Comprehensive management of adults with chronic migraine: Clinical practice guidelines in Mexico

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Abstract

Introduction: Migraine is a polygenic multifactorial disorder with a neuronal initiation of a cascade of neurochemical processes leading to incapacitating headaches. Headaches are generally unilateral, throbbing, 4–72 h in duration, and
associated with nausea, vomiting, photophobia, and sonophobia. Chronic migraine (CM) is the presence of a headache at least 15 days per month for ≥3 months and has a high global impact on health and economy, and therapeutic guidelines are lacking.

**Methods:** Using the Grading of Recommendations, Assessment, Development, and Evaluations system, we conducted a search in MEDLINE and Cochrane to investigate the current evidence and generate recommendations of clinical practice on the identification of risk factors and treatment of CM in adults.

**Results:** We recommend avoiding overmedication of non-steroidal anti-inflammatory drugs (NSAIDs); ergotamine; caffeine; opioids; barbiturates; and initiating individualized prophylactic treatment with topiramate, eptinezumab, galcanezumab, erenumab, fremanezumab, or botulinum toxin. We highlight the necessity of managing comorbidities initially. In the acute management, we recommend NSAIDs, triptans, lasmiditan, and gepants alone or with metoclopramide if nausea or vomiting. Non-pharmacological measures include neurostimulation.

**Conclusions:** We have identified the risk factors and treatments available for the management of CM based on a grading system, which facilitates selection for individualized management.

**Keywords**
chronic, clinical practice guidelines, management, migraine, treatment

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**Introduction**

Headaches are a common occurrence in most people. Recurrent headaches are typically primary (i.e., nosological) entities on their own and are generally frequent, with tension-type headaches and migraines the main culprits. Migraine is a primary headache that has an episodic presentation and is characterized by pulsatile headache; unilateral moderate to intense pain; duration of 4–72 h; and is accompanied by photophobia, sonophobia, nausea and vomiting, and activity intolerance. It is occasionally preceded by an aura 5–60 min duration and sometimes prodrome and postdrome of variable symptomatology. In Mexico, migraine occurs in 12.1% of women and 3.9% of men. Although migraine is second in frequency among primary headaches, disability associated with it significantly impacts family, social, and work life. Unfortunately, therapeutic guidelines are lacking in the scientific literature.

Chronic migraine (CM) is a headache that occurs at least 15 days per month for ≥3 months and ≥8 days per month has migraine characteristics. Patients with CM are challenging to manage, as acute and prophylactic treatments are not always practical. Some of these treatments have not been investigated in controlled clinical trials. Therefore, many are used without sufficient scientific support or are based on acute treatment of patients with episodic migraine (EM). The justification for their use is often based on anecdotal cases or expert recommendations. In addition, epidemiological information in developing countries is scarce. Therefore, we should consider clinical features and comorbidity with psychiatric illnesses, being overweight or obese, and sleep disorders as risk factors for CM. The need to improve physician education and have guidelines in Mexico and other Latin American populations necessitates evidence-based proposals. As such, we (i.e., the Mexican Association of Headache and Migraine [AMCEMIG]) have developed guidelines for the prevention and management of CM. Importantly, we do not attempt to make mandatory recommendations but rather evidence-based suggestions that will help clinicians understand different therapeutic management options and select the most appropriate treatment. It is essential to consider the history of previous treatments that patients have received to reuse options that were not correctly used or avoid returning to what failed previously.

**Methods**

**Working group**

A working group formed by clinical neurologists with knowledge and interest in headaches and migraines, who belong to AMCEMIG, was convened. We questioned the treatment of CM, and aimed to better understand topics and limitations that a guide would address. This created a work schedule to be executed in five face-to-face sessions of 6–8 h each. Before each meeting, the topics and clinical questions were distributed among clinicians for their response and development in two panels. The working group members systematically formulated relevant answers to the questions posed by recommendations for developing Clinical Practice Guidelines (CCPG of the Grading of Recommendations, Assessment, Development, and Evaluation [GRADE] system). Academic sessions were held to review the GRADE system and present our current rules and foundations to unify criteria and systematize the
search, qualification, analysis, argumentation, and writing of specific statements and the derived synopses. Working groups were formed by topic to search and evaluate scientific evidence and the elaboration and argumentation of recommendations.

**GRADE system**

We used the GRADE system to systematize the development of the document and evaluate the evidence to provide certainty about the knowledge and arguments that support each recommendation. Using the GRADE system, we recognize that the available evidence is not always of optimal quality; therefore, we attempted to rate each evidence as high (A: systematic reviews, controlled clinical trials), moderate (B: observational studies, clinical trials with bias), low (C: case series, more consistent studies are required), or very low (D: anecdotal, unlikely for the evidence to be improved), to write specific recommendations. We also rated each recommendation uniformly and efficiently as either 1 (strong: benefits of action outweigh disadvantages, the recommendation is helpful, this is independent of the quality of evidence supporting it) or 2 (weak: benefits of action resemble disadvantages, this is independent of the quality of evidence using the recommendation).

The topics addressed were factors that favor chronicity such as medication overuse and treatments of CM; abortive, preventive, non-pharmacological, monoclonal antibodies, onabotulinum toxin type A, peripheral nerve infiltrations, and CM; and pregnancy.

Subsequently, a search was conducted in Cochrane, MEDLINE and PubMed to assess risk factors, prevention, and treatment of CM in English and Spanish from January 1950 to May 2020. Specific keywords and MeSH terms related to the design of the study, treatment, and disease were as follows: migraine; chronic migraine; headache; chronic headache; treatment; therapy; trial; clinical trial; controlled trial; randomized clinical trial; guideline; meta-analysis; open label study; observational study; risk factors; modifying factors; chronification migraine factors; migraine AND headache; chronic migraine AND headache; headache AND chronic headache; migraine AND treatment; chronic migraine AND treatment; migraine AND therapy; chronic migraine AND therapy; (migraine AND headache) AND treatment; (chronic migraine AND headache) AND treatment; (chronic migraine AND chronic headache) AND treatment; (migraine AND headache) AND therapy; (chronic migraine AND headache) AND therapy; (chronic migraine AND chronic headache) AND therapy; (migraine AND headache OR chronic migraine AND headache OR chronic migraine AND chronic headache) AND (trial, clinical trial, controlled trial, randomized clinical trial, guideline, meta-analysis, open label study, observational study, risk factors, modifying factors, chronification migraine factors, migraine AND headache, chronic migraine AND headache).

**Selection of scientific articles**

The type of article was chosen according to its content and the topic to be developed, privileging the analysis of primary literature (original observational and interventional articles), systematic reviews, and meta-analyses over secondary literature (narrative reviews, synthesis, memoirs, and consensuses); however, the reference list of secondary literature was analyzed to identify sources not identified in the initial searches.

The evidence and recommendations were weighed, rated, and classified into the four categories proposed in the GRADE system: high, moderate, low, and very low quality (Table 1). These categories reflect a confidence gradient in the results offered by each study and how subsequent studies can modify the available results. With the GRADE system, the focus solely of evaluating the quality of evidence is not the methodological criticism of each study but rather the degree of confidence that a panel of experts has in the way that a study answers a PICO question (Patients, Intervention, Comparison, and Outcome) or a clinical problem statement. An attempt was made to reach a consensus; the recommendations are classified as “points of good practice”, provided that the majority approved the statement in its complete and final form.

All statements were reviewed by all authors and compiled into a single document that was then reviewed iteratively until a general agreement was reached. Once consensus was reached on the document’s final version, it was prepared in a single format, the latest version distributed via email for review and approval.

**Results**

**Migraine chronification factors**

Modifiable risk factors include overuse of analgesics for acute migraine, ineffective acute treatment, obesity, depression, and stressful life events. Low educational levels also increase the risk of CM.

**Factors facilitating the presence of headache**

We analyzed the medication-overuse headache (MOH); from medications such as ergotamine, triptans, opiates,
non-opioid analgesics, paracetamol, non-steroidal anti-inflammatory drugs [NSAIDs], acetylsalicylic acid [ASA], or a combination), using the diagnostic criteria of the International Classification of Headache Disorders (ICHD; ICHD-III 2018; strong recommendation, low level of evidence, 1C).

The ICHD-III 2018 considers that any patient with CM may have a concurrent diagnosis of a MOH. Fifty percent of patients with CM are re-classified as having EM after stopping the overuse of migraine medications. Primary or secondary headache must be considered when the patient takes analgesics frequently, as it can become MOH.\(^7\)

MOH is a subtype of secondary headache, which occurs in patients with preexisting primary headache, and develops as a new type of headache or worsening of previous symptoms. The International Headache Society classifies this headache according to the subtype of medication overuse, either individually or in combination (e.g., paracetamol, ASA, or other NSAIDs), and diagnosis requires consuming the medication for at least 15 per month in the last 3 months.\(^1\)

Patients with MOH for opioids, combined analgesics, multiple drugs, or other medication classes for acute and symptomatic treatment of headache have consumed the medication for 10 or more days per month in the last 3 months.\(^2\)

In CM patients who meet MOH criteria, it is recommended to avoid overuse of NSAIDs, ergotamine, caffeine, and opioids/barbiturates (strong recommendation, moderate quality of evidence, 1B). Such medications have a probability of increasing the intensity of pain and frequency of migraine. Also, in patients with CM, daily use of NSAIDs has no protective effect against frequency.\(^2\)

In adults with CM and MOH, a “non-pharmacological intervention” is recommended, which includes highlighting that treatment involves ceasing overused medications (strong recommendation, high quality of evidence, 1A). Such intervention reduces the days of headache and medication use and chronic headache occurrence by 67% and 50%, compared to 3% and 6% when patients are not educated on the importance of ceasing medication overuse, respectively (decrease of 7.3 days/month of headache and 7.9 days/month decrease in medication consumption, respectively).\(^11–13\)

In adults with CM and MOH, abrupt discontinuation of overused medications is recommended rather than restricting their use to reduce the number of

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**Table 1. A step by step of the elaboration of the guidelines proposed by AMCEMIG.**

| Steps | Process | Results |
|-------|---------|---------|
| Call for neurologist members of AMCEMIG with experience and interest in CM | A group of experienced academics and clinicians was selected who had no conflicts of interest and were committed to working on developing clinical guidelines | A committed work team was formed, willing and able to achieve the objective |
| Review the Clinical Practice Guidelines and GRADE system | Unify criteria, systematize the search, qualification, analysis, argumentation, and writing | Use a common language and organize the process to achieve the objective |
| Programming of five sessions 6–8 h of duration | Resources were sought, and a schedule of meetings was generated in comfortable places that did not distract the work of those involved | The meeting was held in a cordial and working environment. Each researcher had a computer, access to the network, and advice that facilitated answering the questions generated |
| MC was selected as a topic and objective to analyze | A series of questions were generated and exchanged among the panelists’ tables | The groups of experts were improving the questions generated in the Population, Intervention, Comparison, and Outcome system |
| The GRADE of recommendation was formulated | I (Strong: benefits of action outweigh disadvantages, the recommendation is helpful, this is independent of the quality of evidence supporting it) and 2 (Weak: benefits of the activity resemble disadvantages, this is independent of the quality of evidence of using the recommendation) | Each therapeutic measure analyzed was rated with a substantial (1) or weak (2) degree of recommendation |
| The quality of evidence was graded according to the type of studies that supported it | High (A: systematic reviews, controlled clinical trials: at least 2 or more), moderate (B: observational studies, clinical trials with bias), low (C: case series, more consistent studies are required), very low (D: anecdotal, unlikely for the evidence to be improved) | Each therapeutic measure was rating according to the quality of the evidence in the medical literature in A (high) until D (very low) |
| Each working group generated a document according to its section | From each document, a group of reviewers made a smaller document a ordered the references | The current document was generated, and the reviewers of the IHS improved it with suggestions and ideas |
headache days and revert to EM (strong recommendation, high quality of evidence, 1A). In cases of opioid, benzodiazepine, and barbiturate abuse, the use of the drug should be gradually decreased, rather than abruptly discontinued (strong recommendation, low quality of evidence, 1C). Patients who abruptly discontinued overused medications versus those who did not reduce the number of headache days by 46% versus 22%, respectively (3.6 versus 7.2 days/month, respectively). Abrupt medication suspension reverts to EM in 70% of patients versus 42% in those who do not restrict the medications' use. For medications derived from ergotamine or triptans, it is preferable to abruptly suspend the analgesics for at least 1 month instead of gradually per month. We recommend warning the patient that symptoms may worsen in the short term before improving and that they may experience withdrawal symptoms. For medications derived from ergotamine or triptans, it is preferable to abruptly suspend the analgesics for at least 1 month instead of gradually per month. We recommend warning the patient that symptoms may worsen in the short term before improving and that they may experience withdrawal symptoms. In adult patients with CM and headaches due to overuse of opioids, benzodiazepines, and barbiturates, suspension should be gradual to avoid withdrawal symptoms.

In adults with CM and uncomplicated medication abuse, outpatient or inpatient treatment is suggested to achieve cessation (weak recommendation, low quality of evidence, 2C). Complicated MOH hospital treatment is recommended (strong recommendation, moderate quality of evidence, 1B). Uncomplicated patients can be treated on an outpatient or inpatient basis, with no preference for either method for stopping the medication abuse. MOH is complicated when it occurs with the following medical conditions: concurrent medical illness; relevant psychiatric comorbidity; a formal diagnosis of anxiety disorder, eating disorder, mood disorder, substance use disorder (including opiates, benzodiazepines, or barbiturates), relapse following previous detoxification or failure to stop medication with outpatient care, daily use of more than three doses of multiple symptomatic medications, or severe withdrawal symptoms (e.g., recurrent vomiting, migraine). In these patients, hospital treatment is more effective in to stopping the misuse.

Discontinuing medication overuse in CM patients and additional preventive measures to avoid headaches

In adults with CM and MOH, the monitoring of withdrawal symptoms when discontinuing overused medications is recommended (strong recommendation, moderate quality of evidence, 1B). When suspending medication overuse, an exacerbation of the headache can occur accompanied by nausea, vomiting, arterial hypotension, tachycardia, anxiety, nervousness, insomnia, and sleep disorders. Symptoms occur 2–14 days after the overuse stops and can last up to 4 weeks. Headaches attributed to substance withdrawal are less common in patients who overuse triptans (4.1 days) than those who overuse ergotamine derivatives (6.7 days) or NSAIDs (9.5 days).

In adults with CM and MOH, preventing overuse drug recurrence is necessary and potential risk factors must be considered (e.g., high frequency of primary headache, excessive use of ergotamine, and high Migraine Disability Assessment Test [MIDAS] scale scores; strong recommendation, moderate quality of evidence, 1B). Independent factors that can predict the outcome include increased age at misuse diagnosis, primary headache onset at a greater age, regular use of benzodiazepines, and having a more significant number of days per month with headache (i.e., high-frequency migraine), a higher score on the MIDAS scale, and abuse of ergotamine compounds. After suspending the abuse, regular follow-up should occur every 4–8 weeks to prevent relapse. Notably, the Spanish MIDAS questionnaire for the Latino population is an effective tool for assessing disabilities that causes migraine.

In adults with CM and MOH, individualized prophylactic treatment (botulinum toxin, topiramate [TPM], or valproate [VPA]) is recommended to improve MOH (strong recommendation, moderate quality of evidence, 1B). With a longer duration of response to a botulinum toxin treatment (high quality of evidence, 1A), treatment is followed by TPM (high quality of evidence, 1A), VPA (moderate quality of evidence, 1B), or amitriptyline (low quality of evidence, 2C). Patients are likely to revert to EM within 4 weeks, with medical advice only; however, most studies recommend prophylactic treatment, which have a better effect than placebo in MOH treatment in reducing the number of headache days. Individualized preventative treatment of the underlying primary headache should be offered in addition to discontinuation of overused medications, with the likelihood that >57% of patients will have permanently discontinued medication abuse with at least 1 year of follow-up. The intention-to-treat analyses demonstrated a 41% decrease at least 50% of the daily intake of medicines and 53% of the number of days with headache. The prophylactic treatment with botulinum toxin 155–195 U in 31–35 sites with a Phase 3 REsearch Evaluating Migraine Prophylaxis Therapy (PREEMPT) scheme was effective and found to improve the number of days with headaches versus placebo in the treatment of CM with MOH even without suspending the medications of abuse. In an randomized controlled trial (RCT), prophylactic therapy with 800 mg/day of sodium VPA for 3 months was superior compared to placebo after discontinuation of medication abuse (45% versus 23% for the treatment of MOH patients). Prophylactic therapy with 100 mg of TPM (maximum 200 mg), even without withdrawing the abused drug, reduces the days of headache per month. In an open pilot study of 33 patients, low-dose amitriptyline (25–75 mg/day) combined with abrupt medication withdrawal effectively reduced the intake of the drug of abuse and decreased the days of headache at 3 months, 64% had reverted to episodic headache within the first year. A 58% of the patients were considered to be responders, 73% continued without drug abuse.
In adults with CM and MOH, we recommend to immediately initiate individualized prophylactic treatment in addition to discontinuation of the drug of abuse for headache improvements (strong recommendation, high quality of evidence, 1A). A systemic review showed that prophylactic treatment from the first day of suspension of the drug of abuse versus later initiation of preventive treatment 2 months later induced a reduction in headache frequency in days/months at 1-year follow-up. There was also a reduction in the consumption of drugs for acute treatment, with an improvement in MIDAS scale, quality of life, anxiety, and depression. An RCT that included 120 adults’ withdrawal therapy combined with preventive treatment from the beginning of the withdrawal was associated with a 30% chance of eliminating MOH.

In adults with CM, it is recommended NOT to use corticosteroids or celecoxib as a bridge therapy when ceasing the overuse and starting prophylaxis (strong recommendation, high quality of evidence, 1A). In an RCT, the use of prednisolone (75 mg) or celecoxib (400 mg) was not found to reduce headache days or the intake of overused medications as a bridge treatment when stopping overuse and initiating prophylactic treatment.

In adults with CM, it is recommended to manage the factors that facilitate relapse of MOH at 1 year (strong recommendation, low quality of evidence, 1C). In an observational study of 177 adults with CM and MOH, the presence of depression and high-frequency CM at least 60 days in the last 3 months was found to demonstrate a threefold increased risk (odds ratio [OR] = 3.02 and 2.94; 33.9% CM relapse) of relapse after 1 year of treatment. There was also an increased risk (OR = 7.16) of admission to the emergency room after treatment. In a prospective study involving 240 adults with MOH treated with prophylactic drugs and withdrawal of the abused drugs after 1 year of treatment, 40% of patients who relapsed had the following predictors: ergotamine use, high-frequency migraine, and severe disability on the MIDAS scale. In a multicenter cohort study of 492 patients with MOH who received prophylactic treatment that controlled the effects of anxiety and depression disorders, we found that headache and MIDAS scale scores were reduced in 58% and 57% of patients from 23 to 10 days and 59.9 to 25.7 points after 6 months, respectively. Depression was reduced in 50% of patients and anxiety disorders in 27.1%. In a prospective 5-year, follow-up cohort of patients with CM and MOH treated with brief hospitalization, cessation of abuse, and preventive treatment, a reduction in the MIDAS scale scores (from 70.8 to 23.3) was observed at 6 months and 34.1 at 12 months after treatment. After 3 and 5 years, these scores remain constant; however, if a patient has a severe disability after 6 months of treatment, it is considered a long-term predictor of relapse.

CM comorbidities to prevent and treat to improve quality of life

We recommend to ruling out sleep disorders in patients with CM and risk factors for obstructive sleep apnea, especially in refractory cases (strong recommendation, low quality of evidence, 1C). Headache presenting upon awakening have been associated with sleep disorders (obstructive sleep apnea syndrome [OSAS]), transformation/chronification of the primary headache, psychological discomfort, intracranial hypertension, among others in the recent ICHD III classification. The diagnosis of OSAS requires signs/symptoms of sleep apnea along with five or more predominantly obstructive respiratory events per hour of sleep during polysomnography (PSG). In the absence of symptoms or associated disorders, ≥15 obstructive respiratory events per hour (respiratory disturbance index ≥ 5). Morning headache has been acknowledged as a symptom related to OSAS severity, but can be exacerbated by depression.

Migraine patients have consistently reported poor sleep both as a trigger and during attacks. Sleep is often thought to have a therapeutic role in ending the pain of an acute migraine attack. Several studies have demonstrated that the high prevalence of sleep disorders is elevated in patients with CM. Moreover, 50% of CM patients have been found to meet the criteria for sleep disorders. Approximately 40% of patients with EM felt their sleep was adequate, compared to 34% of CM participants. Suzuki reports a total proportion of patients with OSAS of 12.3% and 16.6%, according to ICHD-II and ICHD-III beta, respectively. Similarly, the review reports a prevalence of 12–18% of sleep apnea headaches in the middle-aged population. Johnson et al. suggested that of 82 patients with chronic headache with migraine or tension-type headache or both, 63% had concomitant OSAS. Provini et al. determined that OSAS is a common disorder in the general population with an estimated prevalence in the adult population of 2% in women and 4% in men.

The presence of sleep apnea syndrome headache should be investigated in all adult patients with snoring, sleep apnea, and daytime sleepiness; this is especially true in the scrutiny of chronic migraine that does not respond to pharmacological treatment (strong recommendation, low level of evidence, 1C). Patients with OSAS-associated headaches appear to be more likely to respond to treatment with continuous positive airway pressure (CPAP), confirming its efficacy in headaches, which could differentiate other headaches that mimic sleep apnea headaches. The frequency of morning headaches in participants with OSAS (11.8%) compared to those without OSAS (4.16%) in the general population. Patients with CM and OSAS share common risk factors such as obesity, middle age, and snoring. They should be scrutinized and
if they fulfill the criteria, they should undergo PPSG to rule OSAS. Sleep apnea headache should be excluded when evaluating a preexisting primary headache.\textsuperscript{44,45} Adequate treatment of OSAS with chronic headache with CPAP and prophylactic drug therapy proved effective in headaches in 30\% of patients with CM. Other authors such as Goksan et al.\textsuperscript{46} and Loh et al.\textsuperscript{47} demonstrated that 80–90\% of morning headaches improved after appropriate treatment for OSAS.\textsuperscript{48}

Next, weight control (i.e., prevent being overweight or obese) is recommended for adult patients with CM (strong recommendation, high quality of evidence, 1A). Although causality is unknown, there is a clear association in transversal studies of the comorbidity between CM and being overweight or obese (35.3 ± 6.6 kg/m\textsuperscript{2}; i.e., observed in 35\% of overweight and 79\% of obese patients).\textsuperscript{48,49} Some inflammatory mediators are increased in obese individuals, such as interleukins and the calcitonin gene-related peptide (CGRP), which are linked to increased frequency, intensity, and duration of CM attacks.\textsuperscript{49–52}

**Asthma control is recommended for adults with CM to decrease the frequency and severity of migraines episodes** (strong recommendation, low quality of evidence, 1C). Migraine and asthma are two chronic disorders comorbid with episodic attacks. The global prevalence of asthma is 5–10\%.\textsuperscript{53,54} In a cohort study that included 4446 individuals with EM, 17\% had asthma; CM developed in 2.9\% of patients with EM, including 5.4\% (40/746) of asthma versus 2.5\% (91/3700) of non-asthma patients. Mast cell degranulation, autonomic dysfunction, and a combination of genetic and environmental factors may favor this process.\textsuperscript{55–60} A cohort study in South Korea analyzed an adult population (> 20 years) of 113,059 patients with a diagnosis of asthma and 36,044 with CM and their respective controls. Migraineurs had a risk ratio (RR) 1.47 times greater of suffering with asthma compared to controls. Alternatively, the cohort of patients with asthma had a RR 1.37 times greater for migraineurs than controls, demonstrating a bidirectional association between both entities.\textsuperscript{61}

**Mood disorders (i.e., depression and anxiety) are common conditions in CM patients; their modification may improve patient wellbeing** (strong recommendation, high quality of evidence, 1C). Mood disorders occur more frequently in patients with migraines compared to the general population. Importantly, a predictor of CM with an OR of 1.65 (95\% CI = 1.12–2.45) and up to 2.35 (95\% CI = 1.53–3.62) if moderate to severe. Whether mood disorders occur before or due to CM is not always clear.\textsuperscript{62} Nevertheless, although there is evidence on the use of antidepressants as a prophylactic drug in CM, no studies have specifically investigated depression and anxiety as factors that may reduce the chronification of migraine.\textsuperscript{63–67}

The role of depression in the relationship between EM and its transformation to CM is unclear; however, a strong association has been demonstrated, and routine screening for depression should be considered patients with EM and moderate (OR = 1.77; 95\% CI = 1.25–2.52), moderately severe (OR = 2.35; 95\% CI = 1.53–3.62), and severe depression (OR = 2.53; 95\% CI = 1.52–4.21) as they have a higher risk of developing CM.\textsuperscript{63}

It is recommended that chronic overexposure to caffeine be avoided in patients with CM (strong recommendation, low quality of evidence, 1C). The suggested daily caffeine intake to avoid adverse effects is approximately 450 mg/day. Excessive and repeated exposure to caffeine induces a series of metabolic changes that could favor the migraine’s chronification and generate MOH. The chronic effects of caffeine include regulation to the high of adenosine receptors and hypersensitivity. As such, an abrupt suspension of caffeine causes an “adenosine storm” associated with vasodilation and a significant increase in cerebral blood flow. These physiological changes are responsible for caffeine withdrawal headaches.\textsuperscript{68} The prevalence of CM from caffeine abuse is unknown; however, caffeine deprivation or the delayed chronic intake of caffeine (i.e., more than 200 mg/day) has been defined as a risk factor for the presentation and chronification of migraine.\textsuperscript{52,69} A population-based case-control study found that the consumption of more than 241 mg/day of caffeine is a modest risk factor that facilitates an EM becoming chronic in women under 24 years of age.\textsuperscript{70}

The suspension of excessive and frequent use of caffeine improves the control of migraineurs. Therefore, based on prospective controlled clinical studies, we recommend that caffeine consumption be suspended for at least 2 weeks to 3 months in patients with CM to improve the efficacy (72% versus 40.3\% with non-intervention) of acute migraine treatment.\textsuperscript{71–73}

The Chronic Migraine Epidemiology and Outcomes study by Lipton et al. identified several subgroups of individuals that may develop CM. Patients with comorbidities demonstrated the most severe clinical phenotype. Those with only pain syndromes or combinations of respiratory/psychiatric and respiratory/pain disorders had a moderately severe clinical phenotype, whereas those with a low prevalence of comorbidities or cardiovascular comorbidities alone had a milder clinical phenotype. Ongoing studies seek to understand whether any of these classes have a differential effect on migraine progression (from EM to CM) or remittance (from CM to EM).\textsuperscript{74} Also, the Migraine in America Symptoms and Treatment study in 15,133 people with migraine showed cardiovascular, neurological, psychiatric, sleep, respiratory, dermatological, pain, and medical comorbidities. Participants with more comorbidities reported significantly more insomnia (OR = 3.79 [3.6, 4.0]), depression (OR = 3.18 [3.0, 3.3]), anxiety (OR = 3.18 [3.0, 3.3]), gastric ulcers/gastrointestinal bleeding (OR = 3.11 [2.8, 3.5]), angina pectoris (OR = 2.64 [2.4, 3.0]), and epilepsy (OR = 2.33 [2.0, 2.8]).\textsuperscript{75}
**Statement:** To prevent and control CM due to the excess of medication, we recommend appropriately treating any comorbidities and initiating a personalized prophylactic treatment. This is a strong recommendation (i.e., I) with a high quality of evidence (i.e., A; > 2 RCT and systematic reviews).  

*Symptomatic treatment of CM*

This treatment is focused on shortening the duration and severity of acute migraine episodes. With notable exceptions, symptomatic or abortive medicine does not reduce aspects such as the frequency, time, or severity of long-term migraine outbreaks; it should not be used for this purpose. Symptomatic treatments are evaluated in patients with acute headache attacks along the patient’s CM course. Many drugs have not been studied in CM and are only described as tools to manage migraine exacerbation in EM. Unfortunately, the response to symptomatic migraine management is not the same for patients with EM. The alternatives presented are summarized in Figure 1.

Most effective treatments (traditional and new) in CM for acute headaches associated with nausea, vomiting, and disability

The use of 900–1000 mg of oral ASA is recommended as a first-line acute therapy in CM with mild to moderate attacks, not associated with vomiting or severe nausea (strong recommendation, high quality of evidence, 1A). A Cochrane review of 13 studies (4,222 participants) reported that 900 and 1,000 mg of ASA was effective in relieving pain after 2 h compared with placebo (number-needed-to-treat [NNT] = 8.1). For sustained pain relief after 24 h, 1,000 mg ASA had an NNT of 6.6 compared with placebo. ASA alone had comparable efficacy to sumatriptan (50 mg), although higher doses (100 mg) was superior to both ASA and metoclopramide (MTC) combined. ASA reduced symptoms associated with nausea, vomiting, photophobia (NNT = 7.7), and phonophobia (NNT = 6.6) compared to placebo. The addition of MTC further reduced nausea (NNT = 2.6) and vomiting.ASA is a potential gastrointestinal irritant and may cause gastrointestinal ulcers or bleeding; however, adverse effects from short term use are

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**Figure 1.** Algorithm of preventive pharmacological treatment of CM.
primarily mild and transient. ASA should not be used in patients younger than 16 years due to the risk of Reye’s syndrome and is contraindicated during the third trimester of pregnancy.

The use of oral ibuprofen is recommended as first-line symptomatic therapy in adults with mild to moderate acute CM without severe vomiting or nausea. We recommend a dose of 400–600 mg (strong recommendation, high quality of evidence, 1A). Ibuprofen is a recommended NSAID to treat worsening migraines and is a first-line treatment for patients with acute migraines. If this initial dose fails, the dose should be increased to 600 mg in mild-moderate attacks. A multicenter, double-blind, placebo-controlled study of 660 patients demonstrated that 200 and 400 mg of ibuprofen effectively treat an acute migraine, not requiring bed rest in more than 50% of attacks, with associated nausea in more than 20%. Pain improvements to mild or none at 2 h (41.7% and 40.8%, respectively) were higher compared to placebo (28.1%). The 400 mg dose was more effective than the placebo (36.9% versus 21.6%); however, the 200 mg dose did not show statistically significant improvements. Notably, 280 (42.4%) of the enrolled patients withdrew from the study; 272 participants withdrew because they needed other rescue medications. Researchers concluded that ibuprofen at low doses is safe, well-tolerated, and effective in relieving acute migraine attacks and that the 400 mg dose was superior to the 200 mg dose. A subsequent meta-analysis and Cochrane review found ibuprofen to be superior to placebo at doses of 200–600 mg for migraines with improvements in pain after 2 h. In acute migraine patients with moderate basal pain, all doses sustained pain relief at 24 h. The NNT for achieving a pain-free outcome at 2 h was 9.7 for 200 mg and 7.2 for 400 mg.

The use of oral dexketoprofen is suggested as first-line symptomatic therapy in CM patients with mild to moderate attacks without severe vomiting or nausea. We recommend a dose of 50 mg (weak recommendation, moderate quality of evidence, 2B). Dexketoprofen is an NSAID with a relatively short elimination time and maximum plasma concentrations obtained approximately 30 min after administration. A systematic review and meta-analysis evaluated dexketoprofen’s impact on pain control in patients with migraine attacks and confirmed the efficacy of 50 mg, resulting in a reduced need for rescue medication compared to placebo (22.3% versus 55.4%). This analysis demonstrated dexketoprofen’s efficacy alone or combined with a triptan or another analgesic in treating acute migraine and demonstrated pain relief at 15 and 30 min. The parenteral form has been most studied in acute migraine attacks in the emergency room. It is as effective as ibuprofen, although its action appears faster.

The use of oral paracetamol is recommended as first-line symptomatic therapy in patients with CM with mild to moderate attacks without severe vomiting or nausea. We recommend a dose of 1,000 mg (strong recommendation, high quality of evidence, 1A). In an RCT of 351 participants, Lipton et al. demonstrated that 1,000 mg of oral paracetamol was significantly more effective than placebo after 2 h. A Cochrane review identified 11 studies (2,942 participants, with 5,109 attacks) and reported a relative benefit of 1,000 mg paracetamol alone or combined with an antiemetic, demonstrating its superiority to placebo at 2 h (NNT = 12) in patients with mild to moderate acute migraine. This study supported that the combination of paracetamol (1,000 mg) and MTC (10 mg) had a similar efficacy to sumatriptan.

The use of oral naproxen is recommended as first-line symptomatic therapy in patients with CM with mild to moderate attacks without severe vomiting or nausea. We recommend a dose of 500–825 mg (strong recommendation, high quality of evidence, 1A). In a Cochrane meta-analysis that included six RCT assessing naproxen sodium (500–825 mg) was found to be superior to placebo for the acute treatment of migraine after 2 h (NNT = 11 [95% CI 8.7–17]) with a 17% and 8% response to naproxen and placebo, respectively (RR = 2.0 [1.6–2.6], moderate quality). Headache relief was 6.0 (95% CI = 4.8–7.9) with a 45% response with naproxen compared to 29% with placebo (RR = 1.6 [1.4–1.8]). Results were unchanged for doses of 500 mg and 825 mg.

The use of oral diclofenac is recommended as first-line symptomatic therapy in patients with CM with mild to moderate attacks without severe vomiting or nausea. We recommend a dose of 50–100 mg (strong recommendation, high quality of evidence, 1A). Several RCTs and a Cochrane review have demonstrated the efficacy of diclofenac for the acute treatment of migraines compared to placebo. Diclofenac can be administered orally in tablet form or as a water-soluble powder, dissolved in approximately 2 oz of water. For one dose of diclofenac potassium (50 mg) compared to placebo (two studies), the NNT was 8.9, 6.2, and 9.5 for pain-free at 2 h, headache relief at 2 h, and pain-free responses at 24 h, respectively. The adverse events with diclofenac were mild, transient, and comparable to placebo.

A fixed ASA/paracetamol/oral caffeine combination is recommended as first-line symptomatic therapy in CM patients with mild to moderate attacks without vomiting and is helpful in relieving mild nausea, photophobia, phonophobia, and functional disability. We recommend a dose of 500/500/130 mg (strong recommendation, high quality of evidence, 1A). The combination of acetaminophen, ASA, and caffeine was compared to placebo in several studies. Pain intensity was reduced to mild or none 2 h after administration in 59.3% of 602 patients treated with medication compared to 32.8% of 618 patients treated with placebo (P < .001; 95% CI = 55–63% for medication, 29–37% for placebo); 6 h after dosing, 79% versus 52%, respectively, had pain reduced to mild or none (P < 0.001; 95% CI = 75–82%)
versus 48–56%, respectively). Moreover, 6 h after admin-
istration, 50.8% of patients treated with drugs were pain-
free, compared to 23.5% of patients treated with placebo
(P < 0.001; 95% CI = 47–55% for medication, 20–27% for
placebo). Nausea, photophobia, phonophobia, and func-
tional disability were significantly improved 2–6 h after
treatment with the combination of acetaminophen, ASA,
and caffeine compared to placebo.89 The fixed combination
of ASA (250 mg), acetaminophen (200 mg), and caffeine
(50 mg) are more effective than these agents given without
caffeine. This combination’s superior efficacy may also be
depicted in reduced impairment in daily activities and pain
intensity and a low incidence of observed adverse events90; however, the combination of analgesics and their frequent
administration have been shown to increase the risk of
developing a MOH.

The use of combined oral lysine acetylsalicylate (LA) and
MTC is recommended as first-line symptomatic
therapy in patients with mild to moderate attacks
with nausea. We recommend a dose of 1.62 g/10 mg
(strong recommendation, high quality of evidence,
1A). ASA and its prodrug LA are generally administered
at 900–1,000 mg, with a maximum daily dose of 4,000 mg.
They have a relatively long half-life of 6 h, mainly due to
the formation of active salicylate metabolites before their
elimination. Effervescent ASA has a faster onset of action
than ordinary tablets.91 The addition of 10 mg MTC
improved the relief of nausea and vomiting associated with
migraine, while ASL + MTC was as effective as sumatriptan
with a decrease of moderate or severe headache. Both
treatments performed better than placebo.92

In a meta-analysis that included a group who received
step care within attacks (i.e., 800–1,000 mg ASA + 20 mg
MTC) as initial treatment for all attacks found that patients
who did not respond to treatment after 2 h required treat-
ment with zolmitriptan (2.5 mg). A second group who
received step care across attacks (i.e., 800–1,000 mg ASA
+ 10 mg MTC) demonstrated that patients who did not
respond to medication in at least two of the first three
attacks switched to zolmitriptan (2.5 mg) for the subse-
quent three episodes. In a third group (i.e., stratified care),
patients with mild headaches were treated with ASA + MCT,
while those with more severe headaches were treated with
zolmitriptan. The latter two groups had significantly better
outcomes than the first, measured by headache response and
disability time; however, patients in the stratified group had
the highest number of adverse events.93

The use of combined oral paracetamol/tramadol is
suggested as second-line symptomatic therapy or in
patients allergic to NSAIDs with CM with mild to mod-
erate attacks without severe vomiting or nausea. We
recommend a dose of 650/75 mg (weak recommenda-
tion, high quality of evidence, 2A). The combination of
analgesics with opioids (e.g., tramadol) is effective in most
patients; however, it increases the risk of side effects (i.e.,
nausea). Also, frequent administration of these medications
increases the risk of developing a MOH. We suggest the
combination as rescue therapy in acute attacks of moderate
to severe refractory migraine.94,95 The use of combined
oral caffeine/ergotamine is recommended as first-line
symptomatic therapy in CM patients with mild to mod-
erate attacks without severe vomiting or nausea. We
recommend a dose of 100/1 mg (strong recommendation
with moderate quality of evidence, 1B). It is unclear
whether oral ergotamine by itself or other additives pro-
duces a more significant effect that benefits the patient. A
systematic review of RCTs involving caffeine alone or
caffeine plus ergotamine with a dose of 1–5 mg concluded
that the currently available data are conflicting and that
there is no uniformity in the treatment of CM attacks with
this combination; however, they are helpful in the treat-
ment of prolonged migraine attacks (i.e., more than 48 h),
although their use should always be individualized, and
the response is not always satisfactory.

Combined oral ASA/caffeine is recommended as
first-line symptomatic therapy in patients with CM with
mild to moderate attacks without severe vomiting or
nausea. We recommend a dose of 650 at least 100 mg
(strong recommendation, high quality of evidence, 1A).
A Cochrane review included 20 RCT with 4,262 patients
who used a single analgesic dose plus caffeine with the
same analgesic dose alone. Many studies using acetamino-
phen or ibuprofen with 100–130 mg of caffeine showed a
significant, but small, benefit when caffeine was added in
pain management, including headache.96

The use of oral sumatriptan is recommended as first-
line symptomatic therapy in adults with CM with mod-
erate to severe attacks without severe vomiting or
nausea. We recommend a dose of 50–100 mg (strong
recommendation, high quality of evidence, 1A). Suma-
trip坦 is a 5-HT1b and 5-HT1d receptor agonist effective
in treating migraine attacks. Researchers analyzed 61 stud-
ies (37,250 participants) comparing oral sumatriptan to pla-
cebo or an active comparator. Most available data were for
the 50 and 100 mg doses. Sumatriptan outperformed pla-
cebo in all efficacy outcomes (50 mg versus placebo: NNT =
6.1 [5.5 to 6.9]; 100 mg versus placebo: NNT = 3.5
[3.2–3.7]). Almost one-quarter of participants taking
100 mg sumatriptan had no pain after 2 h, which was main-
tained for 24 h without the use of rescue medication, com-
pared with 8% taking placebo.97 The 50 mg dose was
slightly less effective but was associated with fewer
adverse events. While the pain was still mild, treatment
of attacks was more effective than treating established
attacks with moderate or severe pain intensity.98

Naproxen combined with sumatriptan is recom-
mended as first-line therapy in moderate to severe acute
migraine. We recommend 500 mg of naproxen and
85 mg of sumatriptan (strong recommendation, high
quality of evidence, 1A). The combination of naproxen
(500 mg) with sumatriptan (85 mg) may help manage acute
pain in CM, as demonstrated in a 3 month RCT comparing
this combination to the use of naproxen alone. Furthermore, in a Cochrane review, 13 studies were analyzed, where 12 (involving approximately 9,300 participants) assessed the efficacy of the combination of sumatriptan plus naproxen, which was better than placebo at relieving acute migraine attacks in adults. When initial headache intensity was mild, 50% of participants treated with the combination had no pain within 2 h compared to 18% with placebo. Moreover, 58% of participants with moderate or severe pain treated with the combination had mild to no pain after 2 h, compared to 27% with placebo. Overall, 52% of patients administered sumatriptan alone or approximately 44% on naproxen alone responded, demonstrating superior response compared to placebo. Adverse events were shared with sumatriptan (alone or in combination), which differed from placebo or naproxen alone. Overall, these events were mild to moderate in severity and rarely led to withdrawal from studies.

Oral sumatriptan is recommended as first-line symptomatic therapy in patients with moderate to severe attacks without severe vomiting or nausea. We recommend doses of 2.5–5 mg (strong recommendation, high quality of evidence, 1A). A Cochrane systematic review that included 25 RCT studies (20,162 participants), compared sumatriptan (2.5–5 mg) with placebo to treat moderate to severe pain. For all efficacy outcomes, sumatriptan outperformed placebo, including 2.5 mg (NNT = 5.0 for pain suppression at 2 h) with similar 5 mg results. Moreover, 10 mg of sumatriptan was significantly more effective than 5 mg for headache relief at 2 h. Adverse events were primarily transient and mild and more similar to sumatriptan than placebo, with a clear dose-response relationship (1–10 mg). Evidence showed that 2.5 mg and 5 mg oral sumatriptan provided relief at the same rate as 50 mg oral sumatriptan.

Oral eletriptan is recommended as first-line symptomatic therapy in patients with moderate to severe attacks without severe vomiting or nausea. We recommend doses of 40–80 mg (strong recommendation, high quality of evidence, 1A). In a meta-analysis of six RCT of eletriptan involving 3,224 patients, eletriptan in doses of 20, 40, and 80 mg was more effective than placebo. Pain relief was dose-dependent, with 80 mg found to provide significantly greater pain relief than 40 mg at both 2 and 24 h. Eletriptan has consistent and significant clinical efficacy with a good tolerability profile, even in patients with cardiovascular risk without coronary disease. It showed the most favorable clinical response, compared to sumatriptan, zolmitriptan, and rizatriptan; however, it remained contraindicated in patients with high cardiovascular risk.

Oral rizatriptan is recommended as first-line symptomatic therapy in patients with moderate to severe attacks, not associated with severe vomiting or nausea. We recommend doses of 5–10 mg (strong recommendation, high quality of evidence, 1A). Rizatriptan is an oral triptan with the fastest onset of efficacy (30 min) and quickest time to reach maximum plasma levels (60 min), but also has the shortest plasma half-life (2–2.5 h). A systematic review of 24 RCT showed that rizatriptan is an effective treatment for acute migraine. Compared to placebo, rizatriptan (5 and 10 mg) provided significant benefits in all five primary efficacy outcomes (ranging from 1 to 24 h of relief). The 10 mg dose was the most effective; however, the 5 mg dose is indicated if the patient is taking beta-blockers.

The use of oral almotriptan (ALT) is recommended as first-line symptomatic therapy in patients with CM with moderate to severe attacks without severe vomiting or nausea. We recommend a dose of 12.5 mg (strong recommendation, high quality of evidence, 1A). A large RCT found that 12.5 mg of ALT provides optimal pain relief and tolerability. ALT effectively improved pain relief at 2 h, reduced symptoms associated with migraine, and showed low recurrence rates. The pooled analysis of four clinical trials showed reductions in pain (64% versus 35% with placebo), nausea (30.4% versus 45.4%), vomiting (5.0% versus 15.8%), photophobia (27.0% versus 45.8%), and sonophobia (21.2% versus 38.9%). An analysis of data from 255 women with menstrual migraine who participated in a clinical trial comparing 12.5 mg ALT versus 2.5 mg zolmitriptan found no significant differences between the drugs for efficacy endpoints, including pain relief after 2 h and recurrence during menstruation. These trials also showed that results were better if patients took ALT early (i.e., when the pain was still mild). The clinical evidence collected, and comparisons made over a decade of use have demonstrated that ALT is one of the most effective and fast-acting triptans available, showing a tolerability profile similar to placebo.

The use of intravenous metamizole (dipyrone) is recommended as first-line symptomatic therapy in CM patients with moderate to severe attacks associated with severe vomiting or nausea. We recommend a dose of 1,000 mg (strong recommendation with high quality of evidence, 1A [i.e., > 2 systematic reviews]). Four studies with a total of 636 adult participants were evaluated with a generally high methodological quality. Two trials evaluated intravenous dipyrone for migraine, but only one described pain outcomes. Results were statistically significant in favor of dipyrone for pain-free outcomes and headache reduction in adults. Finally, one trial (n = 134) evaluated 1,000 mg intravenous dipyrone versus placebo for pain in patients with migraine and found it to be superior. A systematic review showed that dipyrone is a safe choice, with undesirable effects comparable to other analgesics, with rare agranulocytosis. Evidence also suggests that dipyrone is effective for acute attacks in CM, although there is little existing research.

Intravenous metoclopramide is recommended as first-line symptomatic therapy in adults with CM with moderate to severe attacks associated with severe vomiting or nausea. We recommend a dose of 10 mg
Intravenous ketorolac is recommended as first-line symptomatic therapy in CM patients with moderate to severe attacks without severe vomiting or nausea. We recommend doses of 30–60 mg (strong recommendation, moderate quality of evidence, 1B). A recent study compared the combination of dexamethasone + metoclopramide with intravenous ketorolac, noting a similar response at the end, although it was faster with intravenous ketorolac. In this study, 86 patients were recruited (58.1% males), with a mean age of 37.6 ± 10.3 years. Thirty-five (40.7%) were in the ketorolac group, and 51 (59.3%) were in the dexamethasone + metoclopramide group. Success was defined as a reduction of 3 or more points in pain intensity. At 1 h, the reported pain intensity was 4.7 ± 2.0 in the ketorolac group and 6.2 ± 2.3 in the dexamethasone + metoclopramide group. At 2 h, the pain intensity was 3.4 ± 1.2 in the ketorolac group and 2.9 ± 1.3 in the dexamethasone + metoclopramide group. Thus, the pain reduction time was relatively shorter with ketorolac in acute cases, but the final response was similar between the two groups.115

Intravenous valproic acid is suggested to be second-line symptomatic therapy in CM patients with moderate to severe attacks associated with severe vomiting or nausea. We recommend doses of 500–1000 mg (weak recommendation, low quality of evidence, 2C). To demonstrate the efficacy of intravenous valproic acid in the management of exacerbated symptoms, large trials are needed with a standardized dose and the use of a placebo; therefore, intravenous valproic acid cannot be recommended for acute treatment.116 It was evaluated in a double-blind comparative clinical study involving 330 patients who were randomized to receive 1,000 mg of valproate, 10 mg of metoclopramide, or 30 mg of intravenous ketorolac to assess the management of migraine attacks for 30 months. Patients receiving intravenous valproate improved by a mean of 2.8 (95% CI = 2.3, 3.3) on a 0–10 scale, those receiving intravenous metoclopramide improved by 4.7 (95% CI = 4.2, 5.2), and those receiving intravenous ketorolac improved by 3.9 (95% CI = 3.3, 4.5). In secondary endpoints, 69% (95% CI = 60%, 78%) of patients receiving valproate required rescue medication, compared with 33% (95% CI = 24%, 42%) of patients with metoclopramide and 52% (95% CI = 42%, 63%) of patients given ketorolac. The disappearance of headache was achieved in 4% (95% CI = 0%, 7%), 11% (95% CI = 5%, 17%), and 16% (95% CI = 9%, 23%) of patients who received valproate, metoclopramide, and ketorolac, respectively. Therefore, valproate is a drug that is inferior to metoclopramide and ketorolac in improving acute migraine attacks.117

The sole use of intravenous dexamethasone as a symptomatic therapy is not recommended in CM patients with moderate to severe attacks associated with severe vomiting or nausea; however, we recommend combining it with metoclopramide to avoid recurrence. We recommend doses of 4–16 mg (weak recommendation, low quality of evidence, 2C). Multiple studies have used standard abortive therapy and have subsequently compared a single dose of parenteral dexamethasone with placebo, examining pain relief and headache recurrence within 72 h. Dexamethasone and placebo demonstrated similar reductions in acute pain (weighted mean difference = 0.37; 95% CI = −0.20 to 0.94); however, dexamethasone was more effective than placebo in reducing recurrence rates (RR = 0.74; 95% CI = 0.60–0.90). Moreover, the side effect profiles between the dexamethasone and placebo groups were similar. When added to standard abortive therapy for migraine headaches, a single dose of parenteral dexamethasone was associated with a 26% relative reduction in headache recurrence (NNT = 9) within 72 h.118

The use of 100 mg of tramadol has been suggested as a rescue therapy in patients with acute attacks of CM (weak recommendation, moderate quality of evidence, 2B). In a prospective RCT comparing a single intravenous dose of tramadol, intravenous tramadol was more effective than placebo over 1 h (70.8 versus 35.3), with a 16% recurrence rate in the first 24 h.119 Tramadol differs from other opioids by combining a weak opioid and a monoaminergic mode of action. It can be combined with other analgesics; however, nausea and vomiting occur at the beginning of its
administered. Tramadol should be avoided in epilepsy because it lowers the epileptic seizure threshold and has been shown to facilitate abuse and addiction.\textsuperscript{120–122}

**Intravenous magnesium sulfate is suggested as second-line symptomatic therapy in CM patients with moderate to severe attacks associated with severe vomiting or nausea.** We recommend doses of 1–2 g (weak recommendation, low quality of evidence, 2C). Migraine patients have been suggested to be deficient in magnesium and are suggested to respond when administered intravenously.\textsuperscript{123} A total of 1,203 papers related to this compound were reviewed, providing five RCTs with a total of 295 patients in a meta-analysis. The percentage of patients experiencing headache relief 30 min after treatment was 7% lower in the magnesium groups compared to controls (pooled risk difference = −0.07, 95% CI = −0.23 to 0.09). The percentage of patients with adverse events was higher in the magnesium groups than controls by 37% (pooled risk difference = 0.370, 95% CI = 0.06–0.68). The percentage of patients requiring rescue analgesics was slightly lower in the control groups, but this was not significant (pooled risk difference = −0.021, 95% CI = −0.16 to 0.12).\textsuperscript{124} Meta-analyses have not demonstrated a beneficial effect of intravenous magnesium in reducing pain relief in acute migraine in adults as there is a need for rescue medication and had more adverse events.\textsuperscript{125}

**Intravenous lysine clonixinate as symptomatic therapy in CM patients with moderate to severe attacks associated with severe vomiting or nausea.** We recommend doses of 100–200 mg (weak recommendation, low quality of evidence, 2C). Few studies have involved small groups of patients where the use of lysine clonixinate (200 mg) and placebo are compared. We have not found enough evidence to recommend its use in CM attacks; however, lysine clonixinate improved headache at 60 min (70.6% versus 25.0%) in the placebo group, and adverse events were more frequent (64.7%) in the lysine clonixinate group (e.g., pain at the injection site, hot sensation, dizziness, and fatigue). This study showed that the intravenous lysine clonixinate was effective and well-tolerated in severe migraine attacks.\textsuperscript{126} This finding differs from the oral formulation results, which is effective only in moderate-severity migraine.\textsuperscript{127}

**Oral lasmiditan is recommended as first-line symptomatic therapy in patients with moderate to severe attacks without severe vomiting or nausea and non-severe cardiovascular disease patients.** We recommend doses of 100–200 mg (strong recommendation, high quality of evidence, 1A). Lasmiditan is a serotonin 5-HT\textsubscript{1F} receptor agonist and is not contraindicated in uncontrolled coronary or peripheral vascular disease or hypertension. Studies demonstrate that it is better than a within the first 4 h of an acute migraine attack in adults at doses of 100 and 200 mg by mouth. In a phase three study, lasmiditan was found to be effective, well-tolerated, and safe in cardiovascular risk patients. Phase three studies SPARTAN and SAMURAI were effective at doses of 50, 100, and 200 mg compared with placebo and prophylactic medications from all groups (beta-blockers, antihypertensives, antiepileptics, antidepressants).\textsuperscript{128} Goadsby et al.\textsuperscript{129} assigned patients with migraine to oral lasmiditan 200 mg, 100 mg, 50 mg, or placebo (1:1:1). Most patients (79.2%) had a cardiovascular risk factor at the beginning of the study in addition to migraine. Lasmiditan was associated with greater pain freedom at 2 h (200 mg: 38.8%, OR = 2.3, 95% CI = 1.8–3.1; 100 mg: 31.4%, OR = 1.7, 95% CI = 1.3–2.2; 50 mg: 28.6%, OR = 1.5, 95% CI 1.1–1.9) versus placebo (21.3%). Most adverse events were related to the central nervous system and included dizziness, drowsiness, and paresthesia. Lasmiditan was effective 2 h after administration for the acute treatment of migraine in all tested oral doses. Krege et al. reported no deaths in the SPARTAN and SAMURAI studies and few severe adverse effects (0.2% for all groups), suggesting it is a safe drug. Mild and moderate adverse events occurred in 13.5% of the placebo, 25.4% in the 50 mg, 36.2% in the 100 mg, and 40.6% in the 200 mg groups. No ischemic events, suicidal ideations, or accidents were reported.\textsuperscript{130} Another RCT (GLADIATOR) demonstrated that the effectiveness of lasmiditan at 100 and 200 mg continued after 1 year of treating 19,058 migraine episodes.\textsuperscript{131} The GLADIATOR study also concluded that the reduction in absenteeism and presenteeism presented at school or work during 1 year of use of lasmiditan (100 and 200 mg) and a 50% reduction in MIDAS score.\textsuperscript{132} In the analysis of the subgroups of adult patients with migraine and more than one cardiovascular risk factor, efficacy was maintained and without a significant increase in adverse effects compared to placebo.\textsuperscript{133} Another subgroup analysis reported effects of lasmiditan (100 and 200 mg) after 30 min, with a maximum response at 2 h. Discomfort was improved, except for nausea.\textsuperscript{134} Presently, patients should be advised not to drive or operate machinery within 8 h of administration; this side effect appears to be related to the likely existence of active and inactive metabolites.\textsuperscript{133}

**The use of ubrogepant is recommended as first-line symptomatic therapy in adults with moderate to severe migraine attacks without severe vomiting or nausea in patients with non-severe cardiovascular disease who have not responded to triptan therapy or not using moderate to severe CYP3A4 inhibitors and inducers.** We recommend doses of 50–100 mg (strong recommendation, high quality of evidence, 1A). Ubrogepant is an oral gepant molecularly developed as a peptide antagonist related to CGRP for acute migraine treatment. The safety and efficacy of ubrogepant have been demonstrated in placebo-controlled trials. The ACHIEVE I and II phase trials with single migraine attacks using 50 and 100 mg of ubrogepant showed that freedom rates for headache pain 2 h after administration were significantly higher than placebo.\textsuperscript{135–137} Rates of absence of the most
Table 2. Reasons for hospitalizing a patient with CM and MOH and their management. Modified from Raggi et al.2

| Reasons for hospitalization | Headache frequency of 60 or more days in the last 3 months |
|-----------------------------|----------------------------------------------------------|
| Management                  | Severe mood disorder, History of previous hospitalizations, Strong MOH |
|                             | Intravenous hydration, Steroids for 5 days, Preventive oral choice prophylaxis, Oral benzodiazepines, Metoclopramide oral or IV, Indomethacin in the case of intense rebound headache |

Troublesome symptoms associated with migraine (photophobia, phonophobia, or nausea) at 2 h were significantly higher with ubrogepant (50 and 100 mg) than placebo. A 52-week, RCT, multicenter phase three extension study evaluated the long-term safety and tolerability of intermittent ubrogepant treatment for acute treatment of migraine for 1 year. Long-term intermittent use of 50 and 100 mg of ubrogepant administered in one or two doses per attack for the acute migraine treatment was safe and well-tolerated.138

The use of rimegepant is recommended as first-line symptomatic therapy in patients with moderate to severe attacks associated with mild to moderate vomiting or nausea in patients with non-severe cardiovascular disease who did not respond to triptan therapy. We recommend a dose of 75 mg oro-dispersible tablets (strong recommendation, high quality of evidence, 1A). Rimegepant is an orally administered, small-molecule, CGRP receptor antagonist that is effective in the acute treatment of migraine. Phase three studies have used a 75 mg dose of rimegepant to evaluate relief of pain, nausea, photophobia, and phonophobia at 2 h with benefits maintained and well-tolerated 48 h after administration.139 Subsequently, two RCT, methodologically identical, placebo-controlled phase three trials of 75 mg of rimegepant were conducted. Each trial showed that rimegepant was significantly more effective than placebo at the coprimary efficacy endpoints of pain freedom and troublesome symptoms associated with migraine 2 h post-dose.2140 The bioequivalent rimegepant orally disintegrating tablet allows optimization of its absorption rate without fluid intake, which could be of clinical importance for migraine patients experiencing nausea and vomiting.141,142

Statement: Symptomatic management of CM exacerbation should be individualized. NSAIDs, triptans, lamotriginate, and gepants are beneficial and the combination of sumatriptan and naproxen is highly effective. Administration with metoclopramide and intravenous steroids may be necessary and usually resolves in the emergency department. This is a strong recommendation (i.e., 1) with a high quality of evidence (i.e., A: > 2 RCT and systematic reviews).

Occasionally a patient with CM should be hospitalized to effectively manage their symptoms (Table 2).141

Preventive treatment of CM in adults

Most effective treatments (traditional and new) in CM for preventive management. According to the International Headache Society guidelines, preventative treatment should be utilized; it is crucial to avoid overmedication and consider the comorbidities with CM. They emphasize that in trials of preventive treatment of CM, the choice is limited to only two agents that have shown superiority over placebo: TPM and onabotulinum toxin type A (BTA).143 The alternatives presented are summarized in Figure 2.

The use of oral TPM is recommended as first-line prophylactic therapy in patients with CM at doses of 50–100 mg/day (strong recommendation, high level of evidence, 1A). Bartolini et al.144 reported 49 randomized patients comparing TPM to valproate, with induction doses of 25 mg per day and 250 mg of valproate, escalating to 75 mg TPM (25 mg in the morning and 50 mg in the evening) and 750 mg of valproate (250 mg in the morning and 500 mg in the evening) after 3 months. All patients demonstrated improvements in the post hoc analysis with more significant improvements with TPM than valproate. Notably, MIDAS scores dropped significantly with TPM from 27 to 12 points with a 50% decrease in headache days. In another study, Diener et al.145 demonstrated that TPM is an effective drug for treating CM at doses of 100 mg/day or 500 or 1000 mg/day of sodium valproate every 12 h; however, low doses of 50 mg/day may be effective. In another prospective, randomized study of TPM, 59 patients were included, 32 of which received TPM. A reduction of more than 50% of migraine days was observed in both groups with 35% experiencing adverse effects, suggesting that TPM has adequate tolerability and safety. TPM has similar efficacy compared to BTA.146–148 In conclusion, in adult patients with CM, TPM is associated with more than a 50% reduction of migraine attacks.

Oral sodium valproate is recommended as second-line prophylactic therapy in patients with CM at doses of 1,000–2,000 mg/day (weak recommendation, moderate quality of evidence, 2B). Sodium valproate may reduce the frequency of chronic headaches compared to placebo in preventing CM. In the Yurekli et al.149 RCT, sodium valproate was superior to placebo for CM prophylaxis. A more than 50% reduction in attack frequency at doses of 1,000–2,000 mg/day was found when divided into two doses (n = 70, 29 with CM). The most frequent side effects were tremors, drowsiness, and impotence, which was found in a single patient.

For adults with CM, the use of oral levetiracetam is recommended as a second-line prophylactic therapy at doses of 500–1,500 mg/day (weak recommendation, low...
Levetiracetam is effective in the treatment of CM. In Rapoport’s study, it was used at doses of 1–3 g where 36 patients were included and treated with 750 mg of levetiracetam every 12 h. This study demonstrated a reduction in the frequency of migraine from 24.9 days/month to 16.2 days/month, and the number of days of migraine decreased from 16.8 days/month to 9.7 days/month. The observed adverse effects were somnolence, asthenia, anxiety, weight gain, and concentration difficulties. An RCT with 86 patients comparing 500 mg, 1 g, or 1.5 g of levetiracetam every 12 h demonstrated a decrease in the rate of pain-free days (pain-free days over a stable dose period/number of regular dose days) from 1000 mg to 650 mg. Lethargy and dizziness were also observed as adverse effects.

Oral pregabalin is suggested as second-line prophylactic therapy for patients with CM at doses of 100–300 mg every 24 h (weak recommendation, low level of evidence, 2C). Clinical studies on pregabalin are very scarce. Pizzolato refers that this drug is recommended for focal epileptic seizures and pain associated with herpes zoster, diabetic neuropathy, and fibromyalgia. It acts through mechanisms of reducing excitatory neurotransmitters such as glutamate, noradrenaline, and substance P. Additionally, it restores the hyperexcitability of calcium channels to normal; by these mechanisms, it could affect the glutamatergic mechanisms of the migraine. Using doses of 75–150 mg per day is generally well tolerated; however, 30% of patients reported vertigo and nausea, necessitating the reduction of doses to 75 mg per day, demonstrating a reduction of pain crises. Calandre et al. used 75 mg of pregabalin daily in an open study of CM patients over 12 weeks and found a 40% improvement; however, this study had a small sample size and was not blinded. Pregabalin could be considered in headache prevention, but more RCT are needed to evaluate its efficacy.

Oral propranolol is suggested as a second-line treatment in adult patients with CM at doses of 40–240 mg/day
Amitriptyline was effective in treating CM, and its efficacy increased when combined with aerobic exercise (walking for 40 mins three times per week) for 3 months. The study by Magalhaes et al. compared amitriptyline (25–50 mg depending on response) against BTA (250 U; n = 72 patients). Drugs were distributed in 15 pre-established points for a total of 90 days. BTA proved to be as effective as amitriptyline. Finally, in a double-blind study, Krychantowski et al. compared amitriptyline alone against amitriptyline + fluoxetine in the preventive treatment of transformed migraine (n = 39; duration = 45 days). In the group receiving amitriptyline alone, the medication was titrated every week until reaching a dose of 20 mg, twice per day for 45 days. In the group receiving amitriptyline + fluoxetine, the dose was titrated every week until they reached a threshold of 20 mg/20 mg every 12 h for 45 days. No significant benefits could be demonstrated by adding fluoxetine to amitriptyline over the amitriptyline group alone.

Citalopram is suggested as second-line prophylactic therapy in adult patients with CM. We recommend doses of 20 mg/day (weak recommendation, moderate quality of evidence, 2B). A clinical trial of 88 patients assessed the efficacy and tolerability of amitriptyline and citalopram alone or in combination for 16 weeks in patients with comorbid depression, migraine, and tension-type headache. Both treatments reduced depressive symptoms; however, amitriptyline was more effective than citalopram in reducing tension-type headaches and migraine attacks. The combination must be administered at low doses to avoid serotonin syndrome.

Melatonin use is suggested in adults with CM. We recommend doses of 3 mg/day (weak recommendation, with moderate quality of evidence, 2B). In a previous study, patients were divided into three groups A, B, and C, who were treated with 3 mg of melatonin, 200 mg of sodium valproate, and placebo, respectively. Adjunct melatonin treatment was superior to placebo and had the same clinical efficacy as sodium valproate but was better tolerated. Melatonin may be an adequate substitute for sodium valproate in the prevention of CM.

Non-pharmacological treatment of adults with CM

Most effective treatments (traditional and new) in CM for preventive management. Cefaly (transcutaneous supraorbital nerve stimulation) is recommended for adults with
acute CM attacks and to prevent refractory CM and drug abuse. The use of transcutaneous supraorbital nerve stimulation for 20 min/day for 1 month is recommended (strong recommendation with moderate-quality evidence, 1B). Cefaly (Cefaly Technology, Darien, CT, USA) has proven to be a safe and effective method in self-administered sessions in patients with CM and has been approved for the prevention of migraines since 2015. The device is a band with an electrode in contact with the forehead. The device is approved for use for 20 min sessions, once per day for 3 months as a preventive treatment for migraines. The supraorbital and supratrochlear nerves provide the sensation of the forehead and upper parts of the eyebrow.

Riederer et al. designed a study with 67 patients with at least two migraine attacks per month with a follow-up of 3 months. They found a significant response of 38.5% compared to 12% of patients who received a placebo. Russo et al. confirmed these results in an open study with 24 migraine patients. Finally, Vikelis et al. conducted a study of patients with EM and CM intolerant to TPM. A small but statistically significant decrease in the number of days with headache and the need for acute medication by 3 months was found.

In an open study, Di Fiore et al. assessed 23 patients with CM who received active neurostimulation; 35% reported a good safety profile and satisfaction. In 75% of participants, a reduction greater than 50% was achieved. D’Ostillo et al. conducted a multicenter survey of 2,313 patients with migraines and reported that 53.3% of patients were satisfied with the device with a non-response rate of 18.6%. Importantly, adverse events occurred in 4.3% of the patients, most of which were paresthesia, agitation, or changes in the sleep pattern, and only 2% suspended use of the device.

Neurofeedback

Neurofeedback is recommended as adjuvant first-line therapy to prevent CM and patients that prefer not to take medication, have low tolerance or contraindications to drugs, or have had an insufficient response to pharmacological treatment (strong recommendation, moderate quality of evidence, 1B). Neurofeedback is used in conjunction with cognitive behavioral therapy, meditation, and relaxation to change and control measurable brain activities such as temperature, pulse, muscle contraction, and sweating in response to negative stimuli. Since 2000, neurofeedback has been considered an effective adjuvant therapy in CM. Nestoriuc et al. conducted a review and meta-analysis of 150 studies and selected 94 from 1973 to 2007 with a total of 56 adults and older adults with migraines. The variables of efficacy evaluated were the frequency, duration, and intensity of headache. The most used and evaluated biofeedback modalities (BFB) were thermal and electromyography, and BFB with pulse volume measurement, showing efficacy for reducing the frequency and intensity of pain from 56% to 65%. In 2010, Andrasik concluded that relaxation training combined with thermal BFB and cognitive behavioral therapy is effective in improving symptoms from 56% to 65% in pain severity scale scores and was superior to placebo. A decrease in the risk of recurrence of headaches due to medication overuse and CM was also found. Odawara et al. conducted a pilot study comparing thermal BFB with relaxation techniques in 27 patients and found a decrease in the frequency of pain in 1.9 days and the frequency of days when headache intensity was ≥50 by 2.4 times. Disability, stress, depression, anxiety, and irritability were significantly improved. In a comparative clinical study with pharmacological treatment versus BFB with a Q-electroencephalogram that included 61 patients, 54% of patients achieved complete remission of migraine without aura, demonstrating a reduction >50% in frequency in 39% of the participants. Pregnant or nursing patients, history of pain medication abuse, and patients with significant stress have been suggested to possibly benefit from this treatment option.

Statement: Neurofeedback and Cefaly are non-pharmacological effective and practical prophylactic treatment modalities available for some patients with refractory CM. This is a strong recommendation (i.e., 1) with moderate quality of evidence (i.e., B; <2 RCT and systematic reviews).

Monoclonal antibodies

Molecularly designed monoclonal CGRP treatments for the preventive management of CM. The intravenous use of eptinezumab is recommended as a first-line treatment for CM. Intravenous dosages (300 mg) quarterly 9–12 months are recommended (strong recommendation, high quality of evidence, 1A). Eptinezumab (administered intravenously) is a humanized monoclonal antibody that binds to CGRP and is approved for use in CM. Eptinezumab induces a favorable response of pain reduction (50–67%) in the management of CM and CM using doses of 10, 30, 100, and 300 mg. It is effective at doses of 30 mg demonstrates a very favorable response at 300 mg. The administration of this monoclonal offers a 75% reduction in basal frequency of CM. Studies of CM have compared differing doses of eptinezumab (100 mg versus 300 mg) against placebo with a monthly application for 12 weeks. The reduction of headache days was more significant at 300 mg compared to 100 mg and the placebo. The drug was deemed to be safe, and its undesirable effects were comparable to placebo.

The subcutaneously use of galcanezumab is recommended as the first line of treatment for CM. We recommend dosages of 240 mg (initial) and 120 mg (monthly) for an undefined time 9–12 months (strong recommendation, high quality of evidence, 1A).
Galcanezumab is a humanized immunoglobulin 4 monoclonal antibody that binds to CGRP and is approved for use in both EM and CM. Phase three studies have used doses of 120 and 240 mg, which successfully managed both EM and CM with undesirable effects compared to placebo. Another RCT evaluated this antibody in CM comparing three groups: 240 mg, 120 mg, and placebo. There was no difference in response between the active ingredients, but there was a significant difference between them against placebo. Undesirable effects were similar in all three groups, with only discrete superiority in redness and itching reports at the application site. Other subsequent studies have supported these results.

Subcutaneous erenumab is recommended as the first-line of treatment for CM. We recommend dosages of 70 or 140 mg (monthly) for 9–12 months (strong recommendation, high quality of evidence, IA). Erenumab is a human monoclonal antibody indicated in both EM and CM. It can be administered intravenously and subcutaneously and its undesirable effects are comparable to placebo, with only hot flashes in menopausal women reported. In phase three studies in EM and CM compared monthly doses of 70 and 140 mg and demonstrated favorable response to both doses. In 36% of participants, reductions of headaches were greater than 50% in monthly migraine days (OR = 95%: 2.67 [1.36–5.22]) and 35% (OR = 2.51 [1.28–4.94]). Ashina et al. also evaluated erenumab at 70 and 140 mg against placebo in a controlled clinical trial, showing significant efficacy, with safety comparable to placebo. In 667 adults with CM in a controlled clinical study, 70 mg or 140 mg demonstrated a considerable effect with reduced disability and improvements in quality of life, with comparable safety to placebo. Adequate evidence has been synthesized to recommend erenumab use in CM.

The subcutaneous use of fremanezumab is recommended as a first-line or adjuvant treatment for CM. We recommend dosages of 225 mg (monthly) or 675 mg (quarterly) for 9–12 months (strong recommendation, high quality of evidence, IA). Fremanezumab is a humanized monoclonal antibody aimed at blocking the binding to the CGRP receptor. It modulates the trigeminal sensory pathways that innervate the meninges and vessels that supply these structures. It is indicated for the management of EM and CM, suggesting its subcutaneous application monthly or quarterly. Its use is recommended on its own or with other prophylactic treatments. In CM in a phase three study, a favorable response was found with an initial 675 mg and a monthly 225 mg maintenance.

Silberstein et al. conducted a controlled clinical study with 1,130 participants divided into three groups (the first receiving 675 mg at the beginning and placebo at weeks 4 and 8, the second receiving 675 mg at the beginning and 225 mg at weeks 4 and 8, and the third receiving placebo at the beginning and weeks 4 and 8, subcutaneously). There was no statistical difference between the two groups receiving the active drug; however, the percentage of patients with at least a 50% reduction in the average number of days with headache per month was 38% in the quarterly fremanezumab group, 41% in the monthly fremanezumab group, and 18% in the placebo group. Fremanezumab showed comparable safety to placebo, although application site reactions were common.

Statement: Monoclonal antibodies directed to the CGRP receptor or ligand are safe as first-line or adjuvant treatments, with minimal side effects and monthly or quarterly administration in adult patients with CM. This is strong recommendation (i.e., I) with a high quality of evidence (i.e., A: ≥ 2 RCT and systematic reviews).

BTA in the treatment of CM

Application of BTA and anesthetics alone or in combination with other preventive disease management. It is recommended to use BTA subcutaneously as a second line of treatment in adult patients with CM at doses of 155–195 U, with 5 U per point of application (strong recommendation, high quality of evidence, IA). Three RCT compared BTA to placebo and one unified study had as main objective to evaluate decreases in headache day frequency from the base period to its cut-off point. As secondary objectives, the authors included the reduction of migraine days, removal of moderate to severe headache days, decrease of accumulated headache hours, 50% reduction of headache days frequency, and reduction of analgesic medication intake. Regarding decreases in headache day frequency, headache base days were 19.9 ± 0.1 in the BTA group versus 19.8 ± 0.1 in the placebo group, obtaining a reduction of −8.4 headache days in the BTA group versus −6.6 in the placebo group. The percentage of patients who achieved a 50% decrease in headache days was significantly higher in the BTA group compared to placebo (47.1% versus 35.1%). A reduction in headache days of up to 10.7 days from baseline was observed in the active group, and alongside a 4.4 point reduction in Headache Impact Test-6 score. We found a reduction in abortive medication intake and moderate/severe headache days. The recommended dose is 155–195 U (at the clinician’s discretion) at 31 fixed points and eight pain tracking points every 12 weeks. One study suggested that the 195 U dose is more effective than the 155 U dose. The recommendation for second-line treatment is because there are no studies in patients without previous pharmacological treatment. Studies include patients who have had a therapeutic failure to a preventive medication.

The subcutaneous use of BTA is recommended as the first-line of treatment in adult patients with CM and MOH (strong recommendation, moderate quality of evidence, IB). This recommendation is based on five evidence-based clinical trials and two evidence-based studies in real-life settings in patients with CM. These studies
aimed to reduce the number of headache days by 50% alongside the analgesic medication intake. Roughly 32–50% of patients reported a 50% decrease in headache days throughout the studies. Patients with 22–30 days of headache per month as a baseline reduced the frequency of headache up to 5–7 days. Patients reduced the intake of analgesics from 12 to 30 days per month to 3–6 days per month. A 3 year study with administration every 12 weeks demonstrated a reduction of headache days from 21.5 ± 5.1 at the beginning of the study to 3.4 ± 1.7 at the end of the third year, as well as a reduction of analgesic use from 16.5 ± 7.3 days per month to 2.8 ± 1.3 days per month at the end of the third year. One study suggests that the 195 U dose is more effective than the 155 U dose; however, Pijpers et al. reported no additional benefits with the use of BTA in MOH compared with placebo, making it necessary to withdraw the medication of abuse before applying BTA.

Subcutaneous administration of incobotulinum toxin type A is suggested to treat adults with CM as a second line of treatment (weak recommendation, very low quality of evidence, 2D). In a retrospective clinical case study of 21 patients (40 years of age, 52% women, 43% with previous use of BTA, and 29% with a history of head trauma), researchers used 150 U of incobotulinum toxin type A, which has similar applications to BTA alongside patients who had previously failed four or more oral prophylactics. A significant decrease in headache days per month (19.1 versus 9.1) and intensity (8.3 versus 4.1) was reported; however, the dose or application points are unknown.

Bilateral occipital nerve infiltration with bupivacaine or lidocaine is recommended in adults with CM (strong recommendation, high quality of evidence, 1A). The infiltration of peripheral nerves and pain points is a procedure that improves pain quickly in most patients, in addition to the associated symptoms. Three RCT using bupivacaine with weekly blockade for 4 weeks showed improvement for at least 1 month. Another multicentric study showed a reduction in pain days and the intensity of the pain attacks according to the visual analog scale. The study justifies the use of the infiltration of peripheral nerves as another therapeutic option due to the limited efficacy, the latency of time to have the therapeutic effect of the current preventive medicines, as well as the pharmacological interactions, explaining the use of only 28% in EM and 44.8% in CM.

The painful trigger points found in CM are postulated to result from the excessive release of acetylcholine in the neuromuscular junction and result in tension bands. The peripheral nerves infiltrated in the CM are the major and minor occipital nerves. The local anesthetic drugs used for peripheral nerve blocks are lidocaine, bupivacaine with or without methylprednisolone, dexamethasone, and or triamcinolone reversible inhibition voltage-dependent calcium channels and at low doses selectively on sensitive fibers. Another mechanism proposed in migraine is the nociceptive inhibition of some fibers of the trigeminal-cervical complex. By infiltration in peripheral nerves, inhibition of all systems is achieved. Although the duration of the anesthetic effect is typically in hours, the migraine’s impact could last months, which could be explained by breaking the circle of the pain in CM. The frequency of application varied from 1 to 8 weeks; the marker of success was numbness in the distribution of the blocked nerve, evaluation of the improvement of the headache the day of the application, or improvement in the following days. The effect’s duration is variable; it can be hours to months, most commonly weeks. The vasovagal complications reported are dizziness and pain at the injection site and contraindications include infection, skull defects, allergy to anesthetics, and use of anticoagulants. It is a procedure that, in most cases, is performed in the doctor’s office and is inexpensive.

Statement: BTA at 155 or 195 U is effective and recommended in CM with quarterly administration. Cranial nerve blocks (especially the occipital nerve) can be effective, although of variable duration, in the management of CM. This is a strong recommendation (i.e., 1) with a high quality of evidence (i.e., A; > 2 RCT and systematic reviews).

Migraine and pregnancy

Options for acute and preventive management of CM in pregnancy. We recommend that pregnant women suffering from CM, especially in the first trimester of pregnancy, discontinue drugs of abuse (strong recommendation, high quality of evidence, 1A). The prescription of any medication either for a prophylactic or symptomatic episode of pain should be analyzed to select the best treatment option by the potential possibilities of teratogenesis or abortion, especially because at least 10% of congenital disabilities are due to exposure to drugs in pregnancy, especially in the first trimester. Although analgesics produce few teratogenic effects, ergotamine can initiate uterine activity and increase the risk of prematurity, major congenital malformations, low birth weight, and miscarriage.

In general, drugs to be used in pregnancy are divided into categories by FDA recommendation. Category A is safe (e.g., vitamins and thyroid hormone at substitute doses); Category B demonstrates no evidence of risk in humans or animals, but there are not enough controlled studies for pregnant women; Category C states that the drug has shown risk in animals, but there are no studies in women; and Category D demonstrates that the drug has been shown to cause harm, although the potential benefits may outweigh the risks. A category X would be when the drug is contraindicated in pregnancy.

For acute management, paracetamol seems to be the most recommended drug at 500–1,000 mg; however, other NSAIDs, opioids, and antidopaminergics could
be used with an adequate safety level and evidence for pregnancy (category B: World Health Organization pregnancy; weak recommendation, moderate level of evidence, 2B). The short-term, acute management for the migraine pain crisis is generally conducted with NSAIDs often associated with caffeine. Due to the association with nausea and vomiting, they are frequently used together with an antiepileptic that is usually an antipodalnergic or anticholinergic (muscarinic antagonist). Among these drugs, metoclopramide stands out at a 10 mg rate; metoclopramide is frequently used for hyperemesis gravidarum and its use is approved in controlling nausea and vomiting during pregnancy. None of these possibilities are safe in newborn so its use must be well evaluated in particular. ASA can cause gastrointestinal intolerance, asthmatic crises, and even Reye’s syndrome, and in the first trimester, it favors spontaneous abortion; however, its use has recently been promoted in pregnant patients with thrombophilia (e.g., due to primary antiphospholipid syndrome) at doses of anti-aggregation prophylaxis, although doses of 500 or 1,000 mg can be used to relieve pain during migraine attacks. Cyclooxygenase inhibitors may cause agranulocytosis and may be weakly teratogenic, although no studies support or contraindicate their use in pregnancy. In general, NSAIDs may be associated with pulmonary hypertension in the neonate, and premature ductus arteriosus closure has also been reported. Due to the association with nausea and vomiting, they are frequently used together with an antiepileptic that is usually an antipodalnergic or anticholinergic (muscarinic antagonist). Among these drugs, metoclopramide stands out at a 10 mg rate; metoclopramide is frequently used for hyperemesis gravidarum and its use is approved in controlling nausea and vomiting during pregnancy. None of these possibilities are safe in newborn so its use must be well evaluated in particular. ASA can cause gastrointestinal intolerance, asthmatic crises, and even Reye’s syndrome, and in the first trimester, it favors spontaneous abortion; however, its use has recently been promoted in pregnant patients with thrombophilia (e.g., due to primary antiphospholipid syndrome) at doses of anti-aggregation prophylaxis, although doses of 500 or 1,000 mg can be used to relieve pain during migraine attacks. Cyclooxygenase inhibitors may cause agranulocytosis and may be weakly teratogenic, although no studies support or contraindicate their use in pregnancy. In general, NSAIDs may be associated with pulmonary hypertension in the neonate, and premature ductus arteriosus closure has also been reported. The most commonly used analgesic in pregnancy is paracetamol at doses up to 1 g on a schedule until the pain subsides. Opioids, such as codeine, are safe in pregnancy. Unfortunately, they may favor attention deficit hyperactivity disorder in children requiring special handling if there is already a dependence on morphine in the mother and infant; however, there is always the possibility of creating an addictive effect. Barbiturates and benzodiazepines may be used, but their abuse may cause suppression syndromes in the newborn. Caffeine appears to be safe, as coffee-drinking mothers often have children without problems; however, there is controversy about whether its use can cause miscarriages, premature delivery, and low birth weight. As for ergot derivatives, they are associated with abortion and fetal defects. They are contraindicated in pregnancy and breast-feeding and fall into FDA category X. Triptans have not been associated with congenital malformations or an increase in the number of abortions but could potentially give the infant hepatotoxic effects. For prophylactic management, the use of magnesium, riboflavin, memantine, cyproheptadine, propranolol, and gabapentin are minimally recommended and offer moderate evidence for pregnancy (2B). TPM, valproate, and candesartan (category D and X: FDA pregnancy) should be avoided (low recommendation level and moderate level of evidence, 2B). The prophylactic management of migraine in pregnancy should be practically reserved to the use of propranolol and memantine; for EM, with a level 2B of evidence and for CM, amitriptyline with a level 2C, which is compatible with periconception; first, second, and third trimester, and lactation. Valproate (for EM) and TPM (for CM) are entirely contraindicated because of their teratogenic effects.

Peripheral nerve blocks are suggested for pain management and possibly prophylaxis in pregnancy with targets in the significant occipital, auriculotemporal, supraorbital, and supratrochlear nerve (weak recommendation level, moderate level of evidence, 2B). A peripheral nerve block can be used as a safe alternative with few adverse effects attributed to the procedure. Although this procedure has been studied in migraineurs, it has been proposed as a safe possibility for pregnant women, although in a small sample, with the combination of local anesthetic (lidocaine) and steroids administered topically, with a protective effect of days to months. Prophylactic management could also occur by blocking the branches of the upper cervical nerve (great and minor occipital nerves), as well as the trigeminal branches (auriculo-temporal, supraorbital, and supratrochlear) associated with steroids.

BTA is safe and effective in pregnant women with CM (high recommendation and low level of evidence, 1C). Since 2005, anecdotal cases have been reported. Therefore, they do not provide evidence of pregnant women where it has been used without adverse complications for the development of pregnancy or undesirable effects on the infant that can be attributed to the toxin. The FDA approved the use of the BTA in 2010 with a category C for pregnancy. BTA use has been proposed as a safe alternative for the mother and baby in the prophylactic management of CM. A 24 year study on of use of BTA in 574 pregnant women found no difference in the risk of malformations concerning unexposed population (2.7%), so its administration is deemed to be safe in pregnancy.

Statement: In pregnancy, discontinuation of drugs of abuse is mandatory. Administration of paracetamol is indicated in exacerbation (although other considerations may be helpful if there is resistance, including opioids). Prevention, TPM, valproate, and candesartan should be avoided. Memantine, riboflavin, propranolol, and gabapentin could be considered if preventive treatment is required. BTA and nerve block could be other alternatives. This is strong recommendation: 1, with a very low (D), low (C) or moderate (B) quality of evidence; there are systematic reviews, but lack RCT.

Conclusion
The treatment of CM is a challenge and must be individualized, as it considerably affects quality of life. Fortunately, therapeutic options have increased, and we now have molecularly designed drugs to manage symptoms. Comorbid conditions and pregnancy create additional difficulties in care. The development of clinical guidelines can facilitate
the best therapeutic approach in the affected population. Importantly, the validity of the current guidelines is likely to be transitory. We believe that 5 years of use is recommended, and we hope to have new possibilities and evidence for managing this problem in the future.

**Article highlights**

- There are risk factors for migraine chronification that should be avoided, especially medication abuse, sleep disturbances (especially OSAS), obesity, asthma, and mood disorders (e.g., depression and anxiety).
- Symptomatic management demonstrates an excellent response to NSAIDs and triptans and their combination. Metoclopramide can be used if the migraine is associated with vomiting.
- New options for acute management are lasmiditan and gepants.
- In prevention, TPM and BTA have good evidence; however, monoclonal anti-CGRP ligands or receptor antibodies are a novel molecularly designed safe alternative with robust evidence.
- There are non-pharmacological devices with adequate evidence for the acute and preventive management of CM.
- In pregnancy, discontinuation of drugs of abuse is mandatory. For exacerbation, paracetamol can be safely used. Nerve blocks and botulinum toxin are alternatives that need further assessment, but appear safe.

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The author(s) declare that there is no conflict of interest. The authors have no personal, financial, or institutional interest in any of the drugs, materials, or devices described in this publication.

**Ethical considerations**

These guidelines required no written approval from an Ethics Committee, as there was no clinical intervention or direct participation of subjects for this research. Controlled trials for Chronic Migraine should be performed in accordance with the Declaration of Helsinki II.

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