Toxin type A (Onabotulinum toxin): approved in 2010 by the FDA for the management of chronic migraine [42]. Especially useful in patients with poor tolerance or poor response to oral drugs or polymedicated.
- Other medications used, with limited evidence: Amitriptyline [43], sodium diphosphate [44], and gabapentin [45].
- Monoclonal antibodies against CGRP: specific therapy for migraine, as it would block the release of calcitonin gene-related peptide (CGRP), through antibodies designed against CGRP or its receptor. Results have been positive for both episodic and chronic migraine in studies [46]. Three antibodies have been approved since mid-2018 by the FDA in the USA. In Chile, we have Erenumab, since April of this year. Its current recommendation by expert panels, is for management of migraines that do not respond to conventional therapies, and indicated by specialist physicians [46].

6. Headache Due to Drug Abuse

In migraine patients, excessive consumption of analgesic drugs for more than 3 months can lead to a worsening in frequency and intensity of a headache, even changing its clinical characteristics [47]. It is very difficult to manage. It is currently classified as a secondary headache ("headache attributed to a substance or suppression") [5].

Excess is considered to be: more than 10 tablets per month of ergotamines, opioids or triptans, or more than 15 tablets/month of analgesics (Paracetamol or NSAIDs) [5].

Its management is complex, multidisciplinary, and sometimes requires hospitalization [46]. The current recommendation is to discontinue the analgesic in abuse [48] with the support of some preventive drugs and switch to anti-inflammatory drugs such as acetaminophen or naproxen. However, the most important aspect of this condition is its prevention, with good patient education from the first consultation. Finally, we must remember that many times, patients seem to be refractory to treatment and persist with severe and frequent crises, leading to polymedication or unnecessary procedures and tests.

It is important to always reevaluate the patient before labeling as refractory and consider [49]:

(1) Is the diagnosis of migraine correct and can it be another primary headache?

(2) Are there triggering factors that have not been considered (smoking or poor sleep habits)?

(3) Is the pharmacological therapy adequate (low doses or poor adherence)?

(4) Is there undetected abuse of analgesic drugs?

(5) Is non-pharmacological therapy considered?

(6) Are there any untreated comorbidities?

(7) Does the patient have an unrealistic expectation of treatment?

7. Conclusion

Although migraine most of the time should be managed by a neurologist, the first consultation for a patient with headache is very often with a non-specialist physician. Therefore, we must consider that: (1) Headache is a very frequent cause of consultation; (2) Always remember the "red flags" in the differential diagnosis; (3) It is likely that most of the patients who consult for headache have a migraine; Migraine causes great disability, so it should not be underestimated, and should be treated appropriately.

Therefore, the current challenge for the physician, when faced with a patient with headache, is to look for the diagnosis of migraine. A good clinical history and an initial examination, which may be indicated by the general practitioner, can rule out secondary causes and provide an initial diagnostic approach. Quality of life can be improved through patient education, correct use of analgesics, management of triggers, assessment of comorbidities and referral when appropriate.

Conflicts of Interest

The author declares no conflicts of interest regarding the publication of this paper.

References

[1] Lavados PM, Gomez V, Sawada M, Chomali M, Alvarez M. 2003. Diagnósticos neurológicos en la atención primaria de salud en Santiago, Chile. *Rev Neurol*, 36(6): 518-522.

[2] Headache Classification Committee of the International Headache Society (IHS). 2018. The International Classification of Headache Disorders, 3er edition. *Cephalalgia*, 38(1): 1-211.

[3] Randall C, Clunch D. 2001. Evaluation of acute headache in adults. *Am Fam Physician*, 15(63): 685-693.

[4] Chou D. 2018. Secondary headaches syndromes. *Headache*, 24(4): 1179-1191.

[5] Stovner L, et al. 2018. Global, regional and national burden of migraine and tension-type headache, 1990-2016: a systematic analysis for the Global Burden of Disease Study 2016. *Lancet Neurol*, 17: 954-976.

[6] Steiner TJ. 2004. Lifting the burden: the global campaine to reduce the burden of headache worldwide. *Lancet Neurology*, 3(4):204-205.

[7] World Health Organization (2001). The World Health Report 2001-WHO. Geneva.

[8] Goadsby P. 2009. Pathophysiology of migraine. *Neurol Clin*, 27: 335-368.

[9] Dodick D. 2018. A phase-by-phase review of migraine pathophysiology. *Headache*, 58. (Supp1): 4-16.

[10] Durham P. 2006. Calcitonin Gene - Related Peptide (CGRP) and Migraine. *Headache*, 46(Suppl1): S3-S8.

[11] Evans R, Rozen T, Mechtler L. 2008. Neuroimaging and other diagnostic testing in headache. Silberstein S, Lipton R, Dodick D. *Wolff's Headache (8ºEd),* pp. 63-93.

[12] Detsky M, McDonald D, Baerlocher M, Tomlinson G, McCrory D, Booth C. 2006. Does the patient with headache have a migraine need neuroimaging. *JAMA*, 296: 1274-1283.

[13] Loder E, Weisenbaum E, Frishberg B, et al. 2013. Choosing Wisely in headache medicine: the American Headache Society's list of five things physicians and patient should questions. *Headache*, 53: 1651-1659.

[14] Buse DC, et al. 2013. Psychiatric comorbidities of episodic and chronic migraine. *J Neurik*, 260(8): 1960-1969.

[15] Sevillano-García MD, Manso-Calderón R, Cacabelos-Perez P. 2007. Comorbilidades en la migraña: derpesión, ansiedad, estrés ytrastornos del sueño. *Rev Neurol*, 45: 400-405.

[16] Magalhaes JE, Sampaio PA. 2018. Migraine and cerebrovascular diseases:epidemiology, pathophysiological, and clinical considerations. *Headache*, 1277-1286.

[17] Sun Eldestein C, Manskop A. 2011. Alternatives headaches treatment: nutraceuticals, behavioral and physical treatments. *Headache*, 51(3): 469-483.

[18] Da Silva AN. 2015. Acupuncture for migraine prevention. *Headache*, 55(3): 470-473

[19] Vargas B. 2018. Acute treatment of migraine. *Headache*, pp. 1032-1052.

[20] Evers S, Afra J, Frese A, et al. 2009. EFNS guidelines on the drug treatment of migraine- revised report of an EFNS task force. *Eur J Neurol*, 16: 968-981.

[21] Marmura MJ, Silverstein S. 2015. The acute treatment of migraine in adults: The American Headache Society evidence assessment of migraine pharmacotherapies. *Headache*, 55: 3-20.

[22] Kelley N, Tepper D. 2012. Rescue therapy for acute migraine, part 3: opioids, NSAIDs, steroids, and post discharge medication. *Headache*, 52: 467-482.

[23] Bigal M, Lipton R. 2009. Excessive opioids use and the development of chronic migraine. *Pain*, 142: 179-182.

[24] Tepper SJ. 2012. Opioids should not be used in migraine. *Headache*, 52: S30-34.

[25] Levin M. 2014. Opioids in migraine. *Headache*, 54: 12-21.

[26] Kelley N, Tepper D. 2012. Rescue therapy for acute migraine. Part 1: Triptan, Dihydroergotamine and magnesium. *Headache*, 52(1): 114-128.

[27] Lainez JM, et al. 2013. Optimal management of severa nausea and vomiting in migraine: improving patient outcome. *Patient Relat Outcome Meas*, 4: 61-73.

[28] Lipton RB, et al. 2007. AMPP Advisory Group: migraine prevalence, disease burden, and the need for preventive therapy. *Neurology*, 68(5):343-349.

[29] Schwedt T. 2018. Preventive therapy of migraine. *Headache*, 24(4): 1052-1065.

[30] Silverstein SD, et al. 2012. Evidence-based guideline update: pharmacologic treatments for episodic migraine prevention in adults. *Neurology*, 78: 1337-1345.

[31] Loder E, Burch R, Rizzoli P. 2012. The 2012 AHS/AAN Guidelines for prevention of episodic migraine: a summary and comparison with other recent clinical practice guidelines. *Headache*, 52: 930-945.

[32] Jacson J, Shimeall W, Sessums L, et al. 2010. Tricyclic antidepressant and headaches: systematic review and meta-analysis. *BMJ*, 341: c5250.

[33] Linde M, Mullness W, Chronicle E, McCrory D. 2013. Topiramate for theprophylaxis of episodic migraine in adults. *Cochrane Database Syst Rev*, 6: CD010610

[34] Diener HC, et al. 2007. Topiramate reduces headaches days in chronic migraine: a randomized double-blind placebo controlled study. *Cephalalgia*, 27: 814-823.

[35] Linde M, Mullness W, Chronicle E, McCrory D. 2013. Gabapentin or pregabaline for the prophylaxis of episodic migraine in adults. *Cochrane Database Syst Rev*, 6: CD010609.

[36] Bigal M, Serrano D, Reed M, Lipton R. 2008. Chronic migraine in the population. *Neurology*, 71: 559-566.

[37] Lipton RB, Silverstein SD. 2015. Episodic and chronic migraine headache: breaking down barriers to optimal treatment and prevention. *Headache*, 55(2): 103-122.

[38] May A. 2016. Chronic migraine: risk factors, mechanisms and treatment. *Nat Rev Neurol*, 12(8):455-464.

[39] Cho SJ, Song TJ, Chu MK. 2017. Treatment update of chronic migraine. *Curr Pain Headache Rep*, 21: 26.

[40] Pascual J. 2012. Migraña crónica: tratamiento. *Rev Neurol*, 54(Suppl2): S31-S38.

[41] Silverstein SD, Lipton RB, Dodick DW. 2007. Efficacy and safety of topiramate for the treatment of chronic migraine: a randomized double-blind placebo-controlled trail. *Headache*, 47: 170-180.

[42] Diener H, Dodick D, Aurora S, et al. 2010. PREEMPT 2 Chronic Migraine Study Group. Onabotulinumtoxin A for treatment of chronic migraine: results for the double blind, randomized, placebo-controlled phase of the PREEMPT 2 trial. *Cephalalgia*, 32(5): 804-814.

[43] Couch JR. 2011. Amitriptyline versus placebo study group: amitriptyline in the prophylactic treatment of migraine and chronic daily headache. *Headache*, 51(1): 33-51.

[44] Yurekli VA, et al. 2008. The effect of sodium valproate on chronic daily headache and its subgroups. *J Headache Pain*, 9(1): 37-41.

[45] Spira PJ, Beran R. 2003. Australian gabapentin chronic daily headache group. Gabapentin in the prophylaxis of chronic daily headache: a randomized placebo controlled study. *Neurology*, 61(12): 1753-1759

[46] Sacco S, Bendtsen L, Ashina M, et al. 2019. European headache federation guideline on the use of monoclonal antibodies acting on the calcitonin gene related peptide or its receptor for migraine prevention. *J Headache Pain*, 20(1): 6.

[47] Diener HC, et al. 2016. Medication-overuse headache: risk factors, pathophysiology and management. *Nat Rev Neurol*, 12(10): 575-583.

[48] Carlsen L, Murkjaard S, et al. 2018. Complete detoxification is the most effective treatment of medication-overuse headache. A randomized controlled open-label trial. *Cephalalgia*, 38(2): 225-236.

[49] Lipton R, Silberstein S, Saper J, Bigal M, Goadsby P. 2003. Why headache treatment fails? *Neurology*, 60: 1064-1070.