

Evidence-based guidelines for the pharmacological treatment of migraine, summary version

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Abstract

We here present evidence-based guidelines for the pharmacological treatment of migraine. These guidelines, created by the Italian Society for the Study of Headache and the International Headache Society, aim to offer clear, actionable recommendations to healthcare professionals. They incorporate evidence-based recommendations from randomized controlled trials and expert-based opinions. The guidelines follow the GRADE approach for assessing the quality of evidence. The guideline development involved a systematic review of literature across multiple databases, adherence to Cochrane review methods, and a structured framework for data extraction and interpretation. Although the guidelines provide a robust foundation for migraine treatment, they also highlight gaps in current research, such as the paucity of head-to-head drug comparisons and the need for long-term outcome studies. These guidelines serve as a resource to standardize migraine treatment and promote high-quality care across different healthcare settings.

Keywords

migraine treatment, acute treatment, preventive treatment, drugs, pharmacological treatments

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Introduction

Evidence-based guidelines are pivotal tools to guide treatment. These guidelines distill vast amounts of research into practical recommendations, ensuring that healthcare

professionals can deliver the most effective treatments to patients. By systematically reviewing the latest evidence, guidelines help bridge the gap between research findings and clinical practice, promoting consistency and quality in healthcare delivery. The strength of evidence-based guidelines lies in their ability to synthesize diverse sources of evidence into actionable recommendations. By prioritizing interventions with demonstrated efficacy,

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guidelines empower clinicians to make informed decisions that optimize patient outcomes.

In the migraine field, numerous guidelines exist. Notably, guidelines from the European Headache Federation (1,2) have been meticulously developed utilizing a robust methodology, such as the GRADE approach (3). This methodology includes systematic evaluation of available evidence, quantitative pooled statistical synthesis of data, and rigorous rating of evidence quality (3). However, it is noteworthy that these guidelines primarily focus on a subset of available treatments, notably monoclonal antibodies targeting the calcitonin gene-related peptide (CGRP) pathway and onabotulinumtoxinA (1,2).

Conversely, guidelines from the American Headache Society provide comprehensive coverage of all available pharmacological treatments for migraine (4–6). However, they are not grounded in quantitative analyses of the available data.

In pursuit of promoting optimal care for individuals suffering from migraine, the Italian Society for the Study of Headache (SISC) and the International Headache Society (IHS) have embarked on a collaborative endeavor. This initiative aims to develop a joint evidence-based guideline on the pharmacological treatment of migraine.

The overarching goal of this joint guideline is to furnish healthcare practitioners with evidence-based recommendations for the pharmacological management of migraine to provide clear, actionable guidance for the treatment of migraine. The presentation of this guideline is organized as a summary document to facilitate consultation, the main document with all the information to derive evidence-based recommendations, and a supplementary file with additional information. For each of the considered drug categories, the main document contains quantitative summary of the evidence, the evaluation of the quality of evidence, a summary on safety and tolerability, a summary of the evidence-based guideline, and expert-based opinions to support clinical use.

Methods

Details of the Methods are available in section 2 of the main document available at: <https://doi.org/10.1177/03331024241305381>.

The guideline working group was appointed by the ‘Italian Society for the Study of Headaches’ (*Società Italiana per lo Studio delle Cefalee* – SISC) and by the ‘International Headache Society’ (IHS) and is described in Table 1.

The working group included a chair, a coordination supporting group, external reviewers, administrative supporting persons, and module working subgroups, each assigned to a specific drug class (Table 1). Each subgroup had both SISC and IHS components.

This guideline is based on the best available evidence from randomized controlled trials (RCTs) and a rigorous evaluation of the quality of evidence for each intervention and outcome. The considered interventions were drugs commonly used for the acute treatment of migraine attacks or for migraine prevention.

For the acute treatment of migraine attacks, the following drug classes were considered:

- Non-steroidal anti-inflammatory drugs (NSAIDs) and cyclooxygenase 2 (COX2) inhibitors (Section 3.1)
- Triptans (Chapter 3.2)
- Paracetamol/acetaminophen (Chapter 3.3)
- Combination analgesics (Chapter 3.4)
- Antiemetics (Chapter 3.5)
- Opioids (Chapter 3.6)
- Ditans (Chapter 3.7)
- Gepants for acute treatment (Chapter 3.8)

For migraine prevention, the following classes were considered:

- Antidepressants (Chapter 4.1)
- Anti-seizure medications (Chapter 4.2)
- Beta-blockers (Chapter 4.3)
- Calcium channel blockers and blood-pressure lowering agents (Chapter 4.4)
- Botulinum toxin (Chapter 4.5)
- Gepants for acute treatment (Chapter 4.6)
- Monoclonal antibodies targeting the CGRP pathway (Chapter 4.7)

Those chapters addressed the available evidence of treatments compared with placebo. Head-to-head comparisons between different active drugs were reported in Chapter 3.9 for the acute treatment of migraine attacks and in Chapter 4.8 for migraine prevention.

Clinically relevant questions were framed using the PICO format (Population, Intervention, Comparator, and Outcomes) by members of the guideline panel. To provide clinical guidance, we also used expert-based opinions. The text clearly distinguishes between evidence-based recommendations and expert-based opinions to inform the reader where guidance is based solely on evidence data or where it considers experience and opinions.

For the acute treatment of migraine attacks, the following outcomes were considered:

- pain freedom at 2 h from intake;
- pain relief at 2 h from intake.

For preventive treatment, the following outcomes were considered:

Table 1. Guideline working group.

	Italian Headche Society - Società Italiana per lo studio delle cefalee (SISC)	International Headache Society (IHS)
Chairperson	Simona Sacco	Messoud Ashina
Coordination supporting group	Valeria Caponnetto Raffaele Ornello	—
Internal reviewers	Cristina Tassorelli Innocenzo Rainero	Hans-Christoph Diener Morris Levin
Administrative supporting person	Marisa Morson	Carol Taylor
GUIDELINE CHAPTERS		
Methods	Valeria Caponnetto Raffaele Ornello Simona Sacco	Eva-Maria Hüßler Messoud Ashina
Acute attack treatments		
Non-steroidal anti-inflammatory drugs and cyclooxygenase-2 inhibitors	Maria Pia Prudenzano Adriana Fallacara Anna Laporta Marina de Tommaso	Santiago Crema Maria Teresa Goicochea
Triptans	Marcello Silvestro Ilaria Orologio Alessandro Tessitore Antonio Russo	Kimberly Garces Teshamae Monteith
Paracetamol (Acetaminophen)	Francesco Casillo Gianluca Coppola	Esme Ekizoglu Aynur Özge
Combined analgesics	Ilenia Corbelli Alessia Bellotti Paola Sarchielli	Marcio Nattan Portes Souza Volodymyr Romanenko
Antiemetics	Marina Romozzi Francesco Casillo Paolo Calabresi Gianluca Coppola	Haidar Al-Khazali Mansoureh Togha
Opiates	Daniele Martinelli Franco Granella	Koichi Hirata
Ditans	Marina Romozzi Paolo Calabresi	Li-Ling Hope Pan Shuu-Jiun Wang
Gepants	Carlo Baraldi Simona Guerzoni	Diego Swerts Mario Peres
Head-to-head studies	Valeria Caponnetto Raffaele Ornello Cherubino Di Lorenzo Simona Sacco	Patricia Pozo-Rosich
Preventive treatments		
Antidepressants	Gloria Vaghi Roberto De Icco Grazia Sances	Alejandro Labastida-Ramírez Jan Hoffmann
Anti-seizure medications	Luigi Francesco Iannone Alberto Chiarugi	Chia-Chun Chiang Todd Schwedt
Beta-blockers	Vincenzo Di Stefano Antonino Lupica Filippo Brighina	Mona Hussein Tawfeek Amr Hassan
Blood-pressure lowering agents	Marina Romozzi Francesco Casillo Paolo Calabresi Gianluca Coppola Antonio Granato Edoardo Mampreso	Wooseok Ha Min Kyung Chu
Botulinum toxin	Valentina Favoni Silvia Quattrocchi Sabina Cevoli	Lavindren Luke Panneerchelvam Fayyaz Ahmed
Gepants	Carlo Baraldi Simona Guerzoni	Rune Hackert Christensen Sait Ashina
Monoclonal antibodies targeting the CGRP pathway	Luigi Francesco Iannone Pierangelo Geppetti	Shuli Cheng Bronwyn Jenkins
Head-to-head studies	Raffaele Ornello Valeria Caponnetto Anna Ambrosini Simona Sacco	Messoud Ashina

- persisting monthly headache/migraine days, defined as the residual days reported by patients at the end of the treatment (as reported in headache diaries);
- change in monthly headache/migraine days, defined as the variation in days reported by patients from baseline to the end of follow-up (as reported in headache diaries);
- $\geq 50\%$ responder rate, defined as the proportions of patients reporting a $\geq 50\%$ reduction in monthly headache/migraine days compared with baseline. The $\geq 50\%$ reduction of monthly attacks was also considered for $\geq 50\%$ responder rate whenever the reduction in monthly headache/migraine days was not available.

The chosen outcomes were more extensive than those issued by the International Headache Society guidelines for RCTs of migraine prevention (7,8), in order to include the highest possible number of RCTs. Patient-reported outcomes were not included because of substantial heterogeneity across instruments used. Given the expected minimal impact of serious adverse events, we did not consider safety as an important or critical outcome to derive evidence-based recommendations. We addressed tolerability and used this information to draft expert-based opinion sections.

The final guideline report includes patient populations, interventions, comparators, and outcomes for which the

systematic literature search showed the presence of available RCTs.

Search of available evidence was performed according to the Cochrane guidelines for systematic reviews of interventions (9) and overviews of reviews (10). Cochrane guidelines were also followed for study selection, data extraction and synthesis. Reporting was performed according to relevant items of the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) statement (11).

Literature search was performed between 10 and 11 February 2022 for all topics except for antiemetics, which were included in the search plan in September 2022; related search strings were launched on 8 September 2022. As the process of literature search and analysis took more than 12 months, search strings were re-launched in May 2023 and November 2023 to update the search to the RCTs published from February 2022. Two researchers (VC and RO) performed a literature search for each pharmacological class of acute treatments and migraine preventive drugs. Three scientific databases were searched, namely PubMed, Scopus, and Cochrane Database, since the beginning of indexing, utilizing the PICOM (Patients – Intervention – Comparison – Outcome – Methods) methodology. To ensure a broad coverage of available literature, when building search strings, only Participants (i.e., migraine patients) and Interventions (i.e., drugs) were considered for each topic.

Study selection was performed by each module subgroup.

The inclusion and exclusion criteria for eligibility and inclusion phase are presented in Table 2.

Utilizing an .xlsx spreadsheet template, module subgroups extracted data for each included study.

For each PICO question, all extracted data about outcomes were classified, analyzed, and presented as pooled analyses of the available RCTs for each selected outcome. Results were presented as pooled analyses even when only one RCT was available.

The quality of available evidence was then rated according to the Grading of recommendations, Assessment, Development and Evaluation (GRADE) (12) system, that also drove the development of evidence-based recommendations. For each outcome, we rated the quality of evidence as either high, moderate, low, or very low based on: risk of bias (study limitations), inconsistency (differences between the results of trials), indirectness (differences between the questions investigated in trials and the question of interest), imprecision (random error), and other considerations (other conditions that might affect risk of bias such as conflicting results between two outcomes described in the same study, availability of only one outcome for a comparison). In the presence of different quality of evidence across different outcomes for the same PICO, the overall quality of

evidence was rated as the lowest among them. High quality of evidence indicates situations in which there is high certainty that the true effect lies close to the estimated effect; low or very low quality of evidence indicates situations in which the true effect may be substantially different from the estimated effect.

For each PICO question, the coordination supporting group and the chair derived evidence-based recommendations – if possible – according to the available evidence. Each recommendation was rated as strong or weak. The strength of a recommendation indicates the extent to which one can be confident that adherence to the recommendation will give more benefit than harm. For strong recommendations we used the term “we recommend”; for weak recommendations we used the term “we suggest”. Recommendations can be either for or against an intervention, depending on the results of meta-analyses of RCTs.

To provide clinical guidance, expert-based opinions were also incorporated in addition to evidence-based recommendations. The text clearly distinguishes between the two to inform the reader about the sources of guidance. This section is intended to provide practical suggestions for the management of migraine patients, with a rationale based on the available literature.

Topics and suggestions for expert-based opinions were identified by each module working subgroup and by two experts who were responsible for harmonizing this part across all the sections (AA, CDL). Additionally, these experts developed an introductory chapter to provide general concepts on acute treatment and prevention.

Results

Full results of this guideline are presented in the main document and summarized in Table 3 for the acute treatment, in Table 4 for the prevention of episodic migraine, in Table 5 for the prevention of chronic migraine, and in Table 6 for any migraine (no distinction between episodic and chronic).

It is worth mentioning that for calcium-channel blockers there are no trials meeting the eligibility criteria for providing evidence-based recommendations. Considering the long-standing use of those drugs in the prevention of migraine an expert-based opinion is provided in chapter 4.4 to support their use.

Table 7 reports a summary of guidance for the acute treatment of migraine derived from head-to-head studies. Details for this part can be found in chapter 3.9. The following comparisons were found: NSAIDs vs NSAIDs, triptans vs NSAIDs, triptans vs triptans, triptans vs other analgesics, combination analgesics vs NSAIDs, combination analgesics vs triptans, combination analgesics vs paracetamol, combination analgesics vs combination analgesics, combination analgesics vs other analgesics.

Table 8 reports a summary of guidance for the preventive treatment of migraine derived from head-to-head

Table 2. Inclusion and exclusion criteria for evaluation of references in eligibility and inclusion phases for stage 2.

Phase	Inclusion criteria	Exclusion criteria
Eligibility (evaluation of titles and abstracts)	1) Studies meeting all of the following criteria: - RCT - Performed in patients with migraine - Addressing a pharmacological therapy versus placebo or other drugs 1) Abstract not available 2) Abstract not allowing to fully assess eligibility	1) Study design was not RCT 2) The RCT was not performed in patients with migraine 3) The RCT did not assess the outcome of a pharmacological therapy versus placebo or other drugs
Inclusion (evaluation of full text)	1) Studies meeting all the following criteria: - RCT - Performed in patients with migraine - Addressing a pharmacological therapy versus placebo or other drugs	1) Full text not available (e.g., conference abstracts, conference proceedings) 2) Wrong design (not a RCT) 3) Wrong comparison (the RCT did not assess the outcome of a pharmacological therapy versus placebo or other drugs) 4) Wrong population (the RCT included patients with headache other than migraine, or included mixed samples and no separate findings were reported for patients with migraine) 5) Pediatric population (0–18-year-old subjects) 6) The RCT included only patients with menstrual migraine 7) The RCT only assessed non-commercial and non-approved doses of the selected drugs 8) The RCT tested an intravenous drug for acute treatment 10) Wrong outcomes (i.e., the systematic review/meta-analysis did not evaluate any of the outcomes considered for the present guidelines)

studies. Details for this part can be found in chapter 4.8. The following comparisons were found: NSAIDs vs NSAIDs, triptans vs NSAIDs, triptans vs triptans, triptans vs other analgesics, combination analgesics vs NSAIDs, combination analgesics vs triptans, combination analgesics vs paracetamol, combination analgesics vs combination analgesics, combination analgesics vs other analgesics.

Discussion

This comprehensive guideline represents the first detailed framework for the acute treatment and prevention of migraines, providing evidence-based recommendations grounded in a systematic and quantitative assessment of the available randomized controlled trials (RCTs) on pharmacological treatments. The main strength of this guideline is the use of the well-established GRADE methodology offering a rating of the quality of evidence for each migraine treatment.

Notably, many migraine preventive drugs that have been widely used in clinical practice were investigated in trials conducted many years ago, often not meeting the rigorous quality criteria of modern evidence-based medicine (7,13). While this does not negate the potential effectiveness of these drugs, it does indicate that the existing evidence may not be robust enough to strongly support their use. This consideration should be applied particularly to

the oldest established preventive agents for migraine, including tricyclic antidepressants, beta blockers, and calcium channel blockers. As a general rule, more recent treatments have stronger evidence than the older ones, not only because of their efficacy and safety profile, but also because of improvements over time in the design of RCTs.

Additionally, the field of migraine research suffers from a paucity of head-to-head studies with conclusive results, which hampers the ability to recommend one drug over another, with few exceptions. Therefore, it is crucial for the migraine treatment field to advance using the highest standards to derive unbiased evidence that can guide patient care effectively. There is a strong need to compare the long-term outcomes of different drugs and to understand how these medications can prevent the progression of migraine into difficult-to-treat conditions, such as high-frequency episodic migraine, chronic migraine, medication overuse headache, or refractory migraine.

Although strongly grounded in evidence-based principles, this guideline cannot be considered as a complete guide to migraine treatment. Safety outcomes were excluded from evidence-based recommendations because it is established that the considered drugs are not associated with serious risks for the patients. Besides, several topics that are relevant to clinical practice, such as drug titration, duration of treatment, and treatment combinations, were

excluded from evidence-based recommendations and could only be addressed by expert-based opinions.

This guideline provides a solid foundation for deriving best practices at the national level, considering the available pharmacological treatments and the unique aspects of health systems and resident populations. Ideally, drugs supported by the best evidence regarding efficacy and tolerability profiles should be broadly accessible.

Declaration of conflicting interests

The authors declared the following potential conflicts of interest with respect to the research, authorship, and/or publication of this article:

R.O.: Consulting fees, Allergan-AbbVie, Eli Lilly. Honoraria: Eli Lilly, Novartis, Pfizer, Teva. Support for attending meetings, Allergan-AbbVie, Eli Lilly, Lundbeck, Novartis, Pfizer, Teva. Participating, Allergan-AbbVie, Eli Lilly. Leadership, Jr. Editorial Board member *J Headache Pain*. Receipt of equipment, Novartis, Eli Lilly. Other financial or non-financial, Eli Lilly, Novartis, Teva

V.C.: Honoraria, Teva. Support for attending meetings, Teva

F.A.: Received honorarium to be on the ad board and lecturing from AbbVie, Pfizer, Eli Lilly, TEVA, Lundbeck. Leadership, Treasurer, IHS.

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S.A.: Consulting: Allergan/AbbVie, Eli Lilly, Impel NeuroPharma, Linpharma, Lundbeck, Pfizer, Satsuma, Teva, Theranica. Honoraria, Lectures presentations: AbbVie, Eli Lilly, Teva, Pfizer, Lundbeck. Leadership: Associate Editor for Cephalalgia, BMC Neurology, Frontiers in Neurology, Headache and Pain Research, Neurology Reviews, and Trustee of the International Headache Society Board.

C.B.: Honoraria, AbbVie. Support for meeting attendance, AbbVie, Lilly, Pfizer, Lundbeck

F.B.: Received honoraria for lectures, presentations from: Pfizer, Lilly, TEVA, Alnylam, AbbVie, Lundbeck, Alexion. Support for attending meetings, TEVA, Alnylam, Roche, Sanofi, Biogen, AbbVie, Alexion, Lundbeck, Lilly.

P.C.: Received speaker honoraria from: AbbVie, Bayer Schering, Bial, Biogen-Dompè, Biogen-Idec, Eisai, Genzyme, Lundbeck, Lusofarmaco, Merck-Serono, Novartis, Prexton, Teva, UCB Pharma, Zambon. PC received support to attend national and international conferences from: AbbVie, Bayer Schering, Bial, Biogen-Dompè, Biogen-Idec, Eisai, Genzyme, Lundbeck, Lusofarmaco, Merck-Serono, Novartis, Prexton, Teva, UCB Pharma, Zambon. Participation on Advisory Board for Lilly. Participation in Data Safety, Roche, Therapy for Parkinson's Disease. PC is Past President of the Società Italiana per lo Studio delle Cefalee (SISC)

S.C.: Honoraria for lectures, presentations, speakers bureaus, manuscript writing or educational events for Angelini, Teva, Novartis, AbbVie, Lundbeck, Pfizer. Support for attending meetings and/or travel by AbbVie, Lilly. Participation on Advisory Board for Lilly. Advisor of ANIRCEF. PI for trial of Lilly, Novartis, Teva, Lundbeck.

S.C.: Headache Australia website medical reviewer. AbbVie to attend 2022 Australia New Zealand Neurologist Association ASM.

ordinary committee member on the Australian New Zealand Headache Society- current.

C.C.C.: Research support from the American Heart Association with funds paid to her institution. (Unrelated to this manuscript). Consulting, Satsuma, eNeura. Honoraria, HMP Global for migraine education lectures. Leadership, American Migraine Foundation Editorial Board.

A.C.: Filed patents on novel uses of anti-CGRP biologics and gepants.

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Table 3. Summary of recommendations for acute migraine treatments. Rows report strength of recommendations; columns report quality of evidence.

Quality of evidence/ Strength of the recommendation	High	Moderate	Low	Very low
Strong in favor	Paracetamol 1000 mg oral Almotriptan 12.5 mg oral Eletriptan 20 and 40 mg oral Frovatriptan 2.5 mg oral Naratriptan 1 and 2.5 mg oral Rizatriptan 5 and 10 mg oral Sumatriptan 50 and 100 mg oral Sumatriptan 6 mg/mL subcutaneous Sumatriptan 10 and 20 mg intranasal Zolmitriptan 2.5 mg oral Acetylsalicylic acid 500 mg + Paracetamol 500 mg + Caffeine 130 mg oral Lasmiditan 50, 100 and 200 mg oral Rimegepant 75 mg oral Ubrogepant 50 and 100 mg oral Zavegepant 10 mg intranasal	Acetylsalicylic acid 1000 mg oral Diclofenac 50 mg oral Acetylsalicylic acid 900 mg + Metoclopramide 10 mg oral	Ibuprofen 200, 400, 600 mg oral Sumatriptan 85 mg + Naproxen 500 mg oral Rizatriptan 10 mg + Paracetamol 1000 mg oral	Naproxen 500 and 825 mg oral
Weak in favor	-	Celecoxib 120 mg oral Paracetamol 650 mg + Tramadol 75 mg oral Zavegepant 20 mg intranasal	Diclofenac 50 mg subcutaneous Ketorolac 31.5 mg intranasal Ergotamine 2 mg + Caffeine 200 mg oral	Dexketoprofen 50 mg oral Paracetamol 400 mg + Codeine 25 mg oral Butorphanol 1 mg intranasal

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Table 4. Summary of recommendations for the prevention of any migraine (no distinction between episodic and chronic). Rows report strength of recommendations; columns report quality of evidence.

Quality of evidence/ Strength of the recommendation	High	Moderate	Low	Very low
Strong in favor	-	Rimegepant 75 mg every other day, oral Eptinezumab 100 and 300 mg quarterly, intravenous	-	-
Weak in favor	-	-	Candesartan 16 mg oral Propranolol 160 mg oral	Valproate 500, 1000 and 1500 mg oral Bisoprolol 5 and 10 mg oral Metoprolol 200 mg oral

Table 5. Summary of recommendations for the prevention of episodic migraine. Rows report strength of recommendations; columns report quality of evidence.

Quality of evidence/ Strength of the recommendation	High	Moderate	Low	Very low
Strong in favor	Atogepant 60 mg oral Erenumab 70 and 140 mg every four weeks, subcutaneous Fremanezumab 225 mg monthly and 675 quarterly, subcutaneous Galcanezumab 120 mg monthly, subcutaneous	Topiramate 100 and 200 mg oral Eptinezumab 100 and 300 mg quarterly, intravenous	-	-
Weak in favor	-	Amitriptyline 25 mg oral Candesartan 16 mg oral	Topiramate 50 mg oral Lisinopril 20 mg oral Propranolol 160 mg oral	Valproate 750 mg and 1500 mg oral Lamotrigine 50 mg oral Levetiracetam 1000 mg oral

Council (MRC). Consulting and/or advisory boards for AbbVie, Cannovex, Chordate Medical, Eli Lilly, Lundbeck, Sanofi, Teva. Lectures/speaking/educational events: Chordate Medical, MD-Horizonte, Lundbeck, Teva. Manuscript writing/associate editor work: NEJM Journal Watch, Oxford University Press, Quintessence Publishing, Sage Publishing, Springer Healthcare. Data Monitoring Committee: Chordate Medical. Advisory Board: AbbVie, Chordate Medical, Eli Lilly, Lundbeck, Teva.

Board of Trustees of the International Headache Society. Council Member and Treasurer of the British Association for the Study of Headache. Associate Editor for *Cephalalgia*, *Cephalalgia Reports*, *J Headache Pain*, *Frontiers in Pain Research*, *Journal of Oral & Facial Pain* and *Headache*. Stock options for Chordate Medical.

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Table 6. Summary of recommendations for the prevention of chronic migraine. Rows report strength of recommendations; columns report quality of evidence.

Quality of evidence/Strength of the recommendation	High	Moderate	Low	Very low
Strong in favor	OnabotulinumtoxinA (155–195 IU) intramuscular Atogepant 60 mg oral Eptinezumab 100 and 300 mg quarterly, intravenous Fremanezumab 675 mg quarterly, subcutaneous Galcanezumab 120 mg monthly, subcutaneous	Erenumab 70 and 140 mg every four weeks, subcutaneous Fremanezumab 225 mg monthly, subcutaneous	-	-
Weak in favor	-	-	Topiramate 200 mg oral	Topiramate 50 and 100 mg oral

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Table 7. Summary of recommendations for the treatment of acute migraine attacks derived from head-to-head comparison trials.

Better	Worse	Quality of evidence	Strength of the recommendation
Rizatriptan 10 mg	Ibuprofen 400 mg	Low	Weak
Eletriptan 40 mg	Naratriptan 2.5 mg	Moderate	Weak
Eletriptan 40 mg	Sumatriptan 100 mg	High	Strong
Rizatriptan 10 mg	Naratriptan 2.5 mg	Moderate	Weak
Sumatriptan (50 or 85 mg) + naproxen 500	Naproxen 500 mg	Very low	Weak
Paracetamol 500 mg + acetylsalicylic acid 500 mg + caffeine 130 mg	Sumatriptan 50 mg	Very low	Weak
Eletriptan (40 mg or 80 mg)	Ergotamine 2 mg + caffeine 200 mg	Moderate	Strong
Rizatriptan 10 mg	Ergotamine 2 mg + caffeine 200 mg	Very low	Strong
Sumatriptan 100 mg	Ergotamine 2 mg + caffeine 200 mg	Very low	Strong
Frovatriptan 2.5 mg + dexketoprofen 37.5 mg	Frovatriptan 2.5	Moderate	Weak
Promethazine 25 mg + sumatriptan 50 mg	Sumatriptan 50 mg	Moderate	Weak
Sumatriptan (50 mg or 85) + naproxen 500	sumatriptan (50 mg or 85 mg)	Low	Weak
Trimebutine 200 mg + rizatriptan 10 mg	Rizatriptan 10 mg	Low	weak
Paracetamol 1000 mg + rizatriptan 10 mg	Paracetamol 1000 mg	Low	Weak
Calcium carbasalate 900 mg + metoclopramide 10 mg	ergotamine 1 mg + caffeine 100	Very low	Weak

Table 8. Summary of recommendations for the prevention of migraine attacks derived from head-to-head comparison trials.

Population	Better	Worse	Quality of evidence	Strength of the recommendation
Any migraine	Erenumab 70 or 140 mg every four weeks	Topiramate up to 100 mg daily	Low	Strong
Any migraine	Topiramate 50 mg daily	Propranolol 80 mg daily	Very low	Weak
Any migraine	Flunarizine 10 mg daily	Metoprolol 200 mg daily	Low	Weak
Any migraine	Metoprolol 200 mg daily	Acetylsalicylic acid 300 mg daily	Very low	Weak

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