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WHAT´S LEFT AND NEW IN THE MANAGEMENT OF MIGRAINE?

INTRODUCTION Migraine is a neurological disorder that generally manifests in the form of headache. The treatment of migraine is based on changes in lifestyle, symptomatic treatment and preventive therapies. The pharmacotherapeutic approach to migraine is based on widely-used drugs and novel drugs, which include monoclonal antibodies (mAbs), which emerge as an alternative for patients with poor response to standard preventive treatments. PURPOSE The objective of this study is to assess the efficacy and safety of the medications employed for the symptomatic and preventive treatment of migraine. Another objective is to determine its place in therapeutics and identify the best treatment based on the type of migraine and characteristics of the patient. METHODS A search was performed of clinical practice guidelines, documents from regulatory agencies, systematic reviews and primary studies assessing symptomatic and preventive treatments of migraine. Data related to the use of triptans in Navarra, Spain, was extracted from the prescription database of the Navarre Health Service. Data about patients receiving mAb therapy in our community and their progress was extracted from electronic medical records and the Navarre Health Service pharmacotherapy management system. CONCLUSIONS The symptomatic treatment of choice for mild-moderate migraine includes non-steroidal anti-inflammatory drugs (NSAIDs), whereas triptans are frequently reserved for moderate-severe migraine. Oral drugs are the first-line preventive treatment, with ß-blockers and topiramate as the first choice. Botulinum toxin A is used in patients with chronic migraine who are unresponsive to oral preventive therapies. mAbs emerge as an alternative to prevent chronic or episodic migraine in patients unresponsive to previous treatments. These treatments, however, have a modest efficacy as compared to placebo. In addition, no comparative studies have been published to date about other first-line preventive therapies. The long-term safety and efficacy of mAbs have not yet been established, and their cost is high. MAbs are funded by the public health system only as fourth-line prophylactic therapy for chronic or high-frequency episodic migraine.

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index

INTRODUCTION

Migraine is a neurological disorder characterized by episodic or recurrent headache with concurrent hypersensitivity to external visual, auditory, olfactory and/or cutaneous stimuli (auras) and, occasionally, nausea and vomiting. The duration of episodes ranges from 4 to 72 hours and can be very intense or disabling. Pain is frequently one-sided and pulsates, and is exacerbated by exercise. About 25% of patients also experience symptoms such as hypersensitivity to light, noise or smell. These symptoms or auras generally appear immediately before a headache and may persist even once the headache has disappeared[1].

Diagnosis of migraine is based on clinical criteria.

EPIDEMIOLOGY

Around 14% of the general population suffers from migraine (18% women) and is the most frequent reason of consultation in neurology clinics[2]. Migraine is the second neurological and seventh general cause of disability in middle-aged patients in the world and is associated with high consumption and cost of healthcare and non-healthcare resources[2].

ETIOLOGY

The causes of migraine are not well established. There is an activation of the trigeminovascular system (TVS), which causes the release of different pro-inflammatory mediators and vasodilators, especially the calcitonin gene-related peptide (CGRP)[3]. CGRP is involved in the transmission of painful stimuli, and its levels increase during migraine attacks[4].

The triggers of migraine include:

- Diet habits: missing meals and consumption of alcohol, chocolate, cheese, glutamate-containing foods, nitrites and aspartame.
- Environmental factors, afferent stimuli (flashing lights, intense smells, among others), weather changes and high altitude.
- Sleep-related factors: excess sleep or sleep deficit.
- Psychological factors: stress, anxiety.
- Hormonal factors: menstruation, ovulation.
- Drug use: use of contraceptives.

Migraine is a disabling neurological disorder that negatively affects the quality of life of patients

CLASSIFICATION

Migraine can be episodic (EM) or chronic (CM). When headache occurs nine days a month or less, it is called low-frequency EM. When frequency is 10-14 days a month, it is known as high-frequency EM. CM is established when the patient has had 15 or more monthly headache days in the last three months, and when the headache and the associated symptoms correspond to migraine attacks on at least eight days per month[5].

The term CM also involves medication overuse headache (MOH), a concept that will be explained later.

The annual EM to CM conversion rate is 3%. There are reports of patients with chronic migraine who improve and experience partial (10%) or complete remission (3%)[6].

RISK FACTORS

Risk factors for chronic migraine, some of which are modifiable and actionable, have been identified:

- Female gender
- Advanced age
- Caucasian ethnicity
- Genetic factors
- Low socioeconomic and/or educational level
- Obesity
- History of head and neck lesions
- Idiopathic intracranial hypertension without papilledema
- Cutaneous allodynia or other painful comorbidities
- Psychiatric disorders, anxiety, depression, stress

- Sleep rhythm disorders, sleep apnea syndrome, snoring
- Medication abuse*
- Caffeine abuse
- Very frequent attacks
- Low efficacy of the treatment for acute migraine

COMORBIDITIES

The presence of comorbidities may influence and determine patient response to therapy and migraine course[7]. Targeting comorbidities may be effective in improving treatment outcomes, since comorbidities are also risk factors that predispose the patient to chronic migraine. Comorbidities are classified into:

PSYCHIATRIC
Anxiety, depression, bipolar disorder, and panic disorder.

CARDIOVASCULAR
Obesity, heart disease, stroke, circulatory disorders.

RESPIRATORY
Allergy, asthma, bronchitis, emphysema / bronchopathy, sinusitis.

OTHER
Arthritis, chronic pain, fibromyalgia, temporomandibular joint dysfunction.

TREATMENT

The objectives of the migraine treatment include:

- To relieve pain during attacks and improve functionality
- To reduce the frequency of attacks
- To prevent progression to chronic migraine

Treatment is based on three pillars: lifestyle changes, action on triggers, and use of symptomatic and preventive treatment.

Medication overuse is a risk risk factor for chronic migraine

Lifestyle and triggers

Maintaining a healthy lifestyle is recommended to all migraine patients, which involves regular physical exercise, high quality sleep habits, and not missing meals. These patients must also avoid some types of foods, excess stimuli, insufficient sleep, and stress.

Symptomatic treatment

Symptomatic treatment involves the use of non-steroidal anti-inflammatory drugs (NSAIDs), serotonin 1B/1D agonists or triptans. Ergot derivatives are not considered a suitable choice.

Two novel groups of medications have been recently developed, which are not yet commercialized in Europe: ditans and gepants.

For mild-moderate migraine attacks

Mild-moderate attacks do not interfere with patient's daily activities and are not associated with vomiting or severe nausea.

NSAIDs

NSAIDs are the treatment of choice for patients with mild-moderate migraine attacks. They mainly cause gastrointestinal and renal side effects. These therapies must be used with caution in patients of an advanced age and in patients with gastrointestinal disease, renal insufficiency, arterial hypertension or heart disease. Avoid these therapies in patients with severe renal insufficiency[8].

If attacks are associated with nausea or vomiting, metoclopramide or domperidone are recommended as add-on therapy.

(*) The influence of medication overuse in the development of CM is controversial. Medication abuse is a relevant risk factor for chronic migraine, but it is not a necessary or sufficient condition. Medication abuse is frequently the result of chronic pain, which does not necessarily resolve once medication has been withdrawn[4].

NSAIDs are also used as adjuvant therapy to triptan therapy[8].

No studies have been published to compare the efficacy of different NSAIDs for the treatment of migraine.

The recommended duration of symptomatic treatment with NSAIDs cannot exceed 15 days a month to avoid the occurrence of MOH[5].

Simple analgesics

Paracetamol

It can be administered at a dose of 1 g to a maximum dose of 4 g daily. Its side effects include liver toxicity at high doses, especially in alcoholic or fragile patients.

Metamizol

This medication is widely used in our setting, but there is no solid evidence supporting its efficacy. It is not indicated for use in the treatment of migraine and there are reports of episodes of hypersensitivity and agranulocytosis. Therefore, its use must be very limited, since there are other effective anti-inflammatory drugs available for migraine with milder side effects. The Spanish Agency of Medicines and Medical Devices (AEMPS) issued an information note in 2018 recommending short-term use of metamizol at the minimum effective dose, under close monitoring, and regular blood tests to check for the occurrence of agranulocytosis[9].

The combination of analgesics and codeine, tramadol and/or caffeine should be avoided in order to prevent the occurrence of MOH[10].

Antiemetics (adjuvant)

If during migraine attacks the patient experiences vomiting, a combination of an analgesic with metoclopramide or domperidone is recommended.

Metoclopramide

The neurological effects of this drug led the AEMPS to issue an information note recommending restricting its use to the adult population for the prevention and treatment of nausea and vomiting associated with migraine. Its use is also restricted to 1-18 year-old children as second-line therapy for the prevention of postoperative nausea and vomiting. Metoclopramide is not recommended in infants younger than 1 year[11].

In addition, older patients are more prone to experience extrapyramidal effects such as late dyskinesia (potentially irreversible), especially at high doses or in long-term therapies[8].

NSAIDs, associated with metoclopramide or domperidone in the case of nausea and vomiting, are the treatment of choice for patients with mild-moderate attacks

Dosage: oral or parenteral administration of a single dose of 10 mg is recommended, which can be administered up to three times daily. The recommended maximum daily dose in adults is 30 mg or 0.5 mg/kg of body weight for a maximum of five days. For patients with moderate-severe renal insufficiency (CrCl: 15-60 mL/min) it is recommended to reduce the dose by 50%, and by 75% in patients with end-stage renal insufficiency (CrCl: <15 mL/min)[12].

Avoid the administration of metoclopramide at the end of pregnancy. If metoclopramide is administered, neonatal monitoring is required. Metoclopramide is not recommended for lactating mothers[12].

Domperidone

This medication should be administered with caution to patients with heart disease or significant electrolyte disorders due to the risk for QT interval prolongation, palpitations and arrhythmias[8].

Dosage: the recommended dose is 10 mg taken orally up to three times daily to a maximum dose of 30 mg daily. The duration of the treatment should not exceed one week[12]. It is not indicated for children younger than 12 years or adolescents with a body weight <35 Kg[12].

Children and adolescents

With respect to the treatment of migraine in this population group, the studies retrieved only provide poor-quality evidence in relation to NSAIDs. Paracetamol has not been proven to be effective, and ibuprofen seems to be effective in relieving pain in acute treatment[13]. The recommended daily dose of ibuprofen in 6 month-to-12 year-old children is 20 to 30 mg/kg (body weight), as a function of severity of symptoms distributed in three or four doses[12].

Table 1. Drugs used for mild/moderate migraine attacks.

NSAIDs	Level of evidence[10]	Dosage and maximum daily dose
Ibuprofen	IA	400-600 mg/6-8h; orally. Maximum daily dose: 2400 mg
Naproxen		500 mg/12-24h; orally. Maximum daily dose: 1500 mg
Diclofenac		50 mg/8-12h; orally. Maximum daily dose: 150 mg 100 mg/24h; rectally. 75 mg/24h; parenterally.
Dexketoprofen	IIB	12.5 mg/4-6h or 25 mg/8h; orally. Maximum daily dose: 75 mg 50 mg/8-12h; parenterally. Maximum daily dose: 150 mg
Simple analgesics	**Level of evidence[10]**	**Dosage and maximum daily dose**
Paracetamol	IA	1,000 mg/6-24h; orally. Maximum daily dose: 4000 mg
Metamizol	IA	575 mg/4-24h; orally. Maximum daily dose: 3450 mg
Adjuvants	**Level of evidence[10]**	**Dosage and maximum daily dose**
Metoclopramide	-	10 mg/8-24h; orally. Maximum daily dose: 30 mg or 0.5 mg/kg
Domperidone	-	10 mg/8-24h; orally. Maximum daily dose: 30 mg

For moderate-severe migraine attacks

Triptans (5-hydroxytryptamine [5-HT] or serotonin agonists)

These medications have been proven to be effective in the treatment of migraine[14,15]. There are minimal differences among triptans in terms of efficiency and tolerability, with large between-subject variability. Their rapid action and limited side effects make it the treatment of choice (level of evidence: I; degree of recommendation: A). Triptans are more effective when taken at the first sign of migraine. They are administered orally, by nasal inhalation or subcutaneously. Due to their vasoconstrictor effect, they are contraindicated in patients with uncontrolled arterial hypertension, heart disease, cerebrovascular disease, and peripheral vascular disease.

The duration of symptomatic treatment with triptans should not exceed 10 days monthly, since excess use is associated with medication overuse headache (MOH).

MOH is defined as headache in patients with pre-existing primary headache occurring at least 15 days monthly induced by excess regular use of headache medications for more than three months: 10 or more monthly days in the case of simple analgesics or anti-inflammatories, or 15 monthly days or more in the case of triptans, opioids, ergot drugs or fixed combinations of analgesics[5].

The management of MOH involves the withdrawal of the drugs involved. In patients with excess use of opioids or barbiturates, medical or psychiatric comorbidities that required a more complex approach, or at least two failed attempts of ambulatory cessation, hospitalization should be considered[16].

OMH does not always disappear when stopping an overused symptomatic medication.

Triptans are the treatment of choice for moderate-severe attacks

Evidence of differences in the efficacy/indications of each triptan

The triptans currently available in the market have the same mechanism of action and pharmacodynamics, but show significant differences in their pharmacokinetics that make some triptans more effective for some types of attacks. Table 2 shows the potential indications of each triptan adapted to the clinical context where they would exert more clinical benefits[10].

In patients with nausea and vomiting, triptans can be administered orally as lyophilized powder or nasally. If the patient is unresponsive to these options, the subcutaneous form of sumatriptan can be administered.

Table 2. Triptans, doses and recommendations.

Drug	Dosage	Recommendation
Almotripan	12.5 mg orally	Standard migraine patient
Eletriptan*	20 and 40 mg orally	Long-term, severe pain attack
Frovatriptan*	2.5 mg orally	Long-term mild-moderate attacks
Naratriptan*	2.5 mg orally	Long-term mild-moderate attacks
Rizatriptan	10 mg orally	Short-term, severe pain attack
Sumatriptan*	6 mg subcutaneously 20 mg nasally 10 mg nasally 50 mg orally	Severe pain attack resistant to oral or nasal administration Attack resistant to oral administration and patients with vomiting Children older than 12 years and adolescents[12] Standard migraine patient and in patients of childbearing age
Zolmitriptan*	2.5 and 5 mg orally 5 mg nasally	Standard migraine patient Attack resistant to oral administration and patients with vomiting Children older than 12 years and adolescents[12]

(*) Not recommended in patients older than 65 years[16]

Oral formulations are used in patients from 18 years of age and are not recommended in patients older than 65 years[12]. Only nasal formulations can be used in patients over 12 years of age.

Treatment with oral triptans is ineffective in about a third of patients[17]. A patient who is unresponsive to a triptan in the first attack can be responsive in another attack; therefore, it is recommended that the triptan is used for at least three attacks, unless the patient shows poor tolerance. The evidence obtained in clinical trials indicates that patients with a poor response to a triptan can benefit from subsequent treatments with a different triptan[18–20].

The recurrence of pain within 24 hours after a successful initial treatment occurs in about one third of treated attacks[17,21,22]. In case of recurrence, a second dose of triptan can be taken. If recurrent headache persists, naratriptan or frovatriptan can be considered, as they have a longer half-life than the other triptans. The combination of a triptan and a long-action NSAID such as naproxen can also be considered. The combination of sodium naproxen and sumatriptan is more effective than when these agents are used separately[23].

A meta-analysis of 53 trials in 24,089 patients published in 2002[17] compared the efficacy and tolerability of different triptans (rizatriptan, almotriptan, naratriptan, eletriptan and zolmitriptan) with sumatriptan 100 mg. Results were presented in relation to several aspects:

- Short-term efficacy: rizatriptan was shown to be superior to the other triptans.
- Presence of pain at two hours: Rizatriptan and almotriptan were more effective.
- Tolerability: The best tolerated triptans were naratriptan and almotriptan.

A systematic review published in 2004[24] concluded that the results obtained so far were contradictory and that it was unclear which triptan was the most effective. More specifically, the review showed that:

- Eletriptan may be more effective to relieve pain, as compared to sumatriptan.
- Sumatriptan, rizatriptan and zolmitriptan showed similar efficacy in soothing pain, whereas naratriptan might be less effective.

A total of 51,423 packages of triptans were dispensed in the pharmacies of Navarra in 2020. The total cost of all triptans that year was 752,903 euros (Figures 1 and 2).

Ergot derivatives: ergotamine

In 2013, the Committee for Medicinal Products for Human Use (CHMP) of the European Medicines Agency (EMA) issued a note that restricted the use of ergot derivatives to some specific indications, including the prophylactic treatment of migraine, due to the associated risk of developing irreversible and potentially life-threatening fibrosis due to the late occurrence of symptoms and ergotism. The CHMP considered the risk-benefit balance of these medications to be unfavorable[25].

As a result, the use of these medicines has decreased dramatically. Their oral absorption is erratic and suffer first-pass effect, which results in a very variable clinical response. The combination of ergotamine with caffeine seems to increase intestinal absorption and bioavailability.

Ergot derivates are not recommended in "de novo" patients (level of evidence: III-IV; grade of recommendation: C)[26]. Their use can only be considered in patients who already use them occasionally and show good response.

Ergot derivates are contraindicated in cases of peripheral circulatory disorders, obliterative vascular disease, ischemic heart disease, hypertension, sepsis, renal failure, liver disease, temporal arteritis, hemiplegic or basilar

Figure 1. Number of packages of triptans dispensed in the pharmacies of Navarra in 2020.

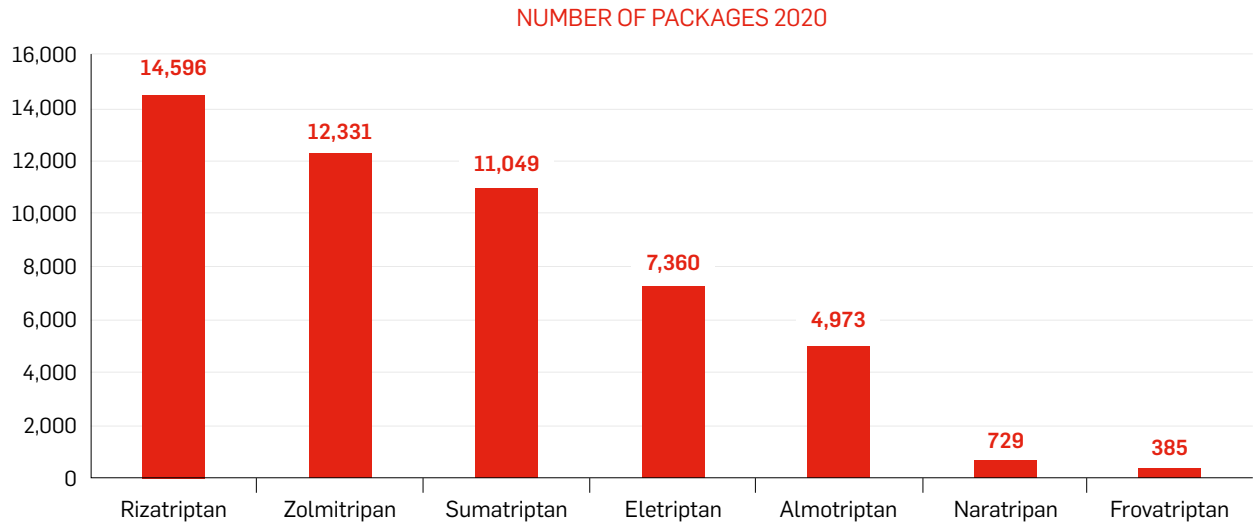
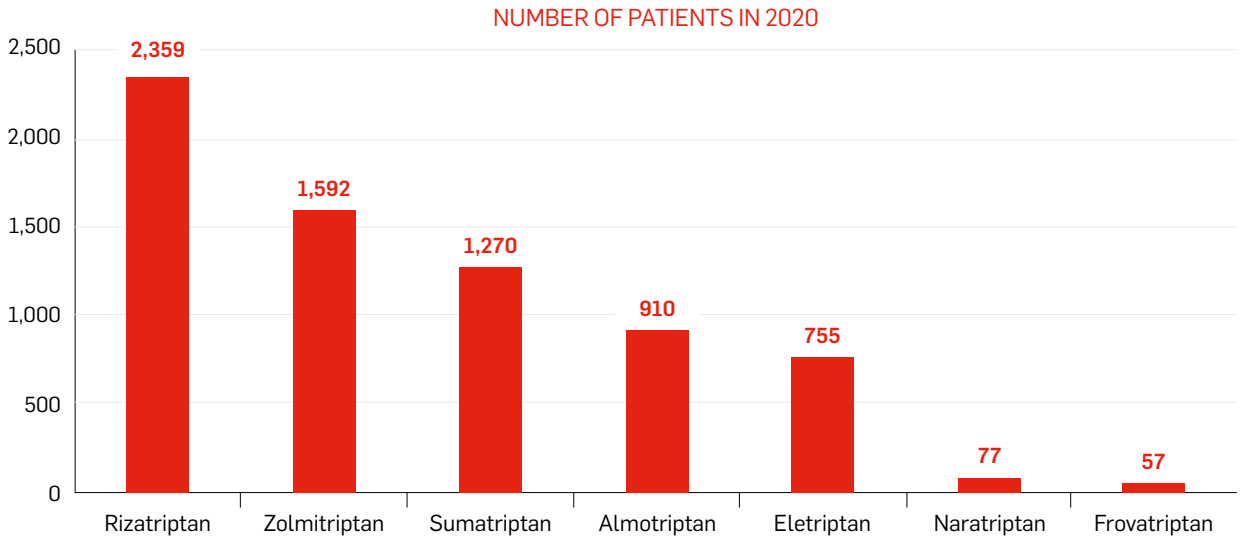


Figure 2. Patients on treatment with triptans in Navarra in 2020.



migraine, concomitant treatment with other drugs that are metabolized by CYP3A4, concomitant treatment with vasoconstrictor agents, pregnancy and lactation[12].

Ditans and gepants

Ditans

Unlike triptans, which act on 5-HT1B, 5-HT1D and 5-HTF receptors, lasmiditan is a high-affinity selective 5HT1F receptor agonist. It targets central and peripheral receptors of trigeminal neurons. Lasmiditan was approved by the US Food and Drug Administration (FDA) in 2019 for the acute treatment of migraine with and without aura in adults. It is not indicated for the preventive treatment of migraine[27]. It has not yet been evaluated by the EMA.

Lasmiditan is administered orally at a single dose of 50-200 mg in a period of 24 hours. Its efficacy versus placebo was demonstrated in two phase III clinical trials assessing lasmiditan at different doses (50 mg, 100 mg and 200 mg). The three doses proved to be effective. The proportion of patients free of pain two hours after the administration of lasmiditan was 7-18% higher compared to placebo (28-39% vs 15-21%). The proportion of patients free of the most bothersome symptom two hours after administration was 8-16% higher (41-49% with lasmiditan vs 30-33% with placebo). The efficacy of a second dose of lasmiditan for rescue treatment of an incompletely treated migraine, or to treat the recurrence of the initial migraine within 24 hours of dosing has not been established. The safety of treating more than 4 migraines attacks in a 30-day period has also not been established. There is no comparative evidence of its efficacy against other symptomatic therapies for migraine[27].

Adverse events of lasmiditan include central nervous system depression with sedation, cognitive and neuropsychiatric adverse events, and serotonergic syndrome. Although this medication has been postulated as a therapeutic option for patients with cardiovascular disease for whom triptans, NSAIDs and dihydroergotamine are contraindicated, the clinical trials showed cardiovascular adverse events, including palpitations, transient increases in blood pressure, and heart rate alterations, albeit with a low frequency. To date, there is limited evidence available to definitely establish the cardiovascular safety of lasmiditan. In addition, cases of lasmiditan abuse were 28.5% vs 7.6% with placebo[27].

Gepants (CGRP antagonists)

The calcitonin gene-related peptide (CGRP) plays a crucial role in the trigemino-vascular reflex and in central sensitivization phenomena that result in chronic migraine[28]. Rimegepant and ubrogepant were approved by the FDA for the acute treatment of migraine with and without aura in adults. However, they are not indicated for the preventive treatment of migraine[29,30]. They have not yet been evaluated by the EMA.

Rimegepant is administered orally at a dose of 75 mg, which is the maximum daily dose. Safety of treating more than 15 migraine attacks with rimegepant during a period of 30 days has not been established. Ubrogepant is administered orally at a dose of 50-100 mg. A second dose can be administered two hours after the starting dose. The maximum daily dose is 200 mg. In patients with severe renal or hepatic insufficiency, the dose must be reduced to 50 mg. Both drugs show interactions at CYP3A and P-glycoprotein level (P-gp)[29,30].

Placebo-controlled clinical trials have shown that rimegepant and ubrogepant are modestly superior in terms of efficacy. The proportion of patients free of pain was 5-10% higher in the rimegepant group vs placebo, and 7-9% higher in the ubrogepant group. The proportion of patients free of the most bothersome symptom was 8-12% higher in the rimegepant group and 10-12% higher in the ubrogepant group vs placebo[29,30]. The efficacy of these medications versus current available therapies for the symptomatic treatment of migraine is unknown.

The most frequent adverse event associated with rimegepant was nausea; and in the case of ubrogepant the most frequent adverse events apart from nausea were viral infections, drowsiness, confusion, dizziness, dry mouth, and abdominal pain. Relevant serious adverse events were not reported in the clinical trials conducted with these medications. Nevertheless, the cardiovascular safety of these medications cannot be determined, since patients with severe cardiovascular diseases were excluded[29,30].

Preventive treatment

The symptomatic treatment of migraine is occasionally insufficient. The decision to start a preventive treatment will depend on the frequency of migraine, the degree of disability they cause and the patient's response to migraine treatment, apart from patient's willingness to start a treatment[31]. It is estimated that at least 25% of patients seen in neurology clinics need preventive treatment[10].

This treatment is reserved for patients with severe, frequent, disabling headache, and for patients unresponsive to acute treatment[32].

As to EM, preventive treatment is indicated in the followed settings[10]:

- Patients with at least three monthly migraine attacks.
- Patients with less than one weekly attack of several days of duration, intense, and with poor response or intolerance to symptomatic medication.
- In the presence of risk for medication overuse (use of symptomatic treatment more than two days per week)
- In the presence of prolonged or atypical auras

The purpose of preventive treatment is to reduce the frequency, severity and duration of attacks, improve patient response to acute treatment, improve patient functionality, and reduce disability[32]. These treatments are also intended to prevent overuse of symptomatic medication.

Preventive treatment is added to symptomatic medication cessation regimens in patients with CM with medication overuse. It is of special relevance for patients with comorbidities who are unresponsive to cessation treatment[10]. This treatment is effective if it reduces the frequency of migraine attacks by at least 50%[33].

Preventive treatment must be used with an educational strategy to make patients aware that the preventive treatment will reduce the frequency and intensity of attacks but will not make them disappear.

The choice of preventive medication will depend on the frequency of attacks (EM vs CM), comorbidities, and individual patient's needs[33].

It is recommended to start the treatment at low doses and progressively escalate to the effective dose for at least three months (the effect may be noticeable at four or six weeks), and to progressively withdraw the preventive treatment after 9-12 months[26].

Below are described the most widely used therapeutic groups for the prevention of migraine:

ß-blockers

ß-blockers are first-line medications for the prevention of migraine, unless they are contraindicated. They are considered the first choice for the prevention of migraine with and without aura, and are especially indicated for patients with concomitant anxiety or stress, hypertension, essential tremor or hyperthyroidism[26].

Both, propranolol and metoprolol have been proven to be superior to placebo in EM, without relevant differences having been found between them in terms of efficacy. In CM, propranolol has not been demonstrated to exert any clinical benefit, as compared to placebo.

Not all ß-blockers effectively treat migraine. ß-blockers with proven efficacy to prevent migraine are propranolol and metoprolol, which are the only ß-blockers marketed and authorized in Spain for that indication[10,12].

A systematic review published in 2019 assessed the efficacy of ß-blockers in the prevention of migraine and tension headache in adults[34]. A total of 108 randomized clinical trials with a duration of 4-64 weeks were included. Most of the studies retrieved were published before 2000. Propranolol and metoprolol were the most-frequently evaluated ß-blockers.

In EM, considering only high-quality evidence and assuming a mean baseline frequency of 4.8 headaches/month, propranolol was associated with a reduction of 1.5 headaches/month at eight weeks (95%CI -2.3 to -0.65) and a reduction of 1.2 headaches/month at 12 weeks (95%CI -1.8 to -0.6) as compared to placebo, with large heterogeneity in the latter. In the case of metoprolol, and assuming a mean baseline frequency of 3.9 headaches/month, the medication reduced the frequency of headache by 0.86 headaches/month (95%CI -1.4 to -0.34) (moderate-quality evidence) with respect to placebo at eight weeks. A network meta-analysis showed no statistically significant differences between propranolol and metoprolol in the frequency of headaches at eight weeks. Metoprolol was superior to placebo in terms of proportion of patients with at least 50% improvement in headaches at 12 weeks (RR 1.4 95%CI 1.1 to 1.8; NNT 5.3 95%CI 3 to 4), but without differences at 42 weeks[34].

In CM, no statistically significant differences were observed between propranolol and placebo in the percentage of patients with at least 50% improvement in headaches at 42 weeks (low-quality evidence). In this context, the efficacy of propranolol was comparable to that of other medications such as flunarizine, topiramate and valproic acid[34].

Frequent side effects of ß-blockers are fatigue, bradycardia and limb coldness; and less frequently, postural hypotension and deterioration of heart failure[12].

ß-blockers are contraindicated in bradycardia, second or third degree heart block, uncontrolled heart failure, cardiogenic shock, Prinzmetal's angina, hypotension, metabolic acidosis and peripheral arterial circulation disorders, among others[12]. Propranolol is also contraindicated in severe bronchial asthma and in patients with a history of bronchospasm[12]. Metoprolol, with its relative cardioselectivity, can be administered with caution to these situations[12].

As to the use of ß-blockers during pregnancy, propranolol and metoprolol belong to FDA Category C and should not be taken during pregnancy unless they are essential, where they should be administered at the lowest effective dose[10,12].

They are excreted in variable amounts in breastmilk, therefore breastfeeding during propranolol treatment is not recommended. In case metoprolol is used during lactation, the infant should be closely monitored[12].

Antiepileptics

Antiepileptics are the treatment of choice when ß-blockers are contraindicated or the patient is unresponsive. They are also indicated in patients with migraine and concomitant epilepsy and/or overweight[10].

Both, topiramate and valproic acid have demonstrated to be effective versus placebo in the prevention of migraine.

Topiramate and sodium valproate are antiepileptics with demonstrated efficacy for the prevention of migraine, although valproate is not authorized in Spain for this indication[10,12].

There is limited evidence available for other antiepileptics such as zonisamide, lamotrigine, carbamazepine, levetiracetam, gabapentin, or pregabalin. The use of these medications for the prevention of migraine has not been approved[10,26]. Recent studies have failed to prove the usefulness of gabapentin as a prophylactic treatment of EM, and its use in this setting is not recommended[10].

A review published in 2015 analyzed the efficacy of a variety of antiepileptics in the prevention of EM in adults through controlled prospective trials[35]. The mean duration of follow-up of studies with topiramate and valproate was 19 and 11 weeks, respectively. As compared to placebo, topiramate and valproic acid were associated with a lower frequency of headache (mean difference (MD) with topiramate: -1.20 95%CI -1.59 to -0.80; MD with valproic acid: -4.31 95%CI -8.32 to -0.30). A higher percentage of patients experienced a ≥50% reduction in the frequency of headache, as compared to placebo (OR 3.18 95%CI 2.10 to 4.82). The studies that analyzed topiramate and most of the studies that assessed valproate were classified as having a high risk of bias. For the rest of antiepileptics, there is no robust evidence supporting their use.

Similar results were obtained in a network review published later, where topiramate was associated with fewer monthly migraine headache days, as compared to placebo (MD: -1.20 95%CI -1.83 to -0.70), and a higher percentage of patients taking topiramate or valproic acid experienced a ≥50% reduction in the number of migraine headache attacks (OR for topiramate: 4.28 95%CI 1.35 to 14.70; OR for valproic acid: 11.38 95%CI 1.31 to 111.11)[36].

Topiramate may cause paresthesia, drowsiness, cognitive impairment, gastrointestinal symptoms, visual disturbances, dyspnea and urinary stones, among other symptoms[12].

ß-blockers and topiramate are first-line medications for the prevention of migraine

Valproic acid is associated with gastrointestinal complaints, weight gain, hematological and coagulation alterations, tremor, confusion, seizures and liver disorders, among others[12]. Its use is contraindicated in patients with liver disease and mitochondrial disorders[12]. Additionally, these drugs are contraindicated in pregnancy and women of childbearing age who are not using an effective contraceptive method[12]. Both topiramate and valproic acid are started at low doses, which are progressively increased to the maximum effective dose[26].

Antidepressants

Antidepressants are not considered as first-line treatment for migraine. They are mainly indicated for patients with migraine and tension headache, or with concomitant depression, anxiety, neuropathic pain or insomnia[26,37].

Amitriptyline is superior to placebo in the prevention of migraine.

The drug of choice is amitriptyline, which is the only antidepressant authorized in Spain for the prevention of migraine in adults[10,12,26]. It is used as prophylactic treatment in patients with EM or CM[38].

A systematic review assessed the evidence available up to July 2016 regarding the efficacy of tricyclic antidepressants in the prevention of migraine[39]. Nine clinical trials assessing amitriptyline were retrieved, with a mean duration of 11 weeks. Statistically significant differences were observed in migraine frequency and index in favor of amitriptyline vs placebo (n=238, MD -0.86 95%CI -1.23 to -0.48).

The anticholinergic and antihistamine activity of amitriptyline cause confusion, agitation, drowsiness, palpitations, tachycardia, orthostatic hypotension, dry mouth, constipation, nausea, urinary retention and weight gain, among others[12]. It should be used with caution in older adults[12]. Its use is contraindicated in patients with recent myocardial infarction, heart block or heart rate disorders and coronary artery failure, in patients taking monoamine oxidase inhibitors or in the presence of severe liver disease[12].

Amitriptyline has been allocated to FDA C category and should not be used in pregnancy unless it is necessary[10,12].

Although at low amounts, it is excreted in breastmilk, and either lactation or amitriptyline treatment should be interrupted in this setting[12].

Calcium antagonists

Calcium antagonists are an option in patients unresponsive or who show poor tolerance to ß-blockers or topiramate, and in thin adults without tendency to depression[26].

Flunarizine is superior to placebo in the prevention of migraine.

Flunarizine is the only calcium antagonist authorized in Spain for the prevention of migraine. More specifically, it is indicated in the prophylaxis of migraine in adults with frequent, severe attacks with poor response to other treatments and/or in the presence of unacceptable side effects[12].

A systematic review assessed the evidence available until 2017 about the efficacy and safety of flunarizine as a preventive treatment in migraine[40]. Nineteen of 25 randomized clinical trials retrieved had a high risk of bias. Flunarizine was superior to placebo in the reduction of the frequency of migraine at three months of treatment (n=249 participants, MD -0.44 95%CI -0.61 to -0.26) and in the proportion of patients with a ≥50% reduction of the frequency of migraine (n=113, OR 8.86 95%CI 3.57 to 22.0), although with a high imprecision. There were no statistically significant differences between flunarizine and placebo in the incidence of adverse events and no severe adverse events were observed. Statistically significant differences were not found between flunarizine and propranolol in the frequency of migraine, intensity of migraine attacks or headache duration.

Flunarizine is associated with weight gain, depression, drowsiness, constipation, and myalgia, among others[12]. It is contraindicated in patients with depression disorders or a history of recurrent depression and in patients with pre-existing symptoms of Parkinson's disease or other extrapyramidal disorders[12].

Since there is no information available in relation to its safety in pregnancy, its use while pregnant should be avoided. Breastfeeding mothers should avoid using flunarizine[12].

Angiotensin-converting enzyme inhibitors (ACEI)/ Angiotensin II receptor blockers (ARB)

Lisinopril and candesartan are used for the prevention of migraine in patients with hypertension in whom ß-blockers are contraindicated or who show poor tolerance to ß-blockers, although they are not indicated for this setting[10,12]. There is limited evidence about their efficacy[38,41].

Botulinum toxin A

Botulinum toxin A is used in patients with CM who are unresponsive or show poor tolerance to oral preventive therapies.

It is superior to placebo in reducing the number of days with CM, but not in EM. There are no differences in terms of efficacy, as compared to oral preventive treatments.

Botulinum toxin blocks the release of acetylcholine at the level of peripheral cholinergic nerve terminals, causing a muscle relaxant effect[12]. Botulinum toxin A is authorized and financed in Spain for the relief of symptoms in adults meeting CM criteria (≥15 monthly headache days, of which at least eight correspond to migraine) with poor response or intolerance to oral prophylactic medications for migraine and in the absence of medication overuse[12,42]. It is not authorized in patients with high-frequency EM.

Botulinum toxin is a hospital medication that must be administered by specialized physicians by intramuscular injection in key muscles of the head and neck that host the sensory nerve terminals responsible for the transmission of painful stimuli[10,12]. The dose is 5 units by injection point. It can be administered in 31-39 points at a time (total dose range: 155-198 units)[12]. Repeat administration is recommended at 12-week intervals[12]. Adverse events associated with this medication include blepharospasm and cervical dystonia[12].

A Cochrane's review assessed the efficacy of botulinum toxin versus placebo or active treatment in adults with CM or EM[43]. The inclusion of studies in which patients were also treated with another preventive or rescue treatment was permitted. A total of 28 studies were identified, with a low or very low quality of evidence in most cases. In CM, at 12 weeks, botulinum toxin reduced the number of migraine days by 3.1 days/month (95%CI -4.7 to -1.4), as compared to placebo, albeit with high heterogeneity. When small studies were excluded, difference was -2 days/month (95%CI -2.8 to -1.1). The only study in patients with EM did not show statistically significant differences in this variable. There were no differences in the number of migraine attacks per month in patients with CM or EM. The three studies that assessed the efficacy of botulinum toxin versus oral preventive treatments did not demonstrate differences in efficacy

Table 3. Preventive treatments for migraine[10,12,26,38]:

Drug	Dosage	Level of evidence[10]	Settings of choice
ß-blockers	Metoprolol 50–200 mg/day in 2 doses, orally	I/A in EM IV In CM	Migraine with hypertension, tremor, anxiety, stress, hyperthyroidism, pregnancy
	Propranolol 40–240 mg/day in 2-3 doses, orally		
Antiepileptics	Topiramate 25–200 mg/day, orally	I/A in EM and CM	Migraine with epilepsy, overweight
	Valproic acid 300-1500 mg/day, orally*	I/A in EM III/C in CM	
Antidepressants	Amitriptyline 10–75 mg/day, orally before going to bed	I/A in EM	They are not considered first line EM and CM Migraine with tension headache, depression, anxiety, neuropathic pain, insomnia
Calcium antagonists	Flunarizine 5-10 mg/day, orally preferably before going to bed	I/A in EM IV/C in CM	Migraine with and without aura unresponsive to ß-blockers and/or topiramate Thin adults without tendency to depression
ACEI/ARB	Lisinopril* 5-20 mg/day, orally	II/B in EM	Migraine with hypertension
	Candesartan* 8-32 mg/day, orally		
Botulinum toxin type A	155-195 units distributed in 31-39 points (5 units/point), intramuscular every 12 weeks	I/A in CM	Financed in patients with CM who are unresponsive or intolerant to oral preventive therapies

(*) Not authorized for migraine in Spain.

measures in patients with CM or EM. Botulinum toxin was associated with a higher incidence of adverse events vs placebo (RR 1.28 95%CI 1.12 to 1.47), but lower as compared to oral preventive treatments (RR 0.76 95%CI 0.59 to 0.98).

Anti-CGRP monoclonal antibodies

In relation to the physiopathology of migraine, it has been postulated that pain may originate from a combination of processes including trigeminal nerve stimulation. This stimulation leads to the release of the calcitonin gene-related peptide (CGRP). Although CGRP is distributed throughout the nervous system, it concentrates in the perivascular sensory afferents of the trigeminal nerve and its nucleus caudalis. It has strong vasodilation effects and causes neuroinflammation and neurotransmission[44]. Increased neurotransmission and the perception of sensory input in the cortex are interpreted as painful stimuli.

CGRP levels have been shown to increase significantly in peripheral blood and cerebrospinal fluid during a migraine attack and return to normal when headache disappears.

Botulinum toxin A is used in patients with chronic migraine who are unresponsive to oral preventive therapies

Nevertheless, and in the absence of other migraine biomarkers, at the present time it cannot be stated that CGRP is a reliable and reproducible marker of migraine in clinical practice[44].

Anti-CGRP monoclonal antibodies (mAbs) are designed to bind and selectively block CGRP (galcanezumab, fremanezumab, eptinezumab) or its receptor (erenumab), and they are used for the prevention of migraine. Their main characteristics are described in Table 4.

To date, the mAbs marketed in Spain include galcanezumab, erenumab and fremanezumab, which are classified as hospital diagnostic drugs and hospital dispensing without a tear-out label, which means that mAbs must be prescribed by neurologists and dispensed (free of charge to the patient) in hospital pharmacy services. Eptinezumab is authorized and marketed in USA.

mAbs have some advantages with respect to oral preventive treatments, especially a low frequency of adverse events (the most frequent being pain or injection site reactions), all of which are mild or moderate, with a drop-out rate under 2.5%[12]. No relevant interactions (they do not interact with symptomatic or other preventive treatments for migraine) or contraindications (except for hypersensitivity to the active substance or its excipients) have been described to date.

Adherence is a pending issue in oral preventive treatments. Indeed, a study in patients with CM[45], showed that only 29% of patients showed a treatment adherence > 80% at six months, and 20% at 12 months. Indeed, adherence to mAbs is expected to be notably higher as administration is subcutaneous or endovenous and monthly or quarterly. Finally, mAbs have a rapid action and their effects can be noticed from the first week of treatment[44], as compared to the 10-15 days needed by ß-blockers, valproic acid and botulinum toxin, or the 20-30 days required by topiramate, flunarizine, or amitriptyline.

Limitations of mAbs include uncertainty about their safety, long-term effectiveness and optimal treatment duration, the appearance of anti-drug antibodies and their effects, and the management of unresponsive patients.

mAb emerge as a new therapeutic alternative of modest efficacy for patients with chronic and episodic migraine who are unresponsive to oral preventive treatments and botulinum toxin

Efficacy of monoclonal antibodies

The efficacy of mAbs in the prevention of migraine has been demonstrated in multicentre, randomized, double-blind, placebo-controlled, three-arm clinical trials, two of which tested the drug at two different doses, with a duration from 12 or 24 weeks. Clinical trials have been conducted in patients with EM, CM and migraine unresponsive to other treatments. These trials are awarded a level of evidence I and a grade of recommendation A[10].

Table 4. Characteristics of anti-CGRP monoclonal antibodie[12,42,46].

Name	GALCANEZUMAB	ERENUMAB	FREMANEZUMAB	EPTINEZUMAB
Pharmaceutical form	Emgality® 120 mg pen injector	Aimovig® 70 mg pen injector Aimovig® 140 mg pen injector	Ajovy® 225 mg 1 prefilled syringe	Vyepti® (FDA) Not marketed in Spain (April 2021)
Molecule	Humanized IgG4 antibody	Human IgG2a antibody	Humanized IgG2a antibody	Humanized IgG1 antibody
Target	CGRP	R- CGRP	CGRP	CGRP
Approved indication	Prophylaxis of migraine in adults with at least four monthly migraine days.			-
Financed indication	Patients with eight or more monthly migraine days (high-frequency EM and CM) and three or more failed treatments used at effective doses for at least three months, one of these treatments including botulinum toxin in the case of CM.			-
Dosage	Loading dose: 240 mg Maintenance dose: 120 mg	70 mg or 140 mg	225 mg/month or 675 mg/3 months	100 mg or 300 mg
Frequency of administration	Monthly	Monthly	Monthly/quarterly	Quarterly
Route of administration	Subcutaneous	Subcutaneous	Subcutaneous	iv infusion 30 min
Special populations	Pediatrics: No data available about patients <18 years old. Older adults: Dose adjustment is not required. Limited data in ≥65 years. Mild-moderate renal or liver insufficiency: dose adjustment is not necessary. Pregnancy: Limited data, avoid use during pregnancy. Breastfeeding: Limited data, its use can be considered only if it is clinically necessary. Effects on fertility: No data available about its effects on fertility in humans.			
Most frequent adverse events	Injection site reaction Pruritus Vertigo Constipation	Injection site reaction Constipation Muscle spams Pruritus Hypersensitivity and skin reactions	Injection site reaction	Nasopharyngitis Hypersensitivity reactions Dizziness Respiratory and urine infections Fatigue Nausea Sinusitis
Anti-drug antibodies	4.8% in CE 12.5% at 12 months	6.3% (70mg) 2,6% (140mg)	0.4% in CE 2.3% at 12 months	18-20.6%
Resource use	The three drugs are prepared for self-administration after the patient has received adequate training from a healthcare professional.			It requires iv administration in a day hospital.

The primary endpoint in all trials was the reduction of monthly migraine days (MMD). A patient was considered to respond to therapy if MMD decreased at least by 50% (50% response) after 12 weeks of therapy (secondary endpoint). Other secondary variables were 75% and 100% response in MMD reduction, MMD reduction with need of acute treatment, disability scales, and daily living activity scales[12,46].

In some clinical trials the inclusion of patients on oral preventive monotherapy at a stable dose was permitted.

The mean baseline MMD was 8.3-9.1 days in EM trials and 16.1-19.4 days in MMD trials[12,46].

All mAbs have been proven to be effective vs placebo in reducing monthly headache and migraine days, the number of days with need of symptomatic treatment, and improving quality of life scores. Nevertheless, their efficacy is insufficient, since mean MMD are only reduced by 1-3 days and less than half the patients achieve a 50% MMD reduction[12,46].

We should not forget the "efficacy of the placebo effect", which to a greater or lesser extent is confirmed in all clinical trials, with almost 40% of patients responding in the placebo arm of some studies. Response to placebo is poorer in refractory migraine studies[47-49].

Tables 5 and 6 summarize the efficacy of the four mAbs in EM and CM in their respective pivotal trials.

Table 7 shows the efficacy of mAbs in refractory migraine to two or four previous preventive treatments.

There are no clinical trials comparing the efficacy and safety between the different mAbs or with other first-line preventive treatments.

An adjusted indirect comparative study of mAbs vs CGRP in CM has been published[50]. This study assessed the relative efficacy in the percentage of patients with a >50% MMD reduction. The results obtained showed no differences among erenumab, fremanezumab and eptinezumab at different dosage schedules in terms of efficacy in reducing MMD by at least 50% or in relation to their safety profile. Therefore, these drugs can be considered equivalent therapeutic alternatives in patients with CM.

A meta-analysis[51] including 11 studies, four with erenumab, four with galcanezumab, two with fremanezumab, and one with eptinezumab concluded there are no significant differences between these drugs in terms of MMD reduction, reduction of monthly days requiring symptomatic treatment, and 50% response rate.

Safety of monoclonal antibodies

Adverse events reported in the clinical trials were similar in the active arms vs placebo, except for local injection site reactions, which were more frequent in patients treated with mAbs. The occurrence of constipation was higher in patients treated with erenumab and galcanezumab vs placebo. Galcanezumab was associated with episodes of vertigo, whereas erenumab was reported to cause muscle cramps. A study assessing the tolerability and cardiovascular safety of long-term use (more than three years) of erenumab demonstrated that the side

Table 5. Efficacy at three months in E.M

Pivotal trials	Drug	MMD reduction		% patients with 50% response			
		Drug vs placebo	MD (95%CI)	Drug vs placebo	Difference	NNT	95%CI
20120296 study[12] Phase III, n: 955, 24 weeks	Erenumab 70 mg/4 weeks	-3.2 vs -1.8	-1,4 (-1.9 to -0.9)	43.3% vs 26.6%	16.7%	6	(5-8)
	Erenumab 140 mg/4 weeks	-3.7 vs -1.8	-1,9 (-2.3 to -1.4)	50.0% vs 26.6%	23.4%	4	(4-6)
CGAH study (EVOLVE-2)[12] Phase III, n: 992, 24 weeks	Galcanezumab 120 mg/month	-4.3 vs -2.3	-2.0 (-2.6 to -1.5)	59.3% vs 36.0%	23.3%	4	(4-6)
	Galcanezumab 240 mg/month	-4.2 vs -2.3	-1.9 (-2.4 to-1.4)	56.5% vs 36.0%	20.5%	5	(5-7)
30050 study (HALO)[12] Phase III, n: 875, 12 weeks	Fremanezumab 225 mg/4 weeks	-3.7 vs -2.2	-1.5 (-1.9 to -0.9)	47.7% vs 27.9%	19.8%	5	(5-7)
	Fremanezumab 675 mg SD	-3.4 vs -2.2	-1.2 (-1.7 to -0.7)	44.4% vs 27.9%	16.5%	6	(5-9)
NCT02559895 study[46] Phase III, n: 665, 12 months	Eptinezumab 100 mg	-3.9 vs -3.2	-0.7 p=0.018	49.8% vs 37.4%	12.4%	8	(6-13)
	Eptinezumab 300 mg	-4.3 vs -3.2	-1.1 p<0.001	56.3% vs 37.4%	18.9%	5	(5-7)

50% response: ≥50% MMD reduction at three months of treatment. **SD:** Single dose.

Table 6. Efficacy at three months in CM.

Pivotal trials	Drug	MMD reduction		% patients with 50% response			
		Drug vs placebo	MD (95%CI)	Drug vs placebo	Difference	NNT	95%CI
20120295 study[12] Phase III, n: 667, 12 weeks	Erenumab 70 mg/4 weeks	-6.6 vs -4.2	-2.4 (-3.5 to -1.4)	39.9% vs 23.5%	16.4%	6	(5-9)
	Erenumab 140 mg/4 weeks	-6.6 vs -4.2	-2.4 (-3.5 to -1.4)	41.2% vs 23.5%	17.7%	6	(5-8)
CGAI study (REGAIN)[12] Phase III, n: 1113, 12 weeks	Galcanezumab 120 mg/month	-4.8 vs -2.7	-2.1 (-2.9 to -1.3)	27.6% vs 15.4%	12.2%	8	(7-12)
	Galcanezumab 240 mg/month	-4.6 vs -2.5	-2.1 (-2.7 to -1.1)	27.5% vs 15.4%	12.1%	8	(7-12)
30049 study (HALO)[12] Phase III, n: 1130, 12 weeks	Fremanezumab 225 mg/4 weeks (D*: 675 mg)	-5.0 vs -3.2	-1.9 (-2.6 to -1.1)	40.8% vs 18.1%	22.7%	4	(4-6)
	Fremanezumab 675 mg SD	-4.9 vs -3.2	-1.7 (-2.4 to -0.9)	37.6% vs 18.1%	19.5%	5	(5-7)
NCT02974153 study[46] Phase III, n: 1072, 6 months	Eptinezumab 100 mg	-7.7 vs -5.6	-2.1 p<0.001	57.6% vs 39.3%	18.3%	5	(5-8)
	Eptinezumab 300 mg	-8.2 vs -5.6	-2.6 p<0.001	61.4% vs 39.3%	22.1%	5	(4-6)

50% response: ≥50% MMD reduction at three months of treatment. **D*:** Loading dose. **SD:** Single dose.

Table 7. Efficacy at three months in refractory migraine.

Study	Drug	MMD reduction		% patients with 50% response			
		Drug vs placebo	MD (95%CI)	Drug vs placebo	Difference	NNT	95%CI
NCT03096834 study Phase III, CM[47]	Erenumab 70 mg	-5.4 vs -2.7	-2.7 (-4.2 a -1.2)	35.6% vs 14.2%	21.4%	5	(4-6)
	Erenumab 140 mg	-7.0 vs -2.7	-4.3 (-5.8 a -2.8)	41.3% vs 14.2%	27.1%	4	(4-5)
CONQUER study[48] Phase III, EM or CM, three months	Galcanezumab 120 mg /month (D*: 240 mg)	-4.1 vs -1	-3.1 (-3.9 a -2.3)	37.7% vs 13.3%	24.4%	4	(4-5)
FOCUS study[49] Phase III, EM (40%) or CM (60%) n: 838, 12 weeks	Fremanezumab 225 mg/4 weeks (in CM 1stD: 675 mg)	-4.1 vs 0.6	-3.5 (-4.2 a-2.8)	34.0% vs 9.0%	25.0%	4	(4-5)
	Fremanezumab 675 mg SD	-3.7 vs 0.6	-3.1 (-3.8 a -2.4)	34.0% vs 9.0%	25.0%	4	(4-5)

50% response: ≥50% MMD reduction at three months of treatment. **D*:** Loading dose. **SD:** Single dose.

effects were similar to those of placebo, except for injection site reactions, constipation and muscle cramps, which were more frequent in the erenumab group, although less frequent than in pivotal clinical trials[52]. Fremanezumab is apparently the mAb with fewest reported adverse effects.

Due to their high molecular weight, mAbs do not cross the blood-brain barrier, and therefore do not cause adverse effects on the central nervous system[10]. They cross the placental barrier and, since there are no data available in pregnant women, they should be avoided in pregnancy.

Inhibition of the vasodilator action of CGRP raises uncertainty about the cardiovascular safety of these medications in patients with underlying or latent cardiovascular diseases, as it may cause exacerbation of ischemic events such as stroke, transient ischemic accident or myocardial infarction, and the risk for eclampsia during pregnancy. It should be noted that patients with migraine have a higher cardiovascular risk. In addition, patients with cardiovascular or cerebrovascular diseases were excluded from most studies, and in those trials that allowed their inclusion, the number of included patients was small. Therefore, there are no safety data available in these patients, nor can safety data be extended to patients with cardiovascular disease. The incidence of cardiovascular events (hypertension, tachycardia, palpitations, increased heart rate) with mAbs was low and similar to those of placebo in studies with a duration of 12-24 weeks. There were isolated cases of severe car-

diovascular events, including myocardial ischemia, although a direct causal relationship could not be established due to confounding factors[58-60].

The risk management plan for the three mAbs marketed in Spain includes the follow-up of cardiovascular events in high-risk patients, severe hypersensitivity, and gestational hypertension and preeclamsia[53–55].

Current situation, indication, funding

To date, the three anti-CGRP mAbs available in Spain (galcanezumab, erenumab and fremanezumab) have the same labelled indication: "prophylaxis of migraine in adults with at least four monthly migraine days"[12].

Although they have been proven to be effective and safe in the prevention of migraine vs placebo, their efficacy is still modest. Moreover, no comparative studies have been performed with standard therapies, and there are limited data available about their long-term efficacy and safety in clinical practice. In addition, incorporating mAbs to migraine therapies has a significant economic impact, not only due to their high prices (150-200 € month/patient; 1800-2300 € year/patient), but also for the high prevalence and chronicity migraine. Therefore, it is necessary that mAbs find their place in the treatment of migraine in the context of other preventive therapies, and to develop guidelines that include criteria for approval by national agencies and funding to guide local clinical practice.

Place in therapeutics

The European Headache Federation (EHF) recommends with the classification as "expert recommendations" the use of anti-CGRP mAbs in patients with EM or CM who have not responded to at least two previous preventive treatments or where other preventive treatments are contraindicated due to the presence of comorbidities, adverse events or poor adherence. As to patients with poor response to an oral preventive treatment, in the case of EM the EHF recommends suspending treatment when mAb therapy is started, and in the case of CM recommends maintaining treatment and consider suspension later. The EHF also recommends suspending mAb therapy at 6-12 months, both in EM and CM. Their use is contraindicated in pregnancy, lactation, alcohol or drug abuse, cardiovascular or cerebrovascular disease or severe mental illness[56].

The American Headache Society (AHS) recommends anti-CGRP mAb therapy in EM patients unresponsive after six weeks of treatment or with poor tolerance to at least two previous preventive treatments. With respect to low-frequency EM (4-7 monthly headache days), it is also required that the patient has moderate-severe disability as measured on the MIDAS (Migraine DisaBility Assessment) (>11) or HIT-6 (Headache Impact Test questionnaire) scales (>50). In relation to CM, the AHS recommends their use in patients unresponsive or with poor tolerance to at least two oral preventive treatments, or to two or more botulinum A toxin infiltrations at three-month intervals. Concomitant use of oral preventive therapies and mAbs is allowed[57].

The maximum duration of treatment with mAB is one year

The AHS recommends evaluating mAbs after three monthly doses, or two doses in case the therapy is administered at three-month intervals, and continue the treatment if at least a 50% reduction in MMD is achieved or if a significant improvement is obtained according to validated impact and life quality scales[57].

In our country, the Ministry of Health and the AEMPS, in their respective therapeutic positioning reports, acknowledge the usefulness of galcanezumab, erenumab and fremanezumab in the prophylaxis of migraine in patients with at least four MMD[12]. However, the authorities restrict state funding and the use of mAbs to patients with 8 or more MMD (high-frequency EM and CM) and three or more failed previous treatments at effective doses administered for at least three months, being one of these treatments botulinum toxin infiltrations in the case of CM[58–60].

Given that the three drugs are considered therapeutic equivalents in terms of efficacy and safety, the choice is based on criteria of efficiency, convenience and profile of adverse events.

In this context, the clinical guidelines for headache of the Spanish Society of Neurology (SEN) recommends using the same criteria as the Ministry of Health and recommends mAbs as fourth-line treatment (level of evidence IV, grade of recommendation GECSEN)[10].

Situation in Navarre

In Navarre in November 2019, the Central Pharmacy Commission approved the request for using mAbs (galcanezumab and erenumab) for the treatment of patients with eight or more MMD (high-frequency EM and CM) and three or more failed treatments administered at suffi-

cient doses for at least three months, which must include two cycles of botulinum toxin at high doses in the case of CM. One year later, in November 2020, the use of fremanezumab was approved under the same conditions.

The protocol for the use of monoclonal antibodies of Navarre Hospital Complex indicates:

- To start with the most cost-effective mAb, considering the profile of adverse events of each therapy and the characteristics of the patient.
- For example, if the patient has previous significant vestibular symptoms, the use of galcanezumab is ruled out. If poor adherence is expected, consider galcanezumab administered on a quarterly basis (dosage not recommended in women of childbearing age).
- Maintain the treatment for at least three months before it is identified as ineffective.
- Consider replacing it with another monoclonal antibody (anti-receptor/anti-ligand) for three more months, in case of poor tolerance or partial effectiveness.
- If the treatment is effective, maintain for a year and then suspend. After a period of observation, if migraine exacerbates, use the same mAb that proved to be effective in that patient.

All treatments are prescribed by the Headache Unit and are dispensed in the hospital pharmacy services.

Given the subjectivity in assessing the response to prophylactic treatment, it is necessary that the patient registers the "headache log" (days with headache, type, intensity, use of symptomatic medication and need for emergency care for migraine), and the completion of quality of life and disability questionnaires (HIT-6 and MIDAS) in each visit.

The long-term safety and efficacy of mAb and the management of unresponsive patients is yet to be established

In addition, coordination of the team of healthcare professionals in the patient care and follow-up is crucial, as well as a structured record of patient progress in their medical history to facilitate the evaluation of response and treatment tolerance.

Between December 2019 and March 2021, 277 patients started an anti-CGRP mAb therapy in Navarre. As for the patients treated in the Navarre Hospital Complex (88% CM, 10% EM and 2% other off-label uses), 91 patients have completed their 12-month treatment with the mAb they started with. Of the 91 patients, the 12-month treatment was effective in 61 (67%); 18 (20%) patients have changed the mAb due to the partial effectiveness and/or adverse effects of the first mAb; and early suspension was necessary in 12 patients (13%) (nine for ineffectiveness and/or intolerance, two drop-outs, and a death).

With regard to safety, 74% of patients treated with galcanezumab and 88% of the patients treated with erenumab did not develop any relevant adverse event, according to their medical history. The most frequent adverse events were vertigo, dizziness and constipation.

Table 8 summarizes recommendations about the management of mAbs in migraine[10].

Table 8. Recommendations for use of anti-CGRP monoclonal antibodies[10] in CM and EM.

Start	Patients meeting CM criteria: if at least three preventive treatments have failed, including a treatment with botulinum toxin A. Patients meeting high-frequency EM criteria: if at least three preventive oral treatments have failed.
Failure of oral preventive treatments	Ineffectiveness: treatment administered for at least 3 months at adequate doses. Lack of tolerability.
Failure of botulinum toxin A	At least two-three cycles of quarterly treatment, at least one-two cycles at a dose of 195 U.
Maintenance	At least three months of treatment and assess response and tolerability: · If it is not effective: suspend. · If it is effective: maintain for at least 12 months. Suspend and reevaluate after withdrawal. · If response is partial: prolong the treatment three more months or consider changing* to another anti-CGRP mAb. Reevaluate at three months. · In case of poor tolerance: change to another anti-CGRP mAb and reevaluate at three months. (*) For the moment, there is no quality scientific evidence to support that changing to a second mAb due to lack of response will be an effective strategy.
Use of other oral preventive treatments	Consider their combination if the patient at least shows a response, although incomplete, to previous treatment. If the patient shows an excellent response, consider suspension of previous preventive treatments.
Do not use in:	Pregnancy. Breastfeeding. Severe cardiovascular and cerebrovascular diseases. Severe mental illness. Concomitant use with other biological agents does not seem to be inadvisable, although there is no evidence.
Objective evaluation	A regular, objective (also subjective) evaluation of clinical outcomes is necessary. The use of headache logs, scales such as HIT-6, MIDAS or quality of life questionnaires to objectively assess effectiveness is recommended

HIT-6: Headache impact test-6. **MIDAS:** Migraine Disability Assessment Scale.

Conclusions

Migraine is a disabling neurological disorder of multifactorial etiology that negatively affects the quality of life of patients.

Differential diagnosis of EM vs CM is based on the number of monthly headache days. MOH is a different entity, being a risk factor for chronic migraine.

The approach to migraine involves changes in lifestyle and triggers, with symptomatic and preventive treatment as needed. These strategies are aimed at relieving pain and reducing the frequencies of headache attacks and prevent progression to chronic migraine.

The symptomatic treatment of choice is based on NSAIDs for mild-moderate attacks, and triptans for moderate-severe attacks.

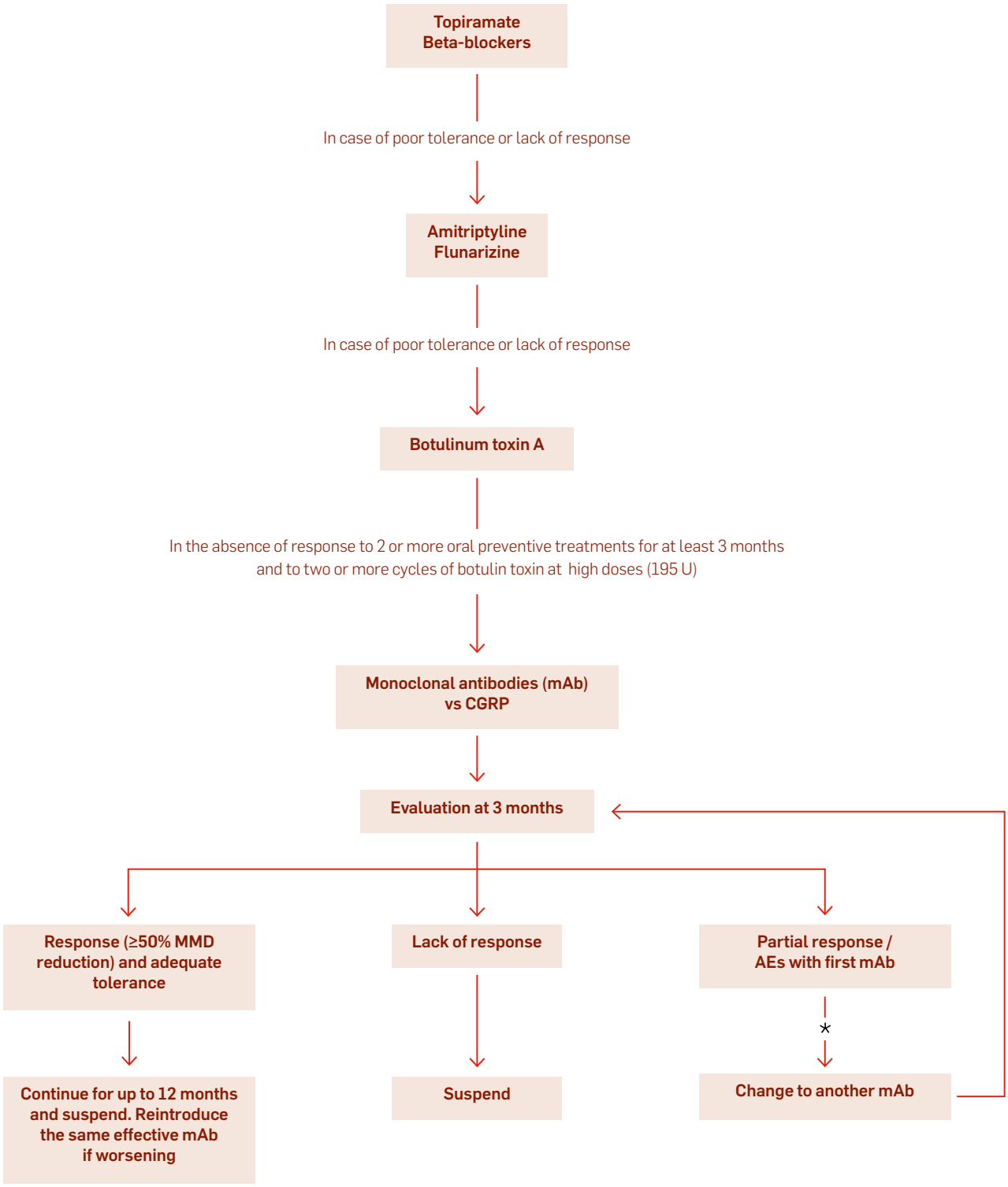
Preventive treatment is reserved for patients with frequent and disabling migraine attacks and for patients who show overuse of symptomatic medication.

Oral drugs are the first-line preventive treatment, being ß-blockers the first-line therapy, along with topiramate.

Botulinum toxin A is used in patients with chronic migraine who are unresponsive to oral preventive therapies.

Anti-CGRP monoclonal antibodies emerge as a new therapeutic alternative for patients with eight or more monthly migraine days who have been unresponsive to three or more treatments administered for at least three months, which must include botulinum toxin A in CM patients. The efficacy of these antibodies vs placebo is modest. There are no comparative studies vs standard therapies. These treatments must be used with caution in patients with a previous history of cardiovascular events.

Figure 3. Algorithm of chronic migraine preventive treatment: headaches 15 or more days per month, of which eight or more correspond to migraine.



AE: Adverse events.

(*) There is no evidence available supporting changing to another mAb.

References

1. Migraña - Trastornos neurológicos - Manual MSD versión para profesionales. Accessed February 1, 2021.

2. Santos Lasaosa S, Irimia P. Recommendations on the use of monoclonal antibodies for treating migraine. Consensus group of Navarre and Aragon. *An Sist Sanit Navar*. 2019;42(2):235-238. doi:10.23938/ASSN.0640

3. Dodick DW. Migraine. *Lancet*. 2018;391(10127):1315-1330. doi:10.1016/S0140-6736(18)30478-1

4. Edvinsson L, Haanes KA, Warfvinge K, Krause DiN. CGRP as the target of new migraine therapies - Successful translation from bench to clinic. *Nat Rev Neurol*. 2018;14(6):338-350. doi:10.1038/s41582-018-0003-1

5. Olesen J, Bes A, Kunkel R, et al. The International Classification of Headache Disorders, 3rd edition (beta version). *Cephalalgia*. 2013;33(9):629-808. doi:10.1177/0333102413485658

6. Bigal ME, Lipton RB. Migraine chronification. *Curr Neurol Neurosci Rep*. 2011;11(2):139-148. doi:10.1007/s11910-010-0175-6

7. Burch RC, Buse DC, Lipton RB. Migraine: Epidemiology, Burden, and Comorbidity. *Neurol Clin*. 2019;37(4):631-649. doi:10.1016/j.ncl.2019.06.001

8. Menéndez AI, D'Elia G, Bajo E. Fisterra. Guías Clínicas: Migraña . 2017[citado el 8 de febrero de 2021].

9. Metamizol y riesgo de agranulocitosis. Nota Informativa de la Agencia Española de Medicamentos y Productos Sanitarios. Referencia: MUH (FV), 15/2018.

10. Santos S, Pozo P. *Manual de Práctica Clínica en Cefaleas. Recomendaciones Diagnóstico-Terapéuticas de La Sociedad Española de Neurología 2020*. Madrid: 2020.

11. Metoclopramida: restricciones de uso, actualización de indicaciones y posología. Nota Informativa de la Agencia Española de Medicamentos y Productos Sanitarios. Referencia: MUH (FV), 22/2013.

12. Fichas técnicas. Agencia Española de Medicamentos y Productos Sanitarios (AEMPS).

13. Richer L, Billinghurst L LM, Russell K, Vandermeer B, Crumley ET, Durec T K, TP HL. Drugs for the acute treatment of migraine in children and adolescents (Review). *Cochrane Database Syst Rev*. 2016;(4):No.: CD005220. doi:10.1002/14651858.CD005220.pub2

14. Riesco N, García-Cabo C, Pascual J. Migraña. *Med Clin (Barc)*. 2016;146(1):35-39. doi:10.1016/j.medcli.2015.07.003

15. 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. doi:10.1111/head.12499

16. González-Oria C, Belvís R, Cuadrado ML, et al. Document of revision and updating of medication overuse headache (MOH). *Neurologia*. 2020;36(3):229-240. doi:10.1016/j.nrl.2020.04.029

17. Ferrari MD, Goadsby PJ, Roon KI, Lipton RB. Triptans (serotonin, 5-HT1B/1D agonists) in migraine: Detailed results and methods of a meta-analysis of 53 trials. *Cephalalgia*. 2002;22(8):633-658. doi:10.1046/j.1468-2982.2002.00404.x

18. Dodick DW. Triptan nonresponder studies: Implications for clinical practice. *Headache*. 2005;45(2):156-162. doi:10.1111/j.1526-4610.2005.05031.x

19. Diener HC, Gendolla A, Gebert I, Beneke M. Almotriptan in migraine patients who respond poorly to oral sumatriptan: A double-blind, randomized trial. In: *European Neurology*. Vol 53. Eur Neurol; 2005:41-48. doi:10.1159/000085061

20. Färkkilä M, Olesen J, Dahlöf C, et al. Eletriptan for the treatment of migraine in patients with previous poor response or tolerance to oral sumatriptan. *Cephalalgia*. 2003;23(6):463-471. doi:10.1046/j.1468-2982.2003.00554.x

21. Pascual J, Mateos V, Roig C, Sanchez-del-Rio M, Jiménez D. Marketed Oral Triptans in the Acute Treatment of Migraine: A Systematic Review on Efficacy and Tolerability. *Headache J Head Face Pain*. 2007;47(8):1152-1168. doi:10.1111/j.1526-4610.2007.00849.x

22. Loder E. *Triptan Therapy in Migraine*. N Engl J Med 2010;363:63-70.

23. Smith TR, Sunshine A, Stark SR, Littlefield DE, Spruill SE, Alexander WJ. Sumatriptan and Naproxen Sodium for the Acute Treatment of Migraine. *Headache J Head Face Pain*. 2005;45(8):983-991. doi:10.1111/j.1526-4610.2005.05178.x

24. Morillo LE. Migraine headache. *Clin Evid (Online)*. 2004;(11):1696-1719.

25. Derivados ergóticos y riesgo de fibrosis y ergotismo: restricción de indicaciones - Agencia Española de Medicamentos y Productos Sanitarios. Accessed March 1, 2021.

26. *Guía Oficial de Cefaleas 2019. Grupo de Estudio de Cefaleas de La Sociedad Andaluza de Neurología (SANCE)*.; 2019.

27. Drug Approval Package: Reyvow (lasmiditan). U.S. Food and Drug Administration (FDA).

28. Ruiz Allende AM. La nueva era de antimigrañosos: más allá de los triptanes. Universidad de Cantabria 2016.

29. Drug Approval Package: Nurtec ODT (rimegepant). U.S. Food and Drug Administration (FDA).

30. Drug Approval Package: Ubrelvy (ubrogepant). U.S. Food and Drug Administration (FDA).

31. Schwedt TJ. Preventive Therapy of Migraine. *Contin Lifelong Learn Neurol*. 2018;24(4-Headache):1052-1065. doi:10.1212/CON.0000000000000635

32. Loder E, Biondi D. General principles of migraine management: The changing role of prevention. *Headache*. 2005;45(Suppl 1:S33-S47). doi:10.1111/j.1526-4610.2005.4501002.x

33. Diener H-C, Holle-Lee D, Nägel S, et al. Treatment of migraine attacks and prevention of migraine: Guidelines by the German Migraine and Headache Society and the German Society of Neurology. *Clin Transl Neurosci*. 2019:1-40. doi:10.1177/2514183x18823377

34. Jackson JL, Kuriyama A, Kuwatsuka Y, et al. *Beta-Blockers for the Prevention of Headache in Adults, a Systematic Review and Meta-Analysis. PLoS ONE 2019;14(3):E0212785*. doi:10.1371/journal.pone.0212785

35. Mulleners WM, McCrory DC, Linde M. Antiepileptics in migraine prophylaxis: An updated Cochrane review. *Cephalalgia*. 2015;35(1):51-62. doi:10.1177/0333102414534325

36. He A, Song D, Zhang L, Li C. Unveiling the relative efficacy, safety and tolerability of prophylactic medications for migraine: pairwise and network-meta analysis. *J Headache Pain*. 2017;18(1):26. doi:10.1186/s10194-017-0720-7

37. Burch R. Antidepressants for Preventive Treatment of Migraine. *Curr Treat Options Neurol*. 2019;21(4). doi:10.1007/s11940-019-0557-2

38. Pharmacological management of migraine. Edinburgh: SIGN; 2018. *Sign*. 2018;155(February).

39. Xu XM, Liu Y, Dong MX, Zou DZ, Wei YD. Tricyclic antidepressants for preventing migraine in adults. *Med (Baltimore*. 2017;96(22):e6989. doi:10.1097/MD.0000000000006989

40. 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. doi:10.1097/j.pain.0000000000001456

41. Dorosch T, Ganzer CA, Lin M, Seifan A. Efficacy of Angiotensin-Converting Enzyme Inhibitors and Angiotensin Receptor Blockers in the Preventative Treatment of Episodic Migraine in Adults. *Curr Pain Headache Rep*. 2019;23(11). doi:10.1007/s11916-019-0823-8

42. BIFIMED: Buscador de la Información sobre la situación de financiación de los medicamentos. Ministerio de Sanidad. Gobierno de España.

43. Herd CP, Tomlinson CL, Rick C, et al. Botulinum toxins for the prevention of migraine in adults. *Cochrane Database Syst Rev*. 2018;2018(6):CD011616. doi:10.1002/14651858.CD011616.pub2

44. Santos-Lasaosa S, Belvís R, Cuadrado ML, et al. Cal-citonin gene–related peptide in migraine: from pathophysiology to treatment. *Neurologia*. July 2019. doi:10.1016/j.nrl.2019.03.013

45. Hepp Z, Dodick DW, Varon SF, Gillard P, Hansen RN, Devine EB. Adherence to oral migraine-preventive medications among patients with chronic migraine. *Cephalalgia*. 2015;35(6):478-488. doi:10.1177/0333102414547138

46. fad. Viepty (Eptinezumab) Prescribing Information. Accessed January 28, 2021.

47. Ashina M, Tepper S, Brandes JL, et al. Efficacy and safety of erenumab (AMG334) in chronic migraine patients with prior preventive treatment failure: A subgroup analysis of a randomized, double-blind, placebo-controlled study. *Cephalalgia*. 2018;38(10):1611-1621. doi:10.1177/0333102418788347

48. Reuter U. Galcanezumab CONQUERs migraine prevention. *Lancet Neurol*. 2020;19(10):798-799. doi:10.1016/S1474-4422(20)30324-0

49. Ferrari MD, Diener HC, Ning X, et al. Fremanezumab versus placebo for migraine prevention in patients with documented failure to up to four migraine preventive medication classes (FOCUS): a randomised, double-blind, placebo-controlled, phase 3b trial. *Lancet*. 2019;394(10203):1030-1040. doi:10.1016/S0140-6736(19)31946-4

50. Briceño-Casado MDP, Gil-Sierra MD, Fénix-Caballero S. Comparación indirecta ajustada de anticuerpos monoclonales contra el péptido relacionado con el gen de la calcitonina en migraña crónica. *Farm Hosp*. 2020;44(5):212-217. doi:10.7399/fh.11419

51. Deng H, Li GG, Nie H, et al. Efficacy and safety of calcitonin-gene-related peptide binding monoclonal antibodies for the preventive treatment of episodic migraine - An updated systematic review and meta-analysis. *BMC Neurol*. 2020;20(1). doi:10.1186/s12883-020-01633-3

52. Ashina M, Kudrow D, Reuter U, et al. Long-term tolerability and nonvascular safety of erenumab, a novel calcitonin gene-related peptide receptor antagonist for prevention of migraine: A pooled analysis of four placebo-controlled trials with long-term extensions. *Cephalalgia*. 2019;39(14):1798-1808. doi:10.1177/0333102419888222

53. *Emgality (Galcanezumab) Public Assessment Report. Committee for Medicinal Products for Human Use (CHMP). European Medicines Agency (EMA). 2018.*

54. *Ajovy (Fremanezumab) Public Assessment Report. Committee for Medicinal Products for Human Use (CHMP). European Medicines Agency (EMA). 2019.*

55. *Aimovig (Erenumab) Public Assessment Report. Committee for Medicinal Products for Human Use (CHMP). European Medicines Agency (EMA). 2019.*

56. Sacco S, Bendtsen L, Ashina M, 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. *J Headache Pain*. 2019;20(1):6. doi:10.1186/s10194-018-0955-y

57. The American Headache Society Position Statement On Integrating New Migraine Treatments Into Clinical Practice. *Headache*. 2019;59(1):1-18. doi:10.1111/head.13456

58. Informe de Posicionamiento Terapéutico de erenumab (Aimovig®) en la profilaxis de migraña. Agencia Española de Medicamentos y Productos Sanitarios (AEMPS) 2019.

59. Informe de Posicionamiento Terapéutico de fremanezumab (Ajovy®) en la profilaxis de migraña. Agencia Española de Medicamentos y Productos Sanitarios (AEMPS) 2020.

60. Informe de Posicionamiento Terapéutico de galcanezumab (Emgality®) en la profilaxis de migraña. Agencia Española de Medicamentos y Productos Sanitarios (AEMPS) 2019.

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