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Evidence-based guidelines for the pharmacological treatment of migraine

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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 Grading of Recommendations, Assessment, Development and Evaluation 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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1. Summary of recommendations

Table 1.1 reports the contents of the guideline. Tables 1.2–1.5 report the summary of all the evidence-based recommendations.

Details on available evidence can be found in each specific section.

2. Guideline methods

Guideline working groups and process

This Guideline was initiated by the Italian Society for the Study of Headaches ('*Società Italiana per lo Studio delle Cefalee*' – SISC) and later continued as a joint guideline

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Table 1.1. Contents of the guideline

Chapter	Title
1	Summary of recommendations
2	Guideline methods
3	Acute treatment
3.1	Non-steroid anti-inflammatory drugs (NSAIDs) and cyclooxygenase 2 (COX2) inhibitors
3.2	Triptans
3.3	Paracetamol (acetaminophen)
3.4	Combination analgesics
3.5	Antiemetics
3.6	Opioids
3.7	Ditans
3.8	Gepants for acute treatment
3.9	Head-to-head comparisons - Acute treatment
4	Preventive treatment
4.1	Antidepressants
4.2	Anti-seizure medications
4.3	Beta blockers
4.4	Calcium channel blockers and other blood pressure-lowering agents
4.5	Botulinum toxin
4.6	Gepants for migraine prevention
4.7	Monoclonal antibodies targeting the CGRP pathway
4.8	Head-to-head comparisons - Preventive treatment

with the International Headache Society (IHS). The SISC Board appointed initial members to form the Guideline Working Group and the IHS added further members. The Guideline Working Group consisted of a chair, a coordination supporting group, internal reviewers, and 19 module subgroups responsible for addressing the different sections of the guideline. One subgroup evaluated the methods, eight the acute treatment of migraine attacks, and seven the preventive treatments. Additionally, the coordination supporting group evaluated head-to-head comparisons of acute and preventive treatments. All subgroups included at least two senior experts in migraine management, defined as physicians with more than 15 years of clinical and research experience in migraine treatment, as verified by the chair and coordination supporting group. The SISC and the IHS Boards were responsible for the selection of senior experts from their respective Societies.

To encompass all the possible pharmacological treatments of migraine, we kept acute and preventive treatments together in one Guideline. Acute and preventive treatments were examined in two different Sections, Section 3 and Section 4, respectively. The final Guideline consists of three parts:

–A full document (the present document);
–A short version for rapid consultation;
–Appendices containing details about literature searches.

To ensure consistency and homogeneity of approach across the groups, a web-based meeting was organized to share the objectives and methodology of the guidelines and to train all researchers involved in the guideline's development. Small groups meetings were held as needed to monitor progress, verify homogeneity of approach across groups, and address any problems encountered during the development process.

The responsibility for study selection, accuracy of extracted data, and data analysis for both placebo-controlled and head-to-head comparative studies was assigned to each group dealing with specific drug classes. The placebo-controlled studies comparisons were assessed in sections dedicated to each specific drug class for the final report. Two additional sections were included to report head-to-head comparisons in acute treatment and prevention, respectively.

The IHS contribution to the guidelines consisted in the addition of an IHS chair to the SISC chair, two IHS members to the internal reviewers' group, and one or two members for each of the 19 SISC subgroups. The IHS members initially revised the literature search performed by the coordination support group and by the SISC groups; afterwards, they performed two updates on the search; finally, they revised the updated manuscripts.

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. Clinically relevant questions were framed using the PICO format (Population, Intervention, Comparator, and Outcomes). An initial set of questions was developed by the SISC chair and coordinating supporting group according to clinical experience and previous guidelines. Additional questions were added based on available evidence. 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.

PICO questions

Clinical questions for evidence-based recommendations were developed according to the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) system as PICO. The PICO format is valuable to clearly define the Population (P), Intervention (I), Comparator (C), and Outcomes (O).

The Population (P) of interest is represented by subjects with migraine. We developed separate PICO questions for episodic and chronic migraine; the group 'any migraine' (no distinction between episodic and chronic) was also considered depending on available data. Intervention (I) was represented by any drug belonging to a class used for the acute or preventive treatment of migraine attacks. Comparators (C) were placebo or active drug(s). Outcomes (O) were different for treatments used for acute and for preventive treatment of migraine attacks and were chosen based on the IHS guidelines for clinical trials for migraine (1–3) because they were rated as important or critical by members of the Guideline Working

Table 1.2. 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

Table 1.3. 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

Groups. For the treatment of acute migraine attack, the following outcomes were considered:

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

Other outcomes such as the absence of the most bothersome symptom at 2 h were not considered as they were measured only in the most recent RCTs.

For preventive treatments, the following outcomes were considered:

Table 1.4. 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

Table 1.5. 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

–persisting monthly headache/migraine days, defined as the residual days reported by subjects in the final period 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);
–≥50% responder rate, defined as the proportions of subjects reporting a ≥50% reduction in monthly headache/migraine days compared with baseline. The ≥50% reduction of monthly attacks was also considered for ≥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 (2,3), 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 groups, interventions, comparators, and outcomes for which the systematic literature search showed the presence of available RCTs.

Literature search

Search of available evidence was performed according to the Cochrane guidelines for systematic reviews of interventions (4) and overviews of reviews (5). 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 (6).

A literature search was performed between 10 and 11 February 2022 for all topics except from antiemetics, which was 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 – namely, non-steroidal anti-inflammatory drugs, triptans, paracetamol, combination analgesics, opioids, ditans, and gepants – and migraine preventive drugs – namely, antidepressants, anti-seizure medications, beta-blockers, calcium channel blockers, blood pressure-lowering medications, botulinum toxin, gepants, and monoclonal antibodies targeting the CGRP pathway. 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. The same search strings were launched in two separate searches. In Search 1, we looked for systematic reviews and meta-analyses, while in Search 2 we looked for RCTs published after the reviews and the meta-analyses retrieved in Search 1. If Search 1 did not allow the retrieval of any systematic reviews or meta-analysis, Search 2 was considered for RCT inclusion since the beginning of indexing of each database. Search 1 was performed at the beginning of the activity, while Search 2 was performed at the beginning and repeated in May 2023 and November 2023. Only published literature was considered for searches. The full search strategies are included in each section of this guideline. Reference management and duplicate removal were performed with EndNote X6®.

Study selection

Study selection was performed by each module subgroup. The selection process was performed in two stages. In Stage 1, systematic reviews and meta-analysis covering the topic of interest were screened to identify eligible studies. In Stage 2, additional RCTs, published after the selected systematic review and meta-analyses were considered for inclusion. In case no systematic reviews and meta-analyses were available, only RCTs were selected.

Stage 1. Each module working subgroup initially received from the coordination supporting group an Excel file containing authors, publication year, title, abstract, and DOI of references retrieved during Search 1 (systematic reviews and meta-analyses) after duplicates were removed. Any further duplicates identified during the study selection process were accounted for in the study selection flowchart. Module subgroups performed the study selection process in two phases, first evaluating titles and abstracts for eligibility, and then evaluating the full text of eligible references for inclusion. Inclusion and exclusion criteria for both phases are reported in Table 2.1. The evaluation process was performed by one rater, with a second rater consulted in case of uncertainty.

Stage 2. Module working subgroups received from the coordination supporting group an Excel file that contained the authors, publication year, title, abstract, and DOI of references retrieved during Search 2 (RCTs) after removing duplicates. To review all the literature that was not included in the selected systematic reviews and meta-analyses, the module working subgroups identified the most recent and comprehensive systematic review or meta-analysis on each pharmacological class and extracted the temporal limit (i.e., the 'until date') of the search. They then evaluated only the studies published after the identified 'until date' following the same evaluation procedure described in Stage 1. The inclusion and exclusion criteria for eligibility and inclusion phase are presented in Table 2.2.

If duplicates were identified during study selection, they were considered and accounted for in the study selection flowchart. Full texts of all RCTs identified in all systematic reviews and meta-analyses included in Stage 1 were evaluated according to the same criteria. Therefore, module subgroups selected the final number of RCTs included in the review. This final number was revised if needed after the literature search updates performed in May 2023 and November 2023.

Data extraction

Utilizing an Excel spreadsheet template, module subgroups extracted the following data for each included study:

- Type of migraine: episodic or chronic or any migraine (no distinction between episodic and chronic) according to the inclusion criteria described in evaluated studies and considering ICHD criteria (7). We considered as separate groups subjects with episodic and chronic migraine when selected studies were specifically aimed to address those groups individually in their primary analyses. In the absence of primary analyses considering episodic and chronic migraine or if it was not possible to individuate those groups according to ICHD criteria, we included the data in the 'any migraine' section;
- Comparison(s): compared drugs, doses, and administration routes;
- Number of subjects: total number and number in each treatment group;

Table 2.1. Inclusion and exclusion criteria for evaluation of references in eligibility and inclusion phases for stage 1

Phase	Inclusion criteria	Exclusion criteria
Eligibility (evaluation of titles and abstracts)	1. Studies meeting all of the following criteria: Systematic review and meta-analysis Including randomized controlled trials Trials performed in patients with migraine Addressing a pharmacological therapy versus placebo or other drugs 2. Abstract not available 3. Abstract not allowing to fully assess eligibility	1. Study design was not a systematic review and meta-analysis 2. The systematic review/meta-analysis did not include studies on migraine 3. The systematic review/meta-analysis did not include studies assessing the outcome of a pharmacological therapy versus placebo or other drugs
Inclusion (evaluation of full texts)	1. Studies meeting all of the following criteria: Systematic review and meta-analysis Including randomized controlled trials 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 systematic review or meta-analysis) 3. Wrong comparison (the systematic review/meta-analysis did not include studies assessing the outcome of a pharmacological therapy versus placebo or other drugs) 4. Wrong population (the systematic review/meta-analysis included studies on other types of headache apart from migraine and did not report separate findings for patients with migraine) 5. Pediatric population (0–18-year-old subjects) 6. Overcome by a more recent systematic review and meta-analysis (i.e., all RCTs included in the systematic review/meta-analysis were also included in another included systematic review/meta-analysis) 7. Wrong outcomes (i.e., the systematic review/meta-analysis did not evaluate any of the outcomes considered for the present guidelines)

Table 2.2. 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 2. Abstract not available 3. 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)	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 9. Wrong outcomes (i.e., the systematic review/meta-analysis did not evaluate any of the outcomes considered for the present guidelines)

–For continuous outcomes: mean and standard deviation or standard error or confidence interval (either 95% or 99%) in each treatment group.

If needed, standard deviations were calculated starting from standard errors or form confidence intervals, using one of the following formulas:

$$\text{Standard deviation} = \sqrt{\text{Standard error}}$$

$$\text{Standard deviation} = \frac{\textit{High limit of 95\% CI} - \textit{mean}}{1.96} * \sqrt{\textit{number of patients}}$$

$$\text{Standard deviation} = \frac{\textit{High limit of 99\% CI} - \textit{mean}}{2.58} * \sqrt{\textit{number of patients}}$$

–For categorical outcomes: number of subjects reporting the outcome in each treatment group. If the required data was not available, the outcome was extracted as reported in the studies. For the outcomes 'persisting monthly migraine days' and 'change in monthly migraine days', assessment time points were retrieved, according to what was reported in the included studies; if these outcomes were reported at different time points, we selected them according to the following priority: 12 weeks, 24 weeks, and others. For the outcomes pain freedom at 2 h and pain relief at 2 h, if outcome data were reported for more than one headache attack, we considered the outcome of the treatment of the first attack described.

If the required data were not available, the outcome was extracted as reported in studies (e.g., outcome of interest expressed as median and not mean).

Data analysis

For each PICO question, all extracted data about outcomes were classified, analyzed, and presented as main evidence or additional evidence as reported below.

Main evidence: it includes results from RCTs with measurable outcomes of interest and reporting a sample size calculation and a study hypothesis for superiority or non-inferiority in the case of comparison between two active principles or an active principle and placebo. For each comparison, data included in this section were meta-analyzed separately for each outcome, introducing, when needed, subgroup analyses to describe the effect of different dosages. Analyses referring to outcomes of interest were considered among main evidence also if those outcomes were secondary outcomes in the included studies, provided that they were pre-specified. To describe all data retrieved in a homogenous way, meta-analyses were conducted also when only one study was available for a comparison and outcome.

Additional evidence: it includes data from RCTs lacking a clear study hypothesis for superiority or non-inferiority or a sample size calculation related to the comparison that is being considered (or, if performed, minimum sample size was not achieved). Data were meta-analyzed with the same procedure adopted for the previous section. This section also includes summaries of data from studies reporting considered outcomes and expressed through indexes not allowing the performance of meta-analyses (e.g., medians or mean without SD).

Meta-analyses were performed using RevMan®, version 5.3. Computed effect sizes were Standardized Mean Difference (SMD) for continuous outcomes and Relative Risk (RR) for categorical outcomes. Pooled effect sizes were computed using the random effect model and expressed with a 95% Confidence Interval (95% CI).

Risk of bias evaluation

The risk of bias of all RCTs was evaluated according to the Cochrane tool (4) and included in the forest plots. This evaluation was performed twice from two different raters of each module working subgroup after a wash-out period of at least 15 days. Disagreements and indecisions were solved by discussion with another member of the module working subgroup. Items included in the risk of bias assessment were the following:

- Random sequence generation (selection bias)
- Allocation concealment (selection bias)
- Blinding of participants and personnel (performance bias)
- Blinding of outcome assessment (detection bias)
- Incomplete outcome data (attrition bias)
- Selective reporting (reporting bias)
- Other bias

Evidence quality rating

The quality of available evidence was then rated according to the Grading of recommendations, Assessment, Development and Evaluation (GRADE) (8) system, which also drove the development of evidence-based recommendations.

The overall quality of evidence for outcomes derived from studies considered in the main evidence was evaluated according to the GRADE methodology and reported in evidence profile tables (5). 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 (e.g., conflicting results between two outcomes described in the same study, availability of only one outcome for a comparison). For the assessment of imprecision, the clinical decision threshold was established as a risk ratio limit of 0.5 to 2.0 (9); thus, if the confidence interval of a RCT was not significant but included those thresholds, the results were considered imprecise.

Imprecision was also considered serious if the numbers of participants included in the RCT were <50 for each arm.

To rate the overall risk of bias in the GRADE evidence profile tables, we used adapted Cochrane criteria as reported in Table 2.3. GRADE tables were built using GradePro®. 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 data included in additional evidence, the quality of evidence was considered by default low and downgraded to very low in the presence of additional limitations. According to the GRADE methodology, we also considered a potential upgrade of the quality of evidence in the case of evidence of large magnitude of the therapeutic effect.

Drafting recommendations

For each PICO question, the coordination supporting group and the chair derived evidence-based recommendations from the main evidence, if available. The additional evidence was used to develop evidence-based recommendations in the absence of the main evidence. For PICO with both main and additional evidence, the overall quality of evidence was derived from the main evidence, but additional evidence was considered to conceptualize the recommendation. Recommendations were issued for each question with available main evidence. For those with only additional evidence, recommendations were issued only if an adequate number of participants (≥50 per each arm of RCTs) were included.

For each recommendation, we provided the quality of evidence and the strength of the recommendation.

Quality of evidence reflects confidence in the estimate as reported above. The strength of a recommendation indicates the extent to which one can be confident that adherence to the recommendation will provide more benefit than harm. Recommendations were rated as "strong" if the addition of further evidence was unlikely to determine a change in the overall result or "weak" if the addition of further evidence was deemed likely to change the overall results. 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. In case of conflicting results (e.g., superiority to placebo in one outcome and neutrality in another outcome), the most precise result – i.e., that with the narrowest confidence interval – was considered.

Expert-based opinions

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 section to provide general concepts on acute treatment and prevention.

Internal review

All data synthesis, evidence-based recommendations, and expert-based opinions were reviewed by four experts (CT, IR, H-CD, ML). The resulting evidence-based recommendations and expert-based opinions were then sent to the entire working group (SISC and IHS) for approval. To be included in the guidelines, statements needed to receive at least 70% approval from the working group. Topics that did not meet the approval threshold were still considered in the document synthesis and discussed in the text.

Table 2.3. Approach for *summary assessments* of the risk of bias for each important outcome (across domains) within and across studies

Risk of bias	Interpretation	Within a study	Across studies
Not serious	Plausible bias unlikely to seriously alter the results.	Low risk of bias for all key domains.	Most information is from studies at low risk of bias.
Serious	Plausible bias that raises some doubt about the results.	Unclear risk of bias for one or more key domains.	Most information is from studies at low or unclear risk of bias.
Very serious	Plausible bias that seriously weakens confidence in the results.	High risk of bias for one or more key domains.	The proportion of information from studies at high risk of bias is sufficient to affect the interpretation of results.

3. Acute treatment

3.1. Non-steroidal anti-inflammatory drugs (NSAIDs) and cycloxygenase 2 (COX2) inhibitors

Introduction

Nonsteroidal anti-inflammatory drugs (NSAIDs) are a class of heterogeneous compounds that largely share therapeutic and adverse effects. The class includes acetylated salicylates (aspirin), non-acetylated salicylates (diflunisal, salsalate), propionic acids (naproxen, ibuprofen), acetic acids (diclofenac, indomethacin), enolic acids (meloxicam, piroxicam), anthranilic acids (meclofenamate, mefenamic acid), naphthylalanine (nabumetone), and diaryl heterocyclic compounds (celecoxib, rofecoxib, parecoxib, etoricoxib, and lumiracoxib) (10).

NSAIDs are approved for use as antipyretic, anti-inflammatory, and analgesic agents.

The main therapeutic effects of NSAIDs derive from their ability to inhibit the prostaglandin synthase enzymes known as cycloxygenases (COXs) (10). There are two forms of COXs, COX1, expressed constitutively in most cells and COX2, which is induced by cytokines, shear stress and tumor promoters (10). COX1 is expressed as the dominant constitutive form in gastric epithelial cells and is considered as the major source of cytoprotective prostaglandin production (10,11).

Traditional NSAIDs inhibit both COX types and are believed to interfere with the homeostatic functions of the constitutively expressed COX1. NSAIDs gastrointestinal (GI) toxicity is related to the inhibition of COX1 and subsequent decrease in GI protection (11).

Aspirin irreversibly inhibits the activity of COXs and the duration of its effects is related to the turnover of COXs in different tissues. For example, platelets are anucleate and have a reduced ability to synthesize proteins, therefore COX1 inhibition lasts the platelet lifetime (10).

When used as general analgesics in non-migraine pain, both unselective (NSAIDs) and selective COX-2 inhibitors (Coxibs) may be less effective than opioids, but lack the opioid adverse effect of depressing the respiratory centers and have less potential for physical dependence (10). These drugs are particularly effective when inflammation has caused peripheral and or central sensitization of pain perception and this explains their usefulness in migraine attack therapy (10).

It is probable that the analgesic and anti-inflammatory actions of NSAIDs are not limited to COX inhibition. At higher concentrations NSAIDS are known to reduce the production of superoxide radicals, decrease NO synthase and pro-inflammatory cytokines, and modify lymphocyte activities *in vitro* (10).

Experimental findings suggest that celecoxib-mediated COX2 inhibition reduces the intensity of migraine headache and potentially terminates an attack via the attenuation of dural macrophages' activation and arterial dilatation outside the blood-brain barrier, and pial macrophages' activation inside the blood-brain barrier (12).

Compared to other NSAIDs, indomethacin may be a more potent vasoconstrictor, that more consistently reduces cerebral blood flow (CBF) and inhibits carbon dioxide (CO2) reactivity (13). In addition, indomethacin reduces cerebrospinal fluid pressure (14).

NSAIDs side effects consist mainly in gastrointestinal adverse events (from gastric pain to gastric or duodenal ulcers), which are mostly due to COX1 inhibition and the Coxibs were designed to reduce the risk of GI side effects, due to their selective inhibition of COX2 (10).

Since the late nineteenth century with the introduction of synthetic acetylsalicylic acid, NSAIDs have been largely used for the acute treatment of migraine – at least in attacks of mild-to-moderate intensity. NSAIDs have been recommended as first-line drugs, particularly for attacks of mild-to-moderate intensity, being the most commonly used analgesic agents worldwide (15–18).

Section-specific methods

This section followed the general procedure to develop this guideline.

Search strings for the guideline on NSAIDs for systematic review/meta-analysis and for additional RCTs are reported in Online Appendix 3.1.1.

Results

Overall, we retrieved 1346 references from searching for systematic reviews and meta-analyses. After duplicate removal and screening stages, we included seven systematic reviews and meta-analyses (19–25) that were considered as sources of RCTs. After analyzing the full texts of these RCTs, we included 17 of them in the quantitative synthesis (26–42) (Figure 3.1.1).

Overall, we retrieved 7973 references from searching for RCTs and after removing duplicates we had 7689 references to analyze. However, considering the most recent included meta-analysis on the topic, the analysis of additional RCTs was performed for studies published since 2010 (31 references). We finally included two additional RCTs (43,44). From the literature search update performed in May 2023, we retrieved 534 references. Further 38 references were retrieved from the November 2023 update. We included one study from this updated search (45) (Figure 3.1.2).

Overall, 20 studies were included in the data synthesis to develop the evidence-based guideline. All the studies reported a comparison between an active drug and placebo and were presented in this section. Eight RCTs also included

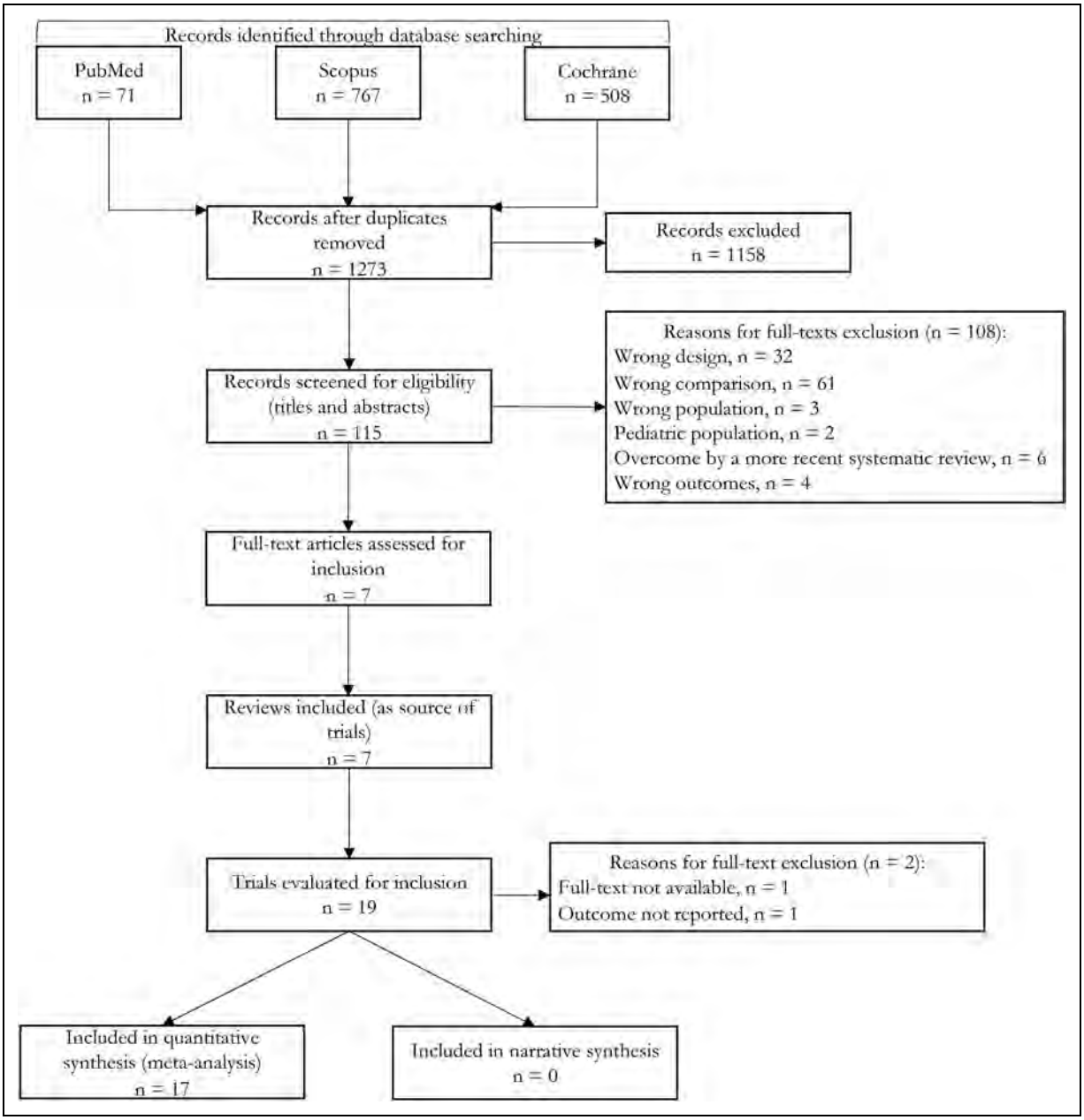


Figure 3.1.1. Meta-analysis selection flow-chart - non-steroidal anti-inflammatory drugs and COX2 inhibitors.

head-to-head comparisons (26,27,29,30,37,38,41,44) and were included in Section 3.9.

Acetylsalicylic acid (Aspirin)

PICO 3.1.1. In subjects with migraine, is acetylsalicylic acid superior to placebo in the acute treatment of migraine attacks (outcomes: pain freedom at 2 h, pain relief at 2 h)?

Main evidence. We found three RCTs (29,33,34) addressing oral acetylsalicylic acid 1000 mg compared to placebo in the treatment of acute migraine attack that met the criteria to be included in main evidence (Figures 3.1.3 and 3.1.4).

The pooled analysis showed the superiority of oral acetylsalicylic acid over placebo considering the outcomes pain freedom at 2 h (Figure 3.1.3) and pain relief at 2 h (Figure 3.1.4). The quality of evidence for both outcomes was considered moderate (Table 3.1.1).

Additional evidence. We found three RCTs (26,30,36) addressing oral acetylsalicylic acid 900 mg and 1000 mg

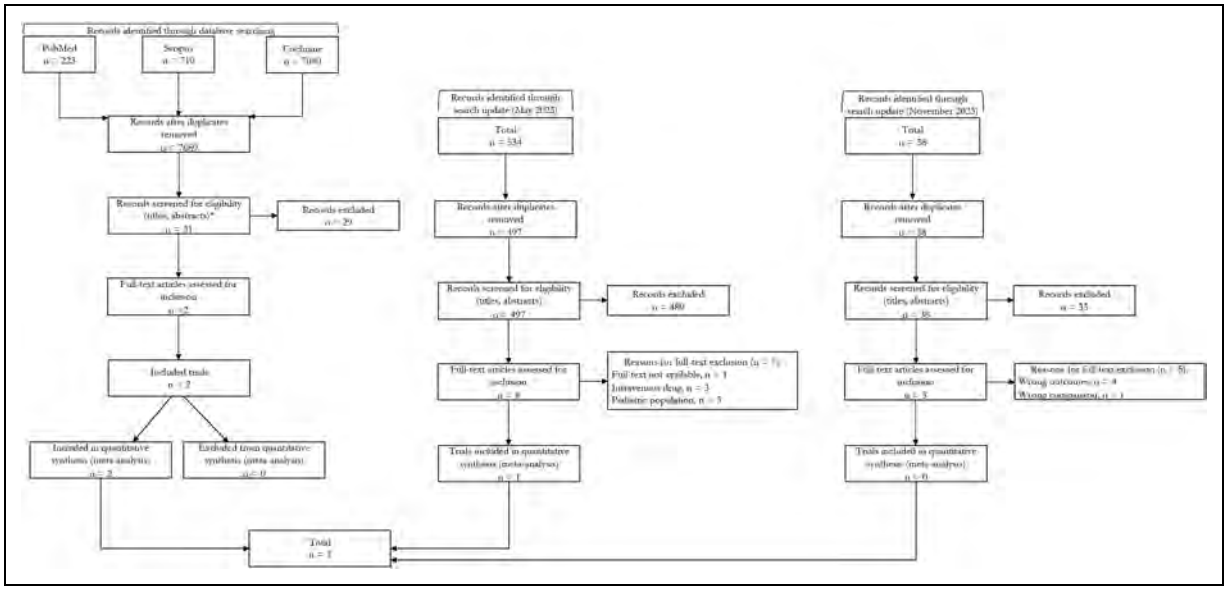


Figure 3.1.2. RCTs selection flow-chart. *trials published since 2010 were screened.

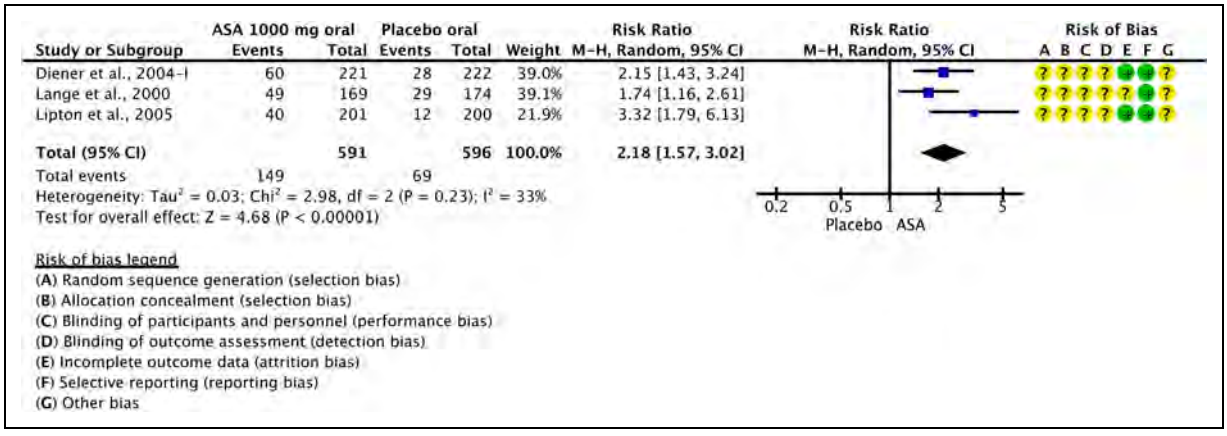


Figure 3.1.3. Forest plot showing the comparison between oral acetylsalicylic acid 1000 mg and oral placebo for the outcome pain freedom at 2 h.

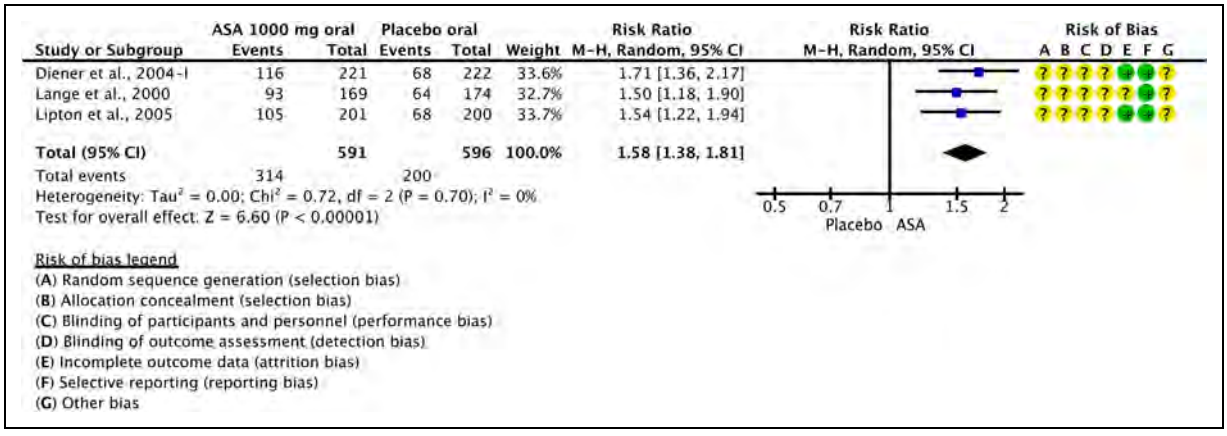


Figure 3.1.4. Forest plot showing the comparison between oral acetylsalicylic acid 1000 mg and oral placebo for the outcome pain relief at 2 h.

Table 3.1.1. GRADE evidence profile table for oral acetylsalicylic acid 1000mg versus oral placebo in patients with migraine

Certainty assessment							№ of patients		Effect			
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Acetylsalicylic acid	Placebo	Relative (95% CI)	Absolute (95% CI)	Quality	Importance
Pain freedom at 2 h – Oral Acetylsalicylic acid 1000mg vs oral Placebo												
3	RCTs	Serious	Not serious	Not serious	Not serious	None	149/591 (25.2%)	69/596 (12.1%)	**RR 2.18** (1.57 to 3.02)	**137 more per 1000** (from 66 more to 234 more)	⊕⊕⊕⊖ Moderate	CRITICAL
Pain relief at 2 h – Oral Acetylsalicylic acid 1000mg vs oral Placebo												
3	RCTs	Serious	Not serious	Not serious	Not serious	None	314/591 (53.1%)	200/596 (33.6%)	**RR 1.58** (1.38 to 1.81)	**195 more per 1000** (from 128 more to 272 more)	⊕⊕⊕⊖ Moderate	CRITICAL

compared to oral placebo in the acute treatment of migraine that did not meet the pre-defined criteria to be included in main evidence. The quality of evidence was considered very low (Figures 3.1.5 and 3.1.6).

The pooled analysis showed the superiority of oral acetylsalicylic acid 1000 mg over oral placebo considering the outcomes pain freedom at 2 h (Figure 3.1.5) and pain relief at 2 h (Figure 3.1.6). The 900 mg oral acetylsalicylic acid dose reached statistical significance only for pain relief.

Evidence-based recommendation for PICO 3.1.1

In subjects with migraine, we recommend oral acetylsalicylic acid 1000 mg for the acute treatment of migraine attacks.
Quality of evidence: Moderate ⊕⊕⊕⊖
Strength of the recommendation: Strong (↑↑).

Safety and tolerability of NSAIDs. NSAIDs mechanism of action (COX1 and COX2 inhibition - see introduction section) is responsible for both effectiveness and adverse effects of this pharmaceutical class. Here we report a general discussion about NSAIDs adverse effects (AE). We will also report some AEs specific to each drug.

Gastrointestinal complaints are the most frequent AEs to NSAIDs and include nausea, vomiting, and dyspepsia. Hypersensitivity to NSAIDs represents one of the major concerns in the use of those drugs, also because allergy to one of these drugs compromises the use of the others by possibly leading to anaphylactic reactions. Other important NSAIDs adverse effects (often therapeutically used) are a major risk of bleeding, especially gastrointestinal bleeding, due to their antiplatelet activity. Renal adverse effects have also been reported in patients with pre-existing renal dysfunction, as have cardiovascular adverse effects (thromboembolic disease, atrial fibrillation) and, less commonly, hepatic damages.

Warnings and Contraindications: Hypersensitivity to NSAIDs and documentation of allergenic cross-reactivity for salicylates, gastrointestinal bleeding history, liver disease, blood clotting disorder. Aspirin must be avoided in pregnant women from 30 weeks to delivery due to risk of premature closure of fetal ductus arteriosus.

Risk of medication overuse (MOH): although to a lesser extent than other painkillers, NSAIDs consumption represents a risk factor for MOH. For this drug class MOH is defined by use on at least 15 days per month for at least three months (7).

Safety and tolerability of acetylsalicylic acid. Warnings and contraindications: No specific data is available from analyzed studies. In general, acetylsalicylic acid is contraindicated in people allergic to ibuprofen – due to

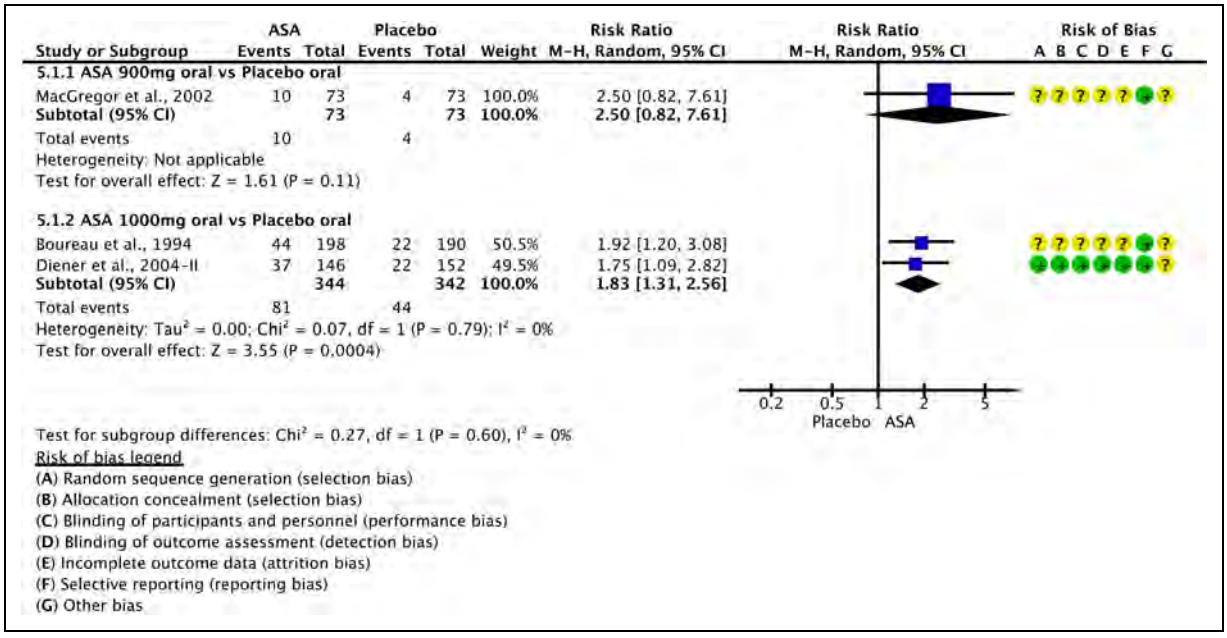


Figure 3.1.5. Forest plot showing the comparison between oral acetylsalicylic acid 900 mg or 1000 mg and oral placebo for the outcome pain freedom at 2 h.

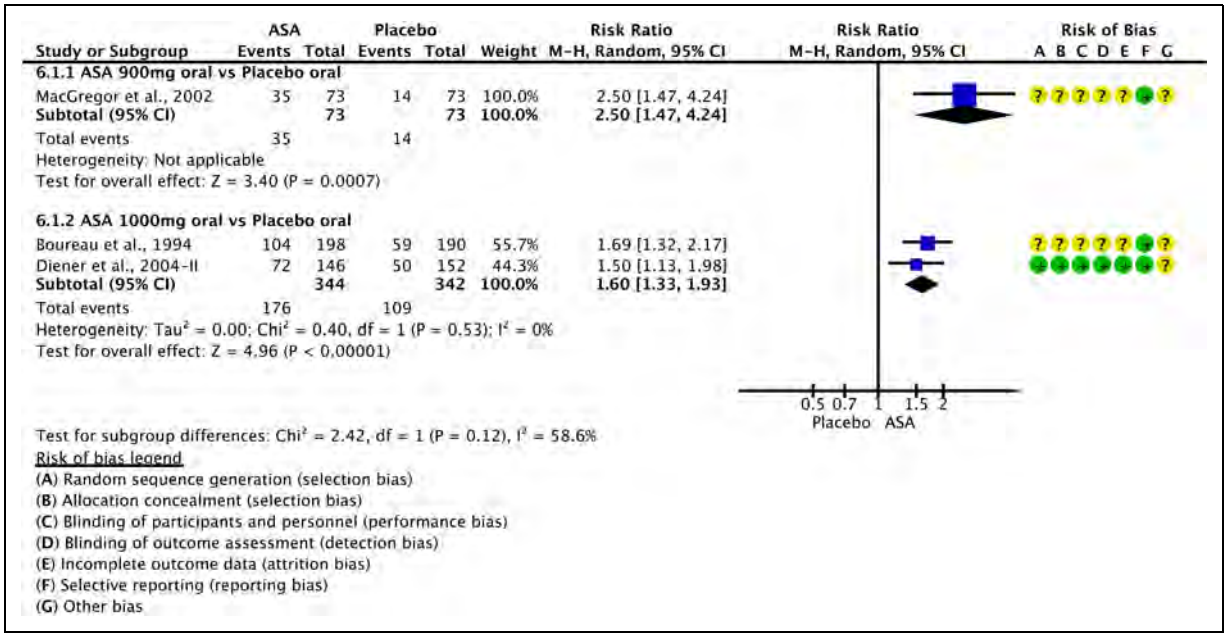


Figure 3.1.6. Forest plot showing the comparison between oral acetylsalicylic acid 900 mg or 1000 mg and oral placebo for the outcome pain relief at 2 h.

cross-reactivity – in patients with asthma or bronchospasm associated with NSAIDs, in patients with peptic ulcer disease or gastritis – due to the increased risk for gastrointestinal bleeding – and in patients with inborn or acquired coagulopathies (46). Acetylsalicylic acid can also trigger intravascular hemolytic anemia in patients with glucose-6-phosphate dehydrogenase deficiency (46). In children with viral infections, the use of acetylsalicylic acid should be avoided to prevent Reye syndrome (47,48).

Serious safety concerns: half of the analyzed studies reported anecdotal serious events, including renal colic, severe abdominal pain, severe nausea, and urticaria.

Tolerability: gastrointestinal complaints were the most frequent AEs. In the examined studies, we found no differences in tolerability and adverse effects between 900 mg and 1000 mg dosage.

Dexketoprofen trometamol

PICO 3.1.2. In subjects with migraine, is oral dexketoprofen trometamol superior to oral placebo in the acute treatment of migraine attacks (outcomes: pain freedom at 2 h, pain relief at 2 h)?

Main evidence. None.

Additional evidence. We found one RCT (42) addressing oral dexketoprofen trometamol 25–50 mg compared to oral placebo in the acute treatment of migraine that did not meet the criteria to be included in the main evidence. The quality of evidence was considered very low (Figures 3.1.7 and 3.1.8).

The study showed superiority of oral dexketoprofen trometamol 50 mg over oral placebo considering the outcomes pain freedom at 2 h (Figure 3.1.7) and pain relief at 2 h (Figure 3.1.8). The benefits of the 25 mg dosing were not proven for the outcome pain freedom at 2 h.

We found one RCT (42) addressing oral dexketoprofen trometamol 25 mg compared to oral dexketoprofen trometamol 50 mg in the acute treatment of migraine that did not meet the criteria to be included in main evidence. The overall risk of bias was considered unclear and the quality of evidence very low (Figures 3.1.9 and 3.1.10).

The study did not show a significant difference between oral dexketoprofen trometamol 50 mg and dexketoprofen 25 mg considering the outcomes pain freedom at 2 h (Figure 3.1.9) and pain relief at 2 h (Figure 3.1.10).

Evidence-based recommendation for PICO 3.1.2

In subjects with migraine, we suggest oral dexketoprofen trometamol 50 mg for the acute treatment of migraine attacks. There is uncertain evidence of the efficacy of the 25 mg dose of oral dexketoprofen.
Quality of evidence: Very low (⊕⊖⊖⊖).
Strength of the recommendation: Weak (↑)

Safety and tolerability of dexketoprofen trometamol. Warnings and contraindications: No data is available from analyzed study except for patients with hypersensitivity to NSAIDs. Overall, contraindications and warnings for dexketoprofen follow the same remarks for the class of NSAIDs (see above).

Serious safety concerns: No serious adverse events reported in the available RCTs.

Tolerability: No significant differences between treatments were found for frequency of AEs. Gastrointestinal complaints were the most frequently reported AEs which is in line with the overall tolerability issues of NSAIDs.

Diclofenac

PICO 3.1.3. In subjects with migraine, is diclofenac superior to placebo in the acute treatment of migraine attacks (outcomes: pain freedom at 2 h, pain relief at 2 h)?

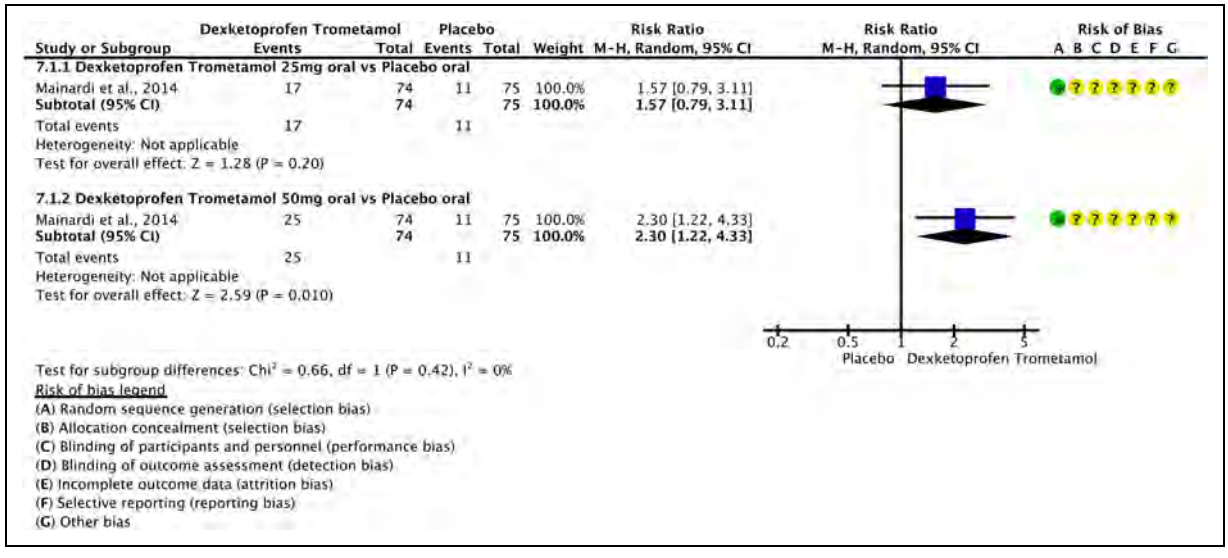


Figure 3.1.7. Forest plot showing the comparison between oral dexketoprofen trometamol 25 mg or dexketoprofen trometamol 50 mg and oral placebo for the outcome pain freedom at 2 h.

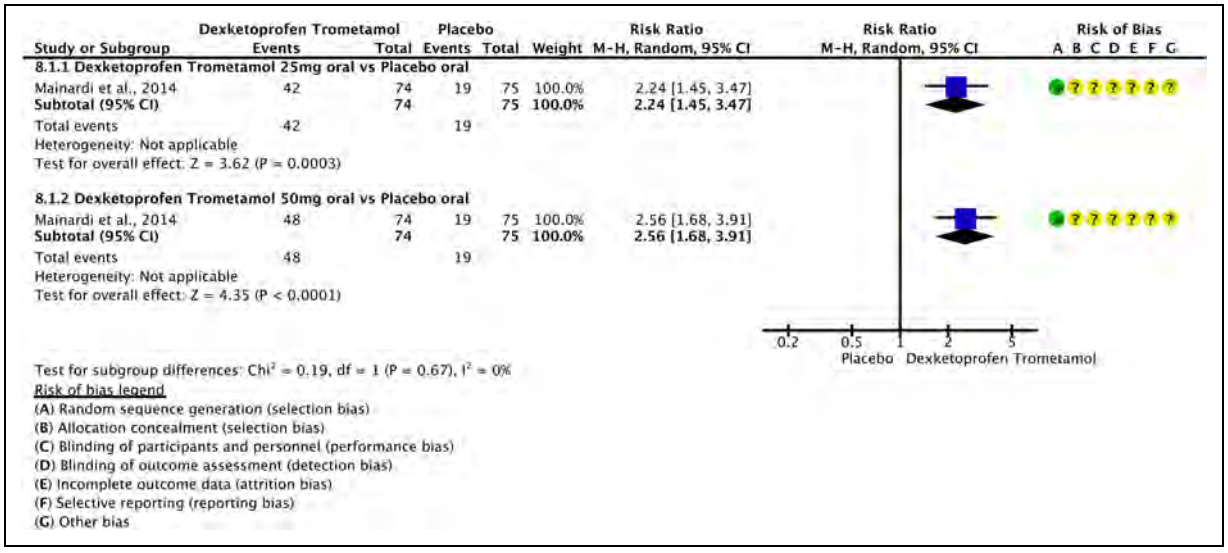


Figure 3.1.8. Forest plot showing the comparison between oral dexketoprofen trometamol 25 mg or dexketoprofen trometamol 50 mg and oral placebo for the outcome pain relief at 2 h.

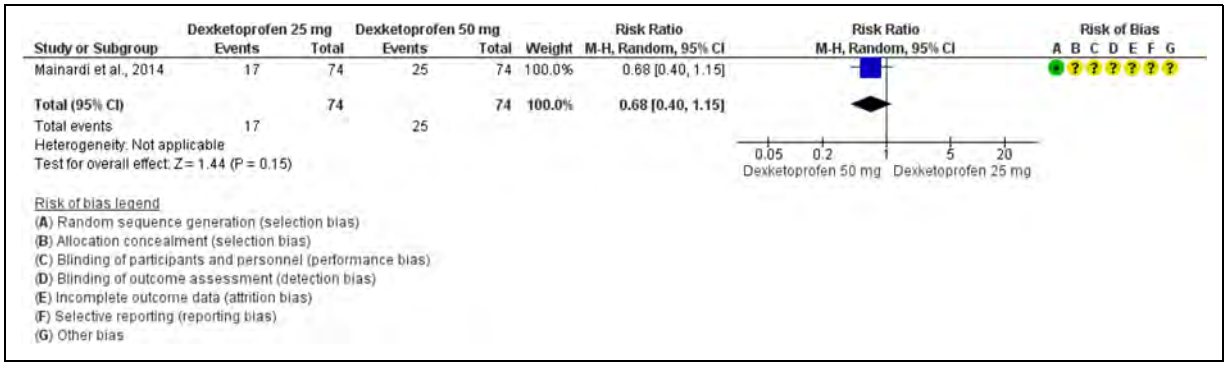


Figure 3.1.9. Forest plot showing the comparison between oral dexketoprofen trometamol 25 mg and oral dexketoprofen trometamol 50 mg for the outcome pain free at 2 h.

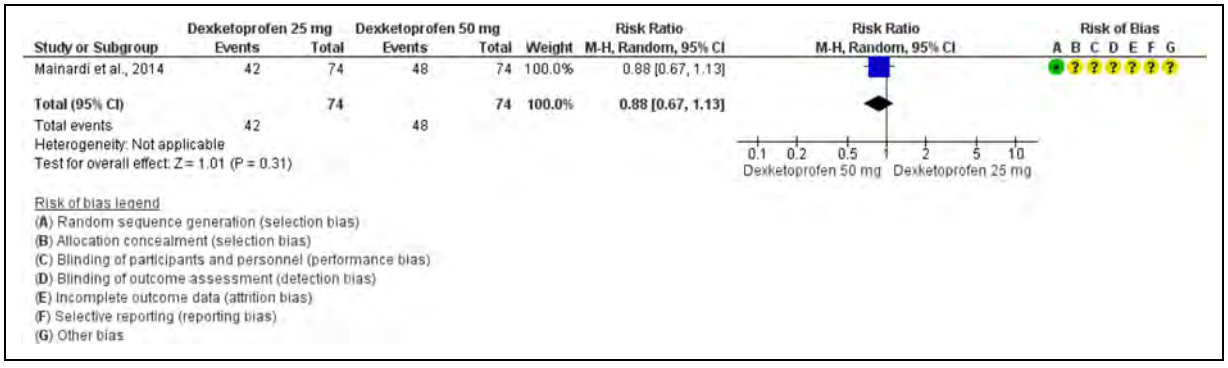


Figure 3.1.10. Forest plot showing the comparison between oral dexketoprofen trometamol 25 mg and oral dexketoprofen trometamol 50 mg for the outcome pain relief at 2 h.

Main evidence. We found two RCTs (31,35) addressing diclofenac potassium 50 mg orally dispersible tablets (ODTs) compared to placebo and one RCT (45) addressing subcutaneous diclofenac sodium compared to subcutaneous placebo in the acute treatment of migraine. All the RCTs met the criteria for main evidence.

The pooled analysis showed benefits of oral diclofenac potassium 50 mg over placebo considering the outcomes pain freedom at 2 h (Figure 3.1.11) and pain relief at 2 h (Figure 3.1.12). Subcutaneous diclofenac sodium was superior to subcutaneous placebo considering the outcome pain relief at 2 h (Figure 3.1.12). The quality of evidence for both outcomes was considered moderate (Table 3.1.2).

Additional evidence. None.

Evidence-based recommendations for PICO 3.1.3

In subjects with migraine, we recommend oral diclofenac potassium 50 mg (tablets or solution) for the acute treatment of migraine attacks.
Quality of evidence: Moderate ⊕⊕⊕⊖
Strength of the recommendation: Strong (↑↑)
In subjects with migraine, we recommend subcutaneous diclofenac sodium 50 mg for the acute treatment of migraine attacks.
Quality of evidence: Low ⊕⊕⊖⊖
Strength of the recommendation: Weak (↑)

Safety and tolerability of diclofenac. Warnings and contraindications: No data is available from analyzed studies. It is important to underline that among NSAIDs, diclofenac is frequently responsible for hepatic and cardiac adverse events (47,49,50). Other warnings and contraindications for diclofenac follow the overall indications that are valid for all NSAIDS (see above).

Serious safety concerns: No serious adverse events were reported in the available RCTs.

Tolerability: Gastrointestinal complaints were the most frequent AEs reported in the available RCTs, including nausea, vomiting, diarrhea, dyspepsia, and abdominal pain. Neurological and psychiatric effects were also reported with no differences between diclofenac and placebo - including nervousness, disorientation, anxiety, confusion, déjà-vu, insomnia, agitation, and restlessness.

Ibuprofen

PICO 3.1.4. In subjects with migraine, is ibuprofen superior to placebo in the acute treatment of migraine attacks (outcomes: pain freedom at 2 h, pain relief at 2 h)?

Main evidence. We found six RCTs (28,30,32,37–39) addressing oral ibuprofen 200 mg, 400 mg or 600 mg as

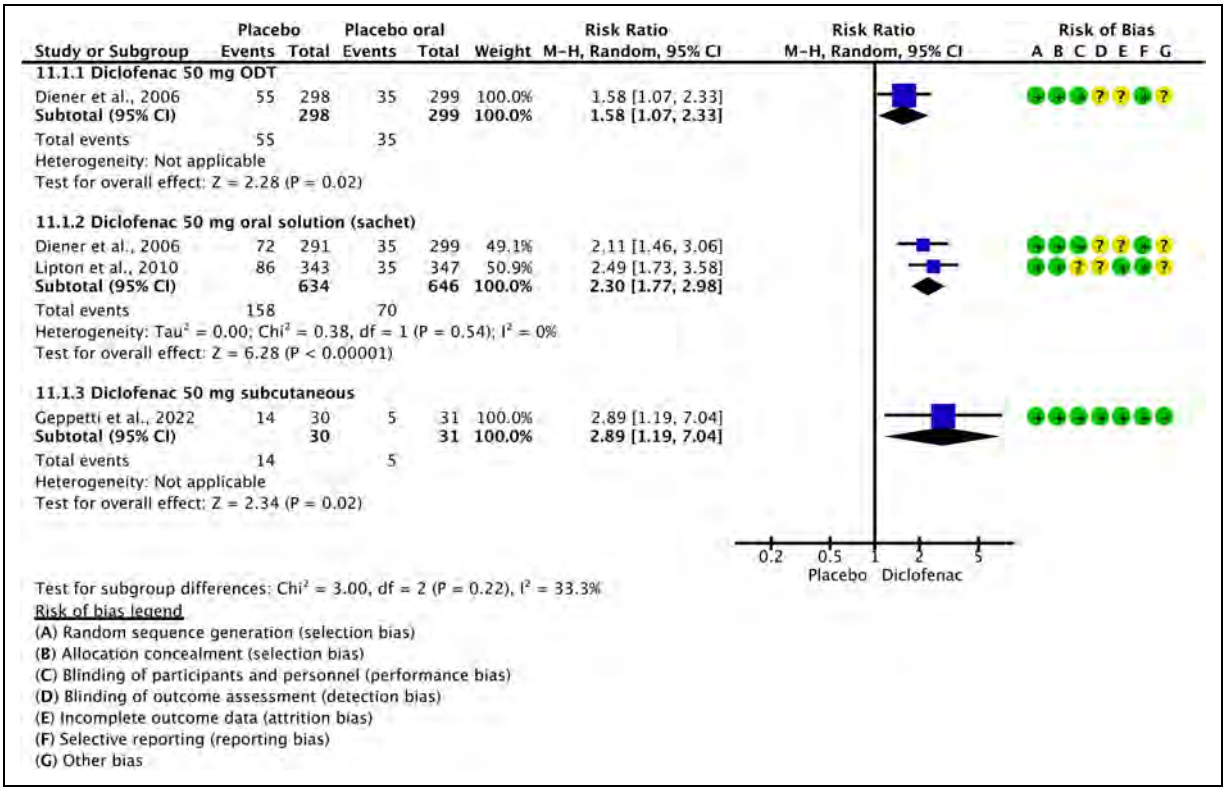


Figure 3.1.11. Forest plot showing the comparison between diclofenac and placebo for the outcome pain freedom at 2 h.

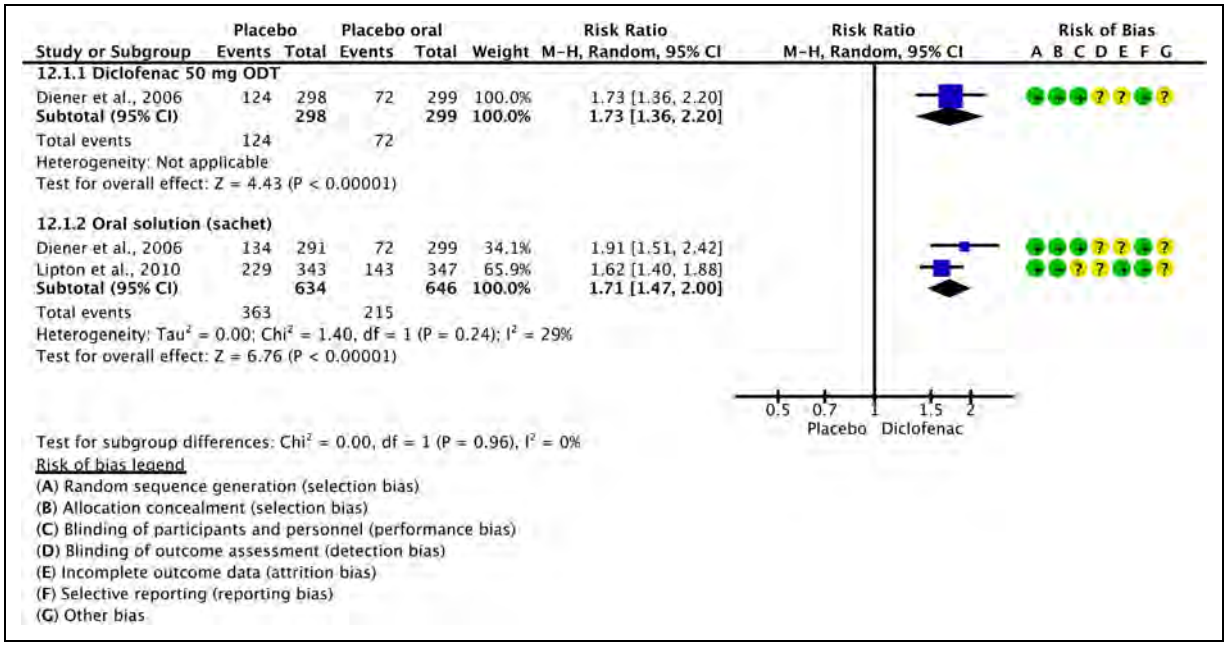


Figure 3.1.12. Forest plot showing the comparison between diclofenac and placebo for the outcome pain relief at 2 h.

compared to placebo in the treatment of acute migraine attack that met the criteria to be included in main evidence.

The pooled analysis showed benefits of ibuprofen 200 mg, 400 mg and 600 mg over placebo considering the outcomes of pain freedom at 2 h (Figure 3.1.13) and pain relief at 2 h (Figure 3.1.14). The quality of evidence for both outcomes was considered moderate (Table 3.1.3).

We found two RCTs (28,32) comparing different dosages of ibuprofen (200 mg, 400 mg, and 600 mg) that met the criteria for main evidence. The pooled analyses did not show significant differences among the different dosages of the drug when considering the outcomes of pain freedom at 2 h and pain relief at 2 h (Figure 3.1.15–Figure 3.1.20). The quality of evidence for all comparisons and both outcomes was considered moderate or low (Table 3.1.4).

Additional evidence. None.

Evidence-based recommendation for PICO 3.1.4

In subjects with migraine, we recommend oral ibuprofen 200–400–600 mg for the acute treatment of migraine attacks.
Quality of evidence: Low ⊕⊕⊖⊖
Strength of the recommendation: Strong (↑↑).

Safety and tolerability of ibuprofen. Warnings and contraindications: No data is available from the analyzed studies. The warnings and contraindications of ibuprofen follow the general indications for all NSAIDs (see above).

Serious safety concerns: Only one analyzed study reported a serious AE in one patient, namely duodenal ulcer (30).

Tolerability: No significant differences between treatments were found for frequency of AEs. Gastrointestinal complaints were the most frequent AE reported, including nausea, dyspepsia, and gastric discomfort. Other reported AEs were dizziness, somnolence, and dry mouth.

Ketorolac

PICO 3.1.5. In subjects with migraine, is ketorolac superior to placebo in the acute treatment of migraine attacks (outcomes: pain freedom at 2 h, pain relief at 2 h)?

Main evidence. We found one RCT (44) addressing ketorolac 31.5 mg nasal spray as compared to placebo in the acute treatment of migraine that met the criteria for main evidence.

The study showed benefits of ketorolac 31.5 mg nasal spray over placebo considering the outcomes of pain freedom at 2 h (Figure 3.1.21) and pain relief at 2 h (Figure 3.1.22). The quality of evidence for both outcomes was considered moderate (Table 3.1.5).

Additional evidence. None.

Evidence-based recommendation for PICO 3.1.5

In subjects with migraine, we suggest ketorolac 31.5 mg nasal spray for the acute treatment of migraine attacks.
Quality of evidence: Low ⊕⊕⊖⊖
Strength of the recommendation: Weak (↑).

Table 3.1.2. GRADE evidence profile table for diclofenac versus placebo in patients with migraine

Certainty assessment							№ of patients		Effect			
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Diclofenac	Placebo	Relative (95% CI)	Absolute (95% CI)	Quality	Importance
Pain freedom at 2 h - Diclofenac potassium 50 mg oral tablet versus placebo oral												
1	RCT	Not serious	Not applicable[a]	Not serious	Not serious	None	55/298 (18.5%)	35/299 (11.7%)	RR 1.58 (1.07 to 2.33)	68 more per 1000 (from 8 more to 156 more)	⊕⊕⊕⊖ Moderate	CRITICAL
Pain freedom at 2 h - Diclofenac potassium 50 mg oral solution (sachet) versus placebo oral												
2	RCT	Not serious	Not serious	Not serious	Not serious	None	158/634 (24.9%)	70/646 (10.8%)	RR 2.30 (1.77 to 2.98)	141 more per 1000 (from 83 more to 215 more)	⊕⊕⊕⊕ High	CRITICAL
Pain freedom at 2 h - Diclofenac sodium 50 mg subcutaneous versus Placebo subcutaneous												
1	RCT	Not serious	Not applicable[a]	Not serious	Serious[b]	None	14/30 (46.7%)	5/31 (16.1%)	RR 2.89 (1.19 to 7.04)	305 more per 1000 (from 31 more to 974 more)	⊕⊕⊖⊖ Low	CRITICAL
Pain relief at 2 h - Diclofenac potassium 50 mg oral tablet versus Placebo oral												
1	RCT	Not serious	Not applicable[a]	Not serious	Not serious	None	124/298 (41.6%)	72/299 (24.1%)	RR 1.73 (1.36 to 2.20)	176 more per 1.000 (from 87 more to 289 more)	⊕⊕⊕⊖ Moderate	CRITICAL
Pain relief at 2 h - Diclofenac potassium 50 mg oral solution (sachet) versus Placebo oral												
2	RCT	Not serious	Not serious	Not serious	Not serious	None	363/634 (57.3%)	215/646 (33.3%)	RR 1.71 (1.47 to 2.00)	236 more per 1.000 (from 156 more to 333 more)	⊕⊕⊕⊕ High	CRITICAL

[a]Only one trial; [b]low numbers of patients.

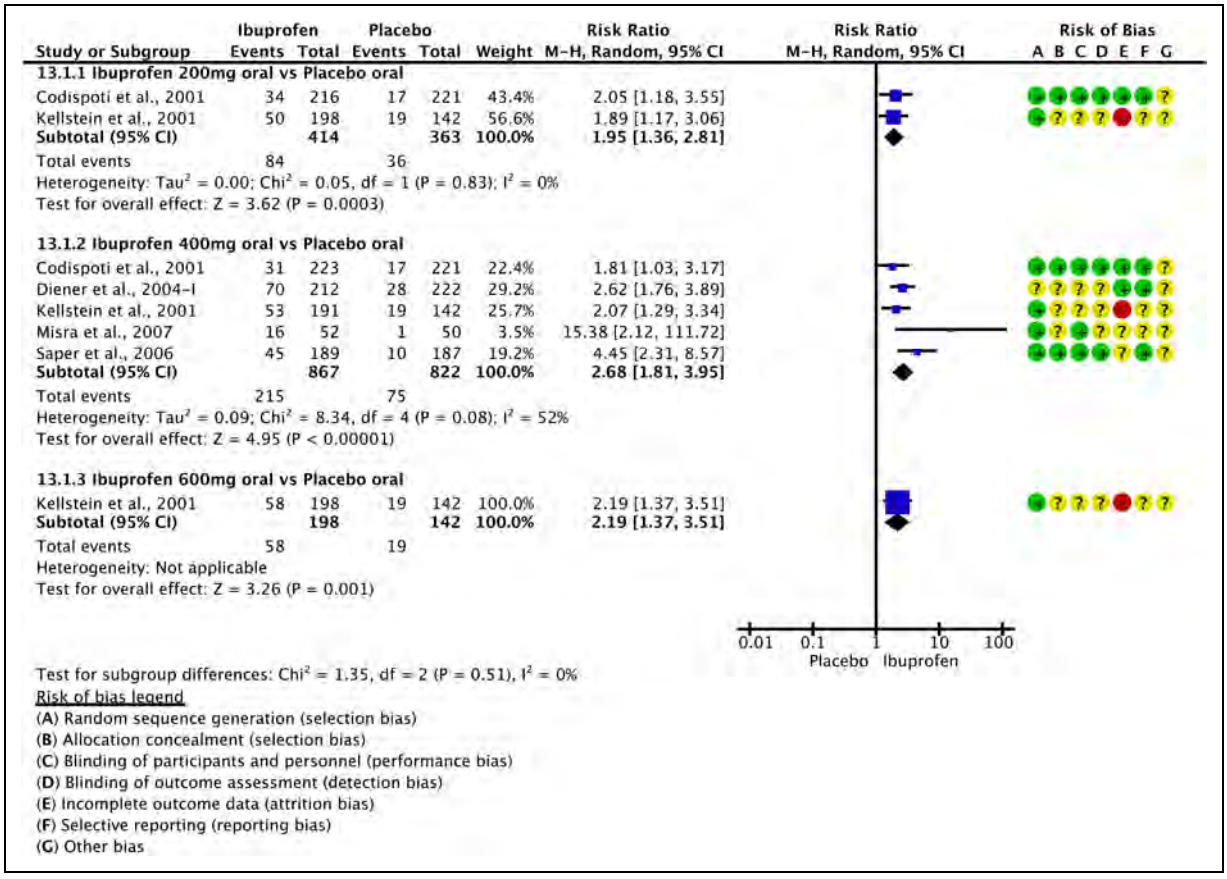


Figure 3.1.13. Forest plot showing the comparison between oral ibuprofen 200–400–600 mg and placebo for the outcome pain freedom at 2 h.

Safety and tolerability of ketorolac. Warnings and contraindications: No data is available from the analyzed study. Ketorolac follows the same warnings and contraindications that are valid for all NSAIDs (see above).

Serious safety concerns: No serious adverse events were reported in the available RCT.

Tolerability: The most common AEs reported by participants treated with ketorolac nasal spray were nasal or throat burning, unusual taste, nasal discomfort, fatigue, dizziness, nausea, and rash.

Naproxen

PICO 3.1.6. In subjects with migraine, is naproxen superior to placebo in the acute treatment of migraine attacks (outcomes: pain freedom at 2 h, pain relief at 2 h)?

Main evidence. None.

Additional evidence. We found three RCTs (27,41) addressing oral naproxen 500–825 mg as compared to placebo in the treatment of acute migraine attack that did not meet the criteria to be included in main evidence. We point out that one RCT (27) reported data from two different studies. The overall risk of bias was considered unclear and the quality of evidence very low (Figures 3.1.23 and 3.1.24).

The pooled analysis showed benefits of naproxen 500 mg and 825 mg over placebo considering the outcomes of pain freedom at 2 h (Figure 3.1.23) and pain relief at 2 h (Figure 3.1.24).

Evidence-based recommendation for PICO 3.1.6

In subjects with migraine, we recommend oral naproxen 500 mg or 825 mg for the acute treatment of migraine attacks.
Quality of evidence: Very low (⊕⊖⊖⊖).
Strength of the recommendation: Strong (↑↑).

Safety and tolerability of naproxen. Warnings and contraindications: No data is available from the analyzed studies. Naproxen follows the same warnings and contraindications that apply to all NSAIDs (see above).

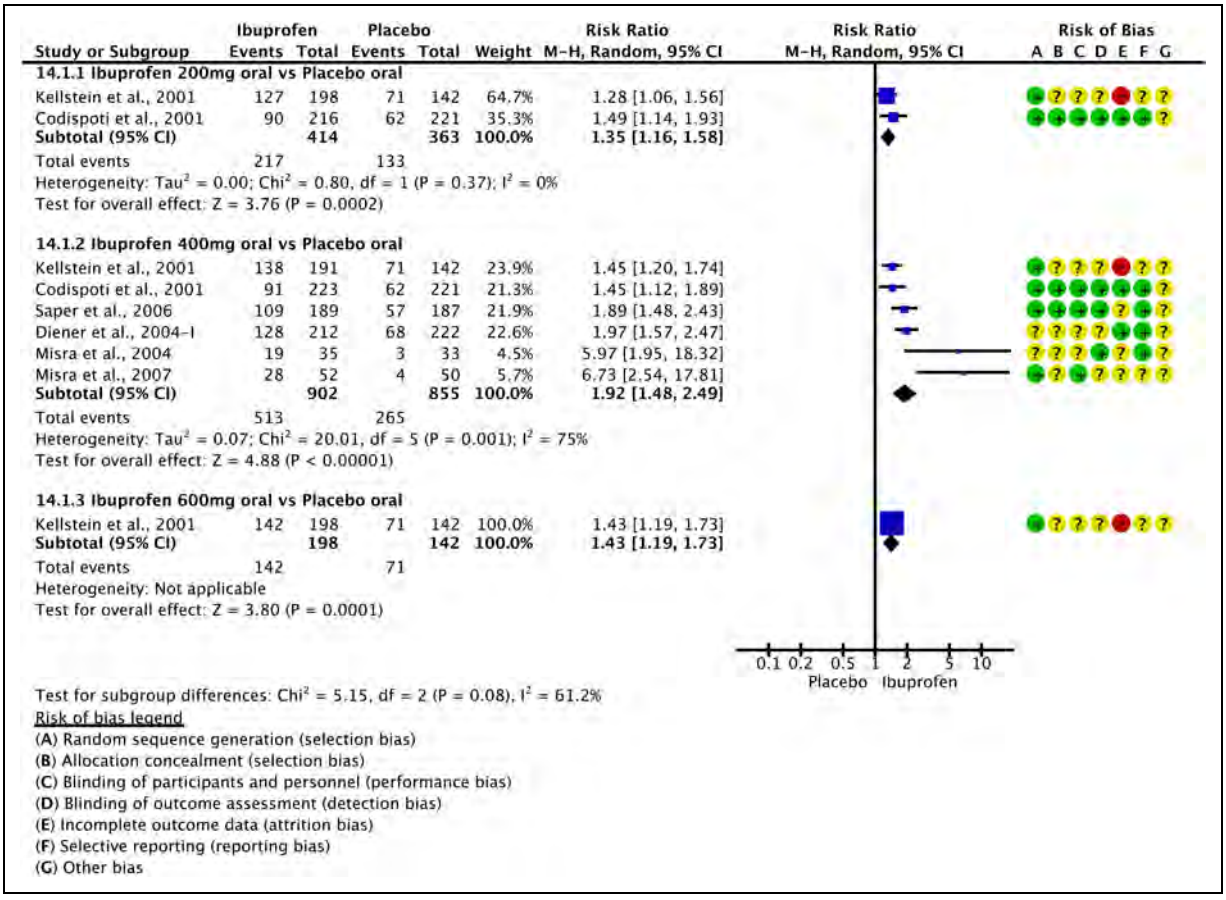


Figure 3.1.14. Forest plot showing the comparison between oral ibuprofen 200–400–600 mg and placebo for the outcome pain relief at 2 h.

Serious safety concerns: No serious adverse events were reported in the available RCTs.

Tolerability: In the available RCTs we found no significant differences between treatments for frequency of adverse events. Gastrointestinal complaints were the most frequently reported event, including nausea, diarrhea, and dyspepsia. Other reported adverse events were dizziness, dry mouth, paresthesia, somnolence, chest tightness, and tinnitus. Naproxen might have a more favorable cardiovascular risk profile compared to coxibs, ibuprofen, and diclofenac (51).

Celecoxib

PICO 3.1.7. In subjects with migraine, is celecoxib superior to placebo in the acute treatment of migraine attacks (outcomes: pain freedom at 2 h, pain relief at 2 h)?

Main evidence. We found one RCT (43) addressing oral celecoxib 120 mg compared to placebo in the acute treatment of migraine attacks that met the criteria to be included in main evidence.

The study showed benefits of celecoxib 120 mg over placebo considering the outcomes of pain freedom at 2 h (Figure 3.1.25) and pain relief at 2 h (Figure 3.1.26). The quality of evidence for both outcomes was considered moderate (Table 3.1.6).

Additional evidence. None.

Evidence-based recommendation for PICO 3.1.7

In subjects with migraine, we recommend oral celecoxib 120 mg for the acute treatment of migraine attacks.
Quality of evidence: Moderate ⊕⊕⊕⊖
Strength of the recommendation: Weak (↑)

Safety and tolerability of coxibs. Coxibs mechanism of action, which is different to common NSAIDs, does not involve COX1 blockage, thus is not responsible for antiplatelet effect. Like non-selective NSAIDs, coxibs bear a cardiovascular risk (including the increased risk of heart attacks and strokes – for these concerns rofecoxib was withdrawn from the market) and of gastrointestinal effects (bleeding and ulceration). In addition, coxibs may worsen hypertension,

Table 3.1.3. GRADE evidence profile table for oral ibuprofen 200, 400, and 600 mg vs placebo in migraine

Certainty assessment							№ of patients		Effect			
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Ibuprofen	Placebo	Relative (95% CI)	Absolute (95% CI)	Quality	Importance
Pain freedom at 2 h - Ibuprofen 200mg oral vs Placebo oral												
2	RCTs	Serious	Not serious	Not serious	Not serious	None	84/414 (20.3%)	36/363 (9.9%)	RR 1.95 (1.36 to 2.81)	94 more per 1.000 (from 36 more to 180 more)	⊕⊕⊕⊖ Moderate	CRITICAL
Pain freedom at 2 h - Ibuprofen 400mg oral vs Placebo oral												
5	RCTs	Serious	Not serious	Not serious	Not serious	None	215/867 (24.8%)	75/822 (9.1%)	RR 2.68 (1.81 to 3.95)	163 more per 1.000 (from 53 more to 343 more)	⊕⊕⊕⊖ Moderate	CRITICAL
Pain freedom at 2 h - Ibuprofen 600mg oral vs Placebo oral												
1	RCT	Very serious	Not applicable[a]	Serious	Not serious	None	58/198 (29.3%)	19/142 (13.4%)	RR 2.19 (1.37 to 3.51)	159 more per 1.000 (from 50 more to 336 more)	⊕⊕⊖⊖ Low	CRITICAL
Pain relief at 2 h - Ibuprofen 200mg oral vs Placebo oral												
2	RCTs	Serious	Not serious	Serious	Not serious	None	217/414 (52.4%)	133/363 (36.6%)	RR 1.35 (1.16 to 1.58)	128 more per 1.000 (from 59 more to 213 more)	⊕⊕⊕⊖ Moderate	CRITICAL
Pain relief at 2 h - Ibuprofen 400mg oral vs Placebo oral												
6	RCTs	Serious	Not serious	Not serious	Not serious	None	513/902 (56.9%)	265/855 (31.0%)	RR 1.92 (1.48 to 2.49)	285 more per 1.000 (from 149 more to 462 more)	⊕⊕⊕⊕ High	CRITICAL
Pain relief at 2 h - Ibuprofen 600mg oral vs Placebo oral												
1	RCT	Very serious	Not applicable[a]	Serious	Not serious	None	142/198 (71.7%)	71/142 (50.0%)	RR 1.43 (1.19 to 1.73)	215 more per 1.000 (from 95 more to 365 more)	⊕⊕⊖⊖ Low	CRITICAL

[a]Only one trial.

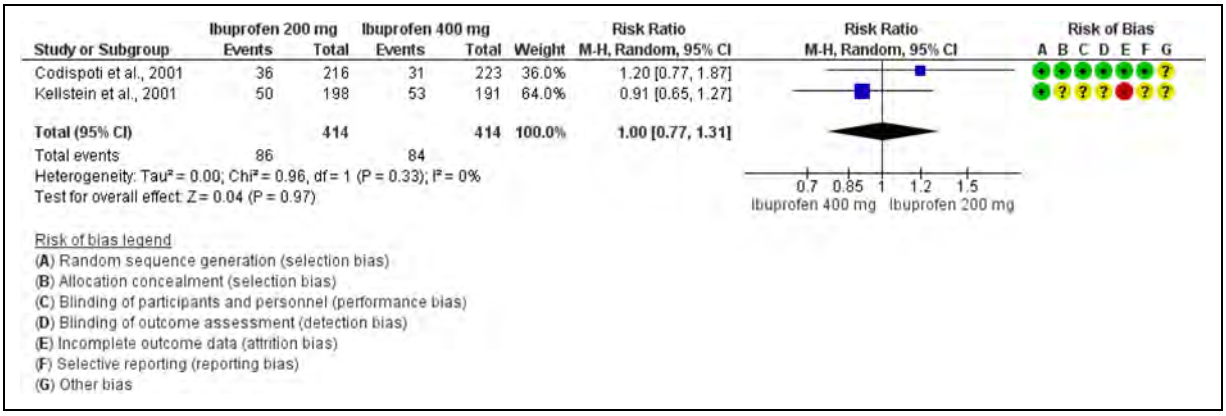


Figure 3.1.15. Forest plot showing the comparison between oral ibuprofen 200 mg and oral ibuprofen 400 mg for the outcome pain freedom at 2 h.

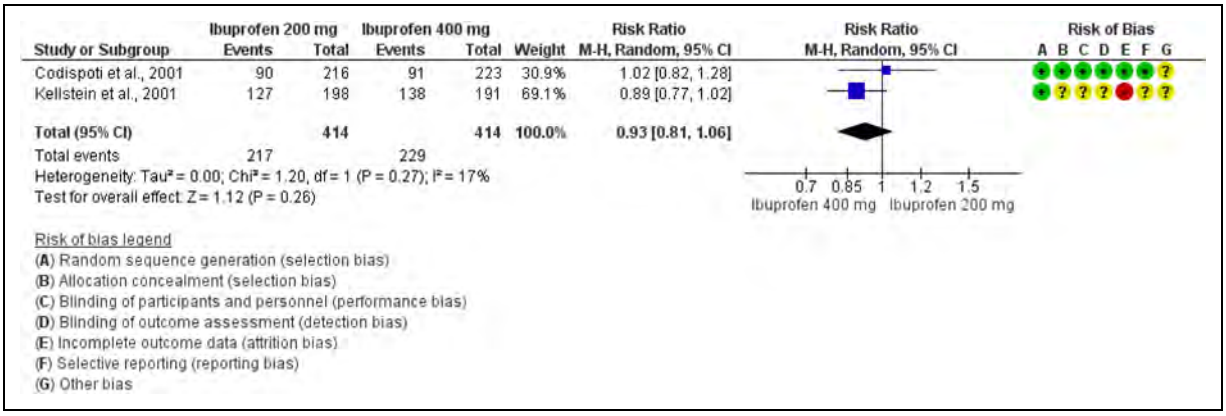


Figure 3.1.16. Forest plot showing the comparison between oral ibuprofen 200 mg and oral ibuprofen 400 mg for the outcome pain relief at 2 h.

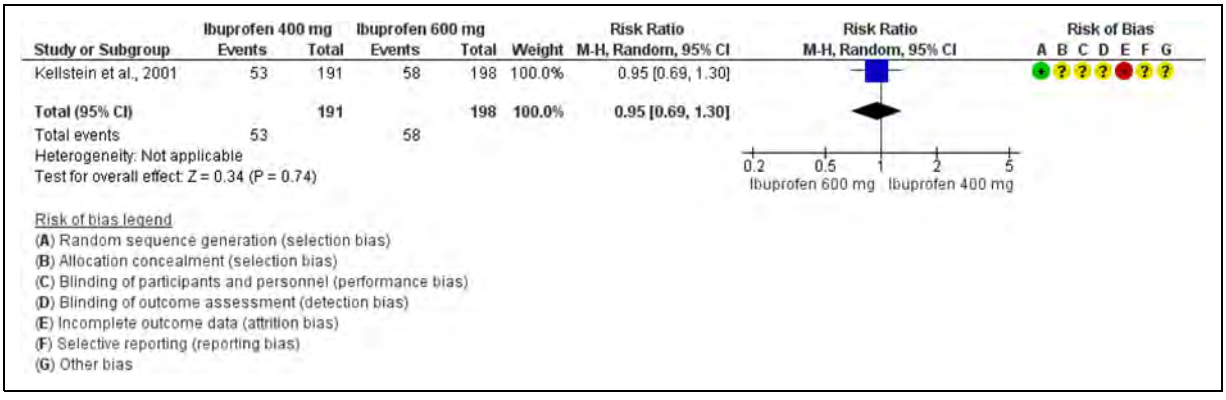


Figure 3.1.17. Forest plot showing the comparison between oral ibuprofen 400 mg and oral ibuprofen 600 mg for the outcome pain freedom at 2 h.

renal and liver failure. Allergic reactions, up to and including anaphylaxis, are described. It should be mentioned that cardiovascular adverse effects of coxibs were reported when the drugs were taken daily for joint or back pain (51,52); it is reasonable to expect that the cardiovascular safety of coxibs is better if they are taken occasionally to treat episodic migraine.

Warnings and contraindications: hypersensitivity to drugs containing sulfonamide group such as some antibiotics, concomitant use of CYP2C9 inhibitors such as

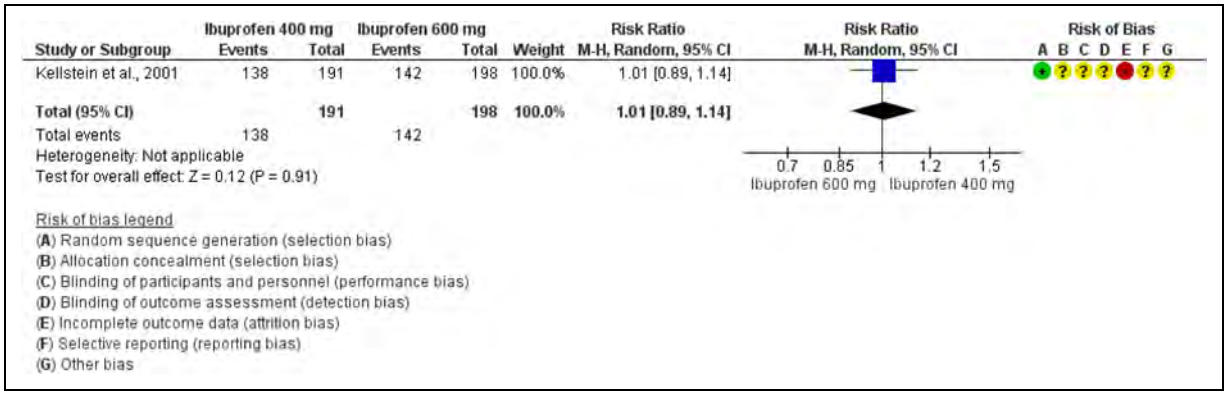


Figure 3.1.18. Forest plot showing the comparison between oral ibuprofen 400 mg and oral ibuprofen 600 mg for the outcome pain relief at 2 h.

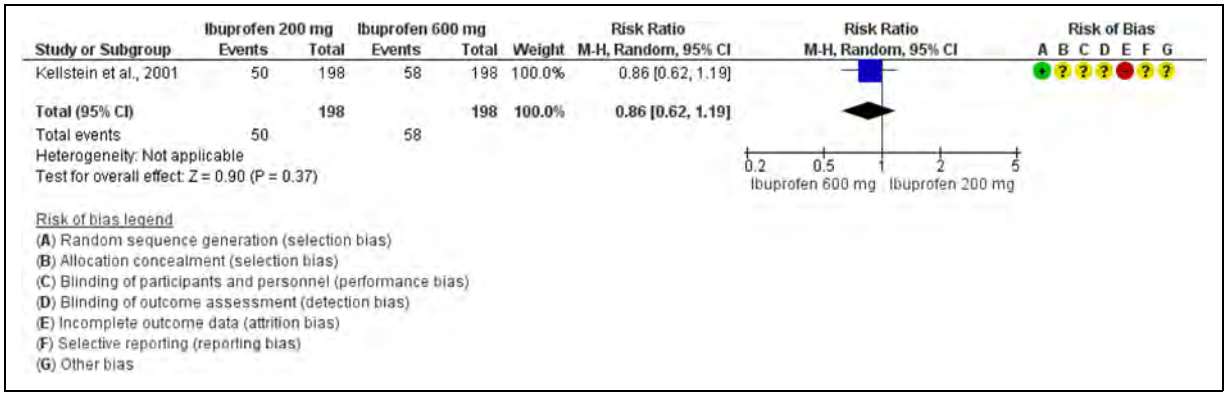


Figure 3.1.19. Forest plot showing the comparison between oral ibuprofen 200 mg and oral ibuprofen 600 mg for the outcome pain freedom at 2 h.

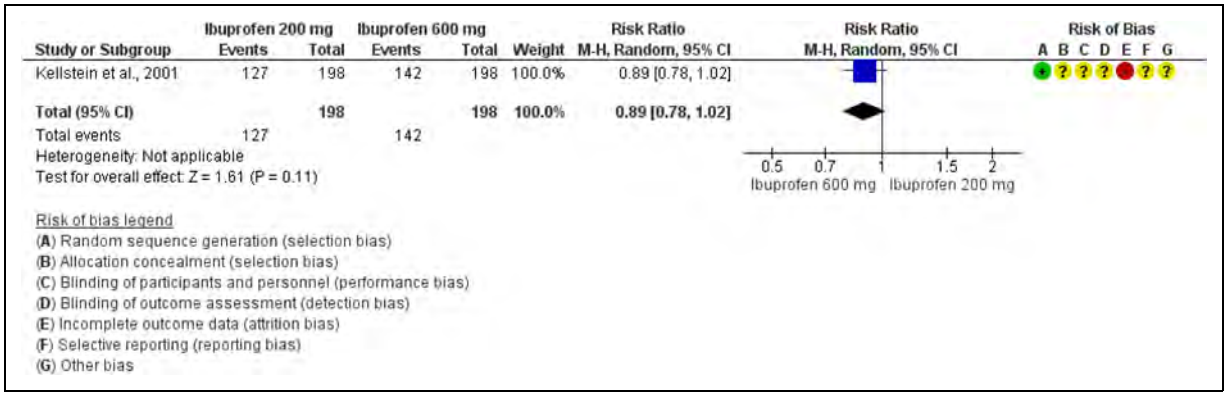


Figure 3.1.20. Forest plot showing the comparison between oral ibuprofen 200 mg and oral ibuprofen 600 mg for the outcome pain relief at 2 h.

fluconazole. Like all NSAIDs, celecoxib should not be taken from the 29th week of pregnancy until delivery. The choice to use a COX2 selective NSAID rather than a nonselective NSAID is based upon its reduced risk of gastroduodenal toxicity compared with nonselective NSAIDs.

Safety and tolerability of celecoxib. Warnings and contraindications: No data is available from the analyzed RCT. Overall, in addition to the warnings and contraindications that apply to all other NSAIDs, celecoxib is contraindicated for the treatment of perioperative pain during coronary

Table 3.1.4. GRADE evidence profile table for oral ibuprofen 200, 400, or 600 mg versus placebo in patients with migraine

Certainty assessment							№ of patients		Effect			
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Ibuprofen 200 mg	Ibuprofen 400 mg main pain free	Relative (95% CI)	Absolute (95% CI)	Quality	Importance
Pain freedom at 2 h - Ibuprofen 200mg oral vs Ibuprofen 400mg oral												
2	RCTs	Serious	Not serious	Not serious	Not serious	None	86/414 (20.8%)	84/414 (20.3%)	**RR 1.00** (0.77 to 1.31)	**0 fewer per 1.000** (from 47 fewer to 63 more)	⊕⊕⊕⊖ Moderate	Critical
Pain relief at 2 h - Ibuprofen 200mg oral vs Ibuprofen 400mg oral												
2	RCTs	Serious	Not serious	Not serious	Not serious	None	217/414 (52.4%)	229/414 (55.3%)	**RR 0.93** (0.81 to 1.06)	**39 fewer per 1.000** (from 105 fewer to 33 more)	⊕⊕⊕⊖ Moderate	Critical
Pain freedom at 2 h - Ibuprofen 400mg oral vs Ibuprofen 600mg oral												
1	RCT	Very serious	Not applicable[a]	Not serious	Not serious	None	53/191 (27.7%)	58/198 (29.3%)	**RR 0.95** (0.69 to 1.30)	**15 fewer per 1.000** (from 91 fewer to 88 more)	⊕⊕⊖⊖ Low	Critical
Pain relief at 2 h - Ibuprofen 400mg oral vs Ibuprofen 600mg oral												
1	RCT	Very serious	Not applicable[a]	Not serious	Not serious	None	138/191 (72.3%)	142/198 (71.7%)	**RR 1.01** (0.89 to 1.14)	**7 more per 1.000** (from 79 fewer to 100 more)	⊕⊕⊖⊖ Low	Critical
Pain freedom at 2 h - Ibuprofen 200mg oral vs Ibuprofen 600mg oral												
1	RCT	Very serious	Not applicable[a]	Not serious	Not serious	None	50/198 (25.3%)	58/198 (29.3%)	**RR 0.86** (0.62 to 1.19)	**41 fewer per 1.000** (from 111 fewer to 56 more)	⊕⊕⊖⊖ Low	Critical
Pain relief at 2 h - Ibuprofen 200mg oral vs Ibuprofen 600mg oral												
1	RCT	Very serious	Not applicable[a]	Not serious	Not serious	None	127/198 (64.1%)	142/198 (71.7%)	**RR 0.89** (0.78 to 1.02)	**79 fewer per 1.000** (from 158 fewer to 14 more)	⊕⊕⊖⊖ Low	Critical

[a]Only one trial.

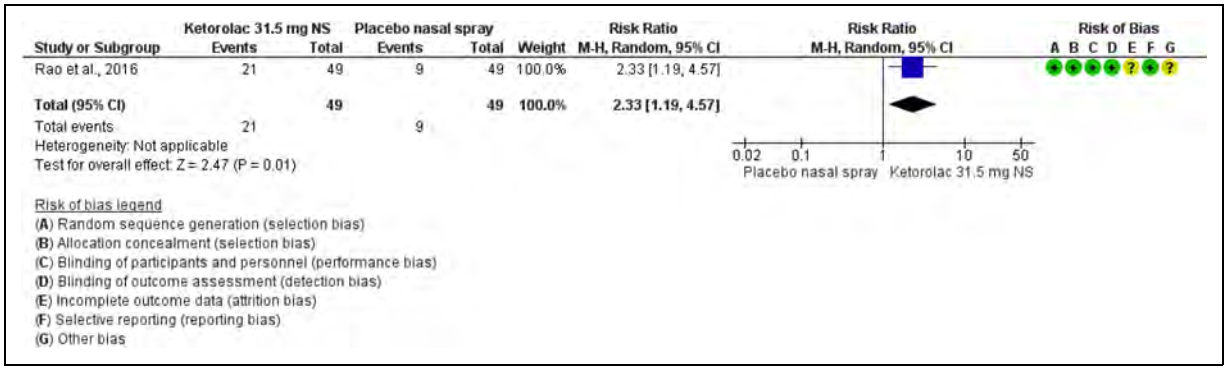


Figure 3.1.21. Forest plot showing the comparison between ketorolac 31.5 mg nasal spray and placebo nasal spray for the outcome pain freedom at 2 h.

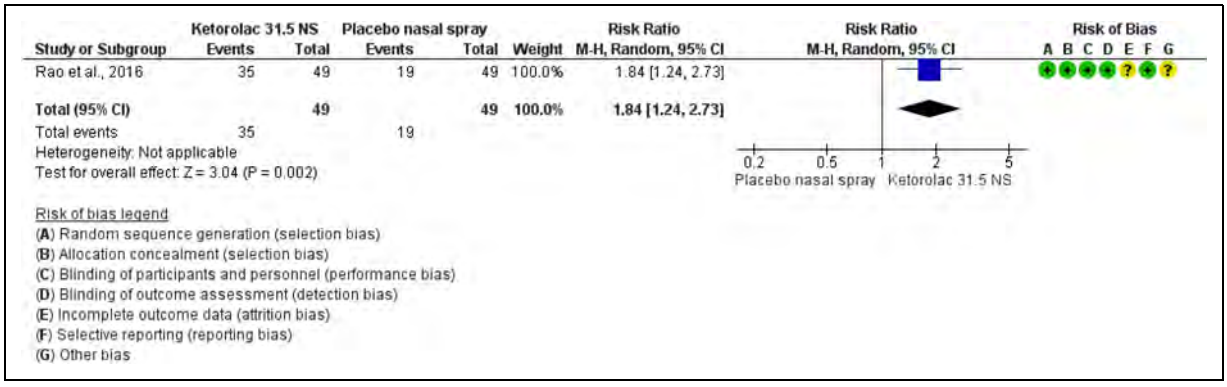


Figure 3.1.22. Forest plot showing the comparison between ketorolac 31.5 mg nasal spray and placebo nasal spray for the outcome pain relief at 2 h.

arterial bypass graft – due to the associated risk of cardiovascular disease (53) – and in patients with prior allergic reaction to antimicrobials containing a sulfonamide group, due to the potential risk for cross-reactivity (54). Caution is also required when using cytochrome CYP2C9 inhibitors such as fluconazole, as that cytochrome metabolizes celecoxib. The use of celecoxib is contraindicated during the first 29 weeks of pregnancy (53) like all other NSAIDs.

Serious safety concerns: No serious AEs reported.

Tolerability: No significant differences between celecoxib and placebo were found for frequency of AEs. Gastrointestinal complaints were the most frequently reported AE, including dysgeusia and nausea.

Evidence-based guideline summary

We found studies on aspirin, dexketoprofen trometamol, diclofenac potassium, ibuprofen, ketorolac, naproxen, and celecoxib to be included for deriving evidence-based recommendations for this guideline. Evidence-based recommendations were possible for several NSAIDs and for celecoxib (Figure 3.1.27).

Expert-based opinions

Topic: Low versus high dosage. Suggestion: We suggest using the lowest effective dose of NSAIDs for the acute treatment of migraine attacks.

Rationale: Choosing the lowest effective dose is reasonable considering the dose-dependent gastrointestinal side effects of NSAIDs.

Topic: Timing to take medication. Suggestion: We suggest taking NSAIDs as soon as possible after pain onset.

Rationale: Even if there is no specific evidence, clinical practice suggests that early intake might enhance the efficacy of NSAIDs.

Topic: NSAIDs versus coxibs. Suggestion: In subjects who tolerate NSAIDs well, we suggest using these rather than coxibs.

Rationale: Coxibs cause less gastrointestinal toxicity but are more likely to cause cardiovascular AEs with no substantial gain in efficacy over NSAIDs (55).

Table 3.1.5. GRADE evidence profile table for ketorolac nasal spray versus placebo in patients with migraine

Certainty assessment							№ of patients		Effect			
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Ketorolac nasal spray	Placebo nasal spray	Relative (95% CI)	Absolute (95% CI)	Quality	Importance
Pain free at 2 h – Ketorolac 31.5 mg nasal spray vs Placebo nasal spray												
1	RCT	Low	Not applicable[a]	Not serious	Serious	None	21/49 (42.9%)	9/49 (18.4%)	**RR 2.33** (1.19 to 4.57)	**244 more per 1.000** (from 35 more to 656 more)	⊕⊕⊖⊖ Low	CRITICAL
Pain relief at 2 h - Ketorolac 31.5 mg nasal spray vs Placebo nasal spray												
1	RCT	Low	Not applicable[a]	Not serious	Serious	None	35/49 (71.4%)	19/49 (38.8%)	**RR 1.84** (1.24 to 2.73)	**326 more per 1.000** (from 93 more to 671 more)	⊕⊕⊖⊖ Low	CRITICAL

[a]Only one trial.

Topic: Which NSAID to use. Suggestion: The choice should be based on the patient's preference for and response to individual NSAIDs.

Rationale: There is no evidence that one NSAID is superior to another. We recommend using the most favorable according to the best efficacy/tolerability profile, always considering patient preference (55).

Topic: Indomethacin. Suggestion: We suggest limiting the use of indomethacin to selected cases.

Rationale: Indomethacin is a potent COX inhibitor largely used in trigeminal autonomic cephalalgias rather than migraine (where there is a lack of trials). The nitric oxide-mediated effect on cerebral blood flow (56) suggests limiting use to patients with low cerebrovascular and cardiovascular risk and for short periods.

3.2 Triptans

Introduction

Triptans have represented a significant advancement in the acute treatment of migraine (57). They were originally developed to address the acute treatment of migraine by emulating ergot-like properties while avoiding its well-known adverse effects (58). Belonging to the tryptamine family and structurally similar to serotonin (5-HT) with substitutions in 3 and 5 positions, triptans act as selective agonist of 5-HT1B/1D receptors (59). Although they were initially chosen based on their vasoactive properties, recent research has challenged the vascular mechanisms of action associated with them. While the precise mechanisms of action remain unknown, triptans are believed to exert their effects at various levels of the nervous system (60,61). Specifically, their activity on the 5-HT_{1B} receptors induces vasoconstriction of meningeal vessels, while their action on the 5-HT_{1D} receptors inhibits the release of vasoactive peptides involved in neurogenic inflammation (62) and pain signaling (63–65).

Since the introduction of sumatriptan, several other triptans have been developed, all administered orally but with some available in different formulations (nasal spray, oral disintegrating tablets, etc.), and marketed (zolmitriptan, rizatriptan, naratriptan, almotriptan, eletriptan and frovatriptan), to date. Due to subtle differences in their chemical structure, triptans demonstrate unique pharmacokinetic characteristics peculiarities leading to differences in efficacy and tolerability profile (66). Herein, we conducted a systematic review and meta-analysis of randomized controlled trials (RCTs) investigating the efficacy and safety of triptans when compared with placebo. Efficacy and tolerability were evaluated across all recommended doses in the meta-analysis of placebo-controlled trials. In addition, this analysis includes comparisons among different doses of the same triptan, while head-to-head comparisons among

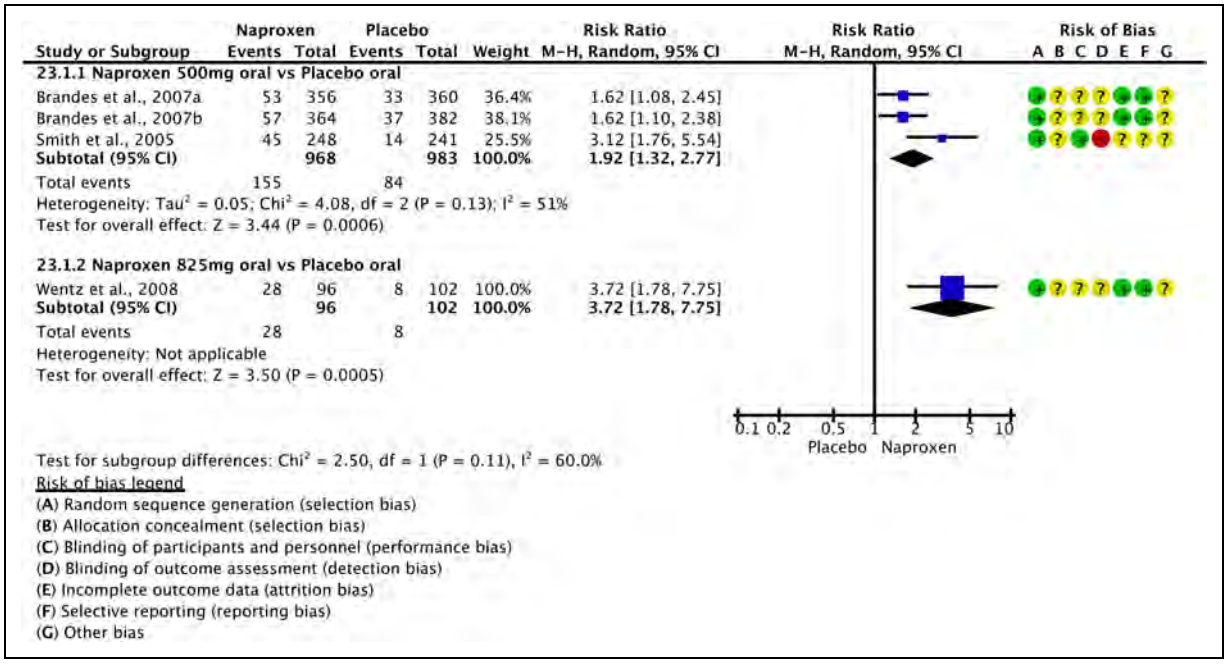


Figure 3.1.23. Forest plot showing the comparison between naproxen 500 mg or naproxen 825 mg and placebo for the outcome pain freedom at 2 h.
One trial (27) *reported results of two studies (a and b).*

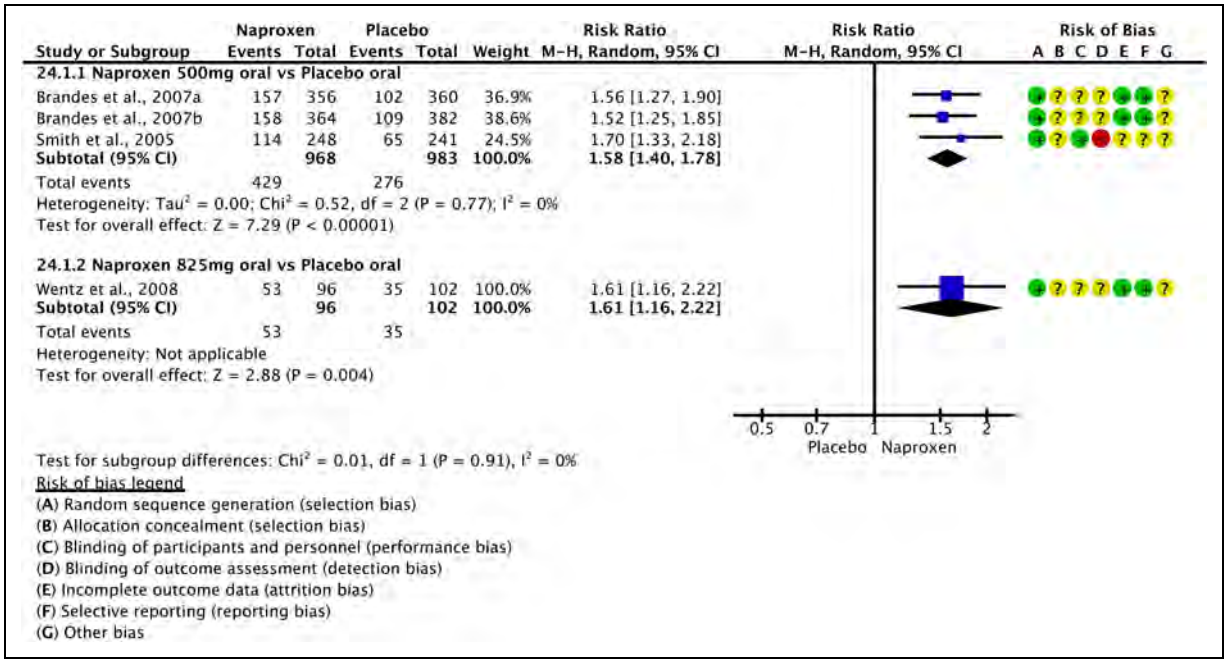


Figure 3.1.24. Forest plot showing the comparison between naproxen 500 mg or naproxen 825 mg and placebo for the outcome pain relief at 2 h.
One trial (27) *reported results of two studies (a and b).*

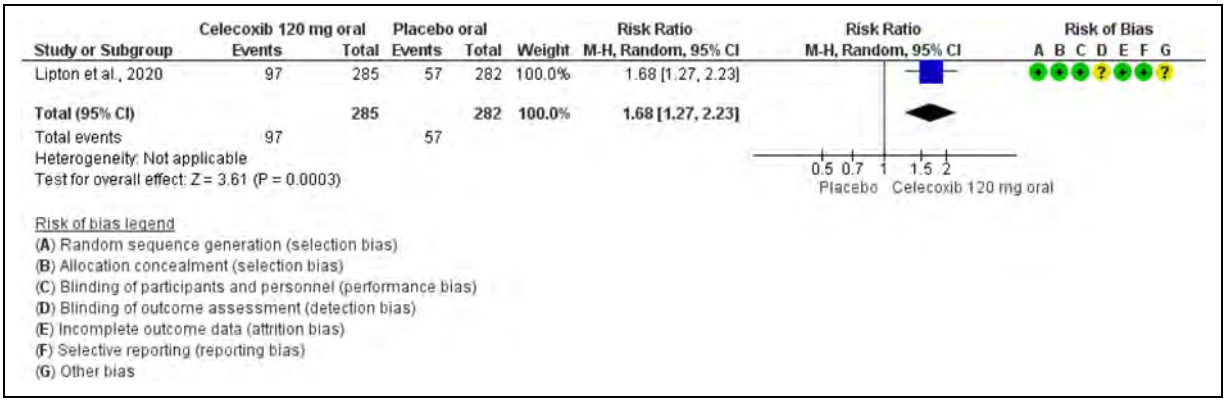


Figure 3.1.25. Forest plot showing the comparison between celecoxib 120 mg and placebo for the outcome pain freedom at 2 h.

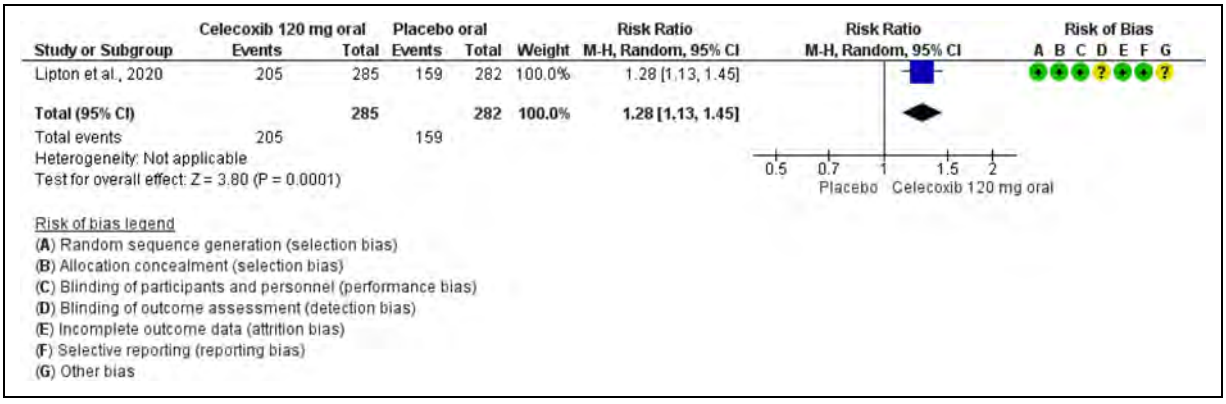


Figure 3.1.26. Forest plot showing the comparison between celecoxib 120 mg and placebo for the outcome pain relief at 2 h.

different triptans are presented in Section 3.9. Combinations of triptans and other acute drugs are presented in Section 3.4.

Section-specific methods

This section followed the general procedure to develop this guideline.

Search strings for the guideline on triptans for systematic review/meta-analysis and for additional RCTs are reported in Online Appendix 3.2.1.

Results

Overall, we retrieved 2445 references from searching for systematic reviews and meta-analyses. After duplicate removal and screening stages, we included 21 systematic reviews and meta-analyses (58, 67–86) that were considered as source of randomized controlled trials (RCTs). After analyzing full texts of these RCTs, we included 119 of them in the quantitative synthesis (27, 29, 38, 41, 44, 87–199) (Figure 3.2.1).

Overall, we retrieved 4616 references from searching for RCTs and after removing duplicates we had 3653 references to analyze. However, considering the most recent included systematic review and meta-analysis (77) on the topic, the analysis of additional RCTs was performed for papers published since 2016 (1114 references). We finally included two additional RCTs (200,201) (Figure 3.2.2).

From the literature search update performed in May 2023, we retrieved 270 references, while 161 further references were retrieved from the update performed in November 2023. We did not include further studies from this additional search.

Overall, 121 studies were included in data synthesis to develop the evidence-based guideline. Among these, 46 reported a comparison between two active drugs and their results are included in Section 3.9.

Almotriptan

PICO 3.2.1. In subjects with migraine, is almotriptan superior to placebo in the acute treatment of migraine attacks (outcomes: pain freedom at 2 h, pain relief at 2 h)?

Table 3.1.6. GRADE evidence profile table for oral celecoxib 120 mg versus placebo in patients with migraine

Certainty assessment							№ of patients		Effect			
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Celecoxib	Placebo	Relative (95% CI)	Absolute (95% CI)	Quality	Importance
Pain free at 2 h – Celecoxib 120 mg oral vs Placebo oral												
1	RCT	Low	Not applicable[a]	Not serious	Not serious	None	97/285 (34.0%)	57/282 (20.2%)	**RR 1.68** (1.27 to 2.23)	**137 more per 1.000** (from 55 more to 249 more)	⊕⊕⊕⊖ Moderate	CRITICAL
Pain relief at 2 h - Celecoxib 120 mg oral vs Placebo oral												
1	RCT	Low	Not applicable[a]	Not serious	Not serious	None	205/285 (71.9%)	159/282 (56.4%)	**RR 1.28** (1.13 to 1.45)	**158 more per 1.000** (from 73 more to 254 more)	⊕⊕⊕⊖ Moderate	CRITICAL

[a]Only one trial.

Main evidence. We found five RCTs (87–91) addressing oral almotriptan compared to placebo in the acute treatment of migraine attacks that met the criteria to be included in the main evidence.

The pooled analysis showed benefits of oral almotriptan 12.5 mg over placebo considering the outcomes of pain freedom at 2 h (Figure 3.2.3) and pain relief at 2 h (Figure 3.2.4). The quality of evidence for both outcomes was considered high (Table 3.2.1).

Additional evidence. None.

Evidence-based recommendation for PICO 3.2.1

In subjects with migraine, we recommend oral almotriptan 12.5 mg for the acute treatment of migraine attacks.
Quality of evidence: High (⊕⊕⊕⊕).
Strength of the recommendation: Strong (↑↑).

Eletriptan

PICO 3.2.2. In subjects with migraine, is eletriptan superior to placebo in the acute treatment of migraine attacks (outcomes: pain freedom at 2 h, pain relief at 2 h)?

Main evidence. We found 11 RCTs (92–101,167) addressing eletriptan as compared to placebo in the acute treatment of migraine attacks that met the criteria for main evidence.

The pooled analysis showed benefits of oral eletriptan 20 and 40 mg over placebo considering the outcomes of pain freedom at 2 h (Figure 3.2.5) and pain relief at 2 h (Figure 3.2.6). The quality of evidence for both outcomes was considered high (Table 3.2.2).

Additional evidence. We found one RCT (101) addressing oral eletriptan 40 mg as compared to placebo in the acute treatment of migraine attack that did not meet the criteria for main evidence. The overall risk of bias was considered low (Figures 3.2.7 and 3.2.8).

The pooled analysis showed benefits of oral eletriptan 40 mg over placebo considering the outcomes pain freedom at 2 h (Figure 3.2.7) and pain relief at 2 h (Figure 3.2.8).

Evidence-based recommendation for PICO 3.2.2

In subjects with migraine, we recommend oral eletriptan 20 and 40 mg for the acute treatment of migraine attacks.
Quality of evidence: High (⊕⊕⊕⊕).
Strength of the recommendation: Strong (↑↑).

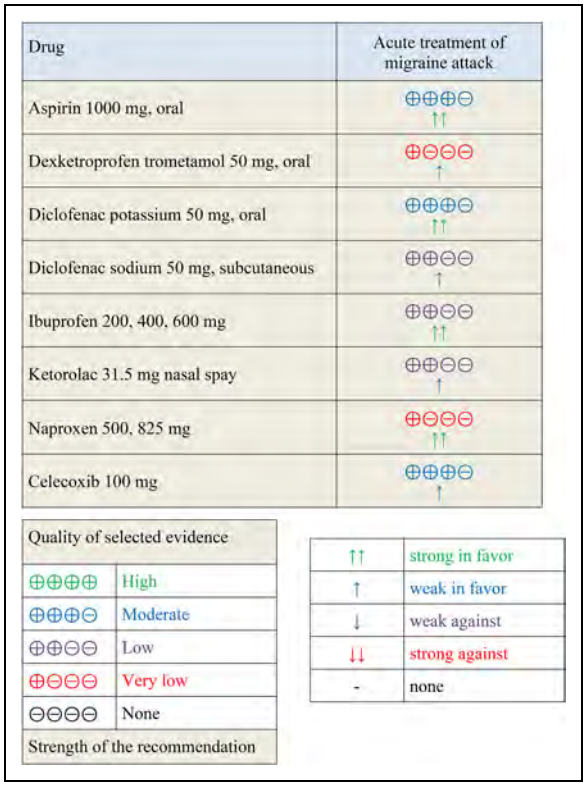


Figure 3.1.27. Summary of evidence-based recommendations on NSAIDs for the acute treatment of migraine attacks.

Frovatriptan

PICO 3.2.3. In subjects with migraine, is frovatriptan superior to placebo in the acute treatment of attacks (outcomes: pain freedom at 2 h, pain relief at 2 h)?

Main evidence. We found three RCTs (102–104) addressing oral frovatriptan compared to placebo in the acute treatment of migraine attacks that met the pre-defined criteria to be included in the main evidence.

The pooled analysis showed benefits of oral frovatriptan 2.5 mg over placebo considering the outcomes of pain freedom at 2 h (Figure 3.2.9) and pain relief at 2 h (Figure 3.2.10). The quality of evidence for pain freedom was considered moderate (due to wide confidence interval) while it was considered high for pain relief (Table 3.2.3).

Additional evidence. We found two RCTs (105,106) addressing oral frovatriptan 2.5 mg compared to placebo in the acute treatment of migraine attack that did not meet the pre-defined criteria to be included in the main evidence. The overall risk of bias was considered low. The pooled analysis showed benefits of frovatriptan over placebo considering both the outcomes of pain freedom at 2 h (Figure 3.2.11) and pain relief at 2 h (Figure 3.2.12).

Evidence-based recommendation for PICO 3.2.3

In subjects with migraine, we recommend oral frovatriptan 2.5 mg for the acute treatment of migraine attacks.
Quality of evidence: High (⊕⊕⊕⊕).
Strength of the recommendation: Strong (↑↑).

Naratriptan

PICO 3.2.4. In subjects with migraine, is naratriptan superior to placebo in the acute treatment of attacks (outcomes: pain freedom at 2 h, pain relief at 2 h)?

Main evidence. We found four RCTs (96,107–109) addressing oral naratriptan as compared to placebo in the acute treatment of migraine attacks that met the criteria to be included in the main evidence.

The pooled analysis showed benefits of oral naratriptan 2.5 mg over placebo considering the outcomes of pain freedom at 2 h (Figure 3.2.13) and pain relief at 2 h (Figure 3.2.14) whereas data from two studies showed benefits of naratriptan 1 mg over placebo considering the outcomes pain-free at 2 h (Figure 3.2.13) and pain relief at 2 h (Figure 3.2.14). The quality of evidence for both outcomes was considered high for naratriptan 2.5 mg and moderate for naratriptan 1 mg (Table 3.2.4).

Additional evidence. We found one RCT (110) addressing oral naratriptan 2.5 mg as compared to placebo in the acute treatment of migraine attacks that did not meet the pre-defined criteria to be included in the main evidence. The overall risk of bias was considered moderate, and the quality of evidence was considered very low (Figures 3.2.15 and 3.2.16).

The results did not confirm benefits of oral naratriptan 2.5 mg over placebo considering the outcomes pain freedom at 2 h (Figure 3.2.15), whereas they showed benefit of naratriptan 2.5 mg considering the outcome of pain relief at 2 h (Figure 3.2.16).

Evidence-based recommendation for PICO 3.2.4

In subjects with migraine, we recommend oral naratriptan 1 mg or 2.5 mg for the acute treatment of migraine attacks.
Quality of evidence: High (⊕⊕⊕⊕).
Strength of the recommendation: Strong (↑↑).

Rizatriptan

PICO 3.2.5. In subjects with migraine, is rizatriptan superior to placebo in the acute treatment of migraine attacks (outcomes: pain freedom at 2 h, pain relief at 2 h)?

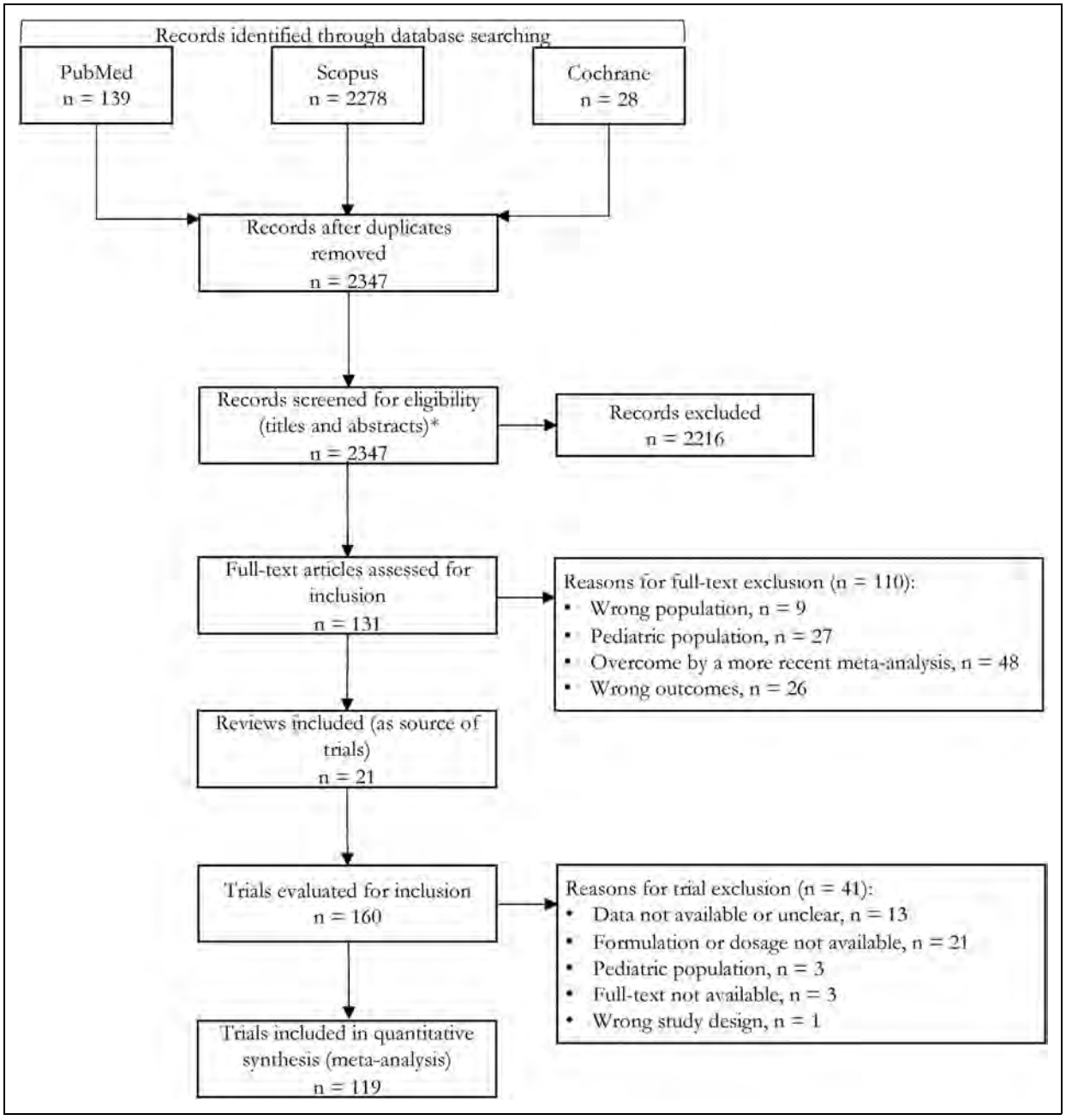


Figure 3.2.1. Meta-analysis selection flow-chart - triptans.

Main evidence. We found 12 RCTs (38,107,111–120) addressing oral rizatriptan as compared to placebo in the acute treatment of migraine attacks that met the criteria to be included in the main evidence.

The pooled analysis showed benefits of oral rizatriptan 5 and 10 mg over placebo considering the outcomes of pain freedom at 2 h (Figure 3.2.17) and pain relief at 2 h (Figure 3.2.18). The quality of evidence for both outcomes was considered high (Table 3.2.5).

Additional evidence. We found one RCT (121) addressing oral rizatriptan as compared to placebo in the acute treatment of migraine attacks that did not meet the predefined criteria to be included in the main evidence. The overall risk of bias was considered high, and the quality of evidence was considered very low (Figures 3.2.19 and 3.2.20).

The results showed benefits of oral rizatriptan over placebo considering the outcomes of freedom at 2 h (Figure 3.2.19) and pain relief at 2 h (Figure 3.2.20).

We found one RCT (115) addressing oral rizatriptan 5 mg as compared to oral rizatriptan 10 mg in the acute treatment of migraine attacks that met the criteria to be included in the main evidence. The overall risk of bias was

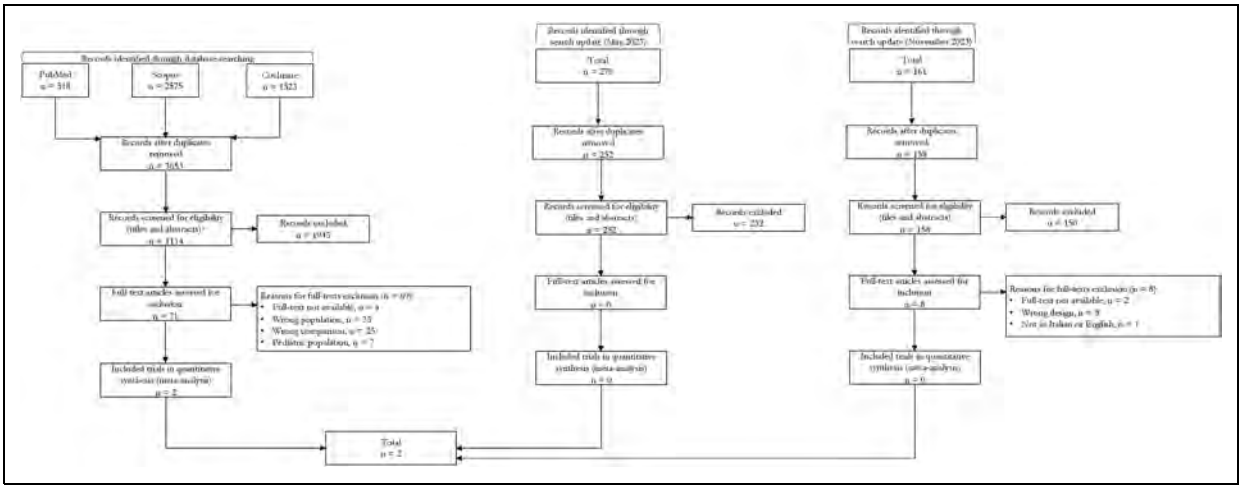


Figure 3.2.2. RCTs selection flow-chart - triptans.
*trials published since 2016 were screened.

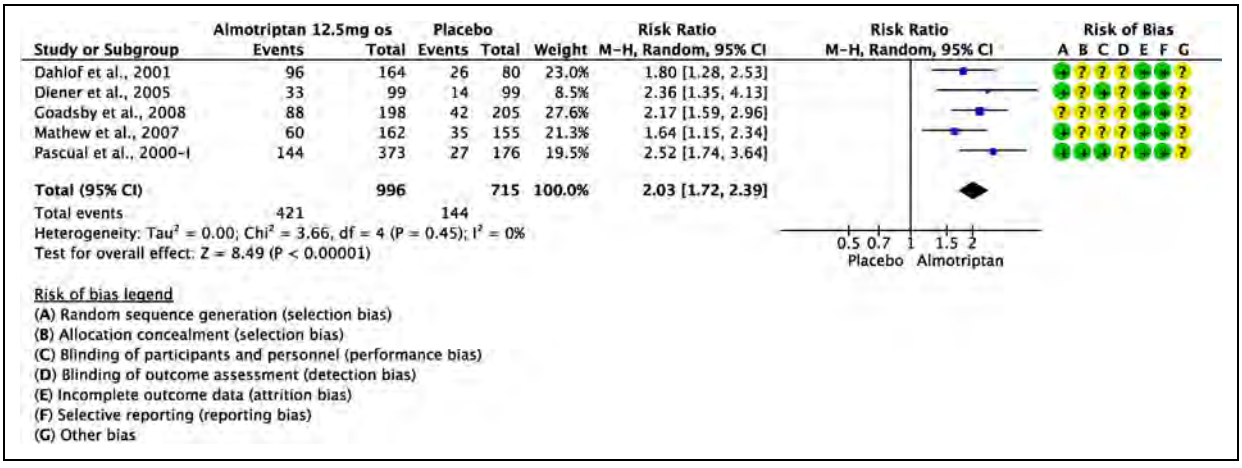


Figure 3.2.3. Forest plot showing the comparison between almotriptan and placebo for the outcome pain freedom at 2 h in patients with migraine.

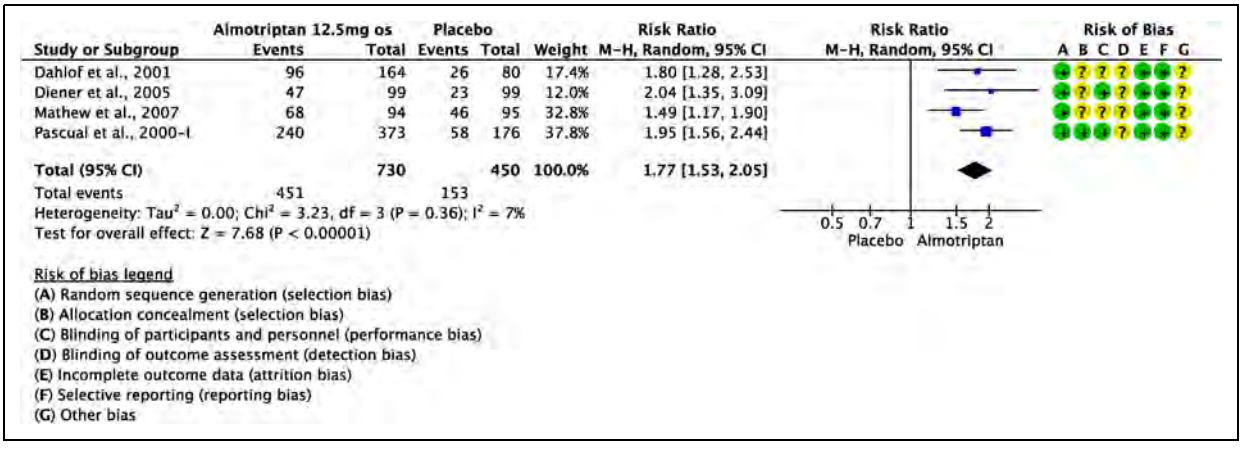


Figure 3.2.4. Forest plot showing the comparison between almotriptan 12.5 mg and placebo for the outcome pain relief at 2 h in patients with migraine.

Table 3.2.1. GRADE evidence profile table of oral almotriptan versus placebo in patients with migraine

Certainty assessment							№ of patients		Effect			
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Almotriptan	Placebo	Relative (95% CI)	Absolute (95% CI)	Quality	Importance
Pain freedom at 2 h – Almotriptan 12.5 mg oral vs. Placebo												
5	RCT	Not serious	Not serious	Not serious	Not serious	None	421/996 (42.3%)	144/715 (20.1%)	**RR 2.03** (1.72 to 2.39)	**207 more per 1.000** (from 145 more to 280 more)	⊕⊕⊕⊕ high	Critical
Pain relief at 2 h – Almotriptan 12.5 mg oral vs. Placebo												
4	RCT	Not serious	Not serious	Not serious	Not serious	None	451/730 (61.8%)	153/450 (34.0%)	**RR 1.77** (1.53 to 2.05)	**262 more per 1.000** (from 180 more to 357 more)	⊕⊕⊕⊕ high	Critical

considered low and the quality of evidence was considered high. The study did not show a significant difference between oral rizatriptan 5 mg and oral rizatriptan 10 mg considering the outcomes of pain freedom at 2 h (Figure 3.2.21). The quality of evidence was considered moderate (Table 3.2.6).

Evidence-based recommendation for PICO 3.2.5

In subjects with migraine, we recommend oral rizatriptan 5 or 10 mg for the acute treatment of migraine attacks.
Quality of evidence: High (⊕⊕⊕⊕).
Strength of the recommendation: Strong (↑↑).

Sumatriptan

PICO 3.2.6. In subjects with migraine, is sumatriptan superior to placebo in the acute treatment of migraine attacks (outcomes: pain freedom at 2 h, pain relief at 2 h)?

Main evidence. We found 27 RCTs (30,41,44,93,97,98,112,114,122–136,176,182,194,198) addressing sumatriptan as compared to placebo in the acute treatment of migraine attacks that met the criteria to be included in the main evidence.

The pooled analysis showed benefits of oral (50 and 100 mg), subcutaneous (6 mg/mL) and nasal spray (10 and 20 mg) sumatriptan over placebo considering the outcomes pain freedom at 2 h (Figure 3.2.22) and pain relief at 2 h (Figure 3.2.23). The quality of evidence for both outcomes was considered high except for sumatriptan 10 mg nasal spray, for which it was considered moderate (Table 3.2.7).

Additional evidence. We found 12 RCTs (29,121,137,139–145,199,202) addressing oral or subcutaneous sumatriptan compared to placebo in the acute treatment of migraine attacks that did not meet the criteria to be included in the main evidence. The pooled analysis showed benefits of oral (50 and 100 mg) and subcutaneous (6 mg/mL) sumatriptan over placebo considering the outcomes of pain freedom at 2 h (Figure 3.2.24) and pain relief at 2 h (Figure 3.2.25).

We found two RCTs (146,147) addressing oral sumatriptan 50 mg compared to oral sumatriptan 100 mg in the acute treatment of migraine attacks that met the criteria to be included in the main evidence. The overall risk of bias was considered low and the quality of evidence was considered high (Figure 3.2.26). The studies showed a significant difference between oral sumatriptan 50 mg and oral sumatriptan 100 mg considering the outcome pain freedom at 2 h (Figure 3.2.26). The pooled analysis showed no benefit of oral sumatriptan 100 mg over oral sumatriptan 50 mg

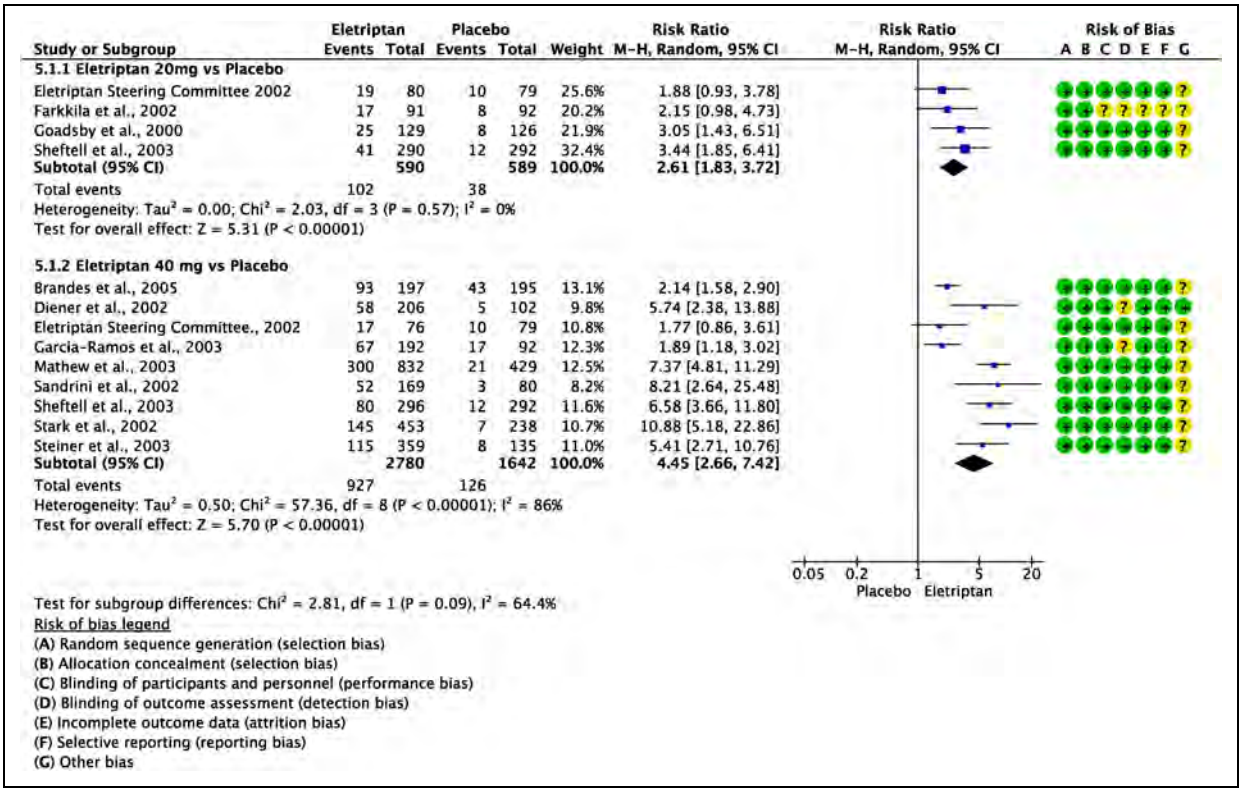


Figure 3.2.5. Forest plot showing the comparison between eletriptan and placebo for the outcome pain freedom at 2 h in patients with migraine.

considering the outcome pain freedom at 2 h. The quality of evidence was considered moderate (Table 3.2.8).

We found one RCT (148) addressing oral sumatriptan 100 mg as compared to oral sumatriptan 50 mg in the acute treatment of migraine attacks that did not meet the criteria to be included in the main evidence. The study did not show a significant difference between oral sumatriptan 50 mg and oral sumatriptan 100 mg considering the outcomes pain freedom at 2 h (Figure 3.2.27) and pain relief at 2 h (Figure 3.2.28).

Evidence-based recommendations for PICO 3.2.6

1) In subjects with migraine, we recommend oral sumatriptan 50 and 100 mg for the acute treatment of migraine attacks.

Quality of evidence: High (⊕⊕⊕⊕).
Strength of the recommendation: Strong (↑↑).

2) In subjects with migraine, we recommend subcutaneous sumatriptan 6 mg/mL for the acute treatment of migraine attacks.

Quality of evidence: High (⊕⊕⊕⊕).
Strength of the recommendation: Strong (↑↑).

3) In subjects with migraine, we recommend sumatriptan nasal spray 10 and 20 mg for the acute treatment of migraine attacks.

Quality of evidence: High (⊕⊕⊕⊕).
Strength of the recommendation: Strong (↑↑)

Zolmitriptan

PICO 3.2.7. In subjects with migraine, is zolmitriptan superior to placebo in the acute treatment of migraine attacks (outcomes: pain freedom at 2 h, pain relief at 2 h)?

Main evidence. We found 11 RCTs (100,120,150–158) addressing zolmitriptan as compared to placebo in the acute treatment of migraine attacks that met the criteria to be included in the main evidence.

The pooled analysis showed benefits of oral zolmitriptan 2.5 mg over placebo considering the outcomes of freedom at 2 h (Figure 3.2.29) and pain relief at 2 h (Figure 3.2.30). The quality of evidence for both outcomes was considered high. Additionally, pooled analysis did not show benefits from zolmitriptan 5 mg nasal spray over placebo considering the outcome pain freedom at 2 h. The outcome pain

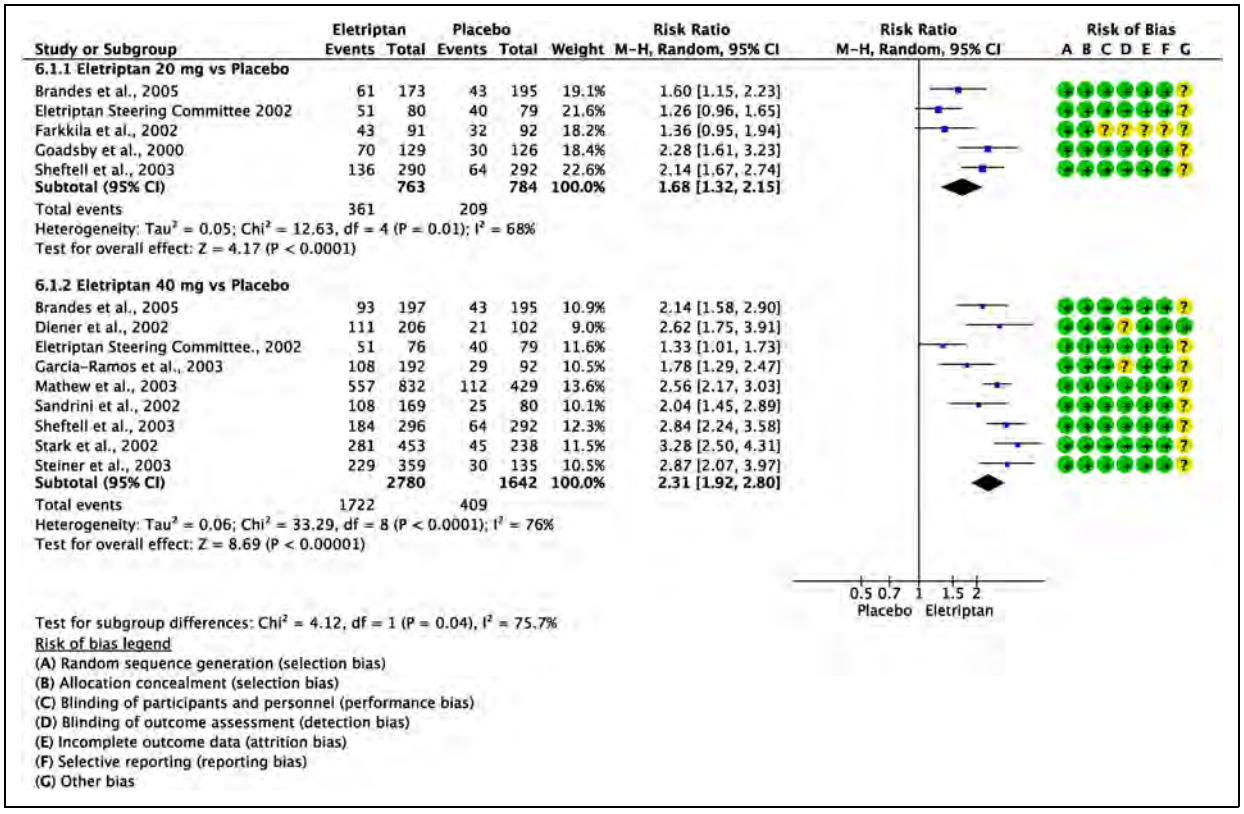


Figure 3.2.6. Forest plot showing the comparison between oral eletriptan and placebo for the outcome pain relief at 2 h in patients with migraine.

relief was not available; quality of evidence was considered low (Table 3.2.9).

We found one RCT (154) addressing oral zolmitriptan 2.5 mg as compared to oral zolmitriptan 5 mg in the acute treatment of migraine attacks that met the criteria to be included in the main evidence. The overall risk of bias was considered high and the quality of evidence was considered very low. The study did not show a significant difference between oral zolmitriptan 2.5 mg and oral zolmitriptan 5 mg considering the outcomes of pain freedom at 2 h (Figure 3.2.31) and pain relief at 2 h (Figure 3.2.32). The pooled analysis did not show benefits of oral zolmitriptan 5 mg over oral zolmitriptan 2.5 mg considering the outcomes of pain freedom at 2 h and pain relief at 2 h (Figures 3.2.31 and 3.2.32). The quality of evidence for both outcomes was considered very low (Table 3.2.10).

We found one RCT (157) addressing oral zolmitriptan 2.5 mg compared to zolmitriptan 5 mg nasal spray in the acute treatment of migraine attacks that met the criteria to be included in the main evidence. The overall risk of bias was considered low. The study did not show a significant difference between oral zolmitriptan 2.5 mg and zolmitriptan 5 mg nasal spray considering the outcome of pain relief at 2 h (Figure 3.2.33). The quality of evidence was considered moderate (Table 3.2.11).

Additional evidence

None.

Evidence-based recommendations for PICO 3.2.7

1) In subjects with migraine, we recommend oral zolmitriptan 2.5 mg for the acute treatment of migraine attacks.

Quality of evidence: High (⊕⊕⊕⊕).
Strength of the recommendation: Strong (↑↑).

2) In subjects with migraine, we suggest against zolmitriptan 5 mg nasal spray for the acute treatment of migraine attacks.

Quality of evidence: Moderate (⊕⊕⊕⊖).
Strength of the recommendation: Weak (↓).

Table 3.2.2. GRADE evidence profile table of oral eletriptan versus placebo in patients with migraine

Certainty assessment							№ of patients		Effect			
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Eletriptan	Placebo	Relative (95% CI)	Absolute (95% CI)	Quality	Importance
Pain freedom at 2 h – Eletriptan 20mg oral vs Placebo												
4	RCT	Not serious	Not serious	Not serious	Not serious	None	102/590 (17.3%)	38/589 (6.5%)	**RR 2.61** (1.83 to 3.72)	**104 more per 1.000** (from 54 more to 175 more)	⊕⊕⊕⊕ high	Critical
Pain freedom at 2 h – Eletriptan 40 mg oral vs Placebo												
9	RCT	Not serious	Not serious	Not serious	Not serious	None	927/2780 (33.3%)	126/1642 (7.7%)	**RR 4.45** (2.66 to 7.42)	**265 more per 1.000** (from 127 more to 493 more)	⊕⊕⊕⊕ high	Critical
Pain relief at 2 h – Eletriptan 20mg oral vs Placebo												
5	RCT	Not serious	Not serious	Not serious	Not serious	None	361/763 (47.3%)	209/784 (26.7%)	**RR 1.68** (1.32 to 2.15)	**181 more per 1.000** (from 85 more to 307 more)	⊕⊕⊕⊕ high	Critical
Pain relief at 2 h – Eletriptan 40 mg oral vs Placebo												
9	RCT	Not serious	Not serious	Not serious	Not serious	None	1722/2780 (61.9%)	409/1642 (24.9%)	**RR 2.31** (1.92 to 2.80)	**326 more per 1.000** (from 229 more to 448 more)	⊕⊕⊕⊕ high	Critical

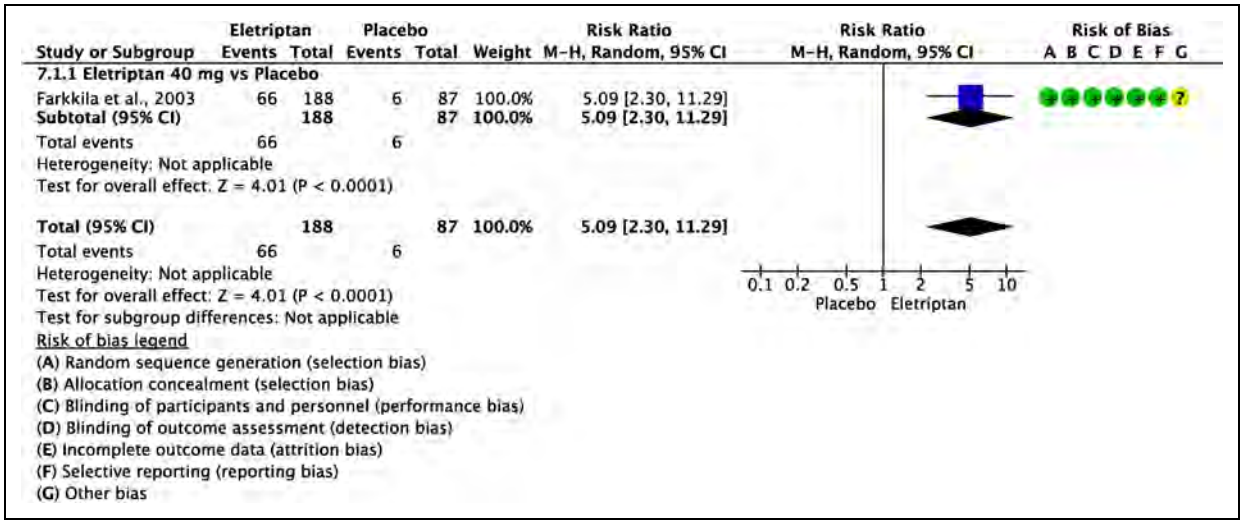


Figure 3.2.7. Forest plot showing the comparison between oral eletriptan and placebo for the outcome pain freedom at 2 h in patients with migraine.

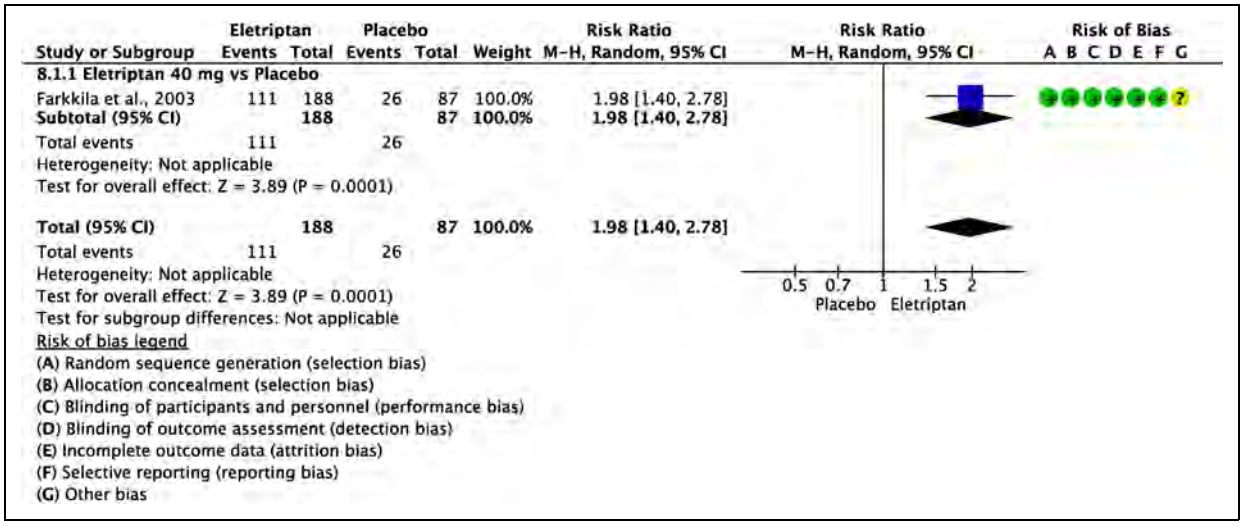


Figure 3.2.8. Forest plot showing the comparison between oral eletriptan and placebo for the outcome pain relief at 2 h in patients with migraine.

Safety and tolerability of triptans. Warnings and contraindications: The vasoconstrictive potential of triptans has led to the exclusion of patients over 65 years with vascular diseases from phase III studies. Therefore, triptans, as specified by the US Food and Drug Administration (FDA), are contraindicated in patients with coronary artery disease or coronary artery vasospasm, history of stroke, transient ischemic attack, hemiplegic or basilar migraine, intracerebral or subarachnoid hemorrhage, hypertensive crisis, Wolff-Parkinson-White syndrome or other cardiac accessory conduction pathway disorders or arrhythmias, peripheral vascular disease, ischemic bowel disease and severe hepatic impairment (203). Moreover, sumatriptan and other triptans are not recommended in patients over 65 years. Nevertheless, several studies reported the use of triptans as safe in patients with stable vascular diseases, including people beyond the age of 65 years (204).

Serious safety concerns: The presence of $5HT_{1B}$ receptors in the coronary arteries has raised several concerns about the risk of triptan-induced coronary arterial narrowing, further supported by individual cases of acute myocardial infarction in close temporal relationship with triptan intake (205). Contrariwise, incidence of triptan-induced serious cardiovascular adverse events in both clinical trials and clinical practice appears to be extremely low and limited to migraine patients with significant

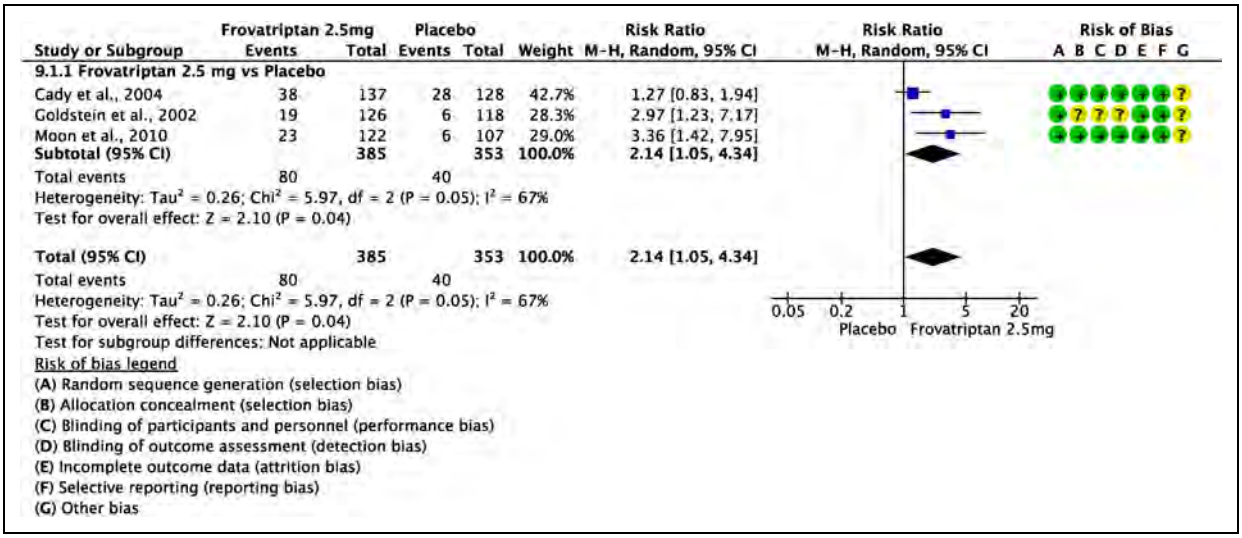


Figure 3.2.9. Forest plot showing the comparison between frovatriptan and placebo for the outcome pain freedom at 2 h in patients with migraine.

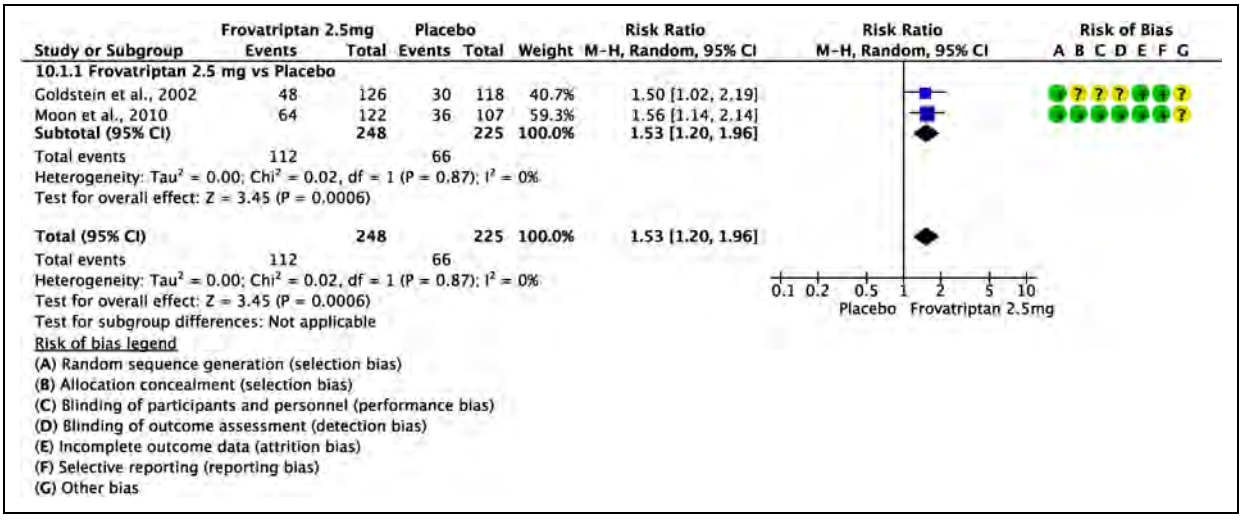


Figure 3.2.10. Forest plot showing the comparison between oral frovatriptan and placebo for the outcome pain relief at 2 h in patients with migraine.

cardiovascular risks or with overt cardiovascular diseases (206,207). In line with these observations, analyses of FDA reports, observational studies, and general practice research databases failed to reveal an increased risk of cardiovascular or cerebrovascular incidents in triptan users in the absence of vascular risk factors (203).

Tolerability: Triptans are associated with a statistically significant increase in odds of any adverse events or treatment-related adverse events compared with placebo, although usually mild to moderate in intensity, transient and spontaneously resolving. Among the most frequent triptan AEs nausea, tingling, paresthesia, as well as flushing and warm sensations in the head, neck, chest, and limbs should be mentioned (208,209).

"Chest-related AEs", also known as "triptan sensation", are not related to myocardial ischemia according to aggregated data from trials, real world experiences and pharmacodynamic instrumental assessments (by electrocardiogram, myocardial scintigraphy and angiography) (210). Therefore, "chest-related AEs" characterized by chest pressure, chest pain, shortness of breath, palpitations, and anxiety, should be considered non-serious AEs. Among different triptans, almotriptan 12.5 mg showed the lowest incidence of 'chest symptoms' (58,59).

Although rare, it is worth mentioning 'central nervous system AEs' (asthenia, abnormal dreams, agitation, aphasia, ataxia, confusion, dizziness, somnolence, headache, speech disorder, thinking abnormal, tremor, vertigo,

Table 3.2.3. GRADE evidence profile table of oral frovatriptan versus placebo in patients with migraine

Certainty assessment							№ of patients		Effect			
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Frovatriptan	Placebo	Relative (95% CI)	Absolute (95% CI)	Quality	Importance
Pain freedom at 2 h - Frovatriptan 2.5 mg oral vs Placebo												
3	RCT	Not serious	Not serious	Not serious	Not serious	None	80/385 (20.8%)	40/353 (11.3%)	**RR 2.14** (1.05 to 4.34)	**129 more per 1.000** (from 6 more to 378 more)	⊕⊕⊕⊕ high	Critical
Pain relief at 2 h - Frovatriptan 2.5 mg oral vs Placebo												
2	RCT	Not serious	Not serious	Not serious	Not serious	None	112/248 (45.2%)	66/225 (29.3%)	**RR 1.53** (1.20 to 1.96)	**155 more per 1.000** (from 59 more to 282 more)	⊕⊕⊕⊕ high	Critical

and other focal neurological symptoms) (211). The "central nervous system AEs" rates of incidence largely overlap among triptans with higher values for eletriptan 80 mg and lower values for almotriptan 12.5 mg (58,59).

Evidence-based guideline summary

We found several studies on triptans to be included for deriving evidence-based recommendations for this guideline. There is high quality of evidence to recommend the use of oral almotriptan 12.5 mg, eletriptan 20 and 40 mg, frovatriptan 2.5 mg, naratriptan 2.5 mg, rizatriptan 5 and 10 mg, sumatriptan 50 and 100 mg, zolmitriptan 2.5 mg and subcutaneous sumatriptan 6 mg for the acute treatment of migraine attacks. (Figure 3.2.34). Additionally, there was moderate quality of evidence to recommend oral naratriptan 1 mg and sumatriptan nasal spray 10 and 20 mg (Figure 3.2.34). On the other hand, evidence did not show benefits from zolmitriptan nasal spray and thus we suggest against its use (Figure 3.2.34).

The decision on the triptan to choose may be guided by several factors including attack characteristics (i.e. rapid onset, severity, duration, presence of recurrence), associated symptoms, such as nausea or vomiting, drug availability and costs, or patients' preference.

Expert-based opinion

Topic: When should triptans be taken during a migraine attack?. Suggestion: Triptans should be administered as soon as possible, ideally within one hour from onset, and possibly when the pain intensity is still mild.

Rationale: Early treatment surely represents a mainstay in the acute treatment of migraine attacks (89, 212–215). Specifically, triptans tend to be more effective when administered in the early phase of the attack before the symptoms are fully blown and features of central sensitization (e.g., allodynia) develop (216). The 'Act when Mild' Study, a randomized, four-arm, multicentre, multinational, double-blind, placebo-controlled trial of almotriptan (12.5 mg), compared early treatment (when pain intensity was mild and within 1 h of headache onset) with late treatment (when pain had become moderate or severe) (89). The study showed that early treatment with almotriptan was statistically and clinically more effective. Furthermore, it has been demonstrated that ictal cutaneous allodynia, a symptom indicative of trigeminal central sensitization, is a negative predictor of response to triptans (65,217).

Topic: When should triptans be given during an attack of migraine with aura?. Suggestion: We suggest waiting for the resolution of the aura and administering triptans at the onset of headache. Waiting for the aura resolution before administering a triptan is also indicated in cases where headache occurs before the end of the aura. In patients

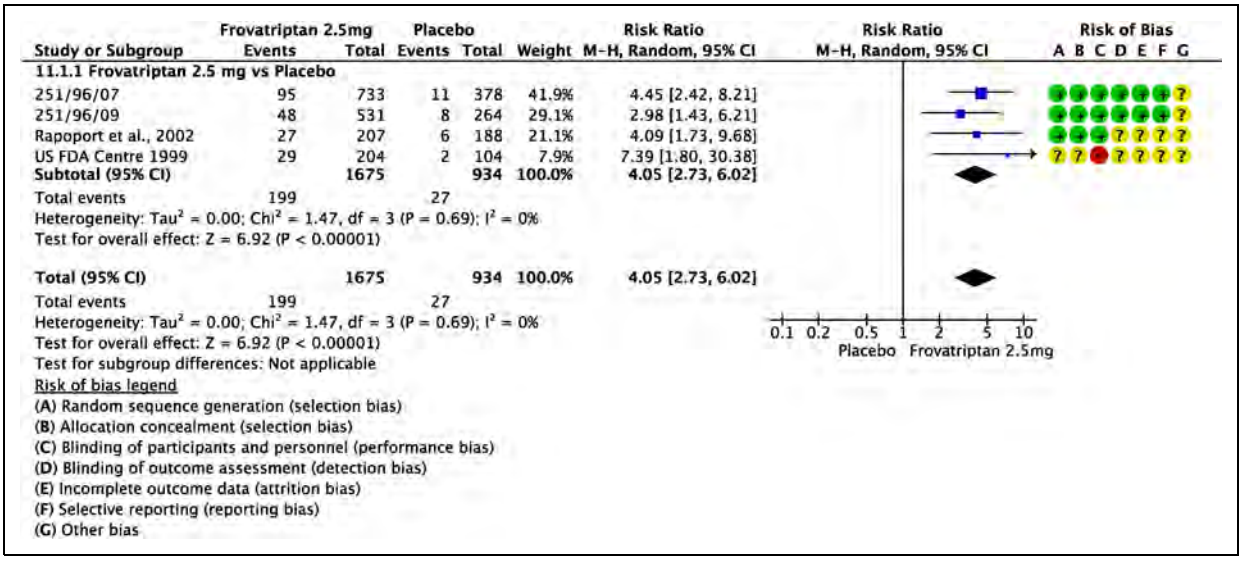


Figure 3.2.11. Forest plot showing the comparison between frovatriptan and placebo for the outcome pain freedom at 2 h in patients with migraine.

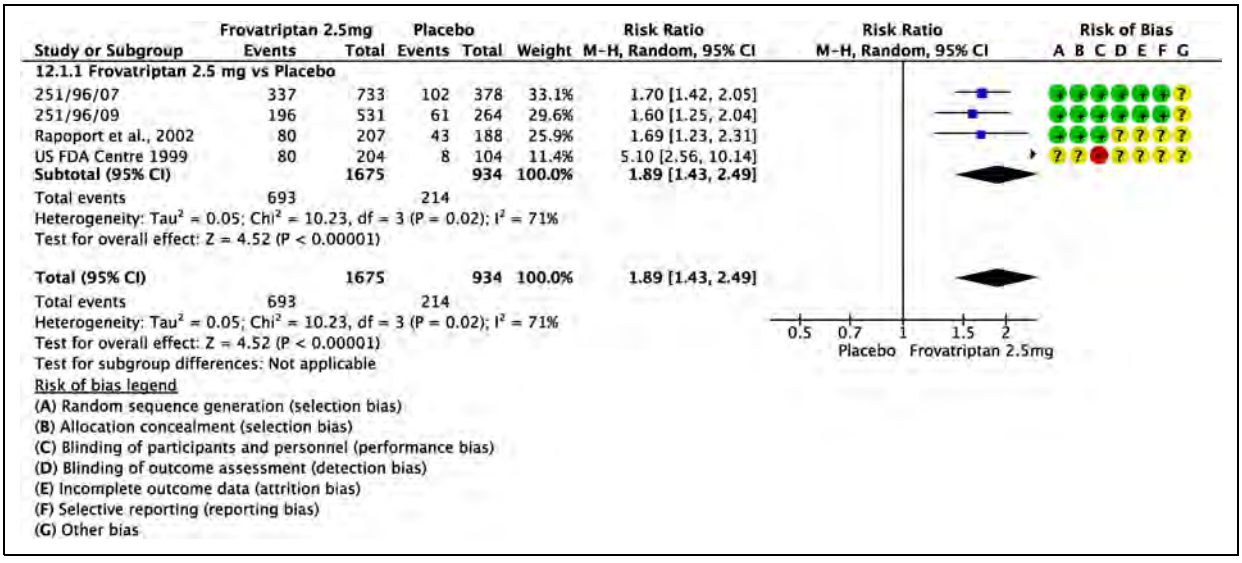


Figure 3.2.12. Forest plot showing the comparison between frovatriptan and placebo for the outcome pain relief at 2 h in patients with migraine.

with hemiplegic migraine, migraine with brainstem aura, and migraine with prolonged aura the administration of triptans is usually avoided due to cerebrovascular concerns, even though cortical spreading depression does not appear to reach ischemic thresholds and some observational studies suggested the safety of triptans even in these conditions (218,219).

Rationale: The right time of triptan administration in the course of a migraine with aura attack is still a matter of debate. Evidence suggests that both subcutaneous sumatriptan and oral eletriptan are not as effective on headache when taken during the aura phase although their use is not related to a higher risk of an adverse effect (220–222). Thus, triptan intake is advisable at the onset of the headache, waiting for the end of the aura symptoms. In the case of patients experiencing headache onset during the aura phase, there is no data about advantages of an early administration during the aura resolution to date.

Several reports showing cerebral vasoconstriction characterizing hemiplegic migraine, migraine with brainstem aura (i.e., former basilar migraine or basilar-type migraine), and migraine with prolonged aura contraindicate triptans

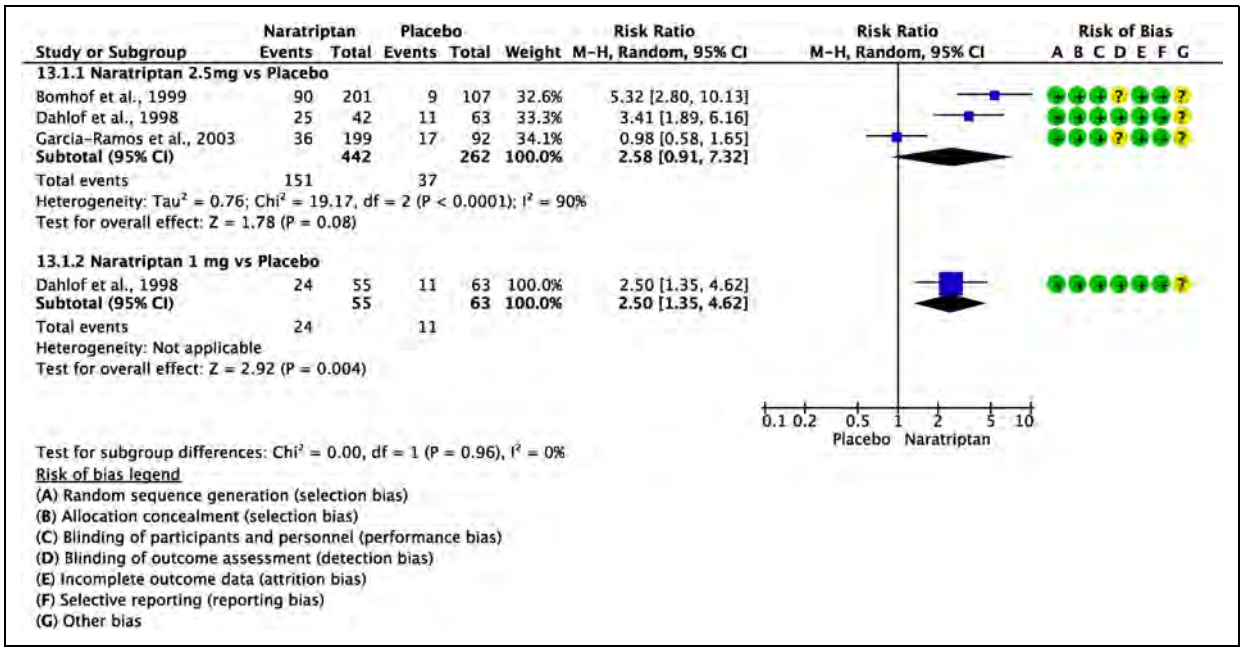


Figure 3.2.13. Forest plot showing the comparison between oral naratriptan and placebo for the outcome pain freedom at 2 h in patients with migraine.

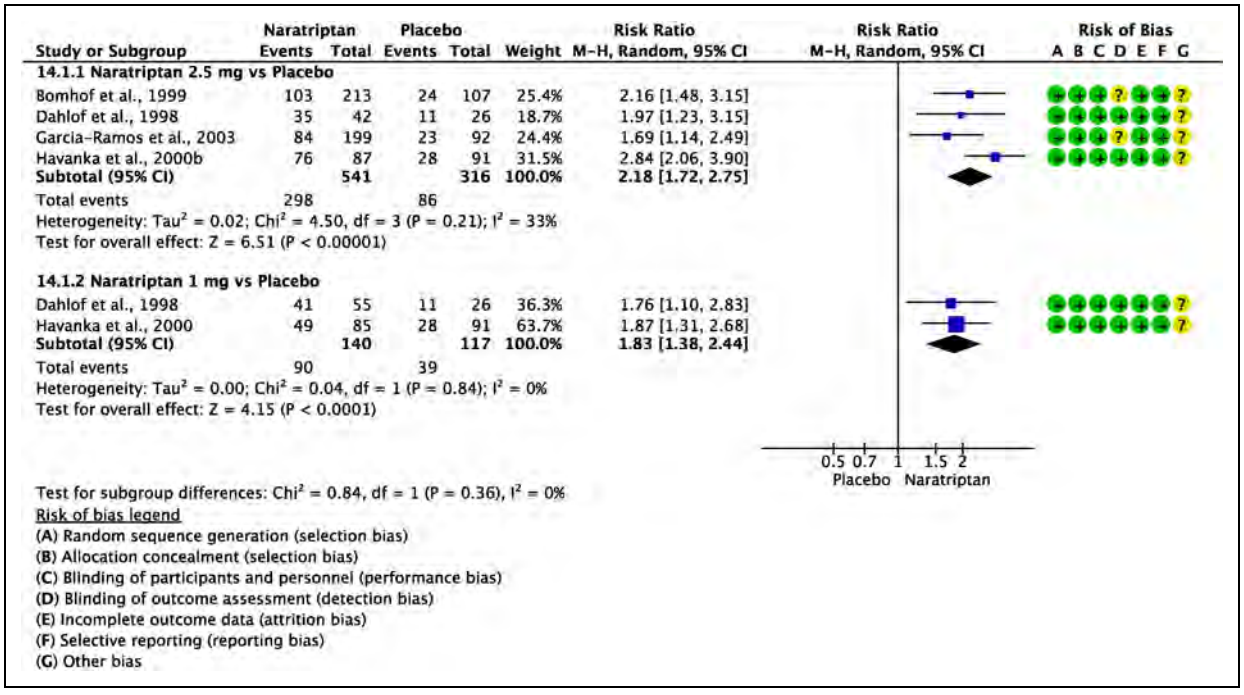


Figure 3.2.14. Forest plot showing the comparison between oral naratriptan and placebo for the outcome pain relief at 2 h in patients with migraine.

for these phenotypes based on the potential vasoconstrictive effects (219,223). However, recent case reports seem to suggest triptans effectiveness and safety when administered during attacks of hemiplegic migraine, migraine with brainstem aura and migraine with prolonged aura. Furthermore, although not specifically studied in RCTs, there is no evidence to date that triptans are unsafe for treatment of brainstem aura or hemiplegic migraine in clinical

Table 3.2.4. GRADE evidence profile table of oral naratriptan versus placebo in patients with migraine

Certainty assessment							№ of patients		Effect			
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Naratriptan	Placebo	Relative (95% CI)	Absolute (95% CI)	Quality	Importance
Pain freedom at 2 h - Naratriptan 2.5 mg oral vs Placebo												
3	RCT	Not serious	Not serious	Not serious	Not serious	None	151/442 (34.2%)	37/262 (14.1%)	**RR 2.58** (0.91 to 7.32)	**223 more per 1.000** (from 13 less to 893 more)	⊕⊕⊕⊕ high	Critical
Pain freedom at 2 h - Naratriptan 1 mg oral vs Placebo												
1	RCT	Not serious	Not applicable[a]	Not serious	Not serious	None	24/55 (43.6%)	11/63 (17.5%)	**RR 2.50** (1.35 to 4.62)	**262 more per 1.000** (from 61 more to 632 more)	⊕⊕⊕⊖ Moderate	Critical
Pain relief at 2 h - Naratriptan 2.5 mg oral vs Placebo												
4	RCT	Not serious	Not serious	Not serious	Not serious	None	298/541 (55.1%)	86/316 (27.2%)	**RR 2.18** (1.72 to 2.75)	**321 more per 1.000** (from 196 more to 476 more)	⊕⊕⊕⊕ high	Critical
Pain relief at 2 h - Naratriptan 1 mg oral vs Placebo												
2	RCT	Not serious	Not serious	Not serious	Not serious	None	90/140 (64.3%)	39/117 (33.3%)	**RR 1.83** (1.38 to 2.44)	**277 more per 1.000** (from 127 more to 480 more)	⊕⊕⊕⊕ high	Critical

[a]Only one trial.

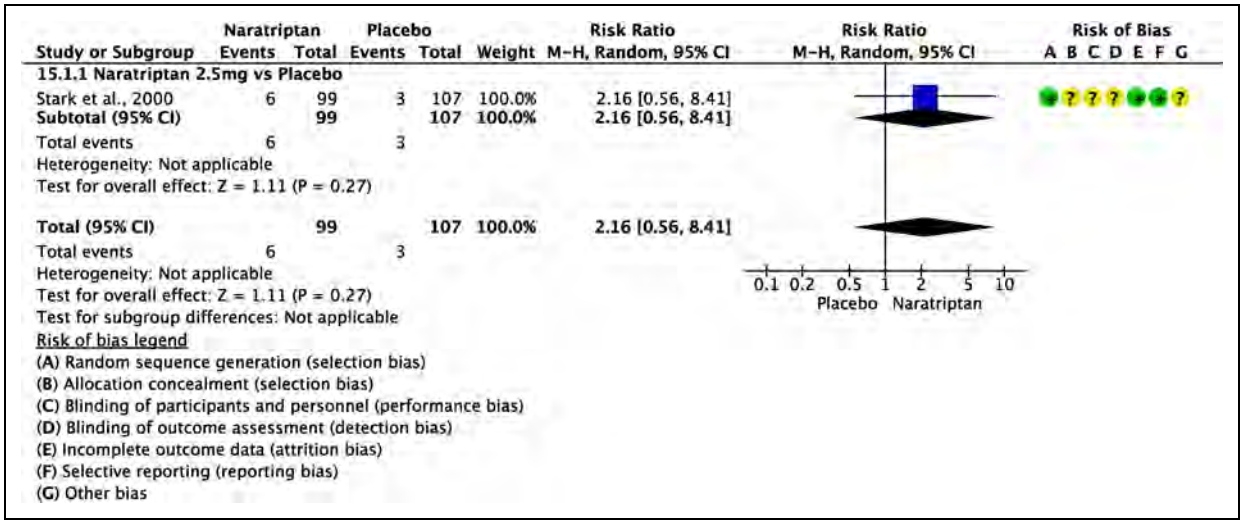


Figure 3.2.15. Forest plot showing the comparison between oral naratriptan and placebo for the outcome pain freedom at 2 h in patients with migraine.

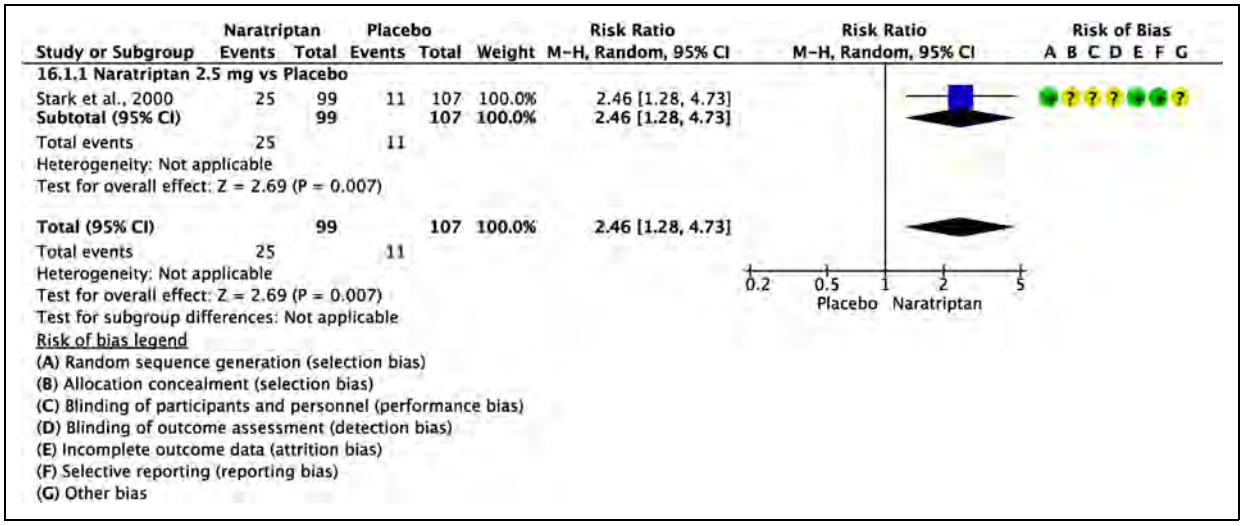


Figure 3.2.16. Forest plot showing the comparison between oral naratriptan and placebo for the outcome pain relief at 2 h in patients with migraine.

practice (219,224). However, more data are required to elucidate the efficacy, tolerability, and safety issues of triptans when administered in patients experiencing these peculiar aura phenomena.

Topic: Which formulation to choose?. Suggestion: We suggest preferring intranasal and orally disintegrating formulations over regular tablets when moderate or severe nausea, or vomiting are present, or a rapid action is needed (e.g., attacks with rapid pain escalation or fully developed upon awakening). Subcutaneous sumatriptan (6 mg/ml) should be considered in case of difficult-to-treat attacks.

Rationale: Although oral administration is easier than non-oral routes, gastric absorption can be delayed during migraine attacks in some individuals due to migraine-related gastroparesis (225,226). Moreover, nausea or vomiting might cause difficulties in oral drug administration. Therefore, alternative routes of administration should be taken into account (227). While for patients without significant nausea regular tablets are appropriate, in patients experiencing mild nausea, nausea exacerbated by drinking, or when fluids are not easily available to swallow tablets, orally disintegrating triptans (i.e., wafers) can be preferable (228). Nevertheless, triptans wafers do not necessarily have a more rapid action compared to

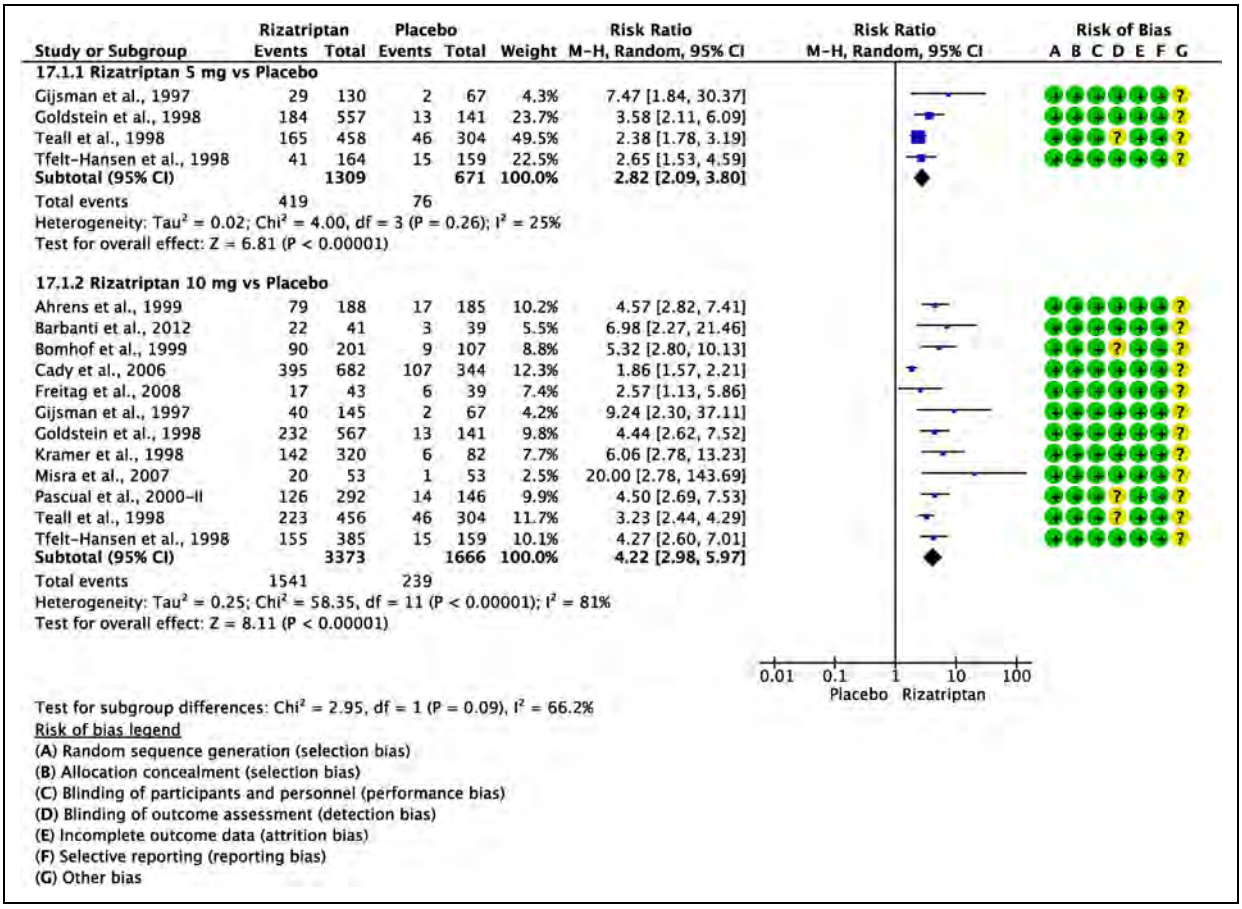


Figure 3.2.17. Forest plot showing the comparison between oral rizatriptan and placebo for the outcome pain freedom at 2 h in patients with migraine.

regular tablets, as triptans are not absorbed through the oral mucosa. For patients with severe nausea or early vomiting in the course of their migraine attacks, nasal sprays formulation of zolmitriptan or sumatriptan, as well as subcutaneous sumatriptan should be considered (229).

Based on the fast absorption property, nasal sprays formulation of zolmitriptan or sumatriptan should also be considered in patients with rapid pain escalation during attacks or full-blown attack upon awakening (230). However, based on the fastest absorption as well as the highest bioavailability resulting in both more rapid action and greater efficacy compared to other triptans formulations (231).

Topic: What to do in case of headache relapse after initial response?. Suggestion: Upon headache relapse after an initially successful treatment, we suggest repeating triptan administration (at least 2 h after the previous intake). However, if the relapse rate is frequent, we suggest switching to another triptan (e.g., eletriptan, frovatriptan and naratriptan) or combining the triptan with a fast-acting formulations of NSAIDs (e.g., naproxen sodium, ibuprofen lysine or diclofenac potassium).

Rationale: Some patients can experience headache relapse, which is defined as a return of symptoms within 48 h after an initially successful treatment, requiring symptomatic drug re-dosing. Indeed, it has been demonstrated that a second dose of the same triptan is effective in case of headache relapse (232). However, patients should be made aware that the higher the number of triptans intake the greater is the risk of developing medication overuse headache (233).

If relapses occur frequently, triptans with longer plasma half-lives ($T_{1/2}$) such as eletriptan, naratriptan, or frovatriptan as well as combination of triptan and NSAID (due to synergistic/additive interaction) should be considered (85,234).

Topic: How many administrations of a triptan are needed to define whether or not a patient is a responder?. Suggestion: we suggest administering a specific triptan at least two more times, in case of no response to the first administration, before declaring the patient as non-responder. A triptan responder is defined by the beneficial effect of the triptan in at least three out of four consecutive attacks.

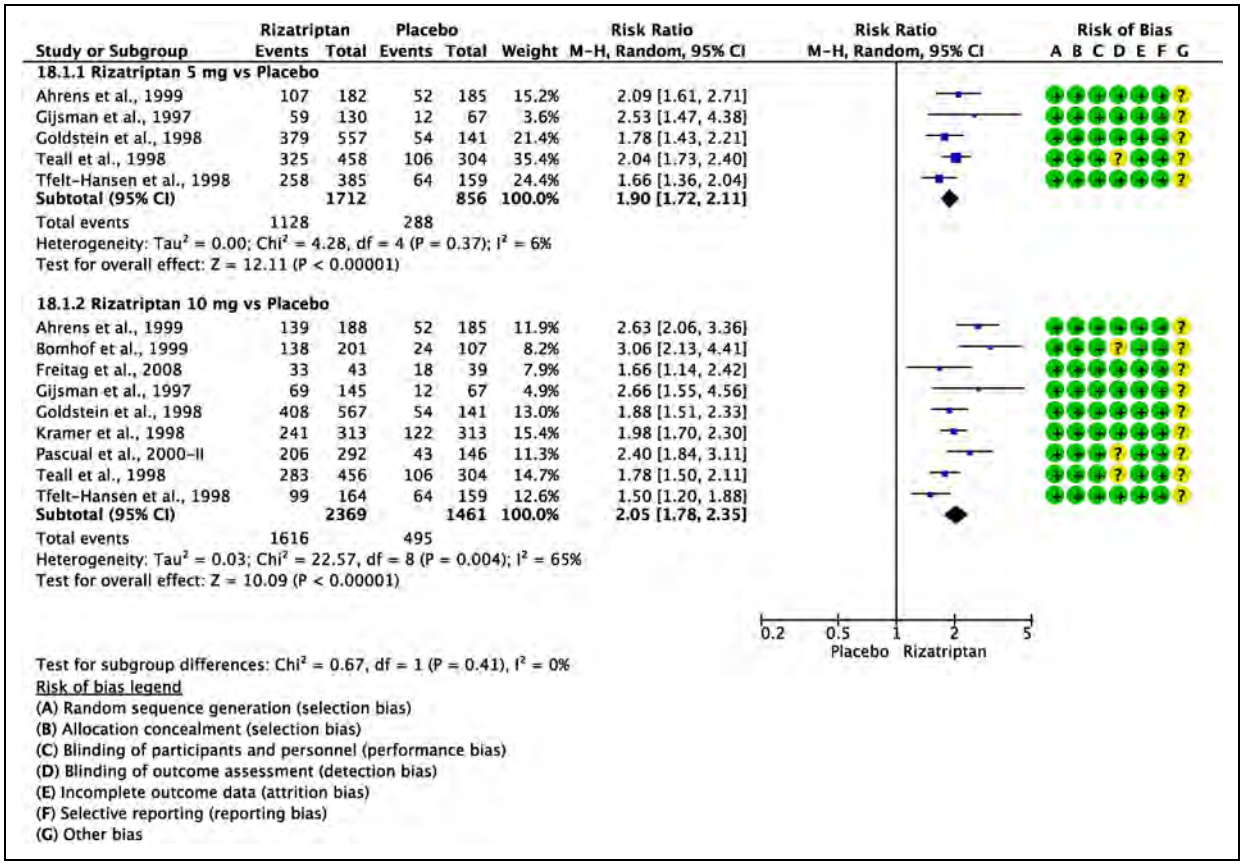


Figure 3.2.18. Forest plot showing the comparison between oral rizatriptan and placebo for the outcome pain relief at 2 h in patients with migraine.

Therefore, if a triptan is not effective after three consecutive attacks, the patient can be declared as non-responder.

Rationale: although triptans trials mainly focused on the response to a single attack, the consistency of response over different attacks surely represents a key factor in the evaluation of the benefit of a symptomatic treatment. According to the Consensus of the European Headache Federation (EHF) on the definition of effective treatment of a migraine attack and triptan failure, patients can be considered responder to a specific triptan when effective treatment is observed in at least three out of four consecutive attacks (235).

Topic: If a patient does not respond to a triptan, does it make sense to try a different triptan?. Suggestion: Lack of response to one triptan does not predict likelihood of responsiveness to a different triptan. We suggest trying at least three triptans before concluding for non-response to triptans (as a class).

Rationale: Several trials evaluated the response to an alternative triptan in patients with no response to a triptan. Despite the heterogeneity among the different trials in terms of study design, definition of triptan "no response", and pain intensity at baseline, they all consistently demonstrated no "class-effect" for triptans (i.e., triptan response failure is not predictive of lack of response to an alternative triptan) (236).

According to the Consensus of the EHF on the definition of effective treatment of a migraine attack and of triptan failure, patients are defined triptan-resistant when they do not respond to at least two different triptans, while patients not responding to at least three different triptans including sumatriptan subcutaneous formulation are defined triptan refractory. Patients can be considered non-responders to a specific triptan when effective treatment is observed in less than three out of four consecutive attacks (235).

Topic: If a triptan is not tolerated, is it reasonable to try another triptan?. Suggestion: If a triptan is not tolerated and AEs are mild to moderate, a lower dose can be considered before discontinuing the drug. Almotriptan should be considered given its favorable tolerability profile.

Rationale: Most triptans AEs are mild to moderate; the risk of severe AEs is low so that reducing the dose or switching is reasonable (237). In clinical practice,

Table 3.2.5. GRADE evidence profile table of oral rizatriptan versus placebo in the acute treatment of migraine attacks

Certainty assessment							№ of patients		Effect			
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Rizatriptan	Placebo	Relative (95% CI)	Absolute (95% CI)	Quality	Importance
Pain freedom at 2 h - Rizatriptan 5 mg oral vs Placebo												
4	RCT	Not serious	Not serious	Not serious	Not serious	None	419/1309 (32.0%)	76/671 (11.3%)	**RR 2.82** (2.09 to 3.80)	**206 more per 1.000** (from 123 more to 317 more)	⊕⊕⊕⊕ high	Critical
Pain freedom at 2 h - Rizatriptan 10 mg oral vs Placebo												
12	RCT	Not serious	Not serious	Not serious	Not serious	None	1541/3373 (45.7%)	239/1666 (14.3%)	**RR 4.22** (2.98 to 5.97)	**462 more per 1.000** (from 284 more to 713 more)	⊕⊕⊕⊕ high	Critical
Pain relief at 2 h - Rizatriptan 5 mg oral vs Placebo												
5	RCT	Not serious	Not serious	Not serious	Not serious	None	1128/1712 (65.9%)	288/856 (33.6%)	**RR 1.90** (1.72 to 2.11)	**303 more per 1.000** (from 242 more to 373 more)	⊕⊕⊕⊕ high	Critical
Pain relief at 2 h - Rizatriptan 10 mg oral vs Placebo												
9	RCT	Not serious	Not serious	Not serious	Not serious	None	1616/2369 (68.2%)	495/1461 (33.9%)	**RR 2.05** (1.78 to 2.35)	**356 more per 1.000** (from 264 more to 457 more)	⊕⊕⊕⊕ high	Critical

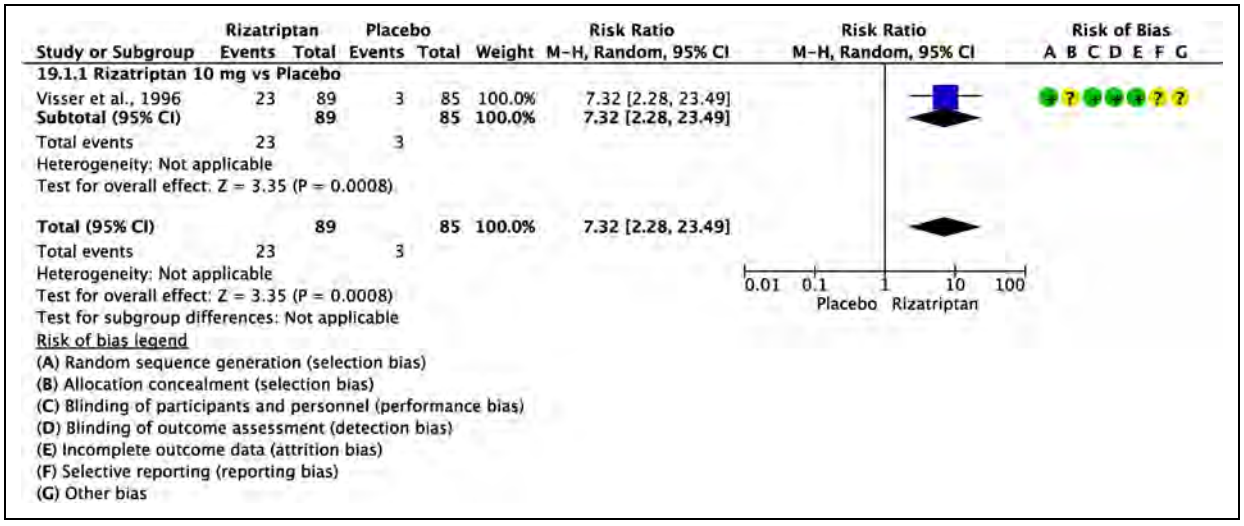


Figure 3.2.19. Forest plot showing the comparison between rizatriptan and placebo for the outcome pain freedom at 2 h in patients with migraine.

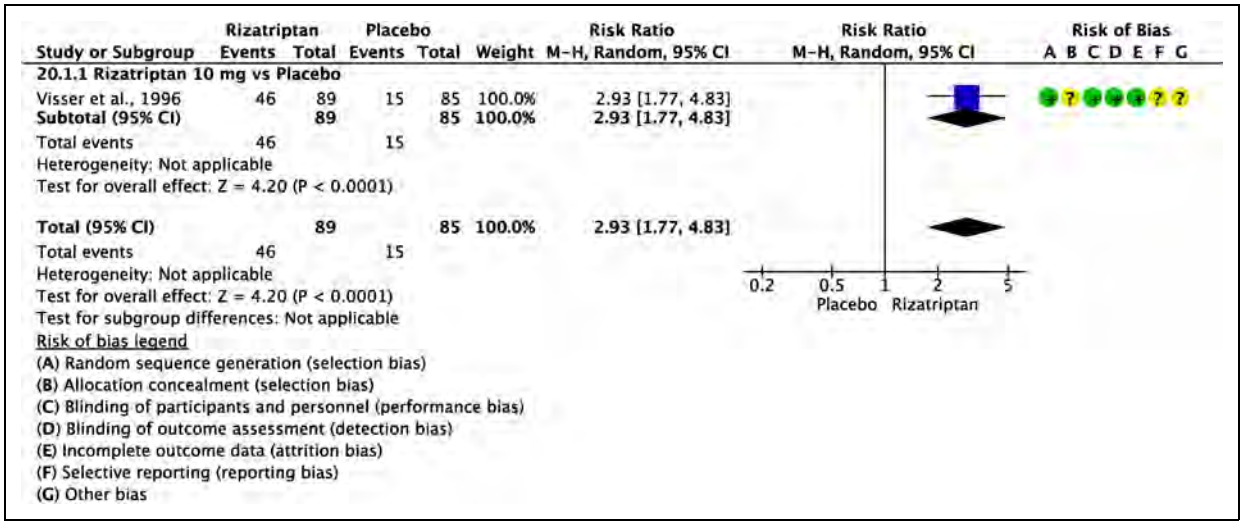


Figure 3.2.20. Forest plot showing the comparison between rizatriptan and placebo for the outcome pain relief at 2 h in patients with migraine.

lowering the dose may be considered as most AEs are associated with a dose-response relationship (i.e., eletriptan, frovatriptan, naratriptan, rizatriptan, sumatriptan, and zolmitriptan).

Topic: How many triptans per month could be administered?.
Suggestion: We suggest limiting the use of triptans to less than 10 days per month in order to decrease the risk of MOH. However, considering that triptans can lead to MOH sooner and at lower doses than other acute headache medications, such as simple analgesics, patients should be advised and trained to put in place corrective measures to limit triptan intake over the month.

Rationale: based on some observational studies showing a greater risk of MOH in patients with more than 10 days of triptans per month, previous expert opinions tend to generally recommend limiting the use of triptans to less than 10 days per month in order to decrease the risk of development of MOH, being the use of triptans on 10 days per month considered overuse according to the International Headache Society criteria for "triptan-overuse headache"(ICHD-3 8.2.2) (7,238).

Topic: Can pharmacokinetic differences affect triptan choice?.
Suggestion: Based on pharmacokinetic differences, frovatriptan, eletriptan or naratriptan should be considered for

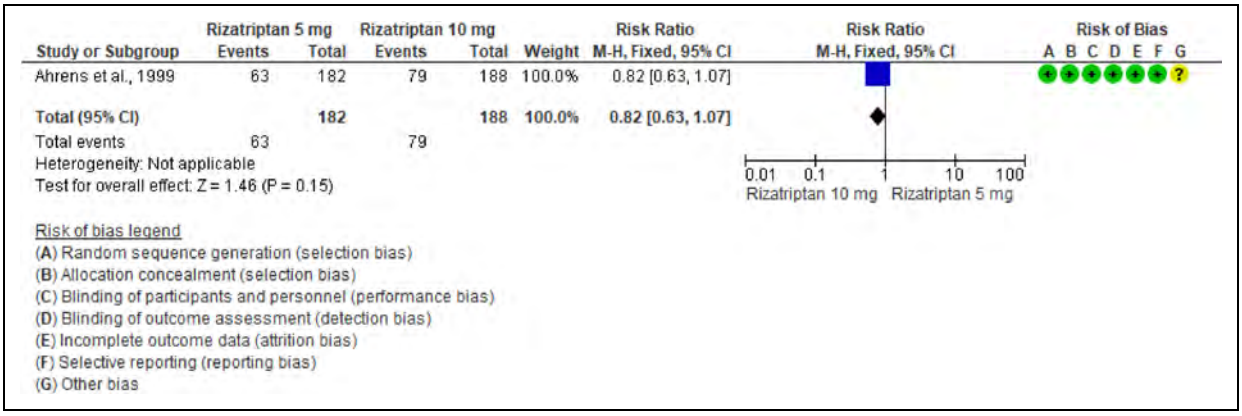


Figure 3.2.21. Forest plot showing the comparison between rizatriptan 5 mg and rizatriptan 10 mg placebo for the outcome pain freedom at 2 h in patients with migraine.

long-lasting migraine attacks as well as for attacks with high relapse rates, while rizatriptan should be considered for attacks with rapid pain escalation or full-blown attack upon awakening.

Rationale: Several pharmacokinetic differences exist among oral triptans, but it is not clear whether these differences among kinetic parameters are relevant in clinical practice (227,239).

Frovatriptan, naratriptan, and eletriptan are characterized by longer plasma half-lives ($T_{1/2}$) compared to the other triptans, with longer duration of action leading to lower migraine relapse rate (59). Rizatriptan is characterized by a shorter time to peak plasma level (T_{max}) compared to other triptans, suggesting a faster onset of action. Almotriptan and naratriptan are characterized by a higher oral bioavailability compared to other triptans, suggesting a more consistent efficacy over multiple attacks. Eletriptan is characterized by higher lipophilicity compared to other triptans, with higher potential to cross the blood-brain-barrier, which suggests central sites of action able to putatively increase the treatment efficacy as well as the risk of central nervous system adverse events (211).

Topic: Do triptans show relevant drug-to-drug interactions?.

Suggestion 1: A dose adjustment of rizatriptan (i.e., reduction of the rizatriptan dose from 10 mg to 5 mg) is recommended in subjects with migraine taking propranolol.

Rationale 1: Rizatriptan is metabolized by monoamine oxidase A (MAO-A) like propranolol metabolites, with a consequent MAO-A competitive interaction that may result in an increase in rizatriptan plasmatic level up to 70% when administered together with propranolol (but not with other β-blockers) (240).

Suggestion 2: Triptans are contraindicated within 24 h from ergotamine administration.

Rationale 2: Based on the shared potential to induce vasoconstriction, triptans should not be administered within 24 h from ergotamine administration (241).

Suggestion 3: Consider frovatriptan, eletriptan or naratriptan in subjects with migraine taking MAO inhibitors. Triptans which are metabolized by MAO (i.e., sumatriptan, rizatriptan, almotriptan and zolmitriptan) are contraindicated within two weeks from MAO inhibitors treatment.

Rationale 3: Some triptans (i.e., sumatriptan, zolmitriptan, rizatriptan, and less so almotriptan) (242) should not be concomitantly administered during the treatment with MAO inhibitors to avoid additive effects potentially resulting in the serotonin syndrome. At least two weeks of MAO inhibitors discontinuation are mandatory to start the administration of triptans metabolized by MAO (59,241).

Suggestion 4: Eletriptan should not be concomitantly administered with moderate or strong CYP3A4 inhibitors drugs.

Rationale 4: Eletriptan is metabolized through the CYP3A4 system (69). Therefore, precautions are needed when concomitantly administered within 72 h of drugs inhibiting CYP3A4 (e.g., antifungal ketoconazole, macrolide erythromycin, anti-HIV drugs, verapamil, grapefruit juice).

Suggestion 5: Triptans can be used in combination with selective serotonin reuptake inhibitors (SSRI) or serotonin noradrenaline reuptake inhibitors (SNRI) drugs.

Rationale 5: Triptans do not act on the 5-HT_{2A} receptors, and, therefore, as already supported by the American Headache Society position paper, the risk of serotonin syndrome does not increase when they are administered in concomitance with SSRI or serotonin noradrenaline reuptake inhibitors (243,244).

Suggestion 6: Almotriptan should be administered with caution with strong CYP3A4 inhibitors drugs. Limit initial almotriptan dose to 6.25 mg and maximum dose to 12.5 mg in any 24-period when used with a strong

Table 3.2.6. GRADE evidence profile table of oral rizatriptan 5 mg versus oral rizatriptan 10 mg in the acute treatment of migraine attacks

Certainty assessment							№ of patients		Effect			
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Rizatriptan 5 mg	Rizatriptan 10 mg	Relative (95% CI)	Absolute (95% CI)	Quality	Importance
Pain freedom at 2 h - Rizatriptan 5 mg oral vs Rizatriptan 10 mg oral												
1	RCT	Not serious	Not applicable[a]	Not serious	Not serious	None	63/182 (34.6%)	79/188 (42.0%)			⊕⊕⊕⊖ Moderate	Critical

[a]Only one trial.

CYP3A4 inhibitor. Avoid concurrent use in patients with impaired hepatic or renal function.

Rationale 6: Almotriptan is metabolized through the CYP3A4 system (245). Strong CYP3A4 inhibitors may increase the serum concentration of the drug. Therefore, precautions are needed when concomitantly administered with drugs inhibiting CYP3A4 (e.g., anti-fungal ketoconazole).

Suggestion 7: Zolmitriptan should be administered with caution with cimetidine. Limit the maximum single dose of zolmitriptan to 2.5 mg, and do not exceed 5 mg in a 24-h period, when co-administered with cimetidine (246).

Rationale 7: Cimetidine may increase the serum concentration of zolmitriptan. The mechanism of this interaction has not been fully investigated, but cimetidine-mediated inhibition of CYP1A2, an enzyme responsible for zolmitriptan metabolism, likely contributes (246).

Topic: How should triptans be used to treat menstrual migraine?. Suggestion: Triptans may be used for the acute treatment of menstrual attacks or for their short-term preventive treatment (short-term prevention) when given two to three days prior to onset of menstruation.

Rationale: Menstrual migraine attacks are often severe and disabling and they warrant migraine-specific treatment and prevention, especially in case of increased frequency, pain severity, and duration. In a review comparing studies investigating acute treatment of menstrual migraine attacks, rizatriptan 10 mg showed the best overall evidence (2 h pain freedom and pain relief between 2 and 24 h) (247). For short-term prevention, Maasumi et al. provided data supporting the use of frovatriptan 2.5 mg daily or twice daily and zolmitriptan 2.5 mg twice or three times daily (247). In a systematic review, naratriptan was least effective when compared to zolmitriptan and frovatriptan (248).

Topic: Can triptans be used during pregnancy?. Suggestion: The use of triptans during pregnancy could be considered as a second line approach in the case of acetaminophen failure. Among triptans, sumatriptan, naratriptan, and rizatriptan should be preferred.

Rationale: Although data from several population-based and registry studies support the safety of triptans during pregnancy in terms of teratogenicity (especially for sumatriptan, naratriptan, and rizatriptan), there are still conflicting results about an increased risk of premature birth (249–251).

Topic: Can triptans be used during lactation?. Suggestion: The use of triptans during lactation could be considered as a second line approach in the case of NSAIDs failure. Among triptans, eletriptan should be preferred. Breastfeeding pause for 12 h after the intake of a triptan can be considered as a cautionary approach.

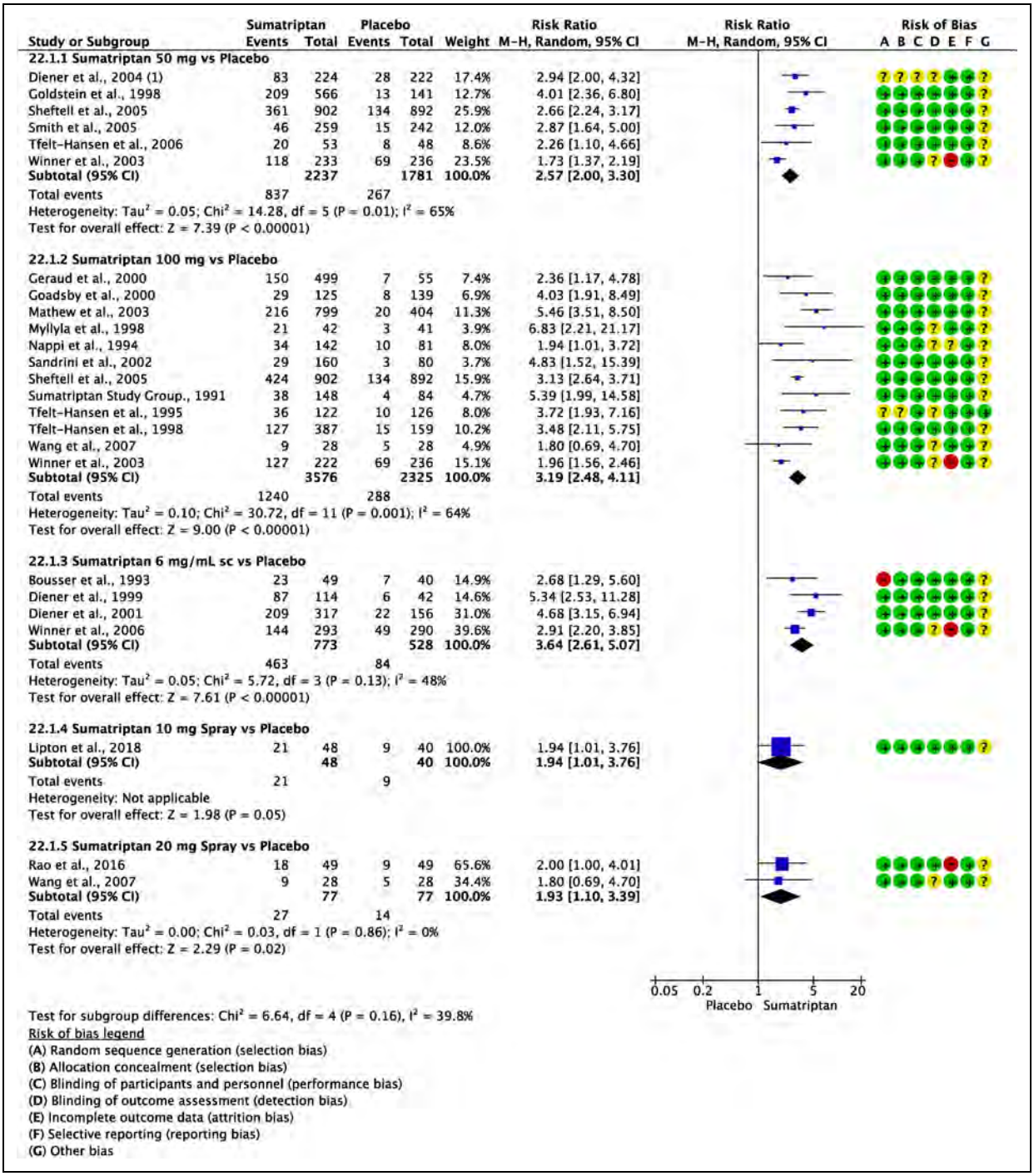


Figure 3.2.22. Forest plot showing the comparison between sumatriptan and placebo for the outcome pain freedom at 2 h in patients with migraine.

Rationale: Triptans efficacy, safety and tolerability during lactation have not been extensively studied although categorized as "usually compatible" with breastfeeding by the American Academy of Pediatrics guidelines/consensus/position paper (252). Among triptans, eletriptan might be theoretically less likely to be transferred into breastmilk, due to its high protein bounding compared to other triptans (253).

Topic: Triptans and renal impairment. Suggestion: In subjects with severe renal impairment (CrCl < 15) almotriptan, rizatriptan and eletriptan are contraindicated while almotriptan

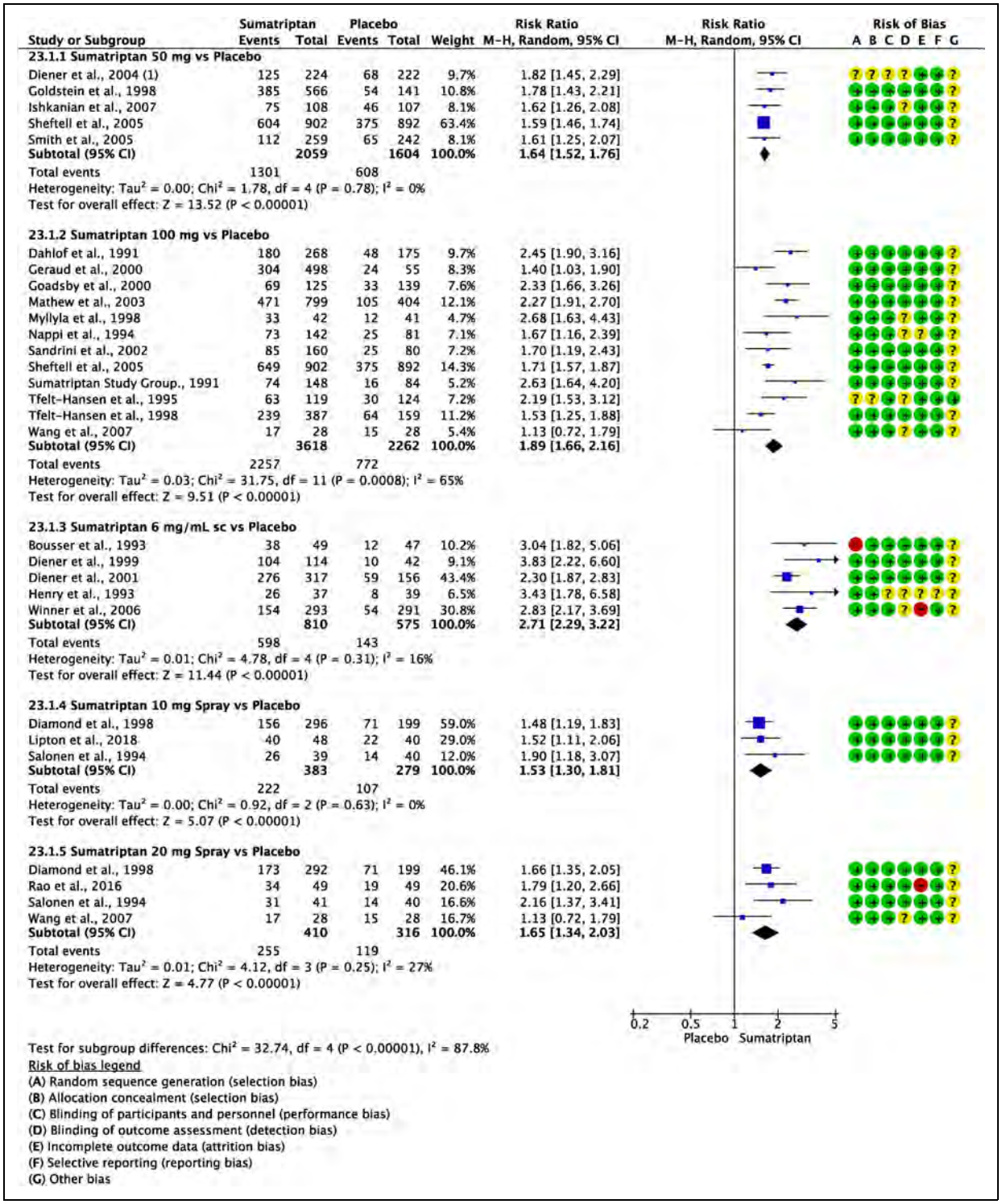


Figure 3.2.23. Forest plot showing the comparison between sumatriptan and placebo for the outcome pain relief at 2 h in patients with migraine.

can be administered at the maximum dose of 12.5 mg over 24 h (254). No dose adjustments are needed for zolmitriptan and frovatriptan. In subjects with mild to moderate renal impairment a dose adjustment is needed for rizatriptan (no more than 5 mg over 24 h) and eletriptan (no more than 20 mg over 24 h) (254).

Table 3.2.7. GRADE evidence profile table of sumatriptan versus placebo in patients with migraine

Certainty assessment							№ of patients		Effect			
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Sumatriptan	Placebo	Relative (95% CI)	Absolute (95% CI)	Quality	Importance
Pain freedom at 2 h – Sumatriptan 50 mg oral vs Placebo												
6	RCT	Not serious	Not serious	Not serious	Not serious	None	837/2237 (37.4%)	267/1781 (15.0%)	**RR 2.57** (2.00 to 3.30)	**235 more per 1.000** (from 150 more to 345 more)	⊕⊕⊕⊕ High	Critical
Pain freedom at 2 h – Sumatriptan 100 mg oral vs Placebo												
12	RCT	Not serious	Not serious	Not serious	Not serious	None	1240/3576 (%)	288/2325 (%)	**RR 3.19** (2.48 to 4.11)	**271 more per 1.000** (from 183 more to 385 more)	⊕⊕⊕⊕ High	Critical
Pain freedom at 2 h – Sumatriptan 6 mg/mL subcutaneous vs Placebo												
4	RCT	Serious	Not serious	Not serious	Not serious	None	463/773 (59.9%)	84/528 (15.9%)	**RR 3.64** (2.61 to 5.07)	**420 more per 1.000** (from 256 more to 648 more)	⊕⊕⊕⊕ High	Critical
Pain freedom at 2 h – Sumatriptan 10 mg nasal spray vs Placebo												
1	RCT	Not serious	Not applicable[a]	Not serious	Serious[b]	None	21/48 (43.8%)	9/40 (22.5%)	**RR 1.94** (1.01 to 3.76)	**212 more per 1.000** (from 2 more to 621 more)	⊕⊕⊕⊖ Moderate	Critical
Pain freedom at 2 h – Sumatriptan 20 mg nasal spray vs Placebo												
2	RCT	Not serious	Not serious	Not serious	Not serious	None	27/77 (35.1%)	14/77 (18.2%)	**RR 1.93** (1.10 to 3.39)	**169 more per 1.000** (from 18 more to 435 more)	⊕⊕⊕⊕ High	Critical
Sumatriptan 50 mg vs Placebo - Pain relief 2h												
5	RCT	Not serious	Not serious	Not serious	Not serious	None	1301/2059 (63.2%)	608/1604 (37.9%)	**RR 1.64** (1.52 to 1.76)	**253 more per 1.000** (from 198 more to 312 more)	⊕⊕⊕⊕ high	Critical

(continued)

Table 3.2.7. (continued)

Certainty assessment							№ of patients		Effect			
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Sumatriptan	Placebo	Relative (95% CI)	Absolute (95% CI)	Quality	Importance
Pain relief at 2 h – Sumatriptan 100 mg oral vs Placebo												
12	RCT	Not serious	Not serious	Not serious	Not serious	None	2257/3618 (62.4%)	772/2262 (34.1%)	**RR 1.89** (1.66 to 2.16)	**304 more per 1.000** (from 225 more to 396 more)	⊕⊕⊕⊕ high	Critical
Pain relief at 2 h – Sumatriptan 6 mg/mL subcutaneous vs Placebo												
5	RCT	Serious	Not serious	Not serious	Not serious	None	598/810 (73.8%)	143/575 (24.9%)	**RR 2.71** (2.29 to 3.22)	**425 more per 1.000** (from 321 more to 552 more)	⊕⊕⊕⊕ high	Critical
Pain relief at 2 h – Sumatriptan 10 mg nasal spray vs Placebo												
3	RCT	Not serious	Not serious	Not serious	Not serious	None	222/383 (58.0%)	107/279 (38.4%)	**RR 1.53** (1.30 to 1.81)	**203 more per 1.000** (from 115 more to 311 more)	⊕⊕⊕⊕ high	Critical
Pain relief at 2 h – Sumatriptan 20 mg nasal spray vs Placebo												
4	RCT	Not serious	Not serious	Not serious	Not serious	None	255/410 (62.2%)	119/316 (37.7%)	**RR 1.65** (1.34 to 2.03)	**245 more per 1.000** (from 128 more to 388 more)	⊕⊕⊕⊕ high	Critical

[a]Only one trial; [b]low numbers of patients.

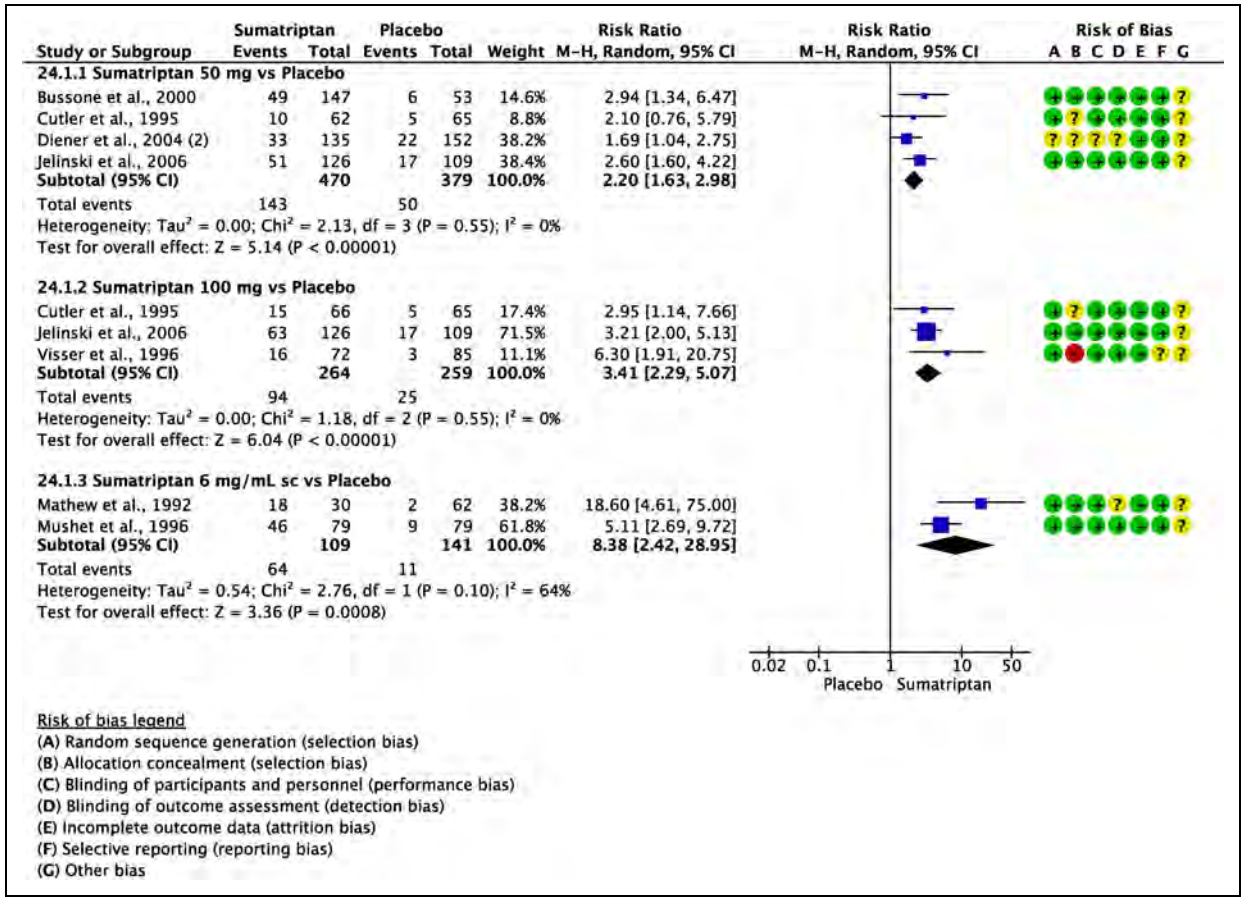


Figure 3.2.24. Forest plot showing the comparison between sumatriptan and placebo for the outcome pain freedom at 2 h in patients with migraine.

Topic: Triptans and hepatic failure. Suggestion: In subjects with severe hepatic impairment all triptans are contraindicated, with the exception of zolmitriptan which, due to its predominantly renal excretion, can be administered at a maximum dose of 5 mg over 24 h (254). In subjects with mild to moderate hepatic impairment no dose adjustments are needed for frovatriptan while a dose adjustment is needed for rizatriptan (no more than 5 mg over 24 h), sumatriptan (no more than 25–50 mg over 24 h), naratriptan (1 mg-2.5 mg over 24 h), zolmitriptan (1.25–5 mg over 24 h), and almotriptan (6.25–12.5 mg over 24 h).

Topic: When should triptans be considered for the acute treatment of migraine attacks?. Suggestion: We suggest triptans as first-line medication in subjects with severe and disabling migraine attacks. Moreover, we suggest considering triptans as second-line medication when over-the-counter analgesics are not effective in subjects with mild to moderate migraine attacks.

Rationale: Two basic approaches to the acute treatment of migraine attacks have been identified based upon attack severity and migraine related disability: the stratified and the step-care-across-attacks approaches (255). In the stratified approach, suggested as the most effective approach based on evidence, the choice of medication is guided by attack severity and disability. Essentially, subjects with migraine attacks characterized by severe pain intensity and great disability are initially started on triptan, whereas subjects with attacks characterized by low pain intensity and disability are started on NSAID first, while triptans will be proposed as second line if NSAID treatment proves unsuccessful. Contrariwise, in the step-care-across-attacks approach, a less expensive non-migraine-specific medication is chosen as the first therapeutic option regardless of attack severity. If the medication proves unsuccessful, migraine-specific options are proposed for subsequent attacks. In other words, NSAIDs or another non-specific analgesic is administered first and, if not beneficial, a triptan should be preferred in subsequent attacks. The "step-care-across-attacks" approach may be burdened by several treatment failures before arriving at the effective medication.

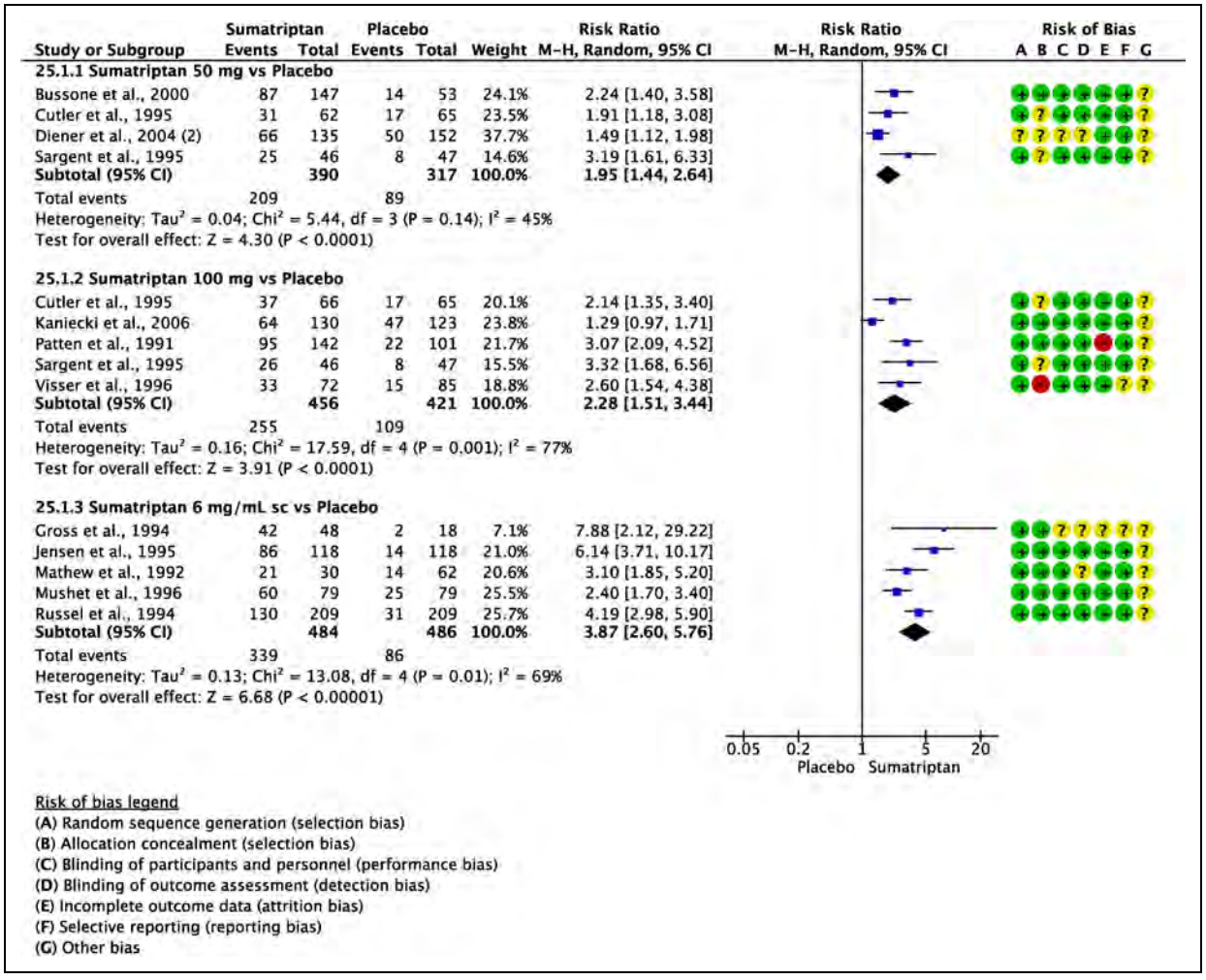


Figure 3.2.25. Forest plot showing the comparison between sumatriptan and placebo for the outcome pain relief at 2 h in patients with migraine.

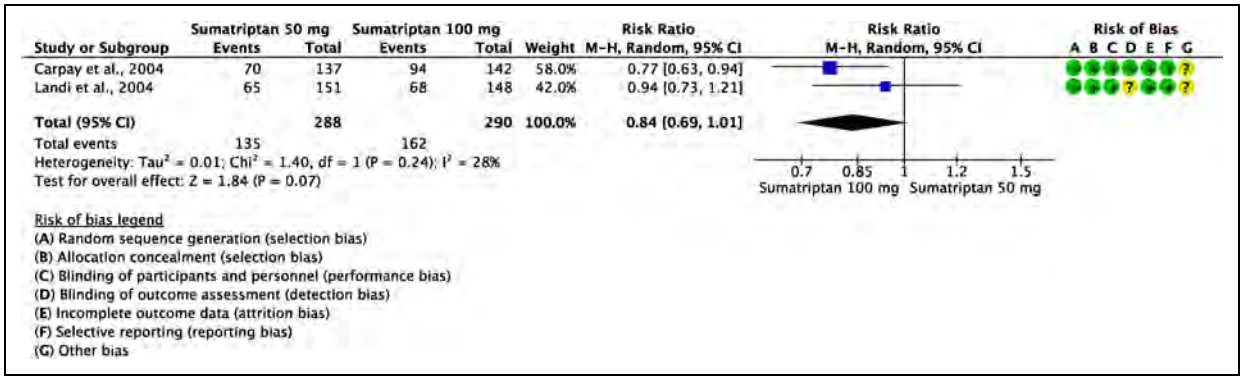


Figure 3.2.26. Forest plot showing the comparison between sumatriptan 50 mg and sumatriptan 100 mg for the outcome pain freedom at 2 h in patients with migraine.

Table 3.2.8. GRADE evidence profile table of sumatriptan 50 mg versus sumatriptan 100 mg in the acute treatment of migraine attacks

Certainty assessment							№ of patients		Effect		Quality	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Sumatriptan	Placebo	Relative (95% CI)	Absolute (95% CI)		
Pain freedom at 2 h – Sumatriptan 50 mg oral vs Sumatriptan 100 mg oral												
2	RCT	Not serious	Not serious	Not serious	Not serious	None	135/288 (46.9%)	162/290 (55.9%)	**RR 0.84** (0.69 to 1.01)	**89 less per 1000** (from 173 less to 6 more)	⊕⊕⊕⊕ High	Critical

*Wide confidence interval.

3.3 Paracetamol (Acetaminophen)

Introduction

Paracetamol, also known as acetaminophen, is one of the most frequently used over-the-counter medications for the treatment of acute pain, including headaches (256). It has a lower risk of gastric bleeding compared to other analgesics, even if at the expense of a risk for liver toxicity (257,258). Paracetamol is often recommended for pediatric migraine. Some clinicians also suggest the use of paracetamol for the treatment of acute migraine attacks during pregnancy, although the evidence on the safety of fetal exposure to the drug is conflicting (259–262).

Paracetamol has a weak anti-inflammatory action and the mechanisms by which it causes analgesia are not fully understood. Various proposed mechanisms include the inhibition of cyclooxygenases (24,263,264), the involvement of serotonergic pathways, and interactions with the endocannabinoid system (265).

This section systematically analyzes existing data on the efficacy of paracetamol, critically evaluating controlled studies that have explored its role in treating acute migraine attacks. The section is concerned with paracetamol alone, while combinations of paracetamol with other acute medication are reviewed in Section 3.4.

Section-specific methods

This section followed the general procedure to develop this guideline.

Search strings for systematic review/meta-analysis and for additional RCTs are reported in Online Appendix 3.3.1.

Results

In total, we retrieved 1152 references for systematic reviews and meta-analyses. Following the removal of duplicates and completion of screening stages, we included 35 articles.

Eventually, we identified two meta-analyses as source of randomized controlled trials (RCTs) (24,264). After thorough analysis of the full texts of these RCTs, we included three of them in the qualitative synthesis (118,266,267) (Figure 3.3.1).

In our search for RCTs, we initially retrieved 1134 references. After removing duplicates, 1026 references remained for analysis. Considering that the most recent included systematic review/meta-analysis on the topic was published in 2014, the analysis of additional RCTs was performed for papers published after that year, ultimately including no additional RCTs. From the literature search update performed in May 2023 and November 2023, we retrieved 115 references. No additional studies were included from this subsequent search (Figure 3.3.2).

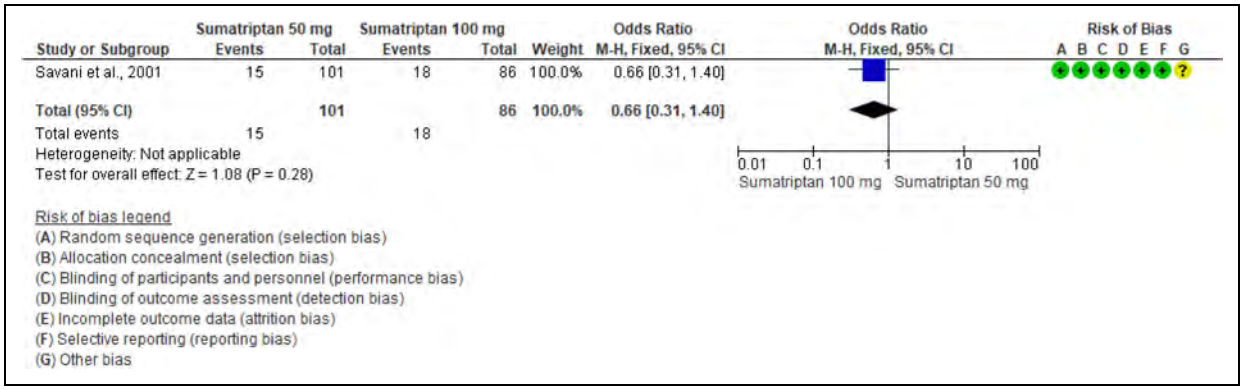


Figure 3.2.27. Forest plot showing the comparison between sumatriptan 50 mg and sumatriptan 100 mg for the outcome pain freedom6 at 2 h in patients with migraine.

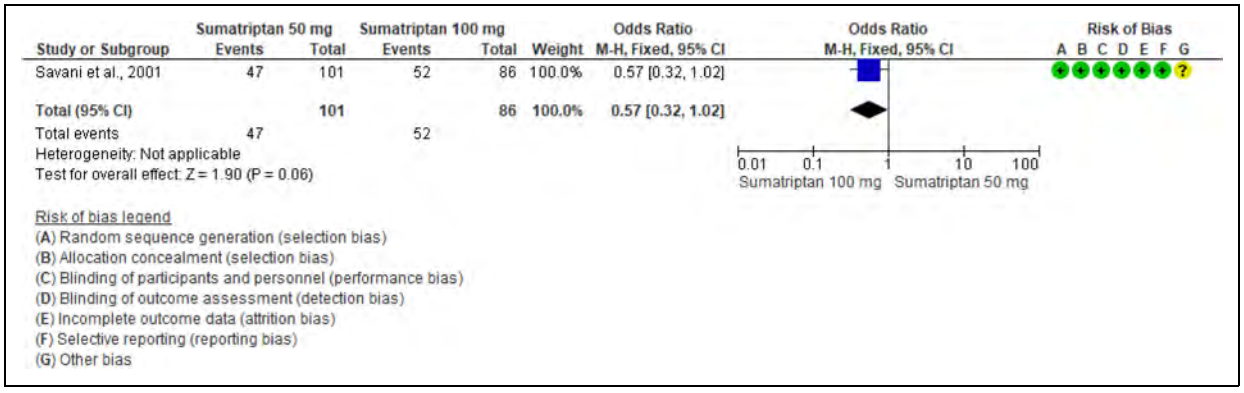


Figure 3.2.28. Forest plot showing the comparison between sumatriptan 50 mg and sumatriptan 100 mg for the outcome pain relief at 2 h in patients with migraine.

In total, three studies were included in the literature review and subsequent quantitative synthesis (meta-analyses) for the development of the evidence-based guideline. All the studies provided a comparison between an active drug and placebo, and all are discussed below.

PICO 3.3.1. In subjects with migraine, is paracetamol superior to placebo in the acute treatment of migraine attacks (outcomes: pain freedom at 2 h, pain relief at 2 h)?

Main evidence. We identified three RCTs (118,266,267) comparing oral paracetamol 1000 mg to placebo in subjects with migraine that met the criteria for main evidence, though they reported an unclear risk of bias (Figures 3.3.3 and 3.3.4).

The pooled analysis of those three studies revealed a significant benefit of orally administered paracetamol (1000 mg) over placebo for both outcomes - pain freedom at 2 h and pain relief at 2 h. The quality of evidence for both outcomes was considered high (Table 3.3.1).

Additional evidence. None.

Evidence-based recommendation for PICO 3.3.1

In subjects with migraine, we recommend oral paracetamol 1000 mg for the acute treatment of migraine attacks.
Quality of evidence: High (⊕⊕⊕⊕)
Strength of the recommendation: Strong (↑↑)

Safety and tolerability of paracetamol. Warnings and contraindications: Cases of severe hemolytic anemia following paracetamol intake have been described in subjects with glucose-6-phosphate dehydrogenase deficiency (268). Paracetamol is also contraindicated for individuals with moderate-to-severe liver failure, as it can transiently increase the levels of liver enzymes two to three weeks after administration (269).

Paracetamol is generally considered safe for managing migraine in children despite the lack of specifically designed controlled trials. Regarding the use of paracetamol during pregnancy, literature is not concord in affirming its safety (270). Some – but not all – studies warn that

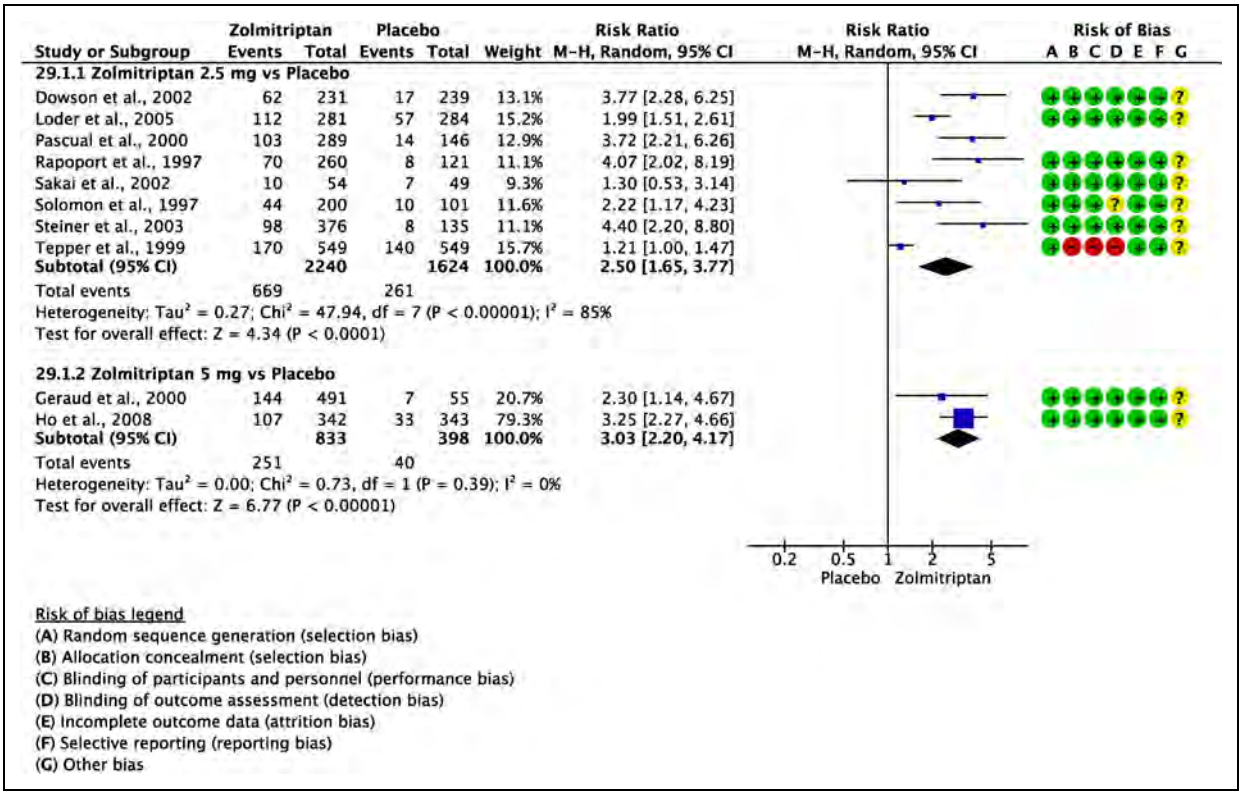


Figure 3.2.29. Forest plot showing the comparison between oral zolmitriptan and placebo for the outcome pain freedom at 2 h in patients with migraine.

paracetamol exposure during pregnancy might be associated with the risk of some neurodevelopmental and endocrine alterations in the newborn (262,271).

Serious safety concerns: Acute severe liver damage has been reported following paracetamol overdosage, even if used to treat migraine attacks (272). Apart from this, a systematic review addressing migraine treatment indicates that the incidence of severe adverse events with paracetamol is comparable to that of placebo (24).

Tolerability: No significant concerns regarding the tolerability of paracetamol have been identified.

Expert-based opinions

Optimization of paracetamol use

Topic: Paracetamol 1000 mg vs Placebo

Suggestion: We recommend administering 1000 mg of paracetamol orally at the onset of migraine symptoms. If the initial dose is not effective, a second dose can be taken after a 6-h interval. We do not recommend more than two 1000-mg doses over a 24-h period. In case of inefficacy of the second dose, we advise using a different acute drug.

Rationale: Paracetamol 1000 mg demonstrated efficacy and safety in managing acute migraine attacks. However, as with other acute drugs including NSAIDs and triptans, when the frequency of intake increases, the risk of developing a medication overuse headache also raises (7,273,274).

3.4 Combination analgesics

Introduction

The complex pathophysiological mechanisms of migraine underpin the variety of migraine symptoms including not only pain, but also nausea, photophobia, phonophobia and other autonomic symptoms. This may explain why none of the currently available monotherapies provides broad coverage of the multiple pathogenic processes in migraine (27,61,63,64,81,275–280). Combining drugs with different mechanisms of action and targeting different peripheral or central migraine mechanisms has a theoretical synergistic therapeutic effect. Furthermore, combining differently acting analgesics could lead to the use of a lower dosage of the individual drugs, with a lower expected incidence of side effects (281–284). Several drug combinations are commercially available, although their availability varies greatly from country to country in both composition and dosage. They include two-drug or three-drug

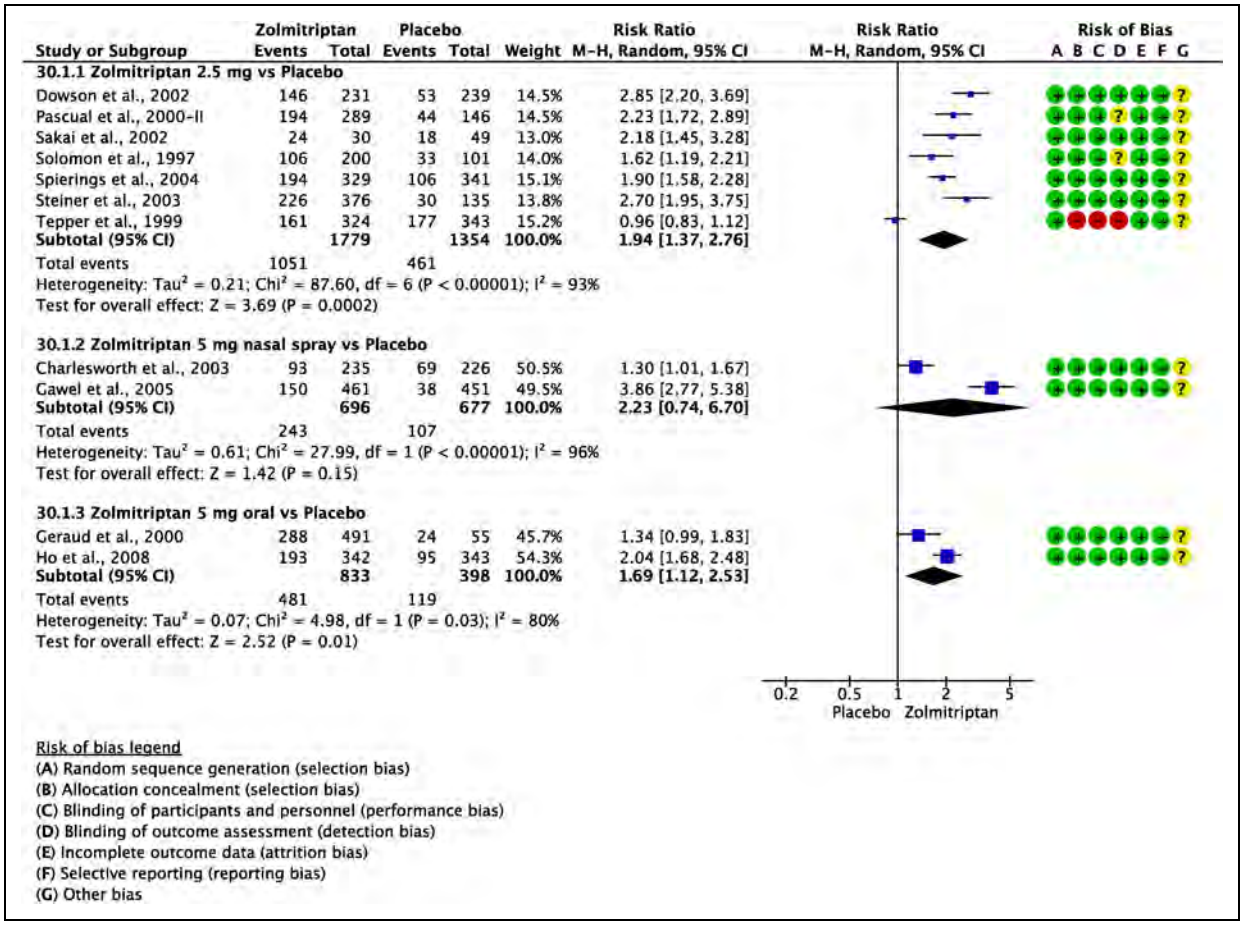


Figure 3.2.30. Forest plot showing the comparison between oral zolmitriptan and placebo for the outcome pain relief at 2 h in patients with migraine.

combinations, such as aspirin, paracetamol, and caffeine (APC), oral metoclopramide plus aspirin, sumatriptan/naproxen and rizatriptan/paracetamol. The three-drug combination APC is the first over-the-counter (OTC) medication registered for acute migraine treatment in the United States (US) in 1998. As for the individual molecules, acetylsalicylic acid mechanisms of action in migraine are based on the inhibition of cyclooxygenase activity resulting in the platelet aggregation and plasma extravasation in the context of neurogenic inflammation, involving meningeal vessels, and its central action on the modulation of pain transmission (285–290). The analgesic property of the non-opioid, non-salicylate medication paracetamol may involve spinal and supraspinal actions, although the exact mechanism of action is unknown (291). On the other hand, caffeine is a methylxanthine used in several analgesic preparations because of its central cholinergic analgesia (292). Its antinociceptive effect is attributed to an inhibition of cyclooxygenase activity and adenosine receptor antagonism both at central and peripheral levels (293). It is used as an adjuvant in the treatment of both pain and headache (294,295). Caffeine alone shows analgesic properties in several clinical pain conditions (296). The observed synergism of acetylsalicylic acid, paracetamol, and caffeine on the inhibition of PGE 2 synthesis in microglial cells, a common model for the COX-2 inhibiting activity of non-steroidal anti-inflammatory drugs, may partly explain these effects (297). Furthermore, coadministration of caffeine and acetylsalicylic acid or other analgesics has been demonstrated to increase plasma acetylsalicylic acid concentration and the mechanism of this increase may involve plasma protein binding displacement (298). The dopamine receptor antagonist metoclopramide is indicated in many pathological conditions to treat nausea and vomiting including migraine (299). Metoclopramide in oral, suppository or parenteral form has been shown to improve gastrointestinal motility enhancing the absorption of other drugs and is effective in relieving nausea and vomiting frequently associated with migraine (300,301). Combinations containing oral metoclopramide plus an analgesic, in particular acetylsalicylic acid, may be a valid therapeutic option for patients when triptans are contraindicated or not tolerated or for those patients who frequently experience nausea and vomiting as associated symptoms (301). Notably, there is

Table 3.2.9. GRADE evidence profile table of oral zolmitriptan versus placebo in the acute treatment of migraine attacks

Certainty assessment							№ of patients		Effect			
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Zolmitriptan	Placebo	Relative (95% CI)	Absolute (95% CI)	Quality	Importance
Pain freedom at 2 h - Zolmitriptan 2.5 mg oral vs Placebo												
8	RCT	Not serious	Not serious	Not serious	Not serious	None	669/2240 (29.9%)	261/1624 (16.1%)	**RR 2.50** (1.65 to 3.77)	**241 more per 1.000** (from 104 more to 445 more)	⊕⊕⊕⊕ High	Critical
Pain relief at 2 h - Zolmitriptan 2.5 mg oral vs Placebo												
7	RCT	Not serious	Not serious	Not serious	Not serious	None	1051/1779 (59.1%)	461/1354 (34.0%)	**RR 1.94** (1.37 to 2.76)	**320 more per 1.000** (from 126 more to 599 more)	⊕⊕⊕⊕ High	Critical
Pain freedom at 2 h - Zolmitriptan 5 mg oral vs Placebo												
2	RCT	Not serious	Not serious	Not serious	Not serious	None	251/833 (30.1%)	40/398 (10.1%)	**RR 3.03** (2.20 to 4.17)	**204 more per 1.000** (from 121 more to 319 more)	⊕⊕⊕⊕ High	Critical
Pain relief at 2 h - Zolmitriptan 5 mg oral vs Placebo												
2	RCT	Not serious	Not serious	Not serious	Not serious	None	243/696 (34.9%)	107/677 (16.0%)	**RR 1.69** (1.12 to 2.53)	**111 more per 1.000** (from 180 more to 245 more)	⊕⊕⊕⊕ High	Critical
Pain relief at 2 h - Zolmitriptan 5 mg nasal spray vs Placebo												
2	RCT	Not serious	Not serious	Not serious	Serious[a]	None	243/696 (34.9%)	107/677 (15.8%)	**RR 2.23** (0.74 to 6.70)	**194 more per 1.000** (from 41 fewer to 901 more)	⊕⊕⊕⊖ Moderate	Critical

[a]Wide confidence intervals.

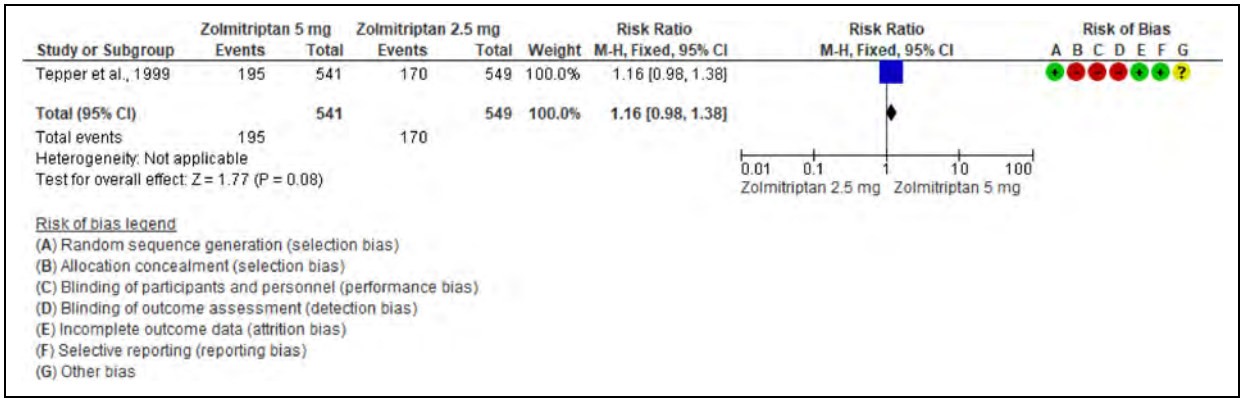


Figure 3.2.31. Forest plot showing the comparison between oral zolmitriptan 5 mg and oral zolmitriptan 2.5 mg for the outcome pain freedom at 2 h in patients with migraine.

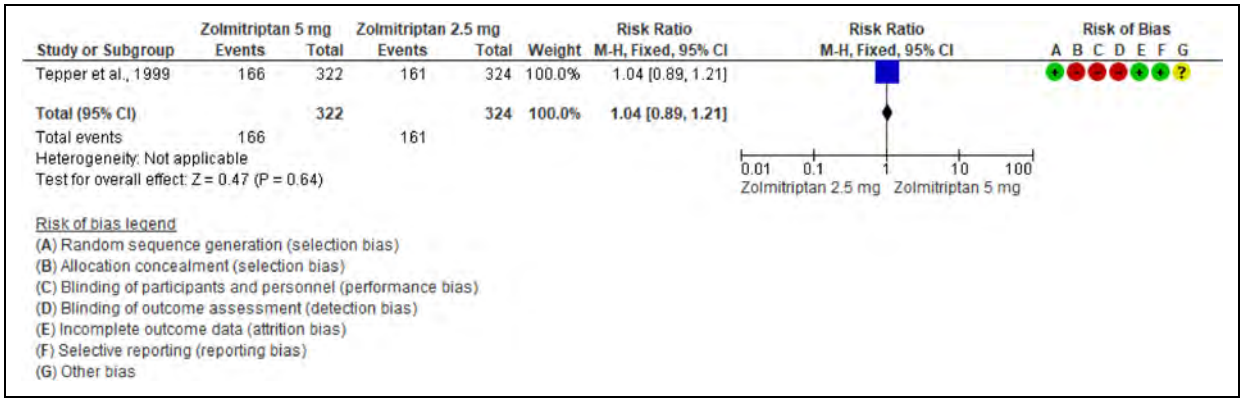


Figure 3.2.32. Forest plot showing the comparison between oral zolmitriptan 5 mg and oral zolmitriptan 2.5 mg for the outcome pain relief at 2 h in patients with migraine.

evidence suggesting that intravenous metoclopramide alone might be effective for migraine treatment in emergency department settings (302–304). Opioids in combination with analgesics are commonly prescribed for the management of acute migraine pain especially in the US (305–307). As far as the mechanism of action is concerned, tramadol specifically appears to reduce pain centrally binding weakly to μ-opioid receptors and inhibiting serotonin and norepinephrine reuptake, and codeine is considered a weak narcotic central analgesic (308).

The combination of ergotamine/caffeine is indicated to treat migraine and cluster headache attacks (309), in patients with severe symptoms or not responding to NSAIDs or other combination-analgesics (310). The main component of the combination is ergotamine tartrate, first used for migraine therapy in the 1920s. Its vasoconstrictor effect is due to its action on the smooth muscle in the arterial walls. It selectively binds to alpha-adrenergic receptors thereby stimulating vascular smooth muscle and causing vasoconstriction in both arteries and veins. Ergotamine also blocks serotonin 5-HT1B receptors, causing vasoconstriction in cerebral blood vessels thereby relieving the pain. It has high affinity for other serotonin receptors, including 5-HT1A, 5-HT2A, 5-HT2B and dopamine D2, but it has a central emetic effect (311). The theoretical basis for using ergotamine tartrate in combination with caffeine consists in the putative enhancement of its absorption (312). Combining drugs containing a triptan and a NSAID/analgesic agent is also an attractive option for the abortive treatment of migraine based on the potential synergy of these drugs both at the central and peripheral levels in the trigeminovascular system. Specifically, NSAIDs reduce meningeal inflammation potentially by inhibiting prostaglandin production. They also have been shown to block neurogenic dural plasma extravasation and trigeminal sensitization caused by CGRP-mediated dural vasodilatation (287). NSAIDs may also be beneficial in treating migraine with allodynia by preventing central sensitization (313,314). Among the NSAIDs, naproxen sodium has a superior safety profile with respect to cardiovascular risk and is an excellent NSAID for the treatment of migraine attacks. It suppresses sensitization of central

Table 3.2.10. GRADE evidence profile table of oral zolmitriptan 2.5 mg versus oral zolmitriptan 5 mg in patients with migraine

Certainty assessment							№ of patients		Effect			
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Zolmitriptan 2.5 mg	Zolmitriptan 5 mg	Relative (95% CI)	Absolute (95% CI)	Quality	Importance
Pain freedom at 2 h - Zolmitriptan 2.5 mg oral vs Zolmitriptan 5 mg oral												
1	RCT	Very serious	Not applicable[a]	Not serious	Not serious	None	195/541 (36.0%)	170/549 (31%)	**RR 1.16** (0.98 to 1.38)	**50 more per 1000** (from 6 less to 118 more)	⊕⊖⊖⊖ Very low	Critical
Pain relief at 2 h - Zolmitriptan 2.5 mg oral vs Zolmitriptan 5 mg oral												
1	RCT	Very serious	Not applicable[a]	Not serious	Not serious	None	166/322 (51.6%)	161/324 (49.7%)	**RR 1.04** (0.89 to 1.21)	**20 more per 1000** (from 55 less to 104 more)	⊕⊖⊖⊖ Very low	Critical

[a]Only one trial.

trigeminovascular neurons in the spinal trigeminal nucleus in an animal model of intracranial pain (315). It has slower absorption but a much longer half-life than ibuprofen and diclofenac (27). Triptans act at the level of trigeminovascular system as agonists of the serotonin receptors (5-HT receptors) 1B/1D by blocking the transmission of signals to the trigeminal nucleus, thereby preventing peripheral sensitization which is involved in head pain maintenance (241). The combination of naproxen with triptans has been proven effective and well tolerated, also in migraine patients with cutaneous allodynia (316,317).

Section-specific methods

This section followed the general procedure to develop this guideline.

Search strings for the Guideline on migraine drug combination for systematic review/meta-analysis and for additional RCTs are reported in Online Appendix 3.4.1.

We considered here as "analgesic" any drug that was intended for the acute treatment of migraine attacks, without selecting any specific classes of medication. As per the Methods (Section 2), we excluded intravenous formulations.

Results

Overall, we retrieved 249 references from searching for systematic reviews and meta-analyses. After duplicate removal and screening, we included 19 systematic reviews and meta-analyses (19,20,57,84,283,284,305,318–329) as source of randomized controlled trials (RCTs) (Figure 3.4.1).

Overall, we retrieved 655 references from searching for RCTs and after removing duplicates we had 607 references to analyze. After screening stages and full text analysis, 33 studies were included in the literature synthesis to develop the evidence-based guideline (26,27,41,118,166,167,177,186,189,194,300,327,330–350). From the literature search update performed in May 2023 and November 2023, we retrieved 62 and 23 additional references, respectively. No further studies were included from the search updates (Figure 3.4.2).

Among RCTs, 19 reported a comparison between an active combination analgesic and placebo and are presented in this section. The remaining 14 RCTs reported head-to-head comparisons and were included in Section 3.9.

Acetylsalicylic Acid + Paracetamol + Caffeine

PICO 3.4.1. In subjects with migraine, is the oral combination of acetylsalicylic acid + paracetamol + caffeine superior to placebo in the acute treatment of migraine attacks (outcomes: pain freedom at 2 h, pain relief at 2 h)?

Main evidence. We found two RCTs (335,340) addressing oral acetylsalicylic acid + paracetamol + caffeine as

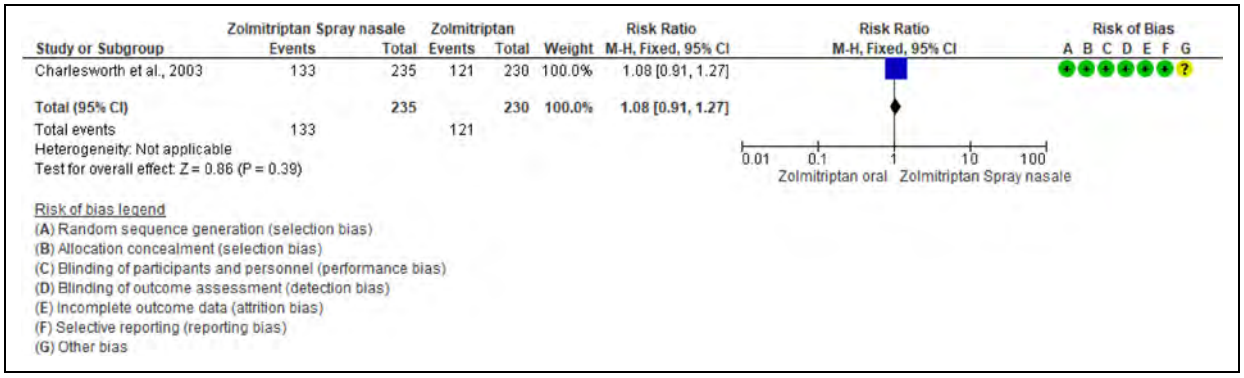


Figure 3.2.33. Forest plot showing the comparison between zolmitriptan 5 mg nasal spray and oral zolmitriptan 2.5 mg for the outcome pain relief at 2 h in patients with migraine.

compared to placebo in the acute treatment of migraine attacks that met the criteria to be included in main evidence (Figure 3.4.3).

The pooled analysis showed benefits of oral acetylsalicylic acid 500 mg + paracetamol 500 mg + caffeine 130 mg over placebo considering the outcome of pain relief at 2 h (Figure 3.4.3). The quality of evidence was considered high (Table 3.4.1).

Additional evidence. We found one RCT addressing oral acetylsalicylic acid + paracetamol + caffeine as compared to placebo in the acute treatment of migraine attacks that did not meet the criteria to be included in main evidence (336).

The study showed benefits of oral acetylsalicylic acid 500 mg + paracetamol 500 mg + caffeine 130 mg over placebo considering the outcome of pain relief at 2 h but not the outcome of pain freedom at 2 h (Figure 3.4.4 and 3.4.5).

We found one RCT (350) addressing the efficacy of oral acetylsalicylic acid 250 mg + paracetamol 250 mg + caffeine 65 mg compared to placebo in the acute treatment of migraine attacks that did not meet the criteria to be included in the quantitative analysis as it was primarily meant to be a head-to-head study against ibuprofen 200 mg and did not consider the outcomes of interest for the present guideline.

The RCT showed benefits of acetylsalicylic acid 250 mg + paracetamol 250 mg + caffeine 65 mg over placebo considering pain intensity scores at 2, 3, and 4 h post-dose.

Evidence-based recommendation for PICO 3.4.1

In subjects with migraine, we recommend the oral combination of acetylsalicylic acid 500 mg + paracetamol 500 mg + caffeine 130 mg for the acute treatment of migraine attacks.
Quality of evidence: High (⊕⊕⊕⊕)
Strength of the recommendation: Strong (↑↑)

Safety and tolerability of acetylsalicylic acid + paracetamol + caffeine. Warnings and contraindications: Subjects with gastrointestinal and liver diseases (in particular, ongoing/recent gastritis and/or peptic ulcer or ulcerative GI disease) should avoid the combination. Nephropathic patients should also use alternative drugs. Patients with a bleeding diathesis should avoid acetylsalicylic acid. Patients with severe hypertension should be advised of the potential risk of using combination containing caffeine, especially on a regular basis. Patients with sleep disturbances should use alternative acute drugs.

Serious safety concerns: No serious adverse events were reported.

Tolerability: The fixed combination of acetylsalicylic acid, paracetamol, and caffeine is in general well tolerated. The percentage of overall AEs is low, although it substantially varies among studies (from 8% to 17%) (284,318,319). The most frequently reported AEs are related to the gastrointestinal system and should be mostly attributed to acetylsalicylic acid and caffeine (351). However, a potential cause of contamination of the results are the gastrointestinal symptoms due to the migraine attack itself. The regular use of acetylsalicylic acid is associated with an increased risk of major bleeding (352). From epidemiological studies there is no clinically meaningful evidence for nephrotoxicity and risk for end-stage renal disease with the use of paracetamol in combined formulation (353,354). Although from the examined meta-analysis and included trials no alteration emerged in liver enzymes, there is an increasing number of registered cases of paracetamol-induced liver intoxication all over the world (355). These should be considered, particularly for the regular, daily use of analgesic combinations containing paracetamol. Regarding caffeine, the use of combinations containing caffeine should be limited to two days per week to avoid the risk of medication overuse (356).

Table 3.2.11. GRADE evidence profile table of oral zolmitriptan 2.5 mg versus zolmitriptan 5 mg nasal spray in patients with migraine

Certainty assessment							№ of patients		Effect			
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Zolmitriptan 2.5 mg	Zolmitriptan 5 mg nasal spray	Relative (95% CI)	Absolute (95% CI)	Quality	Importance
Pain relief at 2 h - Zolmitriptan 2.5 mg oral vs Zolmitriptan 5 mg nasal spray												
1	RCT	Not serious	Not applicable[a]	Not serious	Not serious	None	121/230 (52.6%)	133/235 (56.8%)	**RR 1.08** (0.91 to 1.27)	**45 more per 1000** (from 51 less to 153 more)	⊕⊕⊕⊖ moderate	Critical

[a]Only one trial.

Acetylsalicylic acid + metoclopramide

PICO 3.4.2. In subjects with migraine, is the oral combination of acetylsalicylic acid + metoclopramide superior to placebo in the acute treatment of migraine attacks (outcomes: pain freedom at 2 h, pain relief at 2 h)?

Main evidence. We found two RCTs addressing oral acetylsalicylic acid + metoclopramide as compared to placebo in the treatment of acute migraine attack (194,300).

The pooled analysis showed benefits of oral acetylsalicylic acid 900 mg + metoclopramide 10 mg over placebo considering the outcomes of pain freedom at 2 h and pain relief at 2 h (Figures 3.4.6 and 3.4.7). The quality of evidence for both outcomes was considered moderate (Table 3.4.2).

Additional evidence

None.

Evidence-based recommendation for PICO 3.4.2

In subjects with migraine, we recommend the oral combination of acetylsalicylic acid 900 mg + metoclopramide 10 mg for the acute treatment of migraine attacks.
Quality of evidence: Moderate (⊕⊕⊕⊖)
Strength of the recommendation: Strong (↑↑)

Safety and tolerability of acetylsalicylic acid + metoclopramide.
Warnings and contraindications: Subjects with gastrointestinal diseases (ongoing/recent gastritis and/or peptic ulcer or ulcerative GI disease) should avoid using this combination particularly when the association is frequently used. subjects with a bleeding diathesis should avoid acetylsalicylic acid use. subjects with extrapyramidal disorders should also be advised to avoid acetylsalicylic acid use and metoclopramide combination especially for long term use.

Serious safety concerns: Acetylsalicylic acid use plus metoclopramide is generally well tolerated, with most adverse events being of mild or moderate severity and self-limiting. Overall, single doses of acetylsalicylic acid use, with or without metoclopramide, did not cause significantly more adverse events than placebo in the evaluated studies (321).

Tolerability: There are no specific concerns regarding the tolerability of the combination between acetylsalicylic acid and metoclopramide. Referring to single drugs, adverse events of acetylsalicylic acid include gastrointestinal symptoms (such as stomachache, diarrhea, nausea and vomiting, these latter may be not easily distinguishable from associated symptoms related to migraine attack) drowsiness, dizziness, weakness and rarely extrapyramidal reactions such as acute dystonia or tardive dyskinesia (357–359). There are observations of long-term use of

Drug	Acute treatment of migraine attacks
Almotriptan 12.5 mg oral	⊕⊕⊕⊕ ↑↑
Eletriptan 20 and 40 mg oral	⊕⊕⊕⊕ ↑↑
Frovatriptan 2.5 mg oral	⊕⊕⊕⊕ ↑↑
Naratriptan 1 mg 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 nasal spray	⊕⊕⊕⊕ ↑↑
Zolmitriptan 2.5 mg oral	⊕⊕⊕⊕ ↑↑
Zolmitriptan 5 mg oral	⊕⊕⊕⊕ ↑↑
Zolmitriptan 5 mg nasal spray	⊕⊕⊖⊖ ↓

Quality of selected evidence	
⊕⊕⊕⊕	High
⊕⊕⊕⊖	Moderate
⊕⊕⊖⊖	Low
⊕⊖⊖⊖	Very low
⊖⊖⊖⊖	None
Strength of the recommendation	
↑↑	strong in favor
↑	weak in favor
↓	weak against
↓↓	strong against
-	none

Figure 3.2.34. Summary of evidence-based recommendations on triptans for the acute treatment of migraine attacks.

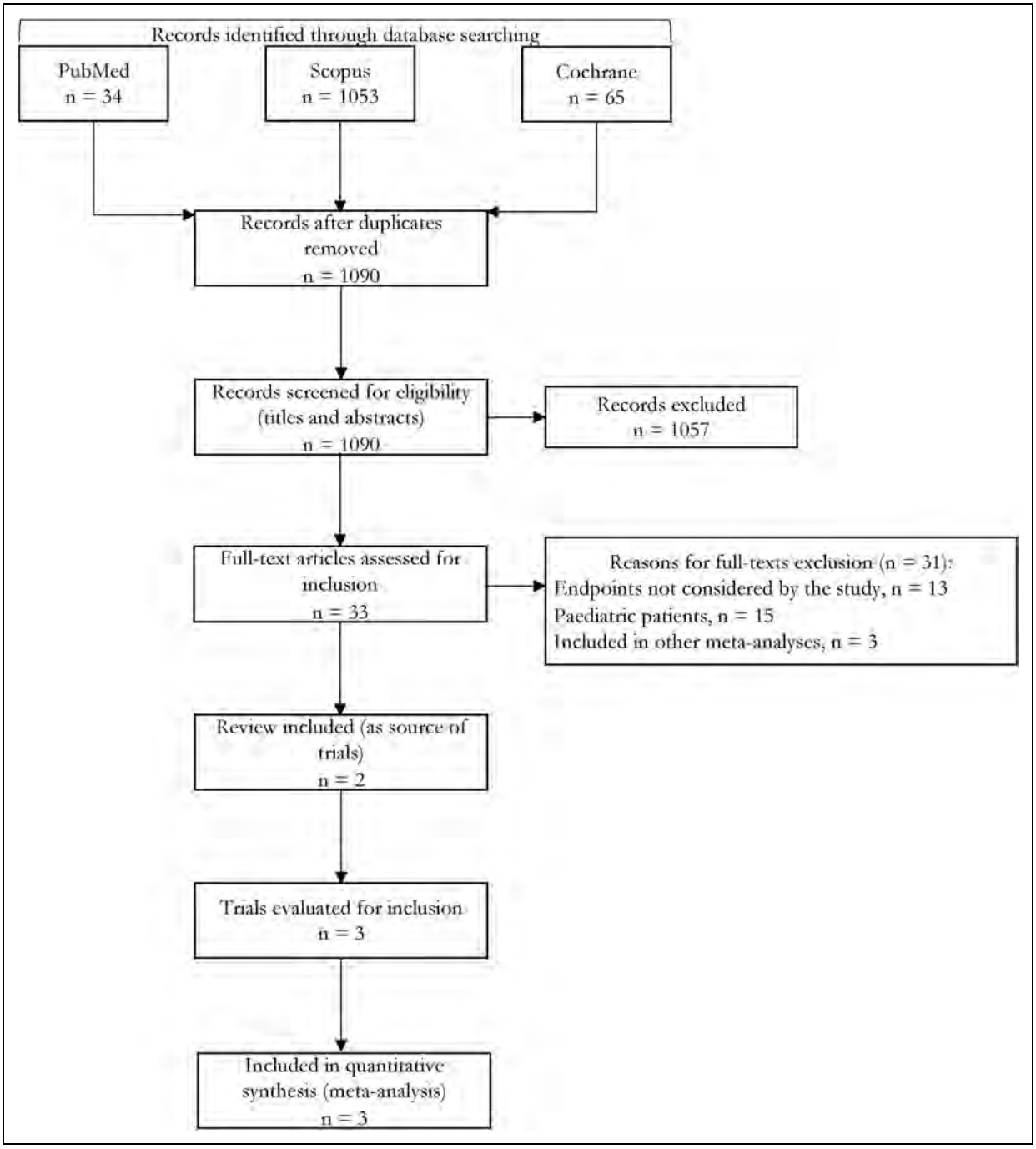


Figure 3.3.1. Meta-analysis selection flow chart - paracetamol.

metoclopramide inducing a Parkinsonian syndrome. However, there are no reports of these symptoms in outpatients using metoclopramide as an adjunctive treatment of migraine attacks (360). The regular use of aspirin is associated with an increased risk of major bleeding (352). This adverse event has not been described in trials assessing aspirin with metoclopramide as migraine acute attack. The risk of medication overuse is theoretically not excluded also for ASA + metoclopramide but description of this secondary headache due to the regular, daily, or almost daily use is lacking in the literature.

Paracetamol + tramadol

PICO 3.4.3. In subjects with migraine, is the oral combination of paracetamol + tramadol superior to placebo in the

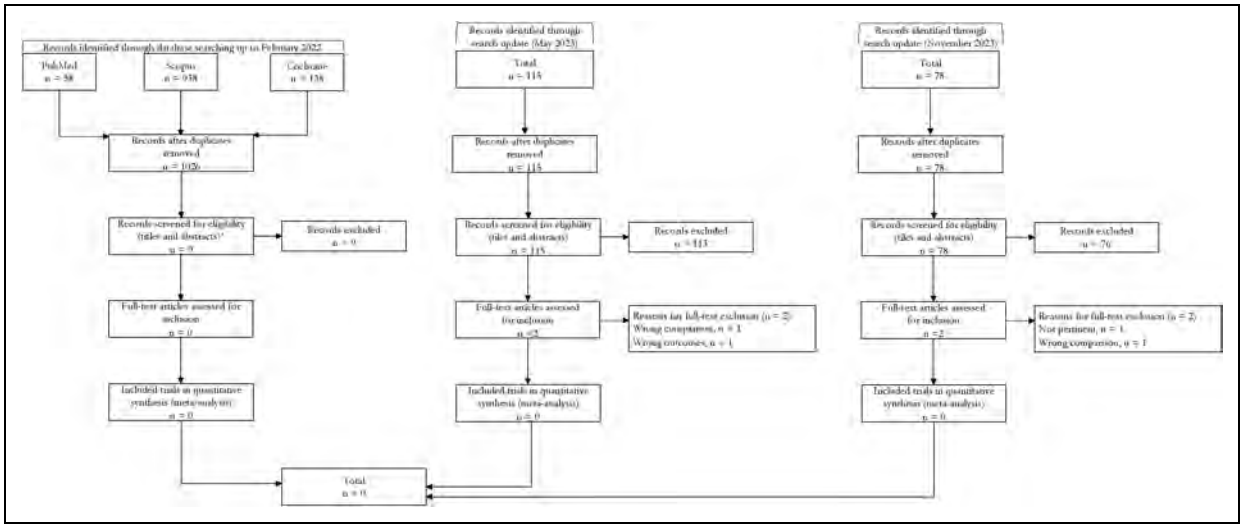


Figure 3.3.2. RCTs selection flow chart - paracetamol.
*trials published since 2014 were screened.

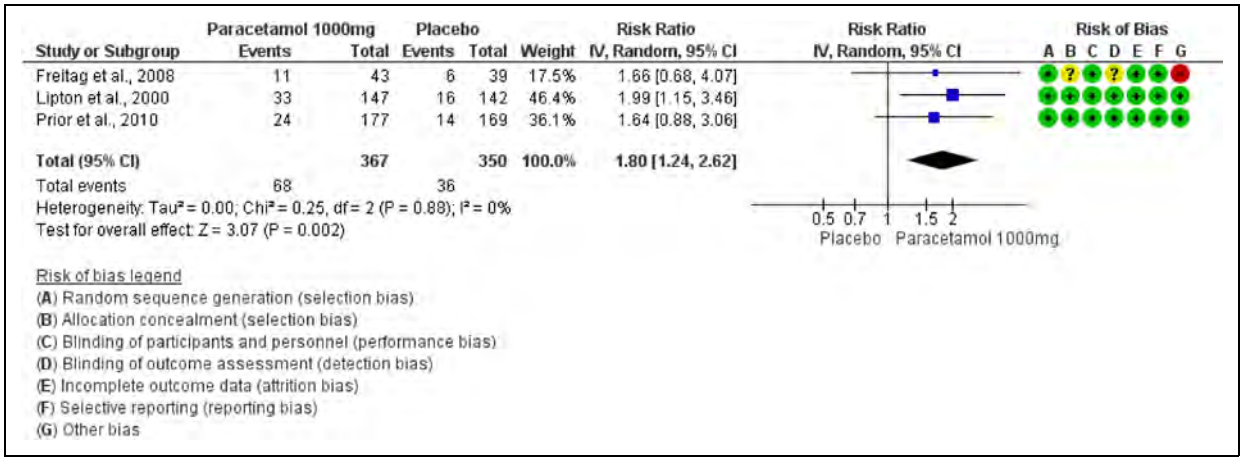


Figure 3.3.3. Forest plot showing the comparison between oral paracetamol 1000 mg and placebo for the outcome pain freedom at 2 h in patients with migraine.

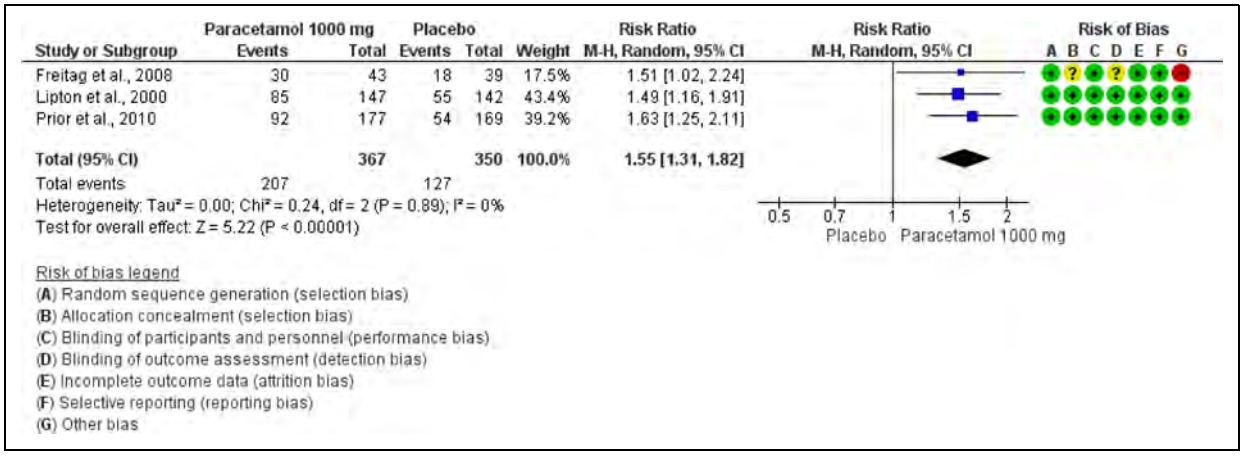


Figure 3.3.4. Forest plot showing the comparison between oral paracetamol 1000 mg and placebo for the outcome pain relief at 2 h in patients with migraine.

Table 3.3.1. GRADE evidence profile table for oral paracetamol 1000 mg versus placebo

Certainty assessment							№ of patients		Effect			
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Paracetamol 1000mg	Placebo	Relative (95% CI)	Absolute (95% CI)	Quality	Importance
Pain freedom at 2 h - Paracetamol 1000 mg oral vs Placebo												
3	RCTs	Not serious	Not serious	Not serious	Not serious	None	68/367 (18.5%)	36/350 (10.3%)	**RR 1.80** (1.24 to 2.62)	**82 more per 1.000** (from 25 more to 167 more)	⊕⊕⊕⊕ High	Critical
Pain relief at 2 h - Paracetamol 1000 mg oral vs Placebo												
3	RCTs	Not serious	Not serious	Not serious	Not serious	None	207/367 (56.4%)	127/350 (36.3%)	**RR 1.55** (1.31 to 1.82)	**200 more per 1.000** (from 112 more to 298 more)	⊕⊕⊕⊕ High	Critical

acute treatment of migraine attacks (outcomes: pain freedom at 2 h, pain relief at 2 h)?

Main evidence. We found one RCT addressing oral paracetamol + tramadol as compared to placebo in the acute treatment of migraine attack (347). The study showed benefits of oral paracetamol 650 mg + tramadol 75 mg over placebo considering the outcomes of pain freedom at 2 h and pain relief at 2 h (Figures 3.4.8 and 3.4.9). The quality of evidence for both outcomes was considered low (Table 3.4.3).

Additional evidence. None.

Evidence-based recommendation for PICO 3.4.3

In subjects with migraine, we recommend the oral combination of paracetamol 650 mg + tramadol 75 mg for the acute treatment of migraine attacks.
Quality of evidence: Moderate (⊕⊕⊕⊖).
Strength of the recommendation: Weak (↑).
[NOTE: Considering the risk associated with the class of opioids, their use in the acute treatment of migraine should be considered only when all the other available options have proved ineffective.]

Safety and tolerability of paracetamol + tramadol. Warnings and contraindications: The use of paracetamol and tramadol association in the acute treatment of migraine should be avoided in people with or at risk for substance abuse or dependence, subjects with liver disease, severe constipation or gastrointestinal obstruction, respiratory problems, and pulmonary impairment (361). It should be noted that tramadol is an opioid linked to a high risk for dependence and that opioid overuse is a serious health concern in the general population (362). Therefore, despite its potential efficacy, the use of drugs containing opioids for headache should be discouraged unless other options have been tried and failed.

Serious safety concerns: Mild adverse events emerged in the trials included in the meta-analysis, in the absence of serious AEs (24).

Tolerability: The evaluated studies did not allow to draw a specific tolerability profile of the combination of paracetamol and tramadol. A previous review showed that the drug is well tolerated when taken occasionally (363). Evidence regarding the safety and tolerability of the repeated use of opioid-containing medications in the treatment of migraine is lacking (324). More common side effects to paracetamol and tramadol combination include nausea, vomiting, constipation, diarrhea, confusion or nervousness, sleep disturbances. In addition, tramadol can cause serotonin syndrome, hypoglycemia, hyponatremia, and seizures

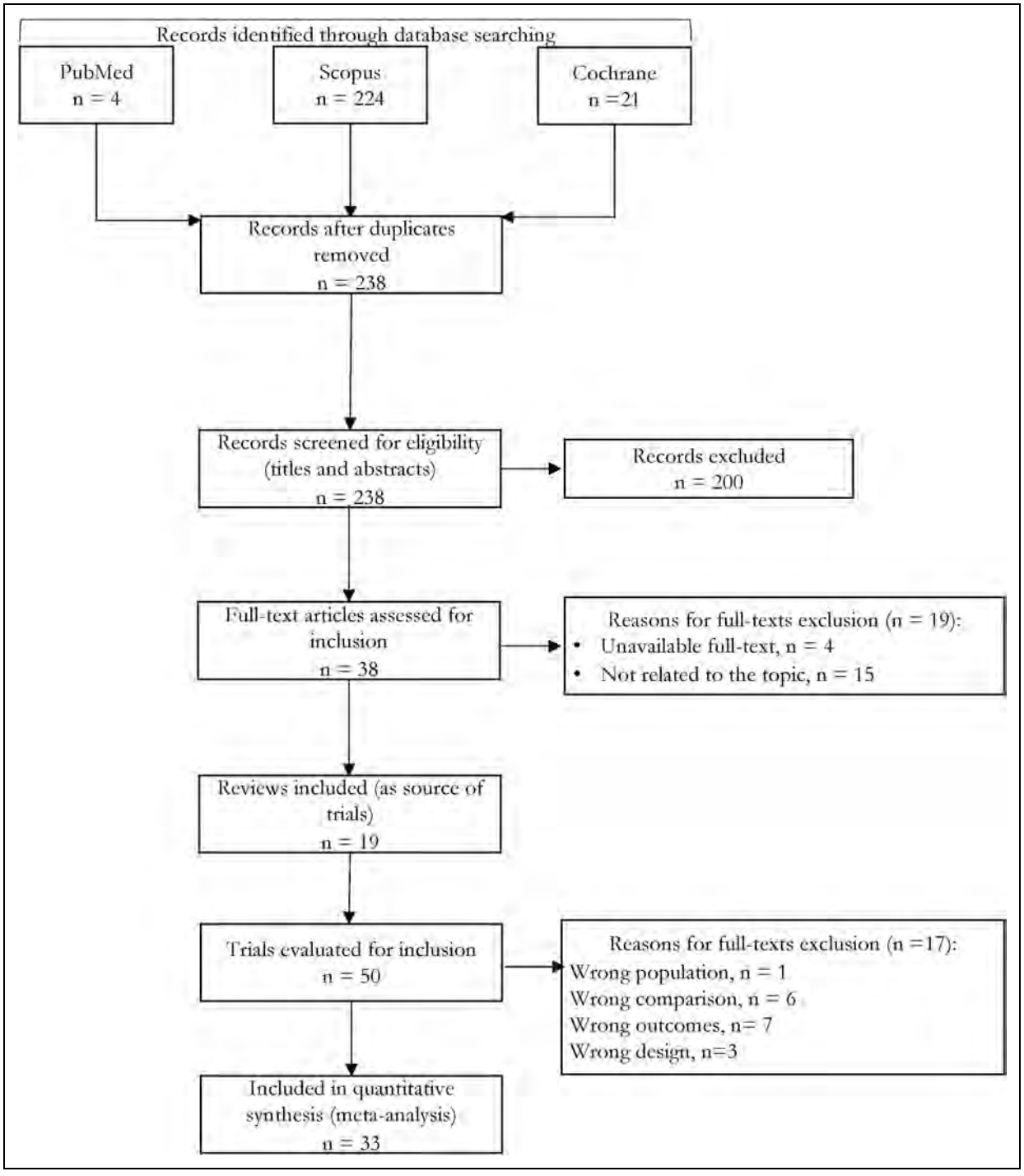


Figure 3.4.1. Meta-analysis selection flow chart - combination analgesics.

(364). The risk of presenting adverse events to this combination is greater in the case of regular and prolonged use. Taking high or repeated doses of the combination should be avoided because they can lead to addiction. Furthermore, there is no evidence that, at equivalent analgesic efficacy, weak opioids carry a lower risk of addiction than low-dose morphine. Patients receiving medications containing opioids have higher risk of developing medication overuse headache (MOH) compared with other treatments. Withdrawal symptoms may occur when these drugs - including the association of paracetamol with tramadol - are stopped abruptly (320).

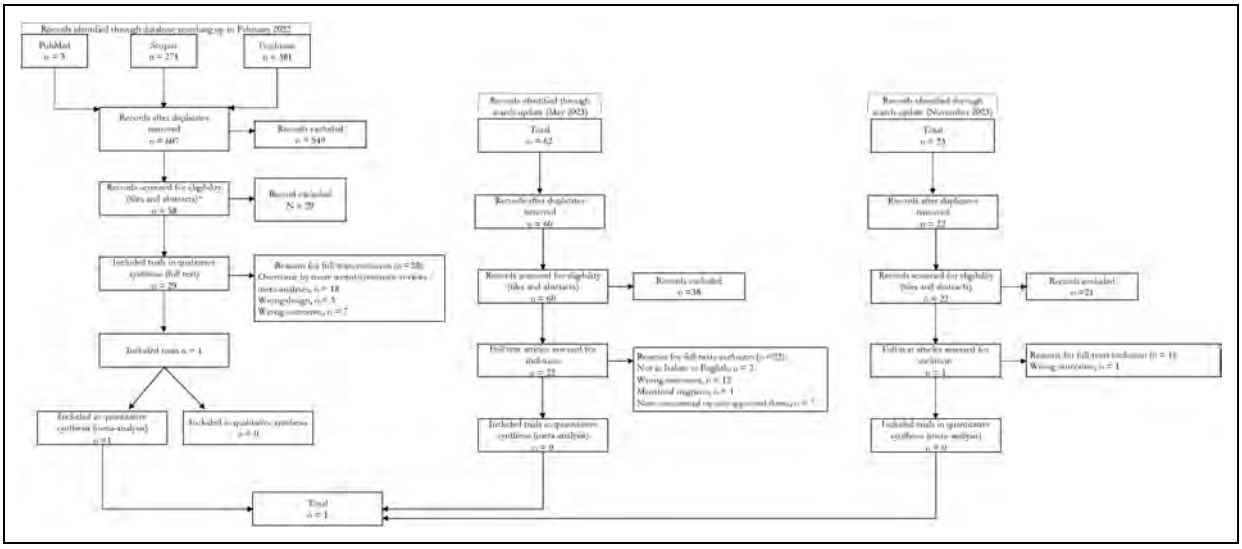


Figure 3.4.2. RCTs selection flow chart - combination analgesics.

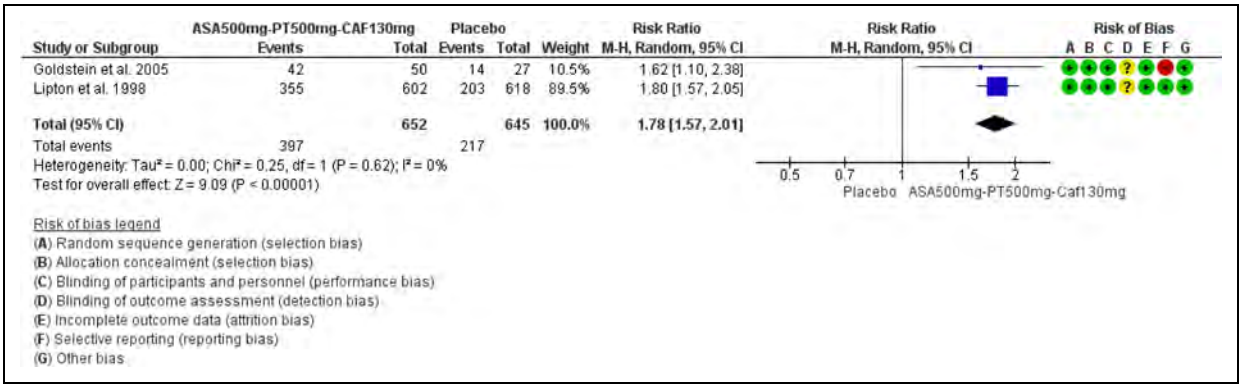


Figure 3.4.3. Forest plot showing the comparison between oral acetylsalicylic acid 500 mg + paracetamol 500 mg + caffeine 130 mg and placebo for the outcome pain relief at 2h in patients with migraine.

Paracetamol + codeine

PICO 3.4.4. In subjects with migraine, is the oral combination of paracetamol + codeine superior to placebo in the acute treatment of migraine attacks (outcomes: pain freedom at 2 h, pain relief at 2 h)?

Main evidence. None.

Additional evidence. We found one RCT comparing oral paracetamol + codeine to placebo in the acute treatment of migraine attacks (26). This RCT did not meet the criteria for main evidence. The quality of evidence was considered very low.

The study showed benefits of oral paracetamol 400 mg + codeine 25 mg over placebo considering the outcomes of pain freedom at 2 h (Figure 3.4.10) and pain relief at 2 h (Figure 3.4.11).

Evidence-based recommendation for PICO 3.4.4

In subjects with migraine, we suggest the oral combination of paracetamol 400 mg + codeine 25 mg for the acute treatment of migraine attacks.
Quality of evidence: Very low (⊕⊖⊖⊖).
Strength of the recommendation: Weak (↑).
[NOTE: Considering the risk associated to the class of opioids, their use in the acute treatment of migraine should be considered only when all the other available options have proved ineffective.]

Table 3.4.1. GRADE evidence profile table for oral acetylsalicylic acid 500 mg + paracetamol 500 mg + caffeine 130 mg vs placebo in patients with migraine

Certainty assessment							№ of patients		Effect				
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Acetylsalicylic acid 500 mg + paracetamol 500 mg + caffeine 130 mg	Placebo	Relative (95% CI)	Absolute (95% CI)	Quality	Importance
Pain relief at 2 h – Acetylsalicylic acid 500 mg + paracetamol 500 mg + caffeine 130 mg oral vs placebo												
2	RCTs	Low	Not serious	Not serious	Not serious	None	397/652 (60.9%)	217/645 (33.6%)	**RR 1.78** (1.57 to 2.01)	**262 more per 1.000** (from 192 more to 340 more)	⊕⊕⊕⊕ High	Critical

Safety and tolerability of paracetamol + codeine. Warnings and contraindications: The association of paracetamol and codeine is contraindicated in patients with hepatic and renal impairment, respiratory depression due to comorbid respiratory disorder, paralytic ileus and intestinal obstruction. Patients with a history of substance abuse should also avoid this therapy and other drugs not centrally-acting should be preferred in relation to the risk of MOH (365). Codeine is an opioid whose use is associated with a high risk for addiction (366).

Serious safety concerns: No serious side effects emerged in the trials included in the meta-analysis. However, considering the risks associated with the class of opioids, their use in the acute treatment of migraine should be proposed only when all the other available options have proved ineffective.

Tolerability: Considering the evidence from RCTs, there is no specific tolerability profile of paracetamol + codeine. Considering the two drugs separately, paracetamol is safe when taken at therapeutic doses; overdose can lead to serious and even fatal hepatotoxicity in 1–2% of patients. Nephrotoxicity becomes evident after hepatotoxicity in most cases, but it should be distinguished from the hepatorenal syndrome complicating fulminant hepatic failure (367). The risk of hepatotoxicity and nephrotoxicity cannot be excluded in patients with regular and sometimes multi-daily use of the combination including those with MOH involving this combination (368). The side effects of codeine are like those of other opioids. Codeine, even when taken at therapeutic doses, may cause constipation, nausea, stomach cramps, dizziness, drowsiness, sedation, and urinary retention. These side effects can occur more frequently in the case of regular daily or multi-daily use of the drug alone or in combination (369).

Sumatriptan + naproxen

PICO 3.4.5. In subjects with migraine, is the oral combination of sumatriptan + naproxen superior to placebo in the acute treatment of migraine attacks (outcomes: pain freedom at 2 h, pain relief at 2 h)?

Main evidence. We found four RCTs (327,332,341,346) addressing oral sumatriptan + naproxen as compared to placebo in the acute treatment of migraine attacks.

The pooled analysis showed benefits of oral sumatriptan 85 mg + naproxen 500 mg versus placebo considering the outcome of pain freedom at 2 h; more limited evidence coming from two RCTs did not show benefits considering the outcome of pain relief at 2 h (Figure 3.4.12 and 3.4.13). The quality of evidence for both outcomes was considered low (Table 3.4.5).

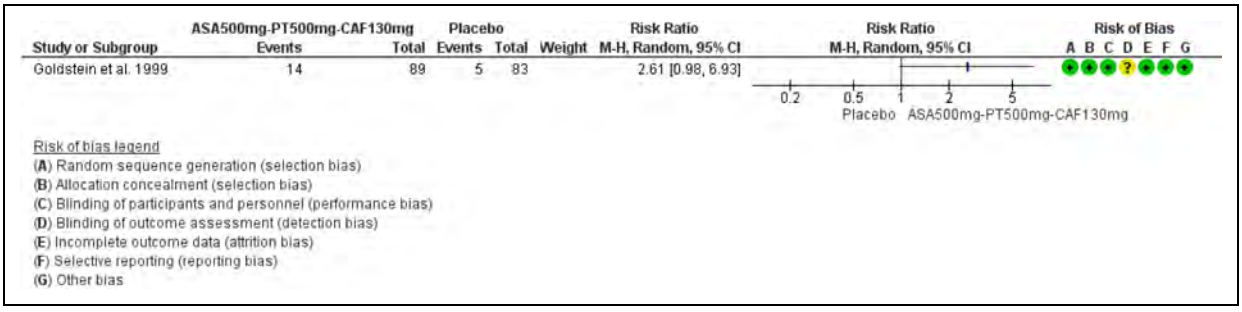


Figure 3.4.4. Forest plot showing the comparison between oral acetylsalicylic acid 500 mg + paracetamol 500 mg + caffeine 130 mg and placebo for the outcome pain freedom at 2h in patients with migraine.

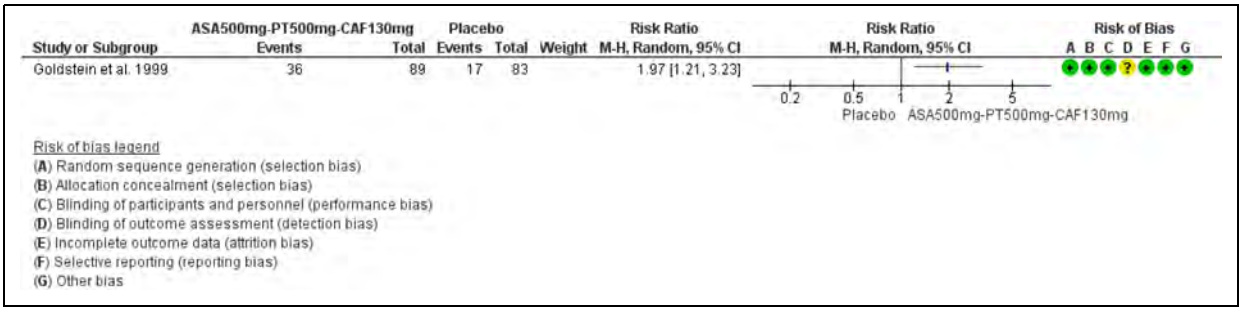


Figure 3.4.5. Forest plot showing the comparison between oral acetylsalicylic acid 500 mg + paracetamol 500 mg + caffeine 130 mg and placebo for the outcomes pain relief at 2h in patients with migraine.

Additional evidence. We found three RCTs (27,41,186) addressing oral sumatriptan + naproxen as compared to placebo in the acute treatment of migraine attacks that did not meet the criteria to be included in main evidence. The overall risk of bias was considered unclear, and the quality of evidence was considered very low.

One RCT (41) showed benefits of oral sumatriptan 50 mg + naproxen 500 mg over placebo considering the outcome pain freedom and pain relief at 2 h; the other two RCTs (27,186) showed benefits of oral sumatriptan 85 mg + naproxen 500 mg versus placebo in the outcomes pain freedom and pain relief at 2 h (Figures 3.4.14 and 3.4.15).

Evidence-based recommendation for PICO 3.4.5

In subjects with migraine, we recommend the oral combination of sumatriptan 85 mg + naproxen 500 mg for the acute treatment of migraine attacks.
Quality of evidence: Low (⊕⊕⊖⊖)
Strength of the recommendation: Strong (↑↑)

Safety and tolerability of sumatriptan + naproxen. Warnings and contraindications: This drug combination should not be used in subjects with heart disease (including Wolff-Parkinson-White syndrome), a history of heart attacks or stroke, uncontrolled high blood pressure, severe liver disease. Naproxen should not be used in patients with actual gastrointestinal disorders, in particular gastritis or ulcers. Patients using Monoamine Oxidase inhibitors in the past 14 days should avoid sumatriptan and naproxen combination due to the potentially dangerous drug interactions (370,371).

Serious safety concerns: Only one serious adverse event was related to study medication in the study of Brandes and collaborators, in a patient with several cardiovascular risk factors who experienced heart palpitations and for this was admitted to hospital (27). Other severe side effects were reported (seven participants in the study by Lipton et al. (186)), none of which were considered related to study medication or occurred within 72 h of receiving study medication.

Tolerability: Adverse events to sumatriptan/naproxen combination are mostly mild or moderate in severity and rarely lead to withdrawal. The most frequently reported side effects include: paresthesia, dizziness, somnolence,

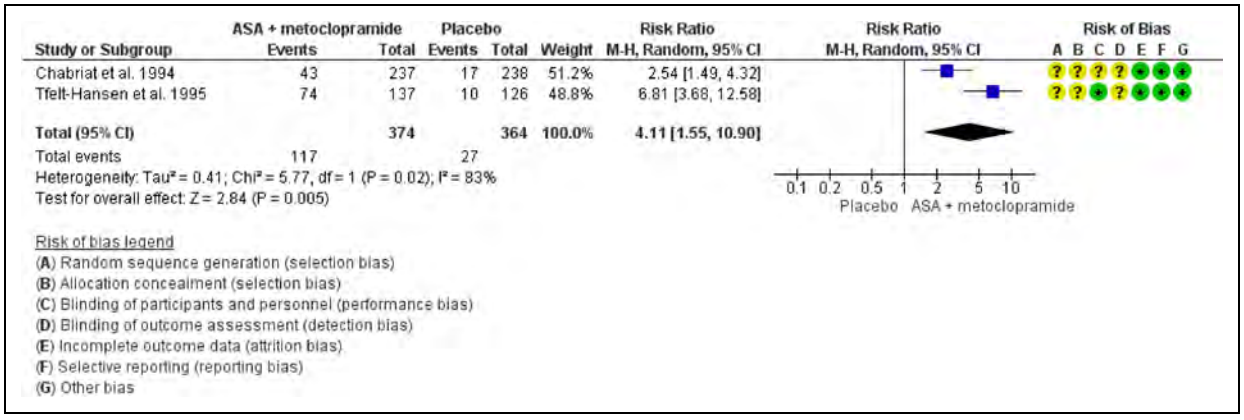


Figure 3.4.6. Forest plot showing the comparison between oral acetylsalicylic acid 900 mg + metoclopramide 10 mg and placebo for the outcome pain freedom at 2h in patients with migraine.

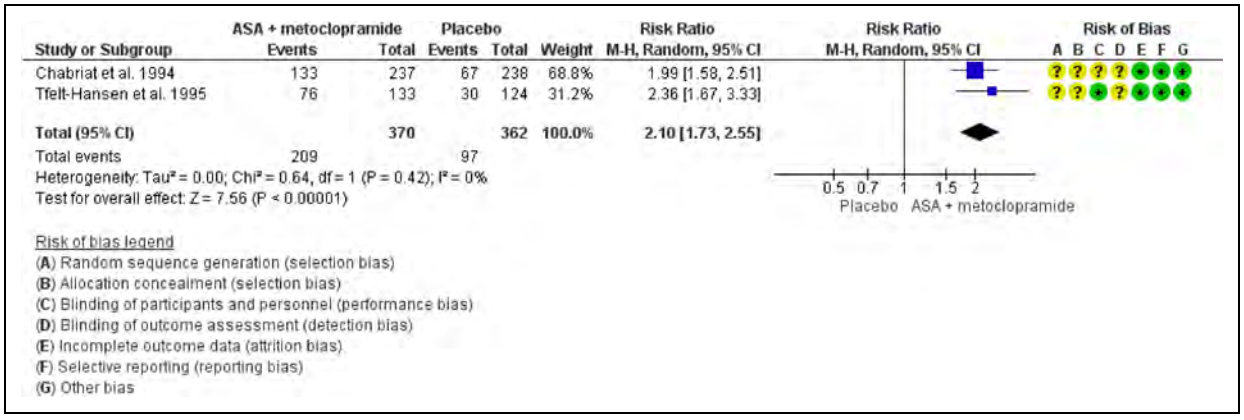


Figure 3.4.7. Forest plot showing the comparison between oral acetylsalicylic acid 900 mg + metoclopramide 10 mg and placebo for the outcome pain relief at 2h in patients with migraine.

nausea, dyspepsia, dry mouth, and chest discomfort (20,317). However, the incidence of any specific event in individual studies is low (less than 4%).

Rizatriptan + paracetamol

PICO 3.4.6. In subjects with migraine, is the combination of oral rizatriptan + paracetamol superior to placebo in the acute treatment of migraine attacks (outcomes: pain freedom at 2 h, pain relief at 2 h)?

Main evidence. We found one RCT (118) addressing oral rizatriptan + paracetamol as compared to placebo in the acute treatment of migraine attacks that met the criteria for main evidence.

The study showed benefits of oral rizatriptan 10 mg + paracetamol 1000 mg over placebo considering the outcomes of pain freedom at 2 h and pain relief at 2 h (Figure 3.4.16 and 3.4.17). The quality of evidence for both outcomes was considered low (Table 3.4.6).

Despite the low quality of evidence and the low number (<100) of subjects included in the trial, we nevertheless provided a strong recommendation for the use of rizatriptan 10 mg + paracetamol 1000 mg, as both drugs alone were associated with high efficacy over placebo (see Sections 3.2 and 3.3).

Additional evidence. None.

Evidence-based recommendation for PICO 3.4.6

In subjects with migraine, we recommend the oral combination of rizatriptan 10 mg + paracetamol 1000 mg for the acute treatment of migraine attacks.
Quality of evidence: Low (⊕⊕⊖⊖)
Strength of the recommendation: Strong (↑↑)

Table 3.4.2. GRADE evidence profile table for oral acetylsalicylic acid 900 mg + metoclopramide 10 mg versus placebo in patients with migraine

Certainty assessment							№ of patients		Effect			
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Acetylsalicylic acid 900 mg + metoclopramide 10 mg	placebo - main	Relative (95% CI)	Absolute (95% CI)	Quality	Importance
Pain freedom at 2 h – Acetylsalicylic acid 900 mg + Metoclopramide 10 mg oral vs Placebo												
2	RCTs	Serious	Not serious	Not serous	Not serious	None	117/374 (31.3%)	27/364 (7.4%)	**RR 4.11** (1.55 to 10.90)	**231 more per 1.000** (from 41 more to 734 more)	⊕⊕⊕⊖ Moderate	Critical
Pain relief at 2 h – Acetylsalicylic acid 900 mg + Metoclopramide 10 mg oral vs Placebo												
2	RCTs	Serious	Not serious	Not serous	Not serious	None	209/370 (56.5%)	97/362 (26.8%)	**RR 2.10** (1.73 to 2.55)	**295 more per 1.000** (from 196 more to 415 more)	⊕⊕⊕⊖ Moderate	Critical

Safety and tolerability of rizatriptan + paracetamol. Warnings and contraindications: The association should be avoided in subjects with contraindications to the individual drugs contained in the combination. They include subjects with cardiovascular, cerebrovascular, and peripheral vascular diseases, renal and hepatic impairment and gastrointestinal diseases (328,372,373).

Serious safety concerns: No serious adverse events have been reported in the single study included in the meta-analysis (118).

Tolerability: The most common side effects are dizziness, hot flashes, nausea or vomiting, sleepiness or unusual drowsiness, tiredness, or weakness. The combination rizatriptan + paracetamol was well tolerated as each of the individual agents (209). The frequent use of this drug association theoretically poses the risk of the development of medication overuse, although no data is available on this specific combination.

Ergotamine + caffeine

PICO 3.4.7. In subjects with migraine, is the oral combination of ergotamine + caffeine superior to placebo in the acute treatment of migraine attacks (outcomes: pain freedom at 2 h, pain relief at 2 h)?

Main evidence. None.

Additional evidence. We found one RCT comparing ergotamine + caffeine to placebo in the acute treatment of migraine attacks (167).

The study did not show benefits of oral ergotamine 2 mg + caffeine 200 mg over placebo considering the outcome pain freedom at 2 h, whereas it showed significant benefit in the outcome pain relief at 2 h (Figure 3.4.18 and 3.4.19). The quality of evidence was downgraded to very low due to the imprecision of results (the clinical decision threshold was included in the confidence interval).

Evidence-based recommendation for PICO 3.4.7

In subjects with migraine, we suggest the oral combination of ergotamine 2 mg + caffeine 200 mg for the acute treatment of migraine attacks.
Quality of evidence: Very low (⊕⊖⊖⊖)
Strength of the recommendation: Weak (↑)

Safety and tolerability of ergotamine + caffeine. Warnings and contraindications: Contraindications to the combination of ergotamine + caffeine are especially related to ergotamine. Ergotamine is contraindicated in patients with peripheral vascular disease, including thromboangiitis obliterans (Buerger's disease), luetic arteritis, severe arteriosclerosis,

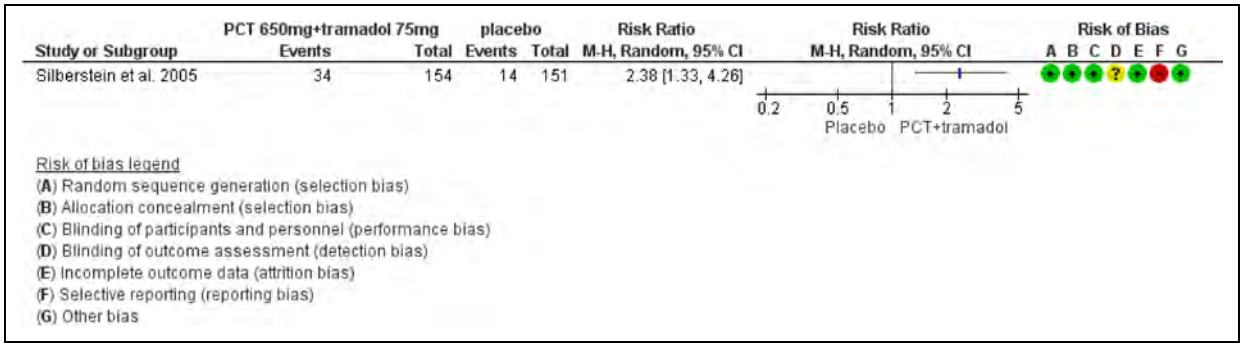


Figure 3.4.8. Forest plot showing the comparison between oral paracetamol 650 mg + tramadol 75 mg and placebo for the outcome pain freedom at 2h in patients with migraine.

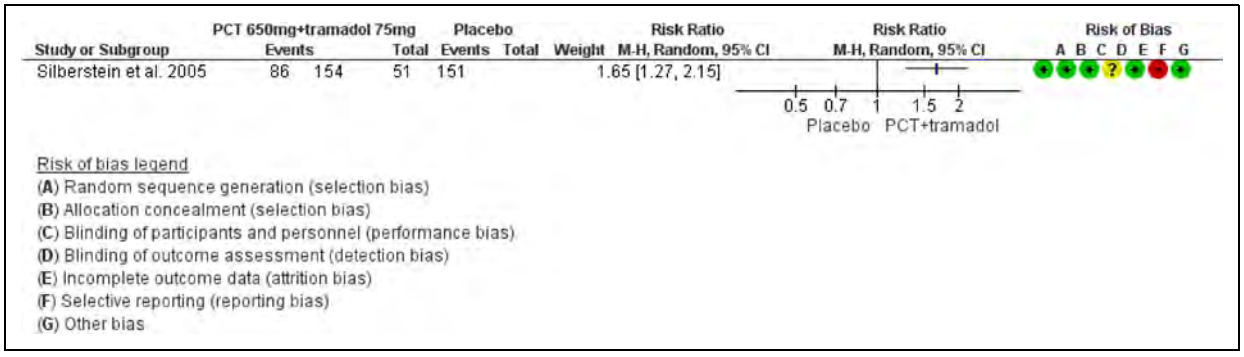


Figure 3.4.9. Forest plot showing the comparison between oral paracetamol 650 mg + tramadol 75 mg and placebo for the outcome pain relief at 2h in patients with migraine.

thrombophlebitis, and Raynaud's phenomenon, coronary artery disease (in particular unstable or vasospastic angina), uncontrolled hypertension, a stroke history, kidney and liver diseases due to the vasoconstrictive effects of the drugs (309).

Serious safety concerns: Serious adverse effects of ergotamine tartrate are related only to excessive dosage or abuse and they include ergotism, resulting in some cases in peripheral or cerebral ischemia and myocardial infarction (374,375). Cases of ergotamine poisoning and overdose symptoms are rare today due the availability of specific anti-migraine medications such as triptans with fewer side effects. In the case of intoxication symptoms, treatment consists of drug withdrawal, which could by itself relieve the above symptoms and, in some cases, also the administration of sodium nitroprusside, along with low molecular weight dextran and heparin (376,377).

Tolerability: In the trials evaluating the efficacy and safety of ergotamine + caffeine combination in the treatment of migraine attacks versus placebo adverse events were mild-to-moderate, transient and did not result in treatment-related discontinuations (167).

Common side effects of the combination of ergotamine + caffeine are nausea and vomiting after both oral and parenteral administration, due to the effect on emetic centers. Insomnia, dizziness cramps and transient lower limb muscle pain have also been described (378). A broad range of side effects can also be attributed to ergotamine because this drug is not specific for the 5HT-1B/1D serotonin receptors. They include chest pain, discomfort, or tightness, cold hands/feet, muscle pain/weakness, numbness/tingling or a bluish color skin of the fingers or toes, continuing loss of appetite, increased frequency of urination, irregular heartbeat, and back pain (379).

Considering the poor safety and tolerability profile of ergotamine and the availability of other safer vasoconstrictive agents for the acute treatment of migraine, combinations containing ergotamine should be proposed only when other options have been tried and failed.

Butalbital + paracetamol + caffeine

PICO 3.4.8. In subjects with migraine, is the oral combination of butalbital + paracetamol + caffeine superior to placebo in the acute treatment of migraine attacks (outcomes: pain freedom at 2 h, pain relief at 2 h)?

Main evidence. We found one RCT (332) addressing oral butalbital 50 mg + paracetamol 325 mg + caffeine 40 mg as compared to placebo in the acute treatment of migraine

Table 3.4.3. GRADE evidence profile table for oral paracetamol 650 mg + tramadol 75 mg versus placebo in patients with migraine

certainty assessment							№ of patients		Effect			
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Paracetamol 650 mg + tramadol 75 mg	placebo - main	Relative (95% CI)	Absolute (95% CI)	Quality	Importance
Pain freedom at 2 h – Paracetamol 650 mg + Tramadol 75 mg oral vs Placebo												
1	RCT	Unclear	Not applicable[a]	Not serious	Not serious	None	34/154 (22.1%)	14/151 (9.3%)	**RR 2.38** (1.33 to 4.26)	**128 more per 1.000** (from 31 more to 302 more)	⊕⊕⊕⊖ Moderate	Critical
Pain relief at 2 h – Paracetamol 650 mg + Tramadol 75 mg oral vs Placebo												
1	RCT	Unclear	Not applicable[a]	Not serious	Not serious	None	86/154 (55.8%)	51/151 (33.8%)	**RR 1.65** (1.27 to 2.15)	**220 more per 1.000** (from 91 more to 388 more)	⊕⊕⊕⊖ Moderate	Critical

[a]Only one trial.

attacks. The analysis showed no benefit of oral butalbital + paracetamol + caffeine versus placebo considering the outcome pain freedom at 2 h (Figure 3.4.20). The quality of evidence was considered moderate due to the availability of only one RCT (Table 3.4.7).

Additional evidence. None.

Evidence-based recommendation for PICO 3.4.8

In subjects with migraine, we suggest against the oral combination of butalbital 50 mg + paracetamol 325 mg + caffeine 40 mg for the acute treatment of migraine attacks.
Quality of evidence: Low (⊕⊕⊖⊖).
Strength of the recommendation: Weak (↓)

Safety and tolerability of butalbital + paracetamol + caffeine. Warnings and contraindications: Contraindications to the use of butalbital include hypersensitivity and porphyria (380). The combination has a warning for hepatotoxicity because of the paracetamol component and for tolerance and addiction because of the butalbital component (380).

Serious safety concerns: Serious adverse effects of butalbital + paracetamol + caffeine have not been reported in the included RCT.

Tolerability: In the RCT evaluating the efficacy and safety of butalbital + paracetamol + caffeine, no differences were reported in tolerability between the drug and placebo.

Evidence-based guideline summary

We found two RCTs (335,340) addressing oral acetylsalicylic acid + paracetamol + caffeine as compared to placebo in the acute treatment of migraine attacks that met the pre-defined criteria to be included in main evidence. The pooled analysis showed benefits of oral acetylsalicylic acid 500 mg + paracetamol 500 mg + caffeine 130 mg over placebo considering the outcome of pain relief at 2 h (Figure 3.4.3). The quality of evidence was considered moderate (Table 3.4.1). The strength of the recommendation was considered strong in favor.

We found two RCTs addressing oral acetylsalicylic acid + metoclopramide as compared to placebo in the acute treatment of migraine attacks (194,300). The pooled analysis showed benefits of oral acetylsalicylic acid 900 mg + metoclopramide 10 mg over placebo considering the outcomes of pain freedom at 2 h and pain relief at 2 h (Figures 3.4.6 and 3.4.7). The quality of evidence for both outcomes was considered moderate (Table 3.4.3). The strength of the recommendation was considered strong in favor.

We found one RCT addressing oral paracetamol + tramadol as compared to placebo in the acute treatment of migraine attacks (347). The study showed benefits of oral

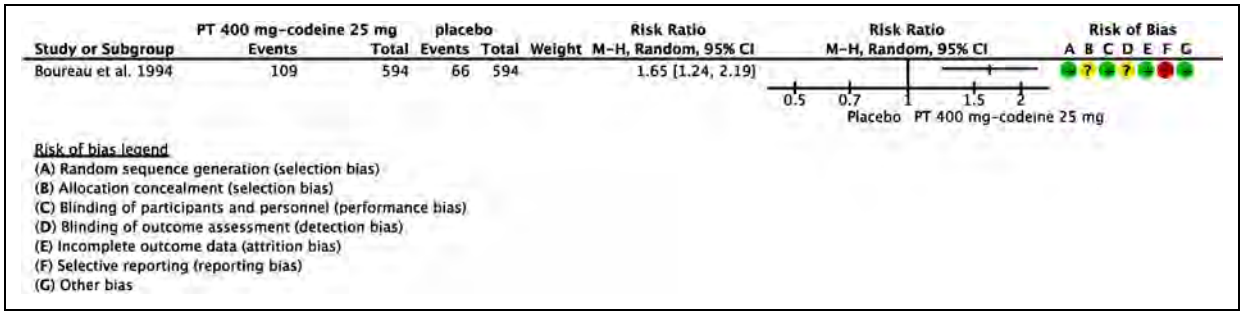


Figure 3.4.10. Forest plot showing the comparison between oral paracetamol 400 mg + codeine 25 mg and placebo for the outcome pain freedom at 2h in patients with migraine.

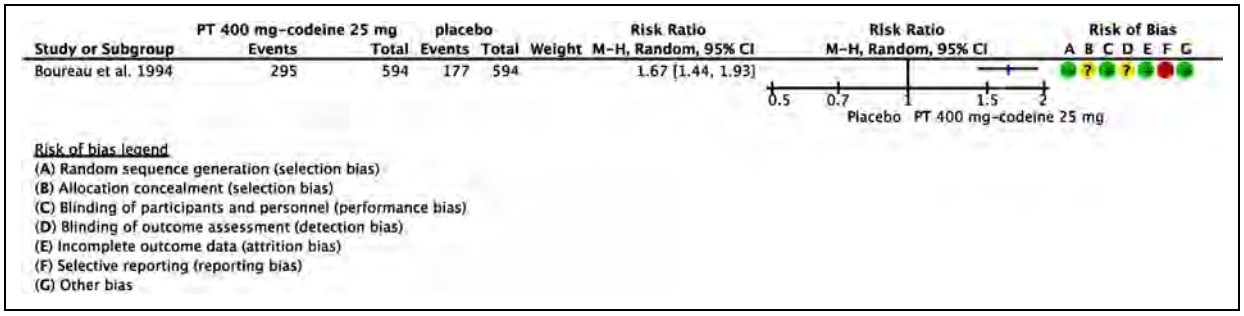


Figure 3.4.11. Forest plot showing the comparison between oral paracetamol 400 mg + codeine 25 mg and placebo for the outcome pain relief at 2h in patients with migraine.

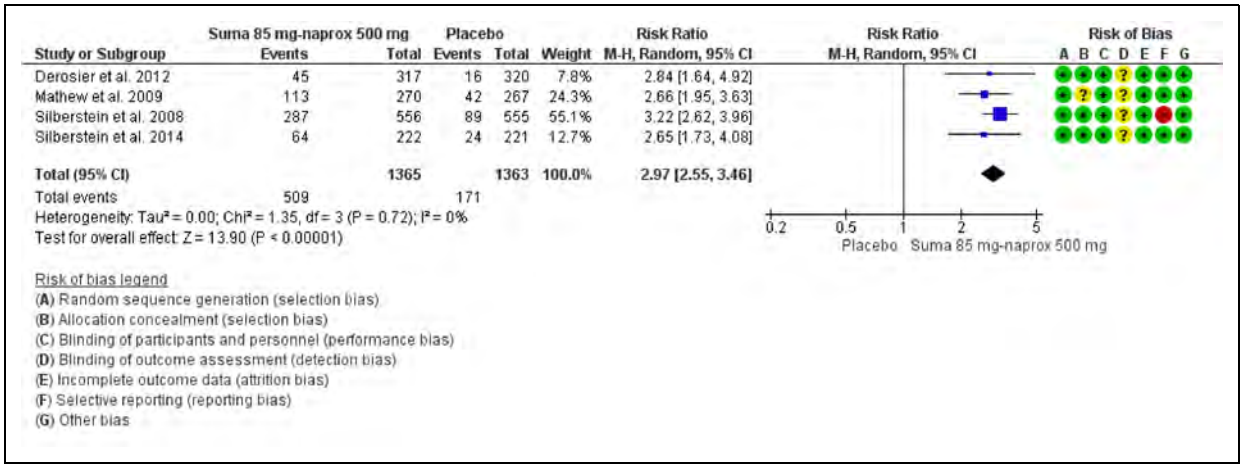


Figure 3.4.12. Forest plot showing the comparison between oral sumatriptan 85 mg + naproxen 500 mg and placebo for the outcome pain freedom at 2h in patients with migraine.

paracetamol 650 mg + tramadol 75 mg over placebo considering the outcomes of pain freedom at 2 h and pain relief at 2 h (Figures 3.4.8 and 3.4.9). The quality of evidence for both outcomes was considered low. The strength of the recommendation was considered strong in favor.

We found one RCT comparing oral paracetamol + codeine to placebo in the acute treatment of migraine attacks (26). This RCT did not meet most of the pre-defined quality criteria and for this reason the quality of evidence was considered very low. The study showed benefits of oral paracetamol 400 mg + codeine 25 mg over placebo

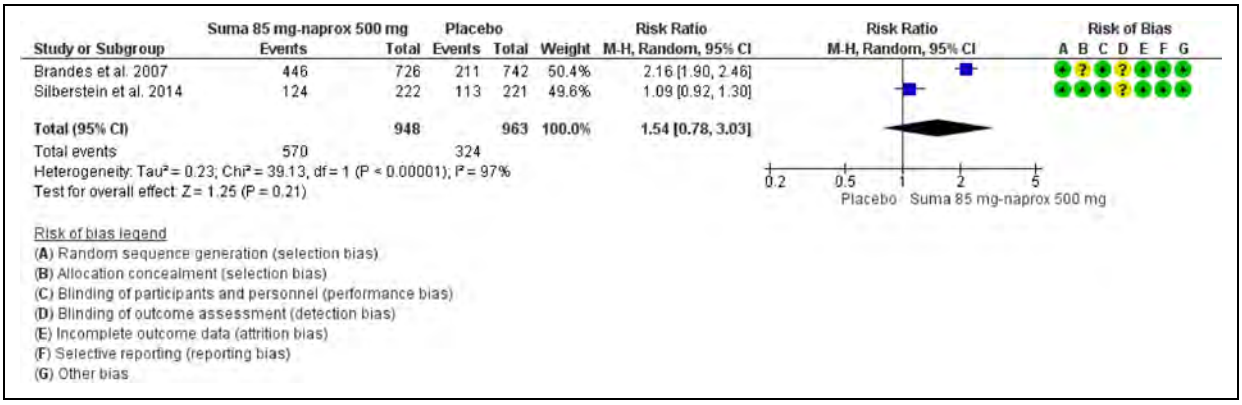


Figure 3.4.13. Forest plot showing the comparison between oral sumatriptan 85 mg + naproxen 500 mg and placebo for the outcome pain relief at 2h in patients with migraine.

considering the outcomes of pain freedom at 2 h and pain relief at 2 h (Figure 3.4.10). The quality of evidence was considered very low. The strength of the recommendation was considered weak in favor. The combination should not be considered as a first choice as we need to consider the potential risk associated with the use of medications containing opioids.

We found four RCTs (327,332,341,346) addressing oral sumatriptan + naproxen as compared to placebo in the acute treatment of migraine attacks. The pooled analysis showed benefits of oral sumatriptan 85 mg + naproxen 500 mg versus placebo considering the outcome pain freedom at 2 h; more limited evidence coming from two RCTs (27,327) did not show benefits considering the outcome pain relief at 2 h (Figure 3.4.12 and 3.4.13). The quality of evidence for both outcomes was considered high (Table 3.4.5). The strength of the recommendation was considered weak in favor.

We found one RCTaddressing oral rizatriptan + paracetamol as compared to placebo in the acute treatment of migraine attacks. This RCT did not meet all the pre-defined quality criteria. The study showed benefits of oral rizatriptan 10 mg + paracetamol 1000 mg over placebo considering the outcomes of pain relief at 2 h and pain freedom at 2 h (Figure 3.4.14 and 3.4.15). The quality of evidence for both outcomes was considered low (Table 3.4.6). The strength of the recommendation was considered strong in favor.

We found one RCTcomparing ergotamine + caffeine to placebo in the treatment of acute migraine attack. The study did not show benefits of oral ergotamine 2 mg + caffeine 200 mg over placebo considering the outcome pain freedom at 2 h, whereas it showed significant benefit in the outcome of pain relief at 2 h (Figure 3.4.18 and 3.4.19). The quality of evidence for both outcomes was considered low. The strength of the recommendation was considered weak in favor.

We found one RCTcomparing butalbital + paracetamol + caffeine to placebo in the acute treatment of migraine attacks. The study did not show benefits of butalbital 50 mg + paracetamol 325 mg + caffeine 40 mg over placebo considering the outcome of pain freedom at 2 h (Figure 3.4.20). The quality of evidence was considered moderate (Table 3.4.7). The strength of the recommendation was considered weak against.

Expert-based opinion

Topic: When should a combination analgesic be taken during a migraine attack?. Suggestion: All oral combinations should be preferentially taken at the beginning of an attack. Oral combinations of symptomatic drugs should be preferred for the treatment of moderate to severe migraine headache that usually does not satisfactorily respond to treatment with a single drug.

Rationale: The mechanism of action of oral combinations of drugs for acute treatment of migraine comes from the summation of the components' effects, each component having a different mechanism of action, resulting in an additional analgesic effect (381,382). Indeed, monotherapy does not always provide rapid, consistent, and complete relief for all subjects with migraine, while polytherapy, modulating two or more biological systems, may be more effective (284). For example, the triple oral combination of acetylsalicylic acid, paracetamol and caffeine, taken early in the attacks, seems to be much quicker and more effective than monotherapy (383). An oral combination of paracetamol + tramadol, or paracetamol + codeine, is indicated for the acute treatment of migraine attacks of moderate intensity, when paracetamol alone fails to effectively relieve headache. Opioid-containing combination analgesics should not be used routinely and as a first-line therapy (320) due to the high risk for addiction and overuse (see above). They should be avoided in attacks because both tramadol and codeine can worsen their symptoms, while the association of acetylsalicylic acid + metoclopramide or paracetamol + domperidone may be the

Table 3.4.5. GRADE evidence profile table for oral sumatriptan 85 mg + naproxen 500 mg versus placebo in migraine

Certainty assessment							№ of patients		Effect			
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Sumatriptan 85 mg + naproxen 500 mg os	Placebo	Relative (95% CI)	Absolute (95% CI)	Quality	Importance
Pain freedom at 2 h – Sumatriptan 85 mg + Naproxen 500 mg oral vs Placebo												
4	RCTs	Low	Not serious	Not serious	Not serious	None	509/1365 (37.3%)	171/1363 (12.5%)	**RR 2.97** (2.55 to 3.46)	**247 more per 1.000** (from 194 more to 309 more)	⊕⊕⊕⊕ High	Critical
Pain relief at 2 h – Sumatriptan 85 mg + Naproxen 500 mg oral vs Placebo												
2	RCTs	Low	Serious[a]	Not serious	Serious[b]	None	570/948 (60.1%)	324/963 (33.6%)	**RR 1.54** (0.78 to 3.03)	**182 more per 1.000** (from 74 fewer to 683 more)	⊕⊕⊖⊖ Low	Critical

[a]Very different results across trials; [b]confidence interval included the threshold for clinical decision.

best choice if migraine headache is accompanied by moderate or severe nausea (300,333).

Oral combination of ergotamine + caffeine can be used when rizatriptan or sumatriptan alone or in combination with naproxen or paracetamol are ineffective or only partially effective (309).

Topic: When should a combination analgesic drug be taken during an attack of migraine with aura?. Suggestion: It is advisable to avoid taking oral combination drugs containing triptans during the aura phase. The combination should be taken when the aura is terminated and possibly at the beginning of the headache phase. This is not the case with a combination of drugs containing paracetamol, acetylsalicylic acid and caffeine, which can be taken preferentially at the beginning of aura with the aim to avoid or reduce headache.

Rationale: Previous studies indicated that triptans, including sumatriptan, were not effective in relieving migraine when taken during the migraine aura phase and other studies also suggest that triptans were unable to reduce headache when it starts during the aura phase. Therefore, based on the lack of evidence of a positive effect on aura, the recommendation to avoid administration at the aura onset can be extended to oral combination drugs containing triptans (221,222,384,385).

Topic: What to do in case of headache relapse after initial response to a combination analgesic?. Suggestion: A reasonable therapeutic option is to use a second dose of the same combination of drugs or use another anti-migraine options (rescue medication), preferring alternative routes (rectal or intramuscular or intravenous in the Emergency Room setting or during hospitalization) when nausea and vomiting are prevalent. Clinicians' decision on which medication to prescribe for recurrence should be guided by considerations such as contra-indications, side effects, and the patient's previous overall experience with these medications.

Rationale: Migraine relapse is one of the main problems in clinical practice. Rates of headache relapse vary consistently among studies and depend on the definition of relapse. Relapse does not appear to be related to initial clinical efficacy but is influenced by the pharmacological and pharmacokinetic properties of the individual drugs in the combinations. If migraine relapses after an initial relief due to an anti-migraine combination drug, an additional dose can be administered at least 2 h after the previous intake (281). When attacks recur very frequently, it is advisable to switch to another anti-migraine formulation (alone or in combination). For combination of drugs containing aspirin and paracetamol, aspirin and metoclopramide, paracetamol combined with mild opioids, triptans should be considered as alternatives, especially those with a longer half-life (e.g., frovatriptan, eletriptan). In the case of partial efficacy, it can be useful to combine the triptan

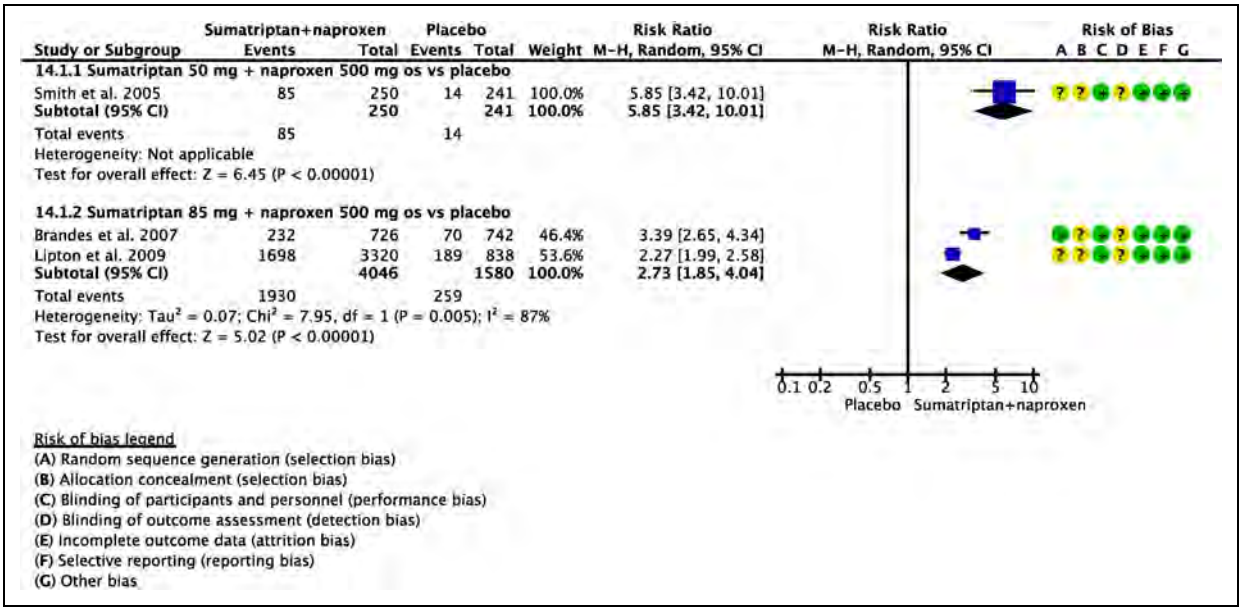


Figure 3.4.14. Forest plot showing the comparison between oral sumatriptan 50 mg + naproxen 500 mg and placebo, or sumatriptan 85 mg + naproxen 500 mg and placebo for the outcome pain freedom at 2 h in patients with migraine.

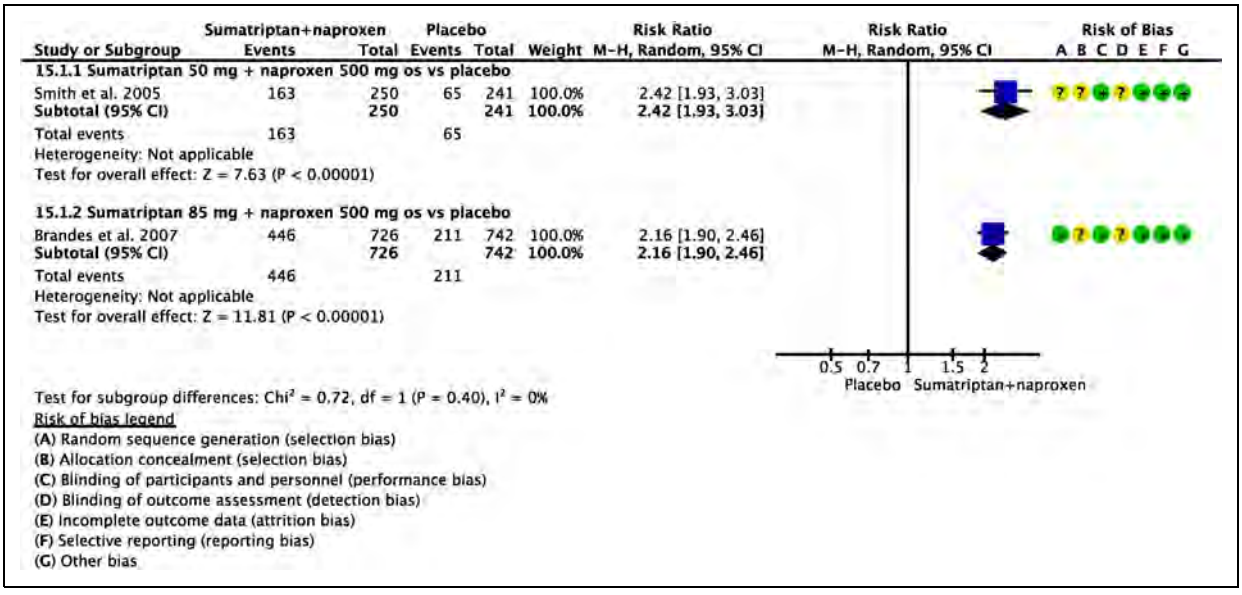


Figure 3.4.15. Forest plot showing the comparison between oral sumatriptan 50 mg + naproxen 500 mg versus placebo, or sumatriptan 85 mg + naproxen 500 mg versus placebo for the outcome pain relief at 2 h in patients with migraine.

with concomitant fast-acting formulations of NSAIDs (e.g., naproxen sodium, ibuprofen) (281).

Topic: How many doses of combination analgesics could be administered per month?. Suggestion: All combination analgesics should be taken for less than 10 days/month in order to decrease the risk of development of MOH, because the use on 10 days per month is considered overuse according to the International Headache Society criteria for "Combination-analgesic-overuse headache"[ICHD-3 8.2.5] (7,234). The misuse or overuse of anti-migraine combination of drugs is a risk factor for migraine chronification.

Rationale: The overuse of combination analgesics can favor the evolution to MOH as with the overuse of simple

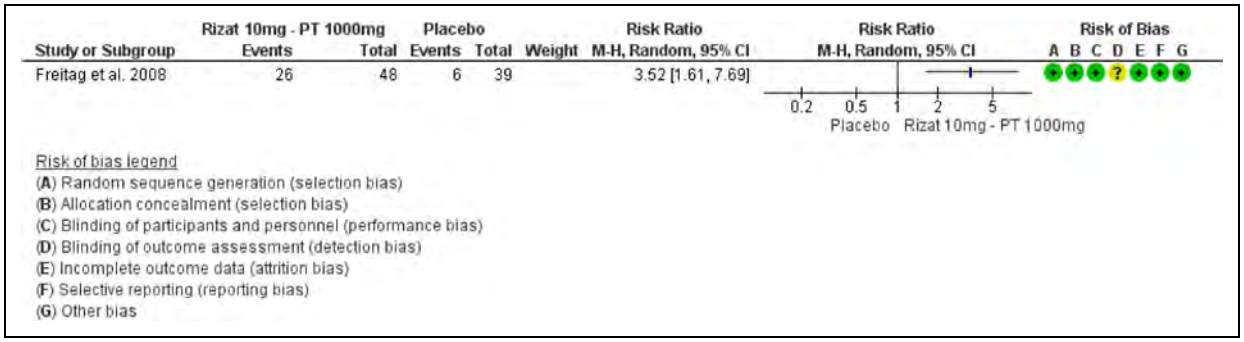


Figure 3.4.16. Forest plot showing the comparison between oral rizatriptan 10 mg + paracetamol 1000 mg and placebo for the outcome pain freedom at 2h in patients with migraine.

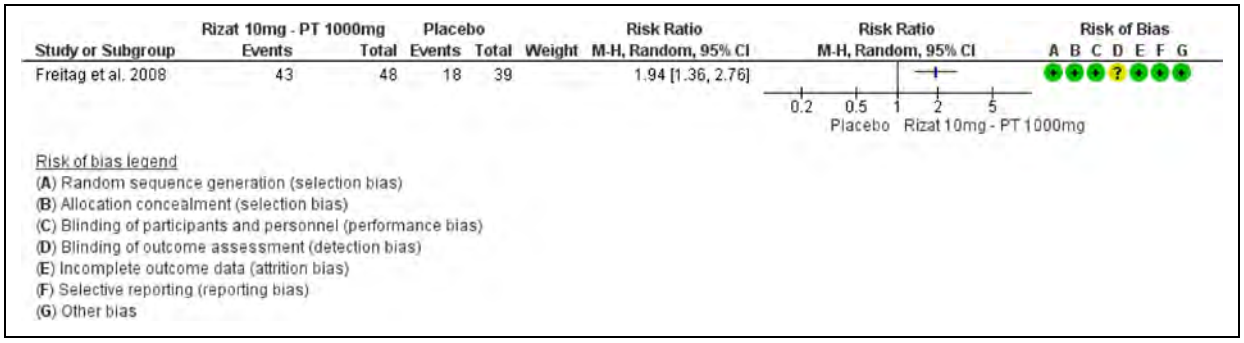


Figure 3.4.17. Forest plot showing the comparison between oral rizatriptan 10 mg + paracetamol 1000 mg and placebo for the outcome pain relief at 2h in patients with migraine.

analgesics and triptans. MOH due to drugs containing triptans, ergotamine, or opioids is more common than those due to simple analgesics and more difficult to treat (273,386,387).

Codeine/tramadol-containing analgesics have a great potential of misuse/overuse or physical and psychological dependence. In particular, codeine is metabolized in the liver like morphine, at a rate which varies consistently among individuals, with quick metabolizers having a higher risk of overuse and addiction (388). Combination drugs containing codeine have been found to increase the risk of MOH in comparison with single analgesics (389). Drugs containing codeine are therefore not recommended for chronic migraine because of the limited clinically relevant improvement in terms of sustained pain reduction and functioning recovery due to codeine in addition to paracetamol compared to paracetamol alone, and in the long run, the risk of dependence outweighs benefits. This is also true for combination drugs containing tramadol (390).

Ergot derivatives and caffeine-containing products increase the risk of transition from episodic to chronic migraine, particularly for those subjects with high headache frequency. It is generally accepted that ergot derivatives—which are marketed in combination with caffeine—exert a relevant influence on the development of MOH, and in recent years, their use has been restricted to those migraine patients with severe but low-frequency attacks (391).

Topic: Can pharmacokinetic and pharmacodynamic differences affect the choice of combination analgesics?. Suggestion: The knowledge of the principal pharmacodynamic and pharmacokinetic properties of the single components of combination analgesics is essential for the identification of specific differences that can affect choice.

Rationale: Drugs containing paracetamol occupy a prominent place among analgesics. These drugs are well tolerated at the gastric level and can therefore be advantageously used in the case of intolerance to salicylates and other NSAIDs or in patients with gastric disorders.

Codeine, in combination with other analgesics such as paracetamol, has a greater analgesic effect than the individual components and a longer lasting efficacy. For combination drugs containing codeine and tramadol, weak metabolizers and ultra-fast metabolizers have been identified, the former having a reduced analgesic effect, the latter an increased risk of side effects due to the two

Table 3.4.6. GRADE evidence profile table for oral rizatriptan 10 mg + paracetamol 1000 mg versus placebo in patients with migraine

Certainty assessment							№ of patients		Effect			
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Rizatriptan 10 mg + paracetamol 1000 mg	Placebo	Relative (95% CI)	Absolute (95% CI)	Quality	Importance
Pain freedom at 2 h – Rizatriptan 10 mg + Paracetamol 1000 mg oral vs Placebo												
1	RCT	Low	Not applicable[a]	Not serious	Serious[b]	None	26/48 (54.2%)	6/39 (15.4%)	**RR 3.52** (1.61 to 7.69)	**388 more per 1.000** (from 94 more to 1.000 more)	⊕⊕⊖⊖ Low	Critical
Pain relief at 2 h – Rizatriptan 10 mg + Paracetamol 1000 mg oral vs Placebo												
1	RCT	Low	Not applicable[a]	Not serious	Serious[b]	None	43/48 (89.6%)	18/39 (46.2%)	**RR 1.94** (1.36 to 2.76)	**434 more per 1.000** (from 166 more to 812 more)	⊕⊕⊖⊖ Low	Critical

[a]Only one trial; [b]low numbers of patients.

weak opioids. The combination of paracetamol and tramadol demonstrated genuine synergy and integrates paracetamol's rapid onset of efficacy with tramadol's prolonged analgesic effect. Combinations containing acetylsalicylic acid, paracetamol and caffeine have the potential of a greater efficacy than the single components with caffeine improving the paracetamol enteric absorption. Paracetamol plus tramadol has comparable efficacy to paracetamol plus codeine, but with reduced somnolence and constipation compared with the codeine combination (392,393).

Caffeine combined with ergotamine can increase the enteric absorption of ergotamine and contribute synergistically to the constriction of cerebral vasculature, thereby providing better efficacy than ergotamine alone and a valid alternative for triptans when they are ineffective (309).

Metoclopramide with his prokinetic action favors acetylsalicylic acid absorption and this is particularly useful for migraine attacks with prevalent nausea and vomiting.

The combination of rizatriptan with paracetamol or of sumatriptan with naproxen did not imply differences in the pharmacodynamic and pharmacokinetic properties of the single drugs in the combination.

Acetylsalicylic acid + paracetamol + caffeine combination. Pharmacodynamic properties: Acetylsalicylic acid belongs to the group of NSAIDs with analgesic, antipyretic and anti-inflammatory properties. Its mechanism of action is based on the irreversible inhibition of the COX enzyme involved in the synthesis of prostaglandins. Paracetamol also inhibits COX activity, but its analgesic effect is mainly attributed to a direct action at the level of the CNS, probably mediated by the opioid and serotonergic systems, as well as by an action of inhibition of prostaglandin synthesis at central level. In addition, paracetamol has a strong antipyretic activity. Caffeine exerts its analgesic activity through the block of the peripheral pronociceptive actions of adenosine and the activation of the central noradrenergic and serotoninergic descending antinociceptive pathways (394).

In primary microglial cells both paracetamol and caffeine dose-dependently inhibited microglial PGE-2 synthesis. In combination with acetylsalicylic acid both substances augmented the inhibitory effect of acetylsalicylic acid on LPS-induced PGE-2 synthesis. Whereas paracetamol inhibited only COX enzyme activity, caffeine also inhibited COX-2 protein synthesis. These results suggest that the clinical activity of paracetamol and caffeine is due to the inhibition of COX and support the clinical experience of an adjuvant analgesic effect of caffeine and paracetamol when combined with acetylsalicylic acid (297).

Additionally, in a pain-induced functional impairment model in rats, caffeine significantly increased the analgesic effect of aspirin at all doses, without modifying aspirin, salicylic acid, or gentisic acid plasma levels. It is concluded that caffeine potentiates the analgesic effect of aspirin by

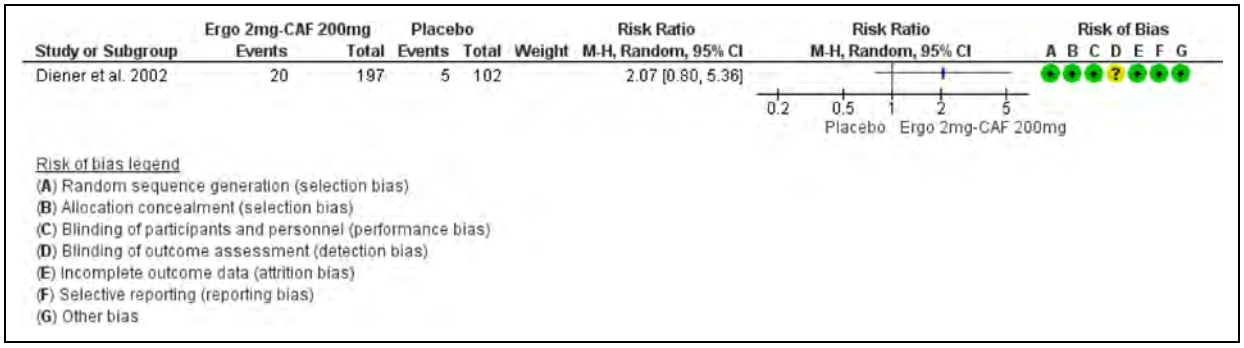


Figure 3.4.18. Forest plot showing the comparison between oral ergotamine 2 mg + caffeine 200 mg and placebo for the outcome pain freedom at 2 h in patients with migraine.

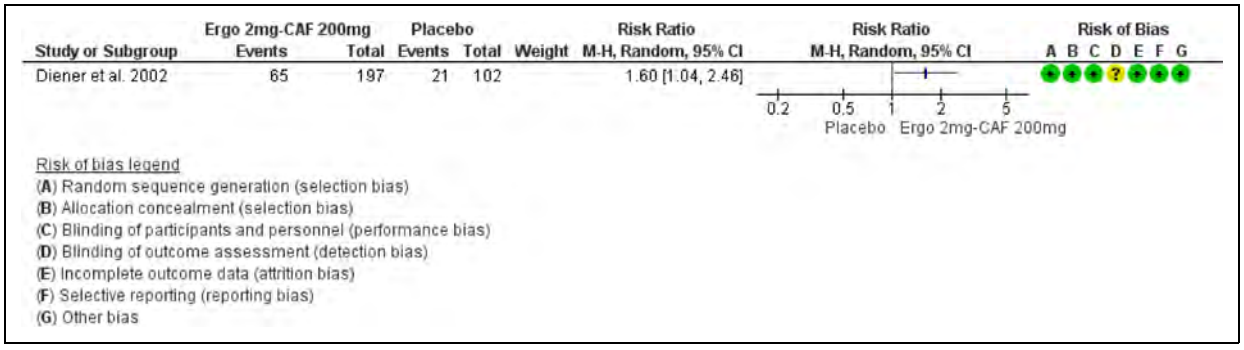


Figure 3.4.19. Forest plot showing the comparison between oral ergotamine 2 mg + caffeine 200 mg and placebo for the outcome pain relief at 2 h in patients with migraine.

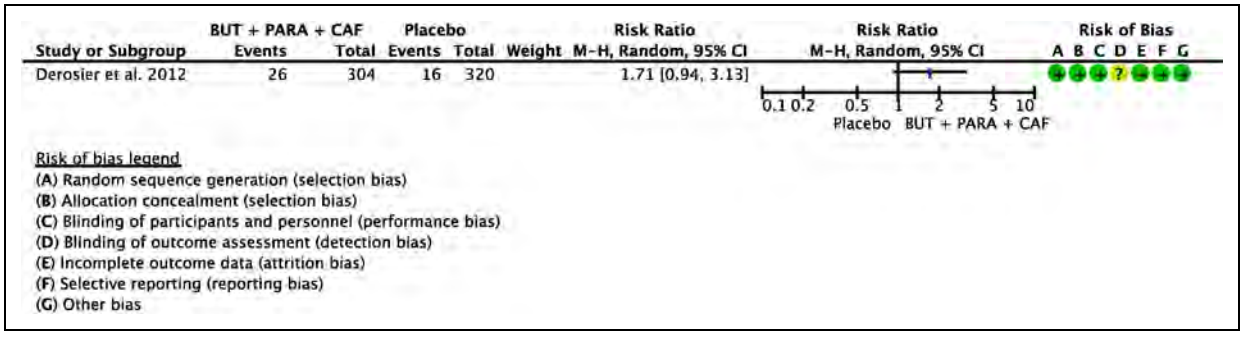


Figure 3.4.20. Forest plot showing the comparison between oral butalbital 50 mg + paracetamol 325 mg + caffeine 40 mg and placebo for the outcome pain freedom at 2 h in patients with migraine.

a pharmacodynamic, but not by a pharmacokinetic mechanism (395).

Pharmacokinetic properties: A slightly positive influence of caffeine on the absorption rate of paracetamol has been observed in a healthy study volunteer (396). Other research confirmed that caffeine accelerated absorption, indicated by enhanced early AUCs and prolonged the analgesic activity of paracetamol (397). Caffeine also significantly increased the rate of appearance as well as the maximum concentration of salicylate in the plasma by about 25% and 17%, respectively. In contrast no change was observed in the plasma half-life, volume of distribution and clearance of salicylate (398).

Caffeine did not affect the pharmacokinetics of ASA and paracetamol when used as an adjuvant in ASA/paracetamol fixed-dose combination under fasting conditions,

Drug	Acute treatment of migraine attacks
Oral combination of acetylsalicylic acid 500 mg + paracetamol 500 mg + caffeine 130 mg	⊕⊕⊕⊕ ↑↑
Oral combination of acetylsalicylic acid 900 mg + metoclopramide 10 mg	⊕⊕⊕⊖ ↑↑
Oral combination of paracetamol 650 mg + tramadol 75 mg	⊕⊕⊕⊖ ↑
Oral combination of paracetamol 400 mg + codeine 25 mg	⊕⊖⊖⊖ ↑
Oral combination of sumatriptan 85 mg + naproxen 500 mg	⊕⊕⊖⊖ ↑↑
Oral combination of rizatriptan 10 mg + paracetamol 1000 mg	⊕⊕⊖⊖ ↑↑
Oral combination of ergotamine 2 mg + caffeine 200 mg	⊕⊕⊖⊖ ↑
Oral combination of butalbital 50 mg + paracetamol 325 mg + caffeine 40 mg	⊕⊕⊖⊖ ↓

Quality of selected evidence	
⊕⊕⊕⊕	High
⊕⊕⊕⊖	Moderate
⊕⊕⊖⊖	Low
⊕⊖⊖⊖	Very low
⊖⊖⊖⊖	None
Strength of the recommendation	
↑↑	strong in favor
↑	weak in favor
↓	weak against
↓↓	strong against
-	none

Figure 3.4.21. Summary of evidence-based recommendations on combinations drugs for the treatment of the acute migraine attack.

Table 3.4.7. GRADE evidence profile table for oral butalbital 50 mg + paracetamol 325 mg + caffeine 40 mg versus placebo in migraine

Certainty assessment								№ of patients		Effect			
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Butalbital 50 mg + paracetamol 325 mg + caffeine 40 mg	placebo - main	Relative (95% CI)	Absolute (95% CI)	Quality	Importance
Pain freedom at 2 h – Butalbital 50 mg + Paracetamol 325 mg + Caffeine 40 mg oral vs Placebo												
1	RCT	Not serious	Not applicable[a]	Not serious	Serious[b]	None	26/304 (8.6%)	16/320 (5.0%)	**RR 1.71** (0.94 to 3.13)	**36 more per 1.000** (from 3 less to 107 more)	⊕⊕⊖⊖ Low	Critical

[a]Only one trial; [b]the confidence interval included the clinical decision threshold.

suggesting that caffeine enhances the analgesic efficacy of these drugs by pharmacodynamic rather than pharmacokinetic interactions (399).

Paracetamol + codeine combination. Pharmacodynamic properties: The association codeine/paracetamol is one of the most widely used central analgesics. Whereas paracetamol exerts its analgesic action by interacting with opioid inhibitory pathways, serotonin pathway, and the endocannabinoid system; codeine, the natural alkaloid of opium, interacts with the CNS and peripheral opiate receptors, exerts its effect through opioid receptors μ, although it has a low affinity for these receptors, and its analgesic action is due to its conversion to morphine (400).

More recent findings showed that codeine activity seems to be related not only to its conversion to morphine but also by itself and through its metabolites, such as norcodeine (NORC) and codeine-6-glucuronide (C-6-G). The addition of codeine to paracetamol significantly improves the analgesic action and reduces the number needed to treat (NNT) from 5 to 2.3–3.1 (401).

Pharmacokinetic properties: Paracetamol did not affect pharmacokinetic and metabolism of codeine in man (402). Likewise, therapeutic doses of codeine do not influence the clearance or metabolism of paracetamol (403). Codeine is rapidly absorbed in the intestine, with a half-life of about 3 h, and excreted via the urine. Codeine is metabolized in the liver mainly by glucuronic conjugation, but through a minor metabolic pathway, such as O-demethylation, it is converted to morphine. This metabolic transformation is catalyzed by the enzyme CYP2D6. About 7% of the Caucasian population has a deficiency of the enzyme CYP2D6 due to genetic variation (404). These subjects are called poor metabolizers and may not benefit from the expected therapeutic effect because they are unable to transform codeine into its active metabolite morphine. Conversely, about 5.5% of the population in Western Europe is made up of ultra-fast metabolizers. These individuals have one or more duplicates of the CYP2D6 gene and therefore may have higher concentrations of morphine in the blood resulting in an increased risk of adverse reactions (405). The existence of ultra-rapid metabolizers should be considered with particular attention in the case of patients with renal impairment in whom an increase in the concentration of the active metabolite morphine-6-glucoronide may occur. Genetic variation for the enzyme CYP2D6 can be ascertained by genetic typing testing (406). These aspects should be considered also when combination of codeine with paracetamol is used as an acute antimigraine drug.

Paracetamol + tramadol combination. Pharmacodynamic properties: Tramadol is a centrally acting opioid analgesic. It is a pure non-selective agonist of μ, δ, and opiate κ receptors with greater affinity for μ receptors. Other mechanisms that contribute to its analgesic effect are the inhibition of

neuronal reuptake of norepinephrine and the increase in serotonin release (364). Unlike morphine, tramadol has no depressant effects on breathing when administered in the analgesic dose range. It also does not affect gastrointestinal motility. The effects on the cardiovascular system are mild. The potency of tramadol is between 1/10 and 1/6 compared to that of morphine (407). Combining agents such as tramadol and paracetamol, which have complementary modes of action and target multiple sites, may potentially provide better analgesia against several types and sources of pain including migraine (408). Indeed, an *in vivo* study in mice showed the combination of tramadol and paracetamol provided synergistic analgesia over a range of dose ratios, and the dose ratio of the fixed-dose combination falls within this range of synergy (409). Moreover, a double-blind, placebo-controlled, crossover study in 17 healthy volunteers showed that the combination of intravenous tramadol and paracetamol had supra-additive analgesic and antihyperalgesic effects (410).

Pharmacokinetic properties: In humans, tramadol is metabolized essentially by demethylation to N and O conjugation of demethylation products to O with glucuronic acid. Only O-desmethyltramadol is pharmacologically active. For the other metabolites, quantitatively, there are significant interindividual differences. Inhibition of one or both types of CYP3A4 and CYP2D6 isoenzymes involved in tramadol biotransformation may alter plasma concentration of tramadol or its active metabolite (411). In the case of a deficiency of CYP2D6 enzyme, the patient may not get an adequate analgesic effect. If the patient is an ultra-rapid metabolizer, there is a risk of developing undesirable effects of opioid toxicity even at commonly prescribed dosages. General symptoms of opioid toxicity include confusion, drowsiness, surface breathing, contracted pupils, nausea, vomiting, constipation, and lack of appetite. In severe cases, this can include symptoms of circulatory and respiratory depression, which can be life-threatening and very rarely be fatal. Co-administration of tramadol 112.5 mg and paracetamol 975 mg had no effects on the single-dose pharmacokinetics of the individual agents in a 3-way crossover study involving 24 healthy volunteers (412). After repeated administration of oral tramadol/paracetamol 37.5/325 mg to steady state in healthy volunteers, the bioavailability of tramadol was lower than those reported after monotherapy, but the bioavailability of paracetamol was unchanged. The area under the plasma concentration-time curve values for tramadol and its O-desmethyl metabolite were slightly reduced by 14–20% compared with those after tramadol monotherapy. The plasma elimination half-life of racemic tramadol increased to between 7 and 9 h after multiple dose administration (413). Evaluation of four pharmacokinetic studies in 84 healthy volunteers showed that after co-administration of tramadol and paracetamol, body weight was the most important determinant of paracetamol clearance and volume of distribution. Gender had no significant impact on paracetamol clearance, or on the pharmacokinetics of tramadol and *O*-desmethyl metabolite. In poor CYP 2D6 metabolizers, tramadol clearance was slightly reduced, and its metabolite formation was reduced by 70% (414). The pharmacokinetics of tramadol/paracetamol have not been studied in patients with renal or hepatic dysfunction or in children. Based on the pharmacokinetics of tramadol and/or paracetamol, the fixed combination tablet is not recommended in patients with severe renal impairment (creatinine clearance < 0.6 L/h [<10 mL/min]) or those with severe hepatic impairment. In those with moderate renal dysfunction (creatinine clearance 0.6–1.8 L/h [10–30 mL/min]), the dosage interval should be increased to 12 h (414).

Acetylsalicilic acid + Metoclopramide combination. Pharmacodynamic properties: Combinations containing oral metoclopramide + acetylsalicylic acid may be an option for patients in whom triptans are contraindicated or who experience intolerable adverse effects (301). In clinical studies the addiction of metoclopramide 10 mg to acetyl salicylic acid 1000 mg improves relief of nausea and vomiting but does not result in a significant better relief compared to acetylsalicylic acid alone (21).

Metoclopramide stimulates and coordinates the motility of the upper gastrointestinal tract, without changing gastric, pancreatic and biliary secretion and has an antiemetic effect. Its mechanism of action is complex, being a competitive antagonist of D1 and D2 dopamine receptors and 5-HT3 serotonin receptors, as well as a nonspecific agonist of 5-HT4 receptors involved in the stimulation of enteric cholinergic neurons. It therefore has intestinal prokinetic activity which results in accelerated gastric emptying and decreased reflux from the duodenum into the stomach and esophagus (299). In an animal model metoclopramide was unable to affect the peripheral response to trigeminovascular activation (neurogenic inflammation), but it did suppress the central response (the trigeminal cervical complex neuronal firing) after dural electrical stimulation, which suggests a possible anti-migraine action of the drug (415).

Pharmacokinetic properties: Metoclopramide is well absorbed, and its bioavailability varies individually between 35 and 100%. The binding affinity with plasma proteins is equal to 40% (416). The drug is metabolized in the liver by simple conjugation processes; slight alterations in liver function, in the presence of normal renal function, do not seem to predispose to significant changes in pharmacokinetic parameters (417). Elimination is dose-dependent, varying between 3 and 5 h after single dose (299). Delayed gastric emptying during migraine attacks may impair the absorption of acetylsalicylic acid. A study suggests that this impaired motility can be overcome by parenteral metoclopramide, but no data are available for oral combinations of the two drugs (418). During migraine

attacks the serum concentrations and the AUC0–5.5 h of metoclopramide were slightly lowered. The impairment of drug absorption during a migraine attack was not related to the duration or severity of the attack. The observed changes in drug absorption during migraine attacks are due to the delay in gastric emptying (419). The relevance of this reduced absorption has never been assessed with regard to the oral absorption of acetylsalicylic acid. No studies are available on the effects of metoclopramide on pharmacokinetics of acetylsalicylic acid but it is conceivable that the antiemetic does not impact acetyl salicylic acid distribution and metabolism based on the effect on other non-steroidal anti-inflammatory drugs such as tolfenamic acid (419).

Sumatriptan + naproxen combination. Pharmacodynamic properties: Sumatriptan is a selective and specific agonist of 5-hydroxytryptamine (HT)-1B/1D receptor on intracranial blood vessels and sensory nerves of the trigeminal system and has no other demonstrated activity on other 5-HT receptors (5HT2–5HT7) (310). The putative antimigraine actions of sumatriptan include vasoconstriction of dilated cranial blood vessels, inhibition of the release of vasoactive neuropeptides such as CGRP, and inhibition of pain signal transmission centrally within the trigeminovascular system. Naproxen has anti-inflammatory and analgesic properties. Its mechanism of action is based on the reversible inhibition of COX (420). A model-based analysis of phase 2 and 3 clinical trial data predicted a statistically significant synergistic interaction between sumatriptan and naproxen sodium in achieving a therapeutic effect in subjects with migraine (282). The pharmacodynamic effects of sumatriptan/naproxen sodium include suppression of the production of several cytokines associated with migraine pain and inflammation. In a rat model, sumatriptan and naproxen sodium suppressed distinct sets of cytokines in the trigeminal ganglia and the spinal trigeminal nuclei (421).

Pharmacokinetic properties: Following the administration of sumatriptan/naproxen sodium, the pharmacokinetics of sumatriptan were largely unchanged versus sumatriptan alone or sumatriptan plus naproxen sodium coadministration, whereas for naproxen sodium, the maximum plasma concentration (C_{max}) was reduced by 36% and time to C_{max} (t_{max}) was increased by ≈4 h versus naproxen alone. Sumatriptan and naproxen pharmacokinetics did not differ between adolescents with migraine and healthy adults (422). The pharmacokinetics of sumatriptan and naproxen sodium were largely unchanged in the elderly, compared with younger adults. A pooled analysis of five clinical trials showed that gender did not affect the systemic exposure of sumatriptan/naproxen sodium (423).

Rizatriptan + paracetamol combination. Pharmacodynamic properties: Like sumatriptan, rizatriptan selectively binds with high affinity to human 5-HT1B and 5-HT1D receptors and its therapeutic activity in the treatment of migraine is attributed to its agonist effect at the level of the 5-HT1B and 5-HT1D receptors of extracerebral intracranial blood vessels and to the inhibition of neuropeptide release leading to reduced inflammation of sensitive tissues and reduced central transmission of the trigeminal pain signal (424). The combination of rizatriptan with paracetamol may provide an additional - although moderate - benefit compared to rizatriptan alone without the safety concerns of nonsteroidal drugs and this offers a further option for the acute treatment of migraine. The rationale of the use of this combination for the acute treatment of migraine attacks is the potential greater benefit in relieving migraine pain from a multi-mechanism therapy (58). Patients with a suboptimal response to rizatriptan can therefore benefit from the combination of this triptan with paracetamol for migraine relief.

Pharmacodynamic properties: No clinical studies are available on the effects of paracetamol on rizatriptan pharmacokinetics.

Ergotamine + caffeine combination. Pharmacodynamic properties: Ergotamine can cause vasoconstriction by stimulating alpha-adrenergic and 5-HT receptors. It shows moderate to high affinity for various subtypes of serotonin receptors, however its effect on migraine is mainly related to the agonistic properties on 5-HT1B and 5-HTID receptors (425). Caffeine may work synergistically with ergotamine by constricting cerebraland this vasoconstrictive effect of caffeine is due to its antagonistic properties at adenosine A1, A2A, and A2B receptors. In the past, the use of the ergotamine + caffeine combination was considered for patients with more severe symptoms and whose attacks did not respond to NSAIDs or combination analgesics. Because there are other medication options for the acute treatment of migraines with fewer side effects - like triptans - clinicians should consider prescribing ergotamine + caffeine only to patients with infrequent but very severe attacks lasting more than 48 h (309). The potential for overuse when attacks are frequent should be taken into account. Overuse of ergotamine + caffeine combination has been associated with physical and psychological dependence resulting in predictable recurrent and/or rebound headaches, and severe withdrawal symptoms, including nausea, upon discontinuation. Overuse of ergotamine + caffeine combination is a risk factor for the development of MOH even if this risk is lower compared to that related to combination analgesics containing opiates or barbiturates overuse (426). In patients with migraine experiencing severe nausea and vomiting during their attacks, the rectal route allows the combination of ergotamine + caffeine to reach the cranial vessels directly, evading the splanchnic vasculature and the liver.

Pharmacokinetic properties: Caffeine increases the absorption of ergotamine from the small intestine and is thought to exert its rate-accelerating effect by increasing the water solubility of ergotamine neutral molecules (427).

Topic: Do combination analgesics show relevant drug interactions?. Suggestion: Many drug interactions have been described for the single components in the combination drugs. For the anti-migraine combination drugs the most relevant interactions with other drugs are reported for each drug in the combination.

Acetylsalicylic acid. Suggestion 1: Concomitant treatment with combination analgesics containing acetyl salicylic acid and drugs that alter hemostasis is not recommended, unless strictly indicated, as they may increase the risk of bleeding (e.g., anticoagulants such as warfarin, thrombolytic and antiplatelet agents e.g., ticlopidine, clopidogrel and dipyridamole, anti-inflammatory drugs and selective serotonin reuptake inhibitors).

Rationale 1: Increased risk of bleeding due to inhibition of thrombocyte function, lesion of the duodenal mucosa and displacement of oral anticoagulants from plasma protein binding site can occur with drugs containing acetylsalicylic acid. The concomitant use and selective serotonin reuptake inhibitors (SSRIs; such as sertraline or paroxetine) also increase the risk of gastrointestinal bleeding (synergistic effect on anti-platelet activity). If these combinations cannot be avoided, close clinical and laboratory monitoring (including bleeding time) is recommended (428,429).

Suggestion 2: The regular or frequent use of compounds containing acetylsalicylic acid can cause an increase in the blood concentration of valproic acid and phenytoin. Combination analgesics containing aspirin should also be used with caution in patients treated with digoxin and lithium.

Rationale 2: Acetylsalicylic acid impairs renal excretion of digoxin and lithium, resulting in increased plasma concentrations. Dosage adjustment may be necessary (430). Acetylsalicylic acid has been reported to reduce valproate and phenytoin binding to serum albumin, thereby increasing free plasma concentrations at steady state. This also may lead to an increased fraction of free phenytoin (431,432).

Naproxen. Suggestion: Naproxen has several potential drug interactions that need to be addressed for their potential clinical relevance, especially if the drug is used regularly or daily or almost daily.

Rationale: Due to the high binding of naproxen to plasma proteins, patients receiving concomitant drugs highly bound to proteins such as anticoagulants should be closely monitored for overdose effects of these drugs. Naproxen like NSAIDs may increase the effects of anticoagulants such as warfarin. With concomitant use of antiplatelet agents and selective serotonin reuptake inhibitors (SSRIs) there is also an increased risk of gastrointestinal bleeding effects (433,434). Naproxen and other nonsteroidal anti-inflammatory drugs may reduce the antihypertensive effect of propranolol and other beta-blockers (430).

Paracetamol. Suggestion: Paracetamol should be used with extreme caution and under close supervision during chronic treatment with drugs that may induce hepatic monooxygenases or in case of exposure to substances that may have such an effect.

Rationale: Rifampicin, cimetidine, antiepileptics such as phenobarbital, carbamazepine may increase the risk of liver toxicity by this mechanism due to paracetamol (435–437). Concomitant administration of phenytoin may result in decreased efficacy of paracetamol and an increased risk of hepatotoxicity. Patients receiving phenytoin should avoid high and/or chronic doses of paracetamol. Patients should be monitored for evidence of hepatotoxicity (438).

Caffeine. Suggestion: The clearance of caffeine can be modified by several drugs, leading to an increased risk of the risk of caffeine toxicity.

Rationale: Caffeine is extensively metabolized by CYP1A2 and drugs that increase or decrease enzyme activity can modulate the metabolic clearance of caffeine. Fluoroquinolones, mexiletine, fluvoxamine and oral contraceptives may increase plasma caffeine exposure (439,440). The association of caffeine with sympathomimetics can lead to an increase in blood pressure (441).

Metoclopramide. Suggestion 1: Metoclopramide potentiates the effects of sedative drugs, neuroleptics and serotoninergic drugs.

Rationale 1: The sedative effects of central nervous system depressing drugs (morphine derivatives, anxiolytics, sedative H1 antihistamines, sedative antidepressants, barbiturates, clonidine) are enhanced by metoclopramide (442). Metoclopramide may have an additive effect on neuroleptics in the case of extrapyramidal disorders. Concurrent administration of metoclopramide and antipsychotic drugs should be avoided due to the potential for additive effects and neuroleptic malignant syndrome (443). Using metoclopramide with serotonergic drugs such as SSRIs may increase the risk of serotonin syndrome (444,445).

Suggestion 2: Metoclopramide influences the absorption, metabolism and bioavailability of many drugs, with different mechanisms of action.

Rationale 2: Levodopa or dopaminergic agonists and metoclopramide antagonize each other; therefore, their concomitant use should be avoided (446). Metoclopramide may reduce the bioavailability of digoxin. Close monitoring of digoxin plasma concentrations is necessary (447). Finally, by reducing intestinal transit of food,

metoclopramide treatment may require insulin dosage adjustment in diabetes (448).

Codeine and tramadol. Suggestion 1: The effects of weak opioids such as codeine and tramadol can be enhanced by other depressant drugs such as sedatives, tranquilizers, and antihistamines.

Rationale 1: Concomitant use of these drugs with sedative medicinal products such as benzodiazepines or related drugs increases the risk of sedation, respiratory depression, coma and death due to the additive depressant effect on the CNS. The dose and duration of concomitant treatment should be kept as low as possible (449).

Suggestion 2: Compounds containing tramadol can favor seizures when used with alcohol, antidepressants and neuroleptics and cannabinoids. Its concomitant use with antidepressant can be responsible for serotonin syndrome.

Rationale 2: Tramadol can induce seizures and potentiate the effect of selective serotonin reuptake inhibitors (SSRIs), serotonin-norepinephrine reuptake inhibitors (SNRIs), tricyclic antidepressants, antipsychotics, and other drugs (such as bupropion, mirtazapine, tetrahydrocannabinol) that lower the seizure threshold (450). Concomitant therapeutic use of tramadol and serotonergic drugs, such as selective serotonin reuptake inhibitors (SSRIs), serotonin-norepinephrine reuptake inhibitors (SNRIs), MAO inhibitors, tricyclic antidepressants and mirtazapine, may result in serotonin syndrome (364).

Suggestion 3: Caution should be exercised during concomitant treatment with tramadol and coumarin derivatives (e.g., warfarin) due to reports of increased international normalized ratio (INR) with major bleeding and bruising in some patients.

Rationale 3: Clinical reports of critical elevations of prothrombin time and INR in patients concomitantly using warfarin and tramadol have been published. Empiric dose reduction of 25–30% in warfarin followed by repeat measurement of the INR within one week in patients using warfarin and who are starting tramadol therapy is suggested (451,452).

Sumatriptan and rizatriptan. Suggestion 1: The use of sumatriptan or rizatriptan within 24 h of using ergot-containing drugs or 5-$HT_{1B/D}$ receptor agonists is contraindicated because of the risk of prolonged vasospastic reactions and additive vasospastic effect of concomitant use of triptans and ergot-derivatives.

Rationale 1: Concomitant administration of triptans and ergot-containing drugs is not recommended due to the potential increased risk of coronary vasospasm. The required interval between the use of sumatriptan and preparations containing ergotamine or other triptans/5-HT1 receptor agonists is unknown. Therefore, it is recommended to wait at least 24 h before taking sumatriptan after using preparations containing ergotamine or other triptans/5-HT1 receptor agonists. In contrast, it is recommended to wait at least 6 h after using sumatriptan before taking an ergotamine-containing product and at least 24 h before taking another triptan/5-HT1 receptor agonist (453).

Suggestion 2: An interaction between combination drugs containing sumatriptan and rizatriptan and MAO inhibitors is possible, and their concomitant administration is therefore contraindicated.

Rationale 2: Co-administration of an inhibitor of MAO-A (a MAOI-A) causes a 2-fold increase in sumatriptan plasma concentrations, and a 40% increase in elimination half-life. A model for sumatriptan pharmacokinetics suggests that a MAOI-A probably has greater effect on elimination kinetics than first-pass metabolism, and that this interaction appears to be overstated in product labeling (322,454). Rizatriptan is metabolized primarily via monoamine oxidase type A (MAO-A). Plasma concentrations of rizatriptan and its active metabolite N-monodactyl were increased by concomitant administration of a selective and reversible MAO-A inhibitor. Due to the risk of coronary artery vasoconstriction and hypertensive episodes, the administration of rizatriptan to patients taking MAO inhibitors is contraindicated (455).

Suggestion 3: Concomitant use of combination drugs containing sumatriptan or rizatriptan with selective serotonin reuptake inhibitors, serotonin norepinephrine reuptake inhibitors or tricyclic antidepressants and lithium may cause serotonin syndrome.

Rationale 3: Some post-marketing cases have been published describing patients with serotonin syndrome (including altered mental status, autonomic instability, and neuromuscular abnormalities) following the use of SSRIs and sumatriptan. Serotonin syndrome has also been reported following concomitant treatment with triptans and SNRIs, there may also be risks of serotonin syndrome with concomitant use of sumatriptan with lithium (456). A lack of clinical, pharmacodynamic and pharmacokinetic interactions has been reported between rizatriptan and the selective serotonin reuptake inhibitor, paroxetine (457).

Suggestion 4: Combinations of analgesics containing rizatriptan are not recommended in patients treated with propranolol.

Rationale: Propranolol increases plasma concentrations of rizatriptan by inhibiting monoamine oxidase-A. When prescribing rizatriptan to migraine patients receiving propranolol for migraine prevention, the 5 mg dose of rizatriptan is recommended. This is not possible for the combination drug containing rizatriptan 10 mg. Administration with other beta-adrenoceptor blockers does not require a dose adjustment (240).

Ergotamine. Suggestion 1: The simultaneous use of cytochrome P450 3A (CYP3A4) inhibitors and ergotamine containing drug combinations should be avoided.

Rationale 1: These associations may result in increased ergotamine plasma concentration and consequent ergot toxicity, with vasospasm and ischemia of the extremities and other tissues. CY3A4-inhibitors include HIV protease inhibitors, HIV reverse transcriptase inhibitors, HCV protease inhibitors, imidazole derivatives, triazole derivatives, tetracyclines and macrolides (e.g., troleandomycin, clarithromycin). An expected interaction to be considered is also with moderate/weak CYP3A4 inhibitors, such as cimetidine, clotrimazole, fluconazole, grapefruit juice, quinupristin/dalfopristin and zileuton, which may increase ergotamine exposure, with possible ergotism and necrosis of the extremities and caution is required for their concomitant use. Ergotism with the possibility of necrosis of the extremities has been described with diltiazem due to the inhibition of hepatic metabolism of ergot alkaloids (375,458).

Suggestion 2: Ergotamine tartrate + caffeine tablets should not be administered with other vasoconstrictors.

Rationale 2: Concomitant use of vasoconstrictors, including drugs containing ergot alkaloids, 5HT1 receptor agonists, nicotine (e.g., excessive smoking) and alpha-sympathomimetics (nasal and/or oral), and indirect sympathomimetics may cause increased vasoconstriction and/or hypertensive crisis (311). The beta-blocker propranolol has been reported to potentiate the vasoconstrictive action of ergotamine tartrate + caffeine tablets. Several cases of arterial spasm with ischemia of the extremities (sum of vascular effects) have been observed. Clinical monitoring should be increased, particularly during the first weeks of administration of the combination (459). As already stated, an increased risk of vasospasm has been observed with the concomitant use of ergotamine/caffeine combination and triptans as well as an increased risk of arterial hypertension, coronary artery disease. Concomitant use of ergotamine with serotonin reuptake inhibitors (for example, amitriptyline), including selective agents (for example, sertraline) may lead to serotonin syndrome and requires caution (243).

Topic: Can combination analgesics be used during pregnancy?.

Suggestion: None of the oral combination analgesics included in this meta-analysis for acute migraine treatment is recommended during pregnancy.

Rationale: Considerations about combination analgesics are based on the observations available for each component in the combinations. Paracetamol is regarded as safe to use in pregnancy, although some studies showed an association with ADHD with long-term use even after adjusting the other risk factors. However, the combination of paracetamol with opioids (such as codeine or tramadol) should only be used after careful benefit/risk assessment and under medical supervision. Since the product crosses the placental barrier, it can induce neonatal respiratory depression; long-term use during pregnancy can also cause withdrawal symptoms in the newborn infant (460).

Aspirin, as well as NSAIDs, usually are not recommended during pregnancy. These drugs should be avoided during pregnancy due to the fetal risks such as renal injury, oligohydramnios, constriction of the ductus arteriosus (with potential for persistent pulmonary hypertension in the newborn), necrotizing enterocolitis, and intracranial hemorrhage (461).

A limited use of caffeine is recommended during pregnancy; therefore, compounds containing caffeine should preferentially be avoided. Indeed, observational studies and meta-analyses suggest an increased risk from maternal caffeine consumption for miscarriage, stillbirth, lower birth weight and/or small for gestational age (462).

The use of triptans and other drugs exhibiting vasoconstrictive properties in pregnant women requires a careful benefits/risks evaluation. There is no data to suggest teratogenicity for any of the triptans, although the most common adverse events recorded with available registries are spontaneous abortion, preterm delivery and low birth weight (463,464). These findings underline the need for a careful evaluation of the potential serious adverse effects of triptans and their potential impact on pregnancy outcome (463). This observation should be extended to the combination drugs containing triptans. Ergotamine is contraindicated in women who are or may become pregnant, since the drug may cause fetal harm. Its use during pregnancy is associated with low birthweight and/or preterm birth which may relate to ergotamine-induced vasoconstriction in the placenta of pregnant women. Ergotamine may cause acute fetal hypoxia and myocardial ischemia. Based on these observations, ergotamine-containing compounds should be avoided (465,466).

Topic: Can combination analgesics be used during lactation?.

Suggestion: Women who are breastfeeding should consult their health care practitioner about all the drugs they are taking or about to start. However, many medications in the anti-migraine oral combinations can be safely taken during breastfeeding, including paracetamol, anti-inflammatory medications such as ibuprofen (being the drug of choice owing to its short elimination half-life, lack of active metabolites, and low excretion in milk), naproxen and diclofenac, and triptans such as eletriptan and sumatriptan.

Caffeine is not harmful for breastfed babies but can make them irritable and may increase the baby's heart and breathing rates.

Therefore, many combination drugs can be used in limited doses during breast-feeding with the exclusion of combinations containing codeine or tramadol.

Compounds containing ergotamine are contraindicated during lactation.

Rationale: Paracetamol is a good choice for nursing mothers. Amounts in milk are much less than doses

usually given to infants and adverse effects in breastfed infants are rare (467). Maternal administration or ingestion of most NSAIDs result in low infant exposure via breast milk, therefore both COX-1 and COX-2 inhibitors are generally considered safe, and preferable to acetylsalicylic acid, when breastfeeding (461). Maternal use of oral combinations containing mild narcotics during breastfeeding can cause infant drowsiness, and severe CNS depression. Furthermore, new-born infants are particularly sensitive to the effects of even small doses of narcotic analgesics. Therefore, the use of narcotic analgesics should be avoided during lactation (468). Infant drug exposure to triptans through breastfeeding appears to be low and this indicates that the use of these drugs alone or in combination with an analgesic/NSAID is compatible with breastfeeding (469). There is limited published evidence on ergotamine effects during breastfeeding. One dated study in which ergotamine was administered to mothers of newborns immediately postpartum, did not show effect on weight gain in the breastfed infants nor difference in the milk production (470). However, WHO contraindicates ergotamine use during breastfeeding due to adverse effects in the infant and decreased milk production (471).

Topic: combination-analgesics and renal impairment. Suggestion: The use of all combination analgesics should be limited to the monthly recommendations for the potential renal impairment due to the single drugs in the combinations. In patients with impaired renal function an altered clearance of these drugs occurs, with the risk of production and accumulation of toxic or therapeutically active metabolites. Some agents in the combinations may also aggravate pre-existing renal disease.

Rationale: Despite paracetamol being recommended as the drug of choice in patients with renal impairment, a recent meta-analysis demonstrated a significantly increased risk of newly developing renal impairment in adults. Therefore, the risk of potential adverse renal effects due to paracetamol should be considered when combination drugs containing this drug are prescribed (472–474). Combinations containing acetylsalicylic acid or other NSAIDs should not be used in the presence of chronic renal failure due to the risk of significant toxicity. Combinations containing acetylsalicylic acid or naproxen sodium should therefore be avoided in the case of renal impairment. No evidence of renal toxicity is available for ergotamine containing compounds used in the recommended dosages (475). Renal impairment can reduce the elimination of certain opioids and their metabolites, and their accumulation and toxicity may occur. Drugs containing codeine should be avoided whereas drugs containing tramadol should be used with caution and in reduced dosages (476). Prolonged renal impairment after chronic ergotamine intoxication has been reported but no evidence of renal impairment was published for a more cautious use of ergotamine alone or in combination (477). There are no reports on renal impairment due to triptans, and there is no need for dosage adjustment in patients with mild-to-severe renal impairment. No particular caution should be made in the case of the use of a drug combination containing rizatriptan and paracetamol. However, the possibility of a paracetamol-induced renal failure becoming evident after paracetamol-induced hepatotoxicity should be taken into account (367). Isolated cases of paracetamol-induced acute kidney injury without hepatic injury have also been described (478). Furthermore, there are a few case reports of renal infarction due to peripheral vasospasm in patients using triptans, including rizatriptan (479).

Topic: Combination-analgesics and hepatic failure. Suggestion: The use of all combination analgesics should be limited to the monthly recommendations for the potential hepatotoxicity of single drugs in the combinations. A limited use of combinations containing paracetamol and mild opioid or triptans and paracetamol should be recommended in the case of hepatic failure.

Rationale: Combination drugs containing paracetamol should be used with caution and in reduced doses in patients with hepatic impairment for a period not exceeding a few days. Combination drugs containing codeine should also be taken in limited doses and for a short period of time, especially if combined with paracetamol. Codeine is metabolized in the liver via the cytochrome P450 system, and a long-term use can be responsible for hepatic injury (480). Moreover, combinations containing tramadol can cause acute liver failure. Pharmacologic doses of tramadol have not been shown to be associated with cases of drug induced liver disease (481). Combinations containing acetylsalicylic acid can also produce hepatotoxic reactions as a cumulative phenomenon, which require days or weeks to develop but also cases of acute liver injury have been described. Complications such as bleeding due to antiplatelet activity, gastrointestinal irritation, and renal failure are more likely to occur with nonsteroidal anti-inflammatory drugs in patients with severe hepatic impairment. Thus, this analgesic class should be avoided in this population (482,483). In contrast, there are some rare individual reports of cholestatic hepatitis after the use of triptans. Combination of a triptan with paracetamol or naproxen sodium can be safe, and only requires caution in the case of hepatic failure (484,485).

3.5 Antiemetics

Introduction

Antiemetics are drugs currently used in several diseases in order to treat nausea and vomiting, belonging to different classes including antagonists of dopamine, serotonin, histamine, muscarinic and neurokinin systems, benzodiazepines

and corticosteroids (486). During the acute phase of a migraine attack, antiemetics can relieve nausea and vomiting, and lead to a reduction in pain (24,486). Antiemetics are often considered the treatment of choice in the emergency room setting, where parenteral routes of administration are often used (304).

Dopamine antagonists, such as metoclopramide, prochlorperazine, domperidone, and chlorpromazine are the mainstay of migraine-related nausea treatment, although 5-HT_3 receptor antagonists (e.g., ondansetron) are also used in the emergency room, especially in the pediatric population. Within the class of antiemetics, metoclopramide and prochlorperazine are dopamine D2 receptor blockers that have the greatest evidence for efficacy in migraine. Metoclopramide exhibits both peripheral and central actions, demonstrating efficacy in reducing nausea and migraine pain, while also enhancing the impact of concurrent analgesics (487,488). Although domperidone and chlorpromazine are good antiemetics, the evidence for their effect in migraine treatment is weaker (489–491).

Antiemetic agents are generally safe and well-tolerated, but they might be associated with adverse events, including extrapyramidal symptoms – such as dystonia and akathisia – and QT interval prolongation (486).

We performed a systematic review and meta-analysis of randomized controlled trials (RCTs) to evaluate the efficacy of antiemetics compared with placebo for the acute treatment of migraine in adults. The primary endpoints in most studies were the number of patients with headache resolution or with reduced headache severity, while the secondary outcome was improvement in quality of life.

Section-specific methods

This section followed the general procedure to develop this guideline (see Section 2).

Search strings for the guideline on antiemetics for systematic review/meta-analysis and for additional RCTs are reported in Online Appendix 3.5.1.

Results

The database search for systematic reviews and meta-analyses resulted in a total of 1042 hits (Figure 3.5.1). After duplicate removal and screening 990 titles and abstracts, one systematic review and meta-analysis was considered as source of RCTs (24) after analyzing full texts of these RCTs, we included no RCTs in the quantitative synthesis (Figure 3.5.1).

Overall, we retrieved 1315 references from searching for RCTs in the context of antiemetics and migraine, and after removing duplicates, we had 1100 references to screen. However, considering the most recent included systematic review and meta-analysis on the topic (24), the analysis of additional RCTs was performed for papers published since 2021 (101 references) (Figure 3.5.2).

Overall, no studies were included in the qualitative or quantitative synthesis (meta-analyses) to develop the evidence-based guideline.

Expert-based opinions

There is a lack of good quality RCTs on acute pharmacological treatment of migraine with antiemetics. Available evidence mostly focused on dopaminergic antagonists, like metoclopramide and prochlorperazine. Therefore, while antiemetics are commonly utilized in the emergency room or at home to manage nausea associated with migraine attacks (487), their use as a standalone acute migraine treatment is discouraged due to the poor quality of published studies (488,489). Of note, a comparative study conducted on a small population suggested that a buccal formulation of prochlorperazine 3 mg produced a faster and more marked efficacy than oral or buccal placebo, or oral ergotamine tartrate 1 mg + caffeine 100 mg (489). In another study metoclopramide was more effective than placebo in relieving nausea, but not migraine pain (488).

Though some reports suggest that antiemetics may alleviate migraine pain, they are indicated for the symptomatic treatment of nausea and vomiting in association to standard acute therapy for migraine attacks (see Section 3.4 on combination analgesics). They can be used alone only when acetaminophen, NSAIDs and migraine-specific drugs for the acute treatment of attacks are ineffective or contraindicated (488).

It is important to keep in mind that antiemetics can also result in side effects such as extrapyramidal symptoms (e.g., akathisia), hypotension, and arrhythmias, including Torsade de Pointes and QT interval prolongation (486).

Overall, antiemetics may thus be a viable alternative for patients who experience intense nausea/vomiting during migraine attacks and are resistant to or have contraindications to acetaminophen, NSAIDs and migraine specific acute treatments (488,489).

3.6 Opioids

Introduction

Opioids are semi-synthetic and synthetic substances that act on opioid receptors to produce morphine-like effects. These receptors are found principally in the central and peripheral nervous system, in the gastrointestinal tract. Their stimulation induces somatic and psychoactive effects, reduces pain, and suppresses cough and diarrhea (492). In the headache field, opioids are potentially useful thanks to their ability to promote immediate relief of moderate to severe acute pain (493). On the other hand, their persistent use is

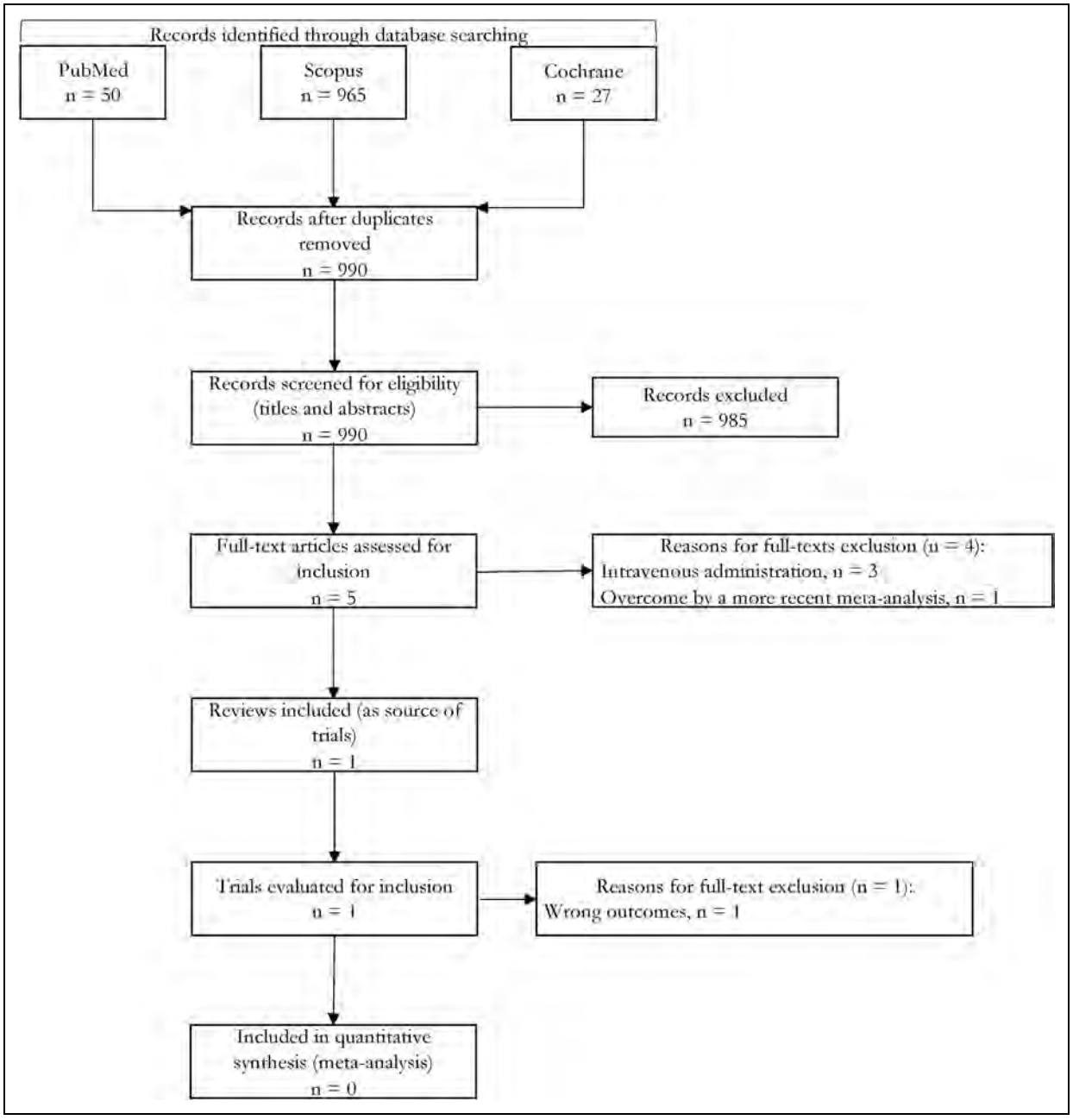


Figure 3.5.1. Meta-analysis selection flow chart - antiemetics.

associated with long-term opioid consequences such as dependence and need of increasing dosage to obtain pain relief; this may also lead to life-threatening overdose (494). Over the last decades, the increased prescription of this class of drugs has led to widespread misuse of both prescription and non-prescription opioids. The soaring increase in opioid prescriptions and misuse in the United States (US) contributed to the so-called "opioid crisis" in North America (495) and was a driver for the onset of the first wave of the epidemic of drug overdose deaths. These alarming phenomena led to an update of the Canadian guideline on opioids for chronic non-cancer pain (CNCP) (496) and to a guideline from the United States (US) Centers for Disease Control (CDC) (497), which focused on harm reduction in relation to opioid prescribing for CNCP.

A large number of randomized placebo-controlled trials (RCTs) were conducted to test the efficacy of opioids in the treatment of CNCP. These have provided evidence of a modest efficacy in pain relief and on the improvement of physical functioning, while underlining clinically relevant adverse events (498).

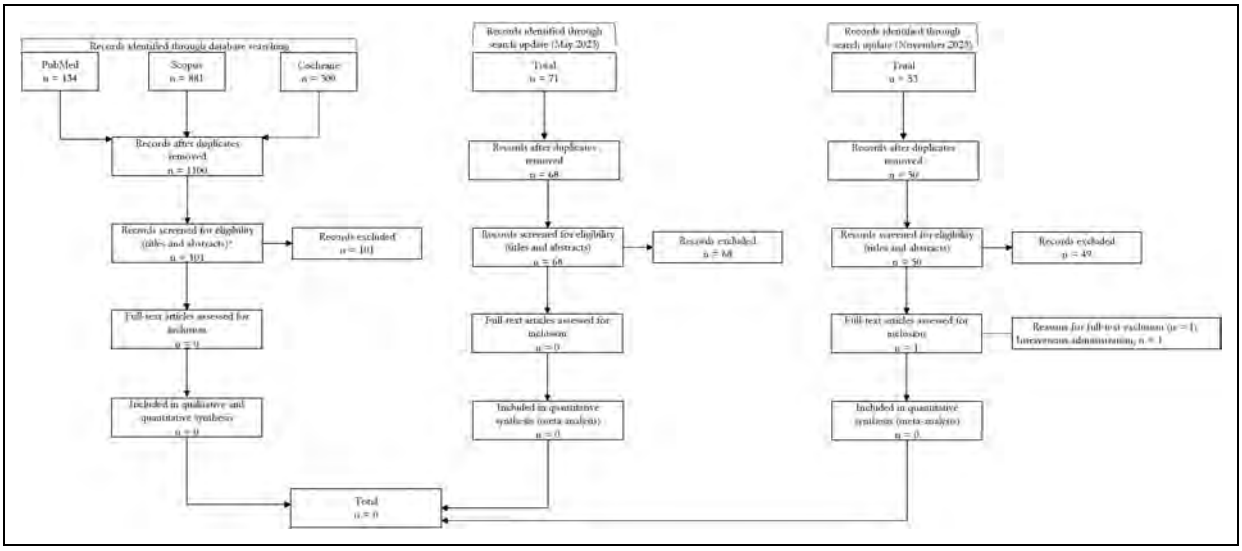


Figure 3.5.2. RCTs selection flow chart. *trials published since 2021 were screened.

In the migraine field, the extent of use of opioids has been recently assessed by a web-based survey conducted in a large representative US population (ObserVational survey of the Epidemiology, tReatment and Care of MigrainE [OVERCOME]) (499). The outcome of the survey shows that among the 12,299 patients with 0–3 monthly headache days (MHDs), 59.0% never used opioids, 26.0% formerly used them, and 15.0% were current opioid users. When considering the 8844 patients with ≥4 MHDs, 44.9% never used opioids, 31.2% formerly used them, and 23.9% were current opioid users.

Although the situation in European countries is far less critical than the opioid crisis observed in North America (500), there are increasing concerns about the safety of long-term opioid therapy for patients with CNCP (501). Therefore, the European Pain Federation released the European clinical practice recommendations on opioids for CNCP, which were endorsed by several other European scientific associations, including the European Academy of Neurology (EAN) and the European Headache Federation (EHF) (502). Notably, in several chronic pain conditions, opioids are considered neither a universal cure nor a universally dangerous threat. They can only be used for some selected chronic noncancer pain syndromes, but it is strongly recommended to consider them only if established non-pharmacological and pharmacological treatment options have failed. In the acute setting, opioids are often prescribed for immediate postoperative pain and other painful conditions for patients in the emergency department and primary care settings. In this framework, opioids should be prescribed only when necessary, at the lowest effective dose, and for the shortest period required (497).

Section-specific methods

Search strings for the Guideline on opiates for systematic review/meta-analysis and for additional RCTs are reported in Online Appendix 3.6.1.

Results

Overall, we retrieved 1096 references from searching for systematic reviews and meta-analyses. After duplicate removal and screening stages, we included one systematic review with meta-analysis (24) that was considered as the source of randomized controlled trials (RCTs). After analyzing full texts of these RCTs, we included one of them in the quantitative synthesis (503) (Figure 3.6.1).

Overall, we retrieved 719 references from searching for RCTs and after removing duplicates we had 693 references to analyze. However, considering the most recent included systematic review with meta-analysis on the topic (24), the analyses of additional RCTs were performed for papers published since 24 February 2021 and did not result in the inclusion of any additional RCTs (Figure 3.6.2).

Overall, one study was included in the quantitative synthesis (meta-analyses) to develop the evidence-based guideline (503). It reported a comparison between an active drug and placebo and was presented in this paper.

Butorphanol

PICO 3.6.1. In patients with episodic migraine, is butorphanol superior to placebo in the acute treatment

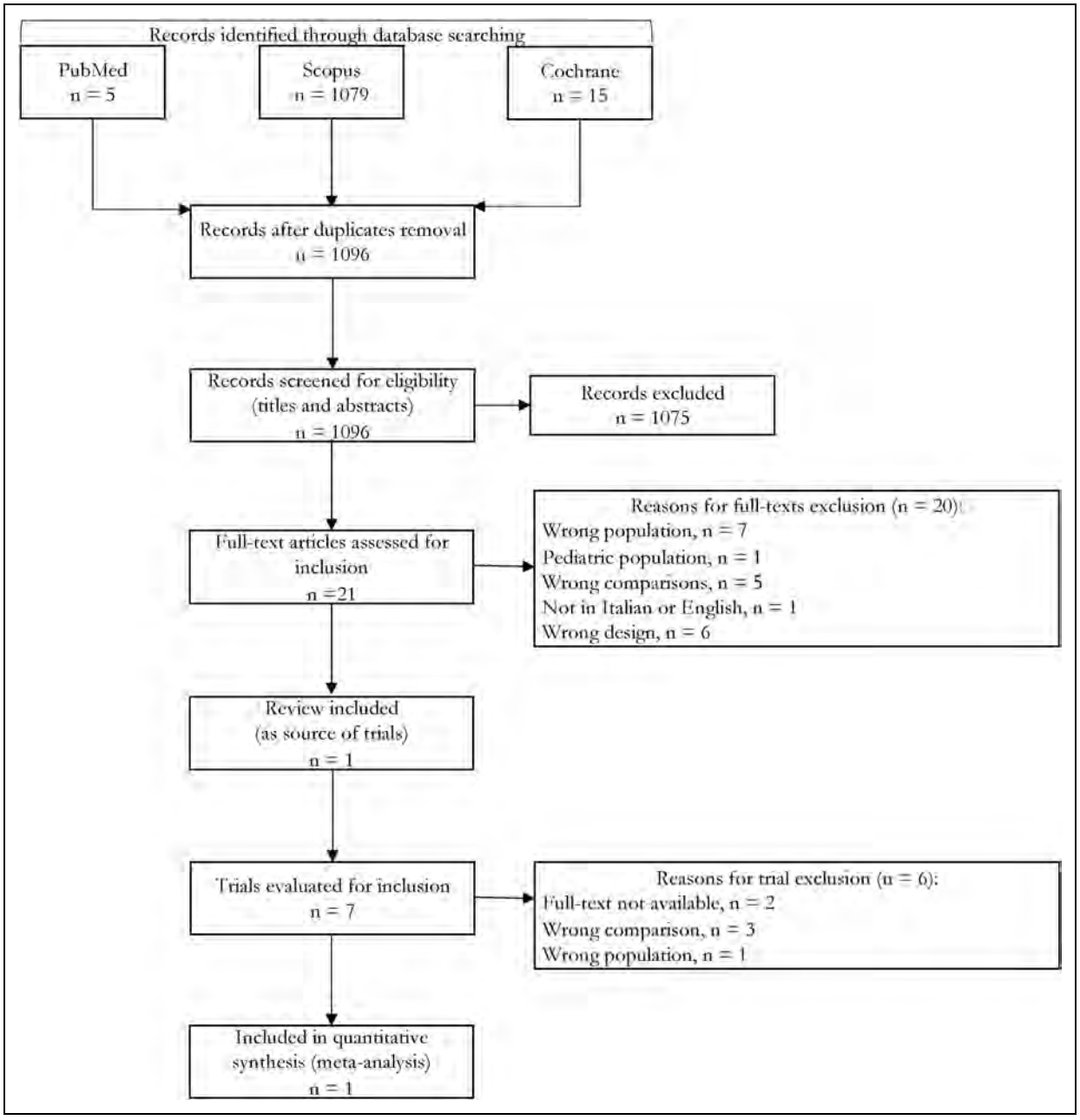


Figure 3.6.1. Meta-analysis selection flow chart - opioids.

of migraine attacks (outcomes: pain freedom at 2 h, pain relief at 2 h)?

Main evidence. None.

Additional evidence. We found one RCT comparing butorphanol to placebo in the acute treatment of migraine attacks (503) that did not meet the criteria to be included in the main evidence. The risk of bias of this study was very serious and the overall quality of evidence was further downgraded to very low (Figures 3.6.3 and 3.6.4).

The study showed benefits of intranasal butorphanol 1 mg over placebo considering the outcomes pain freedom at 2 h (Figure 3.6.3) and pain relief at 2 h (Figure 3.6.4).

Evidence-based recommendation for PICO 3.6.1

In patients with migraine, we suggest intranasal butorphanol 1 mg for the acute treatment of migraine attacks.

Quality of evidence: Very low (⊕⊖⊖⊖)
Strength of the recommendation: Weak (↑)
[NOTE: Considering the risk associated with the class of opioids, their use in the acute treatment of migraine should be considered only when all the other available options have proved ineffective.]

Safety and tolerability of opioids. Warnings and contraindications: Opioids should not be used in pregnant or breastfeeding women, as these populations are not included in RCTs. Breastfeeding is not recommended due to the risk of serious adverse reactions in breastfed infants. Opioids should not be used in patients with significant respiratory depression or acute or severe bronchial asthma.

Serious safety concerns: Seizures can occur within the recommended dose range. Serotonin syndrome, which may be life-threatening, can occur. The concomitant use of opioids with serotonergic drugs, such as SSRIs and triptans, should be avoided. The misuse of opioids can lead to opioid use disorder and MOH (opioid-overuse headache).

Tolerability: Adverse events were more frequent in patients using butorphanol compared to those receiving placebo. Dizziness, nausea, vomiting, and drowsiness were the more frequent adverse events. In the butorphanol RCT, 36% of the adverse events were rated as severe.

Evidence-based guideline summary

We found only one study on butorphanol for deriving evidence-based recommendations for this guideline. There is low quality of evidence to suggest the use of intranasal butorphanol for the acute treatment of migraine attacks. (Figure 3.6.5).

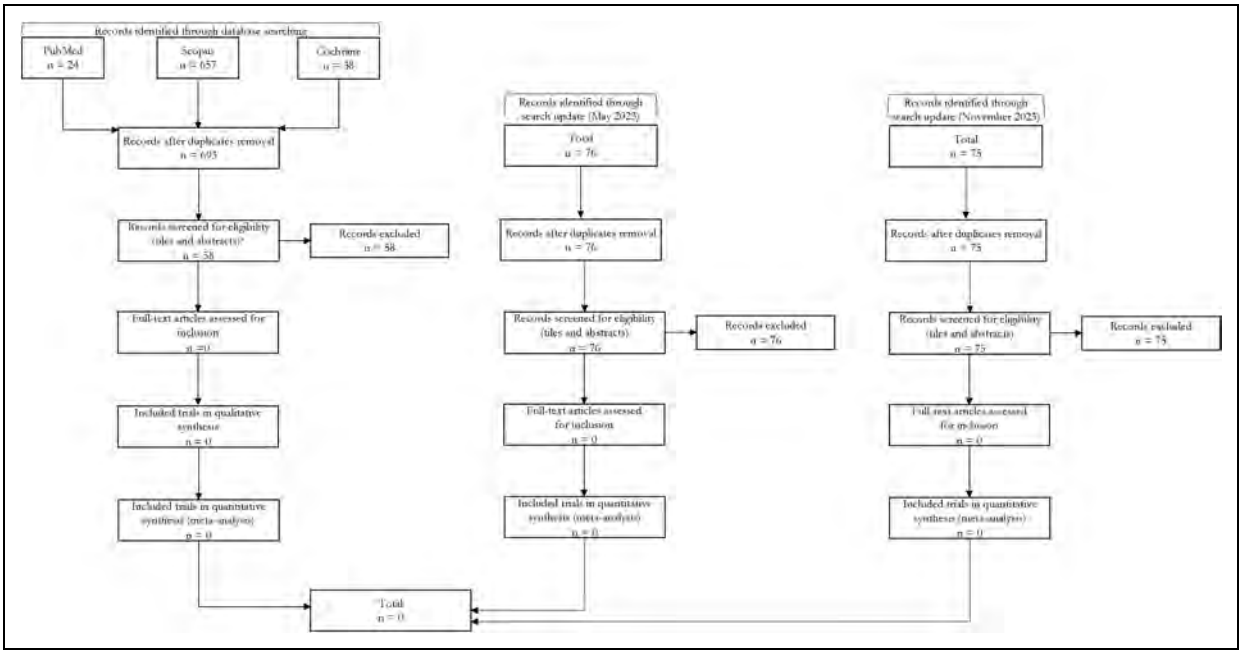


Figure 3.6.2. RCTs selection flow chart - opioids.
*trials published since February 24, 2021 were screened.

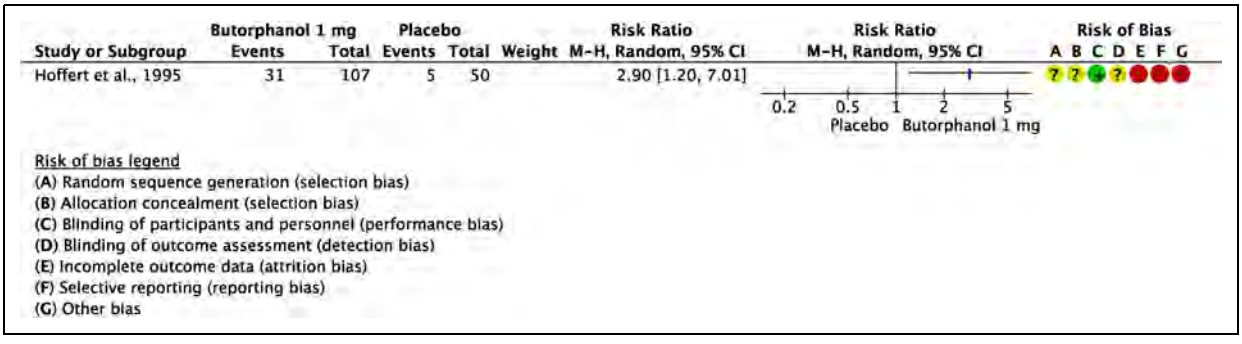


Figure 3.6.3. Forest plot showing the comparison between butorphanol 1 mg intranasal vs placebo for the outcome pain freedom at 2 h in patients with migraine.

Expert-based opinions

Topic: Opioids in the acute treatment of migraine attacks.
Suggestion: The evidence of efficacy of opioids in the acute treatment of migraine attacks is very limited. There is low-quality evidence to suggest the use of intranasal butorphanol, but this drug is not commonly used in the real-life setting.

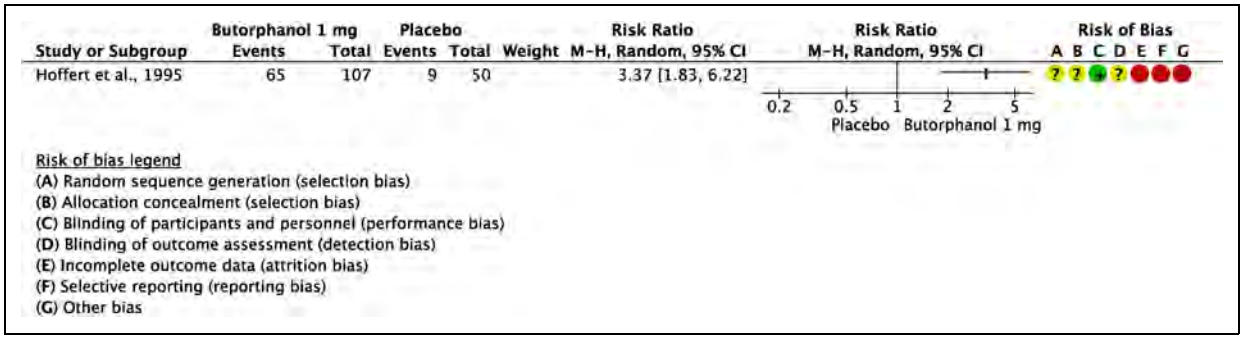


Figure 3.6.4. Forest plot showing the comparison between butorphanol 1 mg intranasal vs placebo for the outcome pain relief at 2 h in patients with episodic migraine.

Drug	Acute treatment of migraine attacks
Butorphanol 1 mg (intranasal)	⊕⊖⊖⊖ ↑

Quality of selected evidence	
⊕⊕⊕⊕	High
⊕⊕⊕⊖	Moderate
⊕⊕⊖⊖	Low
⊕⊖⊖⊖	Very low
⊖⊖⊖⊖	None
Strength of the recommendation	
↑↑	strong in favor
↑	weak in favor
↓	weak against
↓↓	strong against
-	none

Figure 3.6.5. Summary of evidence-based recommendations on opioids for the acute treatment of migraine attacks.

Before considering a trial with opioids, we suggest optimization of nonopioid pharmacotherapy and nonpharmacologic therapy. By a trial with opioids, we mean initiation, titration, and monitoring of response, with discontinuation of opioids if a clinically meaningful improvement in pain or function is not achieved. Opioids should never be used in patients with migraine with concurrent or past substance use disorder or active psychiatric disorders and in patients with MOH.

Rationale: As opioids are associated with low evidence of efficacy, no data replication, and serious risk of tolerance, dependency, and addiction, we suggest against their use, especially in patients prone to overuse. Only selected and properly informed patients with migraine who do not respond or bear contraindications to the agents recommended for the acute treatment of migraine may be eligible for a trial with opioids. Patient education and strict monitoring of the frequency of drug intake are mandatory to prevent opioid misuse, addiction, and overdose. In addition, only short-term use should be considered as prolonged use of opioids may lead to drug dependence (and, in some patients, addiction/opioid use disorder), even at therapeutic doses.

3.7 Ditans

Introduction

Lasmiditan is a first-in-class ditan developed as an acute treatment of migraine. It is a high-affinity, highly selective 5-hydroxytriptamine (serotonin)-1F (5-HT_{1F}) receptor agonist. Lasmiditan has a unique chemical structure based on a pyridinoyl-piperidine scaffold that replaces the indole group of triptans (504).

5-HT1F receptors are expressed at various levels within the CNS and the trigeminovascular system, essential for the pathophysiology of migraine. Lasmiditan exerts its therapeutic effect through the agonistic effects at the 5-HT_{1F} receptor, blocking pain transmission through the trigeminal ganglion and nucleus trigeminalis caudalis and inhibiting CGRP and glutamate release (505,506).

Lasmiditan is highly lipophilic and capable of crossing the blood-brain barrier, resulting in the occurrence of CNS-related adverse events (507).

Unlike triptans, agonists of the 5-HT_{1F} receptor are devoid of vasoconstrictor properties, as demonstrated in preclinical animal models and in vitro human models (508,509). They were demonstrated to be safe and effective also in patients with concomitant cardiovascular risk factors (504,510,511).

Therefore, lasmiditan may address important unmet needs in patients with cardiovascular risk factors, cardiovascular diseases, or patients who respond poorly to other acute treatments.

Section-specific methods

This section followed the general procedure to develop this guideline.

Search strings for the guideline on ditans for systematic review/meta-analysis and for additional RCTs are reported in Online Appendix 3.7.1.

Results

Overall, we retrieved 170 references from searching for systematic reviews and meta-analyses. After duplicate removal and screening stages, we included six systematic reviews and meta-analyses (24,507,512–515) that were considered as sources of RCTs. After analyzing full texts of these RCTs, we included four RCTs in the quantitative synthesis (516–519) (Figure 3.7.1).

Overall, we retrieved 320 references from searching for RCTs and, after removing duplicates, we had 237 references to analyze. However, considering the most recent included systematic review and meta-analysis on the topic, the analysis of additional RCTs was performed for papers published since 2021 (49 references). We finally included one additional RCT (520). No further studies were included from the literature search updates performed in May 2023 and November 2023 (Figure 3.7.2).

Overall, five studies were included in the quantitative synthesis (meta-analyses) to develop the evidence-based guideline. All of them reported a comparison between lasmiditan and placebo and are presented in this section.

Lasmiditan

PICO 3.7.1. In patients with migraine, is lasmiditan superior to placebo in the acute treatment of migraine attacks (outcomes: pain freedom at 2 h, pain relief at 2 h)?

Main evidence. We found five RCTs (516–520) addressing lasmiditan as compared to placebo in the acute treatment of migraine attacks that met the criteria to be included in the main evidence.

The pooled analysis showed benefits of oral lasmiditan 50, 100 and 200 mg over placebo considering the outcomes of pain freedom at 2 h (Figure 3.7.3) and pain relief at 2 h (Figure 3.7.4). The quality of evidence for both outcomes was high (Table 3.7.1)

Additional evidence. None.

Evidence-based recommendation for PICO 3.7.1

In patients with migraine, we recommend lasmiditan 50 mg, 100 mg, or 200 mg for the acute treatment of migraine attacks.

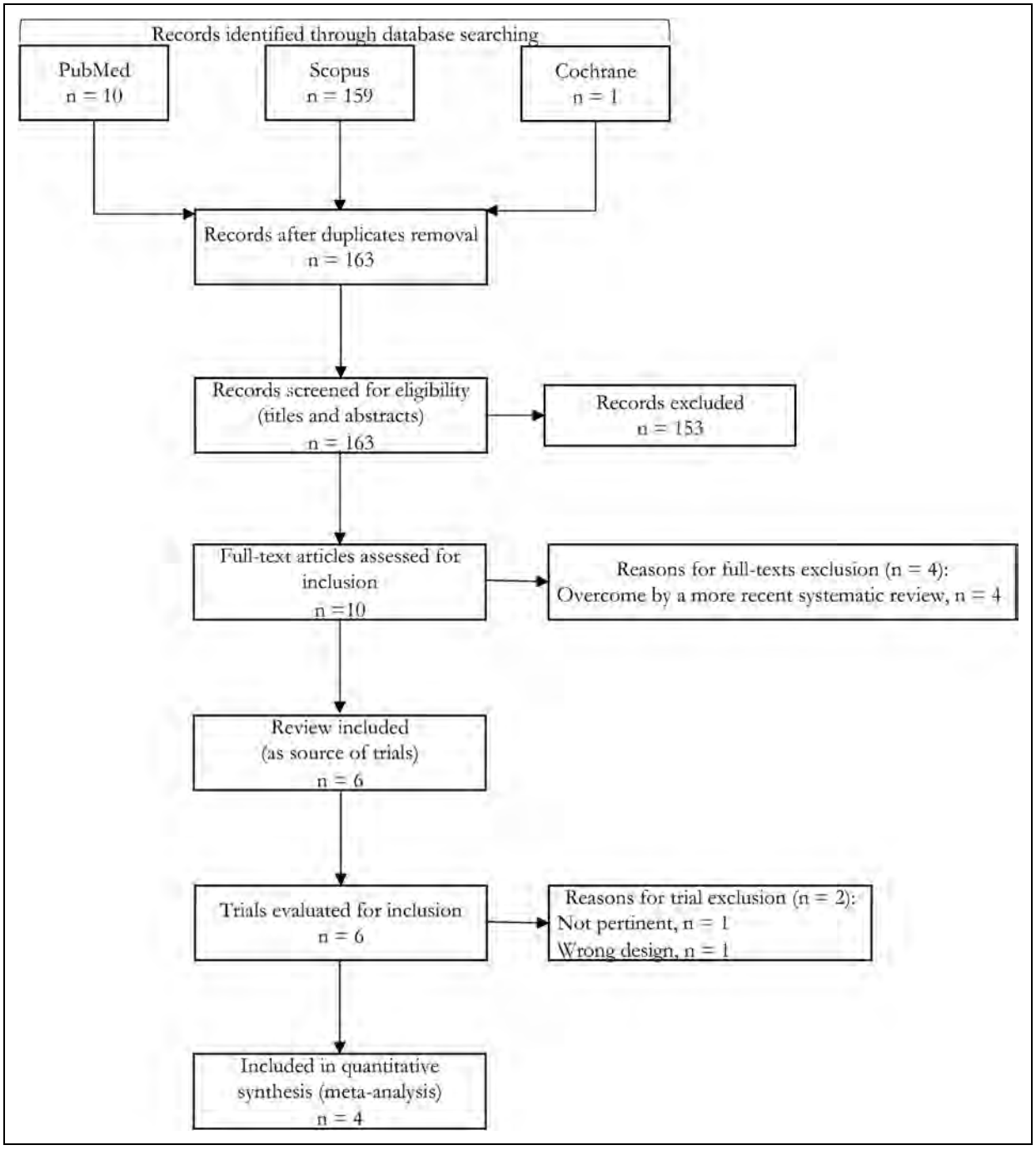


Figure 3.7.1. Meta-analysis selection flow chart - ditans.

Quality of evidence: High (⊕⊕⊕⊕)
Strength of the recommendation: Strong (↑↑)

Safety and tolerability of lasmiditan. Warnings and contraindications: Lasmiditan should not be used during pregnancy and breastfeeding, as insufficient data is available. Lasmiditan is associated with CNS-related adverse events (518), and it should be used with caution if taken in combination with CNS depressants or alcohol.

Serious safety concerns: No serious safety concerns have emerged for treatment with lasmiditan. RCTs have not shown a higher incidence of cardiovascular events in patients treated with lasmiditan (511).

Tolerability: The most common adverse events associated with lasmiditan were dizziness, somnolence, fatigue, paresthesia, nausea, and vertigo. Adverse events

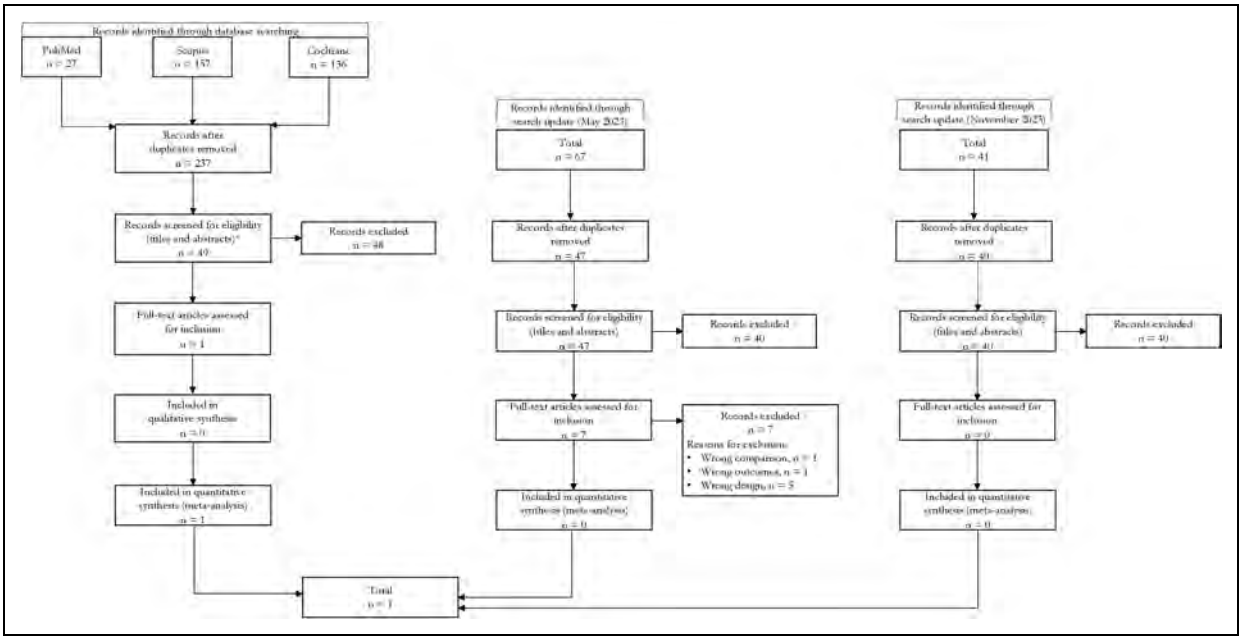


Figure 3.7.2. RCTs selection flow chart - ditans.
*trials published since 2021 were screened.

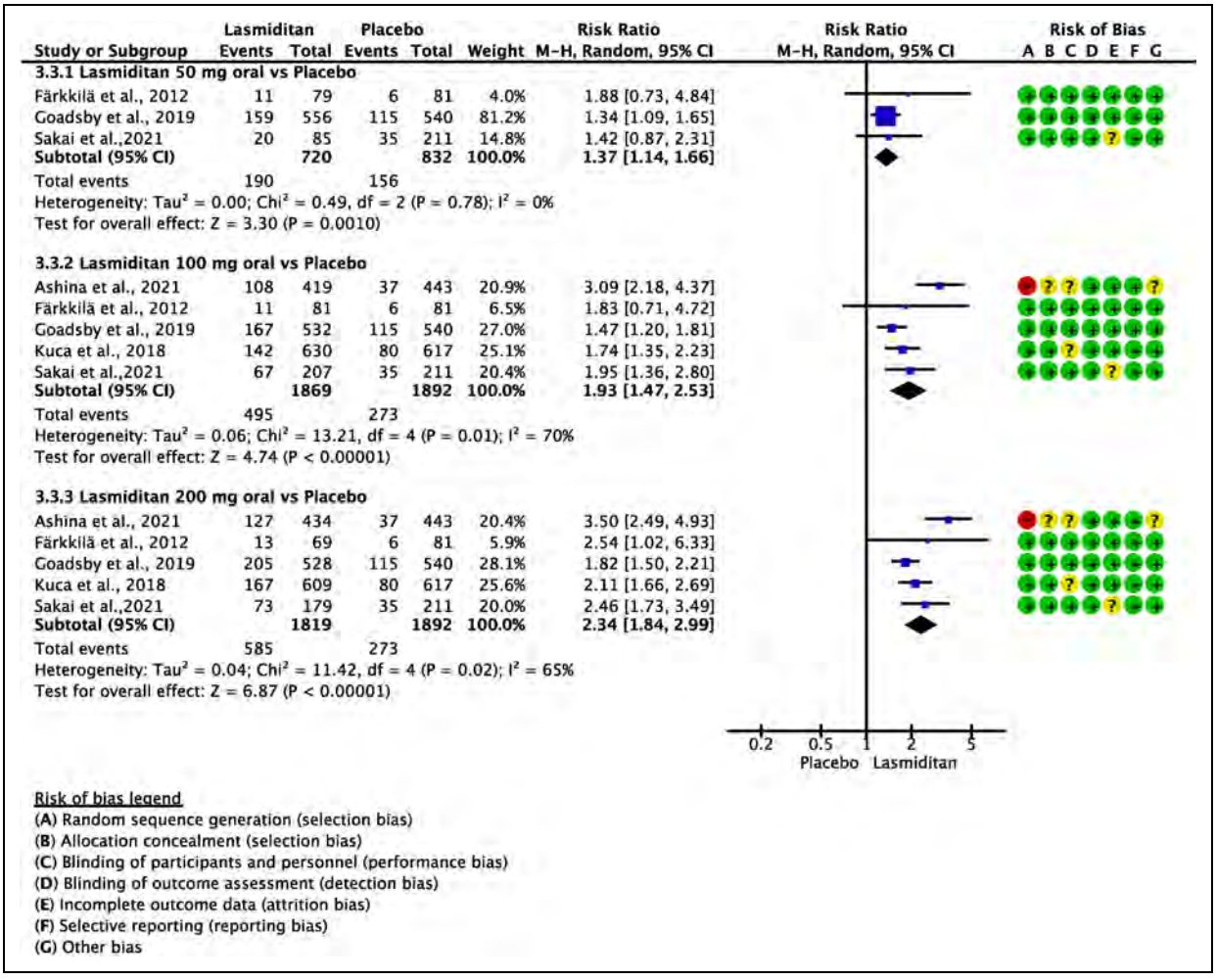


Figure 3.7.3. Forest plot showing the comparison between oral lasmiditan (50, 100, and 200 mg) and placebo for the outcome pain freedom at 2 h in patients with migraine.

were mainly transient and mild to moderate in severity (516). Adverse events were dose-related, with the highest occurrence for lasmiditan 200 mg (517). RCTs showed a higher incidence of adverse events in elderly people compared to patients less than 65 years of age (521). The advice against driving or operating machinery within 8 h from lasmiditan intake (522) might be a tolerability issue and a reason to avoid lasmiditan by patients who usually perform those tasks for working purposes.

Evidence-based guideline summary

We found studies on lasmiditan to be included for deriving evidence-based recommendations for this guideline. There is high quality of evidence to recommend the use of lasmiditan for the acute treatment of migraine attacks (Figure 3.7.5). Notably, lasmiditan lacks head-to-head comparisons with other acute treatments for migraine, such as triptans (please refer to Section 3.9 for other comparisons).

Expert-based opinions

Topic: Lasmiditan dosing. Suggestion: We suggest an initial dose of 100 mg of lasmiditan. If needed, the dose can be decreased to 50 mg for better tolerability or increased to 200 mg for improved efficacy.

Rationale: Higher dosages are probably more effective than lower ones. RCTs provided evidence suggesting higher efficacy of lasmiditan 200 mg and 100 mg compared with lasmiditan 50 mg in the acute treatment of migraine attacks for several migraine-related variables, including the outcomes of pain freedom and pain relief at two hours after treatment (518–520). Dose has also an impact on tolerability as evidence showed a higher incidence of adverse events with increasing lasmiditan dose (518). Dose optimization should be considered according to tolerance and efficacy. Given the higher incidence of adverse events in the elderly compared with younger patients (521), it might be reasonable to start with the 50 mg dose in patients aged 65 years or older.

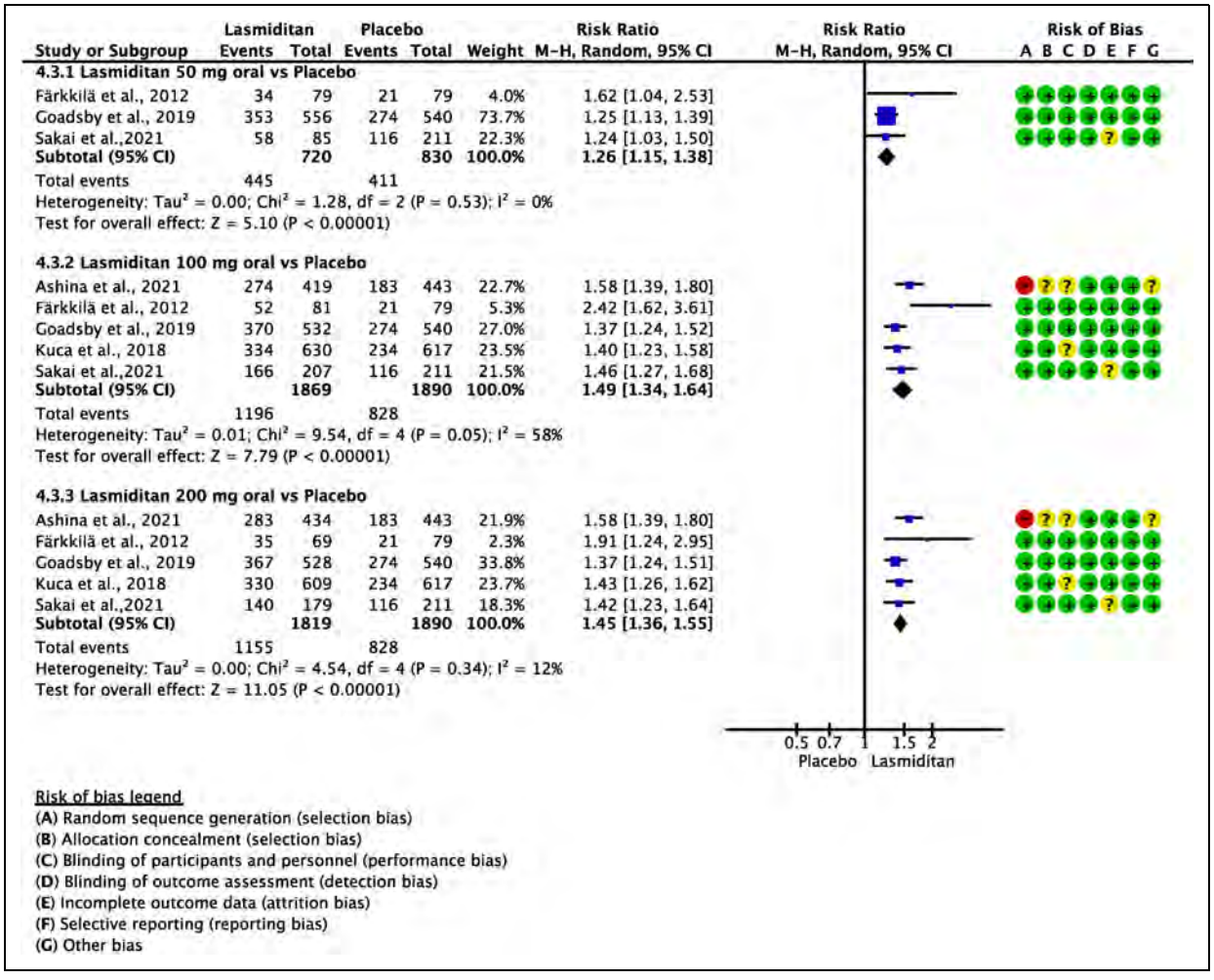
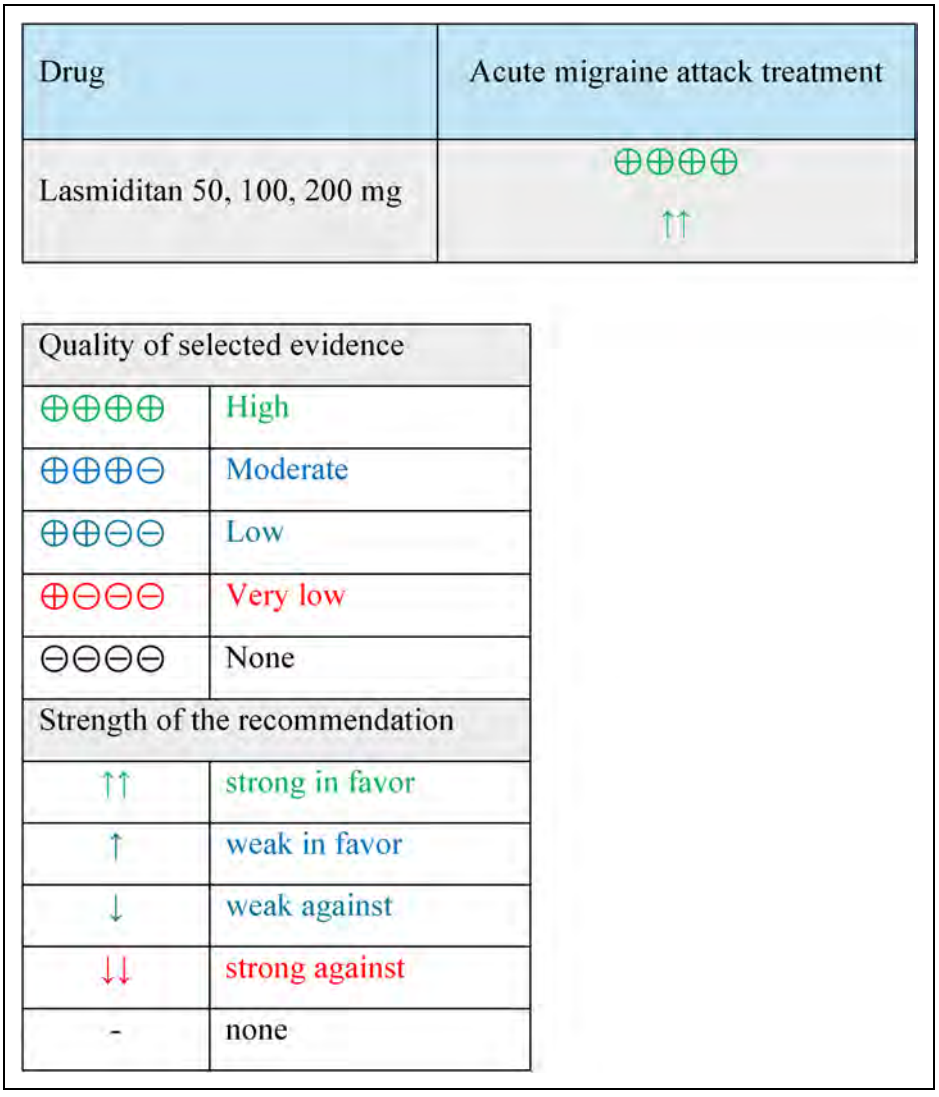


Figure 3.7.4. Forest plot showing the comparison between oral lasmiditan (50, 100, and 200 mg) and placebo for the outcome pain relief at 2 h in patients with migraine.

Table 3.7.1. GRADE evidence profile table for oral lasmiditan versus placebo in migraine

Certainty assessment							№ of patients		Effect			
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Lasmiditan	Placebo	Relative (95% CI)	Absolute (95% CI)	Quality	Importance
Pain freedom at 2 h - Lasmiditan 50 mg oral vs Placebo												
3	RCTs	Low	Not serious	Not serious	Not serious	None	190/720 (26.4%)	156/832 (18.8%)	**RR 1.37** (1.14 to 1.66)	**69 more per 1.000** (from 26 more to 124 more)	⊕⊕⊕⊕ **High**	Critical
Pain freedom at 2 h - Lasmiditan 100 mg oral vs Placebo												
5	RCTs	Low	Not serious[a]	Not serious	Not serious	None	495/1869 (26.5%)	273/1892 (14.4%)	**RR 1.93** (1.47 to 2.53)	**134 more per 1.000** (from 68 more to 221 more)	⊕⊕⊕⊕ **High**	Critical
Pain freedom at 2 h - Lasmiditan 200 mg oral vs Placebo												
5	RCTs	Low	Not serious	Not serious	Not serious	None	585/1819 (32.2%)	273/1892 (14.4%)	**RR 2.34** (1.84 to 2.99)	**193 more per 1.000** (from 121 more to 287 more)	⊕⊕⊕⊕ **High**	Critical
Pain relief at 2h - Lasmiditan 50 mg oral vs Placebo												
3	RCTs	Low	Not serious	Not serious	Not serious	None	445/720 (61.8%)	411/830 (49.5%)	**RR 1.26** (1.15 to 1.38)	**129 more per 1.000** (from 74 more to 188 more)	⊕⊕⊕⊕ **High**	Critical
Pain relief at 2h - Lasmiditan 100 mg oral vs Placebo												
5	RCTs	Low	Not serious	Not serious	Not serious	None	1196/1869 (64.0%)	828/1890 (43.8%)	**RR 1.49** (1.34 to 1.64)	**215 more per 1.000** (from 149 more to 280 more)	⊕⊕⊕⊕ **High**	Critical
Pain relief at 2h - Lasmiditan 200 mg oral vs Placebo												
5	RCTs	Low	Not serious	Not serious	Not serious	None	1155/1819 (63.5%)	828/1890 (43.8%)	**RR 1.45** (1.36 to 1.55)	**197 more per 1.000** (from 158 more to 241 more)	⊕⊕⊕⊕ **High**	Critical



Drug	Acute migraine attack treatment
Lasmiditan 50, 100, 200 mg	⊕⊕⊕⊕ ↑↑

Quality of selected evidence	
⊕⊕⊕⊕	High
⊕⊕⊕⊖	Moderate
⊕⊕⊖⊖	Low
⊕⊖⊖⊖	Very low
⊖⊖⊖⊖	None
Strength of the recommendation	
↑↑	strong in favor
↑	weak in favor
↓	weak against
↓↓	strong against
-	none

Figure 3.7.5. Summary of evidence-based recommendations on lasmiditan for the acute treatment of the migraine attacks.

Topic: Tolerability. Suggestion: We suggest against lasmiditan in patients who cannot follow the advice to avoid driving or operating machinery for at least eight hours after taking lasmiditan (522). Caution should also be used for activities requiring heightened attention.

Rationale: Lasmiditan is associated with impaired driving and machinery use after the administration of single 50 mg, 100 mg and 200 mg doses. Patients are advised not to drive or operate machinery for at least eight hours after taking lasmiditan.

Topic: Use in patients with cardiovascular risk factors and disease. Suggestion: There are no limitations in using lasmiditan in patients with cardiovascular risk factors or disease.

Rationale: Lasmiditan proved safe and effective in patients with cardiovascular risk factors and cardiovascular disease (511). It therefore represents a valid option for patients who have contraindications to triptans. Further studies are, however, needed to assess the long-term safety of lasmiditan in this population.

3.8 Gepants for acute treatment

Introduction

Gepants were developed in the early 2000s as a new symptomatic treatment for migraine. However, their development was soon interrupted due to liver toxicity: telcagepant, a first generation gepant, determined indeed a significant increase in the serum levels of liver

aminotransferase levels compared to placebo (523). Hence, research focused on the chemical manipulation of the first generation gepants led to the second generation gepants, devoid of liver toxicity (524). The Food and Drug Administration (FDA) approved rimegepant 75 mg in 2020 and ubrogepant 50 and 100 mg in 2019 for the acute treatment of migraine attacks (524). The European Medicine Agency (EMA) approved the use of rimegepant in Europe in 2022. More recently, another gepant has been studied: zavegepant, a third generation gepant, characterized by the intranasal administration route (525).

Gepants are small molecules that bind with high affinity to the CGRP receptor, thus inducing an allosteric modulation that prevents CGRP binding. Notably, their specific mechanism of action justifies their good safety profile (526). Gepants do not constrict or tighten blood vessels, although it must be noted that they inhibit vasoconstriction and the opening of collaterals in conditions of ischemia (526).

Section-specific methods

This section followed the general procedure to develop this guideline with the exception of the literature search update, which was performed directly in November 2023 overcoming the May 2023 update.

Search strings for the Guideline on the gepants (acute treatment) for systematic review/meta-analysis and for additional RCTs are reported in Online Appendix 3.8.1.

Results

Overall, we retrieved 173 references from searching for systematic reviews and meta-analyses. After duplicate removal and selection phases, we included eight systematic reviews and meta-analyses (24,237,527–532) as a source of randomized controlled trials (RCTs). After analyzing full texts of these RCTs, we included seven of them in the quantitative synthesis (533–539) (Figure 3.8.1).

Overall, we retrieved 365 references from searching for RCTs and, after removing duplicates, we had 304 references to analyze. However, considering the most recent included systematic review/meta-analysis on the topic, the analysis of additional RCTs was performed for papers published since May 2022 (31 references). We finally included one additional RCT on rimegepant (540) and two RCTs on zavegepant (541,542) (Figure 3.8.2). Notably, the selection of RCTs on zavegepant was performed via a specific search string (see Online Appendix 3.8.1 and Online Appendix 3.8.2).

Overall, 12 studies were included in the quantitative synthesis (meta-analyses) to develop the evidence-based guideline. All the included studies reported a comparison between a gepant and placebo and are presented in this paper.

Rimegepant

PICO 3.8.1. In patients with migraine, is rimegepant superior to placebo in the acute treatment of migraine attacks (outcomes: pain freedom at 2 h, pain relief at 2 h)?

Main evidence. We found five RCTs (533–536,540) addressing rimegepant oral-disintegrating tablets compared to placebo in the acute treatment of migraine attacks that met the criteria to be included in the main evidence. In particular, the studies by Yu et al. (540) and Croop et al. (543) tested rimegepant oral-disintegrating tablets, whilst the others rimegepant tablets (534–536). Since the two formulations were found similarly effective, we discussed them together (544). The pooled analysis showed benefits of oral rimegepant 75 mg daily over placebo considering the outcomes of pain freedom at 2 h (Figure 3.8.3) and pain relief at 2 h (Figure 3.8.4). The quality of evidence for both outcomes was high (Table 3.8.1).

Additional evidence. None.

Evidence-based recommendation for PICO 3.8.1

In patients with migraine, we recommend rimegepant 75 mg oral-disintegrating tablets for the acute treatment of the attacks.
Quality of evidence: High (⊕⊕⊕⊕)
Strength of the recommendation: Strong (↑↑)

Ubrogepant

PICO 3.8.2. In patients with migraine, is ubrogepant superior to placebo for the acute treatment of migraine attacks (outcomes: pain freedom at 2 h, pain relief at 2 h)?

Main evidence. We found five RCTs (537–539,545,546) addressing ubrogepant compared to placebo for the acute treatment of migraine attacks that met the criteria to be included in the main evidence.

The pooled analysis showed benefits of oral ubrogepant 50 and 100 mg over placebo considering the outcomes pain freedom at 2 h (Figure 3.8.5) and pain relief at 2 h (Figure 3.8.6). The quality of evidence for both outcomes was high (Table 3.8.2).

Additional evidence. None.

Evidence-based recommendation for PICO 3.8.2

In patients with migraine, we recommend oral ubrogepant 50 or 100 mg for the acute treatment of attacks.

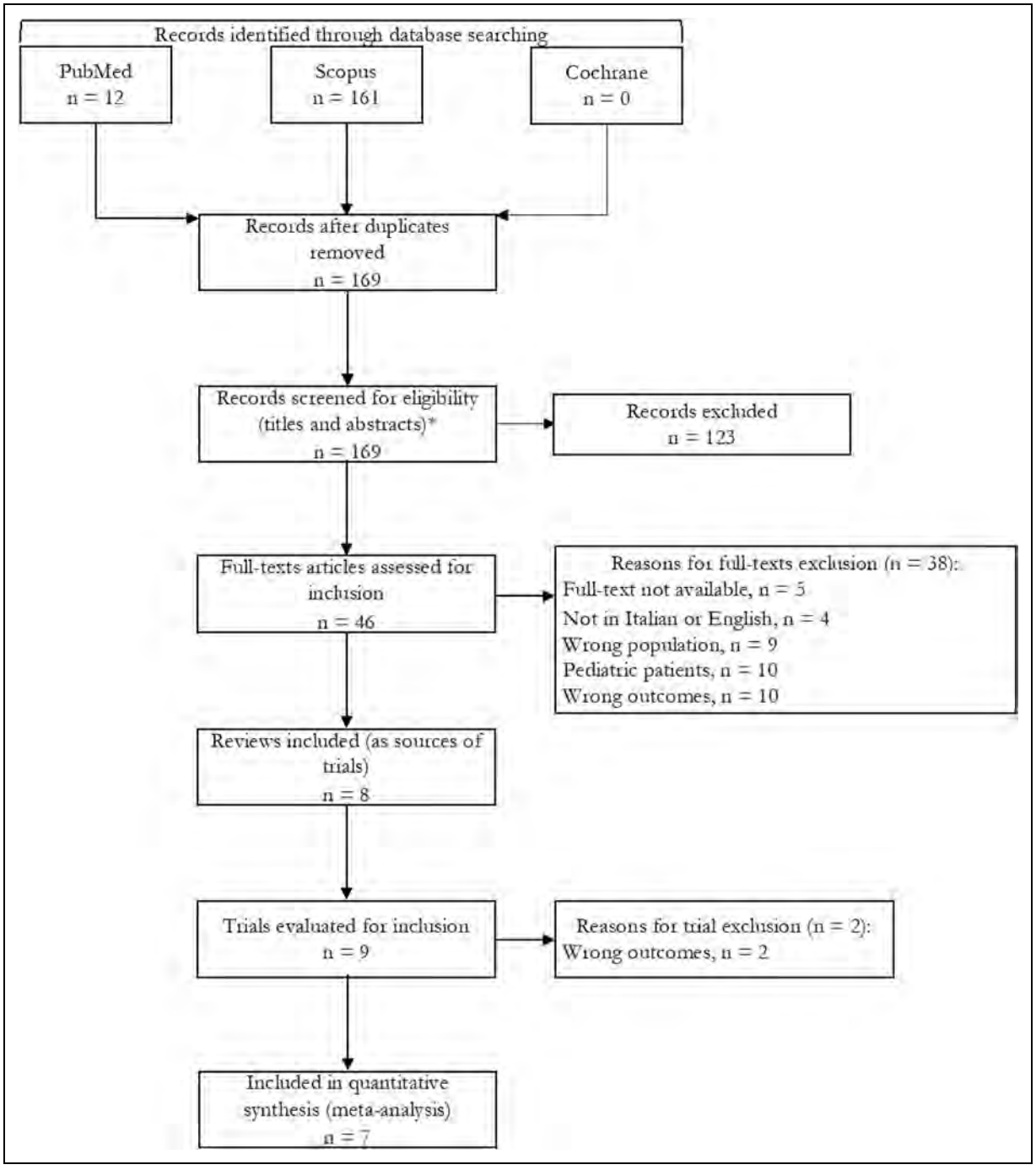


Figure 3.8.1. Meta-analysis selection flow chart - gepants for acute treatment.

Quality of evidence: High (⊕⊕⊕⊕)
Strength of the recommendation: Strong (↑↑)

Zavegepant

The study selection for zavegepant was added following the literature search update. The related flowchart is provided in Online Appendix 3.8.2.

PICO 3.8.3. In patients with migraine, is zavegepant superior to placebo in the acute treatment of the attacks (outcomes: pain freedom at 2 h, pain relief at 2 h)?

Main evidence. We found two RCTs (541,542) addressing zavegepant compared to placebo in the acute treatment of migraine attacks that met the predefined criteria to be included in the main evidence.

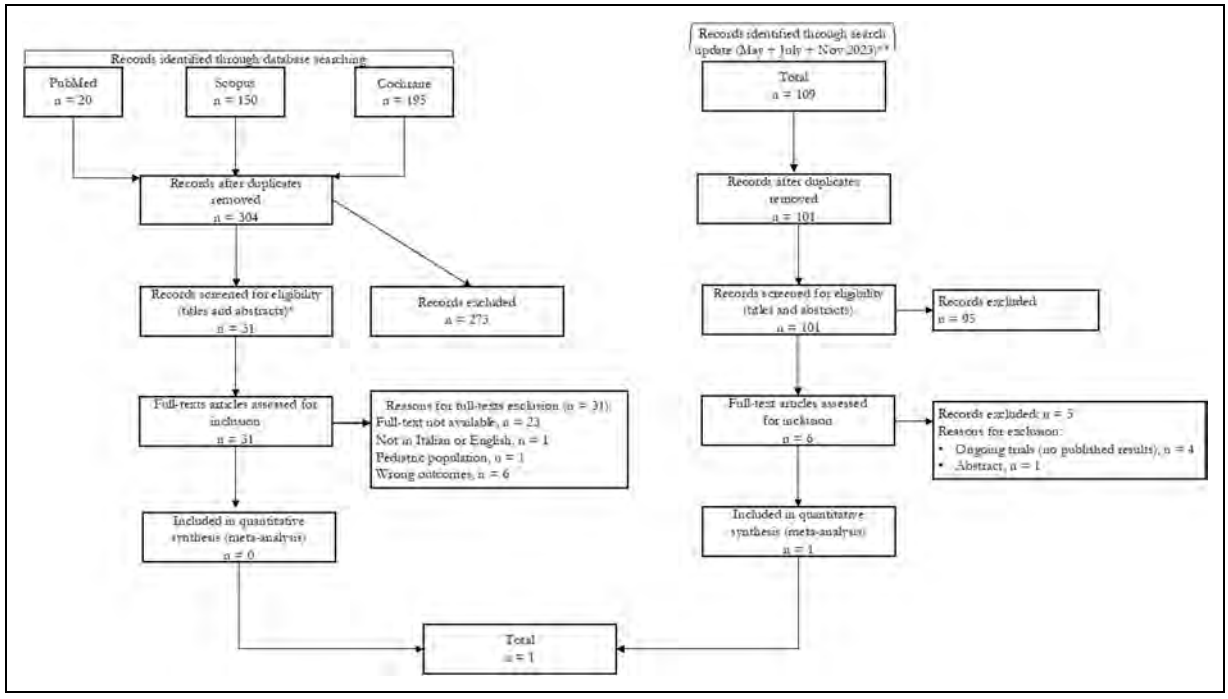


Figure 3.8.2. RCTs selection flow chart - gepants for acute treatment.
*trials published since 01 May 2022 were screened
**Trials on zavegepant assessed with a further search string (see Online Appendix 3.8.1) and flow chart (see Online Appendix 3.8.2).

The pooled analysis showed benefits of zavegepant 5, 10, and 20 mg nasal spray over placebo considering the outcomes of pain freedom at 2 h (Figure 3.8.7) and pain relief at 2 h (Figure 3.8.8). The quality of evidence for both outcomes was high for the 10 mg dosage – due to the presence of two RCTs – and moderate for the 5 mg and 20 mg doses of zavegepant (Table 3.8.3) due to the presence of only one RCT.

Additional evidence. None.

Evidence-based recommendations for PICO 3.8.3

1) In patients with migraine, we recommend intranasal zavegepant 10 mg for the acute treatment of migraine attacks.

Quality of evidence: High (⊕⊕⊕⊕)
Strength of the recommendation: Strong (↑↑)

2) In patients with migraine, we suggest against zavegepant 5 mg nasal spray for the acute treatment of migraine attacks.

Quality of evidence: Moderate (⊕⊕⊕⊖)
Strength of the recommendation: Weak (↓)

3) In patients with migraine, we suggest zavegepant 20 mg nasal spray for the acute treatment of migraine attacks.

Quality of evidence: Moderate (⊕⊕⊕⊖).
Strength of the recommendation: Weak (↑).

Safety and tolerability of rimegepant, ubrogepant, and zavegepant. Warnings and contraindications: Rimegepant and ubrogepant should not be used in patients with hypersensitivity reaction to them or to their excipients. Indeed, in the RCTs serious hypersensitivity reactions have been registered, even delayed, i.e., days after the administration of the drug (535,547). Moreover, considering that rimegepant and ubrogepant are primarily metabolized by the CYP3A4, the FDA advises against their use with strong CYP3A4 inhibitors, such as azoles antimycotics (548,549). Concomitant use may induce higher plasma concentration of the abovementioned gepants, thus leading to a higher rate of AEs. Regarding zavegepant, hypersensitivity reactions were not reported in the RCTs (541,542).

The safety of rimegepant and zavegepant in geriatric patients has not been explored, so they are not recommended in elderly patients with migraine. Ubrogepant has

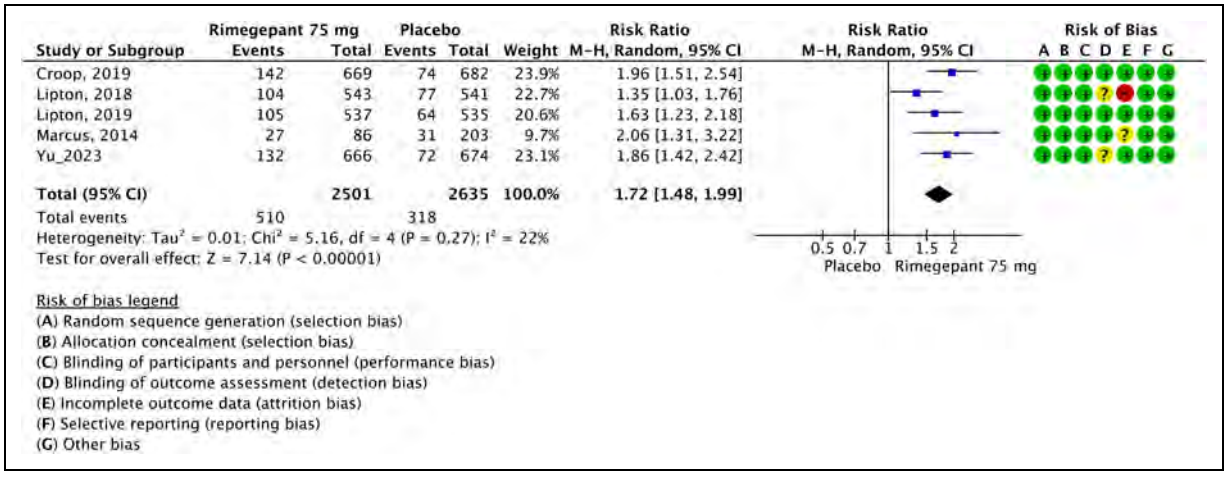


Figure 3.8.3. Forest plot showing the comparison between rimegepant 75 mg oral-disintegrating tablets and placebo for the outcome pain freedom at 2 h.

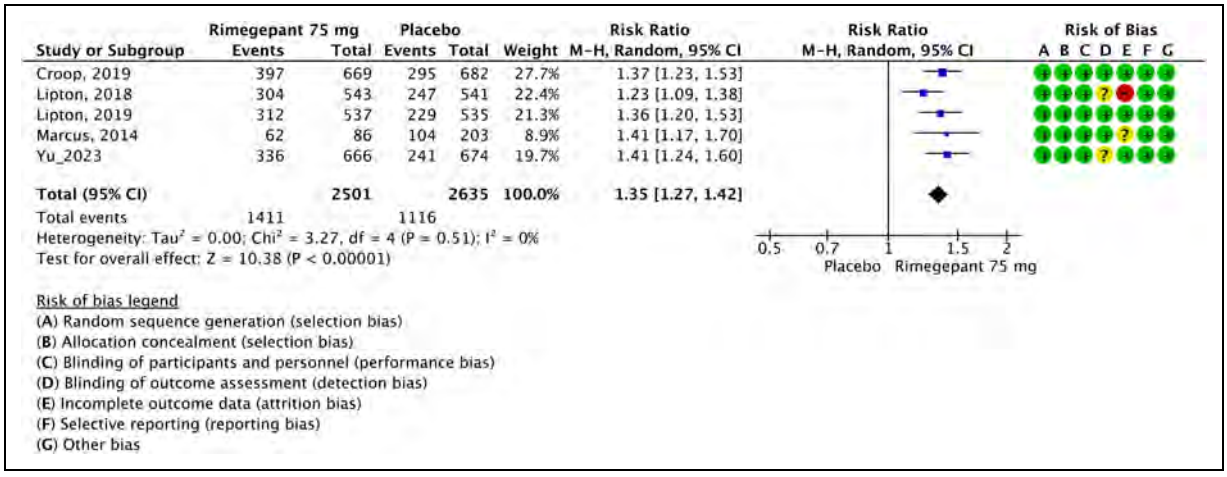


Figure 3.8.4. Forest plot showing the comparison between rimegepant 75 mg oral-disintegrating tablets and placebo for the outcome pain relief at 2 h.

been tested up to 75 years of age. Children and adolescents have not been studied yet, therefore gepants are at present contraindicated below the age of 18 years. Pregnant or lactating women were excluded from RCTs too, hence, gepants are not recommended in these categories. It ought to be taken into consideration that ubrogepant induces fetal toxicity in rats and it passes in the maternal milk in rats, where it has similar concentrations than in the plasma (550). For rimegepant, it has been demonstrated that a single dose can result in its presence in maternal milk (551), even if less than 1%. Hence, rimegepant should be avoided in breastfeeding women (551). Since rimegepant and ubrogepant are metabolized by the liver, they should not be administered in patients with liver impairment (550,552). Finally, as rimegepant and ubrogepant are substrates for the P glycoprotein (P-gp), their use is contraindicated in the presence of severe renal impairment (550,552). Zavegepant excretion is mainly biliary and fecal (525); the drug is mainly metabolized by CYP3A4 and CYP2D6 (525). Mild or moderate liver impairment does not seem to alter the metabolism of zavegepant, while the drug has not been tested in patients with severe liver impairment (525,553). Zavegepant has also not been tested in patients with renal impairment, which however should not be considered a problem given the very small proportion of renal metabolism of the drug (553). The use of zavegepant during pregnancy has not been evaluated in humans and is therefore contraindicated, although animal studies showed no significant increase in birth defects (525,554).

Serious safety concerns: In the study published by Lipton et al. (539) in 2019, five serious adverse events

Table 3.8.1. GRADE evidence profile table for rimegepant 75mg oral-disintegrating tablets versus placebo for the acute treatment of migraine attacks

Certainty assessment							№ of patients		Effect			
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Rimegepant 75 mg	Placebo	Relative (95% CI)	Absolute (95% CI)	Quality	Importance
Pain freedom at 2 h - Rimegepant 75 mg oral-disintegrating tablets vs Placebo												
5	RCTs	Not serious	Not serious	Not serious	Not serious	None	510/2501 (20.4%)	318/2635 (12.1%)	**RR 1.72** (1.48 to 1.99)	**109 more per 1.000** (from 72 more to 149 more)	⊕⊕⊕⊕ High	Critical
Pain relief at 2 h - Rimegepant 75 mg oral-disintegrating tablets vs Placebo												
5	RCTs	Not serious	Not serious	Not serious	Not serious	None	1411/2501 (56.4%)	1116/2635 (42.4%)	**RR 1.35** (1.27 to 1.42)	**53 more per 1.000** (from 41 more to 63 more)	⊕⊕⊕⊕ High	Critical

were registered: two appendicitis, one pericardial effusion, one seizure and one spontaneous abortion. The seizure was considered related to the study drug. Of note, the rate of serious adverse events was comparable to the one achieved in the placebo group. No liver serious safety concerns were noticed. In consideration of liver toxicity associated with the first generation gepants, serum aminotransferase levels were strictly monitored in the patients treated with the gepants of the second generation. In the study by Goadsby et al. (547) there were only seven cases of aminotransferase elevation and only two (one in the placebo and one in the ubrogepant group) were considered treatment-related. Aminotransferase increases in the ubrogepant group were transient and resolved with continued administrations (547). In one RCT of zavegepant, one serious adverse event of leg thrombosis occurred in treated patients and was not related to the drug (541); in the other RCT, no serious adverse events occurred (542). No hepatotoxicity issues emerged with zavegepant (541,542,554). At present, gepants should not be used in patients at high risk of ischemic events such as transient ischemic attack (TIA), ischemic stroke, angina, and Raynaud disease. These patient groups were excluded from the randomized trials and open-label observational studies.

Tolerability: From the published RCTs the most frequent AEs with rimegepant, i.e., those that emerged in more than the 2% of the patients, were nasopharyngitis, nausea, urinary tract infection and upper respiratory tract infections (533–536). Globally, the tolerability of rimegepant was good, even if taken regularly for the preventive treatment of migraine (543). For ubrogepant, the most frequent minor tolerability issues were dry mouth, nausea, fatigue, dizziness, and somnolence. Globally, ubrogepant was well tolerated by most of the patients, also over long treatment periods (552,555). The most frequent adverse events related to zavegepant use were dysgeusia, nausea, and nasal discomfort (541,542).

Evidence-based guideline summary

We found studies on rimegepant, ubrogepant, and zavegepant to be included for deriving evidence-based recommendations for this guideline. There is high quality of evidence to recommend the use of rimegepant, ubrogepant, and zavegepant for the acute treatment of migraine attacks (Figure 3.8.9).

Expert-based opinion

Optimization of ubrogepant use

Topic: Ubrogepant dosing. Suggestion 1: When starting ubrogepant for the acute treatment of migraine attacks, we suggest 50 mg as initial dose; the dose can be increased up to 100 mg if the response is unsatisfactory.

Rationale 1: From the available RCTs the different dosages of ubrogepant displayed a similar efficacy in both the primary and secondary outcome measures. There was only a slight difference regarding the number of AEs, which was higher for the 100 mg dose. Indeed, in the study by Lipton and coworkers, patients receiving ubrogepant 100 mg displayed a higher rate of nausea, somnolence, and dry mouth (539).

Suggestion 2: Ubrogepant can be considered for the acute treatment of migraine attacks during prodromes.

Rationale 2: A RCT compared oral ubrogepant 100 mg for the acute treatment of migraine attacks during prodromes, before the onset of pain (556). This RCT was not included in evidence-based recommendations as it did not consider the outcomes that were chosen for the guideline. The RCT showed that absence of moderate or severe headache within 24 h after a dose occurred after 46% of prodrome events that had been treated with ubrogepant and after 29% of prodrome events that had been treated with placebo ($p < 0{\cdot}0001$). Adverse events that occurred within 48 h after drug administration were reported after 17% of prodrome events that had been treated with ubrogepant and after 12% of events that had been treated with placebo, in the absence of difference between the two groups (556). From these results, the use of ubrogepant might be considered in patients who recognize the prodromes of migraine, even if this suggestion needs confirmation in clinical practice.

Ubrogepant and anti-CGRP monoclonal antibodies

Topic: Ubrogepant co-administered with an anti-CGRP monoclonal antibody. Suggestion: We suggest the possibility to use ubrogepant even in patients who are receiving anti-CGRP monoclonal antibodies for the preventive treatment for migraine.

Rationale: A phase I study from Jakat et al. (557) explored the safety and drug-to-drug interactions of ubrogepant 100 mg with erenumab or galcanezumab. The pharmacokinetic profile of ubrogepant was not significantly affected by the co-administration of erenumab or galcanezumab. Moreover, no safety concerns emerged from the association between ubrogepant 100 mg and erenumab or galcanezumab (557). In clinical practice, we still do not know the effects of long-term use of concomitant CGRP inhibition with monoclonal antibodies and frequent use of gepants; therefore, caution and close monitoring is advisable in patients with concomitant use of the two drug classes.

Zavegepant and oral gepants

Topic: Choice of zavegepant in special cases. Suggestion: Zavegepant nasal spray may be the gepant of choice in patients with severe nausea and/or vomiting during their migraine attacks.

Rationale: The intranasal administration of zavegepant is interesting as the drug bypasses digestive metabolism and can be directly delivered into the blood by the nasal mucosa. This route of administration can be particularly useful for patients with migraine experiencing severe nausea and/or vomiting during their migraine attacks, as those symptoms can be associated with gastroparesis and consequently to decreased absorption of oral drugs. It should be noted that the available RCTs of zavegepant did not test the efficacy of this drug specifically in patients who failed oral acute treatments due to severe nausea and/or vomiting.

3.9 Head-to-head comparisons – Acute treatments

Introduction

Several acute treatments for migraine have been assessed comparatively to test their efficacy and tolerability. In clinical practice, it is important to know those comparisons to have an idea of the possible efficacy of different approaches to treat migraine attacks. However, there is a need for an orderly and rational presentation of those studies and of their results to provide clinicians with evidence-based tools for clinical judgment.

For those reasons, the present section reports a systematic and critical evaluation of the efficacy results of head-to-head studies comparing the different acute treatments for migraine.

Section-specific methods

All RCTs included in this section were retrieved from the search strings of the other sections dedicated to RCTs of acute treatments. We considered only PICOs including at least one drug as intervention or comparator that had an independent comparison against placebo.

At first, we collected all the head-to-head RCTs retrieved from the literature search. Duplicates were removed as an initial step.

All RCTs were considered only once, even if eligible for more than one comparison. Comparisons were structured to be read in either direction, without the concept of a main intervention and its comparator. The terms "intervention" and "comparator" were replaced by "Drug 1" and "Drug 2" in the PICO structure (Table 3.9.1). Nevertheless, given the number of available trials, we classified them into the following groups of comparisons:

- Non-steroidal anti-inflammatory drugs (NSAIDs) vs NSAIDs
- Triptans vs NSAIDs
- Triptans vs triptans

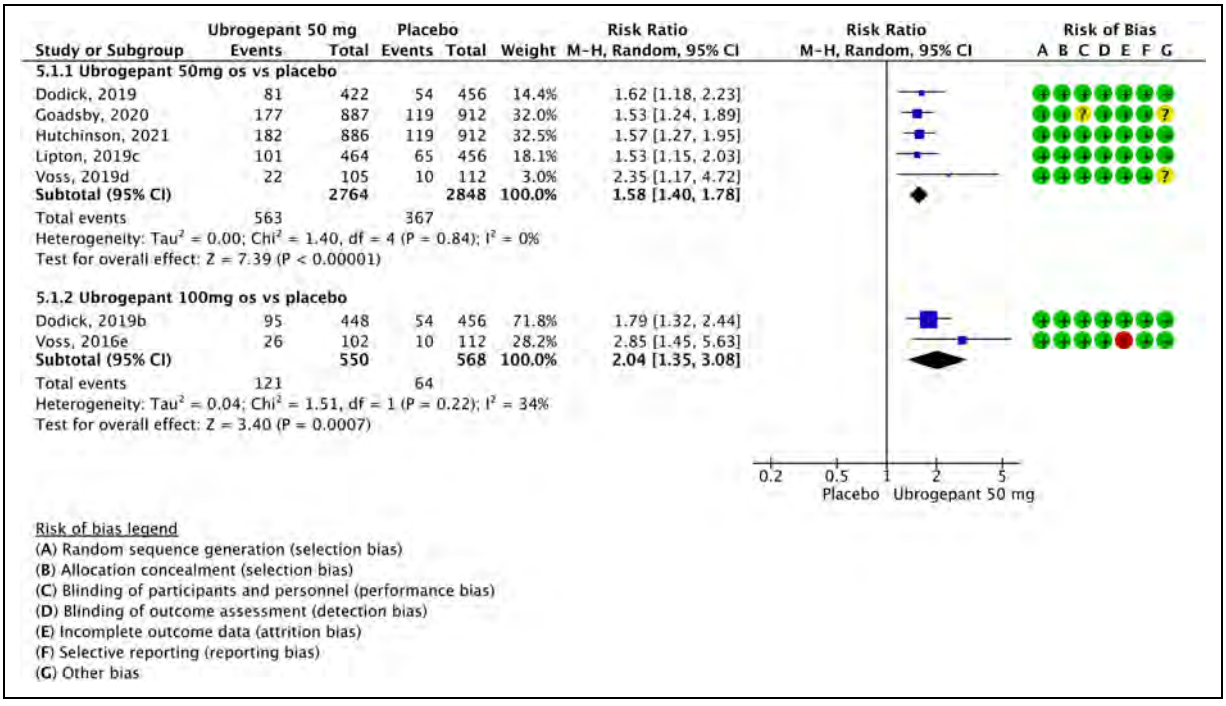


Figure 3.8.5. Forest plot showing the comparison between oral ubrogepant 50 mg or 100 mg and placebo for the outcome pain freedom at 2 h.

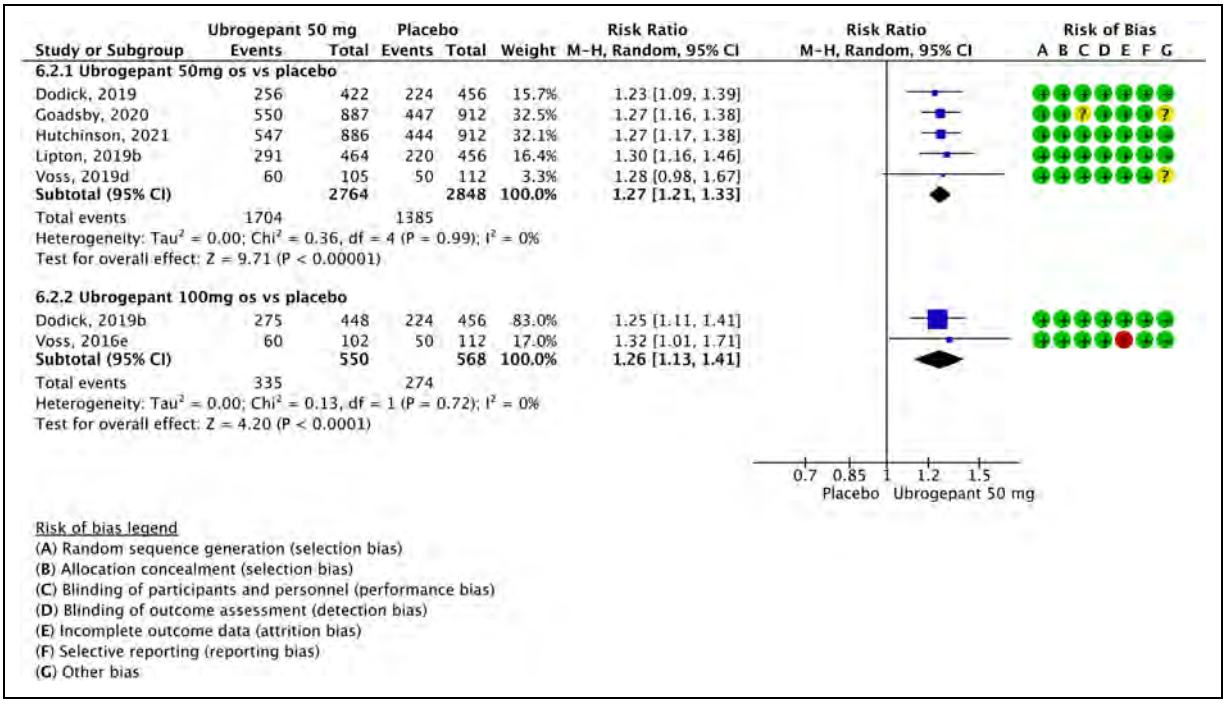


Figure 3.8.6. Forest plot showing the comparison between oral ubrogepant 50 mg or 100 mg and placebo for the outcome pain relief at 2 h.

Table 3.8.2. GRADE evidence profile table for oral ubrogepant versus placebo in the acute treatment of migraine attacks

Certainty assessment							№ of patients		Effect			
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Ubrogepant	placebo 1	Relative (95% CI)	Absolute (95% CI)	Quality	Importance
Pain freedom at 2 h - Ubrogepant 50mg oral vs Placebo												
5	RCTs	Not serious	Not serious	Not serious	Not serious	None	563/2764 (20.4%)	367/2848 (12.9%)	**RR 1.58** (1.40 to 1.78)	**75 more per 1.000** (from 52 more to 101 more)	⊕⊕⊕⊕ High	Critical
Pain freedom at 2 h - Ubrogepant 100mg oral vs Placebo												
2	RCTs	Not serious	Not serious	Not serious	Not serious	None	121/550 (22.0%)	64/568 (11.3%)	**RR 2.04** (1.35 to 3.08)	**117 more per 1.000** (from 39 more to 234 more)	⊕⊕⊕⊕ High	Critical
Pain relief at 2 h - Ubrogepant 50mg oral vs Placebo												
5	RCTs	Not serious	Not serious	Not serious	Not serious	None	1704/2764 (61.6%)	1385/2848 (48.6%)	**RR 1.27** (1.21 to 1.33)	**131 more per 1.000** (from 102 more to 160 more)	⊕⊕⊕⊕ High	Critical
Pain relief at 2 h - Ubrogepant 100mg oral vs Placebo												
2	RCTs	Not serious	Not serious	Not serious	Not serious	None	335/550 (60.9%)	274/568 (48.2%)	**RR 1.26** (1.13 to 1.41)	**125 more per 1.000** (from 63 more to 198 more)	⊕⊕⊕⊕ High	Critical

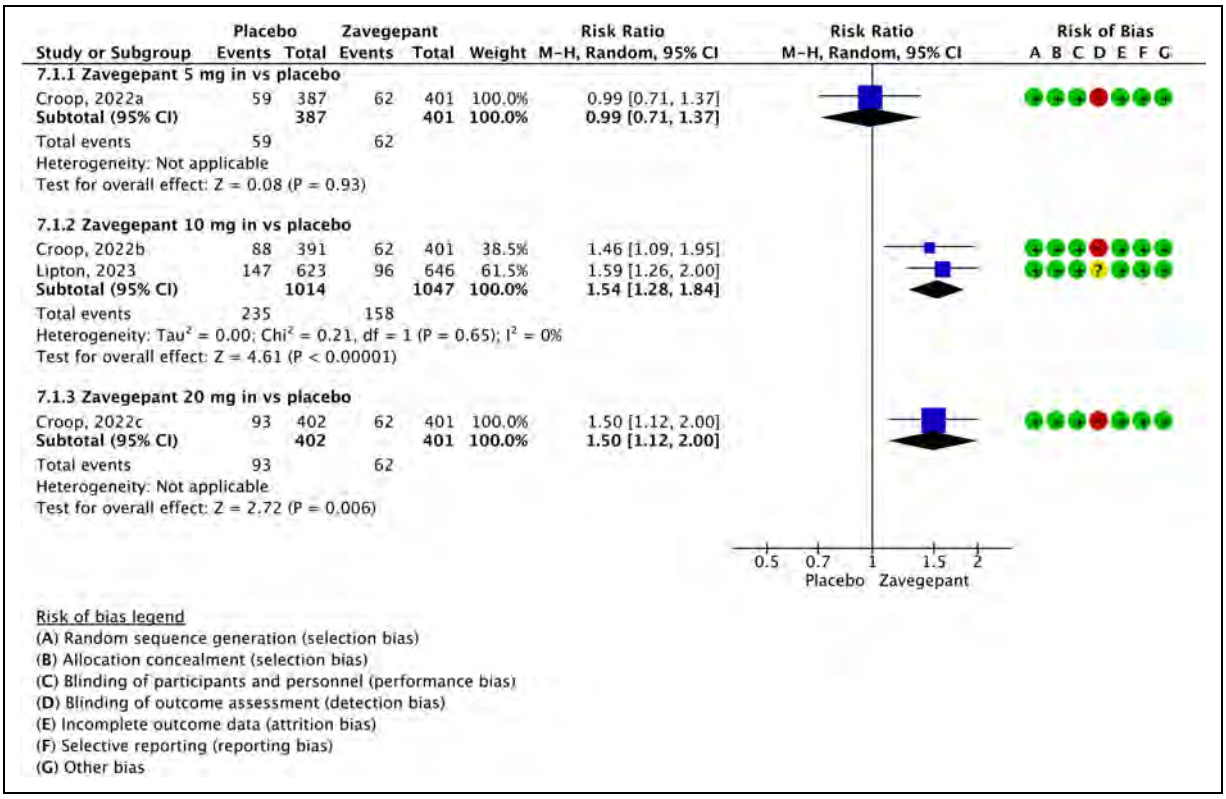


Figure 3.8.7. Forest plot showing the comparison between zavegepant 5 mg, 10 mg, or 20 mg nasal spray and placebo for the outcome pain freedom at 2 h.

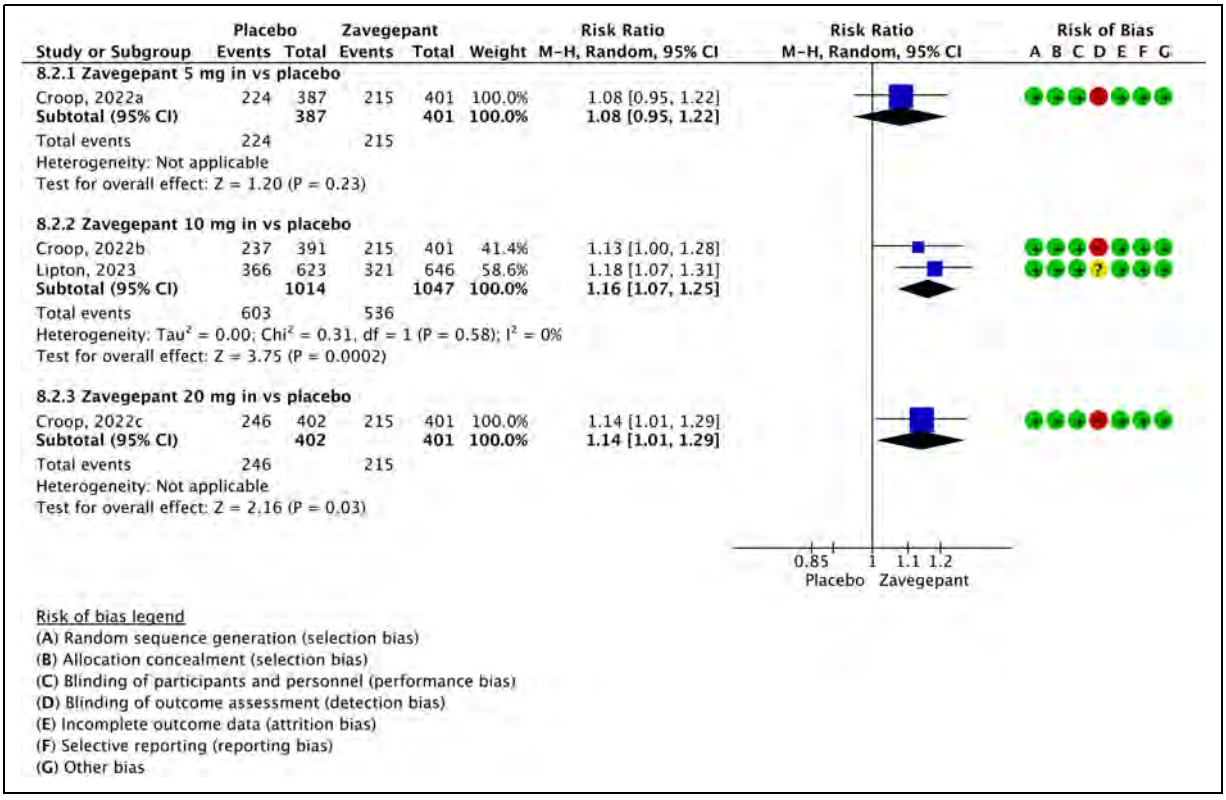


Figure 3.8.8. Forest plot showing the comparison between zavegepant 5 mg, 10 mg, or 20 mg nasal spray and placebo for the outcome pain relief at 2 h.

- 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

RCTs were included in the main evidence if they met all the following criteria:

- A hypothesis of non-inferiority or superiority of one drug over the other was clearly stated
- The study sample size was justified.

All trials not meeting these criteria were excluded from the main evidence and considered for additional evidence.

Only head-to-head comparisons between different drugs were included in the present section.

We restricted comparisons to oral and intranasal drugs, excluding studies comparing parenteral routes of administration of drugs. This choice was made to decrease the heterogeneity of comparisons and to adhere to the outpatient settings in which oral and intranasal drugs are the most used.

Figure 3.9.1 reports the results of the literature search. Table 3.9.1 reports the PICO question structure of the present section.

It is important to note that PICO questions referring to the present section were structured after the literature search, as there were no expected results prior to the search.

Table 3.9.1 reports the comparisons that were included in the present section, while Figure 3.9.87 reports a summary of each recommendation.

Comparison between different non-steroidal anti-inflammatory drugs

PICO 3.9.1. In patients with migraine, are acetylsalicylic acid and ibuprofen equivalent for the acute treatment of migraine attacks (outcomes: pain freedom at 2 h, pain relief at 2 h)?

Main evidence. We found one RCT comparing oral acetylsalicylic acid 1000 mg to oral ibuprofen 400 mg in patients with migraine (30) that met the criteria to be included in the main evidence. The risk of bias was unclear (Figures 3.9.2 and 3.9.3). The RCT showed no difference between oral acetylsalicylic acid 1000 mg and oral ibuprofen 400 mg considering the outcomes of pain freedom at 2 h (Figure 3.9.2) and pain relief at 2 h (Figure 3.9.3). The quality of evidence for both outcomes was considered low (Table 3.9.2).

Additional evidence. None.

Evidence-based recommendation for PICO 3.9.1

In patients with migraine, we suggest acetylsalicylic acid 1000 mg and ibuprofen 400 mg as equivalent options for the acute treatment of migraine attacks.
Quality of evidence: Low (⊕⊕⊖⊖)
Strength of the recommendation: =

Comparisons between triptans and non-steroidal anti-inflammatory drugs

PICO 3.9.2. In patients with migraine, are rizatriptan and ibuprofen equivalent for the acute treatment of migraine attacks (outcomes: pain freedom at 2 h, pain relief at 2 h)?

Main evidence. We found one RCT comparing rizatriptan 10 mg to ibuprofen 400 mg in patients with migraine (38) that met the criteria to be included in the main evidence. The risk of bias was low (Figures 3.9.4 and 3.9.5). The RCT showed no difference between oral rizatriptan 10 mg and oral ibuprofen 400 mg considering the outcome pain freedom at 2 h (Figure 3.9.4) while oral rizatriptan 10 mg was slightly superior to oral ibuprofen 400 mg considering the outcome pain relief at 2 h (Figure 3.9.5). The quality of evidence for both outcomes was considered low to moderate (Table 3.9.3).

Additional evidence. None.

Evidence-based recommendation for PICO 3.9.2

In patients with migraine, we suggest oral rizatriptan 10 mg over oral ibuprofen 400 mg for the acute treatment of migraine attacks.
Quality of evidence: Low (⊕⊕⊖⊖)
Strength of the recommendation: Weak (↑)

PICO 3.9.3. In patients with migraine, are sumatriptan and acetylsalicylic acid equivalent for the acute treatment of migraine attacks (outcomes: pain freedom at 2 h, pain relief at 2 h)?

Main evidence. We found two RCTs comparing sumatriptan 50 mg to acetylsalicylic acid 1000 mg in patients with migraine (29,30) that met the criteria to be included in the main evidence. The risk of bias was unclear (Figures 3.9.6 and 3.9.7). The RCTs showed no difference between sumatriptan 50 mg and acetylsalicylic acid 1000 mg considering the outcomes of pain freedom at 2 h (Figure 3.9.6) and pain relief at 2 h (Figure 3.9.7). The quality of evidence for both outcomes was considered moderate (Table 3.9.4).

Table 3.8.3. GRADE evidence profile table for zavegepant nasal spray versus placebo in the acute treatment of migraine attacks

Certainty assessment							№ of patients		Effect			
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Zavegepant	Placebo	Relative (95% CI)	Absolute (95% CI)	Quality	Importance
Pain freedom at 2 h – Zavegepant 5 mg nasal spray vs Placebo												
1	RCTs	Not serious	Not applicable[a]	Not serious	Not serious	None	59/387 (15.2%)	62/401 (15.5%)	**RR 0.99** (0.71 to 1.37)	**2 less per 1.000** (from 45 less to 57 more)	⊕⊕⊕⊖ Moderate	Critical
Pain freedom at 2 h – Zavegepant 10 mg nasal spray vs Placebo												
2	RCTs	Not serious	Not serious	Not serious	Not serious	None	235/1014 (23.2%)	158/1047 (15.1%)	**RR 1.54** (1.28 to 1.84)	**81 more per 1.000** (from 42 more to 127 more)	⊕⊕⊕⊕ High	Critical
Pain freedom at 2 h – Zavegepant 20 mg nasal spray vs Placebo												
1	RCTs	Not serious	Not applicable[a]	Not serious	Not serious	None	93/402 (23.1%)	62/401 (15.5%)	**RR 1.50** (1.12 to 2.00)	**75 more per 1.000** (from 18 more to 151 more)	⊕⊕⊕⊖ Moderate	Critical
Pain relief at 2 h – Zavegepant 5 mg nasal spray vs Placebo												
1	RCTs	Not serious	Not applicable[a]	Not serious	Not serious	None	224/387 (57.9%)	215/401 (53.6%)	**RR 1.08** (0.95 to 1.22)	**43 more per 1.000** (from 27 less to 118 more)	⊕⊕⊕⊖ Moderate	Critical
Pain relief at 2 h – Zavegepant 10 mg nasal spray vs Placebo												
2	RCTs	Not serious	Not serious	Not serious	Not serious	None	603/1014 (59.5%)	536/1047 (51.2%)	**RR 1.16** (1.07 to 1.25)	**24 more per 1.000** (from 11 more to 38 more)	⊕⊕⊕⊕ High	Critical
Pain relief at 2 h – Zavegepant 20 mg nasal spray vs Placebo												
1	RCTs	Not serious	Not applicable[a]	Not serious	Not serious	None	246/402 (61.2%)	215/401 (53.6%)	**RR 1.14** (1.01 to 1.29)	**21 more per 1.000** (from 2 more to 44 more)	⊕⊕⊕⊖ Moderate	Critical

[a]Only one trial.

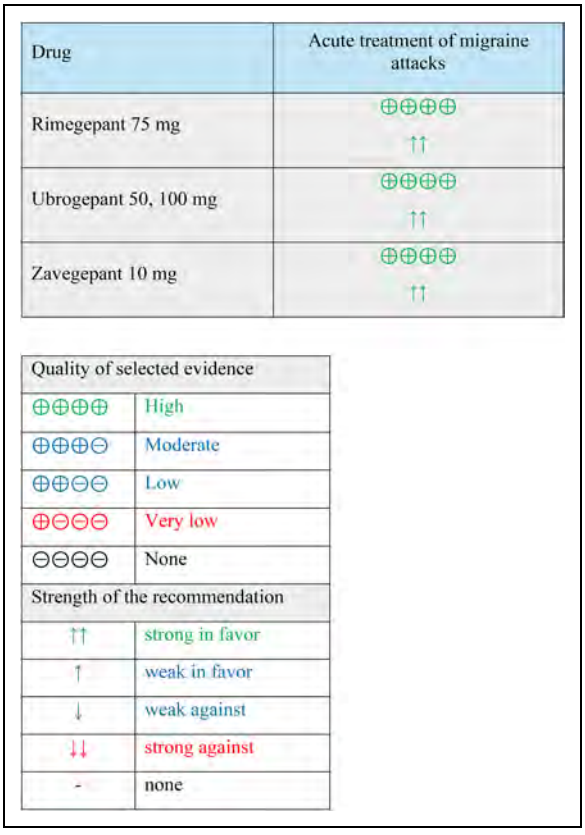


Figure 3.8.9. Summary of evidence-based recommendations on gepants for the acute treatment of migraine attacks.

Additional evidence. None.

Evidence-based recommendation for PICO 3.9.3

In patients with migraine, we suggest oral sumatriptan 50 mg and oral acetylsalicylic acid 1000 mg as equivalent options for the acute treatment of migraine attacks.
Quality of evidence: Moderate (⊕⊕⊕⊖)
Strength of the recommendation: =

PICO 3.9.4. In patients with migraine, are sumatriptan and ibuprofen equivalent for the acute treatment of migraine attacks (outcomes: pain freedom at 2 h, pain relief at 2 h)?

Main evidence. None.

Additional evidence. We found one RCT comparing oral sumatriptan 50 mg and ibuprofen 400 mg (30) that did not meet the criteria for main evidence due to the lack of a sample size calculation. The risk of bias was considered unclear (Figures 3.9.8 and 3.9.9). The RCT found no difference between oral sumatriptan 50 mg and oral ibuprofen 400 mg considering the outcomes of pain freedom at 2 h (Figure 3.9.8) and pain relief at 2 h (Figure 3.9.9). The quality of evidence was considered very low due to the availability of only one RCT with unclear risk of bias.

Evidence-based recommendation for PICO 3.9.4

In patients with migraine, we suggest sumatriptan 50 mg and ibuprofen 400 mg as equivalent options for the acute treatment of migraine attacks.
Quality of evidence: Very low (⊕⊖⊖⊖)
Strength of the recommendation: =

PICO 3.9.5. In patients with migraine, are sumatriptan nasal spray and ketorolac nasal spray equivalent for the acute treatment of migraine attacks (outcomes: pain freedom at 2 h, pain relief at 2 h)?

Main evidence. We found one RCT comparing sumatriptan 20 mg nasal spray to ketorolac 31.5 mg nasal spray in patients with migraine (44) that met the criteria to be included in the main evidence. The risk of bias was high (Figures 3.9.10 and 3.9.11). The RCT showed no difference between sumatriptan 20 mg nasal spray and ketorolac 31.5 mg nasal spray considering the outcomes of pain freedom at 2 h (Figure 3.9.10) and pain relief at 2 h (Figure 3.9.11). The quality of evidence for both outcomes was considered very low (Table 3.9.5) due to the availability of only one RCT with high risk of bias and low numbers of patients (<50 per group).

Additional evidence. None.

Evidence-based recommendation for PICO 3.9.5

In patients with migraine, we suggest sumatriptan 20 mg nasal spray and ketorolac 31.5 mg nasal spray as equivalent options for the acute treatment of migraine attacks.
Quality of evidence: Very low (⊕⊖⊖⊖)
Strength of the recommendation: =

PICO 3.9.6. In patients with migraine, are sumatriptan and naproxen equivalent for the acute treatment of migraine attacks (outcomes: pain freedom at 2 h, pain relief at 2 h)?

Main evidence. We found one RCT comparing oral sumatriptan 100 mg with oral naproxen 500 mg (174) that met the criteria for main evidence. The risk of bias was unclear (Figure 3.9.12). The RCT showed no difference between oral sumatriptan 100 mg and oral naproxen 500 mg considering the outcome pain freedom at 2 h

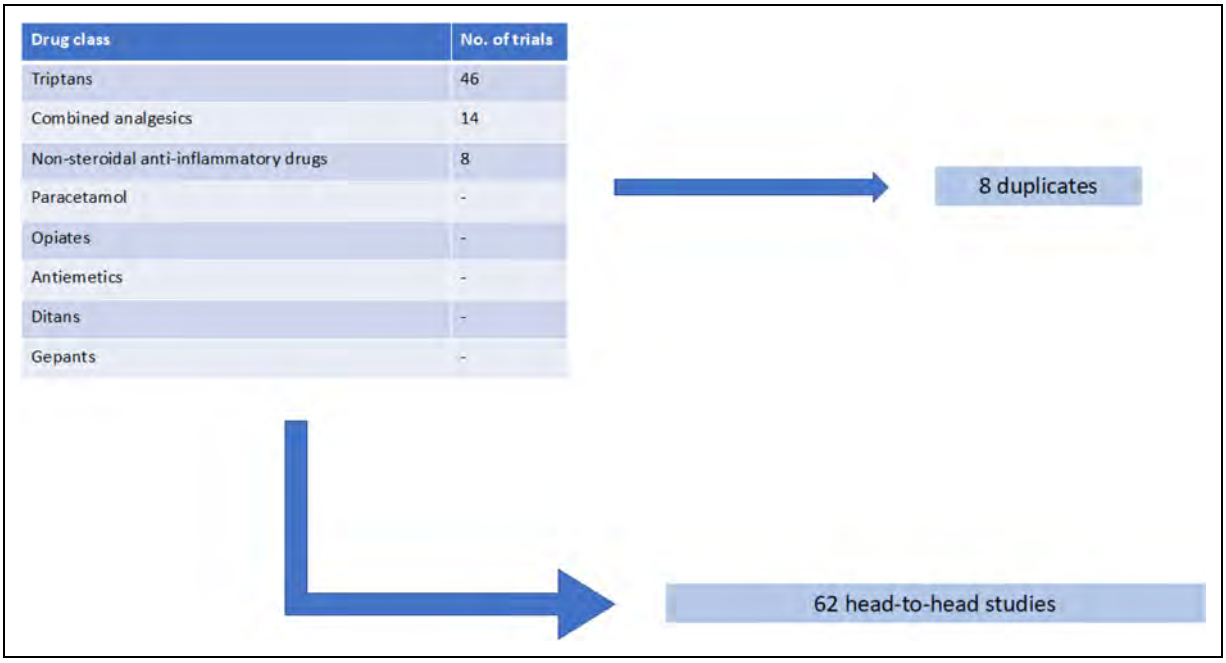


Figure 3.9.1. Flowchart of study selection for the present chapter.

(Figure 3.9.12). The quality of evidence was considered low (Table 3.9.6).

Additional evidence. We found two RCTs comparing oral sumatriptan 50 mg or 85 mg with oral naproxen 500 mg (27,41). Those RCTs did not meet the criteria for main evidence as they did not report criteria for sample size calculation. The risk of bias was unclear (Figures 3.9.13 and 3.9.14). Overall, the RCTs showed that the 85 mg dose of oral sumatriptan was superior to oral naproxen 500 mg considering the outcomes pain freedom at 2 h (Figure 3.9.13) and pain relief at 2 h (Figure 3.9.14), while the 50 mg dose of oral sumatriptan was not more effective than oral naproxen 500 mg. The quality of evidence was considered very low due to the availability of RCTs with unclear risk of bias.

Evidence-based recommendation for PICO 3.9.6

In patients with migraine, we suggest oral sumatriptan 50 mg or 100 mg and oral naproxen 500 mg as equivalent options for the acute treatment of migraine attacks; there is very low evidence to suggest sumatriptan 85 mg over naproxen 500 mg.
Quality of evidence: Very low (⊕⊖⊖⊖)
Strength of the recommendation: =

Comparisons between two different triptans

PICO 3.9.7. In patients with migraine, are almotriptan and frovatriptan equivalent for the acute treatment of migraine attacks (outcomes: pain freedom at 2 h, pain relief at 2 h)?

Main evidence. We found one RCT comparing oral almotriptan 12.5 mg with oral frovatriptan 2.5 mg (160) that met the criteria for inclusion in main evidence. The risk of bias was low (Figures 3.9.15 and 3.9.16). The RCT found no difference between oral almotriptan and oral frovatriptan considering the outcomes of pain freedom at 2 h (Figure 3.9.15) and pain relief at 2 h (Figure 3.9.16). The quality of evidence was considered moderate (Table 3.9.7) due to the availability of only one RCT.

Additional evidence. None.

Evidence-based recommendation for PICO 3.9.7

In patients with migraine, we suggest almotriptan 12.5 mg and frovatriptan 2.5 mg as equivalent options for the acute treatment of migraine attacks.
Quality of evidence: Moderate (⊕⊕⊕⊖)
Strength of the recommendation: =

PICO 3.9.8. In patients with migraine, are almotriptan and sumatriptan equivalent for the acute treatment of migraine attacks (outcomes: pain freedom at 2 h, pain relief at 2 h)?

Table 3.9.1. PICO structure of randomized controlled trials included in the present chapter. ASA, acetylsalicylic acid; CAs, combination analgesics

Comparison	PICO Question	Reference	Drug 1	Drug 2
NSAIDs vs NSAIDs	1	(30)	ASA	Ibuprofen
Triptans vs NSAIDs	2	(38)	Rizatriptan	Ibuprofen
	3	(29)	Sumatriptan	ASA
	3	(30)	Sumatriptan	ASA
	4	(30)	Sumatriptan	Ibuprofen
	5	(44)	Sumatriptan	Ketorolac
	6	(171)	Sumatriptan	Naproxen
	6	(27)	Sumatriptan	Naproxen
	6	(41)	Sumatriptan	Naproxen
Triptans vs triptans	7	(157)	Almotriptan	Frovatriptan
	8	(169)	Almotriptan	Sumatriptan
	8	(170)	Almotriptan	Sumatriptan
	8	(190)	Almotriptan	Sumatriptan
	9	(175)	Almotriptan	Zolmitriptan
	10	(93)	Eletriptan	Naratriptan
	11	(192)	Eletriptan	Rizatriptan
	12	(90)	Eletriptan	Sumatriptan
	12	(94)	Eletriptan	Sumatriptan
	12	(95)	Eletriptan	Sumatriptan
	13	(97)	Eletriptan	Zolmitriptan
	14	(187)	Frovatriptan	Rizatriptan
	15	(195)	Frovatriptan	Zolmitriptan
	16	(104)	Naratriptan	Rizatriptan
	17	(109)	Rizatriptan	Sumatriptan
	17	(181)	Rizatriptan	Sumatriptan
	17	(111)	Rizatriptan	Sumatriptan
	17	(118)	Rizatriptan	Sumatriptan
	17	(554)	Rizatriptan	Sumatriptan
	18	(117)	Rizatriptan	Zolmitriptan
	19	(172)	Zolmitriptan	Sumatriptan
	19	(173)	Zolmitriptan	Sumatriptan
	19	(176)	Zolmitriptan	Sumatriptan
Triptans vs other	20	(122)	Sumatriptan	Tolfenamic acid
CAs vs NSAIDs	21	(26)	Paracetamol + codeine	ASA
	22	(27)	Sumatriptan + naproxen	Naproxen
	22	(41)	Sumatriptan + naproxen	Naproxen
CAs vs triptans	23	(332)	Paracetamol + ASA + caffeine	Sumatriptan
	24	(330)	Paracetamol + domperidone	Sumatriptan
	25	(115)	Paracetamol + rizatriptan	Rizatriptan
	26	(341)	Almotriptan + aceclofenac	Almotriptan
	27	(184)	ASA + metoclopramide	Sumatriptan
	27	(191)	ASA + metoclopramide	Sumatriptan
	28	(174)	ASA + metoclopramide	Zolmitriptan
	29	(164)	Ergotamine + caffeine	Eletriptan
	30	(328)	Ergotamine + caffeine	Rizatriptan
	31	(346)	Ergotamine + caffeine	Sumatriptan
	32	(339)	Ergotamine + sumatriptan	Sumatriptan
	33	(555)	Frovatriptan + dexketoprofen	Frovatriptan
	33	(556)	Frovatriptan + dexketoprofen	Frovatriptan
	34	(163)	Indomethacin + prochlorperazine + caffeine	Sumatriptan
	34	(186)	Indomethacin + prochlorperazine + caffeine	Sumatriptan
	35	(331)	Isometheptene + dichloralphenazone + paracetamol	Sumatriptan

(continued)

Table 3.9.1. (continued)

Comparison	PICO Question	Reference	Drug 1	Drug 2
	36	(327)	Promethazine + sumatriptan	Sumatriptan
	37	(342)	Sumatriptan + metoclopramide	Sumatriptan
	38	(27)	Sumatriptan + naproxen	Sumatriptan
	38	(41)	Sumatriptan + naproxen	Sumatriptan
	39	(335)	Trimebutine + rizatriptan	Rizatriptan
CAs vs paracetamol	40	(115)	Paracetamol + rizatriptan	Paracetamol
CAs vs CAs	41	(336)	ASA + metoclopramide	Ergotamine + caffeine
	42	(329)	Sumatriptan + naproxen	Paracetamol + butalbital + caffeine
CAs vs other	43	(334)	ASA + butalbital + codeine + caffeine	Butorphanol

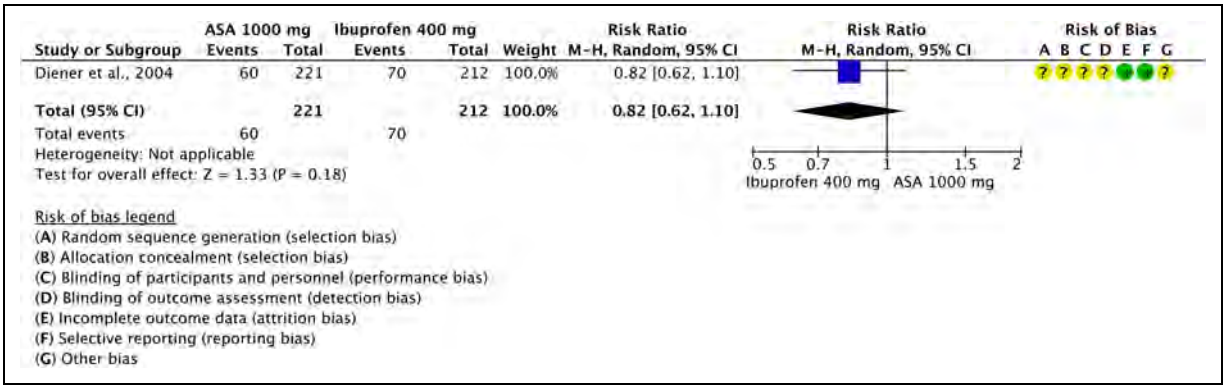


Figure 3.9.2. Forest plot showing the comparison between oral acetylsalicylic acid 1000 mg and oral ibuprofen 400 mg for the outcome pain freedom at 2 h in patients with migraine.

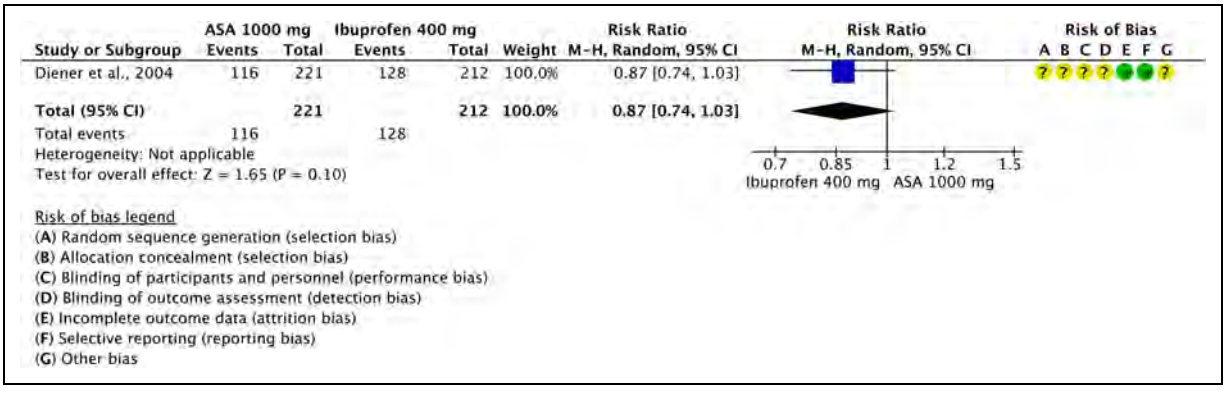


Figure 3.9.3. Forest plot showing the comparison between oral acetylsalicylic acid 1000 mg and oral ibuprofen 400 mg for the outcome pain relief at 2 h in patients with migraine.

Main evidence. We found two RCTs comparing oral almotriptan 12.5 mg with oral sumatriptan 50 mg or 100 mg (150,193) that met the criteria for main evidence. The risk of bias was considered low (Figures 3.9.17 and 3.9.18). The two RCTs found that oral almotriptan was inferior to oral sumatriptan 50 mg and equivalent to oral sumatriptan 100 mg considering the outcome pain freedom at 2 h (Figure 3.9.17), while oral almotriptan and oral sumatriptan

Table 3.9.2. GRADE evidence profile table for oral acetylsalicylic acid 1000 mg versus oral ibuprofen 400 mg in patients with migraine

Certainty assessment							№ of patients		Effect			
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Acetylsalicylic acid 1000 mg	Ibuprofen 400 mg	Relative (95% CI)	Absolute (95% CI)	Quality	Importance
Pain freedom at 2 h – Acetylsalicylic acid 1000 mg oral vs ibuprofen 400 mg oral												
1	RCT	Serious	Not applicable[a]	Not serious	Not serious	None	60/221 (27.1%)	70/212 (33.0%)	**RR 0.82** (0.62 to 1.10)	**59 less per 1000** (from 125 less to 33 more)	⊕⊕⊖⊖ Low	Critical
Pain relief at 2 h – Acetylsalicylic acid 1000 mg oral vs ibuprofen 400 mg oral												
1	RCT	Serious	Not applicable[a]	Not serious	Not serious	None	116/221 (52.5%)	128/212 (60.4%)	**RR 0.87** (0.74 to 1.03)	**78 less per 1000** (from 157 less to 18 more)	⊕⊕⊖⊖ Low	Critical

[a]Only one trial.

were equivalent considering the outcome pain relief at 2 h (Figure 3.9.18). The quality of evidence was considered moderate (Table 3.9.8).

Additional evidence. We found one RCT comparing oral almotriptan 12.5 mg to oral sumatriptan 100 mg for the acute treatment of migraine attacks (173) that did not meet the criteria for main evidence as it did not specify a sample size calculation for pain freedom at 2 h. The risk of bias was low (Figure 3.9.19). The RCT showed no difference between oral almotriptan 12.5 mg and oral sumatriptan 100 mg considering the outcome pain freedom at 2 h (Figure 3.9.19).

Evidence-based recommendation for PICO 3.9.8

In patients with migraine, we suggest oral almotriptan 12.5 mg and oral sumatriptan – 50 mg or 100 mg – as equivalent options for the acute treatment of migraine attacks.
Quality of evidence: Moderate (⊕⊕⊕⊖)
Strength of the recommendation: **=**

PICO 3.9.9. In patients with migraine, are almotriptan and zolmitriptan equivalent for the acute treatment of migraine attacks (outcomes: pain freedom at 2 h, pain relief at 2 h)?

Main evidence. We found one RCT comparing oral almotriptan 12.5 mg with oral zolmitriptan 2.5 mg (178) that met the criteria for main evidence. The risk of bias was considered low (Figures 3.9.20 and 3.9.21). The RCT showed no difference between oral almotriptan 12.5 mg and oral zolmitriptan 2.5 mg considering the outcome of pain freedom at 2 h (Figure 3.9.20) and pain relief at 2 h (Figure 3.9.21). The quality of evidence was considered moderate (Table 3.9.9).

Additional evidence. None.

Evidence-based recommendation for PICO 3.9.9

In patients with migraine, we suggest oral almotriptan 12.5 mg and oral zolmitriptan 2.5 mg as equivalent options for the acute treatment of migraine attacks.
Quality of evidence: Moderate (⊕⊕⊕⊖)
Strength of the recommendation: weak (=)

PICO 3.9.10. In patients with migraine, are eletriptan and naratriptan equivalent for the acute treatment of migraine attacks (outcomes: pain freedom at 2 h, pain relief at 2 h)?

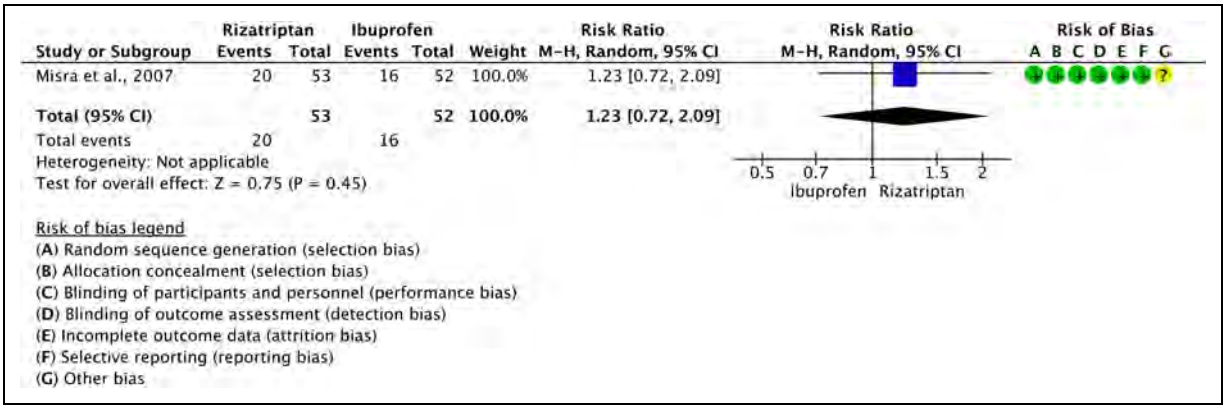


Figure 3.9.4. Forest plot showing the comparison between oral rizatriptan 10 mg and oral ibuprofen 400 mg for the outcome pain freedom at 2 h in patients with migraine.

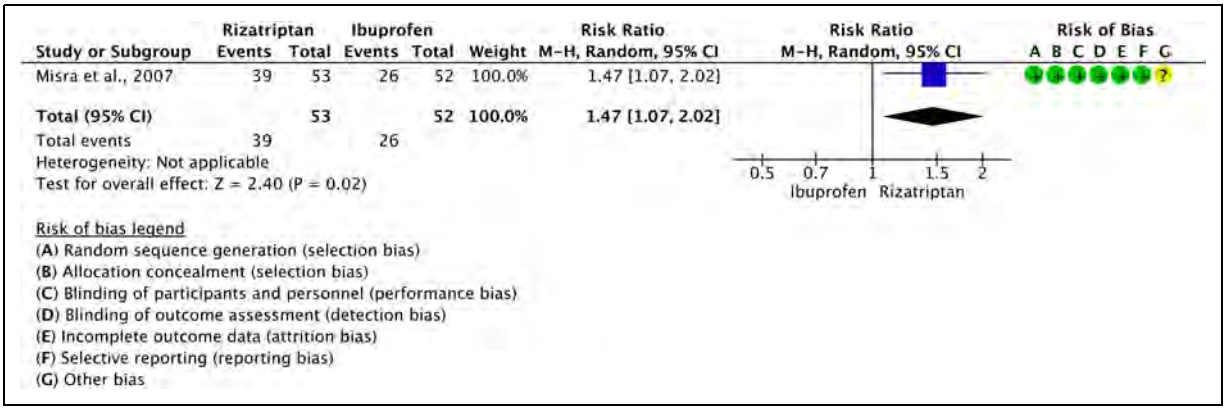


Figure 3.9.5. Forest plot showing the comparison between oral rizatriptan 10 mg and oral ibuprofen 400 mg for the outcome pain relief at 2 h in patients with migraine.

Main evidence. We found one RCT comparing oral eletriptan 40 mg to oral naratriptan 2.5 mg (96) that met the criteria for main evidence. The risk of bias was considered unclear (Figures 3.9.22 and 3.9.23). The RCT found that oral eletriptan 40 mg was superior to oral naratriptan 2.5 mg considering the outcomes pain freedom at 2 h (Figure 3.9.22) and pain relief at 2 h (Figure 3.9.23). The quality of evidence was considered low (Table 3.9.10).

Additional evidence. None.

Evidence-based recommendation for PICO 3.9.10

In patients with migraine, we suggest eletriptan 40 mg over naratriptan 2.5 mg for the acute treatment of migraine attacks.
Quality of evidence: Moderate (⊕⊕⊕⊖)
Strength of the recommendation: Weak (↑)

PICO 3.9.11. In patients with migraine, are eletriptan and rizatriptan equivalent for the acute treatment of migraine attacks (outcomes: pain freedom at 2 h, pain relief at 2 h)?

Main evidence. None.

Additional evidence. We found one RCT comparing oral eletriptan 40 mg with oral rizatriptan 10 mg (195) that did not meet the criteria for main evidence due to the lack of a sample size calculation. The risk of bias was considered high (Figures 3.9.24 and 3.9.25). The RCT showed that oral eletriptan 40 mg was equivalent to oral rizatriptan 10 mg considering the outcome pain freedom at 2 h (Figure 3.9.24) and superior to oral rizatriptan 10 mg considering the outcome pain relief at 2 h (Figure 3.9.25). Due to the small number of patients (<50 in each treatment arm), no recommendation was issued.

Table 3.9.3. GRADE evidence profile table for oral rizatriptan 10 mg versus oral ibuprofen 400 mg in patients with migraine

Certainty assessment							№ of patients		Effect			
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Rizatriptan 10 mg	Ibuprofen 400 mg	Relative (95% CI)	Absolute (95% CI)	Quality	Importance
Pain freedom at 2 h – Rizatriptan 10 mg oral vs Ibuprofen 400 mg oral												
1	RCT	Not serious	Not applicable[a]	Not serious	Serious[b]	None	20/53 (37.7%)	16/52 (30.8%)	**RR 1.23** (0.72 to 2.09)	**71 more per 1000** (from 86 less to 335 more)	⊕⊕⊖⊖ Low	Critical
Pain relief at 2 h – Rizatriptan 10 mg oral vs Ibuprofen 400 mg oral												
1	RCT	Not serious	Not applicable[a]	Not serious	Not serious	None	39/53 (73.6%)	26/52 (50.0%)	**RR 1.37** (1.01 to 1.84)	**235 more per 1000** (from 35 more to 510 more)	⊕⊕⊕⊖ Moderate	Critical

[a]Only one trial; [b]the confidence interval included the threshold for clinical decision.

Evidence-based recommendation for PICO 3.9.11

None.
Quality of evidence: -
Strength of the recommendation: -

PICO 3.9.12. In patients with migraine, are eletriptan and sumatriptan equivalent for the acute treatment of migraine attacks (outcomes: pain freedom at 2 h, pain relief at 2 h)?

Main evidence. We found three RCTs comparing oral eletriptan 40 mg with oral sumatriptan 100 mg (93,97,98) that met the criteria for main evidence. The risk of bias was considered low (Figures 3.9.26 and 3.9.27). The RCTs found that oral eletriptan 40 mg was superior to oral sumatriptan 100 mg considering the outcomes pain freedom at 2 h (Figure 3.9.26) and pain relief at 2 h (Figure 3.9.27). The quality of evidence was considered high (Table 3.9.11).

Additional evidence. None.

Evidence-based recommendation for PICO 3.9.12

In patients with migraine, we recommend eletriptan 40 mg over sumatriptan 100 mg for the acute treatment of migraine attacks.
Quality of evidence: High (⊕⊕⊕⊕)
Strength of the recommendation: Strong (↑↑)

PICO 3.9.13. In patients with migraine, are eletriptan and zolmitriptan equivalent for the acute treatment of migraine attacks (outcomes: pain freedom at 2 h, pain relief at 2 h)?

Main evidence. We found one RCT comparing oral eletriptan 40 mg with oral zolmitriptan 2.5 mg (100) that met the criteria for main evidence. The risk of bias was considered low (Figures 3.9.28 and 3.9.29). The RCT showed that oral eletriptan 40 mg and oral zolmitriptan 2.5 mg were equivalent considering the outcomes of pain freedom at 2 h (Figure 3.9.28) and pain relief at 2 h (Figure 3.9.29). The quality of evidence was considered moderate (Table 3.9.12).

Additional evidence. None.

Evidence-based recommendation for PICO 3.9.13

In patients with migraine, we suggest eletriptan 40 mg and zolmitriptan 2.5 mg as equivalent options for the acute treatment of migraine attacks.

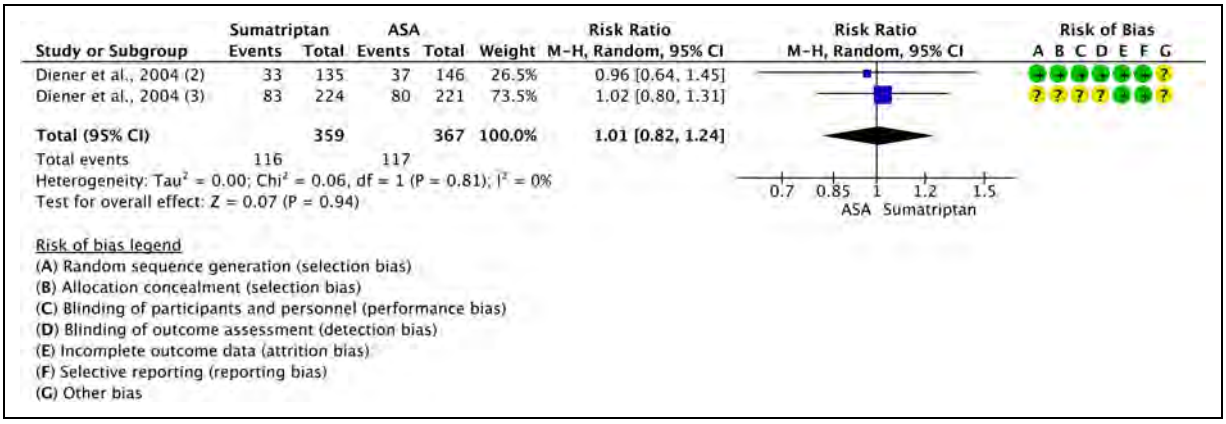


Figure 3.9.6. Forest plot showing the comparison between oral sumatriptan 50 mg and oral acetylsalicylic 1000 mg for the outcome pain freedom at 2 h in patients with migraine.

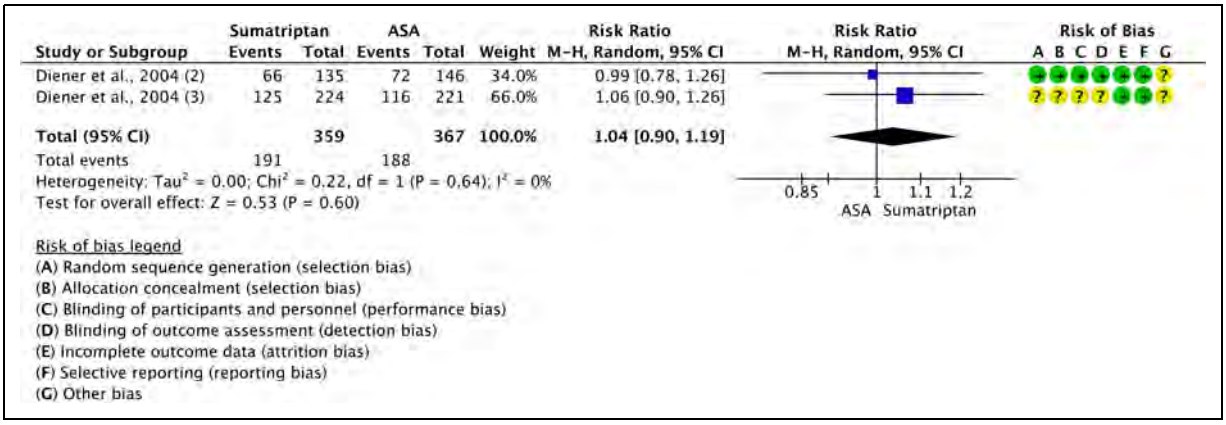


Figure 3.9.7. Forest plot showing the comparison between oral sumatriptan 50 mg and oral acetylsalicylic 1000 mg for the outcome pain relief at 2 h in patients with migraine.

Quality of evidence: Moderate (⊕⊕⊕⊖)
Strength of the recommendation: =

PICO 3.9.14. In patients with migraine, are frovatriptan and rizatriptan equivalent for the acute treatment of migraine attacks (outcomes: pain freedom at 2 h, pain relief at 2 h)?

Main evidence. We found one RCT comparing oral frovatriptan 2.5 mg and oral rizatriptan 10 mg (190) that met the criteria for main evidence. The risk of bias was considered low (Figures 3.9.30 and 3.9.31). The RCT showed no difference between oral frovatriptan 2.5 mg and oral rizatriptan 10 mg considering the outcomes of pain freedom at 2 h (Figure 3.9.30) and pain relief at 2 h (Figure 3.9.31). The quality of evidence was considered moderate (Table 3.9.13).

Additional evidence. None.

Evidence-based recommendation for PICO 3.9.14

In patients with migraine, we suggest frovatriptan 2.5 mg and rizatriptan 10 mg as equivalent options for the acute treatment of migraine attacks.
Quality of evidence: Moderate (⊕⊕⊕⊖)
Strength of the recommendation: =

PICO 3.9.15. In patients with migraine, are frovatriptan and zolmitriptan equivalent for the acute treatment of migraine attacks (outcomes: pain freedom at 2 h, pain relief at 2 h)?

Main evidence. We found one RCT comparing oral frovatriptan 2.5 mg with oral zolmitriptan 2.5 mg (200) that

Table 3.9.4. GRADE evidence profile table for oral sumatriptan 50 mg versus oral acetylsalicylic acid 1000 mg in patients with migraine

Certainty assessment							№ of patients		Effect			
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Rizatriptan 10 mg	Ibuprofen 400 mg	Relative (95% CI)	Absolute (95% CI)	Quality	Importance
Pain freedom at 2 h – Sumatriptan 50 mg oral vs Acetylsalicylic acid 1000 mg oral												
2	RCT	Serious	Not serious	Not serious	Not serious	None	116/359 (32.3%)	117/367 (51.2%)	**RR 1.01** (0.82 to 1.24)	**3 more per 1000** (from 57 less to 77 more)	⊕⊕⊕⊖ Moderate	Critical
Pain relief at 2 h – Sumatriptan 50 mg oral vs Acetylsalicylic acid 1000 mg oral												
2	RCT	Serious	Not serious	Not serious	Not serious	None	191/359 (53.2%)	188/367 (51.2%)	**RR 1.04** (0.90 to 1.19)	**20 more per 1000** (from 51 less to 97 more)	⊕⊕⊕⊖ Moderate	Critical

met the criteria for main evidence. The risk of bias was low (Figures 3.9.32 and 3.9.33). The RCT showed no difference between oral frovatriptan 2.5 mg and oral zolmitriptan 2.5 mg considering the outcomes of pain freedom at 2 h (Figure 3.9.32) and pain relief at 2 h (Figure 3.9.33). The quality of evidence was considered moderate (Table 3.9.14) due to the availability of only one RCT.

Additional evidence. None.

Evidence-based recommendation for PICO 3.9.15

In patients with migraine, we suggest frovatriptan 2.5 mg and zolmitriptan 2.5 mg as equivalent options for the acute treatment of migraine attacks.
Quality of evidence: Moderate (⊕⊕⊕⊖)
Strength of the recommendation: =

PICO 3.9.16. In patients with migraine, are naratriptan and rizatriptan equivalent for the acute treatment of migraine attacks (outcomes: pain freedom at 2 h, pain relief at two hours)?

Main evidence. We found one RCT comparing oral naratriptan 2.5 mg with oral rizatriptan 10 mg (107) that met the criteria for main evidence. The risk of bias was considered low (Figures 3.9.34 and 3.9.35). The RCT showed that oral rizatriptan 10 mg was superior to oral naratriptan 2.5 mg considering the outcomes of pain freedom at 2 h (Figure 3.9.34) and pain relief at 2 h (Figure 3.9.35). The quality of evidence was considered moderate (Table 3.9.15).

Additional evidence. None.

Evidence-based recommendation for PICO 3.9.16

In patients with migraine, we suggest rizatriptan 10 mg over naratriptan 2.5 mg for the acute treatment of migraine attacks.
Quality of evidence: Moderate (⊕⊕⊕⊖)
Strength of the recommendation: weak (↑)

PICO 3.9.17. In patients with migraine, are rizatriptan and sumatriptan equivalent for the acute treatment of migraine attacks (outcomes: pain freedom at 2 h, pain relief at 2 h)?

Main evidence. We found four RCTs comparing oral rizatriptan 5 or 10 mg to oral sumatriptan 50 or 100 mg (112,114,121,184) that met the criteria for main evidence. The risk of bias was considered low (Figures 3.9.36 and 3.9.37). Overall, the RCTs showed no difference between rizatriptan and sumatriptan considering the outcomes of

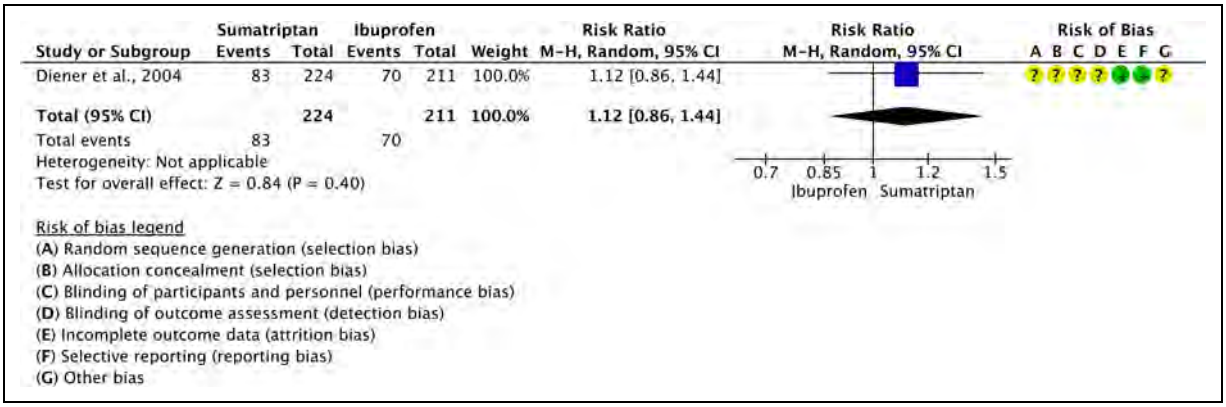


Figure 3.9.8. Forest plot showing the comparison between oral sumatriptan 50 mg and oral ibuprofen 400 mg for the outcome pain freedom at 2 h in patients with migraine.

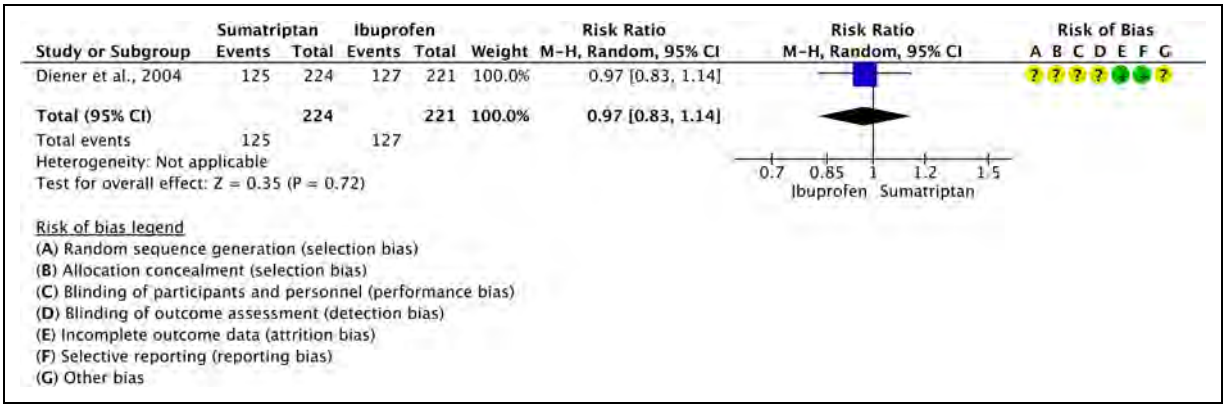


Figure 3.9.9. Forest plot showing the comparison between oral sumatriptan 50 mg and oral ibuprofen 400 mg for the outcome pain relief at 2 h in patients with migraine.

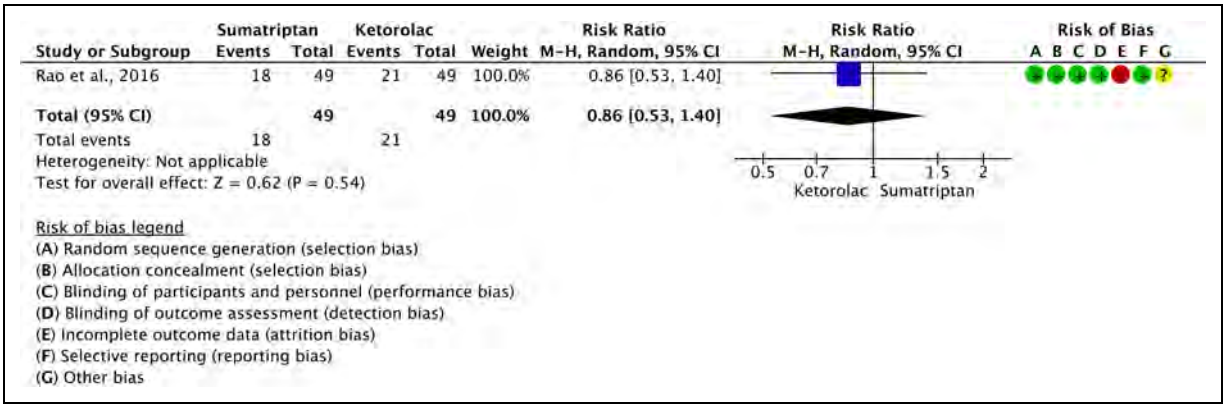


Figure 3.9.10. Forest plot showing the comparison between sumatriptan 20 mg nasal spray and ketorolac 31.5 mg nasal spray for the outcome pain freedom at 2 h in patients with migraine.

pain freedom at 2 h (Figure 3.9.36) and pain relief at 2 h (Figure 3.9.37). The quality of evidence was considered moderate-to-high (Table 3.9.16).

Additional evidence. We found one RCT comparing oral rizatriptan 10 mg with oral sumatriptan 50 mg (558) that did not meet the criteria for main evidence as it did not

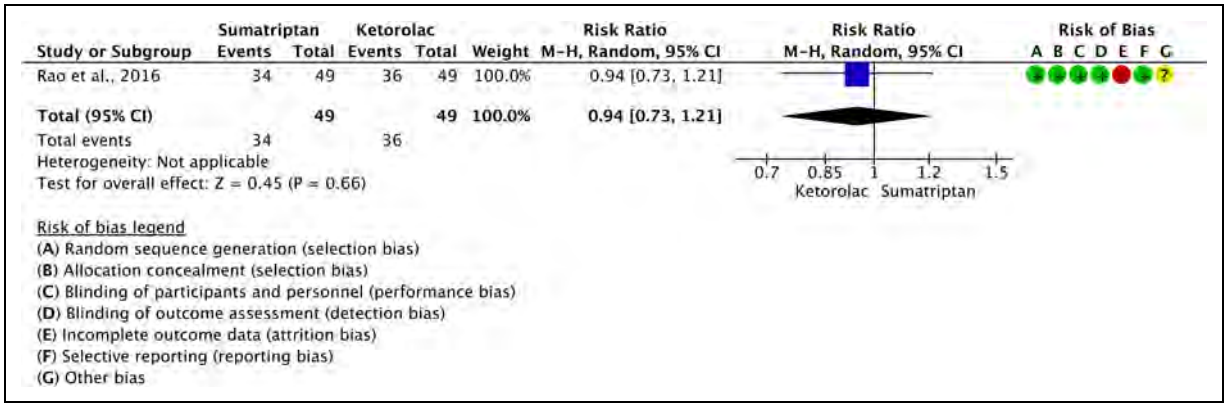


Figure 3.9.11. Forest plot showing the comparison between sumatriptan 20 mg nasal spray and ketorolac 31.5 mg nasal spray for the outcome pain relief at 2 h in patients with migraine.

report a sample size calculation. The risk of bias was considered unclear (Figure 3.9.38). The RCT showed no difference between oral rizatriptan 10 mg and oral sumatriptan 50 mg considering the outcome pain freedom at 2 h (Figure 3.9.38).

Evidence-based recommendation for PICO 3.9.17

In patients with migraine, we suggest rizatriptan (5 mg or 10 mg) and sumatriptan (50 mg or 100 mg) as equivalent options for the acute treatment of migraine attacks.
Quality of evidence: Moderate (⊕⊕⊕⊖)
Strength of the recommendation: =

PICO 3.9.18. In patients with migraine, are rizatriptan and zolmitriptan equivalent for the acute treatment of migraine attacks (outcomes: pain freedom at 2 h, pain relief at 2 h)?

Main evidence. We found one RCT comparing oral rizatriptan 10 mg with oral zolmitriptan 2.5 (120) that met the criteria for main evidence. The risk of bias was considered low (Figures 3.9.39 and 3.9.40). The RCT showed no difference between oral rizatriptan 10 mg and oral zolmitriptan 2.5 mg considering the outcomes of pain freedom at 2 h (Figure 3.9.39) and pain relief at 2 h (Figure 3.9.40). The quality of evidence was considered moderate (Table 3.9.17).

Additional evidence. None.

Evidence-based recommendation for PICO 3.9.18

In patients with migraine, we suggest oral rizatriptan 10 mg and oral zolmitriptan 2.5 mg as equivalent options for the acute treatment of migraine attacks.
Quality of evidence: Moderate (⊕⊕⊕⊖)
Strength of the recommendation: =

PICO 3.9.19. In patients with migraine, are zolmitriptan and sumatriptan equivalent for the acute treatment of migraine attacks (outcomes: pain freedom at 2 h, pain relief at 2 h)?

Main evidence. We found two RCTs comparing oral zolmitriptan 2.5 or 5 mg with oral sumatriptan 50 or 100 mg (176,179) that met the criteria for main evidence. The risk of bias was considered low or unclear (Figures 3.9.41 and 3.9.42). The RCTs showed no difference between oral zolmitriptan and oral sumatriptan considering the outcomes of pain freedom at 2 h (Figure 3.9.41) and pain relief at 2 h (Figure 3.9.42). The quality of evidence was considered low or moderate (Table 3.9.18).

Additional evidence. We found one RCT comparing oral zolmitriptan (2.5 or 5 mg) with oral sumatriptan 50 mg (175) that did not meet the criteria for main evidence due to the lack of a formal sample size calculation. The risk of bias was considered low (Figure 3.9.43). The RCT showed no difference between oral zolmitriptan (2.5 or 5 mg) and oral sumatriptan 50 mg considering the outcome of pain relief at 2 h (Figure 3.9.43). The quality of evidence was considered moderate due to the availability of only one RCT.

Evidence-based recommendation for PICO 3.9.19

In patients with migraine, we suggest zolmitriptan (2.5 or 5 mg) and sumatriptan (50 mg or 100 mg) as equivalent options for the acute treatment of migraine attacks.
Quality of evidence: Low (⊕⊕⊖⊖)
Strength of the recommendation: =

Table 3.9.5. GRADE evidence profile table for sumatriptan 20 mg nasal spray versus ketorolac 31.5 mg nasal spray in patients with migraine

Certainty assessment							№ of patients		Effect			
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Sumatriptan	Ketorolac	Relative (95% CI)	Absolute (95% CI)	Quality	Importance
Pain freedom at 2 h – Sumatriptan 20 mg nasal spray vs Ketorolac 31.5 mg nasal spray												
1	RCT	Serious	Not applicable[a]	Not serious	Serious[b]	None	18/49 (36.7%)	21/49 (42.9%)	**RR 0.86** (0.53 to 1.40)	**60 less per 1000** (from 201 less to 171 more)	⊕⊖⊖⊖ Very Low	Critical
Pain relief at 2 h – Sumatriptan 20 mg nasal spray vs Ketorolac 31.5 mg nasal spray												
1	RCT	Serious	Not applicable[a]	Not serious	Serious[b]	None	34/49 (69.4%)	36/49 (73.5%)	**RR 0.94** (0.73 to 1.21)	**44 less per 1000** (from 198 less to 154 more)	⊕⊖⊖⊖ Very Low	Critical

[a]Only one trial; [b]Low numbers of patients.

Comparisons between triptans and other analgesics

PICO 3.9.20. In patients with migraine, are sumatriptan and tolfenamic acid equivalent for the acute treatment of migraine attacks (outcomes: pain freedom at 2 h, pain relief at 2 h)?

Main evidence. None.

Additional evidence. We found one RCT comparing oral sumatriptan 100 mg with oral tolfenamic acid 200 mg (125) that did not meet the criteria for main evidence due to the lack of a sample size calculation. The risk of bias was considered unclear (Figures 3.9.44 and 3.9.45). The RCT showed no difference between oral sumatriptan 100 mg and oral tolfenamic acid 200 mg considering the outcomes of pain freedom at 2 h (Figure 3.9.44) and pain relief at 2 h (Figure 3.9.45). No recommendation was issued due to low numbers of patients (<50 per group).

Evidence-based recommendation for PICO 3.9.20

None.
Quality of evidence: -
Strength of the recommendation: -

Comparisons between combination analgesics and non-steroidal anti-inflammatory agents

PICO 3.9.21. In patients with migraine, are paracetamol + codeine and acetylsalicylic acid equivalent for the acute treatment of migraine attacks (outcomes: pain freedom at 2 h, pain relief at 2 h)?

Main evidence. None.

Additional evidence. We found one RCT comparing oral paracetamol 400 mg + codeine 25 mg with oral acetylsalicylic acid 1000 mg (26) that did not meet the criteria for main evidence as it did not report a sample size calculation. The risk of bias was considered high (Figures 3.9.46 and 3.9.47). The RCT showed no difference between oral paracetamol 400 mg + codeine 25 mg and oral acetylsalicylic acid 1000 mg considering the outcomes of pain freedom at 2 h (Figure 3.9.46) and pain relief at 2 h (Figure 3.9.47). The quality of evidence was considered very low due to the inclusion of only one RCT with a high risk of bias.

Evidence-based recommendation for PICO 3.9.21

In patients with migraine, we suggest oral paracetamol 400 mg + codeine 25 mg and oral acetylsalicylic acid 1000 mg as equivalent options for the acute treatment of migraine attacks.
Quality of evidence: Very low (⊕⊖⊖⊖)

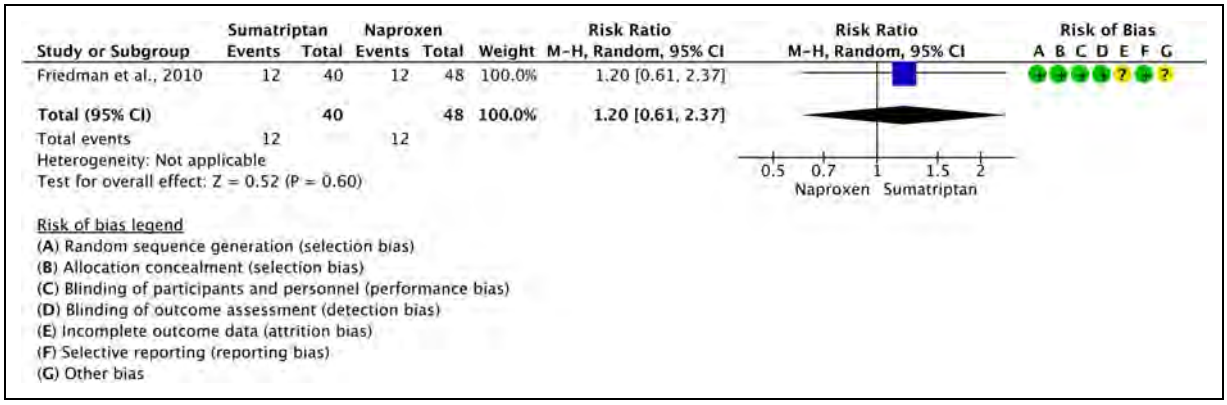


Figure 3.9.12. Forest plot showing the comparison between oral sumatriptan 100 mg and oral naproxen 500 mg for the outcome pain freedom at 2 h in patients with migraine.

Strength of the recommendation: =
[NOTE: Opioids such as codeine present safety risks and should be used with caution. Please refer to Sections 3.4 and 3.6].

PICO 3.9.22. In patients with migraine, are sumatriptan + naproxen and naproxen alone equivalent for the acute treatment of migraine attacks (outcomes: pain freedom at 2 h, pain relief at 2 h)?

Main evidence. None.

Additional evidence. We found two RCTs comparing oral sumatriptan (50 or 85 mg) + naproxen 500 mg with naproxen 500 mg alone (27,41) that did not meet the criteria for main evidence as they did not report a sample size calculation. The risk of bias was considered unclear (Figures 3.9.48 and 3.9.49). The RCT showed that oral sumatriptan (50 or 85 mg) + naproxen 500 mg was superior to oral naproxen 500 mg alone considering the outcomes of pain freedom at 2 h (Figure 3.9.48) and pain relief at 2 h (Figure 3.9.49). The quality of evidence was considered very low due to the inclusion of RCTs with unclear risk of bias.

Evidence-based recommendation for PICO 3.9.22

In patients with migraine, we suggest oral sumatriptan (50 or 85 mg) + naproxen 500 mg over oral naproxen 500 mg alone for the acute treatment of migraine attacks.
Quality of evidence: Very low (⊕⊖⊖⊖)
Strength of the recommendation: Weak (↑)

Comparisons between combination analgesics and triptans

PICO 3.9.23. In patients with migraine, are paracetamol + acetylsalicylic acid + caffeine and sumatriptan equivalent for the acute treatment of migraine attacks (outcomes: pain freedom at 2 h, pain relief at 2 h)?

Main evidence. We found one RCT comparing oral paracetamol 500 mg + acetylsalicylic acid 500 mg + caffeine 130 mg with oral sumatriptan 50 mg (335) that met the criteria for main evidence. The risk of bias was considered high (Figure 3.9.50). The RCT showed that oral paracetamol 500 mg + acetylsalicylic acid 500 mg + caffeine 130 mg was superior to oral sumatriptan 50 mg considering the outcome of pain freedom at 2 h (Figure 3.9.50). The quality of evidence was considered very low (Table 3.9.19) due to the availability of only one RCT with a high risk of bias and low numbers of patients (<50 in one of the groups).

Additional evidence. None.

Evidence-based recommendation for PICO 3.9.23

In patients with migraine, we suggest oral paracetamol 500 mg + acetylsalicylic acid 500 mg + caffeine 130 mg over oral sumatriptan 50 mg for the acute treatment of migraine attacks.
Quality of evidence: Very low (⊕⊖⊖⊖)
Strength of the recommendation: Weak (↑)

PICO 3.9.24. In patients with migraine, are paracetamol + domperidone and sumatriptan equivalent for the acute treatment of migraine attacks (outcomes: pain freedom at 2 h, pain relief at 2 h)?

Table 3.9.6. GRADE evidence profile table for oral sumatriptan 100 mg versus oral naproxen 500 mg in patients with migraine

Certainty assessment							№ of patients		Effect			
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Sumatriptan	Ketorolac	Relative (95% CI)	Absolute (95% CI)	Quality	Importance
Pain freedom at 2 h – Sumatriptan 100 mg oral vs Naproxen 500 mg oral												
1	RCT	Serious	Not applicable[a]	Not serious	Serious[b]	None	12/40 (30.0%)	12/48 (25.0%)	**RR 1.20** (0.61 to 2.37)	**50 more per 1000** (from 98 less to 343 more)	⊕⊖⊖⊖ Very low	Critical

[a]Only one trial; [b]low numbers of patients (<50 per group).

Main evidence. None.

Additional evidence. We found one RCT comparing oral paracetamol 1000 mg + domperidone 20 mg with oral sumatriptan 50 mg (333) that did not meet the criteria for main evidence due to the lack of a sample size calculation. The risk of bias was considered low (Figure 3.9.51). The RCT showed no difference between paracetamol 1000 mg + domperidone 20 mg and sumatriptan 50 mg considering the outcome of pain relief at 2 h (Figure 3.9.51). The quality of evidence was considered low (Figure 3.9.51).

Evidence-based recommendation for PICO 3.9.24

In patients with migraine, we suggest oral paracetamol 1000 mg + domperidone 20 mg and oral sumatriptan 50 mg as equivalent options for the acute treatment of migraine attacks.
Quality of evidence: Low (⊕⊕⊖⊖)
Strength of the recommendation: =

PICO 3.9.25. In patients with migraine, are paracetamol + rizatriptan and rizatriptan alone equivalent for the acute treatment of migraine attacks (outcomes: pain freedom at 2 h, pain relief at 2 h)?

Main evidence. None.

Additional evidence. We found one RCT comparing oral paracetamol 1000 mg + rizatriptan 10 mg with oral rizatriptan 10 mg alone (118) that did not meet the criteria for main evidence due to the lack of a sample size calculation. The risk of bias was considered low (Figures 3.9.52 and 3.9.53). The RCT showed no difference between oral paracetamol 1000 mg + rizatriptan 10 mg and oral rizatriptan 10 mg alone considering the outcomes of pain freedom at 2 h (Figure 3.9.52) and pain relief at 2 h (Figure 3.9.53). The quality of evidence was considered very low due to the availability of only one RCT with low numbers of patients (<50 patients per group).

Evidence-based recommendation for PICO 3.9.25

In patients with migraine, we suggest oral paracetamol 1000 mg + rizatriptan 10 mg and oral rizatriptan 10 mg alone as equivalent options for the acute treatment of migraine attacks.
Quality of evidence: Very low (⊕⊖⊖⊖)
Strength of the recommendation: =

PICO 3.9.26. In patients with migraine, are almotriptan + aceclofenac and almotriptan alone equivalent for the acute treatment of migraine attacks (outcomes: pain freedom at 2 h, pain relief at 2 h)?

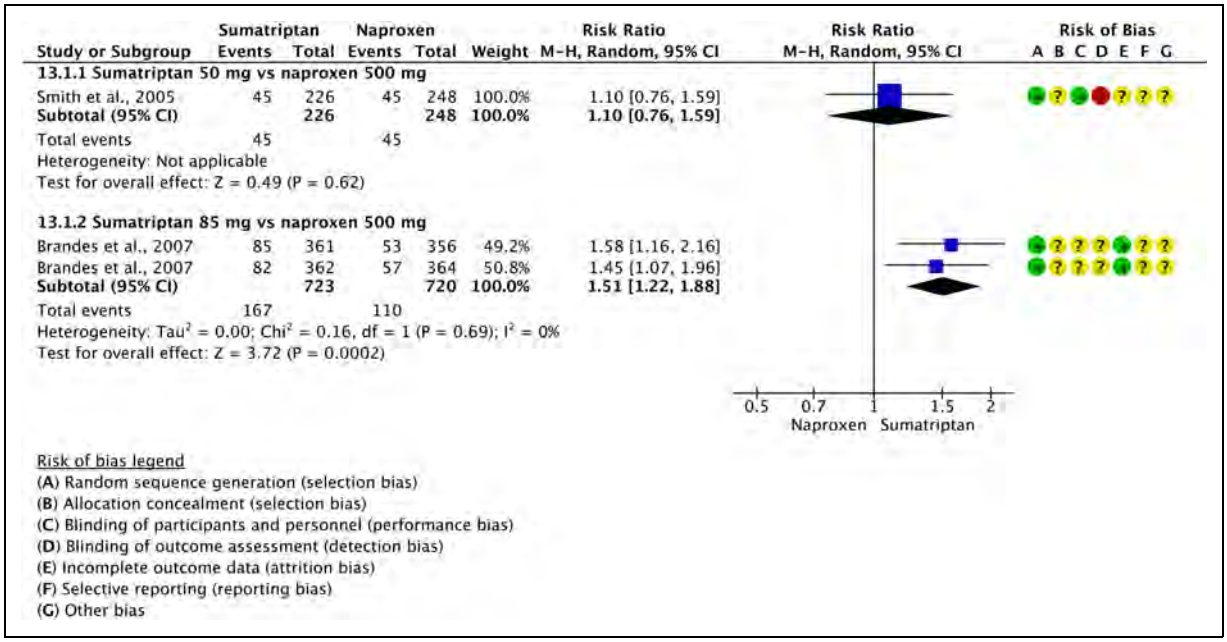


Figure 3.9.13. Forest plots showing the comparison between oral sumatriptan (50 mg or 85 mg) and oral naproxen 500 mg for the outcome pain freedom at 2 h in patients with migraine.

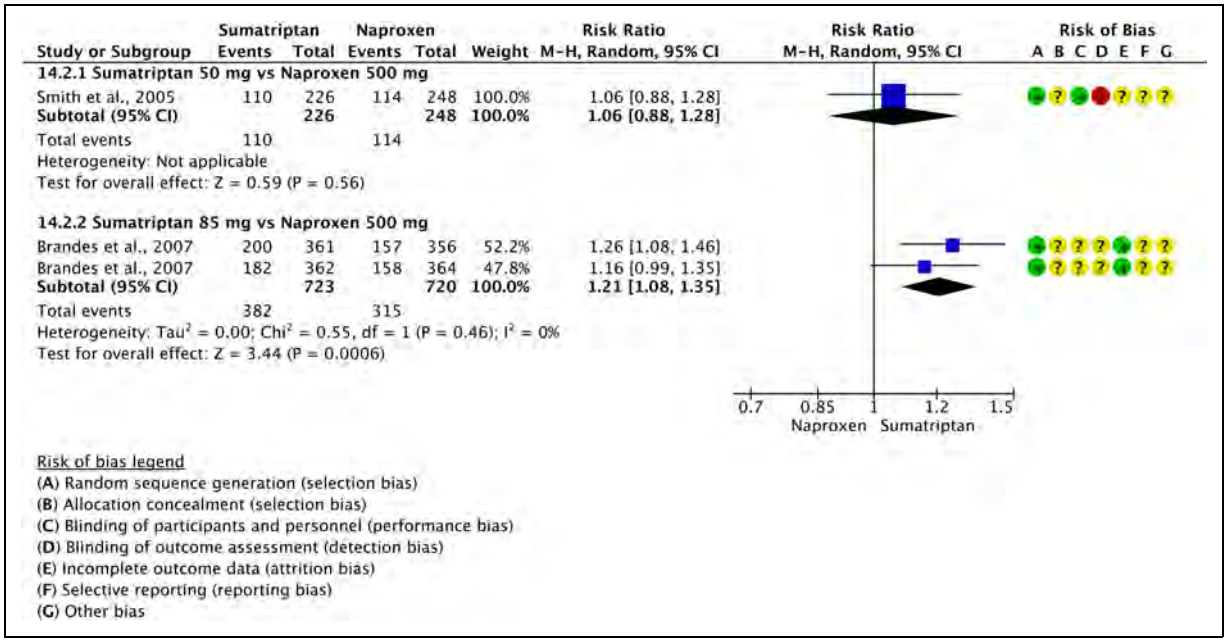


Figure 3.9.14. Forest plot showing the comparison between oral sumatriptan (50 mg or 85 mg) and oral naproxen 500 mg for the outcome pain relief at 2 h in patients with migraine.

Main evidence. None.

Additional evidence. We found one RCT comparing oral almotriptan 12.5 mg + aceclofenac 100 mg with oral almotriptan 12.5 mg alone (344) that did not meet the criteria for main evidence due to the lack of a sample size calculation. The risk of bias was considered unclear (Figure 3.9.54). The RCT showed no difference between oral almotriptan 12.5 mg + aceclofenac 100 mg and oral almotriptan 12.5 mg alone considering the outcome of pain freedom at 2 h (Figure 3.9.54). The quality of evidence was considered

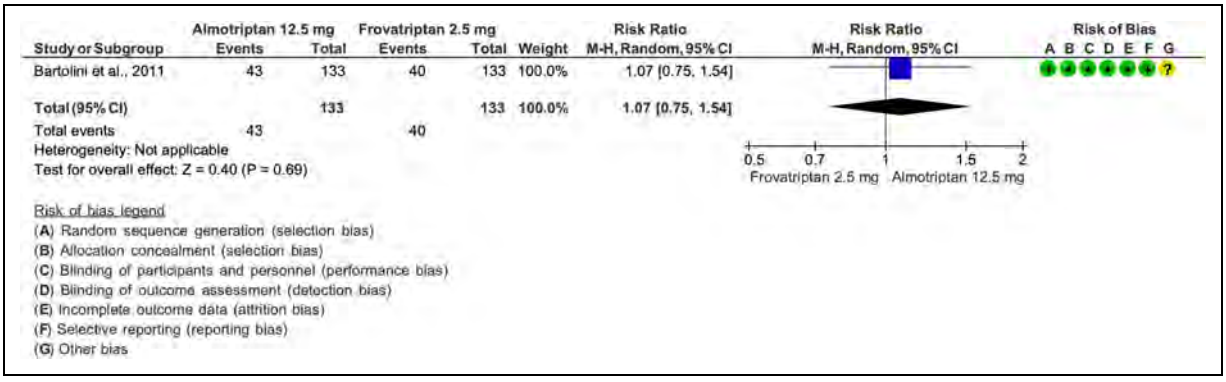


Figure 3.9.15. Forest plot showing the comparison between oral almotriptan 12.5 mg and oral frovatriptan 2.5 mg for the outcome pain freedom at 2 h in patients with migraine.

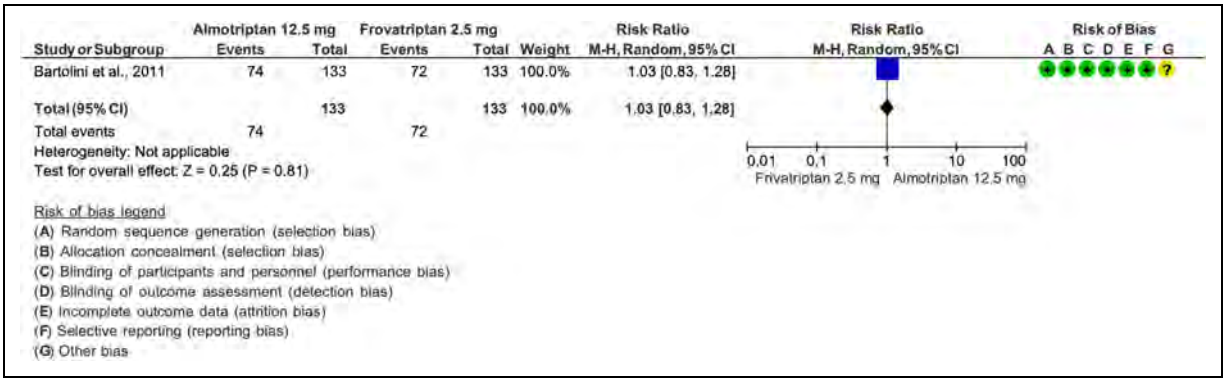


Figure 3.9.16. Forest plot showing the comparison between oral almotriptan 12.5 mg and oral frovatriptan 2.5 mg for the outcome pain relief at 2 h in patients with migraine.

very low due to the availability of only one RCT with an unclear risk of bias and low numbers of patients (<50 in one of the groups).

Evidence-based recommendation for PICO 3.9.26

In patients with migraine, we suggest either oral almotriptan 12.5 mg + aceclofenac 10 mg or oral almotriptan 12.5 mg alone as equivalent options for the acute treatment of migraine attacks.
Quality of evidence: Very low (⊕⊖⊖⊖)
Strength of the recommendation: =

PICO 3.9.27. In patients with migraine, are acetylsalicylic acid + metoclopramide and sumatriptan equivalent for the acute treatment of migraine attacks (outcomes: pain freedom at 2 h, pain relief at 2 h)?
Main evidence. We found two RCTs comparing oral acetylsalicylic acid 900 mg + metoclopramide 10 mg with oral sumatriptan 100 mg (187,194) that met the criteria for main evidence. The risk of bias was considered unclear (Figures 3.9.55 and 3.9.56). The RCTs showed no difference between oral acetylsalicylic acid 900 mg + metoclopramide 10 mg and oral sumatriptan 100 mg considering the outcome of pain freedom at 2 h (Figure 3.9.55) and pain relief at 2 h (Figure 3.9.56). The quality of evidence was considered moderate (Table 3.9.20) due the availability of RCTs with an unclear risk of bias.

Additional evidence. None.

Evidence-based recommendation for PICO 3.9.27

In patients with migraine, we suggest oral acetylsalicylic acid + metoclopramide 10 mg and oral sumatriptan 100 mg as equivalent options for the acute treatment of migraine attacks.
Quality of evidence: Moderate (⊕⊕⊕⊖)
Strength of the recommendation: =

Table 3.9.7. GRADE evidence profile table for almotriptan 12.5 mg versus frovatriptan 2.5 mg for the acute treatment of migraine attacks

Certainty assessment							№ of patients		Effect			
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Almotriptan	Frovatriptan	Relative (95% CI)	Absolute (95% CI)	Quality	Importance
Pain freedom at 2 h – Almotriptan 12.5 mg oral vs Frovatriptan 2.5 mg oral												
1	RCT	Not serious	Not applicable[a]	Not serious	Not serious	None	43/133 (32.3%)	40/133 (30.1%)	**RR 1.07** (0.75 to 1.54)	**21 more per 1000** (from 75 less to 162 more)	⊕⊕⊕⊖ Moderate	Critical
Pain relief at 2 h – Almotriptan 12.5 mg oral vs Frovatriptan 2.5 mg oral												
1	RCT	Not serious	Not applicable[a]	Not serious	Not serious	None	74/133 (55.4%)	72/133 (54.1%)	**RR 1.03** (0.83 to 1.28)	**16 more per 1000** (from 92 less to 152 more)	⊕⊕⊕⊖ Moderate	Critical

[a]Only one trial.

PICO 3.9.28. In patients with migraine, are acetylsalicylic acid + metoclopramide and zolmitriptan equivalent for the acute treatment of migraine attacks (outcomes: pain freedom at 2 h, pain relief at 2 h)?

Main evidence. We found one RCT comparing oral acetylsalicylic acid 900 mg + metoclopramide 10 mg with oral zolmitriptan 2.5 mg (177) that met the criteria for main evidence. The risk of bias was considered low (Figures 3.9.57 and 3.9.58). The RCT showed no difference between oral acetylsalicylic acid 900 mg + metoclopramide 10 mg and oral zolmitriptan 2.5 mg considering the outcomes pain freedom at 2 h (Figure 3.9.57) and pain relief at 2 h (Figure 3.9.58). The quality of evidence was considered moderate (Table 3.9.21) due to the availability of only one RCT.

Additional evidence. None.

Evidence-based recommendation for PICO 3.9.28

In patients with migraine, we suggest acetylsalicylic acid + metoclopramide 10 mg and zolmitriptan 2.5 mg as equivalent options for the acute treatment of migraine attacks.
Quality of evidence: Moderate (⊕⊕⊕⊖)
Strength of the recommendation: =

PICO 3.9.29. In patients with migraine, are ergotamine + caffeine and eletriptan equivalent for the acute treatment of migraine attacks (outcomes: pain freedom at 2 h, pain relief at 2 h)?

Main evidence. We found one RCT comparing oral ergotamine 2 mg + caffeine 200 mg with oral eletriptan (40 mg or 80 mg) (167) that met the criteria for main evidence. The risk of bias was considered low (Figures 3.9.59 and 3.9.60). The RCT found that both dosages of oral eletriptan were superior to oral ergotamine 2 mg + caffeine 200 mg considering the outcomes of pain freedom at 2 h (Figure 3.9.59) and pain relief at 2 h (Figure 3.9.60). The quality of evidence was considered moderate (Table 3.9.22) due to the availability of only one RCT.

Additional evidence. None.

Evidence-based recommendation for PICO 3.9.29

In patients with migraine, we recommend oral eletriptan (40 mg or 80 mg) over oral ergotamine 2 mg + caffeine 200 mg for the acute treatment of migraine attacks.
Quality of evidence: Moderate (⊕⊕⊕⊖)
Strength of the recommendation: strong (↑↑)

PICO 3.9.30. In patients with migraine, are ergotamine + caffeine and rizatriptan equivalent for the acute treatment

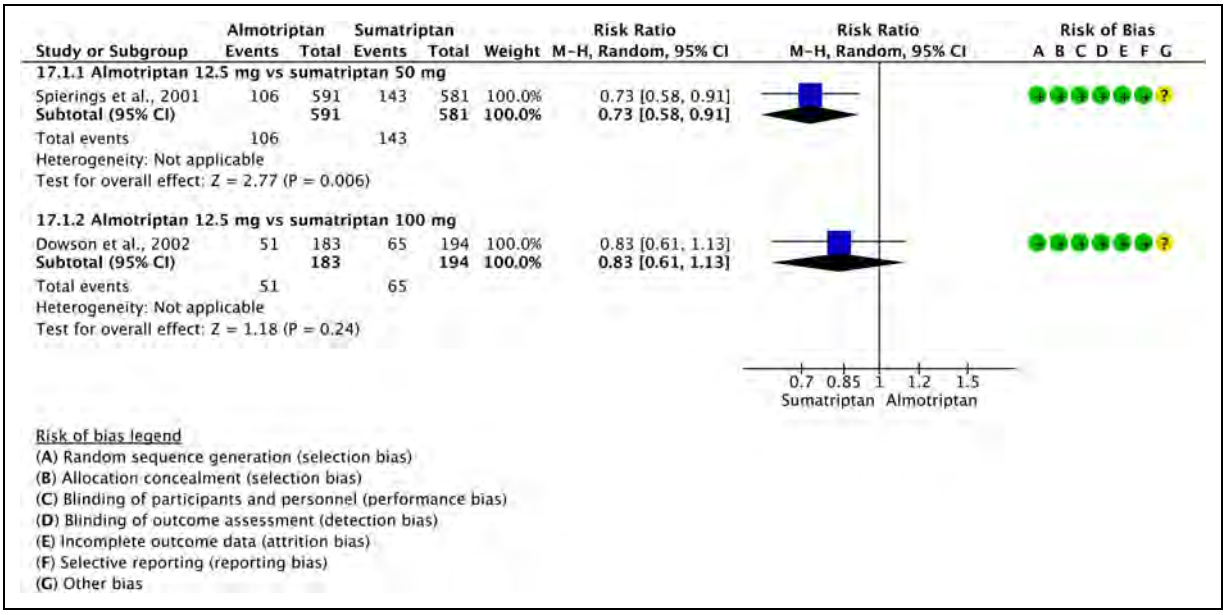


Figure 3.9.17. Forest plot showing the comparison between oral almotriptan 12.5 mg and oral sumatriptan 50 mg or 100 mg for the outcome pain freedom at 2 h in patients with migraine.

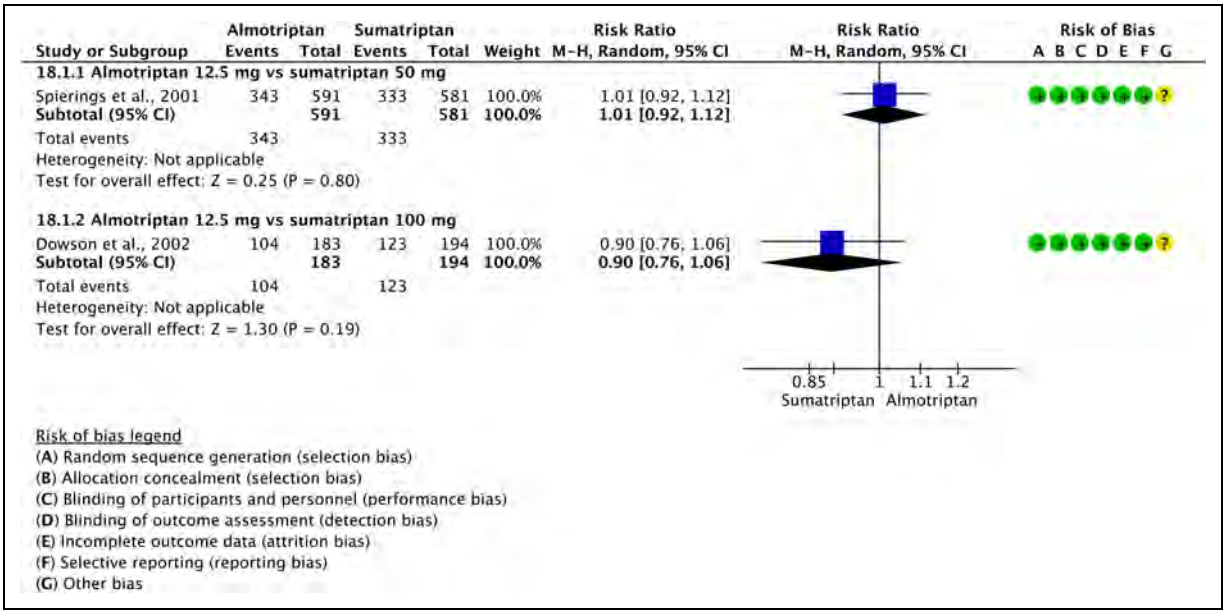


Figure 3.9.18. Forest plot showing the comparison between oral almotriptan 12.5 mg and oral sumatriptan 50 mg or 100 mg for the outcome pain relief at 2 h in patients with migraine.

of migraine attacks (outcomes: pain freedom at 2 h, pain relief at 2 h)?

Main evidence. We found one RCT comparing oral ergotamine 2 mg + caffeine 200 mg with oral rizatriptan 10 mg (331) that met the criteria for main evidence. The risk of bias was considered high (Figures 3.9.61 and 3.9.62). The RCT found that oral rizatriptan 10 mg was superior to oral ergotamine 2 mg + caffeine 200 mg considering the outcomes of pain freedom at 2 h (Figure 3.9.61) and pain relief at 2 h (Figure 3.9.62). The quality of evidence was considered very low (Table 3.9.23) due to the availability of only one RCT with a high risk of bias.

Additional evidence. None.

Table 3.9.8. GRADE evidence profile table for oral almotriptan 12.5 mg versus oral sumatriptan 50 mg or 100 mg in patients with migraine

Certainty assessment							№ of patients		Effect			
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Almotriptan	Sumatriptan	Relative (95% CI)	Absolute (95% CI)	Quality	Importance
Pain freedom at 2 h – Almotriptan 12.5 mg oral vs Sumatriptan 50 mg oral												
1	RCT	Not serious	Not applicable[a]	Not serious	Not serious	None	106/591 (17.9%)	143/581 (24.6%)	**RR 0.73** (0.58 to 0.91)	**66 less per 1000** (from 103 less to 22 less)	⊕⊕⊕⊖ Moderate	Critical
Pain relief at 2 h – Almotriptan 12.5 mg oral vs Sumatriptan 50 mg oral												
1	RCT	Not serious	Not applicable[a]	Not serious	Not serious	None	343/591 (58.0%)	333/581 (57.3%)	**RR 1.01** (0.92 to 1.12)	**6 more per 1000** (from 46 less to 69 more)	⊕⊕⊕⊖ Moderate	Critical
Pain freedom at 2 h – Almotriptan 12.5 mg oral vs Sumatriptan 100 mg oral												
1	RCT	Not serious	Not applicable[a]	Not serious	Not serious	None	51/183 (27.9%)	65/194 (33.5%)	**RR 0.83** (0.61 to 1.13)	**57 less per 1000** (from 131 less to 44 more)	⊕⊕⊕⊖ Moderate	Critical
Pain relief at 2 h – Almotriptan 12.5 mg oral vs Sumatriptan 100 mg oral												
1	RCT	Not serious	Not applicable[a]	Not serious	Not serious	None	104/183 (56.8%)	123/194 (63.4%)	**RR 0.90** (0.76 to 1.06)	**63 less per 1000** (from 152 less to 38 more)	⊕⊕⊕⊖ Moderate	Critical

[a]Only one trial.

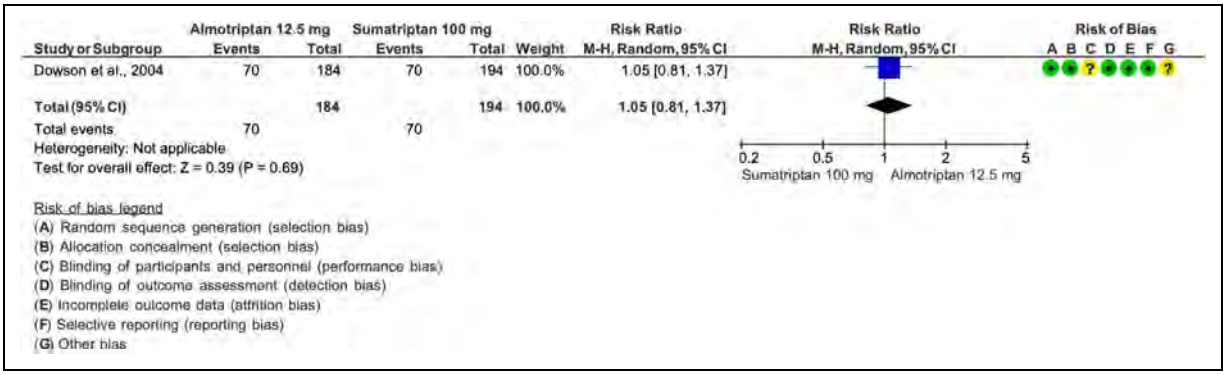


Figure 3.9.19. Forest plot showing the comparison between oral almotriptan 12.5 mg and oral sumatriptan 100 mg for the outcome pain freedom at 2 h in patients with migraine.

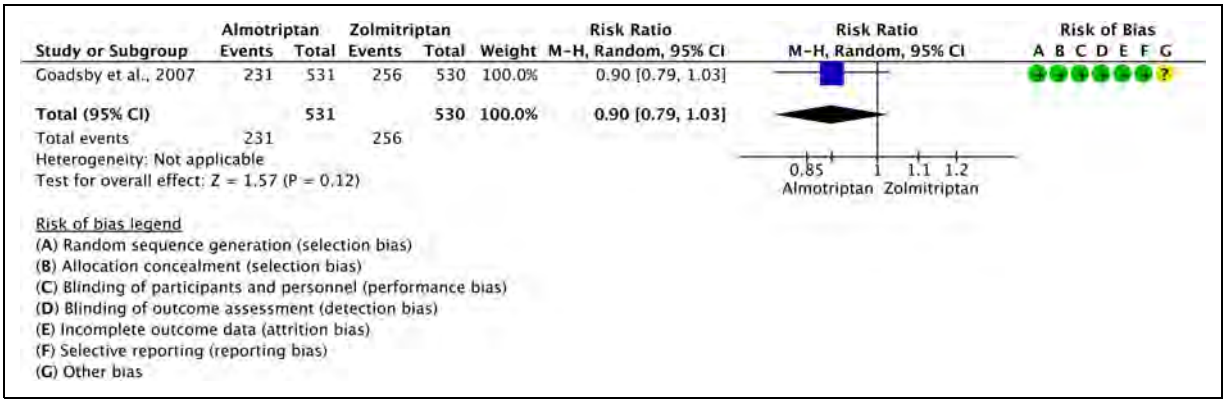


Figure 3.9.20. Forest plot showing the comparison between oral almotriptan 12.5 mg and oral zolmitriptan 2.5 mg for the outcome pain freedom at 2 h in patients with migraine.

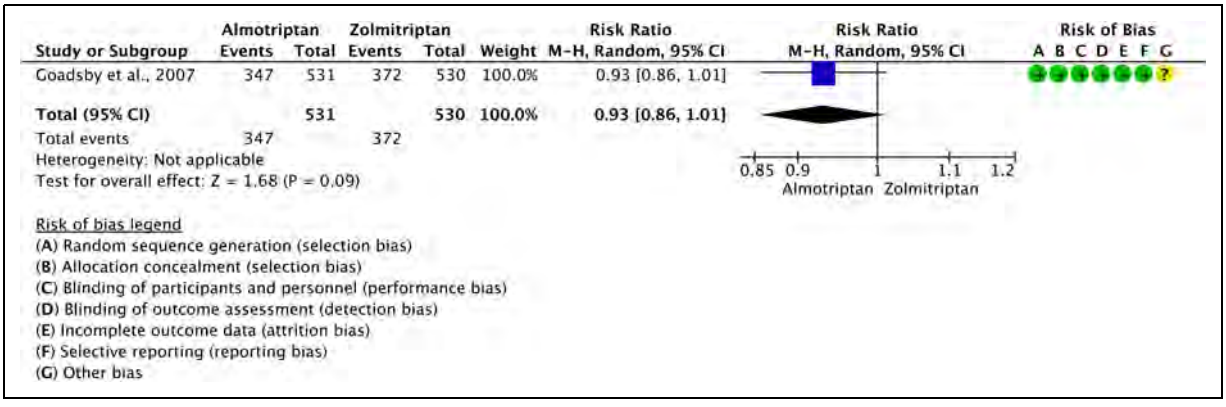


Figure 3.9.21. Forest plot showing the comparison between oral almotriptan 12.5 mg and oral zolmitriptan 2.5 mg for the outcome pain relief at 2 h in patients with migraine.

Evidence-based recommendation for PICO 3.9.30

In patients with migraine, we recommend rizatriptan 10 mg over ergotamine 2 mg + caffeine 200 mg for the acute treatment of migraine attacks.

Quality of evidence: Very low (⊕⊖⊖⊖)
Strength of the recommendation: strong (↑↑)

PICO 3.9.31. In patients with migraine, are ergotamine + caffeine and sumatriptan equivalent for the acute

Table 3.9.9. GRADE evidence profile table for oral almotriptan 12.5 mg versus oral zolmitriptan 2.5 mg in patients with migraine

Certainty assessment							№ of patients		Effect			
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Almotriptan	Zolmitriptan	Relative (95% CI)	Absolute (95% CI)	Quality	Importance
Pain freedom at 2 h – Almotriptan 12.5 mg oral vs Zolmitriptan 2.5 mg oral												
1	RCT	Low	Not applicable[a]	Not serious	Not serious	None	231/531 (43.5%)	256/530 (48.3%)	**RR 0.90** (0.79 to 1.03)	**48 less per 1000** (from 101 less to 14 more)	⊕⊕⊕⊖ Moderate	Critical
Pain relief at 2 h – Almotriptan 12.5 mg oral vs Zolmitriptan 2.5 mg oral												
1	RCT	Moderate	Not applicable[a]	Not serious	Not serious	None	347/531 (65.3%)	372/530 (70.2%)	**RR 0.93** (0.86 to 1.01)	**49 less per 1000** (from 98 less to 7 more)	⊕⊕⊕⊖ Moderate	Critical

[a]Only one trial.

treatment of migraine attacks (outcomes: pain freedom at 2 h, pain relief at 2 h)?

Main evidence. We found one RCT comparing oral ergotamine 2 mg + caffeine 200 mg with oral sumatriptan 100 mg (349) that met the criteria for main evidence. The risk of bias was considered high (Figures 3.9.63 and 3.9.64). The RCT found that oral sumatriptan 100 mg was superior to oral ergotamine 2 mg + caffeine 200 mg considering the outcomes of pain freedom at 2 h (Figure 3.9.63) and pain relief at 2 h (Figure 3.9.64). The quality of evidence was considered very low (Table 3.9.24) due to the availability of only one RCT with a high risk of bias.

Additional evidence. None.

Evidence-based recommendation for PICO 3.9.31

In patients with migraine, we suggest oral sumatriptan 100 mg over oral ergotamine 2 mg + caffeine 200 mg for the acute treatment of migraine attacks.
Quality of evidence: Very low (⊕⊖⊖⊖)
Strength of the recommendation: strong (↑↑)

PICO 3.9.32. In patients with migraine, are ergotamine + sumatriptan and sumatriptan alone equivalent for the acute treatment of migraine attacks (outcomes: pain freedom at 2 h, pain relief at 2 h)?

Main evidence. None.

Additional evidence. We found one RCT comparing oral ergotamine + sumatriptan (unspecified dose) with oral sumatriptan (unspecified dose) (342) that did not meet the criteria for main evidence due to the lack of a clear hypothesis of superiority. The risk of bias was considered unclear (Figure 3.9.65). The RCT found that oral ergotamine + sumatriptan was superior to oral sumatriptan alone considering the outcome of pain freedom at 2 h (Figure 3.9.65). The quality of evidence was considered very low due to the availability of only one RCT with an unclear risk of bias.

Evidence-based recommendation for PICO 3.9.32

In patients with migraine, we suggest oral ergotamine + sumatriptan (unspecified dose) over sumatriptan alone (unspecified dose) for the acute treatment of migraine attacks.
Quality of evidence: Very low (⊕⊕⊖⊖)
Strength of the recommendation: Weak (↑)

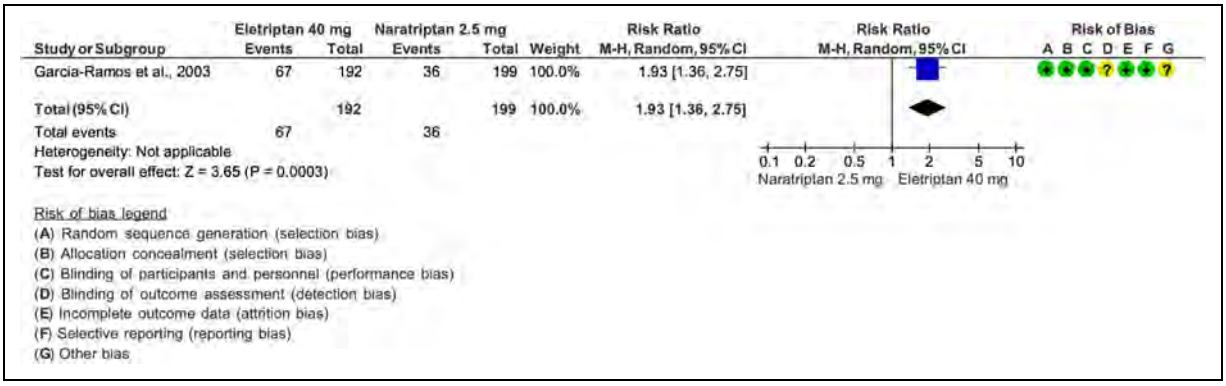


Figure 3.9.22. Forest plot showing the comparison between oral eletriptan 40 mg and oral naratriptan 2.5 mg for the outcome pain freedom at 2 h in patients with migraine.

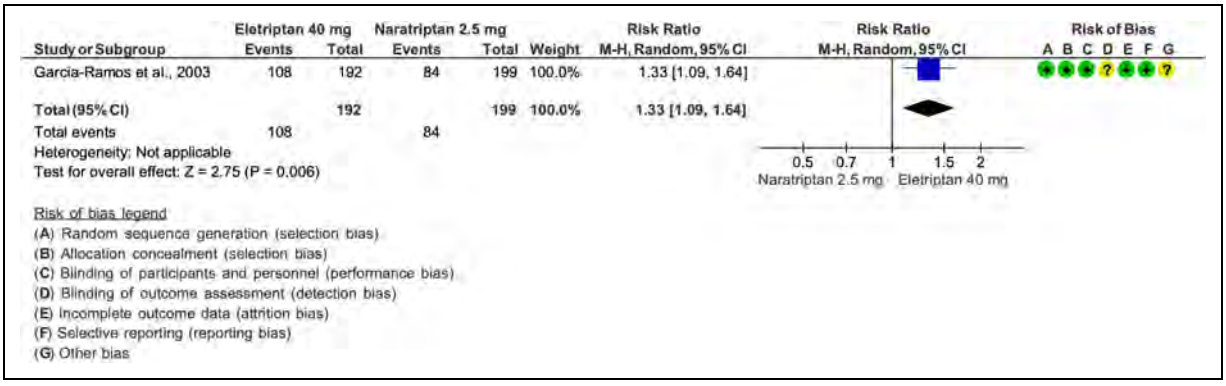


Figure 3.9.23. Forest plot showing the comparison between oral eletriptan 40 mg and oral naratriptan 2.5 mg for the outcome pain relief at 2 h in patients with migraine.

[NOTE. This recommendation is based upon comparative efficacy data. Given the poor overall quality of evidence and the small number of subjects and the limited exposure they had to the combination ergotamine + sumatriptan (which does not allow to draw definite conclusion about the safety of use of the combination), the Guideline Committee considers sumatriptan alone a better choice than the combination with ergotamine.]

PICO 3.9.33. In patients with migraine, are frovatriptan + dexketoprofen and frovatriptan alone equivalent for the acute treatment of migraine attacks (outcomes: pain freedom at 2 h, pain relief at 2 h)?

Main evidence. We found one RCT comparing oral frovatriptan 2.5 mg + dexketoprofen 37.5 mg with frovatriptan 2.5 mg alone (559) that met the criteria for main evidence. The risk of bias was considered low (Figures 3.9.66 and 3.9.67). The RCT found that oral frovatriptan 2.5 mg + dexketoprofen 37.5 mg was superior to oral frovatriptan 2.5 mg alone considering the outcomes of pain freedom at 2 h (Figure 3.9.66) and pain relief at 2 h (Figure 3.9.67). The quality of evidence was considered moderate (Table 3.9.25) due to the availability of only one RCT.

Additional evidence. None.

Evidence-based recommendation for PICO 3.9.33

In patients with migraine, we suggest oral frovatriptan 2.5 mg + dexketoprofen 37.5 mg over oral frovatriptan 2.5 mg alone for the acute treatment of migraine attacks.
Quality of evidence: Moderate (⊕⊕⊕⊖)
Strength of recommendation:

PICO 3.9.34. In patients with migraine, are indomethacin + prochlorperazine + caffeine and sumatriptan equivalent for the acute treatment of migraine attacks (outcomes: pain freedom at 2 h, pain relief at 2 h)?

Main evidence. We found one RCT comparing indomethacin 25 mg + prochlorperazine 4 mg + caffeine 75 mg suppositories and oral sumatriptan 25 mg (166) that met the criteria for

Table 3.9.10. GRADE evidence profile table for oral eletriptan 40 mg vs oral naratriptan 2.5 mg in patients with migraine

Certainty assessment							№ of patients		Effect			
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Eletriptan	Naratriptan	Relative (95% CI)	Absolute (95% CI)	Quality	Importance
Pain freedom at 2 h – Eletriptan 40 mg oral vs naratriptan 2.5 mg oral												
1	RCT	Not serious	Not applicable[a]	Not serious	Not serious	None	67/192 (34.9%)	36/199 (18.1%)	**RR 1.93** (1.36 to 2.75)	**168 more per 1000** (from 65 more to 317 more)	⊕⊕⊕⊖ Moderate	Critical
Pain relief at 2 h – Eletriptan 40 mg oral vs naratriptan 2.5 mg oral												
1	RCT	Not serious	Not applicable[a]	Not serious	Not serious	None	108/192 (56.3%)	84/199 (42.2%)	**RR 1.33** (1.09 to 1.64)	**139 more per 1000** (from 38 more to 270 more)	⊕⊕⊕⊖ Moderate	Critical

[a]Only one trial.

main evidence. The risk of bias was high (Figures 3.9.68 and 3.9.69). The RCT showed that the suppositories of indomethacin 25 mg + prochlorperazine 4 mg + caffeine 75 mg were equivalent to oral sumatriptan 25 mg considering the outcomes pain freedom at 2 h (Figure 3.9.68) and pain relief at 2 h (Figure 3.9.69). The quality of evidence was considered very low (Table 3.9.26).

We found a further RCT comparing oral indomethacin 25 mg + prochlorperazine 2 mg + caffeine 75 mg and oral sumatriptan 50 mg (189) that met the criteria for main evidence. The risk of bias was considered low (Figures 3.9.70 and 3.9.71). The RCT showed no difference between oral indomethacin 25 mg + prochlorperazine 2 mg + caffeine 75 mg and oral sumatriptan 50 mg for the outcomes pain freedom at 2 h (Figure 3.9.70) and pain relief at 2 h (Figure 3.9.71). The quality of evidence was considered moderate (Table 3.9.27).

Additional evidence. None.

Evidence-based recommendations for PICO 3.9.34

In patients with migraine, we suggest indomethacin + prochlorperazine + caffeine suppositories and oral sumatriptan (25 mg or 50 mg) as equivalent options for the acute treatment of migraine attacks.
Quality of evidence: Very low (⊕⊖⊖⊖)
Strength of the recommendation: =
In patients with migraine, we suggest oral indomethacin + prochlorperazine + caffeine and oral sumatriptan (25 mg or 50 mg) as equivalent options for the acute treatment of migraine attacks.
Quality of evidence: Moderate (⊕⊕⊕⊖)
Strength of the recommendation: =

PICO 3.9.35. In patients with migraine, are isometheptene + dichloralphenazone + paracetamol and sumatriptan equivalent for the acute treatment of migraine attacks (outcomes: pain freedom at 2 h, pain relief at 2 h)?

Main evidence. None.

Additional evidence. We found one RCT comparing oral isometheptene 65 mg + dichloralphenazone 100 mg + paracetamol 325 mg with oral sumatriptan 25 mg (334) that did not meet the criteria for main evidence due to the lack of a sample size calculation. The risk of bias was considered low (Figure 3.9.72). The RCT found no difference between oral isometheptene 65 mg + dichoralphenazone 100 mg + paracetamol 325 mg and oral sumatriptan 25 mg considering the outcome of pain relief at 2 h (Figure 3.9.72). The quality of evidence was considered low.

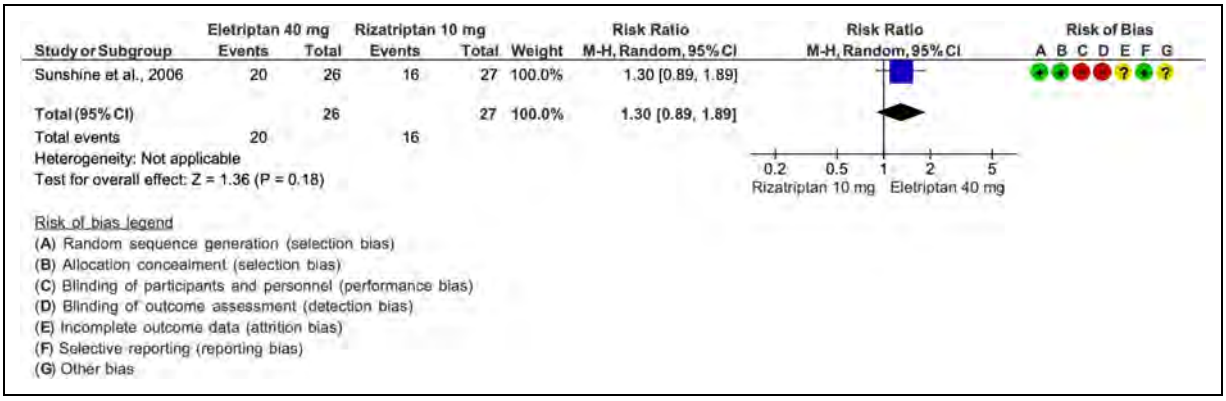


Figure 3.9.24. Forest plot showing the comparison between eletriptan 40 mg and rizatriptan 10 mg for the outcome pain freedom at 2 h in patients with migraine.

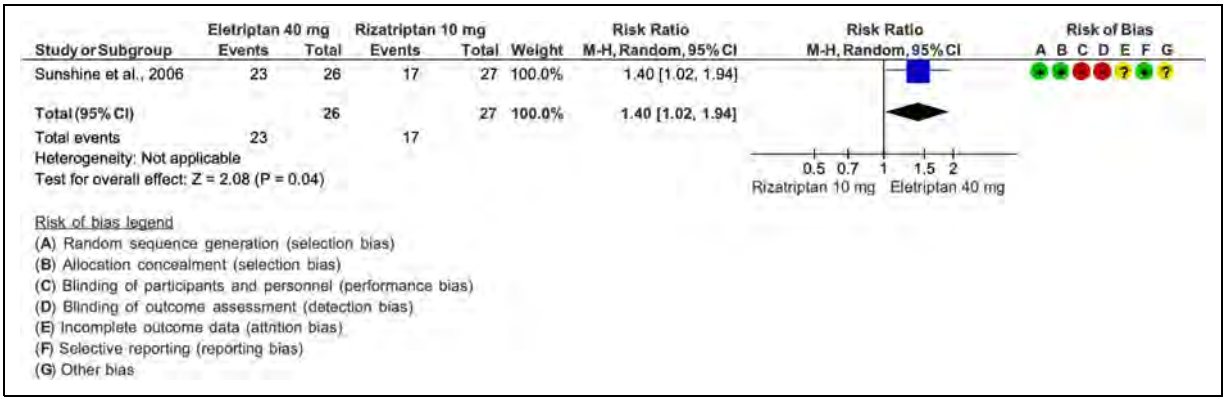


Figure 3.9.25. Forest plot showing the comparison between eletriptan 40 mg and rizatriptan 10 mg for the outcome pain relief at 2 h in patients with migraine.

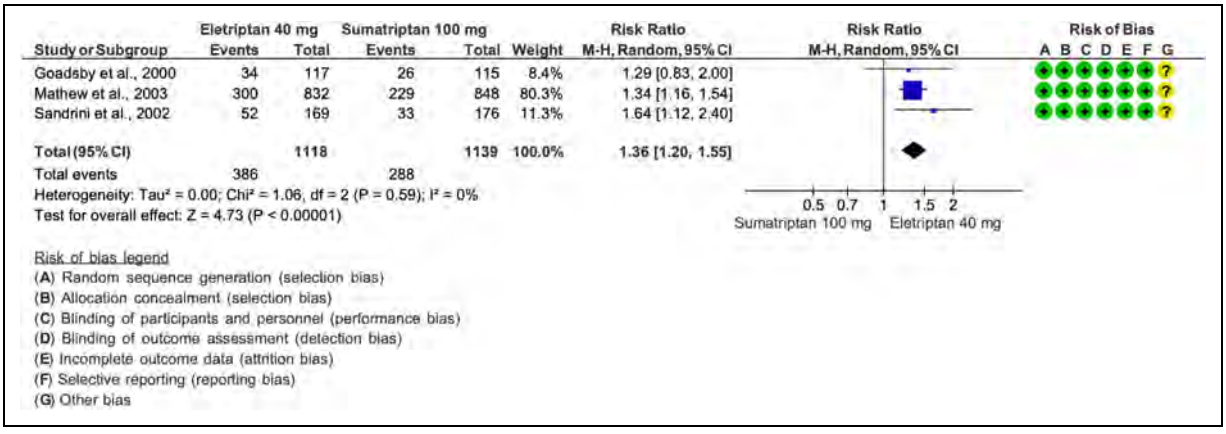


Figure 3.9.26. Forest plot showing the comparison between oral eletriptan 40 mg and oral sumatriptan 100 mg for the outcome pain freedom at 2 h in patients with migraine.

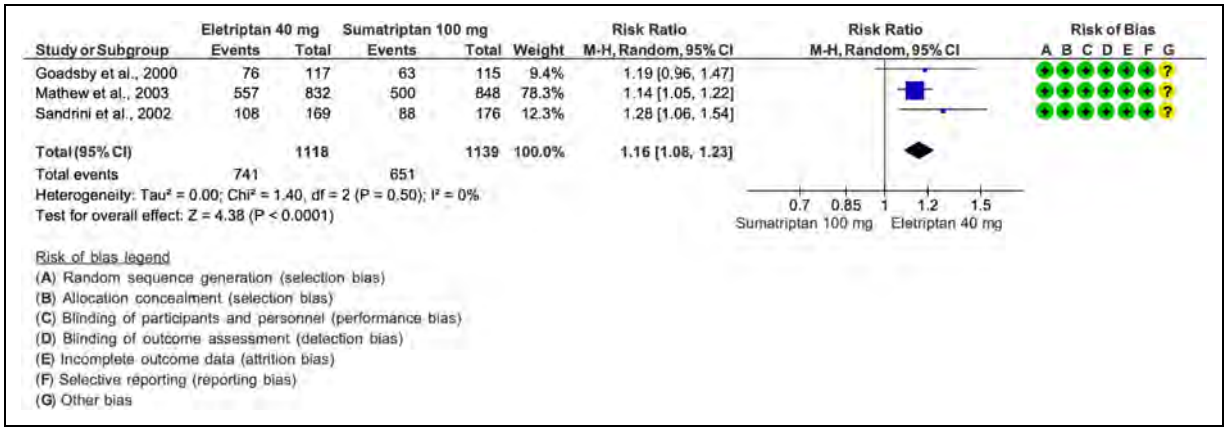


Figure 3.9.27. Forest plot showing the comparison between oral eletriptan 40 mg and oral sumatriptan 100 mg for the outcome pain relief at 2 h in patients with migraine.

Evidence-based recommendation for PICO 3.9.35

In patients with migraine, we suggest isometheptene 65 mg + dichloralphenazone 100 mg + paracetamol 325 mg and sumatriptan 25 mg as equivalent options for the acute treatment of migraine attacks.
Quality of evidence: Low (⊕⊕⊖⊖)
Strength of the recommendation: =

PICO 3.9.36. In patients with migraine, are promethazine + sumatriptan and sumatriptan alone equivalent for the acute treatment of migraine attacks (outcomes: pain freedom at 2 h, pain relief at 2 h)?

Main evidence. We found one RCT comparing oral promethazine 25 mg + sumatriptan 50 mg with oral sumatriptan 50 mg alone (330) that met the criteria for main evidence. The risk of bias was considered low (Figures 3.9.73 and 3.9.74). The RCT showed that oral promethazine 25 mg + sumatriptan 50 mg was superior to oral sumatriptan 50 mg alone considering the outcomes pain freedom at 2 h (Figures 3.9.73) and pain relief at 2 h (Figure 3.9.74). The quality of evidence was considered moderate (Table 3.9.28) due to the availability of only one RCT.

Additional evidence. None.

Evidence-based recommendation for PICO 3.9.36

In patients with migraine, we suggest promethazine 25 mg + sumatriptan 50 mg over sumatriptan 50 mg alone for the acute treatment of migraine attacks.
Quality of evidence: Moderate (⊕⊕⊕⊖)
Strength of the recommendation: Weak (↑)

PICO 3.9.37. In patients with migraine, are sumatriptan + metoclopramide and sumatriptan alone equivalent for the acute treatment of migraine attacks (outcomes: pain freedom at 2 h, pain relief at 2 h)?

Main evidence. None.

Additional evidence. We found one RCT comparing oral metoclopramide 10 mg + sumatriptan 50 mg with oral sumatriptan 50 mg alone (345) that did not meet the criteria for main evidence. The risk of bias was considered unclear (Figure 3.9.75). The RCT showed no difference between oral metoclopramide 10 mg + sumatriptan 50 mg and oral sumatriptan 50 mg alone considering the outcome pain relief at 2 h (Figure 3.9.75). The quality of evidence was considered very low due to the availability of only one RCT with an unclear risk of bias and low numbers of patients (<50 per group).

Evidence-based recommendation for PICO 3.9.37

In patients with migraine, we suggest oral metoclopramide 10 mg + sumatriptan 50 mg and oral sumatriptan 50 mg alone as equivalent options for the acute treatment of migraine attacks.
Quality of evidence: Very low (⊕⊖⊖⊖)
Strength of the recommendation: Weak (=)

PICO 3.9.38. In patients with migraine, are sumatriptan + naproxen and sumatriptan alone equivalent for the acute treatment of migraine attacks (outcomes: pain freedom at 2 h, pain relief at 2 h)?

Main evidence. None.

Table 3.9.11. GRADE evidence profile table for eletriptan 40 mg vs sumatriptan 100 mg in patients with migraine

Certainty assessment							№ of patients		Effect			
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Eletriptan	Sumatriptan	Relative (95% CI)	Absolute (95% CI)	Quality	Importance
Pain freedom at 2 h – Eletriptan 40 mg oral vs Sumatriptan 100 mg oral												
3	RCT	Not serious	Not serious	Not serious	Not serious	None	386/1118 (34.5%)	268/1139 (23.5%)	**RR 1.36** (1.20 to 1.55)	**85 more per 1000** (from 47 more to 129 more)	⊕⊕⊕⊕ High	Critical
Pain relief at 2 h – Eletriptan 40 mg oral vs Sumatriptan 100 mg oral												
3	RCT	Not serious	Not serious	Not serious	Not serious	None	741/1118 (66.3%)	651/1139 (57.2%)	**RR 1.16** (1.08 to 1.23)	**91 more per 1000** (from 46 more to 131 more)	⊕⊕⊕⊕ High	Critical

Additional evidence. We found two RCTs comparing oral sumatriptan (50 mg or 85 mg) + naproxen 500 mg to oral sumatriptan (50 mg or 85 mg) alone (27,41) that did not meet the criteria for main evidence due to the lack of a clear hypothesis of superiority. The risk of bias was considered unclear or high (Figures 3.9.76 and 3.9.77). The RCTs showed that oral sumatriptan (50 mg or 85 mg) + naproxen 500 mg was superior to oral sumatriptan (50 mg or 85 mg) alone considering the outcomes pain freedom at 2 h (Figure 3.9.76) and pain relief at 2 h (Figure 3.9.77). The quality of evidence was considered low.

Evidence-based recommendation for PICO 3.9.38

In patients with migraine, we suggest oral sumatriptan (50 mg or 85) + naproxen 500 mg over oral sumatriptan (50 mg or 85 mg) alone for the acute treatment of migraine attacks.
Quality of evidence: Low (⊕⊕⊖⊖)
Strength of the recommendation: Weak (↑)

PICO 3.9.39. In patients with migraine, are trimebutine + rizatriptan and rizatriptan alone equivalent for the acute treatment of migraine attacks (outcomes: pain freedom at 2 h, pain relief at 2 h)?

Main evidence. None.

Additional evidence. We found one RCT comparing oral trimebutine 200 mg + rizatriptan 10 mg with oral rizatriptan 10 mg alone (338) that did not meet the criteria for main evidence due to the lack of sample size calculation. The risk of bias was considered low (Figure 3.9.78). The RCT showed that oral trimebutine 200 mg + rizatriptan 10 mg was superior to oral rizatriptan 10 mg alone considering the outcome pain freedom at 2 h (Figure 3.9.78). The quality of evidence was considered low.

Evidence-based recommendation for PICO 3.9.39

In patients with migraine, we suggest oral trimebutine 200 mg + rizatriptan 10 mg over oral rizatriptan 10 mg alone for the acute treatment of migraine attacks.
Quality of evidence: Low (⊕⊕⊖⊖)
Strength of the recommendation: Weak (↑)

Comparisons between combination analgesics and paracetamol

PICO 3.9.40. In patients with migraine, are paracetamol + rizatriptan and paracetamol alone equivalent for the acute

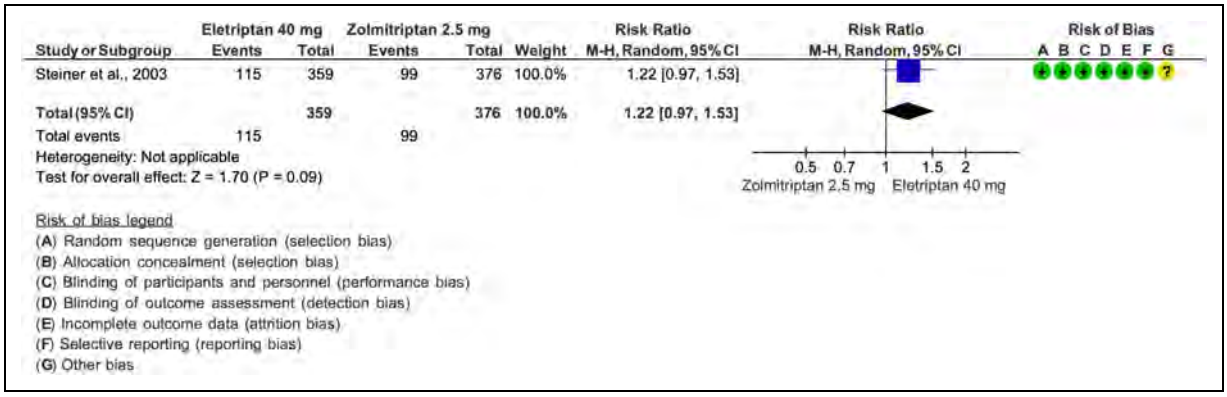


Figure 3.9.28. Forest plot showing the comparison between oral eletriptan 40 mg and oral zolmitriptan 2.5 mg for the outcome pain freedom at 2 h in patients with migraine.

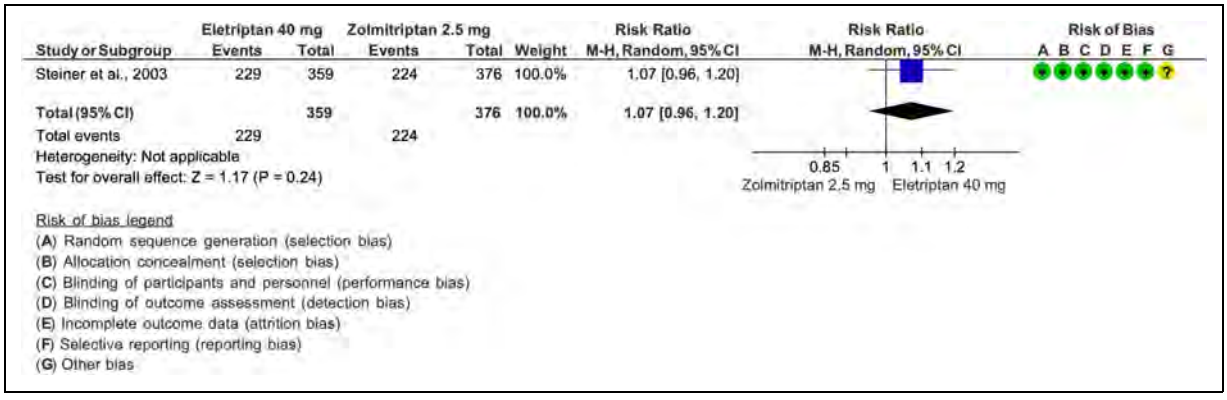


Figure 3.9.29. Forest plot showing the comparison between oral eletriptan 40 mg and oral zolmitriptan 2.5 mg for the outcome pain relief at 2 h in patients with migraine.

treatment of migraine attacks (outcomes: pain freedom at 2 h, pain relief at 2 h)?

Main evidence. None.

Additional evidence. We found one RCT comparing oral rizatriptan 10 mg + paracetamol 1000 mg with oral paracetamol 1000 mg alone (118) that did not meet the criteria for main evidence due to the lack of a sample size calculation. The risk of bias was considered low (Figures 3.9.79 and 3.9.80). The RCT showed that oral paracetamol 1000 mg + rizatriptan 10 mg was superior to oral paracetamol 1000 mg alone considering the outcomes pain freedom at 2 h (Figure 3.9.79) and pain relief at 2 h (Figure 3.9.80). The quality of evidence was considered very low due to the availability of only one RCT with low numbers of patients (<50 per group).

Evidence-based recommendation for PICO 3.9.40

In patients with migraine, we suggest oral paracetamol 1000 mg + rizatriptan 10 mg over oral paracetamol 1000 mg alone for the acute treatment of migraine attacks.
Quality of evidence: Low (⊕⊕⊖⊖)
Strength of the recommendation: Weak (↑)

Comparisons between two combination analgesics

PICO 3.9.41. In patients with migraine, are calcium carbasalate + metoclopramide and ergotamine + caffeine equivalent for the acute treatment of migraine attacks (outcomes: pain freedom at 2 h, pain relief at 2 h)?

Main evidence. We found one RCT comparing oral calcium carbasalate (equivalent to acetylsalicylic acid 900 mg) + metoclopramide 10 mg and oral ergotamine 1 mg + caffeine 100 mg (339) that met the criteria for main evidence. The risk of bias was considered high (Figures 3.9.81 and 3.9.82). The RCT showed that oral calcium carbasalate + metoclopramide 10 mg was superior to oral ergotamine 1

Table 3.9.12. GRADE evidence profile table for oral eletriptan 40 mg vs oral zolmitriptan 2.5 mg in patients with migraine

Certainty assessment							№ of patients		Effect			
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Eletriptan	Zolmitriptan	Relative (95% CI)	Absolute (95% CI)	Quality	Importance
Pain freedom at 2 h – Eletriptan 40 mg oral vs Zolmitriptan 2.5 mg oral												
1	RCT	Not serious	Not applicable[a]	Not serious	Not serious	None	115/359 (32.0%)	99/376 (26.3%)	**RR 1.22** (0.97 to 1.53)	**58 more per 1000** (from 8 less to 140 more)	⊕⊕⊕⊖ Moderate	Critical
Pain relief at 2 h – Eletriptan 40 mg oral vs Zolmitriptan 2.5 mg oral												
1	RCT	Not serious	Not applicable[a]	Not serious	Not serious	None	229/359 (63.8%)	224/376 (59.6%)	**RR 1.07** (0.96 to 1.20)	**42 more per 1000** (from 24 less to 119 more)	⊕⊕⊕⊖ Moderate	Critical

[a]Only one trial.

mg + caffeine 100 mg considering the outcomes pain freedom at 2 h (Figure 3.9.81) and pain relief at 2 h (Figure 3.9.82). The quality of evidence was considered very low (Table 3.9.29) due to the availability of only one RCT with a high risk of bias.

Additional evidence. None.

Evidence-based recommendation for PICO 3.9.41

In patients with migraine, we suggest oral calcium carbasalate 900 mg + metoclopramide 10 mg over oral ergotamine 1 mg + caffeine 100 mg for the acute treatment of migraine attacks.
Quality of evidence: Very low (⊕⊖⊖⊖)
Strength of the recommendation: Weak (↑)

PICO 3.9.42. In patients with migraine, are sumatriptan + naproxen and paracetamol + butalbital + caffeine equivalent for the acute treatment of migraine attacks (outcomes: pain freedom at 2 h, pain relief at 2 h)?

Main evidence. We found one RCT comparing oral sumatriptan 85 mg + naproxen 500 mg with oral paracetamol 325 mg + butalbital 50 mg + caffeine 40 mg (332) that met the criteria for main evidence. The risk of bias was considered low (Figure 3.9.83). The RCT showed no difference between oral sumatriptan 85 mg + naproxen 500 mg and oral paracetamol 325 mg + butalbital 50 mg + caffeine 40 mg considering the outcome of pain freedom at 2 h (Figure 3.9.83). The quality of evidence was considered moderate (Table 3.9.30) due to the availability of only one RCT.

Additional evidence. None.

Evidence-based recommendation for PICO 3.9.42

In patients with migraine, we suggest oral sumatriptan 85 mg + naproxen 500 mg and oral paracetamol 325 mg + butalbital 50 mg + caffeine 40 mg as equivalent options for the acute treatment of migraine attacks.
Quality of evidence: Moderate (⊕⊕⊕⊖)
Strength of the recommendation: =

Comparisons between combination analgesics and other analgesics

PICO 3.9.43. In patients with migraine, are oral acetylsalicylic acid + butalbital + codeine + caffeine and butorphanol nasal spray equivalent for the acute treatment of migraine attacks (outcomes: pain freedom at 2 h, pain relief at 2 h)?

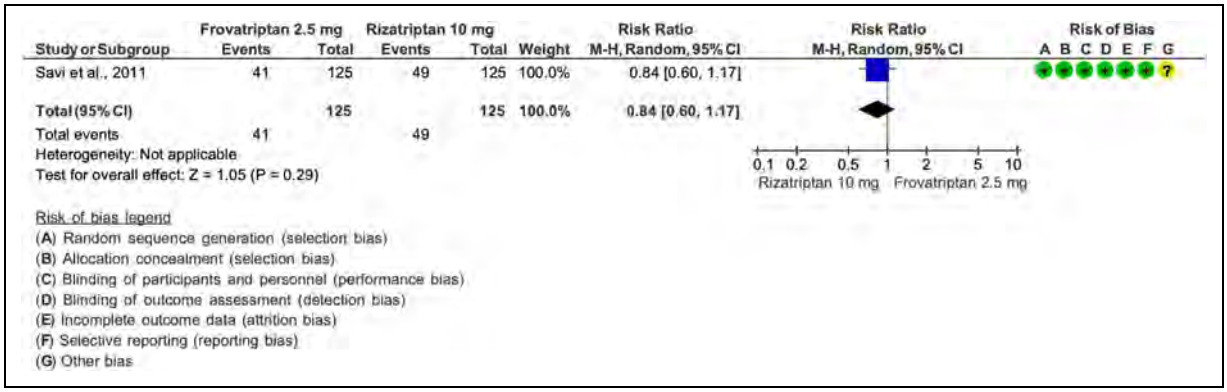


Figure 3.9.30. Forest plot showing the comparison between oral frovatriptan 2.5 mg and oral rizatriptan 10 mg for the outcome pain freedom at 2 h in patients with migraine.

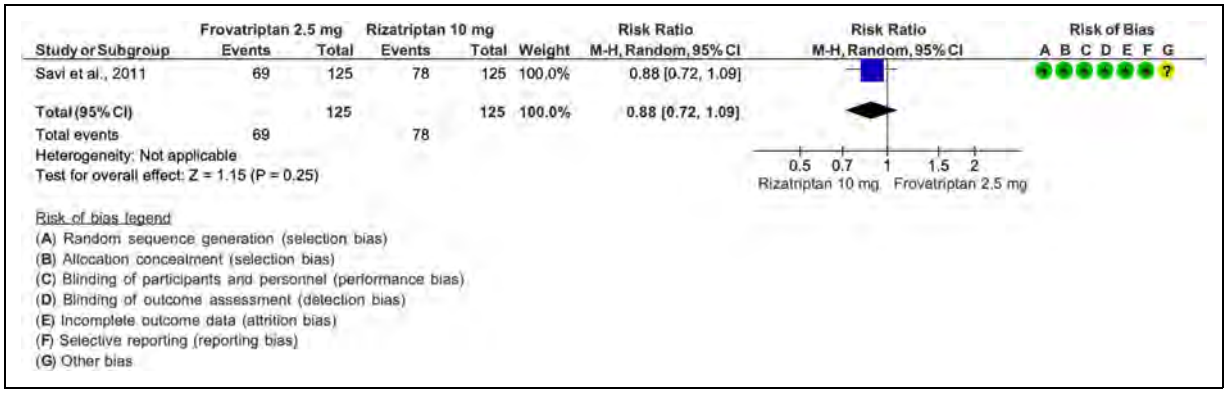


Figure 3.9.31. Forest plot showing the comparison between oral frovatriptan 2.5 and oral rizatriptan 10 mg for the outcome pain relief at 2 h in patients with migraine.

Main evidence. We found one RCT comparing oral acetylsalicylic acid 325 mg + butalbital 50 mg + codeine 30 mg + caffeine 40 mg with butorphanol 2 mg nasal spray (337) that met the criteria for main evidence due to the lack of a sample size calculation. The risk of bias was low (Figure 3.9.84). The RCT showed no difference between oral acetylsalicylic acid 325 mg + butalbital 50 mg + codeine 30 mg + caffeine 40 mg and butorphanol 2 mg nasal spray considering the outcome of pain relief at 2 h (Figure 3.9.84). The quality of evidence was considered moderate (Table 3.9.31) due to the availability of only one RCT.

Additional evidence. None.

Evidence-based recommendation for PICO 3.9.43

In patients with migraine, efficacy data suggest the superiority of butorphanol 2 mg nasal spray over oral acetylsalicylic acid 325 mg + butalbital 50 mg + codeine 30 mg + caffeine 40 mg.

Quality of evidence: Moderate (⊕⊕⊕⊖)
Strength of the recommendation: Weak (↑)
[NOTE: This recommendation is based on comparative efficacy data. However, given the safety risks of opioids and of barbiturates, the Guidelines Committee suggests caution in the use of both drugs.]

Summary of evidence for head-to-head comparisons of acute treatments for migraine

Figure 3.9.85 shows the summary of evidence for head-to-head comparisons of acute treatments for migraine attacks.

Expert-based opinion

Oral combination of paracetamol + acetylsalicylic acid + caffeine

Topic: Is the oral combination of paracetamol + acetylsalicylic acid + caffeine superior to each of the drugs alone for the

Table 3.9.13. GRADE evidence profile table for frovatriptan 2.5 mg vs rizatriptan 10 mg in patients with migraine

Certainty assessment							№ of patients		Effect			
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Frovatriptan	Rizatriptan	Relative (95% CI)	Absolute (95% CI)	Quality	Importance
Pain freedom at 2 h – Frovatriptan 2.5 mg oral vs Rizatriptan 10 mg oral												
1	RCT	Not serious	Not applicable[a]	Not serious	Not serious	None	41/125 (32.8%)	49/125 (39.2%)	**RR 0.84** (0.60 to 1.17)	**63 less per 1000** (from 157 less to 67 more)	⊕⊕⊕⊖ Moderate	Critical
Pain relief at 2 h – Frovatriptan 2.5 mg oral vs Rizatriptan 10 mg oral												
1	RCT	Not serious	Not applicable[a]	Not serious	Not serious	None	69/125 (55.2%)	78/125 (62.4%)	**RR 0.88** (0.72 to 1.09)	**75 less per 1000** (from 175 less to 56 more)	⊕⊕⊕⊖ Moderate	Critical

[a]Only one trial.

acute treatment of migraine attacks?. Suggestion: The oral combination of paracetamol 200 mg + acetylsalicylic acid 250 mg + caffeine 50 mg might be superior to each of the drugs alone for the acute treatment of migraine attacks.

Rationale: We found one RCT comparing acetylsalicylic acid 250 mg + paracetamol 200 mg + caffeine 50 mg with acetylsalicylate 500 mg (560) that did not meet the criteria to be included in the recommendations as it did not measure the outcomes of interest. The RCT showed that the combination of acetylsalicylic acid 250 mg + paracetamol 200 mg + caffeine 50 mg was superior to acetylsalicylic acid 500 mg considering the outcomes time to pain relief ($p = 0.0398$), time needed to reduce pain intensity to 10 mm ($p = 0.0002$), and pain intensity difference at 2 h (44.7 mm vs 40.7 mm; $p = 0.0228$). It also showed the superiority of the combination over paracetamol 200 mg alone (pain intensity difference at 2 h 44.7 mm vs 39.5 mm, $p = 0.0032$), paracetamol 200 mg + acetylsalicylic acid 250 mg (44.7 mm vs 40.2 mm, $p = 0.0019$), and caffeine alone (44.7 mm vs 31.4 mm, $p < 0.0001$). Pain intensity was expressed in mm as it was reported on a 100-mm Visual Analogue Scale.

We found one RCT comparing paracetamol 500 mg + acetylsalicylic acid 500 mg + caffeine 130 mg with ibuprofen 200 mg (350). The RCT did not meet the criteria for main evidence as it did not assess the outcomes of interest for the evidence-based guideline. In the RCT, oral paracetamol 500 mg + acetylsalicylic acid 500 mg + caffeine 130 mg showed a higher weighted sum of pain relief scores than oral ibuprofen 200 mg ($p = 0.03$) and an onset of pain relief 20 min earlier ($p = 0.036$).

Choice of acute treatments for migraine

Topic: Are there differences among NSAIDs used for the acute treatment of migraine attacks?. Suggestion: There are no clear differences among NSAIDs used for the acute treatment of migraine attacks.

Rationale: There are few head-to-head RCTs comparing NSAIDs, and either ibuprofen or acetylsalicylic acid showed similar efficacy. Therefore, there is no clear preference of NSAIDs that can be advised in clinical practice. Individual efficacy and safety profiles should be carefully monitored in headache centers.

Topic: Which class of acute medications should be advised as a first approach in patients with migraine?. Suggestion: Based upon efficacy data, triptans should be considered as a first choice for the acute treatment of migraine; the potential risk for overuse should be monitored.

Rationale: Head-to-head RCTs showed that rizatriptan was superior to ibuprofen and sumatriptan was superior to naproxen, while other comparisons between triptans and NSAIDs were neutral. However, none of the comparisons

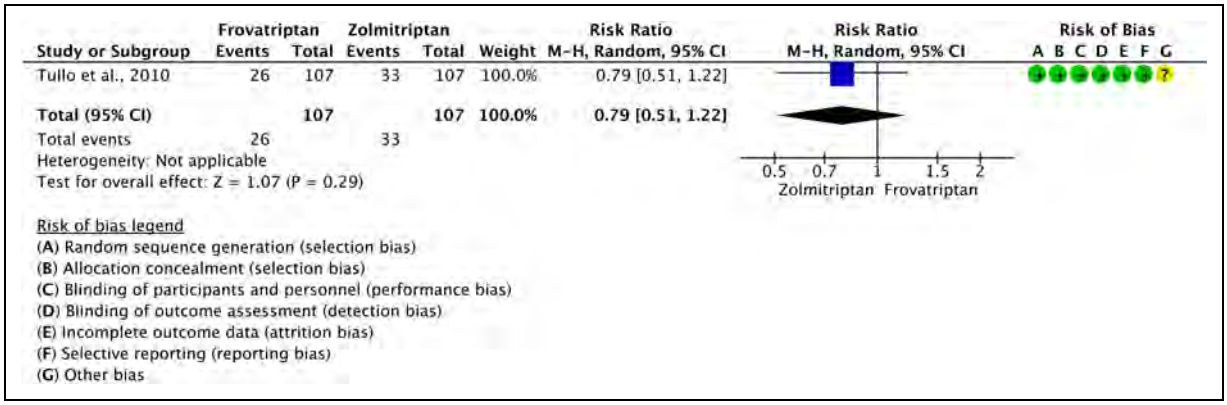


Figure 3.9.32. Forest plot showing the comparison between oral frovatriptan 2.5 mg and oral zolmitriptan 2.5 mg for the outcome pain freedom at 2 h in patients with migraine.

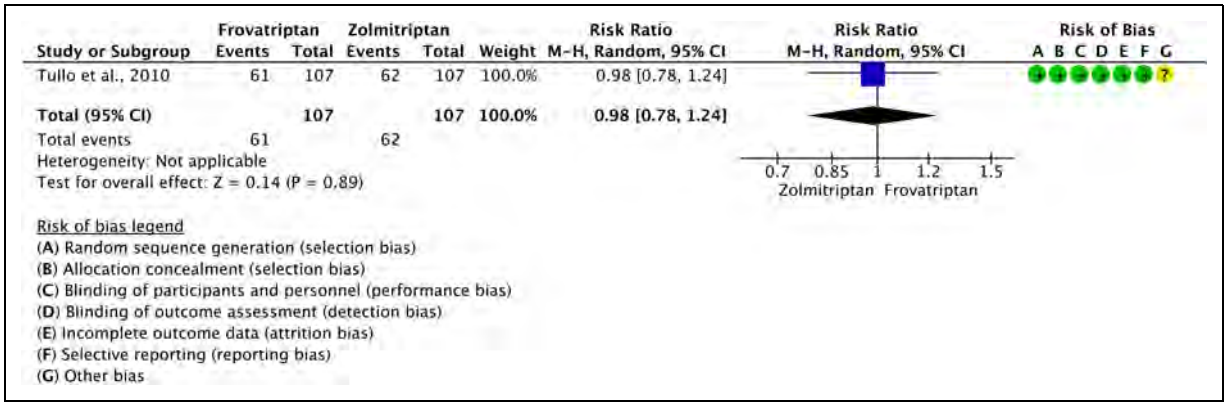


Figure 3.9.33. Forest plot showing the comparison between oral frovatriptan 2.5 mg and oral zolmitriptan 2.5 mg for the outcome pain relief at 2 h in patients with migraine.

showed a superiority of a NSAID alone over a triptan alone. Therefore, we can conclude that triptans should be preferred over other analgesics, unless their use is contraindicated or they are poorly tolerated. This suggestion can be applied to patients with a relatively low consumption of acute medication. In patients with high risk for medication overuse, triptans should not be considered as a first choice over NSAIDs due to their high risk for overuse (see Section 3.2).

Topic: Should different acute medications be used in the same patient for the acute treatment of migraine attacks?. Suggestion: The same patients with migraine can be treated with a more potent medication – such as a triptan – for moderate-to-severe attacks and with a less potent but safer medication – such as a NSAID – for mild attacks.

Rationale: Triptans generally showed a higher efficacy than other acute migraine medication in head-to-head comparisons; however, they present a high risk for medication overuse (see Section 3.2). To reduce the risk for triptan overuse, other analgesics can be advised in the same patient to be used as rescue medications or as first choice in mild attacks.

Topic: In patients with poor response to a triptan, is switching to a combination analgesic containing a triptan an effective option?. Suggestion: A combination between a triptan and a NSAID can be considered in patients with poor response to a triptan alone. The risk for medication overuse should be closely monitored.

Rationale: Combinations between a triptan and a NSAID – such as sumatriptan + naproxen or frovatriptan + dexketoprofen – proved more effective than their individual components taken alone. For this reason, those combinations can be advised in patients with migraine attacks that are resistant to triptans alone. However, combination analgesics have a very high risk for medication overuse (see Section

Table 3.9.14. GRADE evidence profile table for frovatriptan 2.5 mg vs zolmitriptan 2.5 mg in patients with migraine

Certainty assessment							№ of patients		Effect			
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Frovatriptan	Zolmitriptan	Relative (95% CI)	Absolute (95% CI)	Quality	Importance
Pain freedom at 2 h – Frovatriptan 2.5 mg oral vs zolmitriptan 2.5 mg oral												
1	RCT	Not serious	Not applicable[a]	Not serious	Not serious	None	26/107 (24.3%)	33/107 (30.8%)	**RR 0.79** (0.51 to 1.22)	**65 less per 1000** (from 151 less to 68 more)	⊕⊕⊕⊖ Moderate	Critical
Pain relief at 2 h – Frovatriptan 2.5 mg oral vs zolmitriptan 2.5 mg oral												
1	RCT	Not serious	Not applicable[a]	Not serious	Not serious	None	61/107 (57.0%)	62/107 (57.9%)	**RR 0.98** (0.78 to 1.24)	**12 less per 1000** (from 127 less to 139 more)	⊕⊕⊕⊖ Moderate	Critical

[a]Only one trial.

3.4) which should be closely monitored. Besides, the use of different substances might be associated with an increased risk for adverse events.

Topic: In patients with poor response to a triptan, is switching to a combination analgesic not containing a triptan an effective option?. Suggestion: There is no efficacy rationale for switching from a triptan to a combination analgesic not containing a triptan. Safety considerations can be applied to choose a combination not containing a triptan over a triptan.

Rationale: The only combination analgesic not containing a triptan that showed superiority over a triptan (sumatriptan) is paracetamol + acetylsalicylic acid + caffeine, which could be associated with adverse events given the combination of different analgesics. Therefore, the preference of a combination analgesics not containing a triptan over triptans should be reserved to patients who have contraindication or poorly tolerate triptans.

4. Preventive treatment

4.1 Antidepressants

Introduction. Since the 1970s, antidepressants have been widely prescribed for migraine prevention, and still represent one of the most frequently used drug classes (561). Antidepressants share a complex mechanism of action, primarily involving the serotoninergic and noradrenergic pathways (562), and modulate the descending pain control system irrespective of their antidepressant effect (563).

A possible role in migraine prevention was first based on serendipity, considering their positive effects for treating several forms of chronic pain.

Tricyclics have been available since the 1950s and share a common three-ringed chemical structure associated with a secondary or tertiary amine. Their main mechanism of action involves the reuptake inhibition of serotonin and norepinephrine in the presynaptic terminals. They also act in the postsynaptic terminals as competitive antagonists of histaminergic, muscarinic cholinergic and adrenergic receptors (564). Reflecting their multifaceted actions, their clinical role in migraine prevention is probably linked to synergistic effects more than to a key single action (565).

Selective serotonin reuptake inhibitors (SSRIs) and serotonin-norepinephrine reuptake inhibitors (SNRIs) have been available since the 1980s and have a more defined mechanism of action.

SSRIs inhibit the presynaptic serotonin transporter with different degrees of specificity and probably determine up and/or downregulation of serotonin transporters in different brain areas (566).

SNRIs exert a dual action inhibiting reuptake of both serotonin and norepinephrine, leading to an increased availability in the synaptic cleft (567). They consist of a group of different structurally unrelated molecules with a similar mechanism of action and slight differences

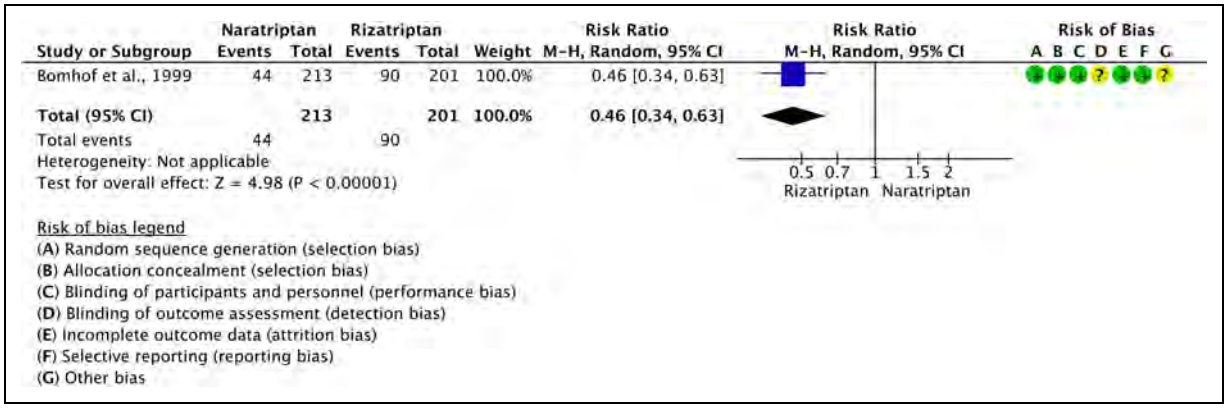


Figure 3.9.34. Forest plot showing the comparison between oral naratriptan 2.5 mg and oral rizatriptan 10 mg for the outcome pain freedom at 2 h in patients with migraine.

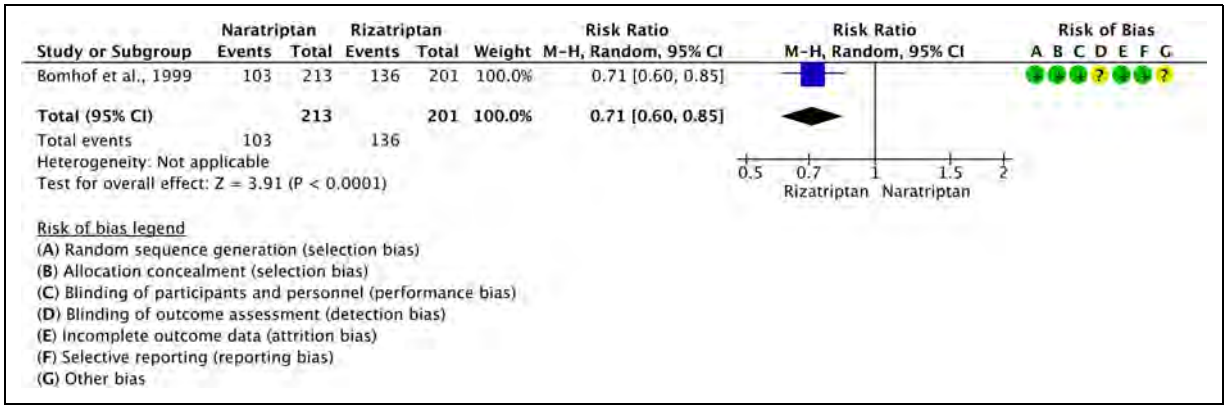


Figure 3.9.35. Forest plot showing the comparison between oral naratriptan 2.5 mg and oral rizatriptan 10 mg for the outcome pain relief at 2 h in patients with migraine.

in pharmacodynamic and pharmacokinetic properties (568).

Previous pre-clinical and clinical evidence supported the hypothesis of a complex monoamine neurotransmitters' interplay in migraine pathophysiology (562).

The serotoninergic system involves several areas strictly related to migraine pathophysiology such as the raphe nuclei, the trigeminal nucleus caudalis, the thalamus, and the sensory cortex (569).

The same is true for the noradrenergic system, predominantly originating from the locus coeruleus in the dorsal rostral pons. It modulates different networks with both descending (as main source of noradrenergic innervation to the spinal dorsal horn, regulating nociception) and ascending projections (regulating nociception, stress response, arousal, and cognition) (570).

Serotonin fluctuates across the migraine cycle, leading to the hypothesis of an interictal low serotonin availability. Low plasma serotonin levels were described between attacks with a plasma peak during the ictal phase (571,572). In the ictal phase, an increased urinary excretion of 5-hydroxyindoleacetic acid (5-HIAA), the main serotonin metabolite, was also detected (573). The 5-HIAA metabolite was found to be increased in the cerebrospinal fluid of migraine patients, too (572).

Low monoaminergic brainstem activity was considered one of the pivotal mechanisms involved in the migraine-related phenomenon of lack of habituation (574). Noteworthy, habituation normalizes during attacks (575) and after administration of 5-HT reuptake inhibitors (576).

Finally, the role of serotonin is supported by the efficacy of acute and preventive drugs specifically acting on the serotoninergic system, namely triptans (5-HT1B/1D receptor agonists), ditans (5-HT1F agonists) and pizotifen (5-HT2A/2C antagonist), respectively.

The noradrenergic system showed an important repercussion on pain regulation and migraine, as well. Indeed, the antinociceptive actions of antidepressants are suppressed by the blockade of alpha-2 adrenoreceptor in animal models (577). In addition, detection of cerebral hypoperfusion after locus coeruleus stimulation in animal models could be a possible link to cortical spreading depression (578).

Table 3.9.15. GRADE evidence profile table for oral naratriptan 2.5 mg vs oral rizatriptan 10 mg in patients with migraine

Certainty assessment							№ of patients		Effect			
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Naratriptan	Rizatriptan	Relative (95% CI)	Absolute (95% CI)	Quality	Importance
Pain freedom at 2 h – Naratriptan 2.5 mg oral vs Rizatriptan 10 mg oral												
1	RCT	Not serious	Not applicable[a]	Not serious	Not serious	None	44/213 (20.7%)	90/201 (44.8%)	**RR 0.46** (0.34 to 0.63)	**242 less per 1000** (from 296 less to 166 less)	⊕⊕⊖⊖ Moderate	Critical
Pain relief at 2 h – Naratriptan 2.5 mg oral vs Rizatriptan 10 mg oral												
1	RCT	Not serious	Not applicable[a]	Not serious	Not serious	None	103/213 (48.4%)	136/201 (68.7%)	**RR 0.71** (0.60 to 0.85)	**196 less per 1000** (from 271 less to 101 less)	⊕⊕⊖⊖ Moderate	Critical

[a]Only one trial.

A role for serotonergic and noradrenergic pathways during the migraine cycle is also confirmed by neuroimaging evidence: the raphe nuclei was activated during spontaneous attacks and an altered connectivity in the dorsal rostral pons was recorded during pre-ictal and ictal phases (579–581).

Section-specific methods. This section followed the general procedure to develop this guideline.

Search strings for the guideline on antidepressants for systematic review/meta-analysis and for additional RCTs are reported in Online Appendix 4.1.1.

Results. Overall, we retrieved 3416 references from searching for systematic reviews and meta-analyses. After duplicate removal and screening stages, we included seven systematic reviews and meta-analyses (561,582–587) that were considered as sources of RCTs. After analyzing full texts of these RCTs, we included eight of them in the quantitative synthesis (588–595) and four of them in the narrative synthesis (596–599) (Figure 4.1.1).

Overall, we retrieved 2691 references from searching for RCTs and after removing duplicates we had 2550 references to analyze. However, considering the most recent included systematic review/meta-analysis on the topic, the analysis of additional RCTs was performed for papers published since 2016 for tricyclic antidepressants and since 2018 for SSRI/SNRI (1075 references). We finally included two additional RCTs (600,601) (Figure 4.1.2).

Overall, 14 RCTs (588–601) were included in the literature synthesis to develop the evidence-based guideline. Among these, 10 were included in quantitative synthesis (meta-analysis) and four in qualitative synthesis. Six RCTs (592–595,597,598) reported a comparison between an active drug and placebo and were presented in this section. Nine RCTs reported head-to-head comparisons that were included in Section 4.8.

Amitriptyline

PICO 4.1.1. In patients with any migraine (no distinction between episodic and chronic), is amitriptyline superior to placebo for migraine prevention (outcome: persisting monthly migraine days, change in monthly migraine days, $\geq 50\%$ response rate)?

Main evidence. None.

Additional evidence. We found two RCTs (592,593) comparing oral amitriptyline to placebo in subjects with migraine. These trials did not meet the criteria to be included in the main evidence. The RCTs did not show benefits for migraine prevention from oral amitriptyline administered with a gradual titration up to 100 mg daily. Overall, the risk of bias of included studies was high (Figure 4.1.3) and the quality of evidence was downgraded to very low.

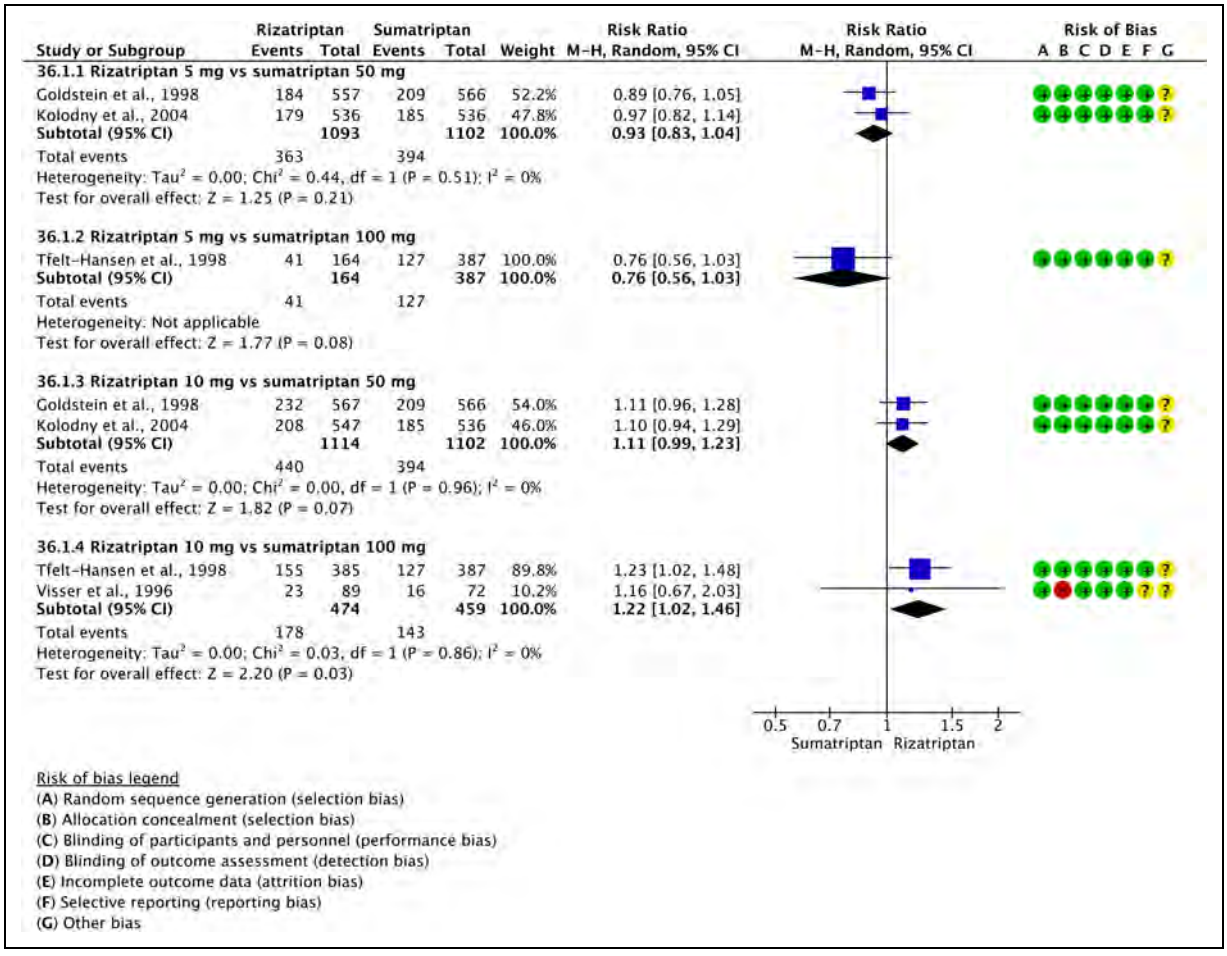


Figure 3.9.36. Forest plot showing the comparison between oral rizatriptan (5 or 10 mg) and oral sumatriptan (50 or 100 mg) for the outcome pain freedom at 2 h in patients with migraine.

Evidence-based recommendation for PICO 4.1.1

In subjects with migraine (no distinction between episodic and chronic), we suggest against oral amitriptyline 25–100 mg daily for migraine prevention.
Quality of evidence: Very low (⊕⊖⊖⊖)
Strength of the recommendation: Weak (↓)

PICO 4.1.2. In subjects with episodic migraine, is amitriptyline superior to placebo for migraine prevention (outcome: persisting monthly migraine days, change in monthly migraine days, ≥ 50% response rate)?

Main evidence. We found one RCT comparing oral amitriptyline 25 mg daily to placebo (595) in subjects with episodic migraine that met the criteria to be included in the main evidence.

This single study showed a significant improvement considering the outcome persisting monthly migraine days in patients treated with oral amitriptyline; no other outcomes were available. The study had a low risk of bias (Figure 4.1.4). The quality of evidence was considered moderate (Table 4.1.1).

Additional evidence. None.

Evidence-based recommendation for PICO 4.1.2

In subjects with episodic migraine, we suggest oral amitriptyline 25 mg daily for migraine prevention.
Quality of evidence: Moderate (⊕⊕⊕⊖)
Strength of recommendation: Weak (↑)
[NOTE. The present recommendation, together with that of PICO 1, points out that amitriptyline is superior to placebo in subjects with episodic migraine, while its superiority to placebo is uncertain in subjects with chronic migraine.]

Safety and tolerability of amitriptyline. Warnings and contraindications: Amitriptyline is contraindicated in subjects

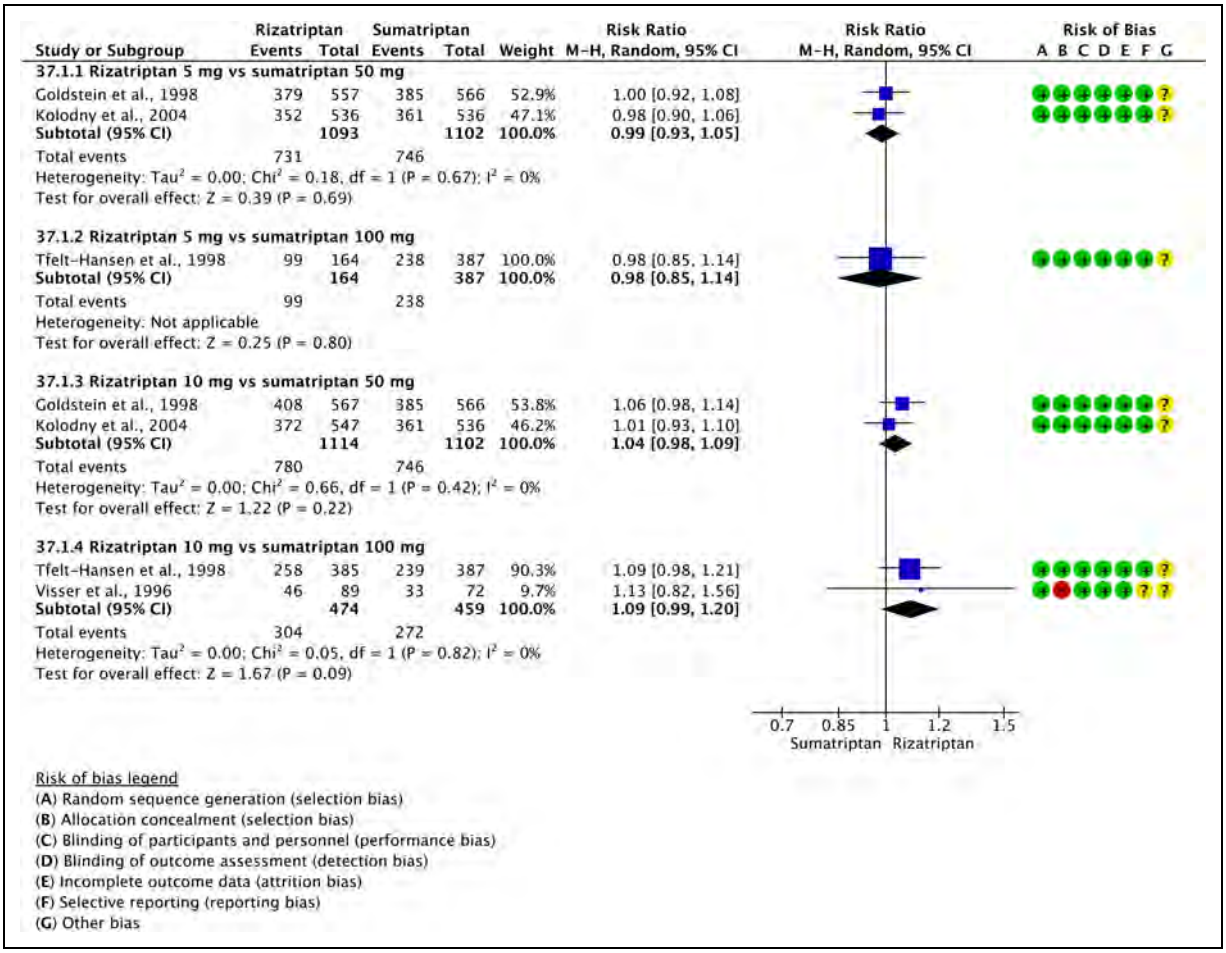


Figure 3.9.37. Forest plot showing the comparison between oral rizatriptan (5 or 10 mg) and oral sumatriptan (50 or 100 mg) for the outcome pain relief at 2 h in patients with migraine.

with severe liver injury for its hepatic metabolism. Due to the risk of arrhythmias, it should not be used in recent myocardial infarction, coronary artery disease, congestive heart failure and heart block to any degree. Concomitant use of amitriptyline and monoamine oxidase inhibitors (MAOI) should be avoided for the risk of serotonergic syndrome (602).

Its use should be avoided in pregnant and breastfeeding women, as these populations are not included in RCTs. Moreover, clinical data indicate that amitriptyline could cross the placenta and can be excreted in the milk with higher risk of congenital malformations (especially in the first trimester), lethargy and withdrawal symptoms (in the third trimester and during lactation) (603,604). Preventive therapies during pregnancy and breastfeeding should be limited to special situations. In cases of strong indication to continue its use during pregnancy, a careful evaluation of the risk/benefit ratio is mandatory to decide whether to continue or interrupt treatment. In case of its continuation during pregnancy, amitriptyline should be interrupted at least seven days before delivery for the above-mentioned risk of withdrawal symptoms (15). Extreme caution should be used in patients with a history of seizures because amitriptyline lowers the seizure threshold. Considering the risk of QT interval at electrocardiography prolongation and arrhythmias, attention is needed in subjects with long QT interval, arrhythmias and uncontrolled hypertension.

Serious safety concerns: RCTs and real world-evidence highlighted some serious safety concerns. Real-world evidence demonstrated potential hypomanic reactions and increased suicidal attempts (both ideation and behavior) in depressed subjects aged under 24 years (605–610). Due to its prominent anticholinergic effects, amitriptyline use was associated with angle-closure glaucoma for increased intraocular pressure in predisposed subjects, worsening of symptoms associated with prostatic benign hypertrophy and paralytic ileus. Caution is necessary in older subjects that could be more sensitive to anticholinergic, cardiovascular and hypotensive effects. Moreover, some reported cases of hyponatremia in this population were described.

Table 3.9.16. GRADE evidence profile table for rizatriptan (5 or 10 mg) versus sumatriptan (50 or 100 mg) in patients with migraine

Certainty assessment							№ of patients		Effect			
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Rizatriptan	Sumatriptan	Relative (95% CI)	Absolute (95% CI)	Quality	Importance
Pain freedom at 2 h – Rizatriptan 5 mg oral vs sumatriptan 50 mg oral												
2	RCT	Not serious	Not serious	Not serious	Not serious	None	363/1093 (33.2%)	394/1102 (35.8%)	**RR 0.93** (0.83 to 1.04)	**25 less per 1000** (from 61 less to 14 more)	⊕⊕⊕⊕ High	Critical
Pain relief at 2 h – Rizatriptan 5 mg oral vs sumatriptan 50 mg oral												
2	RCT	Not serious	Not serious	Not serious	Not serious	None	731/1093 (66.9%)	746/1102 (67.7%)	**RR 0.99** (0.93 to 1.05)	**7 less per 1000** (from 47 less to 34 more)	⊕⊕⊕⊕ High	Critical
Pain freedom at 2 h – Rizatriptan 5 mg oral vs sumatriptan 100 mg oral												
1	RCT	Not serious	Not applicable[a]	Not serious	Not serious	None	41/164 (25.0%)	127/387 (32.8%)	**RR 0.76** (0.56 to 1.03)	**79 less per 1000** (from 144 less to 10 more)	⊕⊕⊕⊖ Moderate	Critical
Pain relief at 2 h – Rizatriptan 5 mg oral vs sumatriptan 100 mg oral												
1	RCT	Not serious	Not applicable[a]	Not serious	Not serious	None	99/164 (60.4%)	238/387 (61.5%)	**RR 0.98** (0.85 to 1.14)	**12 less per 1000** (from 92 less to 86 more)	⊕⊕⊕⊖ Moderate	Critical
Pain freedom at 2 h – Rizatriptan 10 mg oral vs sumatriptan 50 mg oral												
2	RCT	Not serious	Not serious	Not serious	Not serious	None	440/1114 (39.5%)	394/1102 (35.8%)	**RR 1.11** (0.99 to 1.23)	**39 more per 1000** (from 4 less to 82 more)	⊕⊕⊕⊕ High	Critical
Pain relief at 2 h – Rizatriptan 10 mg oral vs sumatriptan 50 mg oral												
2	RCT	Not serious	Not serious	Not serious	Not serious	None	780/1114 (70.0%)	746/1102 (67.7%)	**RR 1.04** (0.98 to 1.09)	**27 more per 1000** (from 14 less to 61 more)	⊕⊕⊕⊕ High	Critical
Pain freedom at 2 h – Rizatriptan 10 mg oral vs sumatriptan 100 mg oral												
2	RCT	Not serious	Not serious	Not serious	Not serious	None	178/474 (37.6%)	143/459 (31.2%)	**RR 1.22** (1.02 to 1.46)	**69 more per 1000** (from 6 more to 143 more)	⊕⊕⊕⊕ High	Critical
Pain relief at 2 h – Rizatriptan 10 mg oral vs sumatriptan 100 mg oral												
2	RCT	Not serious	Not serious	Not serious	Not serious	None	304/474 (64.1%)	272/459 (59.3%)	**RR 1.09** (0.99 to 1.20)	**53 more per 1000** (from 6 less to 119 more)	⊕⊕⊕⊕ High	Critical

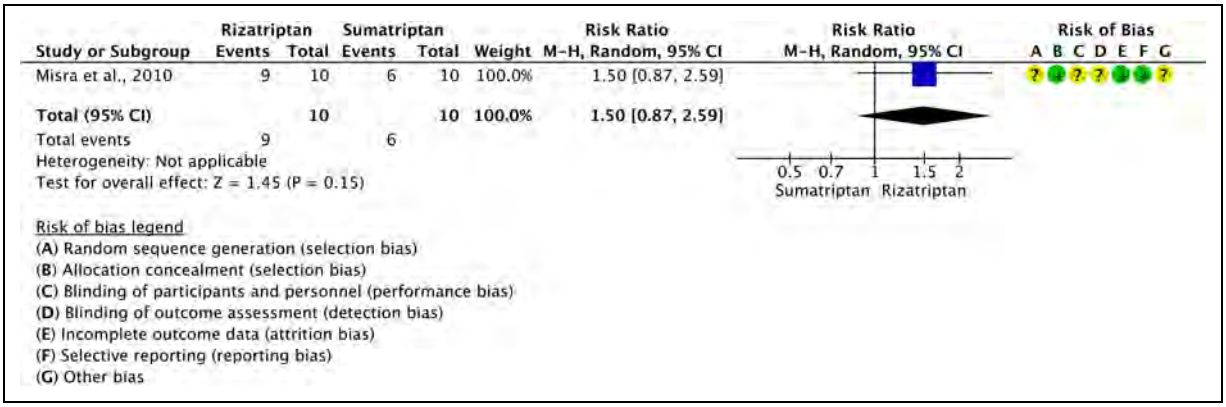


Figure 3.9.38. Forest plot showing the comparison between oral rizatriptan (5 or 10 mg) and oral sumatriptan (50 or 100 mg) for the outcome pain relief at 2 h in patients with migraine.

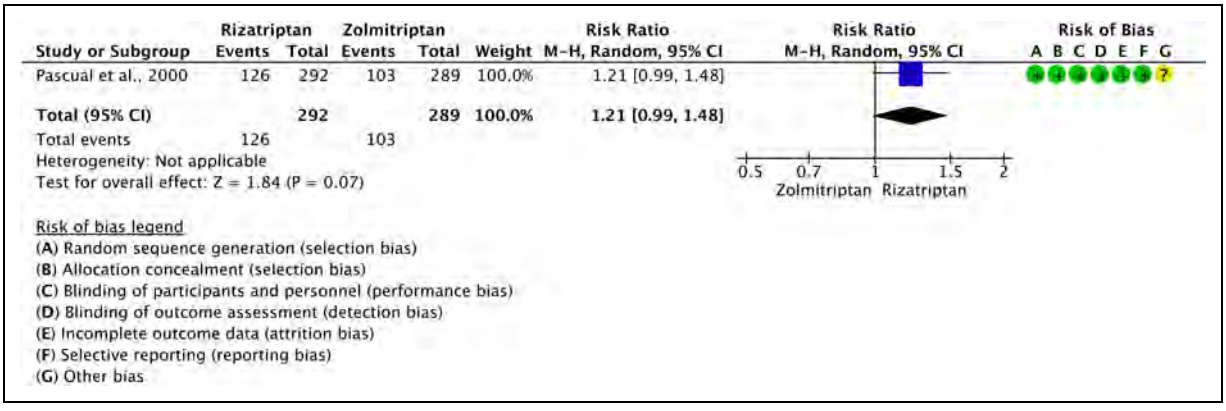


Figure 3.9.39. Forest plot showing the comparison between oral rizatriptan 10 mg and oral zolmitriptan 2.5 mg for the outcome pain freedom at 2 h in patients with migraine.

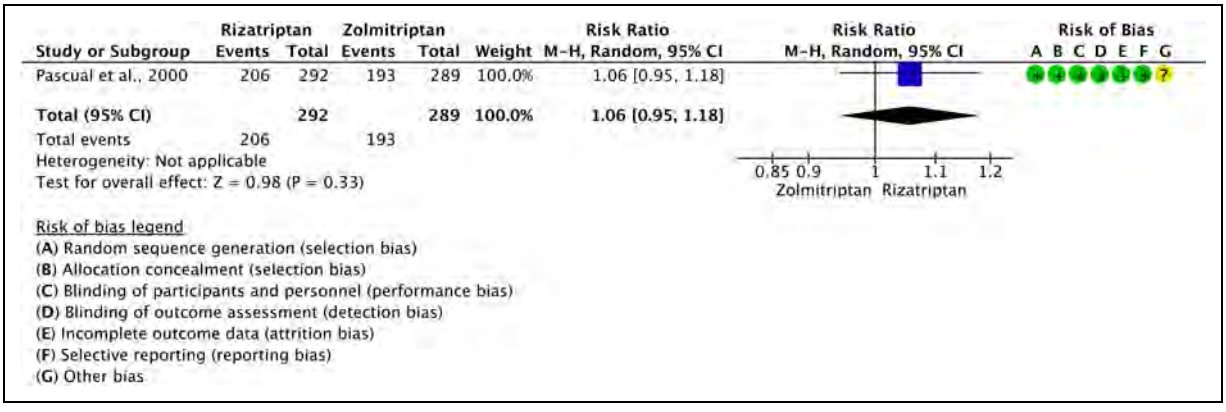


Figure 3.9.40. Forest plot showing the comparison between oral rizatriptan 10 mg and oral zolmitriptan 2.5 mg for the outcome pain relief at 2 h in patients with migraine.

Table 3.9.17. GRADE evidence profile table for oral rizatriptan 10 mg versus oral zolmitriptan 2.5 mg in patients with migraine

Certainty assessment							№ of patients		Effect			
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Rizatriptan	Zolmitriptan	Relative (95% CI)	Absolute (95% CI)	Quality	Importance
Pain freedom at 2 h – Rizatriptan 10 mg oral vs zolmitriptan 2.5 mg oral												
1	RCT	Low	Not applicable[a]	Not serious	Not serious	None	126/292 (43.2%)	103/289 (35.6%)	**RR 1.21** (0.99 to 1.48)	**75 more per 1000** (from 4 less to 171 more)	⊕⊕⊕⊖ Moderate	Critical
Pain relief at 2 h – Rizatriptan 10 mg oral vs zolmitriptan 2.5 mg oral												
1	RCT	Low	Not applicable[a]	Not serious	Not serious	None	206/292 (70.5%)	193/289 (66.8%)	**RR 1.06** (0.95 to 1.18)	**40 more per 1000** (from 33 less to 120 more)	⊕⊕⊕⊖ Moderate	Critical

[a]Only one trial.

Tolerability: Amitriptyline presents different adverse events that could limit its use in the general population. They are mostly associated with its competitive antagonism of histaminergic, muscarinic cholinergic and adrenergic receptors. Cholinergic blockade is responsible for sedation, xerostomia, constipation, tachycardia, blurred vision, and urinary retention. Histaminergic blockade is associated with weight gain, confusion, and concentration deficits. Dizziness and orthostatic hypotension are linked to alpha-1 adrenergic receptor blockade. Other less specific adverse events are frequently reported, such as nausea and vomiting, probably related to the area postrema stimulation, as well as asthenia, anxiety or agitation, altered sleep architecture, and vivid dreams. Amitriptyline is also responsible for sexual dysfunctions, as loss of libido, impotence, or difficulty in reaching orgasm, linked to the anticholinergic and antidopaminergic effects. Finally, cutaneous reactions (photosensitivity, pruritus, alopecia, purpura), galactorrhea, extrapyramidal symptoms, increased risk of bleeding and bone marrow suppression are rarely reported.

Duloxetine. **PICO 4.1.3**. In subjects with episodic migraine, is duloxetine superior to placebo for migraine prevention (outcome: persisting monthly migraine days, change in monthly migraine days, $\geq 50\%$ response rate)?

Main evidence. None.

Additional evidence. We found one RCT comparing oral duloxetine 60 mg once a day to placebo (594) in subjects with episodic migraine that did not meet the criteria to be included in the main evidence. Overall, the risk of bias of the included RCT was not serious (Figure 4.1.5); however, the low numbers of participants included (<50 subjects per group) led to downgrading the quality of evidence to very low. This single study did not show benefits of duloxetine over placebo.

Evidence-based recommendation for PICO 4.1.3

In subjects with episodic migraine, we suggest against duloxetine 60 mg for migraine prevention.
Quality of evidence: Very low (⊕⊖⊖⊖)
Strength of recommendation: Weak (↓)

Evidence-based guideline summary. We found studies on amitriptyline and duloxetine to be included for deriving evidence-based recommendations for this guideline. No studies on other antidepressants met eligibility criteria.

For amitriptyline, evidence covered any migraine and episodic migraine. No studies were included for chronic migraine. For duloxetine, evidence covered episodic migraine. No studies were included for any migraine or chronic migraine.

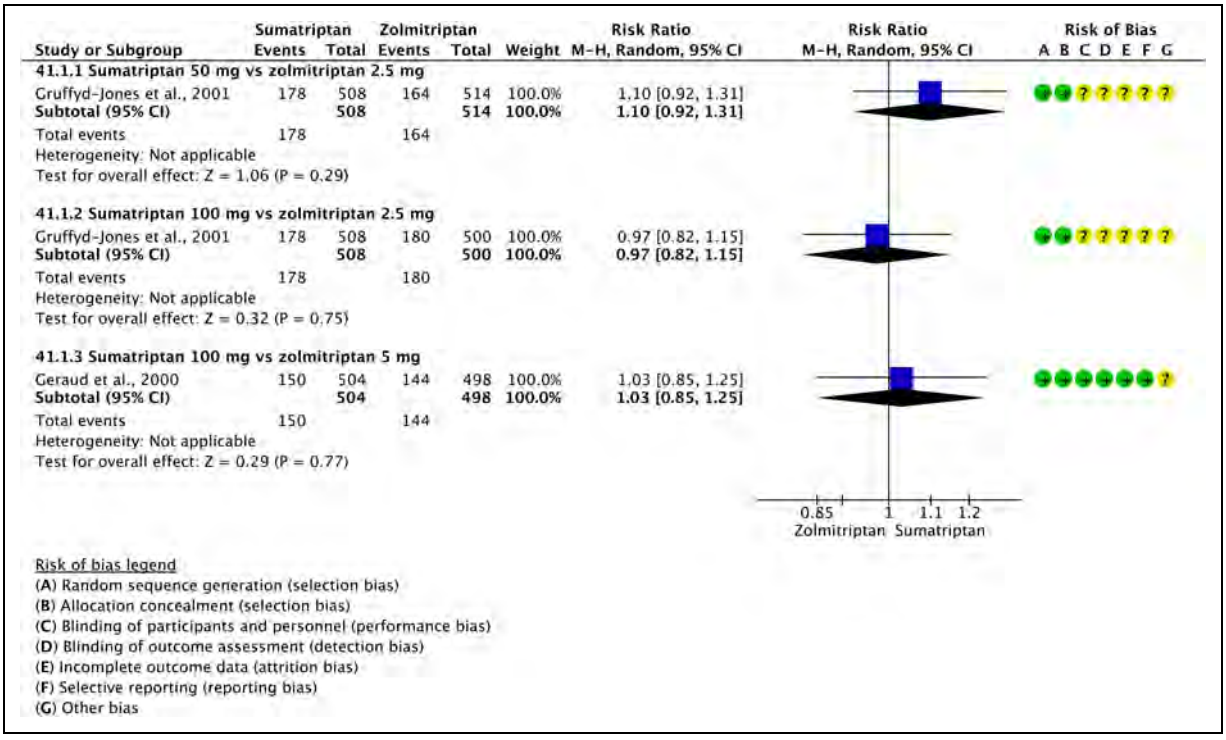


Figure 3.9.41. Forest plot showing the comparison between oral zolmitriptan (2.5 or 5 mg) and oral sumatriptan (50 or 100 mg) for the outcome pain freedom at 2 h in patients with migraine.

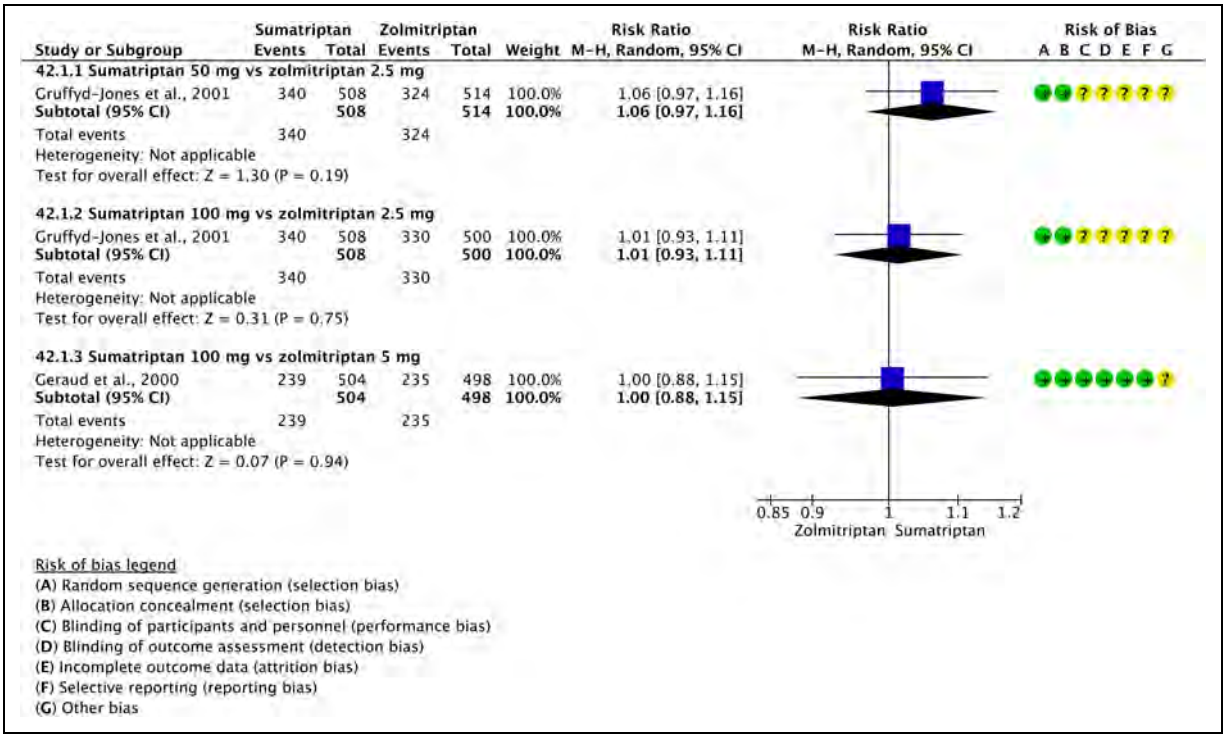


Figure 3.9.42. Forest plot showing the comparison between oral zolmitriptan (2.5 or 5 mg) and oral sumatriptan (50 or 100 mg) for the outcome pain relief at 2 h in patients with migraine.

Table 3.9.18. GRADE evidence profile table for oral zolmitriptan (2.5 or 5 mg) versus oral sumatriptan (50 or 100 mg) in patients with migraine

Certainty assessment							№ of patients		Effect			
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Sumatriptan	Zolmitriptan	Relative (95% CI)	Absolute (95% CI)	Quality	Importance
Pain freedom at 2 h – Sumatriptan 50 mg oral vs Zolmitriptan 2.5 mg oral												
1	RCT	Serious	Not applicable[a]	Not serious	Not serious	None	178/508 (35.0%)	164/514 (31.9%)	**RR 1.10** (0.92 to 1.31)	**36 more per 1000** (from 26 less to 99 more)	⊕⊕⊖⊖ Low	Critical
Pain relief at 2 h – Sumatriptan 50 mg oral vs Zolmitriptan 2.5 mg oral												
1	RCT	Serious	Not applicable[a]	Not serious	Not serious	None	340/508 (66.9%)	324/514 (63.0%)	**RR 1.06** (0.97 to 1.16)	**38 more per 1000** (from 19 less to 101 more)	⊕⊕⊖⊖ Low	Critical
Pain freedom at 2 h – Sumatriptan 100 mg oral vs zolmitriptan 2.5 mg oral												
1	RCT	Serious	Not applicable[a]	Not serious	Not serious	None	178/508 (35.0%)	180/500 (36.0%)	**RR 0.97** (0.82 to 1.15)	**11 less per 1000** (from 65 less to 54 more)	⊕⊕⊖⊖ Low	Critical
Pain relief at 2 h – Sumatriptan 100 mg oral vs zolmitriptan 2.5 mg oral												
1	RCT	Serious	Not applicable[a]	Not serious	Not serious	None	340/508 (66.9%)	330/500 (64.2%)	**RR 1.01** (0.93 to 1.11)	**6 more per 1000** (from 45 less to 71 more)	⊕⊕⊖⊖ Low	Critical
Pain freedom at 2 h – Sumatriptan 100 mg oral vs zolmitriptan 5 mg oral												
1	RCT	Not serious	Not applicable[a]	Not serious	Not serious	None	150/504 (29.8%)	144/498 (28.9%)	**RR 1.03** (0.85 to 1.25)	**9 more per 1000** (from 43 less to 72 more)	⊕⊕⊕⊖ Moderate	Critical
Pain relief at 2 h – Sumatriptan 100 mg oral vs zolmitriptan 5 mg oral												
1	RCT	Not serious	Not applicable[a]	Not serious	Not serious	None	239/504 (47.4%)	235/498 (47.2%)	**RR 1.00** (0.88 to 1.15)	**0 less per 1000** (from 57 less to 71 more)	⊕⊕⊕⊖ Moderate	Critical

[a]Only one trial.

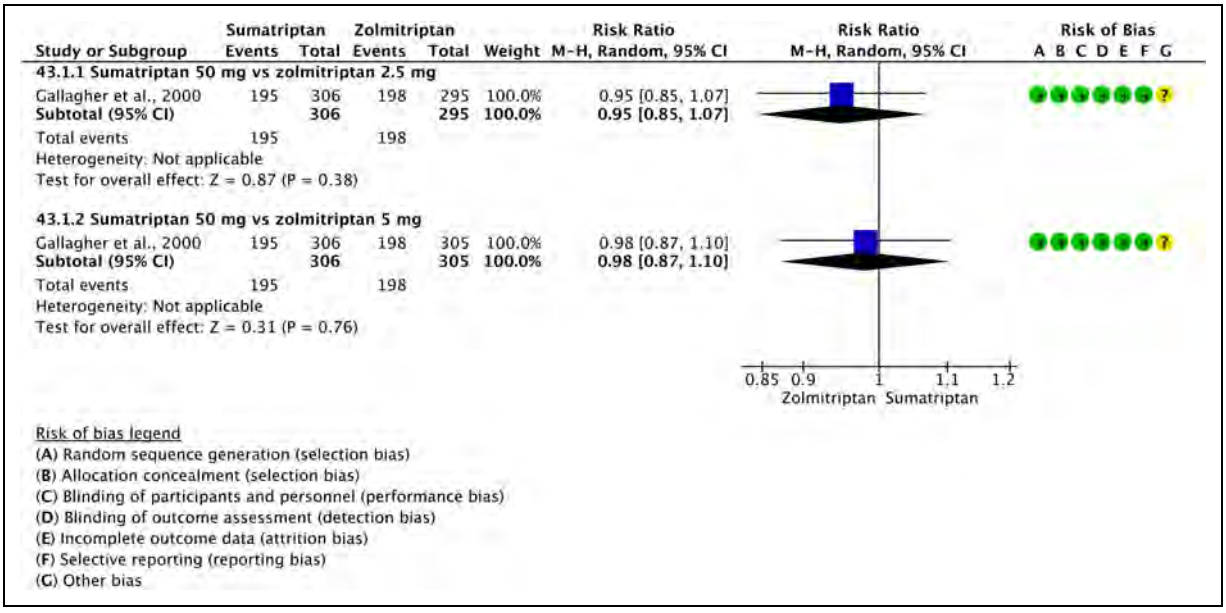


Figure 3.9.43. Forest plot showing the comparison between oral zolmitriptan (2.5 or 5 mg) and oral sumatriptan 50 mg for the outcome pain relief at 2 h in patients with migraine.

There is moderate quality of evidence to suggest the use of amitriptyline for the prevention of episodic migraine. Data do not indicate benefits from duloxetine use (Figure 4.1.6). This evidence-based recommendation refers to subjects with migraine independently from the presence of comorbid depression or other conditions that may need treatment with antidepressants.

Expert-based opinion

Topic: Antidepressants in subjects with migraine and psychiatric or other pain comorbidities. Suggestion: In subjects who may benefit from antidepressants because of comorbidities, those drugs should be used and their benefit on migraine outcomes checked before starting a migraine-specific preventive treatment.

Rationale: Antidepressants were first introduced as preventive migraine therapies when no other migraine-specific preventive agents were available. Migraine is often comorbid with depression and anxiety, which also represent risk factors for migraine worsening (570,605). This provides a rationale to use antidepressants in subjects with migraine and they may remain a reasonable option for subjects having migraine and a comorbid condition that may benefit from antidepressants.

Topic: Antidepressants other than amitriptyline. Suggestion 1: In subjects with migraine there might be an advantage for oral venlafaxine (75 mg or 150 mg daily) for migraine prevention.

Rationale 1: Venlafaxine is used in clinical practice as a migraine preventive agent and it was recommended as probably effective, or level B, in previous guidelines for migraine prevention (18). However, we did not find robust evidence to support its use. There was only one study comparing venlafaxine 75 mg and 150 mg extended release with placebo (597). This study did not meet the inclusion criteria of this guideline because of different outcome measures. Indeed, a generic "number of headache days" was used as the primary outcome measure. The RCT was a 10-week long study which included overall 60 subjects subdivided into three groups. The RCT did not provide mean and standard deviation of monthly headache days. A between-groups comparison demonstrated that the 150 mg group showed a significantly higher reduction in headache days ($p = 0.006$) when compared to the 75 mg and placebo groups. All three groups (75 mg, 150 mg and placebo) showed a reduction in headache days at the end of the 10-week treatment compared to the respective baseline values.

Suggestion 2: In subjects with migraine, there is no advantage of oral fluoxetine 40 mg daily over placebo for migraine prevention.

Rationale 2: We found one RCT comparing oral fluoxetine 40 mg daily to placebo (598) in subjects with migraine that did not meet the criteria to be included in the main evidence and did not provide enough data to be meta-analyzed. The study included overall 53 subjects and concluded that, after 12 weeks of treatment, no significant differences could be established between fluoxetine and placebo regarding monthly migraine days frequency.

Optimization of amitriptyline use

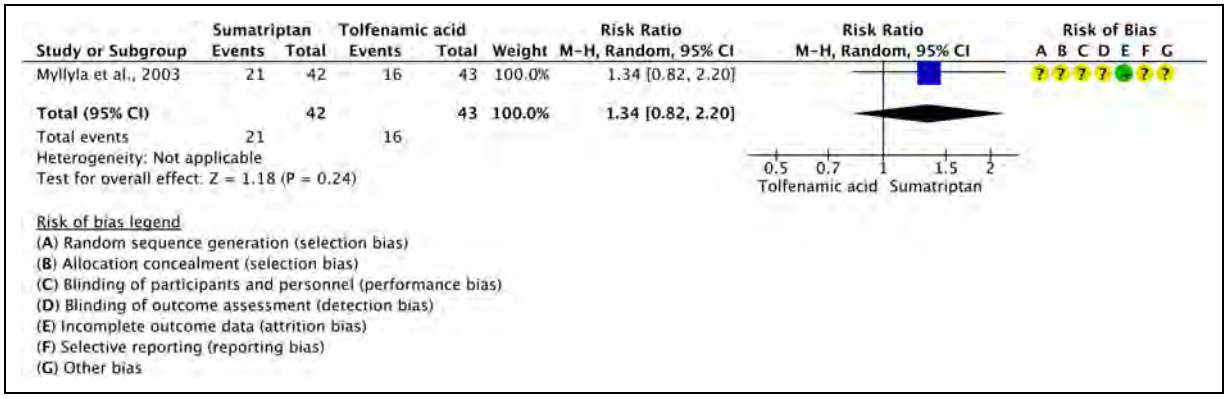


Figure 3.9.44. Forest plot showing the comparison between oral sumatriptan 100 mg and oral tolfenamic acid 200 mg for the outcome pain freedom at 2 h in patients with migraine.

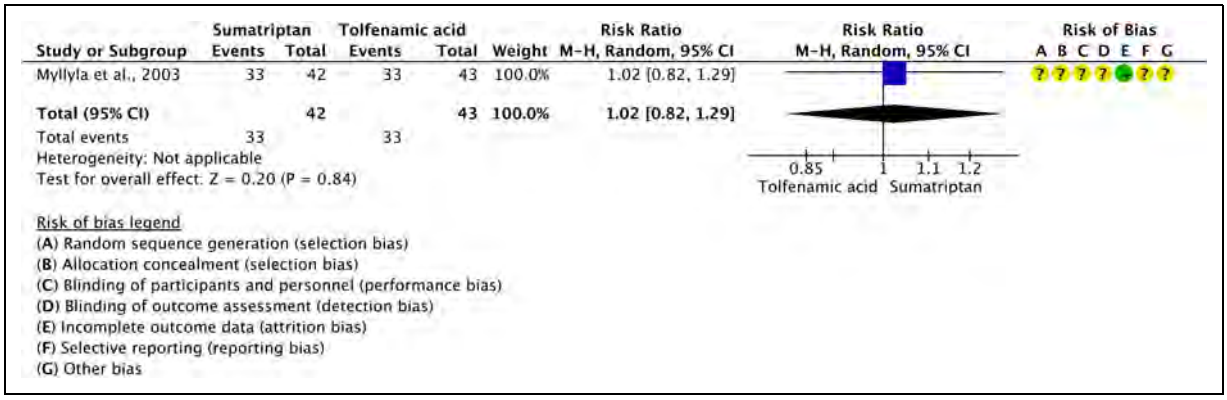


Figure 3.9.45. Forest plot showing the comparison between oral sumatriptan 100 mg and oral tolfenamic acid 200 mg for the outcome pain relief at 2 h in patients with migraine.

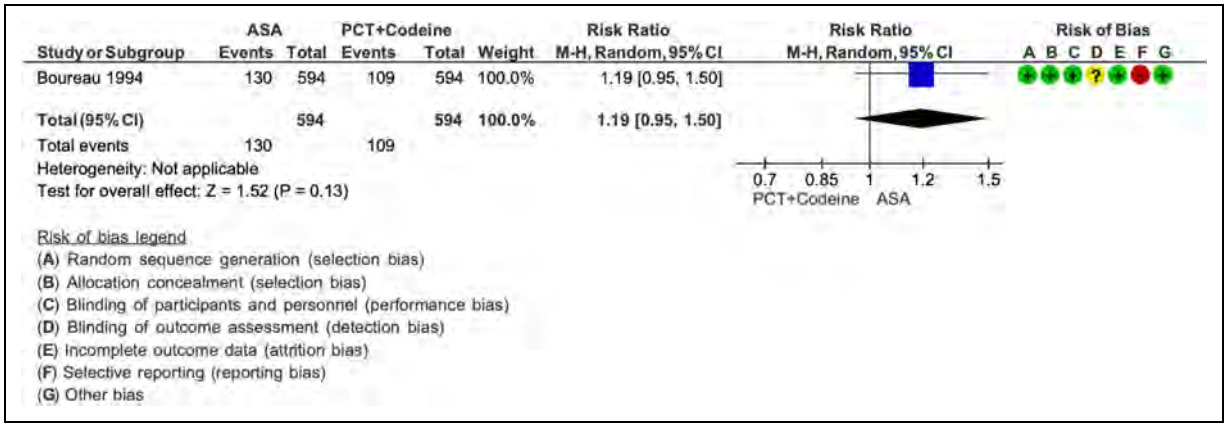


Figure 3.9.46. Forest plot showing the comparison between oral paracetamol 400 mg + codeine 25 mg and oral acetylsalicylic acid 1000 mg for the outcome pain freedom at 2 h in patients with migraine.

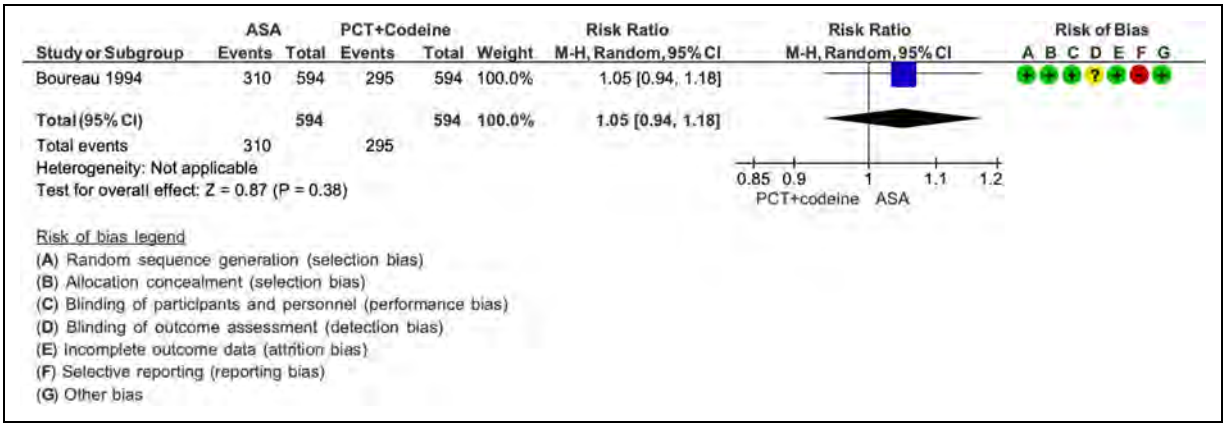


Figure 3.9.47. Forest plot showing the comparison between oral paracetamol 400 mg + codeine 25 mg and oral acetylsalicylic acid 1000 mg for the outcome pain relief at 2 h in patients with migraine.

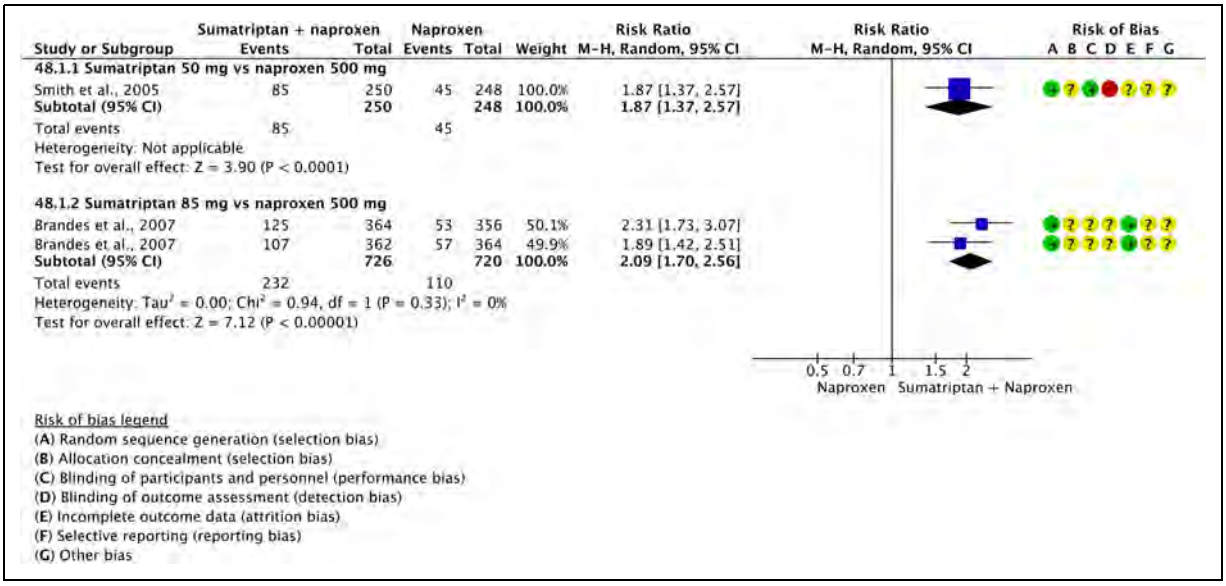


Figure 3.9.48. Forest plot showing the comparison between oral sumatriptan (50 or 85 mg) + naproxen 500 mg and oral naproxen 500 mg alone for the outcome pain freedom at 2 h in patients with migraine. NOTE: One study (27) is reported twice because it included two different populations.

Topic: Amitriptyline titration and dosing. Suggestion: When starting amitriptyline in individuals with episodic migraine, we suggest an initial dose of 10 mg at bedtime. We then suggest a two-step titration of the dose, with a first increase to 15–20 mg after the first week, and a second increase to 25 mg after the second week. In individuals with less than 50% reduction in monthly migraine days after at least four weeks of treatment, the dose should be gradually increased by weekly increments of 10–25 mg up to 25 mg twice a day or up to 50 mg once a day in the evening. Higher doses (75 to 150 mg per day) could be reached in subjects with comorbid depression – taking into due consideration the poor efficacy-to-tolerability ratio of this drug.

Rationale: Amitriptyline is better tolerated if gradually increased from lower starting doses (606). One RCT showed a significant improvement of monthly migraine days in subjects with episodic migraine treated with amitriptyline 25 mg daily administered for three months (595). Older clinical trials included doses up to 100–150 mg/day (589,607). Italian guidelines suggest a daily dose from 10 mg to 75 mg a day (15), while American and European guidelines propose a daily dose from 25 mg to 150 mg (608,609).

In the real-world setting, dosages are generally lower than the ones tested in RCTs and should be gradually increased to reduce adverse events. Indeed, in clinical practice our experience is that doses higher than 25–50 mg per day are associated with a poor efficacy-to-tolerability ratio.

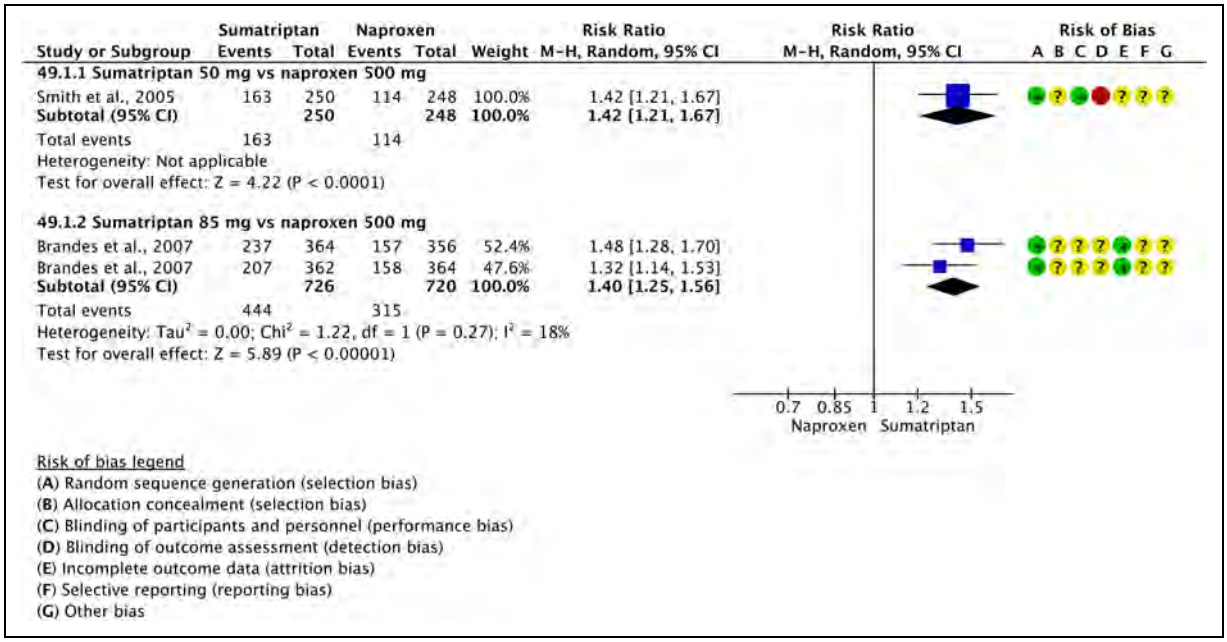


Figure 3.9.49. Forest plot showing the comparison between oral sumatriptan (50 or 85 mg) + naproxen 500 mg and oral naproxen 500 mg alone for the outcome pain relief at 2 h in patients with migraine. NOTE: One study (27) is reported twice because it included two different populations.

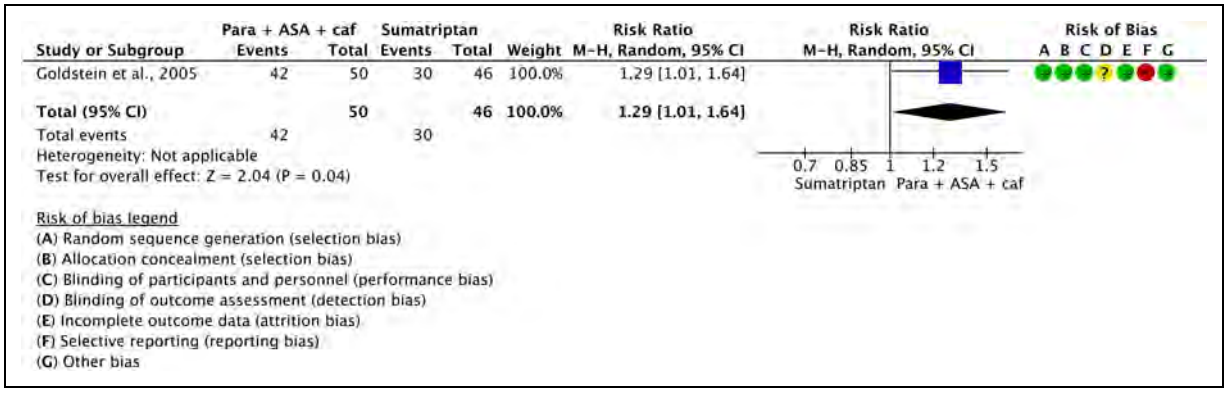


Figure 3.9.50. Forest plot showing the comparison between oral paracetamol 500 mg + acetylsalicylic acid 500 mg + caffeine 130 mg and oral sumatriptan 50 mg for the outcome pain freedom at 2 h in patients with migraine.

Amitriptyline should be given at the lowest effective dose. Dose modifications should be accurately personalized balancing efficacy and adverse events (610). In subjects with comorbid depression, compared with those without, it might be reasonable to prescribe higher doses of amitriptyline, which are adjusted to treat comorbid depression. It is estimated that 40 mg daily of fluoxetine are equivalent to 122.3 mg daily of amitriptyline (611), which is a much higher dose than the 25 mg daily dose tested in subjects with migraine.

4.2 Anti-seizure medications

Introduction. Anti-seizure medications (ASMs) are the mainstay of therapy for epilepsy, and approximately 30 different ASMs with various mechanisms of action (MoA) are available to date (612,613). Several ASMs are approved treatments for non-epileptic conditions, including migraine, neuropathic pain, and psychiatric disorders (612,614). ASMs are usually characterized by a wide spectrum of therapeutic activities and different tolerability profiles.

The use of ASM in the treatment of migraine is based on their potential actions on the general modulation of pain systems or more specifically to systems involved in the pathophysiology of migraine. The specific mechanism(s) responsible for their anti-migraine efficacy is still unknown. Generally, ASMs act by stabilizing neuronal membrane potential through their effect on voltage and

Table 3.9.19. GRADE evidence profile for the comparison between oral paracetamol 500 mg + acetylsalicylic acid 500 mg + caffeine and oral sumatriptan 50 mg in patients with migraine

Certainty assessment								№ of patients		Effect				
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Paracetamol + acetylsalicylic acid + caffeine	Sumatriptan	Relative (95% CI)	Absolute (95% CI)	Quality	Importance
Pain freedom at 2 h –Paracetamol 500 mg + Acetylsalicylic 500 mg + Caffeine 130 mg oral vs Sumatriptan 50 mg oral												
1	RCT	Very serious	Not applicable[a]	Not serious	Serious[b]	None	42/50 (84.0%)	30/46 (65.2%)	**RR 1.29** (1.01 to 1.64)	**189 more per 1000** (from 7 more to 417 more)	⊕⊖⊖⊖ Very Low	Critical

[a]Only one trial; [b]low numbers of patients.

receptor-gated ion channels and reducing the release of pro-algesic neuropeptides (615).

Recent evidence suggests that ASMs might also exert their antimigraine activity by attenuating neurogenic inflammation in the trigeminal vascular system or directly in the release of CGRP, or by several additional MoAs in the central and peripheral nervous system (616). Numerous ASMs have been tested for migraine prevention by RCTs and open-label studies, with very different and sometimes inconsistent results. Only two ASMs, sodium valproate/divalproex sodium and topiramate, are currently approved for migraine prevention. Indeed, although several other ASMs were specifically investigated for migraine in different clinical trial phases (lamotrigine, zonisamide, gabapentin, pregabalin, carbamazepine, oxcarbazepine, levetiracetam, perampanel, lacosamide, carisbamate, clonazepam, tiagabine and vigabatrin), none of them have indication for migraine/headache (616).

Clinical practice guidelines for using ASMs for migraine treatment must consider the evidence regarding their efficacy, tolerability, and adverse events, including the risk of teratogenicity, which is particularly important considering that migraine is most prevalent in women of childbearing potential.

Section-specific methods. This section followed the general procedure to develop this guideline.

Search strings for the Guideline on ASMs for systematic review/meta-analysis and for additional RCTs are reported in Online Appendix 4.2.1.

Results. Overall, we retrieved 1662 references from searching for systematic reviews and meta-analyses. After duplicate removal and screening, we included seven systematic reviews and meta-analyses (617–623) as sources of RCTs. After analyzing full texts of these RCTs, we included 33 of them in the quantitative synthesis (596,624–655) (Figure 4.2.1).

Considering the most recently included systematic review/meta-analysis on the topic, the analysis of additional RCTs was performed for papers published since June 2020. Overall, we retrieved 1744 references from searching for RCTs and after removing duplicates we had three references to analyze (656–658). From the literature search updates performed in May and November 2023, we included 9 additional RCTs (656–664) (Figure 4.2.2).

Overall, 42 studies were considered for inclusion in the quantitative synthesis (meta-analyses) to develop the evidence-based guideline. However, 11 trials were excluded because they included medications that are not available on the market, the comparison was not pertinent, or they did not compare the ASM with another medication or placebo. Among the remaining 31 RCTs, 16 reported a comparison between active drugs and placebo and were presented in

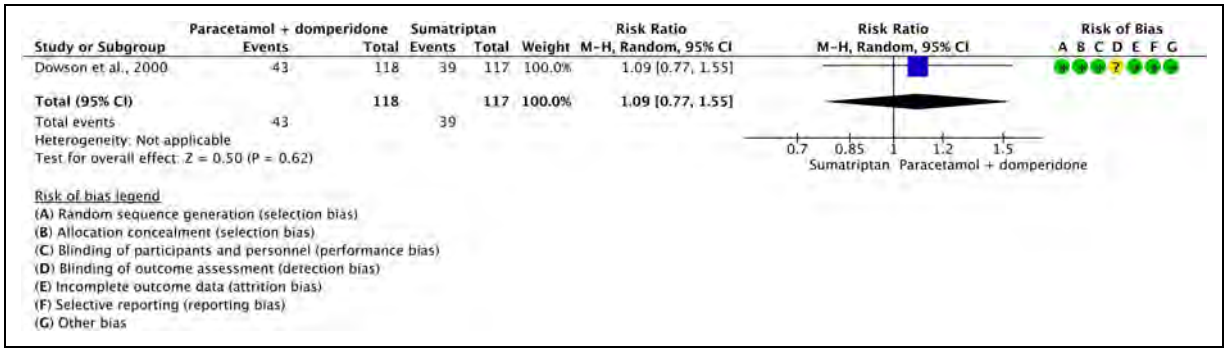


Figure 3.9.51. Forest plot showing the comparison between oral paracetamol 1000 mg + domperidone 20 mg and oral sumatriptan 50 mg for the outcome pain relief at 2 h in patients with migraine.

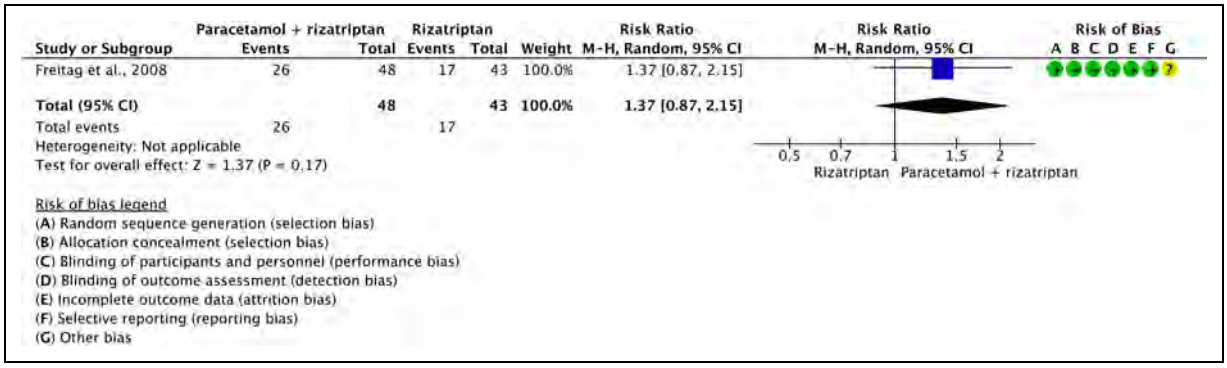


Figure 3.9.52. Forest plot showing the comparison between oral paracetamol 1000 mg + rizatriptan 10 mg and oral rizatriptan 10 mg alone for the outcome pain freedom at 2 h in patients with migraine.

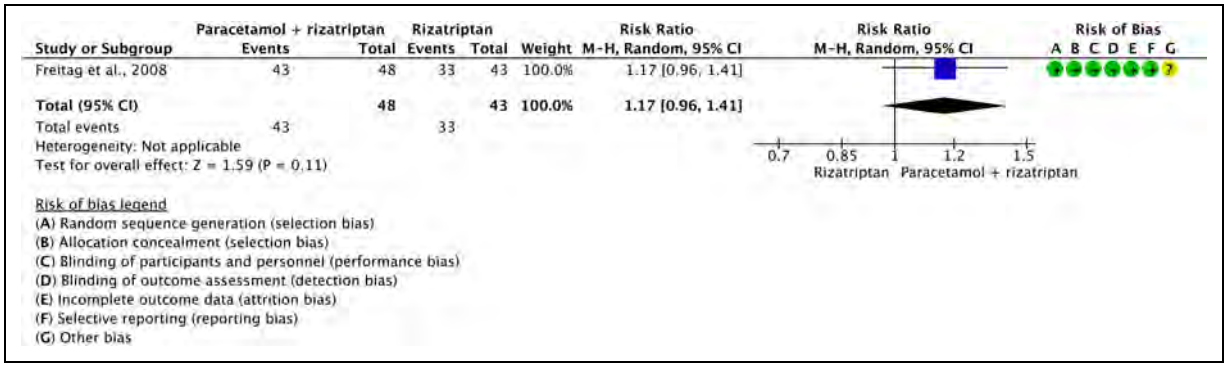


Figure 3.9.53. Forest plot showing the comparison between oral paracetamol 1000 mg + rizatriptan 10 mg and oral rizatriptan 10 mg alone for the outcome pain relief at 2 h in patients with migraine.

this section, while the 15 RCTs reporting head-to-head comparisons only are presented in Section 4.8.

Topiramate. **PICO 4.2.1**. In subjects with episodic migraine, is topiramate superior to placebo for migraine prevention (outcomes: persisting monthly migraine days, change in monthly migraine days, ≥ 50% response rate)?

Main evidence. We found four RCTs comparing topiramate to placebo in subjects with episodic migraine (625,628,630,664) that met the criteria to be included in the main evidence.

The pooled analysis of two RCTs (630,664) showed a significant improvement considering the outcome persisting monthly migraine days in patients treated with oral topiramate 100 mg and 200 mg daily as compared to placebo

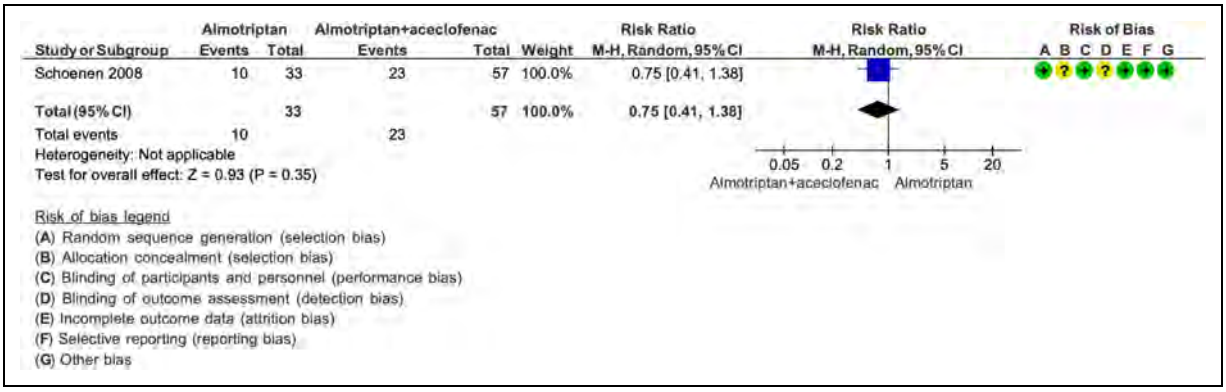


Figure 3.9.54. Forest plot showing the comparison between oral almotriptan 12.5 mg + aceclofenac 100 mg and oral almotriptan 12.5 mg alone for the outcome pain freedom at 2 h in patients with migraine.

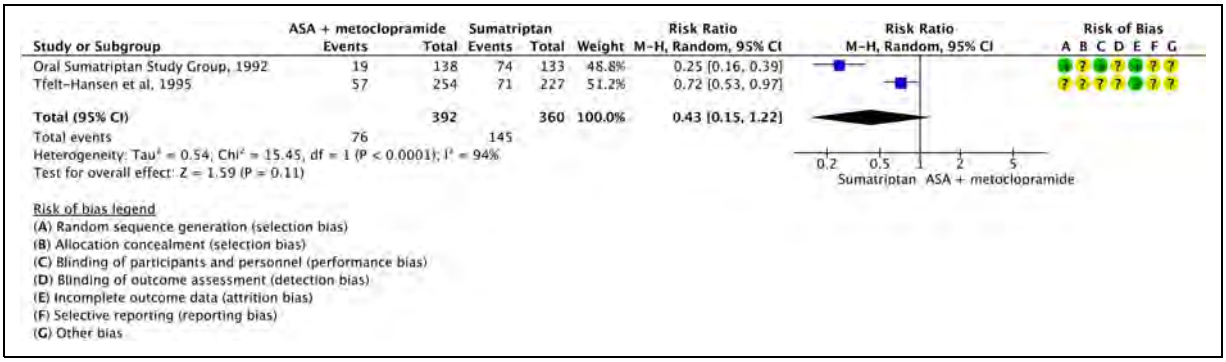


Figure 3.9.55. Forest plot showing the comparison between oral acetylsalicylic acid 900 mg + metoclopramide 10 mg and oral sumatriptan 100 mg for the outcome pain freedom at 2 h in patients with migraine.

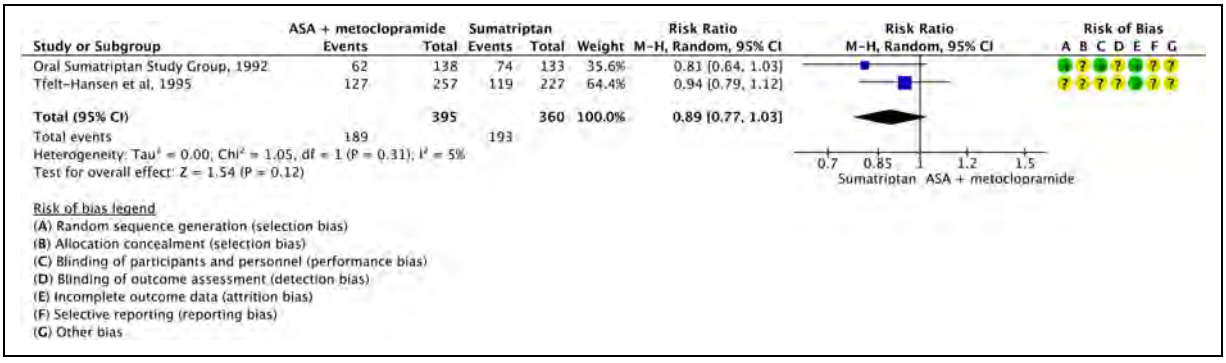


Figure 3.9.56. Forest plot showing the comparison between oral acetylsalicylic acid 900 mg + metoclopramide 10 mg and oral sumatriptan 100 mg for the outcome pain relief at 2 h in patients with migraine.

(Figure 4.2.3), while results did not show benefit of oral topiramate 50 mg daily over placebo for the same outcome. The quality of evidence for the outcome persisting monthly migraine days was considered low for the 50 mg daily dose and moderate for the 100 and 200 mg daily doses (Table 4.2.1).

Three RCTs reported the outcome change in monthly migraine days (625,628,630) (Figure 4.2.4). The pooled

Table 3.9.20. GRADE evidence profile for oral acetylsalicylic acid 900 mg + metoclopramide 10 mg versus oral sumatriptan 100 mg in patients with migraine

Certainty assessment							№ of patients		Effect			
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Acetylsalicylic acid + metoclopramide	Sumatriptan	Relative (95% CI)	Absolute (95% CI)	Quality	Importance
Pain freedom at 2 h – Acetylsalicylic acid 900 mg + metoclopramide 10 mg oral vs Sumatriptan 100 mg oral												
2	RCT	Serious	Not serious	Not serious	Not serious	None	76/392 (19.4%)	145/360 (40.3%)	**RR 0.43** (0.15 to 1.42)	**230 less per 1000** (from 342 less to 169 more)	⊕⊕⊕⊖ Moderate	Critical
Pain relief at 2 h – Acetylsalicylic acid 900 mg + metoclopramide 10 mg oral vs Sumatriptan 100 mg oral												
2	RCT	Serious	Not serious	Not serious	Not serious	None	189/395 (48.2%)	193/360 (53.6%)	**RR 0.89** (0.77 to 1.03)	**59 less per 1000** (from 123 less to 16 more)	⊕⊕⊕⊖ Moderate	Critical

analysis of those studies showed benefits of oral topiramate 100 mg daily but not of oral topiramate 200 mg daily over placebo. No data for this outcome was available for the 50 mg daily dose. The quality of evidence for the outcome change in monthly migraine days was considered moderate for the 100 dose and low for the 200 mg dose (Table 4.2.1).

Two studies reported the outcome ≥50% responder rate (628,630). The pooled analysis of the two studies showed benefits of oral topiramate 100 and 200 mg daily dose over placebo (Figure 4.2.5). Only one of them addressed the 50 mg daily dose and showed benefits of the active treatment over placebo. The quality of evidence for the outcome ≥50% response rate was considered low for the 50 mg dose and moderate for the 100 and 200 mg dose (Table 4.2.1).

Additional evidence. We found three RCTs comparing topiramate to placebo in subjects with episodic migraine (627,629,638) that did not meet the criteria to be included in the main evidence. Overall, the risk of bias of included studies was very serious (Figures 4.2.6–4.2.8).

One study showed significant benefits of topiramate 50 mg daily over placebo considering the outcome change in monthly migraine days (629) (Figure 4.2.7), and another study showed significant benefits of topiramate 100 mg over placebo for the outcome ≥50% response rate (638) (Figure 4.2.8). The third study did not show significant benefits of topiramate 200 mg daily over placebo considering the outcomes persisting monthly migraine days (Figure 6) and ≥50% response rate (627) (Figure 4.2.8).

Evidence-based recommendation for PICO 4.2.1

1) In subjects with episodic migraine, we recommend oral topiramate 100 mg daily for migraine prevention.

Quality of evidence: Moderate (⊕⊕⊕⊖)
Strength of the recommendation: Strong (↑↑)

2) In subjects with episodic migraine, we recommend oral topiramate 200 mg daily for migraine prevention.

Quality of evidence: Moderate (⊕⊕⊕⊖)
Strength of the recommendation: Strong (↑↑)

3) In subjects with episodic migraine, we suggest oral topiramate 50 mg daily for migraine prevention.

Quality of evidence: Low (⊕⊕⊖⊖)
Strength of the recommendation: Weak (↑)

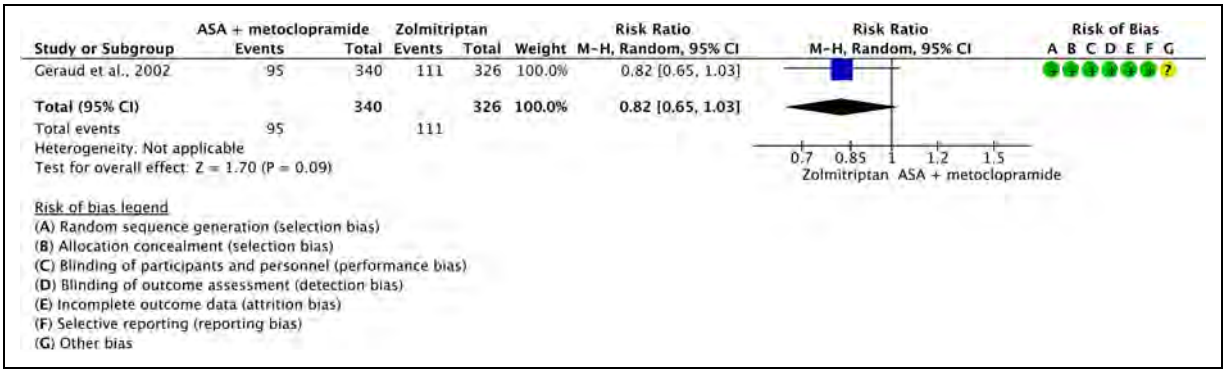


Figure 3.9.57. Forest plot showing the comparison between oral acetylsalicylic acid 900 mg + metoclopramide 10 mg and oral zolmitriptan 2.5 mg for the outcome pain freedom at 2 h in patients with migraine.

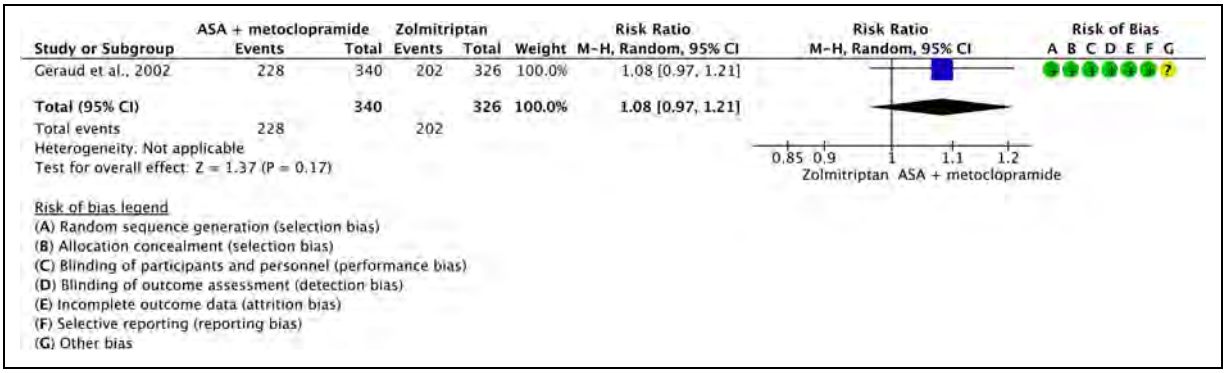


Figure 3.9.58. Forest plot showing the comparison between oral acetylsalicylic acid 900 mg + metoclopramide 10 mg and oral zolmitriptan 2.5 mg for the outcome pain relief at 2 h in patients with migraine.

PICO 4.2.2. In subjects with chronic migraine, is topiramate superior to placebo for migraine prevention (outcomes: persisting monthly migraine days, change in monthly migraine days, ≥ 50% responder rate)?

Main evidence. We found one RCT comparing topiramate to placebo in subjects with chronic migraine (660) that met the criteria to be included in the main evidence. This study showed a significant improvement considering the outcome change in monthly migraine days in subjects treated with oral topiramate 200 mg daily as compared to placebo (Figure 4.2.9), while the results did not show benefit of oral topiramate 200 mg over placebo for the outcome 50% response (Figure 4.2.10). The quality of evidence for the outcomes change in monthly migraine days and ≥50% response was considered low (Table 4.2.2).

Additional evidence. We found three RCTs comparing topiramate to placebo in subjects with chronic migraine (626,647,661) that did not meet the criteria to be included in the main evidence. Overall, the risk of bias of included studies was very serious (Figure 4.2.11–4.2.13) and for this reason the quality of evidence was considered very low.

Two RCTs showed significant benefits of oral topiramate 50 and 100 mg daily over placebo considering the outcome persisting monthly migraine days (626,661) (Figure 4.2.11), while the third RCT did not show significant benefit of 100 mg daily over placebo considering the outcome change in monthly migraine days (647) (Figure 4.2.12).

The three RCTs considered the outcome ≥50% response rate and one (626) showed significant benefit of oral topiramate 50 mg over placebo, while the pooled analysis of the other two RCTs (647,661) did not show significant improvement with oral topiramate 100 mg over placebo (Figure 4.2.13).

Evidence-based recommendation for PICO 4.2.2

1) In subjects with chronic migraine, we suggest oral topiramate 50 mg daily for migraine prevention.

Quality of evidence: Very low (⊕⊖⊖⊖)

Table 3.9.21. GRADE evidence profile for oral acetylsalicylic acid 900 mg + metoclopramide 10 mg versus oral zolmitriptan 2.5 mg in patients with migraine

Certainty assessment							№ of patients		Effect			
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Acetylsalicylic acid + metoclopramide	Zolmitriptan	Relative (95% CI)	Absolute (95% CI)	Quality	Importance
Pain freedom at 2 h – Acetylsalicylic acid 900 mg + metoclopramide 10 mg oral vs Zolmitriptan 2.5 mg oral												
1	RCT	Low	Not applicable[a]	Not serious	Not serious	None	95/340 (27.9%)	111/326 (34.0%)	**RR 0.82** (0.65 to 1.03)	**61 less per 1000** (from 119 less to 10 more)	⊕⊕⊕⊖ Moderate	Critical
Pain relief at 2 h – Acetylsalicylic acid 900 mg + metoclopramide 10 mg oral vs Zolmitriptan 2.5 mg oral												
1	RCT	Low	Not applicable[a]	Not serious	Not serious	None	228/340 (67.1%)	202/326 (62.0%)	**RR 1.08** (0.97 to 1.21)	**50 more per 1000** (from 19 less to 130 more)	⊕⊕⊕⊖ Moderate	Critical

[a]Only one trial.

Strength of recommendation: Weak (↑)

2) In subjects with chronic migraine, we suggest oral topiramate 100 mg daily for migraine prevention.

Quality of evidence: Very low (⊕⊖⊖⊖)
Strength of recommendation: Weak (↑)

3) In subjects with chronic migraine, we suggest oral topiramate 200 mg daily for migraine prevention.

Quality of evidence: Low (⊕⊕⊖⊖)
Strength of recommendation: Weak (↑)

Safety and tolerability of topiramate. Warnings and contraindications: Topiramate should not be used in pregnant and nursing women with migraine due to its teratogenic effects of increasing the risk of cleft lip and/or palate. Similarly, in women of childbearing potential who are not using highly effective contraception methods, topiramate should be avoided (665). It is important to note that topiramate is a CYP450 enzyme-inducing drug, which has the potential to reduce the effectiveness of oral contraceptives containing estrogen. However, this effect is dose-dependent and does not appear to be clinically significant at doses lower than 200 mg/day (665–667). Topiramate should not be used in subjects with severe renal or hepatic impairment. Reduced dose to 50% and slow titration is suggested for subjects with renal impairment CrCl <70 ml/minute/1.73 m^2, and, as topiramate clearance may be reduced in hepatic impairment, cautious use is recommended. Additionally, caution should be exercised when prescribing topiramate in combination with other carbonic anhydrase inhibitors or drugs that can cause metabolic acidosis (668). Its use should also be avoided in subjects on a ketogenic diet due to an increased risk of nephrolithiasis (669).

Serious safety concerns: Topiramate has been associated with rare but significant adverse effects including acute myopia and secondary angle closure glaucoma that can lead to permanent visual loss with untreated increased intraocular pressure. Therefore, careful monitoring of subjects taking topiramate is necessary to detect any visual disturbances or eye-related symptoms. In addition, topiramate requires monitoring for cognitive problems, language disturbances, behavior disturbances, and the rare risk of suicidal ideation (616,665,670). Other potential adverse effects of topiramate include the risk of nephrolithiasis and weight loss. It is important to be aware of these risks and to monitor subjects appropriately during treatment.

Tolerability: The most commonly reported side effects of topiramate, as observed in RCTs and real-world studies, include paresthesia, anorexia, weight loss, altered taste, memory impairment, fatigue, insomnia, nausea, diarrhea, somnolence, and dizziness (671,672). It is worth

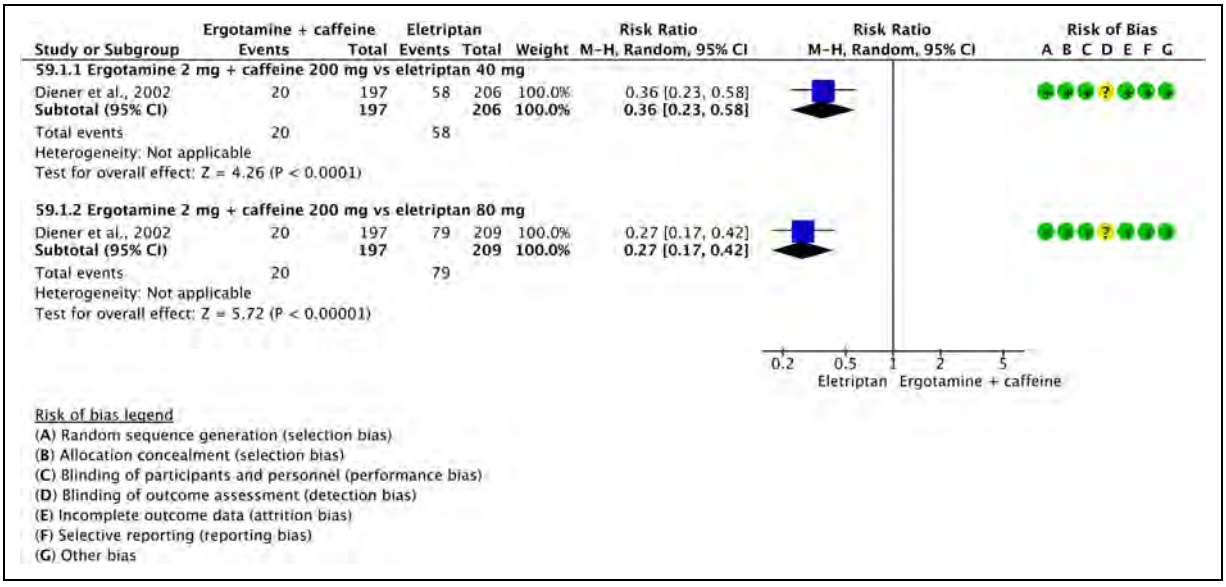


Figure 3.9.59. Forest plot showing the comparison between oral ergotamine 2 mg + caffeine 200 mg and oral eletriptan (40 mg or 80 mg) for the outcome pain freedom at 2 h in patients with migraine.

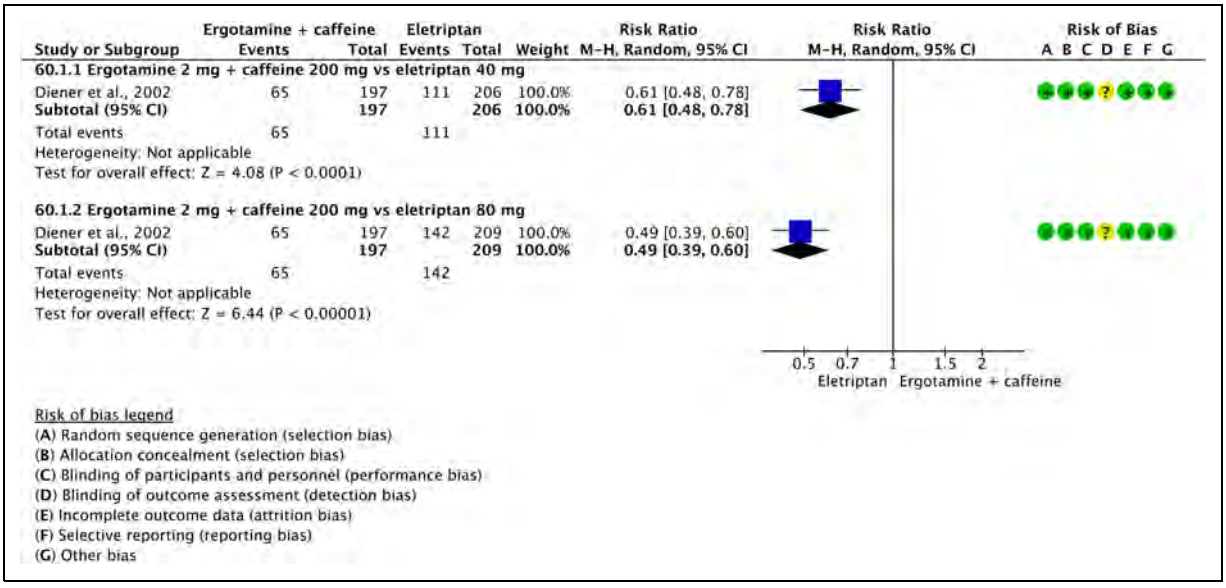


Figure 3.9.60. Forest plot showing the comparison between ergotamine 2 mg + caffeine 200 mg and eletriptan (40 mg or 80 mg) for the outcome pain relief at 2 h in patients with migraine.

noting that these side effects are dose-dependent, and generally, the tolerability of the 100 mg/day dose is better than the 200 mg/day dose. Topiramate has been associated with a distinct cognitive syndrome characterized by difficulties in word-finding, slowed thinking or mental processing, attention and memory difficulties, and psychiatric or behavioral disturbances such as depression and mood problems (616,670). Notably, neurocognitive symptoms and paresthesia are more prominent in subjects treated with topiramate for migraine than for epilepsy. Treatment with topiramate is also associated with a 10-fold increased risk of nephrolithiasis due to an increase in urinary bicarbonate excretion and urinary pH, and a reduction in urinary citrate (669). For the immediate release formulation, no contraindications are listed in the manufacturer's labeling. However, for the extended-release formulation, recent alcohol use (within 6 h prior to and 6 h after medication intake), and use of topiramate by subjects with metabolic acidosis concomitantly taking metformin are contraindications.

Table 3.9.22. GRADE evidence profile for oral ergotamine 2 mg + caffeine 200 mg versus oral eletriptan (40 mg or 80 mg) in patients with migraine

Certainty assessment							№ of patients		Effect			
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Ergotamine + caffeine	Eletriptan	Relative (95% CI)	Absolute (95% CI)	Quality	Importance
Pain freedom at 2 h – Ergotamine 2 mg + caffeine 200 mg oral vs Eletriptan 40 mg oral												
1	RCT	Not serious	Not applicable[a]	Not serious	Not serious	None	20/197 (10.2%)	58/206 (28.2%)	**RR 0.36** (0.23 to 0.58)	**180 less per 1000** (from 217 less to 118 less)	⊕⊕⊕⊖ Moderate	Critical
Pain relief at 2 h – Ergotamine 2 mg + caffeine 200 mg oral vs Eletriptan 40 mg oral												
1	RCT	Not serious	Not applicable[a]	Not serious	Not serious	None	65/197 (33.0%)	111/206 (53.9%)	**RR 0.61** (0.48 to 0.78)	**210 less per 1000** (from 280 less to 119 less)	⊕⊕⊕⊖ Moderate	Critical
Pain freedom at 2 h – Ergotamine 2 mg + caffeine 200 mg oral vs Eletriptan 80 mg oral												
1	RCT	Not serious	Not applicable[a]	Not serious	Not serious	None	20/197 (10.2%)	79/209 (37.8%)	**RR 0.27** (0.17 to 0.42)	**276 less per 1000** (from 314 less to 219 less)	⊕⊕⊕⊖ Moderate	Critical
Pain relief at 2 h – Ergotamine 2 mg + caffeine 200 mg oral vs Eletriptan 80 mg oral												
1	RCT	Not serious	Not applicable[a]	Not serious	Not serious	None	65/197 (33.0%)	142/209 (67.9%)	**RR 0.49** (0.39 to 0.60)	**347 less per 1000** (from 414 less to 272 less)	⊕⊕⊕⊖ Moderate	Critical

[a]Only one trial.

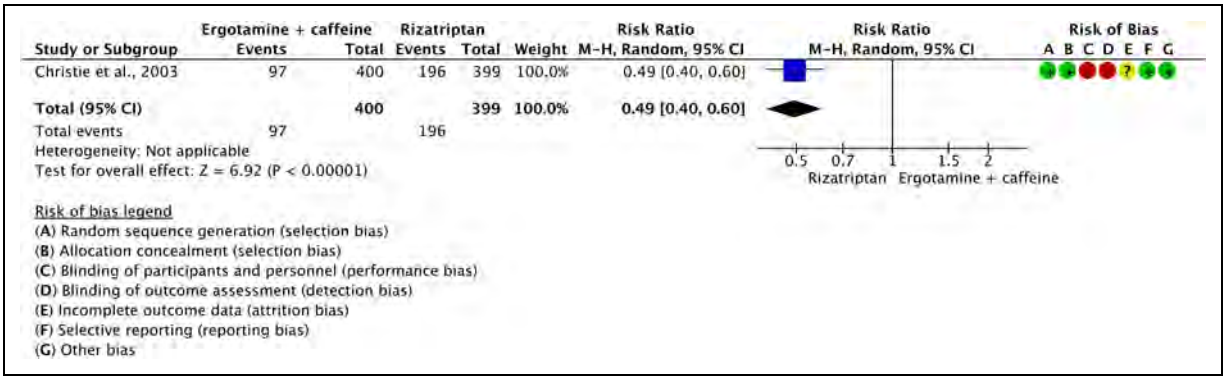


Figure 3.9.61. Forest plot showing the comparison between oral ergotamine 2 mg + caffeine 200 mg and oral rizatriptan 10 mg for the outcome pain freedom at 2 h in patients with migraine.

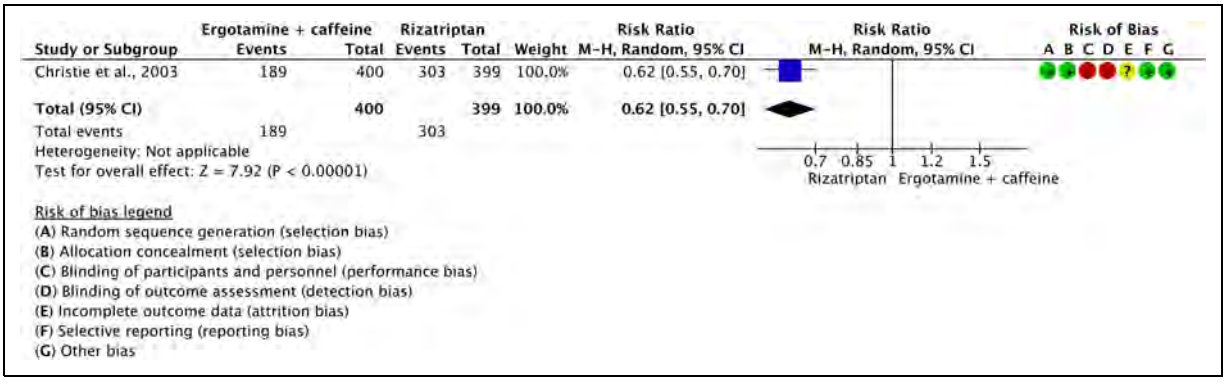


Figure 3.9.62. Forest plot showing the comparison between oral ergotamine 2 mg + caffeine 200 mg and oral rizatriptan 10 mg for the outcome pain relief at 2 h in patients with migraine.

Valproate. **PICO 4.2.3.** In subjects with episodic migraine, is valproate superior to placebo for migraine prevention (outcomes: persisting monthly migraine days, change in monthly migraine days, ≥ 50% response rate)?

Main evidence. None.

Additional evidence. We found three RCTs comparing valproate to placebo in subjects with episodic migraine (632,633,639) that did not meet the criteria to be included in the main evidence. Overall, the risk of bias of included studies was very serious (Figures 4.2.14 and 4.2.15) and for this reason the quality of evidence was downgraded to very low.

One RCT considered the outcome change in monthly migraine days and showed significant benefit of oral valproate 1500 mg daily over placebo (633) (Figure 4.2.14), even if with low numbers of participants (<50 per group).

Two RCTs showed significant benefits of valproate 750 mg and 1500 mg daily over placebo considering the outcome ≥50% response rate (632,639), while the third RCT (633) did not show significant benefit of valproate 800 mg daily over placebo considering the same outcome (Figure 4.2.15).

Evidence-based recommendation for PICO 4.2.3

1) In subjects with episodic migraine, we suggest oral valproate 750 mg daily for migraine prevention.

Quality of evidence: very low (⊕⊖⊖⊖)
Strength of recommendation: weak (↑)

2) In subjects with episodic migraine, there is not enough evidence to establish the efficacy of oral valproate 800 mg daily for migraine prevention.

Quality of evidence: Very low (⊕⊖⊖⊖)
Strength of recommendation: -.

3) In subjects with episodic migraine, we suggest oral valproate 1500 mg daily for migraine prevention.

Quality of evidence: very low (⊕⊖⊖⊖)
Strength of recommendation: weak (↑)

Table 3.9.23. GRADE evidence profile for oral ergotamine 2 mg + caffeine 200 mg versus oral rizatriptan 10 mg in patients with migraine

Certainty assessment							№ of patients		Effect			
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Ergotamine + caffeine	Rizatriptan	Relative (95% CI)	Absolute (95% CI)	Quality	Importance
Pain freedom at 2 h – Ergotamine 2 mg + caffeine 200 mg vs rizatriptan 10 mg												
1	RCT	Very serious	Not applicable[a]	Not serious	Not serious	None	97/400 (24.3%)	196/399 (49.1%)	**RR 0.49** (0.40 to 0.60)	**251 less per 1000** (from 295 less to 196 less)	⊕⊖⊖⊖ Very Low	Critical
Pain relief at 2 h – Ergotamine 2 mg + caffeine 200 mg vs rizatriptan 10 mg												
1	RCT	Very serious	Not applicable[a]	Not serious	Not serious	None	189/400 (47.3%)	303/399 (75.9%)	**RR 0.62** (0.55 to 0.70)	**289 less per 1000** (from 342 less to 228 less)	⊕⊖⊖⊖ Very Low	Critical

[a]Only one trial.

PICO 4.2.4. In subjects with migraine (no distinction between episodic and chronic), is valproate superior to placebo for migraine prevention (outcomes: persisting monthly migraine days, change in monthly migraine days, ≥ 50% response rate)?

Main evidence. We found two RCTs comparing oral valproate to placebo in subjects with migraine (no distinction between episodic and chronic) (636,651) that met the criteria to be included in the main evidence. The RCTs showed a significant improvement considering the outcome ≥50% response rate in subjects treated with oral valproate 500 mg and 1500 mg daily compared to placebo, while results did not show benefit of oral valproate 1000 mg over placebo for the same outcome (Figure 4.2.16). The quality of evidence for the outcome ≥50% response rate was considered very low (Table 4.2.3).

Additional evidence. We found two RCTs comparing oral valproate to placebo in subjects with migraine (no distinction between episodic and chronic) (631,653) that did not meet the criteria to be included in the main evidence. Overall, the risk of bias of included studies was very serious (Figures 4.2.17 and 4.2.18) and for this reason the quality of evidence was downgraded to very low. No recommendation could be issued given the low numbers of subjects (<50 per group) in each RCT.

One RCT considered the outcome persisting monthly migraine days (631) and showed significant benefit of oral valproate 800 mg daily over placebo (Figure 4.2.17).

One study considered the outcome ≥50% response rate (653) and showed significant benefit of valproate 500 mg daily over placebo (Figure 4.2.18).

Evidence-based recommendation for PICO 4.2.4

In subjects with migraine (no distinction between episodic and chronic), we suggest oral valproate (500–1500 mg) daily for migraine prevention.
Quality of evidence: Very low (⊕⊖⊖⊖)
Strength of recommendation: Weak (↑)

Safety and tolerability of valproate. Warnings and contraindications: Valproate should not be used in pregnant and nursing women with migraine due to the significant risk of congenital malformations, particularly neural tube defects, and neurodevelopmental disorders. Valproate is also contraindicated in subjects with compromised liver function, urea cycle disorders, and mitochondrial disorders (673,674). Women of childbearing potential should also avoid valproate due to its teratogenicity risk (674,675).

Serious safety concerns: Severe hepatotoxicity, although rare, can occur within the first six months of treatment. Subjects should be closely monitored for potential liver

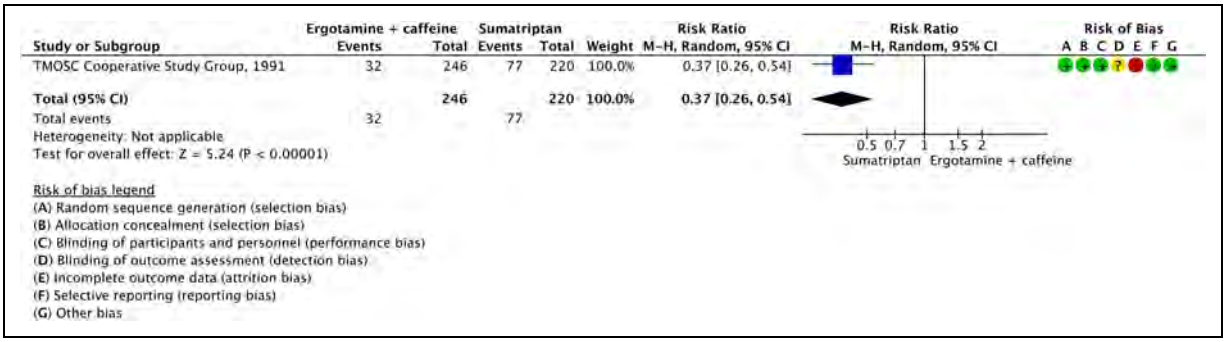


Figure 3.9.63. Forest plot showing the comparison between oral ergotamine 2 mg + caffeine 200 mg and oral sumatriptan 100 mg for the outcome pain freedom at 2 h in patients with migraine.

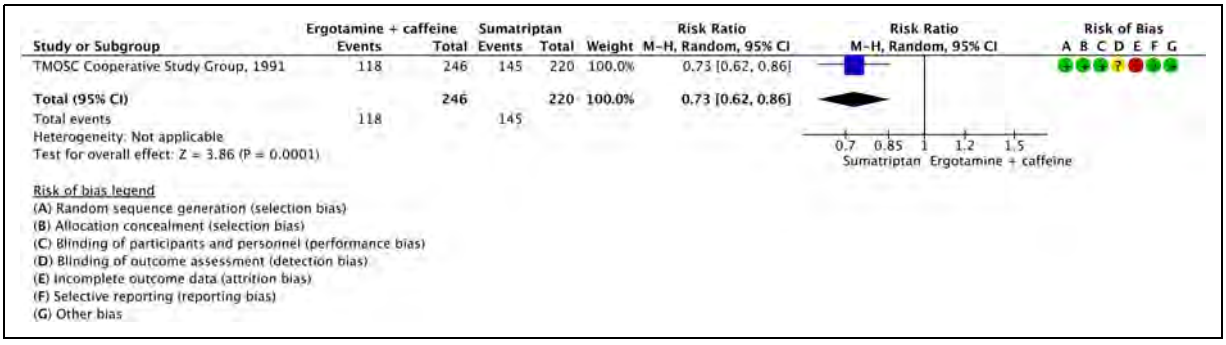


Figure 3.9.64. Forest plot showing the comparison between oral ergotamine 2 mg + caffeine 200 mg and oral sumatriptan 100 mg for the outcome pain relief at 2 h in patients with migraine.

failure and pancreatitis, although these adverse events are infrequent. Valproate has also been associated with an increased risk of suicidal thoughts or behavior.

Tolerability: Clinical trials for migraine prevention have reported fatigue, weight gain, dizziness, nausea, abdominal pain, and tremor as the most clinically significant adverse events associated with valproate use.

Gabapentin. **PICO 4.2.5**. In subjects with episodic migraine, is gabapentin superior to placebo for migraine prevention (outcomes: persisting monthly migraine days, change in monthly migraine days, ≥ 50% responder rate)?

Main evidence. We found one RCT comparing gabapentin to placebo in subjects with migraine (635) that met the criteria to be included in the main evidence. The RCT considered only the outcome ≥50% response rate. The results did not show benefit of oral gabapentin 1200 to 3000 mg daily over placebo (Figure 4.2.19).

The overall quality of evidence for the outcome was considered very low (Table 4.2.4).

Additional evidence. None.

Evidence-based recommendation for PICO 4.2.5

In subjects with episodic migraine, we suggest against gabapentin for migraine prevention.
Quality of evidence: Very low (⊕⊖⊖⊖)
Strength of recommendation: Weak (↓)

Lamotrigine. **PICO 4.2.6**. In subjects with episodic migraine, is lamotrigine superior to placebo for migraine prevention (outcomes: persisting monthly migraine days, change in monthly migraine days, ≥ 50% responder rate)?

Main evidence. We found two RCTs comparing lamotrigine to placebo in subjects with episodic migraine (638,641) that met the criteria to be included in the main evidence. One RCT (641) did not show any benefit of oral lamotrigine 200 mg daily over placebo for the outcome persisting monthly migraine days (Figure 4.2.20) whereas the other RCT showed significant improvement in the outcome change in monthly migraine days for oral lamotrigine 50 over placebo (638) (Figure 4.2.21). The overall quality of evidence for the outcome was considered

Table 3.9.24. GRADE evidence profile for oral ergotamine 2 mg + caffeine 200 mg versus oral sumatriptan 100 mg in patients with migraine

Certainty assessment							№ of patients		Effect			
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Ergotamine + caffeine	Sumatriptan	Relative (95% CI)	Absolute (95% CI)	Quality	Importance
Pain freedom at 2 h – Ergotamine 2 mg + caffeine 200 mg oral vs Sumatriptan 100 mg oral												
1	RCT	Very serious	Not applicable[a]	Not serious	Not serious	None	32/246 (13.0%)	77/220 (35.0%)	**RR 0.37** (0.26 to 0.54)	**220 less per 1000** (from 259 less to 161 less)	⊕⊖⊖⊖ Very Low	Critical
Pain relief at 2 h – Ergotamine 2 mg + caffeine 200 mg oral vs Sumatriptan 100 mg oral												
1	RCT	Very serious	Not applicable[a]	Not serious	Not serious	None	118/246 (48.0%)	145/220 (65.9%)	**RR 0.73** (0.62 to 0.86)	**178 less per 1000** (from 250 less to 92 less)	⊕⊖⊖⊖ Very Low	Critical

[a]Only one trial.

very low for both persisting monthly migraine days and change in monthly migraine days (Table 4.2.5).

Additional evidence. None.

Evidence-based recommendation for PICO 4.2.6

In subjects with episodic migraine, we suggest oral lamotrigine 50 mg for migraine prevention.
Quality of evidence: Very low (⊕⊖⊖⊖)
Strength of the recommendation: Weak (↑)

[NOTE: The suggestion in favor of lamotrigine was based upon the RCT that provided the most precise results. The RCT showing no benefit of lamotrigine over placebo had imprecise results. Further guidance on the use of lamotrigine for migraine prevention is provided in the Expert-Based Opinion Section.]

Levetiracetam. **PICO 4.2.7.** In subjects with episodic migraine, is levetiracetam superior to placebo for migraine prevention (outcomes: persisting monthly migraine days, change in monthly migraine days, ≥ 50% response rate)?

Main evidence. We found one RCT comparing oral levetiracetam to placebo in subjects with episodic migraine (640) that met the criteria to be included in the main evidence. The RCT considered only the outcome persisting monthly migraine days. The results showed significant benefit from oral levetiracetam 1000 mg daily over placebo (Figure 4.2.22).

The overall quality of evidence for the outcome was considered very low (Table 4.2.6).

Additional evidence. None.

Evidence-based recommendation for PICO 4.2.7

In subjects with episodic migraine, we suggest oral levetiracetam 1000 mg for migraine prevention.
Quality of evidence: Very low (⊕⊖⊖⊖)
Strength of the recommendation: Weak (↑)

[NOTE: The results from the included RCT are imprecise due to the low number of included subjects. Nevertheless, a recommendation was issued as the RCT was included in main evidence. Additional guidance is provided in the expert-based opinion section.]

PICO 4.2.8. In subjects with migraine (no distinction between episodic and chronic), is levetiracetam superior to placebo for migraine prevention (outcomes: persisting monthly migraine days, change in monthly migraine days, ≥ 50% response rate)?

Main evidence. None.

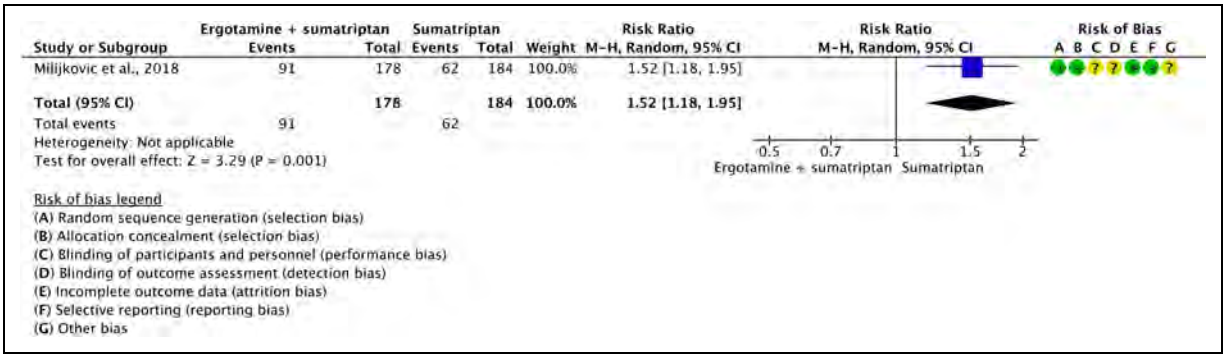


Figure 3.9.65. Forest plot showing the comparison between ergotamine + sumatriptan and sumatriptan for the outcome pain freedom at 2 h in patients with migraine.

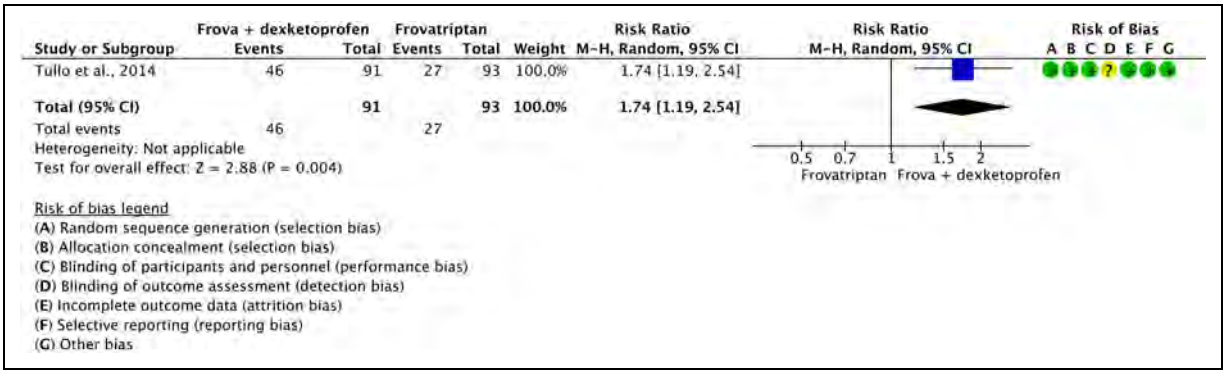


Figure 3.9.66. Forest plot showing the comparison between oral frovatriptan 2.5 mg + dexketoprofen 37.5 mg and oral frovatriptan 2.5 mg alone for the outcome pain freedom at 2 h in patients with migraine.

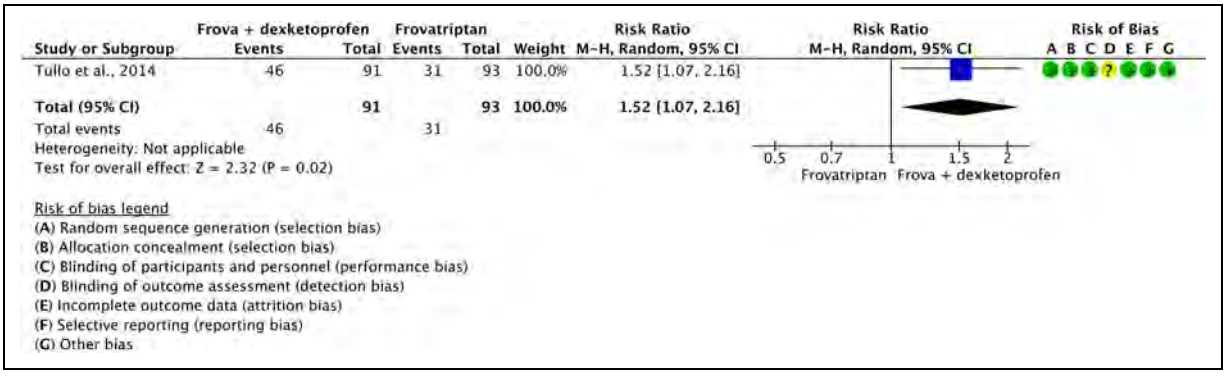


Figure 3.9.67. Forest plot showing the comparison between oral frovatriptan 2.5 mg + dexketoprofen 37.5 mg and oral frovatriptan 2.5 mg alone for the outcome pain relief at 2 h in patients with migraine.

Additional evidence. We found one RCT comparing oral levetiracetam to placebo in subjects with migraine (no distinction between episodic and chronic) (653) that did not meet the criteria to be included in the main evidence. The risk of bias for this study was very serious (Figure 4.2.23) and for this reason the quality of evidence was downgraded to very low. This study considered the outcome ≥50% response rate and showed significant benefit of oral levetiracetam 500 mg daily over placebo (Figure 4.2.23). A recommendation could

Table 3.9.25. GRADE evidence profile table for frovatriptan 2.5 mg + dexketoprofen 37.5 mg versus frovatriptan 2.5 mg alone in patients with migraine

Certainty assessment							№ of patients		Effect			
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Frovatriptan	Frovatriptan + dexketoprofen	Relative (95% CI)	Absolute (95% CI)	Quality	Importance
Pain freedom at 2 h – Frovatriptan 2.5 + dexketoprofen 37.5 mg oral vs Frovatriptan 2.5 alone oral												
1	RCT	Moderate	Not applicable[a]	Not serious	Not serious	None	46/91 (50.5%)	27/93 (29.0%)	**RR 1.74** (1.19 to 2.54)	**215 more per 1000** (from 55 more to 447 more)	⊕⊕⊕⊖ Moderate	Critical
Pain relief at 2 h – Frovatriptan 2.5 + dexketoprofen 37.5 mg oral vs Frovatriptan 2.5 alone oral												
1	RCT	Moderate	Not applicable[a]	Not serious	Not serious	None	46/91 (50.5%)	31/93 (33.3%)	**RR 1.52** (1.07 to 2.16)	**173 more per 1000** (from 23 more to 387 more)	⊕⊕⊕⊖ Moderate	Critical

[a]Only one trial.

not be issued given the low numbers of participants (<50 per group).

Evidence-based recommendation for PICO 4.2.8

In subjects with migraine (no distinction between episodic and chronic), there is not enough evidence to recommend levetiracetam over placebo for migraine prevention.
Quality of evidence: -
Strength of the recommendation: -

Vigabatrin. **PICO 4.2.9**. In subjects with migraine (no distinction between episodic and chronic), is vigabatrin superior to placebo for migraine prevention (outcomes: persisting monthly migraine days, change in monthly migraine days, ≥ 50% responder rate)?

Main evidence. None.

Additional evidence. We found one RCT comparing oral vigabatrin to placebo in subjects with migraine (no distinction between episodic and chronic) (650) that did not meet the criteria to be included in the main evidence. The risk of bias for this RCT was very serious (Figure 4.2.24) and for this reason the quality of evidence was downgraded to very low.

The RCT did not show benefits of oral vigabatrin 2000 mg daily over placebo considering the outcome persisting monthly migraine days (Figure 4.2.24). A recommendation could not be issued given the low numbers of subjects (<50 per group).

Evidence-based recommendation for PICO 4.2.9

In subjects with migraine (no distinction between episodic and chronic), there is not enough evidence to recommend vigabatrin over placebo for migraine prevention.
Quality of evidence: -
Strength of recommendation: -

Oxcarbazepine. **PICO 4.2.10.** In subjects with migraine (no distinction between episodic and chronic), is oxcarbazepine superior to placebo for migraine prevention (outcomes: persisting monthly migraine days, change in monthly migraine days, ≥ 50% responder rate)?

Main evidence. We found one RCT comparing oral oxcarbazepine to placebo in subjects with migraine (no distinction between episodic and chronic) (637) that met the criteria to be included in the main evidence. This study did not show benefits of oral oxcarbazepine 1200 mg daily as compared to placebo (Figure 4.2.25). The quality of evidence for the outcome persisting

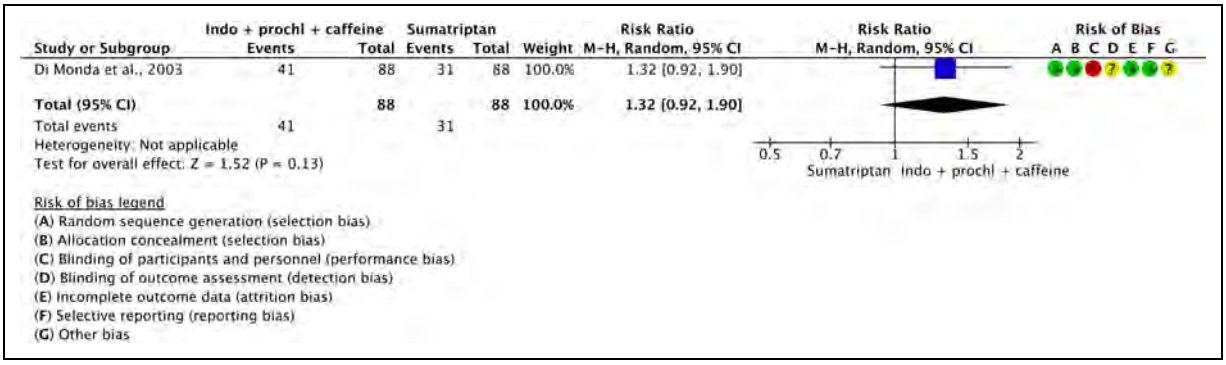


Figure 3.9.68. Forest plot showing the comparison between indomethacin 25 mg + prochlorperazine 4 mg + caffeine 75 mg suppositories and oral sumatriptan 25 mg for the outcome pain freedom at 2 h in patients with migraine.

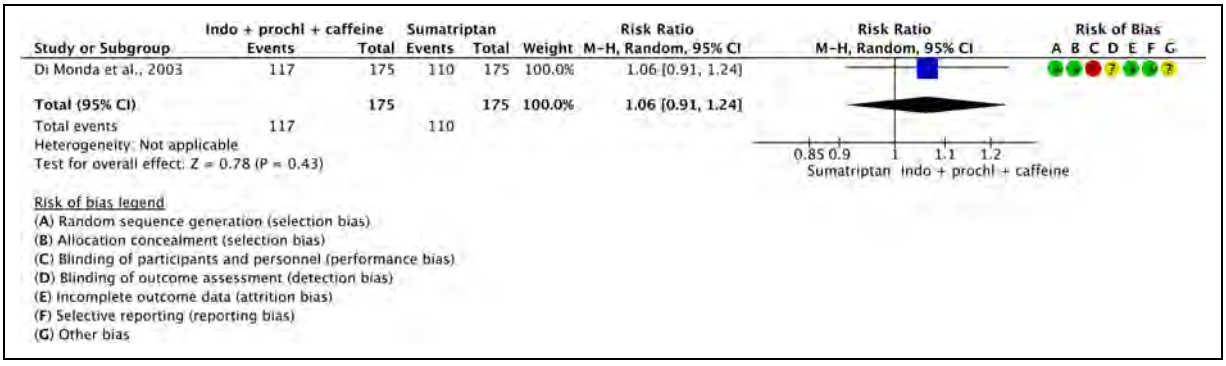


Figure 3.9.69. Forest plot showing the comparison between indomethacin 25 mg + prochlorperazine 4 mg + caffeine 75 mg suppositories and oral sumatriptan 25 mg for the outcome pain relief at 2 h in patients with migraine.

monthly migraine days was considered very low (Table 4.2.7).

Accordingly, there was no difference in the outcome ≥50% response rate in subjects treated with oxcarbazepine 1200 mg daily as compared to placebo (Figure 4.2.26). The quality of evidence for the outcome ≥50% response rate was considered very low (Table 4.2.7).

Additional evidence. None.

Evidence-based recommendation for PICO 4.2.10

In subjects with migraine, we suggest against oral oxcarbazepine for migraine prevention.
Quality of evidence: Very low (⊕⊖⊖⊖)
Strength of recommendation: Weak (↓)

Evidence-based guideline summary. Based on clinical trial results and the quality of evidence, the use of topiramate for episodic and chronic migraine prevention is recommended. There is limited evidence to support the use of valproate for episodic and chronic migraine and the use of lamotrigine and levetiracetam for episodic migraine. There is inadequate evidence to support the use of other anti-seizure medications (Figure 4.2.27).

Expert-based opinions

Optimization of topiramate use

Topic: Topiramate titration and dosing. Suggestion: We suggest the use of topiramate at a daily dosage of 100 mg for both episodic and chronic migraine. It is advisable to establish an initial target dose of 100 mg, and patients should be advised to discontinue titration if the maximum dose is reached, optimal effectiveness is achieved, or if adverse events become intolerable. A four-week titration period is recommended, with a weekly increase of 25 mg to reach the target dose. The consideration of a dosage of 200 mg daily should be evaluated on a case-by-case basis.

Rationale: RCTs have consistently demonstrated the effectiveness of topiramate at a dosage of 100 mg compared

Table 3.9.26. GRADE evidence profile table for indomethacin 25 mg + prochlorperazine 4 mg + caffeine 75 mg suppositories versus oral sumatriptan 25 mg in patients with migraine

Certainty assessment							№ of patients		Effect				
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Indomethacin + prochlorperazine + caffeine	Sumatriptan	Relative (95% CI)	Absolute (95% CI)	Quality	Importance
Pain freedom at 2 h – Indomethacin 25 mg + prochlorperazine 4 mg + caffeine 75 suppositories vs Sumatriptan 25 mg oral												
1	RCT	Very serious	Not applicable[a]	Not serious	Not serious	None	41/88 (46.6%)	31/88 (35.2%)	**RR 1.32** (0.92 to 1.90)	**113 more per 1000** (from 28 less to 317 more)	⊕⊖⊖⊖ Very Low	Critical
Pain relief at 2 h – Indomethacin 25 mg + prochlorperazine 4 mg + caffeine 75 suppositories vs Sumatriptan 25 mg oral												
1	RCT	Very serious	Not applicable[a]	Not serious	Not serious	None	117/175 (66.9%)	110/175 (62.9%)	**RR 1.06** (0.91 to 1.24)	**38 more per 1000** (from 57 less to 151 more)	⊕⊖⊖⊖ Very Low	Critical

[a]Only one trial.

to placebo in both subjects with episodic and chronic migraine. Additionally, some RCTs that have explored multiple doses of topiramate, along with real-world evidence, suggest that a dosage of 200 mg may not be more effective and could potentially be less tolerated (622). When appropriately titrated, topiramate at a dosage of 100 mg is generally considered safe for use in the treatment of migraine, despite its poorer tolerability profile in migraine subjects (670). Similar to other ASMs, a slow titration is recommended to minimize the occurrence of adverse events and improve treatment adherence. Abrupt discontinuation of topiramate should be avoided (612).

Topic: Selection of candidates for migraine prevention with topiramate. Suggestion: We suggest considering topiramate as a preventive treatment option for subjects with both episodic and chronic migraine, irrespective of medication overuse. It may be particularly advantageous for subjects with comorbidities such as epilepsy or obesity.

However, topiramate should not be used during pregnancy or lactation, and caution should be exercised when prescribing it to subjects with a history of nephrolithiasis, narrow-angle glaucoma, or moderate/severe renal or hepatic impairment. For women of childbearing potential, it is essential to inform them about the potential teratogenic effects of topiramate, and the use of a highly effective method of contraception should be strongly recommended.

Rationale: There is substantial evidence supporting the effectiveness of topiramate in reducing the frequency of migraine attacks in both subjects with and without aura. Additionally, treatment effects of topiramate appear to be independent of medication overuse, suggesting that it may not be necessary to discontinue medication overuse prior to initiating topiramate treatment (676). Because of its propensity to promote weight loss, it has potential added benefits for subjects who are overweight, have concerns about weight gain, or have co-existing conditions that could be exacerbated by weight gain (677). Topiramate is classified as pregnancy category D by the FDA, indicating positive evidence of fetal risk based on studies showing a twofold increased risk of cleft lip, and less commonly cleft palate, when topiramate is used during pregnancy (678). Breastfeeding infants typically have plasma levels of topiramate at approximately 10% to 20% of the maternal levels. Approximately one-quarter of patients discontinue topiramate due to side effects, thus careful monitoring is necessary for cognitive problems, language and behavior disturbances, as well as the risk of nephrolithiasis, glaucoma, visual defects, and weight loss (refer to the safety and tolerability section above).

Topic: Selection of candidates for migraine prevention with topiramate. Suggestion: We suggest using topiramate for episodic or chronic migraine prevention in men or women without childbearing potential.

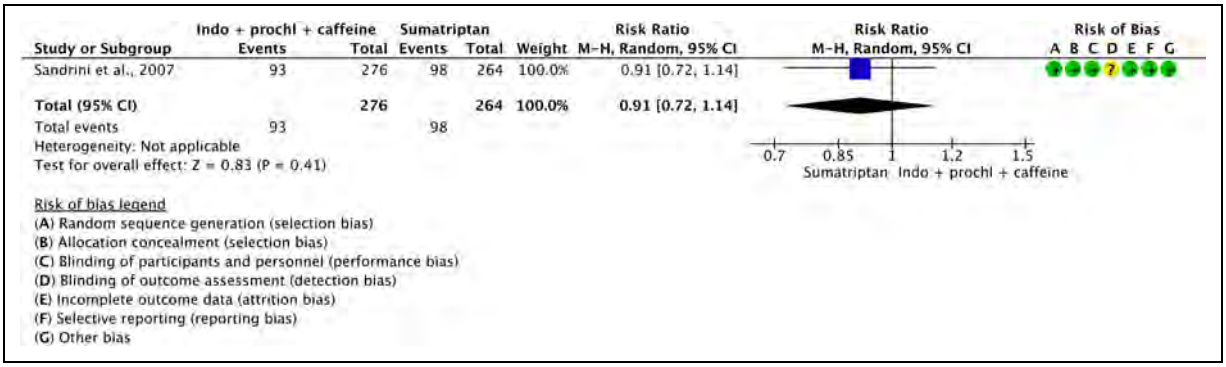


Figure 3.9.70. Forest plot showing the comparison between oral indomethacin 25 mg + prochlorperazine 2 mg + caffeine 75 mg and oral sumatriptan 50 mg for the outcome pain freedom at 2 h in patients with migraine.

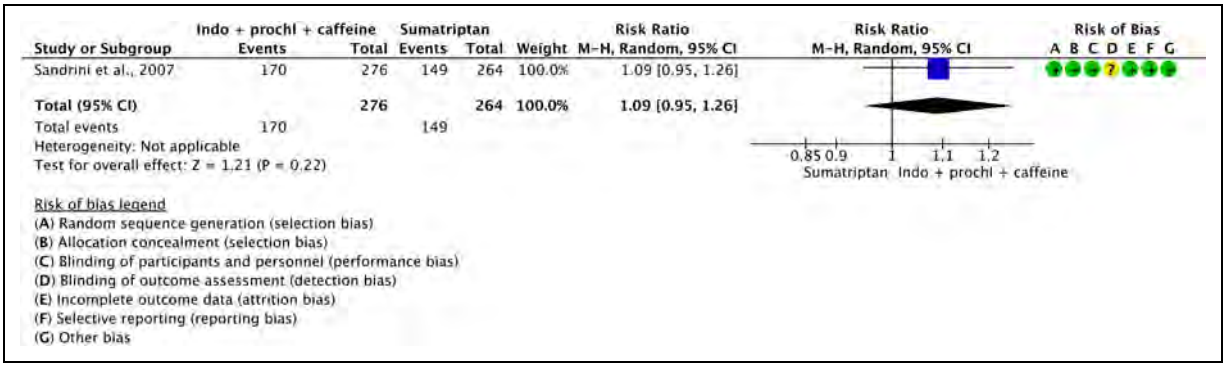


Figure 3.9.71. Forest plot showing the comparison between oral indomethacin 25 mg + prochlorperazine 2 mg + caffeine 75 mg and oral sumatriptan 50 mg for the outcome pain relief at 2 h in patients with migraine.

Rationale: Recent evidence showed that women exposed to topiramate during pregnancy have a risk of neurodevelopmental disorders and autism in offspring that is comparable to that of women exposed to valproate (679). For this reason, it is advisable to avoid the use of topiramate and other ASMs – in women with childbearing potential (680). Other migraine preventative medications without teratogenic risks should be preferred.

Optimization of valproate use

Topic: Valproate titration and dosing. Suggestion: Although the quality of the evidence is low and the recommendation is weak, sodium valproate 600–1500 mg oral once daily can be considered for episodic migraine. We suggest setting an initial target dose to be reached after a slow titration, instructing patients to stop the titration if the maximal dose is reached, or efficacy is optimal, or when AEs become intolerable. Sodium valproate could be started at 200 or 250 mg daily, increased to 200–250 mg twice a day after a week, and then increased on a weekly basis according to target dose. An extended-release formulation could be used starting at 500 mg once daily for one week.

Rationale: Despite some statistical inconsistencies with some dosages, valproate has demonstrated efficacy as a preventive treatment for migraine based on evidence from RCTs, open-label studies, and real-world evidence (620). The suggested dosage for valproate in this context typically falls within the range of 500 to 1500 mg/day. Like other ASMs, a slow titration approach is advisable to minimize the occurrence of adverse events and improve treatment adherence. It is important to note that valproate should not be abruptly discontinued (612).

Topic: Selection of candidates for migraine prevention with valproate. Suggestion: We suggest using valproate for the prevention of episodic or chronic migraine in men or in women without childbearing potential. Valproate should be avoided in patients with liver disease and thrombocytopenia due to the associated risks. However, valproate may

Table 3.9.27. GRADE evidence profile table for oral indomethacin 25 mg + prochlorperazine 2 mg + caffeine 75 mg versus oral sumatriptan 50 mg in patients with migraine

Certainty assessment							№ of patients		Effect			
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Indomethacin + prochlorperazine + caffeine	Sumatriptan	Relative (95% CI)	Absolute (95% CI)	Quality	Importance
Pain freedom at 2 h – Indomethacin 25 mg + prochlorperazine 2 mg + caffeine 75 oral vs Sumatriptan 50 mg oral												
1	RCT	Low	Not applicable[a]	Not serious	Not serious	None	93/276 (33.7%)	98/264 (37.1%)	**RR 0.91** (0.72 to 1.14)	**53 less per 1000** (from 104 less to 52 more)	⊕⊕⊕⊖ Moderate	Critical
Pain relief at 2 h – Indomethacin 25 mg + prochlorperazine 2 mg + caffeine 75 oral vs Sumatriptan 50 mg oral												
1	RCT	Low	Not applicable[a]	Not serious	Not serious	None	170/276 (61.6%)	149/264 (56.4%)	**RR 1.09** (0.95 to 1.26)	**51 more per 1000** (from 28 less to 147 more)	⊕⊕⊕⊖ Moderate	Critical

[a]Only one trial.

be a preferable option for patients with comorbid epilepsy or bipolar disorder.

Rationale: The Food and Drug Administration (FDA) and the European Medicines Agency (EMA) recommend against the use of valproate during pregnancy (classified as category X) and in women of childbearing potential. This precaution is due to the significant risk of congenital malformations and neurodevelopmental disorders associated with valproate use (675). Valproate should also be avoided in patients with compromised liver function or thrombocytopenia.

Topic: ASMs treatment duration. Suggestion: The evaluation of effectiveness should be conducted after a minimum of 8–12 weeks at the target therapeutic dose. Patients who experience a partial response should be informed that cumulative benefits may be observed over a period of 6 to 12 months with continued use. It is important to acknowledge that certain patients may require even longer treatment durations. In cases where there is no response to the treatment after at least 8–12 weeks, switching to an alternative preventive treatment is recommended. The decision to continue or discontinue treatment should be based on pragmatic therapeutic goals that are agreed upon between the patient and the clinician, and therapeutic response should be reassessed after a maximum of 6 months

Rationale: RCTs and real-world evidence have indicated that the majority of patients can experience clinical benefits from treatment within the initial three months of therapy, and there is a potential for further improvement over time (681). Early discontinuation, usually at subtherapeutic doses, could lead to ineffectiveness. Given the fluctuating nature of migraine attack frequency and the possibility of migraine improvement or remission, it is essential to regularly reassess the therapeutic response. This assessment will determine whether to continue treatment, gradually reduce the dosage, or discontinue treatment altogether if the patient no longer meets the criteria for preventive therapy (17). Since the response to treatment in migraine is highly individualized, the decision to discontinue established therapies should be based on evaluating the onset and magnitude of treatment effects.

Topic: Lamotrigine in migraine prevention. Suggestion: We suggest considering the use of lamotrigine in the range of 50 to 200 mg/day, with a slow titration, for subjects diagnosed with migraine with aura.

Rationale: Lamotrigine has primarily been studied for the prevention of migraine with aura and has demonstrated effectiveness, even for more severe types of auras such as brainstem aura and hemiplegic migraine (682,683). However, its efficacy for migraine without aura remains uncertain. The effective dose of lamotrigine has varied across studies, but a recommended dose range of 50 to

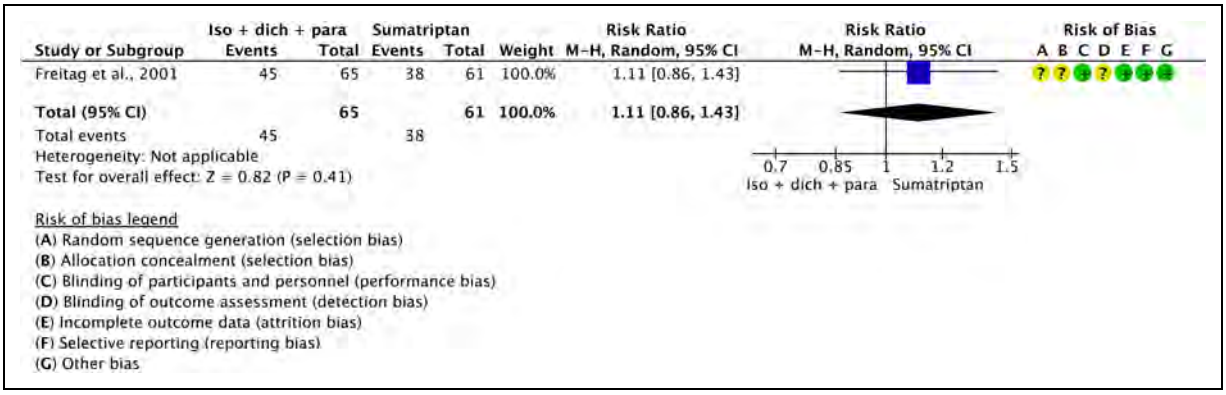


Figure 3.9.72. Forest plot showing the comparison between oral isometheptene 65 mg + dichloralphenazone 100 mg + paracetamol 325 mg and oral sumatriptan 25 mg for the outcome pain relief at 2 h in patients with migraine.

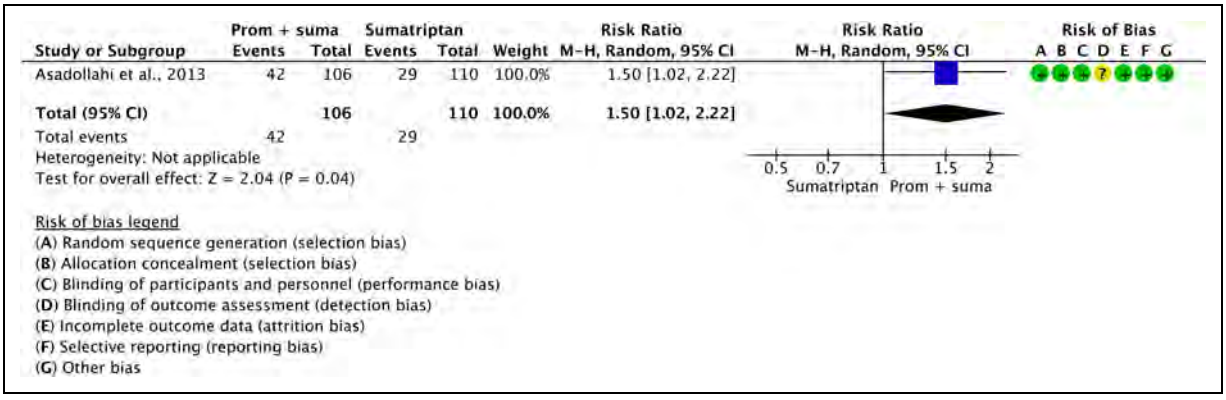


Figure 3.9.73. Forest plot showing the comparison between oral promethazine 25 mg + sumatriptan 50 mg and oral sumatriptan 50 mg alone for the outcome pain freedom at 2 h in patients with migraine.

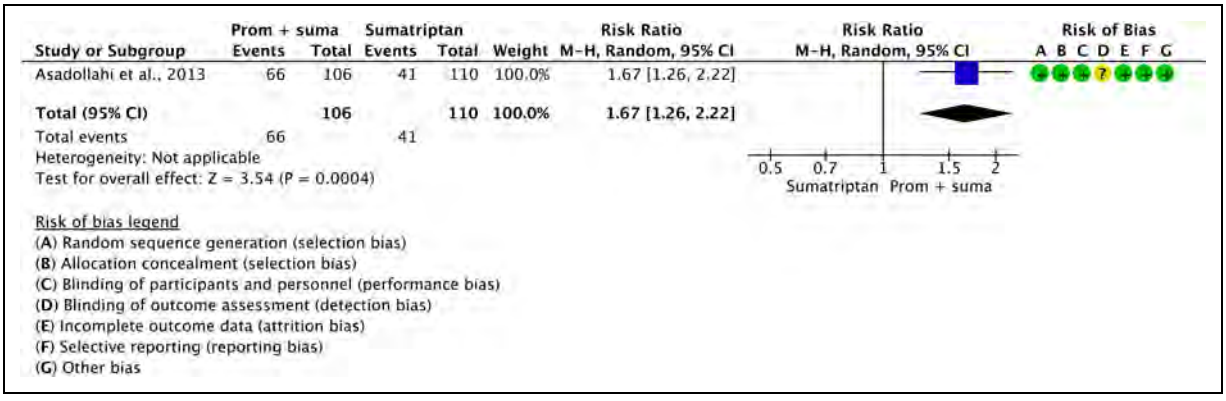


Figure 3.9.74. Forest plot showing the comparison between oral promethazine 25 mg + sumatriptan 50 mg and oral sumatriptan 50 mg alone for the outcome pain relief at 2 h in patients with migraine.

Table 3.9.28. GRADE evidence profile table for oral promethazine 25 mg + sumatriptan 50 mg versus oral sumatriptan 50 mg alone in patients with migraine

Certainty assessment							№ of patients		Effect			
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Promethazine + sumatriptan	Sumatriptan	Relative (95% CI)	Absolute (95% CI)	Quality	Importance
Pain freedom at 2 h – Promethazine 25 mg + sumatriptan 50 mg oral vs Sumatriptan 50 mg oral alone												
1	RCT	Low	Not applicable[a]	Not serious	Not serious	None	42/106 (39.6%)	29/110 (26.4%)	**RR 1.50** (1.02 to 2.22)	**132 more per 1000** (from 5 more to 322 more)	⊕⊕⊕⊖ Moderate	Critical
Pain relief at 2 h – Promethazine 25 mg + sumatriptan 50 mg oral vs Sumatriptan 50 mg oral alone												
1	RCT	Low	Not applicable[a]	Not serious	Not serious	None	66/106 (62.3%)	41/110 (37.3%)	**RR 1.67** (1.26 to 2.22)	**250 more per 1000** (from 97 more to 455 more)	⊕⊕⊕⊖ Moderate	Critical

[a]Only one trial.

200 mg/day has been suggested, with higher doses associated with an increased risk of skin rashes (684). Slower titration of lamotrigine can help mitigate the risk of cutaneous adverse events, as reported in both clinical trials and real-world studies (684).

Topic: Levetiracetam in migraine prevention. Suggestion: We propose considering the use of levetiracetam at a daily dosage range of 500 to 1000 mg for subjects experiencing episodic or chronic migraine who have encountered multiple ineffective prior treatment trials, contraindications, or intolerance issues with other classes of migraine preventive treatments, including valproate and/or topiramate.

Rationale: In the few trials and real-world studies available, levetiracetam demonstrated low to moderate levels of efficacy as a preventive treatment for subjects with migraine, although a significant difference compared to placebo was not obtained in some studies (681). Levetiracetam has generally been well-tolerated as a preventive treatment for migraine. However, the most commonly reported adverse events include somnolence, dizziness, irritability, anxiety, weight gain, asthenia, memory problems, and lack of concentration. It is important to note that levetiracetam necessitates monitoring of renal function, and patients with renal impairment may require dose adjustment when taking levetiracetam (612,619).

Topic: Switching among antiseizure medications. Suggestion: We suggest switching to alternative ASM if intolerance or lack of effectiveness is observed with one ASM following an appropriate trial at therapeutic doses.

Rationale: Given the diverse and multifaceted mechanisms of action of ASMs and the unclear mechanisms involved in migraine treatment, it is not assumed that there is a class effect for ASMs (612,616). Consequently, the ineffectiveness of treatment or the development of adverse effects with one ASM cannot predict or determine the suitability of other antiseizure medications.

4.3 Beta-blockers

Introduction. Beta-blockers are available worldwide and used for many different conditions in medicine ranging from the discovery of beneficial effects for angina pectoris in the mid-1950s to the more recent use for migraine prevention (685). Nowadays, propranolol is listed among the most commonly used preventive drugs for migraine (686–688). In 2012, the American Academy of Neurology guideline recommended beta-blockers, specifically propranolol and metoprolol, as first line therapy for preventing migraine (689). Since then, several systematic reviews and meta-analysis supported the use of beta-blockers for migraine prevention (688), but, although they were employed in clinical practice, widely used in Europe, and recommended from international guidelines, the evidence for the efficacy of beta-blockers in

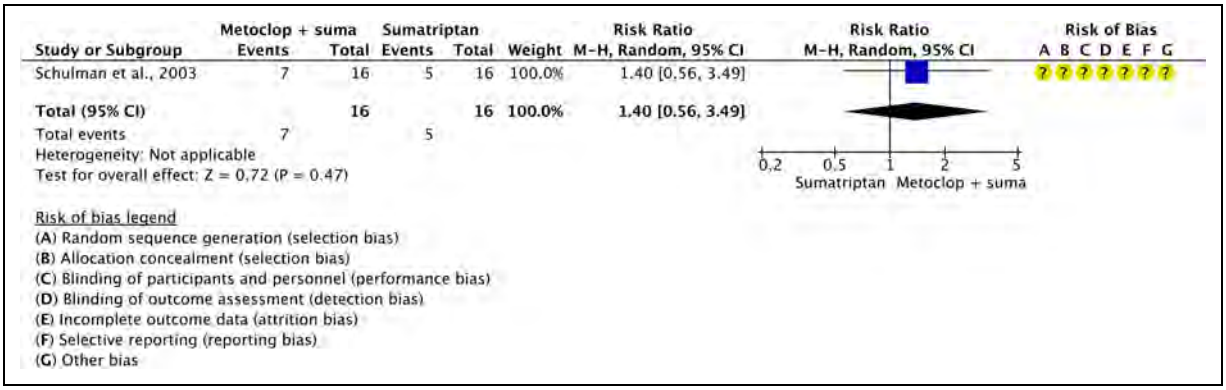


Figure 3.9.75. Forest plot showing the comparison between oral metoclopramide 10 mg + sumatriptan 50 mg and oral sumatriptan 50 mg alone for the outcome pain relief at 2 h in patients with migraine.

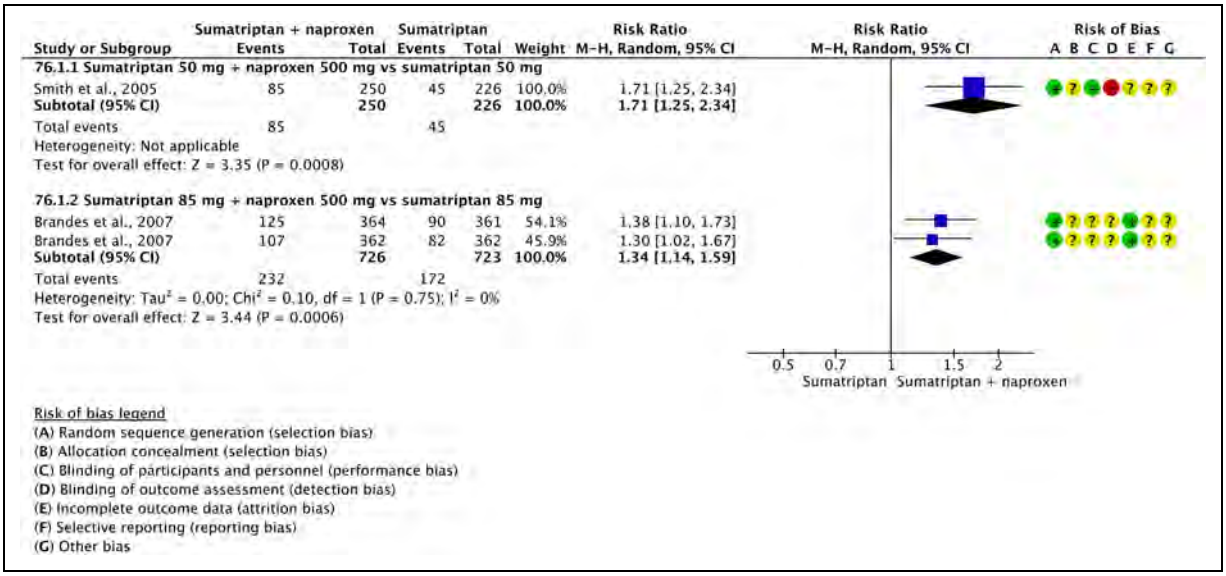


Figure 3.9.76. Forest plot showing the comparison between oral sumatriptan (50 mg or 85 mg) + naproxen 500 mg and oral sumatriptan (50 mg or 85 mg) alone for the outcome pain freedom at 2 h in patients with migraine.

migraine prevention still comes from old studies performed in the late 1970–80s (690–696). Of note, the mechanism of action of beta-blockers in migraine prevention is still not understood. It has been hypothesized that beta-blockers might penetrate the blood-brain barrier and interact with the catecholaminergic system and serotonin receptor in the brain, but the exact mechanism of action in migraine is still not understood (697,698). Beta-blockers are well-tolerated in general and considered safe in the absence of contraindications (asthma, congestive heart failure, cardiac dysrhythmia, depression), but adverse effects are reported in a minority of cases (691,699).

Section-specific methods. This section followed the general procedure to develop this guideline. However, in addition to those procedures, we also considered the outcomes of change in monthly migraine attacks and of persisting monthly migraine attacks. This choice was made to include even the oldest RCTs of beta-blockers. As the additional outcomes were not initially considered for the guideline, the resulting quality of evidence was considered by definition as very low.

Search strings for the Guideline on beta-blockers for systematic review/meta-analyses and for additional RCTs are reported in Online Appendix 4.3.1.

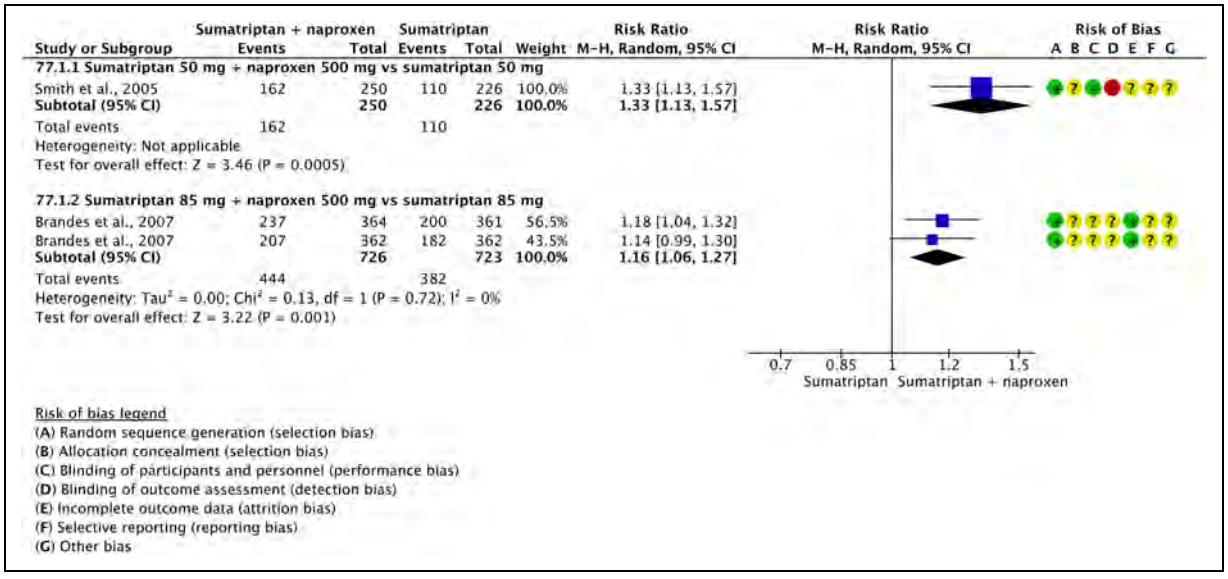


Figure 3.9.77. Forest plot showing the comparison between oral sumatriptan (50 mg or 85 mg) + naproxen 500 mg and oral sumatriptan (50 mg or 85 mg) alone for the outcome pain relief at 2 h in patients with migraine.

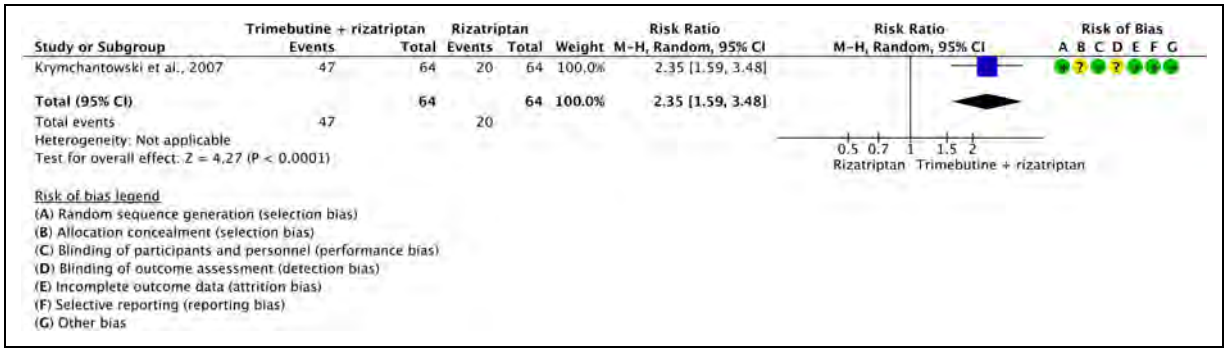


Figure 3.9.78. Forest plot showing the comparison between oral trimebutine 200 mg + rizatriptan 10 mg and oral rizatriptan 10 mg alone for the outcome pain freedom at 2 h in patients with migraine.

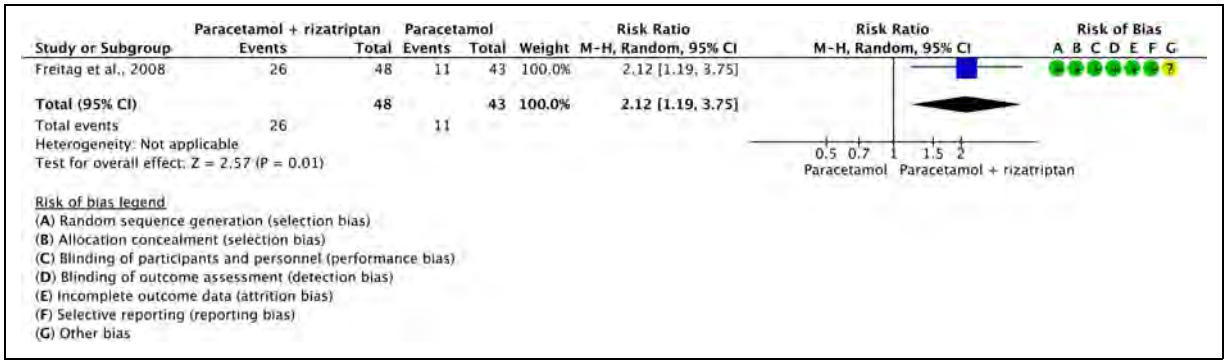


Figure 3.9.79. Forest plot showing the comparison between oral rizatriptan 10 mg + paracetamol 1000 mg and oral paracetamol 1000 mg alone for the outcome pain freedom at 2 h in patients with migraine.

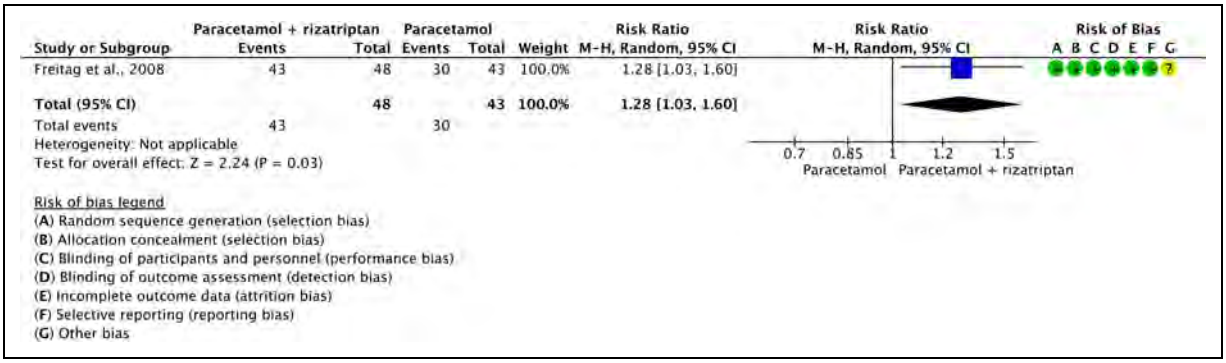


Figure 3.9.80. Forest plot showing the comparison between oral rizatriptan 10 mg + paracetamol 1000 mg and oral paracetamol 1000 mg alone for the outcome pain relief at 2 h in patients with migraine.

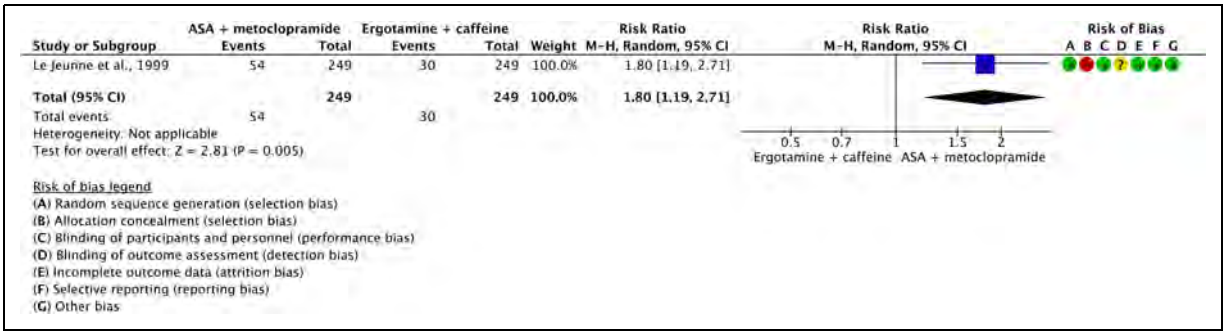


Figure 3.9.81. Forest plot showing the comparison between oral calcium carbasalate + metoclopramide 10 mg and oral ergotamine 1 mg + caffeine 100 mg for the outcome pain freedom at 2 h in patients with migraine.

Results. Overall, we retrieved 2841 references from searching for systematic reviews and meta-analyses. After duplicate removal and screening stages, we included four systematic reviews and meta-analyses (686–688,700) that were considered as sources of randomized controlled trials (RCTs). After analyzing full texts of RCTs included in these reviews, we included 21 of them in qualitative or quantitative synthesis (628,649,691,696,697,699,701–715) (Figure 4.3.1).

Overall, we retrieved 2386 references from searching for RCTs and after removing duplicates we had 2211 references to analyze. However, considering the most recent included meta-analysis on the topic (688), the analysis of additional RCTs was performed for papers published since 21 August 2018 (623 references). No additional RCT was included in meta-analyses (Figure 4.3.2). The literature update performed in May 2023 and November 2023 led to the inclusion of one further RCT (656) (Figure 4.3.2).

Overall, 22 RCTs were included in the literature synthesis to develop the evidence-based guideline. Among these studies, 12 reported a comparison between an active drug and placebo that could be included in quantitative analyses and generate recommendations, while the remaining 10 only reported head-to-head comparisons and were included in Section 4.8.

Results

Bisoprolol. **PICO 4.3.1**. In subjects with migraine (no distinction between episodic and chronic), is bisoprolol superior to placebo for migraine prevention (outcomes: persisting monthly migraine days, change in monthly migraine days, $\geq 50\%$ response rate)?

Main evidence. None.

Additional evidence. We found one RCT comparing oral bisoprolol 5 mg and 10 mg for 12 weeks to placebo (710) in subjects with migraine (no distinction between episodic and chronic) that did not meet the criteria to be included in the main evidence. The study had a very serious risk of bias, and the quality of evidence was further downgraded to very low (Figures 4.3.3 and 4.3.4).

The study showed benefits of oral bisoprolol 5 mg and 10 mg for 12 weeks over placebo considering the outcomes persisting monthly migraine days (Figure 4.3.3) and change in monthly migraine days (Figure 4.3.4).

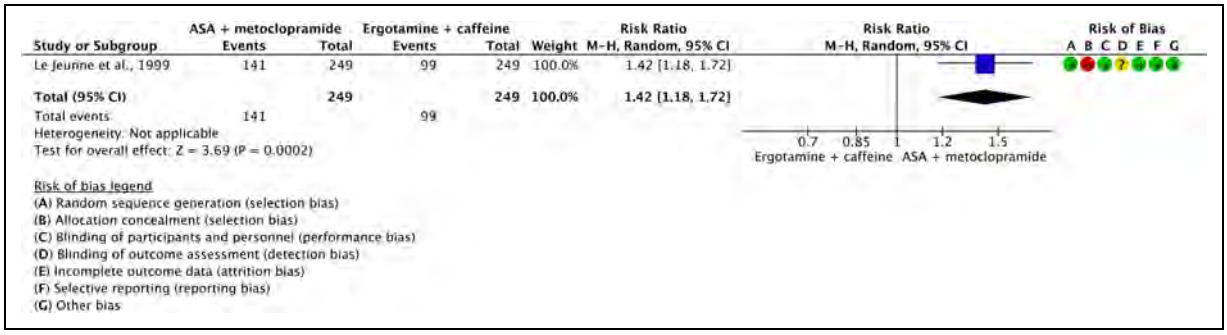


Figure 3.9.82. Forest plot showing the comparison between oral calcium carbasalate + metoclopramide 10 mg and oral ergotamine 1 mg + caffeine 100 mg for the outcome pain relief at 2 h in patients with migraine.

Evidence-based recommendation for PICO 4.3.1

In subjects with any migraine (no distinction between episodic and chronic), we suggest oral bisoprolol 5 or 10 mg daily for migraine prevention.
Quality of evidence: Very low (⊕⊖⊖⊖)
Strength of recommendation: Weak (↑)

Metoprolol. **PICO 4.3.2**. In subjects with any migraine (no distinction between episodic and chronic), is metoprolol superior to placebo for migraine prevention (outcomes: persisting monthly migraine days, change in monthly migraine days, ≥ 50% response rate)?

Main evidence. None.

Additional evidence. We found two RCTs comparing metoprolol for 8 or 12 weeks to placebo (703,708) in subjects with any migraine (no distinction between episodic and chronic) that did not meet the criteria to be included in the main evidence. These studies showed high risk of bias and the evidence was downgraded to very low.

One study showed no differences between oral metoprolol 50 mg twice a day for eight weeks and placebo (708), while the other study showed benefits of oral metoprolol 200 mg for 12 weeks over placebo considering the outcomes persisting monthly migraine days (703) (Figure 4.3.5). Regarding the outcome change in monthly migraine days, one of the studies showed benefits of oral metoprolol 200 mg for 12 weeks over placebo (703) (Figure 4.3.6).

Evidence-based recommendation for PICO 4.3.2

1) In subjects with migraine (no distinction between episodic and chronic), we suggest against oral metoprolol 50 mg twice a day for migraine prevention.

Quality of evidence: Very low (⊕⊖⊖⊖)
Strength of recommendation: Weak (↓)

2) In subjects with any migraine (no distinction between episodic and chronic), we suggest oral metoprolol 200 mg daily for migraine prevention.

Quality of evidence: Very low (⊕⊖⊖⊖)
Strength of recommendation: Weak (↑)

PICO 4.3.3. In subjects with episodic migraine, is propranolol superior to placebo for migraine prevention (outcomes: persisting monthly migraine days, change in monthly migraine days, ≥ 50% responder rate)?

Main evidence. We found one RCT comparing propranolol to placebo in subjects with episodic migraine (628) that met the criteria for main evidence. The risk of bias was considered serious (Figures 4.3.7 and 4.3.8). The RCT showed benefit of oral propranolol 160 mg daily over placebo considering the outcomes of change in monthly migraine days (Figure 4.3.7) and ≥50% responder rate (Figure 4.3.8). The quality of evidence was considered low (Table 4.3.1).

Additional evidence. None.

Evidence-based recommendation for PICO 4.3.3

In subjects with episodic migraine, we suggest oral propranolol 160 mg daily over placebo for migraine prevention.
Quality of evidence: Low (⊕⊕⊖⊖)
Strength of recommendation: Weak (↑)

PICO 4.3.4. In subjects with migraine (no distinction between episodic and chronic), is propranolol superior to placebo for migraine prevention (outcomes: persisting monthly migraine days, change in monthly migraine days, ≥ 50% responder rate)?

Table 3.9.29. GRADE evidence profile table for oral calcium carbasalate + metoclopramide 10 mg versus oral ergotamine 1 mg + caffeine 100 mg in patients with migraine

Certainty assessment							№ of patients		Effect			
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	ASA + metoclopramide	Ergotamine + caffeine	Relative (95% CI)	Absolute (95% CI)	Quality	Importance
Pain freedom at 2 h – Acetylsalicylic acid 900 mg + Metoclopramide 10 mg oral vs Ergotamine 1 mg + Caffeine 100 mg oral												
1	RCT	High	Not applicable[a]	Not serious	Not serious	None	54/249 (21.7%)	30/249 (12.0%)	**RR 1.80** (1.19 to 2.71)	**96 more per 1000** (from 23 more to 206 more)	⊕⊖⊖⊖ Very Low	Critical
Pain relief at 2 h – Acetylsalicylic acid 900 mg + Metoclopramide 10 mg oral vs Ergotamine 1 mg + Caffeine 100 mg oral												
1	RCT	High	Not applicable[a]	Not serious	Not serious	None	141/249 (56.6%)	99/249 (39.8%)	**RR 1.42** (1.18 to 1.72)	**167 more per 1000** (from 72 more to 286 more)	⊕⊖⊖⊖ Very Low	Critical

[a]Only one trial.

Main evidence. We found one RCT comparing propranolol to placebo (709) that met the criteria for main evidence. The risk of bias was considered not serious (Figures 4.3.9 and 4.3.10). The RCT showed no benefits of oral propranolol 160 mg daily over placebo considering the outcomes of persisting monthly migraine days (Figure 4.3.9) and ≥50% responder rate (Figure 4.3.10). The quality of evidence was considered moderate (Table 4.3.2) due to the availability of only one RCT.

Additional evidence. We found eight RCTs comparing propranolol to placebo (691,696,697,707,712–715) that did not meet the criteria for main evidence. The overall risk of bias was considered serious (Figures 4.3.11 and 4.3.12). The RCTs showed benefits of oral propranolol 80 mg and 160 mg daily over placebo considering the outcome of ≥50% responder rate (Figure 4.3.11) and of oral propranolol 160 mg daily over placebo considering the outcome of persisting monthly migraine attacks (Figure 4.3.12). The quality of evidence was considered very low due to the assessment of an additional outcome – persisting monthly migraine attacks – that was not considered for the rest of the guideline.

Evidence-based recommendation for PICO 4.3.4

1) In subjects with migraine (no distinction between episodic and chronic), we suggest oral propranolol 160 mg daily over placebo for migraine prevention.
Quality of evidence: Very Low (⊕⊖⊖⊖)
Strength of recommendation: Weak (↑)

2) In subjects with migraine (no distinction between episodic and chronic), we suggest against propranolol 80–120 mg daily over placebo for migraine prevention.
Quality of evidence: Very Low (⊕⊖⊖⊖)
Strength of recommendation: Weak (↓)

[NOTE: The recommendation in favor of propranolol 160 mg daily was based upon the large number of positive RCTs available, even if the only RCT that could be included in the main evidence suggests against the benefit of propranolol. Evidence in favor of propranolol 160 mg daily refers to the slow-release formulation].

Safety and tolerability of beta-blockers. Warnings and contraindications: Beta-blockers are contraindicated in patients with asthma, congestive heart failure, cardiac dysrhythmia, depression (688,704,716). Indeed, due to the risk of bradyarrhythmia, they should not be used in recent myocardial infarction, coronary artery disease, congestive heart failure (716). Extreme caution is to be used in patients with a history of asthma due to concerns of decreasing pulmonary function and inducing bronchospasm (711,716). Data from

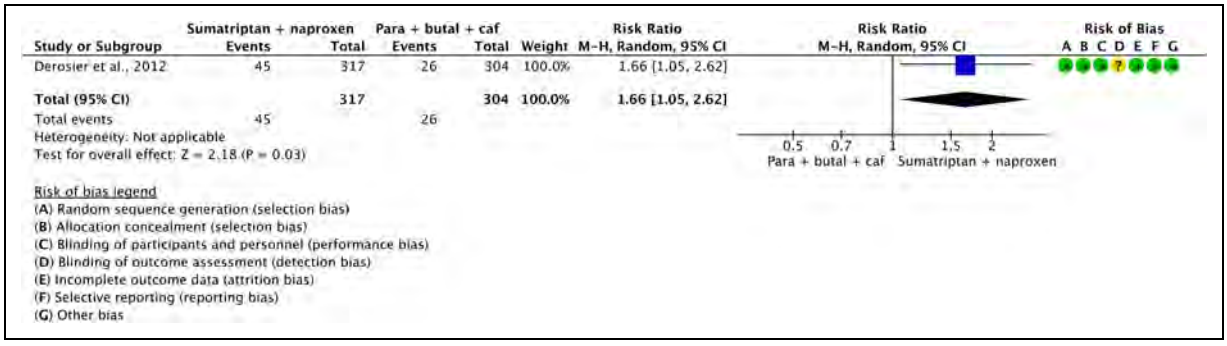


Figure 3.9.83. Forest plot showing the comparison between oral sumatriptan 85 mg + naproxen 500 mg and oral paracetamol 325 mg + butalbital 50 mg + caffeine 40 mg for the outcome pain freedom at 2 h in patients with migraine.

the literature indicates that depression is commonly reported after the use of beta-blockers (688,704,709). In patients taking triptans more caution should be used, as beta-blockers have been shown to increase plasma concentrations of triptans (716). Considering the risk of myasthenic crisis exacerbation, attention is needed in patients with myasthenia gravis (717). Finally, beta-blockers should not be used in hemiplegic migraine, as safety of these populations was not investigated, even if the literature is lacking on this issue (716). Bradycardia and hypotension may limit their use in cardiopathic patients.

Serious safety concerns: RCTs and real world-evidence highlighted some serious safety concerns. Real world evidence demonstrated a potentially fatal outcome in patients with asthma (716). Caution is necessary in older cardiopathic subjects. These patients may benefit from the use of low dose of cardioselective beta-blockers (688,716).

Tolerability: Beta-blockers present some adverse events that might limit their use in the general population. These effects, typical of non-cardioselective beta-blockers, are mostly associated with the antagonism of beta-2 receptors located in smooth muscle cells in the lungs, pancreas, bladder, uterus, blood vessels, and gastrointestinal system, thus affecting smooth muscle relaxation in bronchioles, blood vessels, and the uterus, as well as altering metabolic processes such as glycogenolysis and insulin release from pancreatic beta cells (716). Moreover, lipophilic beta-blockers could cross the blood–brain barrier, leading to depression, fatigue, and sleep disorders (688,704,709,716). Also, beta-blockers can cause impaired glucose metabolism, with new-onset diabetes (709,716). Also, gastrointestinal complaints, with nausea, abdominal cramps and diarrhea, weight gain, paresthesia, and Raynaud's phenomenon, dizziness and vertigo are reported (688,695,704,709,711,716,718).

Evidence-based guideline summary

There is low-quality evidence to suggest oral bisoprolol 5–10 mg, oral metoprolol 200 mg, and oral propranolol 160 mg for migraine prevention (Figure 4.3.7).

Expert based opinions

Topic: Beta-blockers other than bisoprolol, metoprolol, and propranolol. Suggestion: In subjects with migraine, we suggest considering timolol (20 or 30 mg daily) or atenolol 100 mg daily as an alternative to bisoprolol, metoprolol, and propranolol for migraine prevention.

Rationale: Along with bisoprolol, metoprolol, and propranolol, several other beta-blockers were tested against placebo in RCTs, including acebutolol 800 mg, alprenolol 200 mg, atenolol 100 mg, nadolol (80 to 240 mg), oxprenolol 240 mg, pindolol 7.5 mg to 15 mg, and timolol 20 to 30 mg (688). According to the most recent meta-analysis on the topic, atenolol 100 mg proved more effective than placebo with low quality of evidence, timolol 20 or 30 mg proved more effective than placebo with moderate quality of evidence and atenolol 100 mg proved more effective than placebo with low quality of evidence, while acebutolol, alprenolol, nadolol, oxprenolol, and pindolol proved not effective against placebo (688).

Optimization of beta-blockers

Topic: Bisoprolol titration and dosing. Suggestion: When starting migraine prevention with bisoprolol we suggest a dosage of 5 mg daily.

Rationale: a single RCT provided low evidence that administration of bisoprolol 5 mg provides the same benefits compared with bisoprolol 10 mg. The incidence of AEs for both dosages were similar.

Topic: Metoprolol titration and dosing. Suggestion: When starting metoprolol in individuals with episodic or chronic migraine, we suggest 200 mg daily. We suggest starting with 100 mg, increasing to 200 mg after the first week. Dose modifications should be accurately personalized balancing efficacy and AEs.

Rationale: Metoprolol is a cardio-selective beta-blocker. We found one RCT showing superiority of metoprolol 200 mg for 12 weeks versus placebo (703) in subjects with

Table 3.9.30. GRADE evidence profile table for oral sumatriptan 85 mg + naproxen 500 mg versus oral paracetamol 325 mg + butalbital 50 mg + caffeine 40 mg in patients with migraine

Certainty assessment							№ of patients		Effect			
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Sumatriptan + Naproxen	Paracetamol + Butalbital + Caffeine	Relative (95% CI)	Absolute (95% CI)	Quality	Importance
Pain freedom at 2 h – Sumatriptan 85 mg + Naproxen 500 mg oral vs Paracetamol 325 mg + Butalbital 50 mg + Caffeine 40 mg oral												
1	RCT	Low	Not applicable[a]	Not serious	Not serious	None	45/317 (14.2%)	26/304 (8.6%)	**RR 1.56** (1.05 to 2.62)	**48 more per 1000** (from 4 more to 139 more)	⊕⊕⊕⊖ Moderate	Critical

[a]Only one trial.

migraine. A minority of patients experienced bradycardia and fatigue, with a low rate of discontinuation. Metoprolol has been shown to have a positive effect on the frequency as well as on the intensity of migraine attacks in an open study (719).

Topic: Propranolol titration and dosing. Suggestion: When starting propranolol in subjects with episodic or chronic migraine, we suggest starting with a 40 mg dose and increasing by 40 mg every week for a maximum total dose of 160 mg.

Rationale: In the RCTs of propranolol that were included in the present guideline, the drug was given in multiple daily administrations of 40 mg each to ensure safety. Starting with lower doses and gradually increasing would ensure an adequate monitoring of adverse events. A drop of heart rate and/or blood pressure might require withdrawal of the drug or the use of a decreased dose.

4.4 Calcium channel blockers and blood pressure-lowering agents

Introduction. Calcium channel blockers and drugs acting on the renin-angiotensin system (RAS), such as angiotensin-converting-enzyme (ACE) inhibitors and angiotensin receptor blockers (ARBs), have been used for migraine prevention.

Flunarizine is one of many preventive treatment options for migraine (720–722). Flunarizine is a nonselective calcium antagonist, which has also been shown to block voltage-gated sodium channels. Action at these two sites may reduce neuronal excitability and normalize cortical hyperexcitability in migraine. Furthermore, flunarizine acts as a D2 dopamine antagonist and has in this regard been shown to possess (at high doses) comparable antipsychotic efficacy as haloperidol (723). It has also been shown that flunarizine can reduce the number and duration of cortical spreading depolarization (CSD) waves (724) and can alleviate CSD-induced mitochondrial injury (725). Finally, flunarizine increases leptin levels, and this activity has been suggested to reflect leptin resistance, which may potentially explain the treatment-related weight gain (565). Flunarizine is largely regarded as effective, inexpensive, and easy to use with its once-daily dosing (721).

ACE inhibitors and angiotensin receptor blockers (ARBs) modulate RAS, which contributes to control of maintenance of extracellular volume homeostasis and blood pressure (726). Renin is a plasmatic enzyme produced by kidneys. It converts angiotensinogen to angiotensin I, which is subsequently converted to angiotensin II by ACE. Angiotensin II can bind to specific receptors (AT), the most important being AT1 and AT2 (727). AT1 receptors are implicated in mediating vasoconstriction, sympathetic nervous system activation and cardiovascular

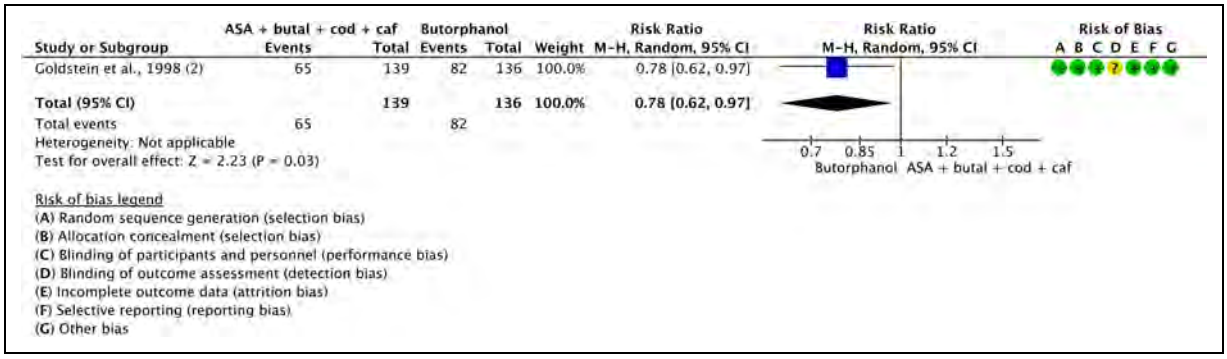


Figure 3.9.84. Forest plot showing the comparison between oral acetylsalicylic acid 325 mg + butalbital 50 mg + codeine 30 mg + caffeine 40 mg and butorphanol 2 mg nasal spray for the outcome pain relief at 2 h in patients with migraine.

remodeling, while AT2 activation results in vasodilation, antiproliferative effects and apoptosis (728,729). RAS involvement in migraine is not fully understood. Centrally, RAS may influence endorphin metabolism altering nociception, cerebrovascular blood flow, neurohormone levels, neurotransmitter levels, mast cells degranulation, proinflammatory cytokines and NO production, oxidative stress, vasodilation and neurogenic inflammation (730,731). Moreover, RAS modulates cerebrovascular blood flow, and inhibition and blockade of RAS may provide protection against cortical oligemia that occurs during a migraine attack. There may also be a genetic association between RAS and migraine. In fact, the ACE-D allele is significantly more frequent in subjects with migraine compared to controls (732,733), and the ACE-DD genotype positively correlated with a higher frequency of migraine attacks (734). ACE inhibitors (captopril, enalapril, lisinopril) are suggested to be effective for the prevention of migraine because they block the ACE enzyme preventing the conversion of angiotensin I to angiotensin II. ARBs represent another option for pharmacological prevention of migraine (735), because they compete directly with angiotensin II at its receptor (736). Candesartan and telmisartan are selective and competitive ARB at the AT1. In this way, they inhibit the sympathetic tone by reducing angiotensin II-induced vasopressin and adrenal catecholamine release and decreasing expression of nitric oxide-synthase (737). Furthermore, ARBs can partially agonize peroxisome proliferator-activated receptor gamma which exerts an anti-inflammatory action in the brain, by reducing levels of tumor necrosis factor and inducible nitric oxide (730).

Section-specific methods. This section followed the general procedure to develop this guideline.

Search strings for the guideline on antihypertensives for systematic review/meta-analysis and for additional RCTs are reported in Online Appendix 4.4.1.

Results. Overall, we retrieved 1498 references from searching for systematic reviews and meta-analyses. After duplicate removal and screening stages, we included eight systematic reviews and meta-analyses that were considered as sources of randomized controlled trials (RCTs). After analyzing full texts of these RCTs, we included four RCTs in the quantitative synthesis (709,736,738,739) (Figure 4.4.1).

Overall, we retrieved 1525 references from searching for RCTs and after removing duplicates we had 1438 references to analyze. However, considering the most recent included systematic review and meta-analysis on the topic, the analysis of additional RCTs was performed for papers published since January 2020 (217 references). We finally included no additional RCTs (Figure 4.4.2). No additional RCTs were included after the literature update performed in May and in November 2023 (Figure 4.4.2).

Overall, four studies were included in the literature review and quantitative synthesis (meta-analyses) to develop the evidence-based guideline (709,736,738,739). All of them reported a comparison between an active drug and placebo and were presented in this section. One RCT also included a head-to-head comparison (709) which was reported in Section 4.8.

Candesartan. **PICO 4.4.1.** In subjects with any migraine (no distinction between episodic and chronic), is candesartan superior to placebo in migraine prevention (outcomes: persisting monthly migraine days, change in monthly migraine days, ≥ 50% responder rate)?

Main evidence. We found one RCT comparing oral candesartan to placebo (709) in subjects with migraine that met the criteria to be included in main evidence. The risk of bias was considered not serious (Figures 4.4.3 and 4.4.4). The study did not show a significant benefit of oral candesartan 16 mg compared to placebo considering the outcome persisting monthly migraine days while it showed significant benefit for the outcome ≥50% responder rate (Figures

Table 3.9.31. GRADE evidence profile table for oral acetylsalicylic acid 325 mg + butalbital 50 mg + codeine 30 mg + caffeine 40 mg versus butorphanol 2 mg nasal spray in patients with migraine

Certainty assessment							№ of patients		Effect			
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	ASA + butalbital + codeine + caffeine	Butorphanol	Relative (95% CI)	Absolute (95% CI)	Quality	Importance
Pain freedom at 2 h –Acetylsalicylic acid 325 mg + codeine 30 mg + caffeine 40 mg oral vs Butorphanol 2 mg nasal spray												
1	RCT	Low	Not applicable[a]	Not serious	Not serious	None	65/139 (46.8%)	82/136 (60.3%)	**RR 0.78** (0.62 to 0.97)	**100 less per 1000** (from 173 less to 14 less)	⊕⊕⊕⊖ Moderate	Critical

[a]Only one trial.

4.4.3 and 4.4.4). The quality of evidence for both outcomes was considered low (Table 4.4.1).

Additional evidence. None.

Evidence-based recommendation for PICO 4.4.1

In subjects with migraine (no distinction between episodic and chronic), we suggest oral candesartan 16 mg for migraine prevention.
Quality of evidence: Low (⊕⊕⊖⊖).
Strength of the recommendation: Weak (↑)

PICO 4.4.2. In subjects with episodic migraine, is candesartan superior to placebo in migraine prevention (outcomes: persisting monthly migraine days, change in monthly migraine days, ≥ 50% responder rate)?

Main evidence. We found one RCT comparing oral candesartan to placebo (738) in subjects with episodic migraine that met the criteria to be included in main evidence. The study showed a significant benefit of oral candesartan 16 mg compared to placebo considering the outcome persisting monthly migraine days (Figure 4.4.5). The quality of evidence for the selected outcomes was considered moderate (Table 4.4.2).

Additional evidence. None.

Evidence-based recommendation for PICO 4.4.2

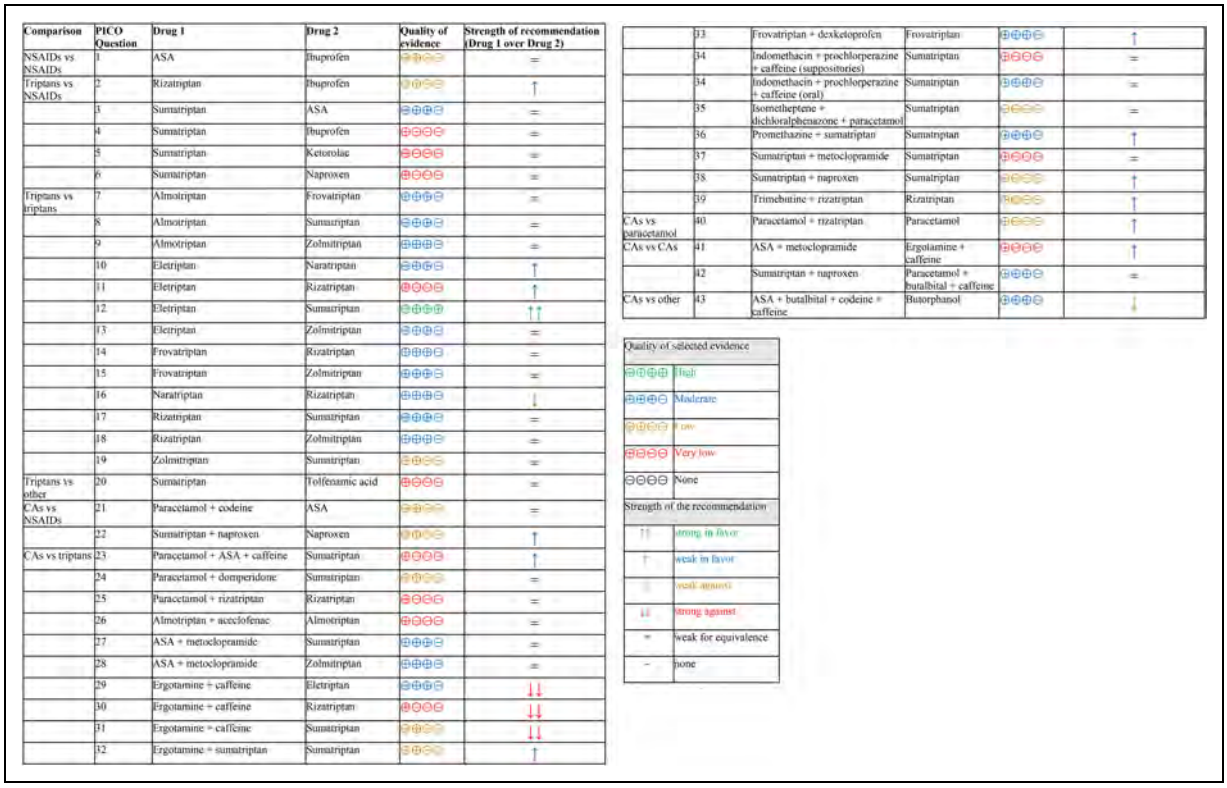
In subjects with episodic migraine, we suggest oral candesartan 16 mg for migraine prevention.
Quality of evidence: Moderate (⊕⊕⊕⊖)
Strength of the recommendation: Weak (↑)

Lisinopril. **PICO 4.4.3.** In subjects with episodic migraine, is lisinopril superior to placebo in migraine prevention (outcomes: persisting monthly migraine days, change in monthly migraine days, ≥ 50% responder rate)?

Main evidence. We found one RCT comparing oral lisinopril to placebo (739) in subjects with migraine that met pre-defined criteria to be included in main evidence (Figure 4.4.6).

Its analysis showed a significant benefit of oral lisinopril 20 mg compared to placebo for the outcome persisting monthly migraine days (Figure 4.4.6). No other outcome was reported. The quality of evidence was considered low (Table 4.4.3).

Additional evidence. None.



Comparison	PICO Question	Drug 1	Drug 2	Quality of evidence	Strength of recommendation (Drug 1 over Drug 2)
NSAIDs vs NSAIDs	1	ASA	Ibuprofen	⊕⊕⊖⊖	=
Triptans vs NSAIDs	2	Rizatriptan	Ibuprofen	⊕⊕⊖⊖	↑
	3	Sumatriptan	ASA	⊕⊕⊕⊖	=
	4	Sumatriptan	Ibuprofen	⊕⊖⊖⊖	=
	5	Sumatriptan	Ketorolac	⊖⊖⊖⊖	=
	6	Sumatriptan	Naproxen	⊕⊖⊖⊖	=
Triptans vs triptans	7	Almotriptan	Frovatriptan	⊕⊕⊕⊖	=
	8	Almotriptan	Sumatriptan	⊕⊕⊕⊖	=
	9	Almotriptan	Zolmitriptan	⊕⊕⊕⊖	=
	10	Eletriptan	Naratriptan	⊕⊕⊖⊖	↑
	11	Eletriptan	Rizatriptan	⊕⊖⊖⊖	↑
	12	Eletriptan	Sumatriptan	⊕⊕⊕⊕	↑↑
	13	Eletriptan	Zolmitriptan	⊕⊕⊕⊖	=
	14	Frovatriptan	Rizatriptan	⊕⊕⊕⊖	=
	15	Frovatriptan	Zolmitriptan	⊕⊕⊕⊖	=
	16	Naratriptan	Rizatriptan	⊕⊕⊕⊖	↓
	17	Rizatriptan	Sumatriptan	⊕⊕⊕⊖	=
	18	Rizatriptan	Zolmitriptan	⊕⊕⊕⊖	=
	19	Zolmitriptan	Sumatriptan	⊕⊕⊖⊖	=
Triptans vs other	20	Sumatriptan	Tolfenamic acid	⊕⊖⊖⊖	=
CAs vs NSAIDs	21	Paracetamol + codeine	ASA	⊕⊕⊖⊖	=
	22	Sumatriptan + naproxen	Naproxen	⊕⊕⊖⊖	↑
CAs vs triptans	23	Paracetamol + ASA + caffeine	Sumatriptan	⊕⊖⊖⊖	↑
	24	Paracetamol + domperidone	Sumatriptan	⊕⊕⊖⊖	=
	25	Paracetamol + rizatriptan	Rizatriptan	⊕⊖⊖⊖	=
	26	Almotriptan + aceclofenac	Almotriptan	⊕⊖⊖⊖	=
	27	ASA + metoclopramide	Sumatriptan	⊕⊕⊕⊖	=
	28	ASA + metoclopramide	Zolmitriptan	⊕⊕⊕⊖	=
	29	Ergotamine + caffeine	Eletriptan	⊕⊕⊕⊖	↓↓
	30	Ergotamine + caffeine	Rizatriptan	⊕⊖⊖⊖	↓↓
	31	Ergotamine + caffeine	Sumatriptan	⊕⊕⊖⊖	↓↓
	32	Ergotamine + sumatriptan	Sumatriptan	⊕⊕⊖⊖	↑
	33	Frovatriptan + dexketoprofen	Frovatriptan	⊕⊕⊕⊖	↑
	34	Indomethacin + prochlorperazine + caffeine (suppositories)	Sumatriptan	⊕⊖⊖⊖	=
	34	Indomethacin + prochlorperazine + caffeine (oral)	Sumatriptan	⊕⊕⊕⊖	=
	35	Isometheptene + dichloralphenazone + paracetamol	Sumatriptan	⊕⊖⊖⊖	=
	36	Promethazine + sumatriptan	Sumatriptan	⊕⊕⊕⊖	↑
	37	Sumatriptan + metoclopramide	Sumatriptan	⊕⊖⊖⊖	=
	38	Sumatriptan + naproxen	Sumatriptan	⊕⊖⊖⊖	↑
	39	Trimebutine + rizatriptan	Rizatriptan	⊕⊖⊖⊖	↑
CAs vs paracetamol	40	Paracetamol + rizatriptan	Paracetamol	⊕⊖⊖⊖	↑
CAs vs CAs	41	ASA + metoclopramide	Ergotamine + caffeine	⊕⊖⊖⊖	↑
	42	Sumatriptan + naproxen	Paracetamol + butalbital + caffeine	⊕⊕⊕⊖	=
CAs vs other	43	ASA + butalbital + codeine + caffeine	Butorphanol	⊕⊕⊕⊖	↓

Quality of selected evidence	
⊕⊕⊕⊕	High
⊕⊕⊕⊖	Moderate
⊕⊕⊖⊖	Low
⊕⊖⊖⊖	Very low
⊖⊖⊖⊖	None
Strength of the recommendation	
↑↑	strong in favor
↑	weak in favor
↓	weak against
↓↓	strong against
=	weak for equivalence
-	none

Figure 3.9.85. Summary of evidence for head-to-head comparisons of preventive treatments.

Evidence-based recommendation for PICO 4.4.3

In subjects with episodic migraine, we suggest oral lisinopril 20 mg for migraine prevention.
Quality of evidence: Low (⊕⊕⊖⊖)
Strength of the recommendation: Weak (↑)

Telmisartan. **PICO 4.4.4.** In subjects with episodic migraine, is telmisartan superior to placebo in migraine prevention (outcomes: persisting monthly migraine days, change in monthly migraine days, ≥ 50% response rate)?

Main evidence. We found one RCT comparing oral telmisartan to placebo (736) in subjects with migraine that met the criteria to be included in main evidence (Figures 4.4.7 and 4.4.8). Its analysis did not show a significant benefit of oral telmisartan 80 mg compared to placebo for the outcomes change in monthly migraine days and for the outcome ≥50% response rate (Figure 4.4.7 and 4.4.8). The quality of evidence for the selected outcomes varies from moderate to low and the overall quality of evidence across both outcomes was rated as low (Table 4.4.4).

Additional evidence. None.

Evidence-based recommendation for PICO 4.4.4

In subjects with episodic migraine, we suggest against oral telmisartan 80 mg for migraine prevention.
Quality of evidence: Low (⊕⊕⊖⊖)
Strength of the recommendation: Weak (↓)

Safety and tolerability

Calcium-channel blockers. Warnings and contraindications: Parkinson disease or extrapyramidal disturbances (740), obesity (741), pregnancy, and breast feeding represent contraindications to the use of calcium channel blockers.

Serious safety concerns: The adverse effects of flunarizine can be minimized by selecting the appropriate dose, giving drug holidays, prescribing the drug at night and avoiding its use in older individuals; the most relevant safety warning regards subjects with depression (720).

Tolerability: Adverse events to flunarizine include somnolence, asthenia, weight gain, depression and extrapyramidal symptoms in the long-term treatment and occur more frequently in elderly subjects (720,740).

ACE inhibitors. Warnings and contraindications: ACE inhibitors are contraindicated in patients with a history of

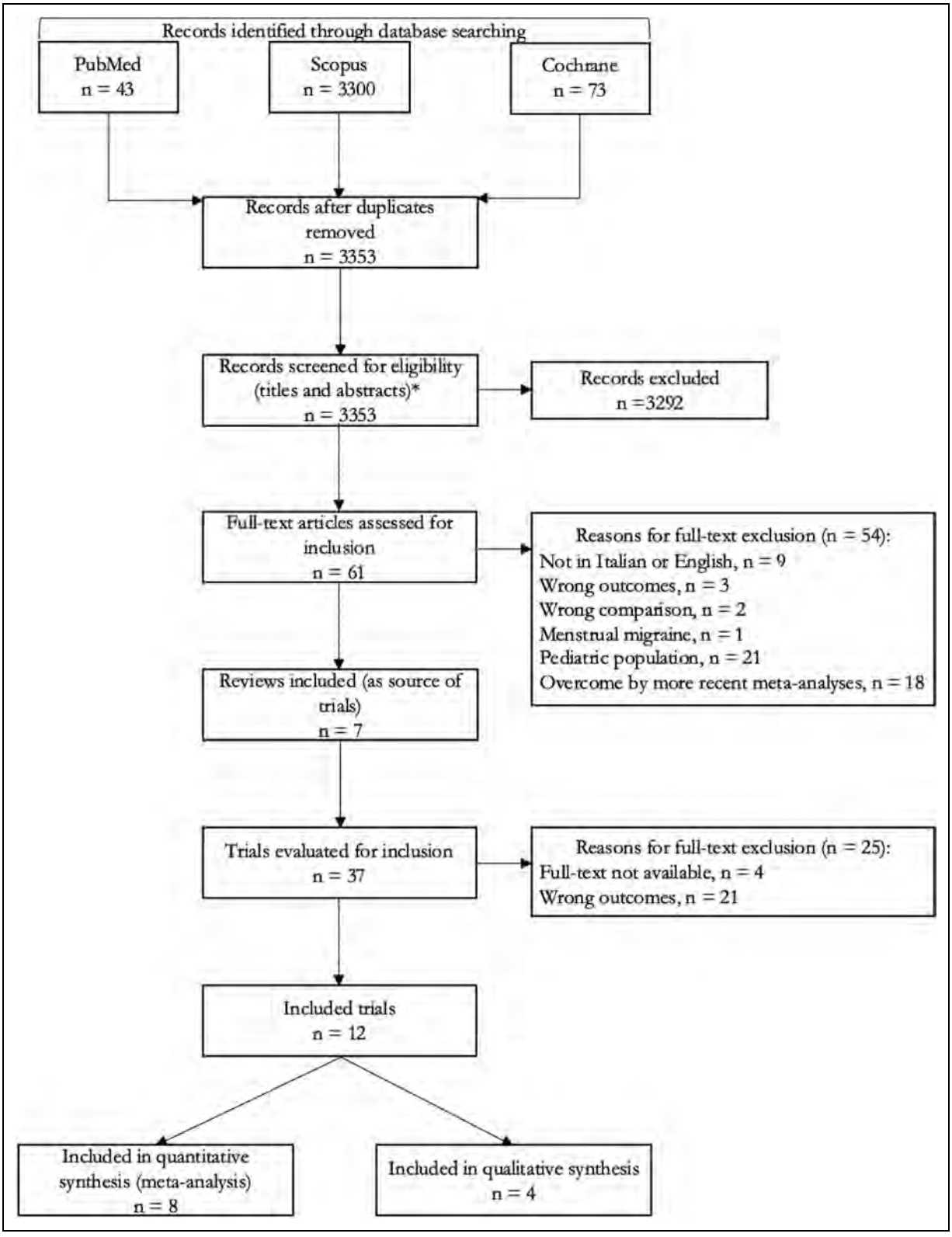


Figure 4.1.1. Meta-analysis selection flow chart - antidepressants.

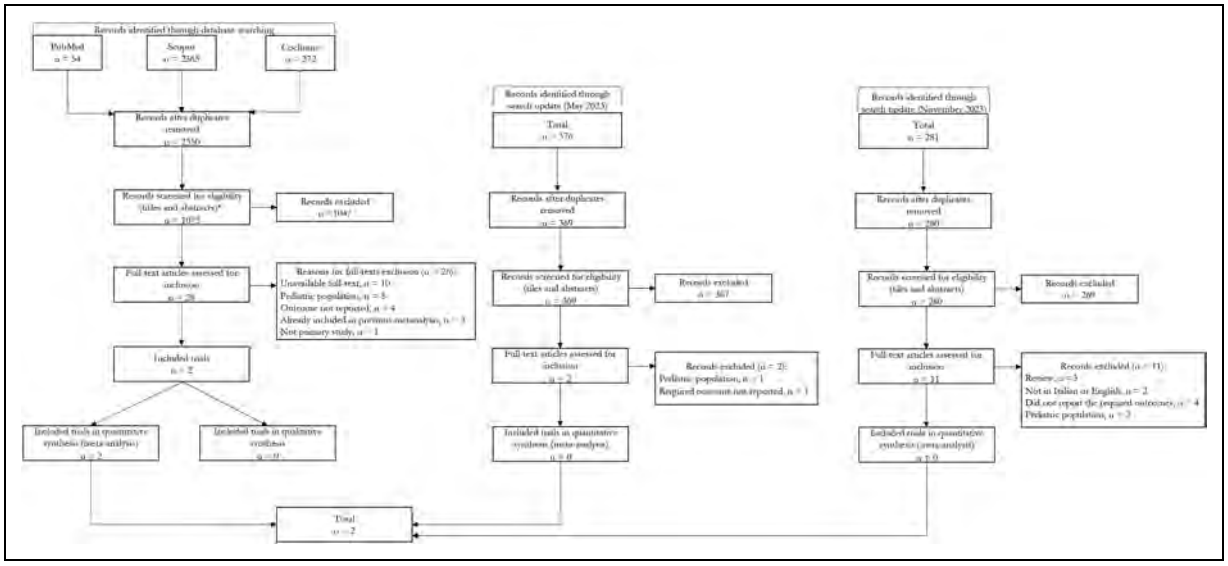


Figure 4.1.2. RCT selection flow chart - antidepressants.
*trials published since 2018 (for SSRIs/SNRIs) and since 2016 (for tricyclics) were screened.

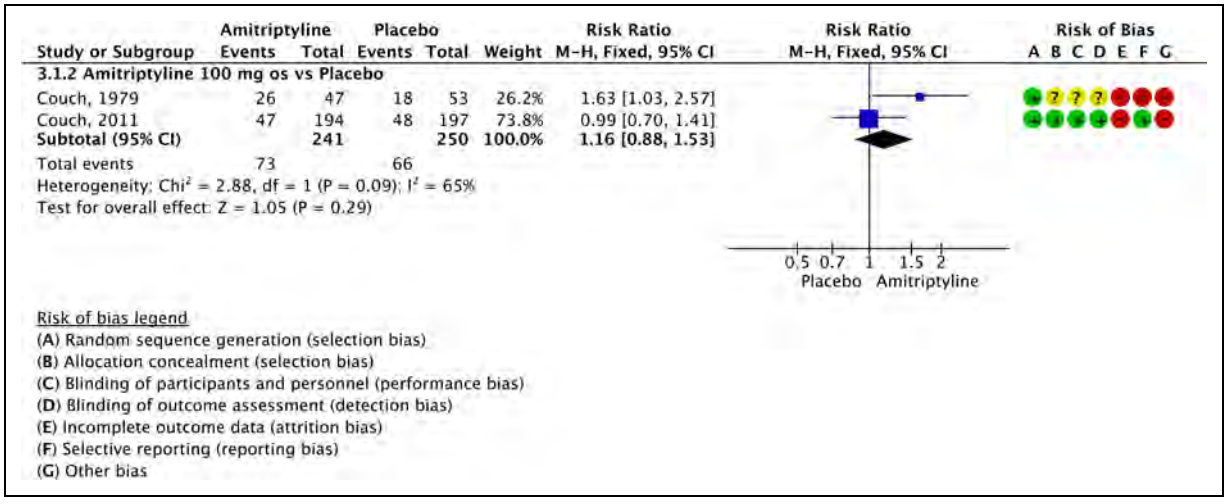


Figure 4.1.3. Forest plot showing the comparison between oral amitriptyline and placebo for the outcome ?50% responder rate in patients with migraine (no distinction between episodic and chronic).

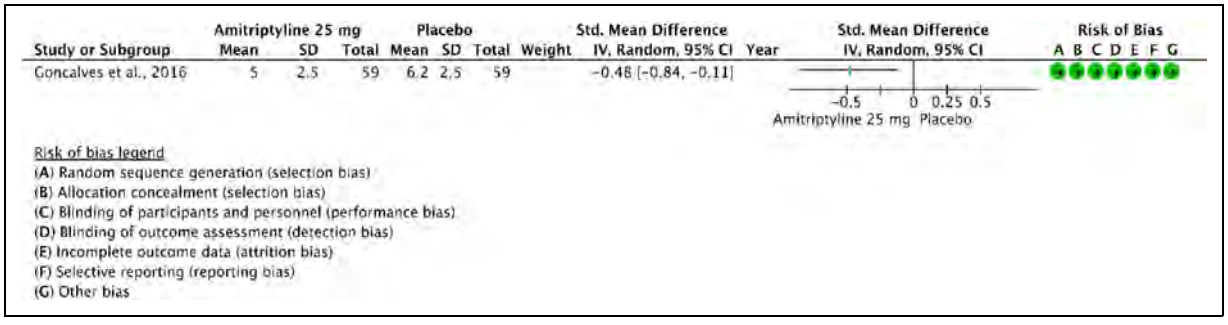


Figure 4.1.4. Forest plot showing the comparison between oral amitriptyline and placebo for the outcome persisting monthly migraine days in patients with episodic migraine.

Table 4.1.1. GRADE evidence profile table for oral amitriptyline versus placebo in patients with episodic migraine

Certainty assessment							№ of patients		Effect			
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Amitriptyline	Placebo	Relative (95% CI)	Absolute (95% CI)	Quality	Importance
Persisting monthly migraine days - Amitriptyline 25 mg oral vs Placebo												
1	RCT	Not serious	Not applicable[a]	Not serious	Not serious	None	59	59	-	SMD **0.48 lower** (0.84 lower to 0.11 lower)	⊕⊕⊖⊖ Low	Critical
≥50% responder rate - Amitriptyline 25 mg oral vs Placebo												
1	RCT	Not serious	Not applicable[a]	Not serious	Not serious	None	23/59 (39.0%)	12/59 (20.3%)	**RR 1.92** (1.05 to 3.48)	**187 more per 1000** (from 10 more to 504 more)	⊕⊕⊖⊖ Low	Critical

[a]Only one RCT.

angioedema, in patients already taking a direct renin inhibitor such as aliskiren, during pregnancy and in patients with diabetes mellitus or renal impairment. The combination therapy of ACE inhibitors and ARBs can worsen renal indices and cause life-threatening hyperkalemia (742–744).

Serious safety concerns: Angioedema has a higher rate of incidence in the African American population, it is rare but life-threatening. Life-threatening anaphylactoid reactions have occurred in patients receiving dialysis with high-flux membranes (bradykinins effect) and patients undergoing concomitant Hymenoptera venom desensitization immunotherapy (histaminergic effect) (745,746). Cholestatic jaundice or hepatitis is another rare but serious adverse effect that can progress to hepatic necrosis and sometimes death (747).

Tolerability: ACE inhibitors may be associated with an increased risk of dry cough, hypotension, hyperkalemia, and dizziness (748). Dry cough is the most common adverse effect and is not dose- or duration-dependent; enalapril yields the lowest risk for dry cough compared to other ACE inhibitors (748). The mechanism of ACE-inhibitor-induced dry cough may be related to a bradykinin-induced sensitization of airway sensory nerves and an accumulation of substance P in the respiratory tracts. Hypotension is attributable to reduced angiotensin II formation. Hyperkalemia is uncommon and occurs when ACE inhibitors are concomitantly prescribed with potentially interacting drugs, such as spironolactone or chlorothiazide or with chronic kidney disease. ACE inhibitors are associated with dizziness that is likely a symptom of orthostatic hypotension.

ARBs. Warnings and contraindications: ARBs are contraindicated in patients suffering from renal artery stenosis, chronic kidney disease, congestive heart failure, hypotension, or assuming other potassium-increasing drugs, such as ACEi. Moreover, ARBs should not be used during pregnancy, due to the risk of fetal malformations (749).

Serious safety concerns: During treatment with ARBs, sudden difficulty breathing and swelling of extremities or glottis must alert, because it could be due to angioedema, a rare but life-threatening side effect (750).

Tolerability: The most common side effects of ARBs are dizziness, fatigue, hypotension, renal dysfunction, and hyperkalemia.

Evidence-based guideline summary

We found only studies on ARBs and ACE inhibitors and not studies on calcium-channel blockers to be included for deriving evidence-based recommendations for this guideline. Evidence was available for candesartan, lisinopril and telmisartan.

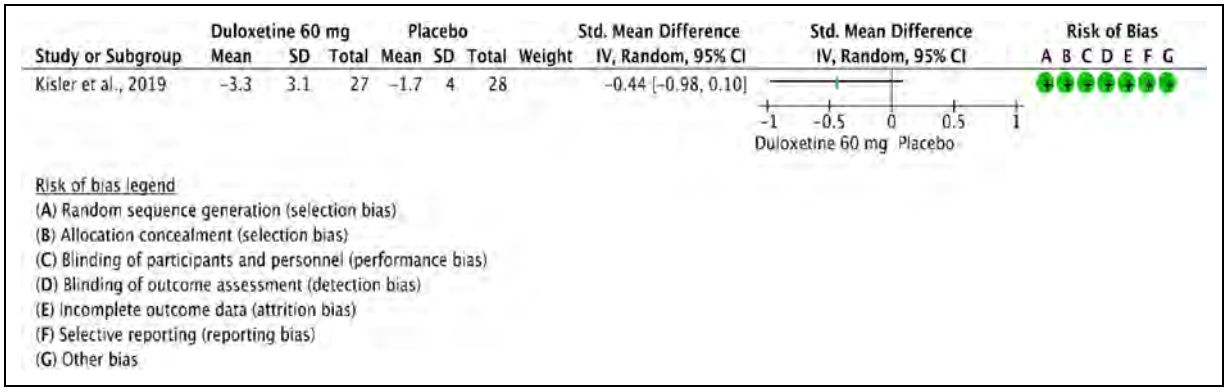


Figure 4.1.5. Forest plot showing the comparison between oral duloxetine 60 mg daily and placebo for the outcome changing in monthly headache days in patients with episodic migraine.

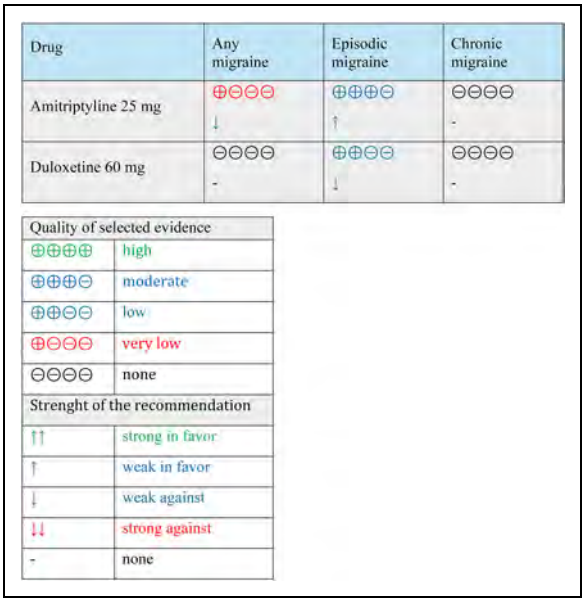


Figure 4.1.6. Summary of evidence-based recommendations on antidepressants for migraine prevention.

The available evidence is limited to migraine (no distinction between episodic and chronic) and episodic migraine. No studies were included for chronic migraine.

There is evidence to recommend the use of candesartan for episodic migraine prevention while other agents' studies do not allow to establish any recommendation (Figure 4.4.9).

Expert based opinions

Calcium channel blockers

Topic: Calcium-channel blockers in migraine prevention.

Suggestion 1: We suggest oral flunarizine (5–10 mg daily) for the prevention of any migraine (no distinction between episodic and chronic).

Rationale 1: Flunarizine is widely used for the prevention of migraine in clinical practice since the 1980s (751,752). Flunarizine has been extensively studied in several RCTs; meta-analyses of those RCTs showed that flunarizine was more effective than placebo in decreasing monthly migraine attacks, even if at the expense of increased adverse events as compared with placebo (681,722). For those reasons, flunarizine has been included in several recommendations and guidelines for migraine prevention (15,608,753). A systematic review focused on the largest and highest quality RCTs showed a possible benefit of flunarizine over placebo in the prevention of migraine (722) (Table 4.4.5), even if the efficacy results from the available RCTs could not be pooled into a meta-analysis.

RCTs assessing the efficacy and safety of flunarizine for migraine prevention could not be included in our guidelines as either main or additional evidence as they did not measure the outcomes that were required to be included in the present guideline. Nevertheless, given the large amount of available data, positive results against placebo, and clinical experience, we would like to provide guidance on the use of flunarizine for migraine prevention.

According to evidence from RCTs and clinical experience, there is no need to titrate flunarizine. The 10 mg oral dose, taken once daily, is the one with the best evidence for efficacy (721). However, a head-to-head RCT did not show any difference in efficacy between the 5 mg and the 10 mg dose of flunarizine (704). The 5 mg dose of flunarizine was associated with a lower proportion of adverse events compared with the 10 mg dose, although not significantly (704). Therefore, it might be reasonable to employ a 5 mg dose of flunarizine in subjects with high expected probability of adverse events, such as those with low weight or depressive symptoms, or in those reporting adverse effects with the 10 mg dose. It might also be

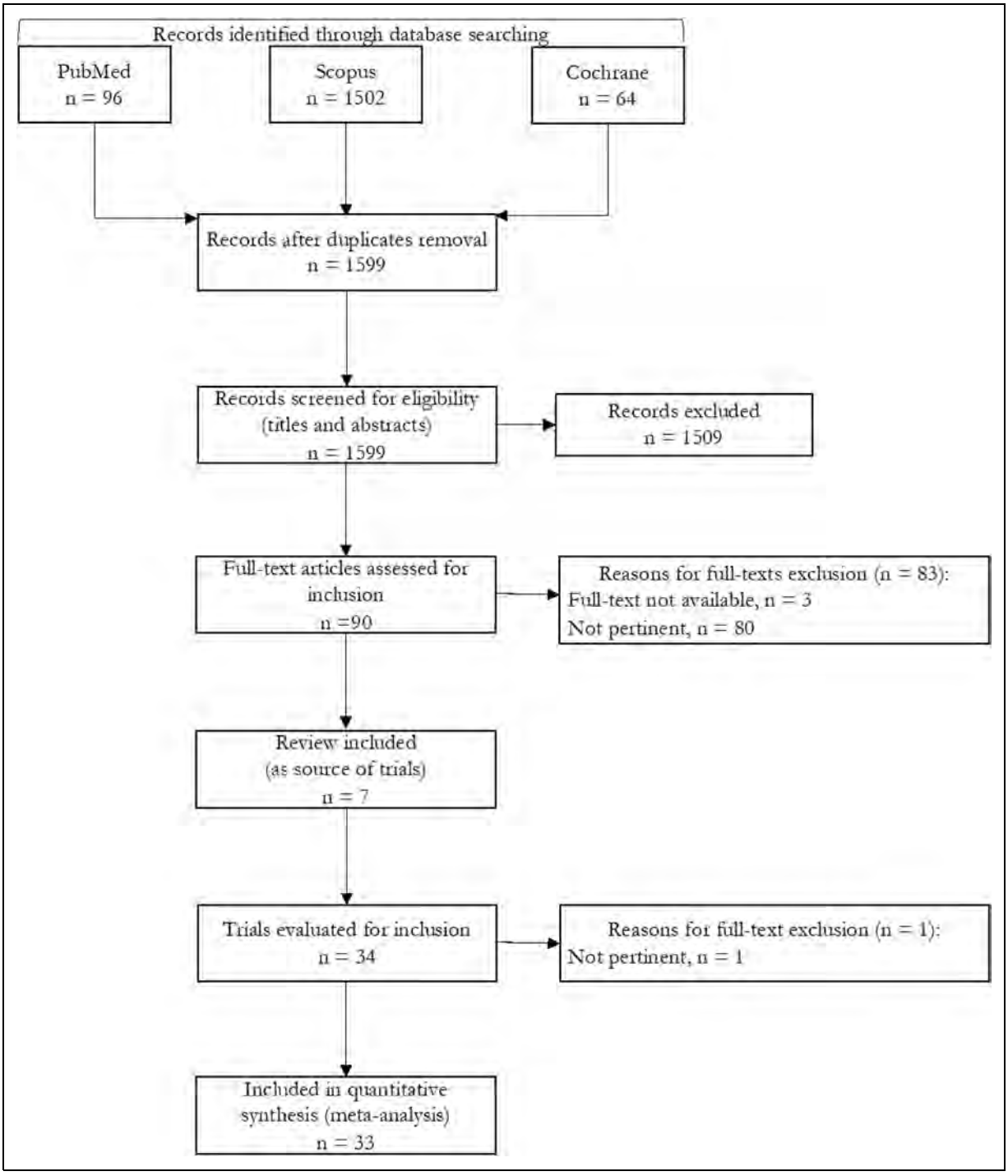


Figure 4.2.1. Meta-analysis selection flow chart - anti-seizure medications.

reasonable to take the drug in the evening due to the possible drug-related sedation.

Suggestion 2: We suggest oral cinnarizine 75 mg for migraine prevention, especially if associated with vestibular symptoms.

Rationale 2: The evidence for efficacy of cinnarizine is more sparse compared with that on flunarizine; nevertheless, according to some studies that were summarized in a narrative review (754), it showed some evidence of efficacy for the prevention of migraine and especially in those forms

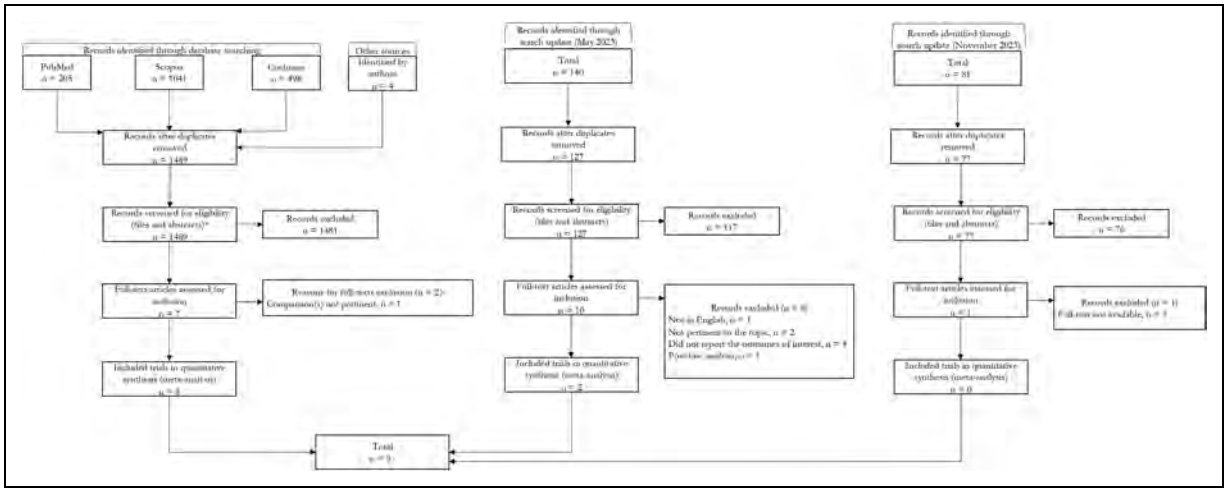


Figure 4.2.2. RCT selection flow chart - anti-seizure medications.
*trials published since June 2020 were screened.

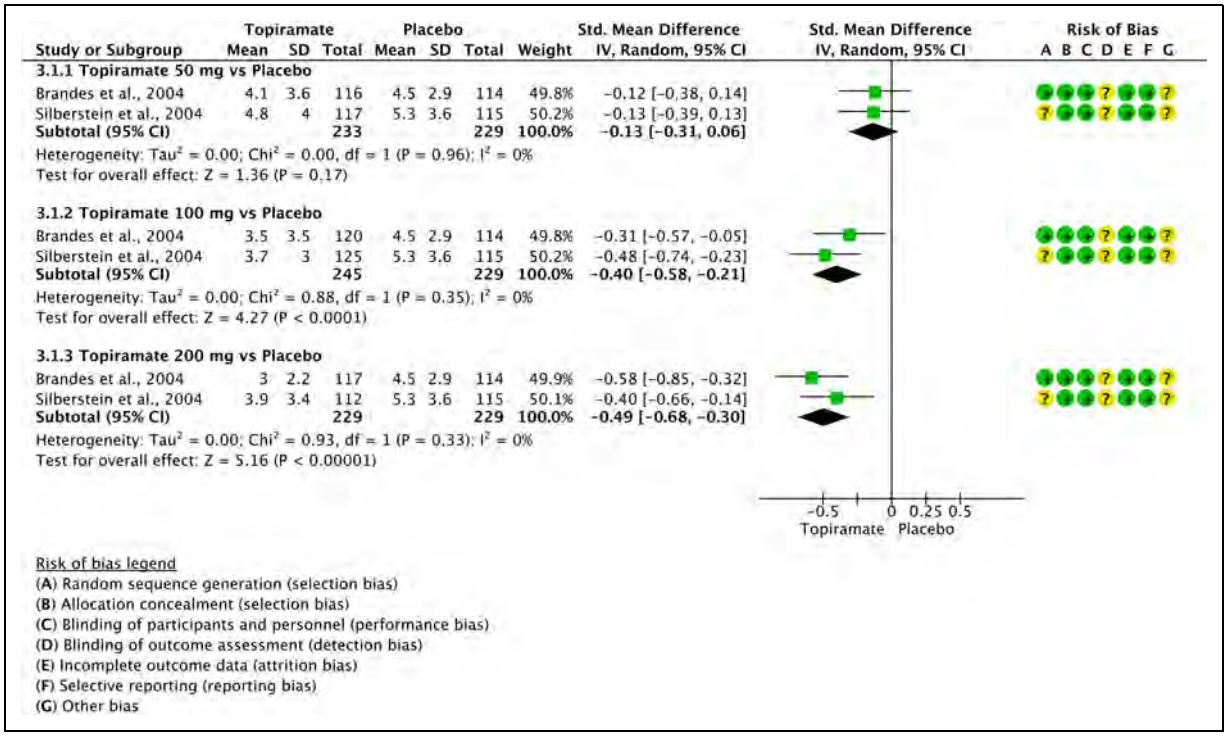


Figure 4.2.3. Forest plot showing the comparison between oral topiramate (50, 100 or 200 mg) and placebo for the outcome persisting monthly migraine days in patients with episodic migraine.

associated with vestibular symptoms (754). Based upon RCTs evidence and clinical experience, a total daily dose of 75 mg in two or three daily administrations, without prior titration, is advisable (754).

Optimization of candesartan use

Topic: Candesartan titration and dosing. Suggestion: In subjects with migraine, we suggest using a 16 mg daily dose of candesartan for migraine prevention; titration of the drug can be useful to assess tolerability.

Rationale: The available RCT of candesartan tested the 16 mg daily dose (738). Therefore, there is no reason to increase the dose beyond 16 mg daily for migraine prevention. If a 16 mg dose is not effective for migraine prevention, switching to other preventive agents could be advisable over increasing the dose of candesartan. Titration of the drug is useful to monitor its effects on

Table 4.2.1. GRADE evidence profile table of oral topiramate versus placebo in patients with episodic migraine

Certainty assessment							№ of patients		Effect			
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Topiramate	Placebo	Relative (95% CI)	Absolute (95% CI)	Quality	Importance
Persisting monthly migraine days – Topiramate 50 mg oral vs Placebo												
2	RCTs	Serious	Not serious	Not serious	Not serious	None	233	229	-	SMD **0.13 lower** (0.3 lower to 0.06 higher)	⊕⊕⊕⊖ Moderate	Critical
Persisting monthly migraine days – Topiramate 100 mg oral vs Placebo												
2	RCTs	Serious	Not serious	Not serious	Not serious	None	245	229	-	SMD **0.40 lower** (0.5 lower to 0.2 lower)	⊕⊕⊕⊖ Moderate	Critical
Persisting monthly migraine days – Topiramate 200 mg oral vs Placebo												
2	RCTs	Serious	Not serious	Not serious	Not serious	None	229	229	-	SMD **0.49 lower** (0.6 lower to 0.3 lower)	⊕⊕⊕⊖ Moderate	Critical
Change in monthly migraine days – Topiramate 100 mg oral vs Placebo												
3	RCTs	Serious	Not serious	Not serious	Not serious	None	378	368	-	SMD **1.63 lower** (3.5 lower to 0.3 lower)	⊕⊕⊕⊖ Moderate	Critical
Change in monthly migraine days – Topiramate 200 mg oral vs Placebo												
2	RCTs	Serious	Not serious	Not serious	Not serious	None	260	257	-	SMD **2.7 lower** (7.8 lower to 2.5 higher)	⊕⊕⊕⊖ Moderate	Critical
≥50% responder rate – Topiramate 50 mg oral vs Placebo												
1	RCT	Serious	Not applicable[a]	Not serious	Not serious	None	45/116 (38.8%)	28/114 (24.6%)	**RR 1.58** (1.06 to 2.34)	**142 more per 1.000** (from 15 more to 329 more)	⊕⊕⊖⊖ Low	Critical
≥50% responder rate – Topiramate 100 mg oral vs Placebo												
2	RCTs	Serious	Not serious	Not serious	Not serious	None	110/259 (42.5%)	59/257 (23.0%)	**RR 1.85** (1.42 to 2.41)	**195 more per 1.000** (from 96 more to 324 more)	⊕⊕⊕⊖ Moderate	Critical
≥50% responder rate – Topiramate 200 mg oral vs Placebo												
2	RCTs	Serious	Not serious	Not serious	Not serious	None	105/260 (40.4%)	59/257 (23.0%)	**RR 1.76** (1.35 to 2.30)	**174 more per 1.000** (from 80 more to 298 more)	⊕⊕⊕⊖ Moderate	Critical

[a]Only one trial.

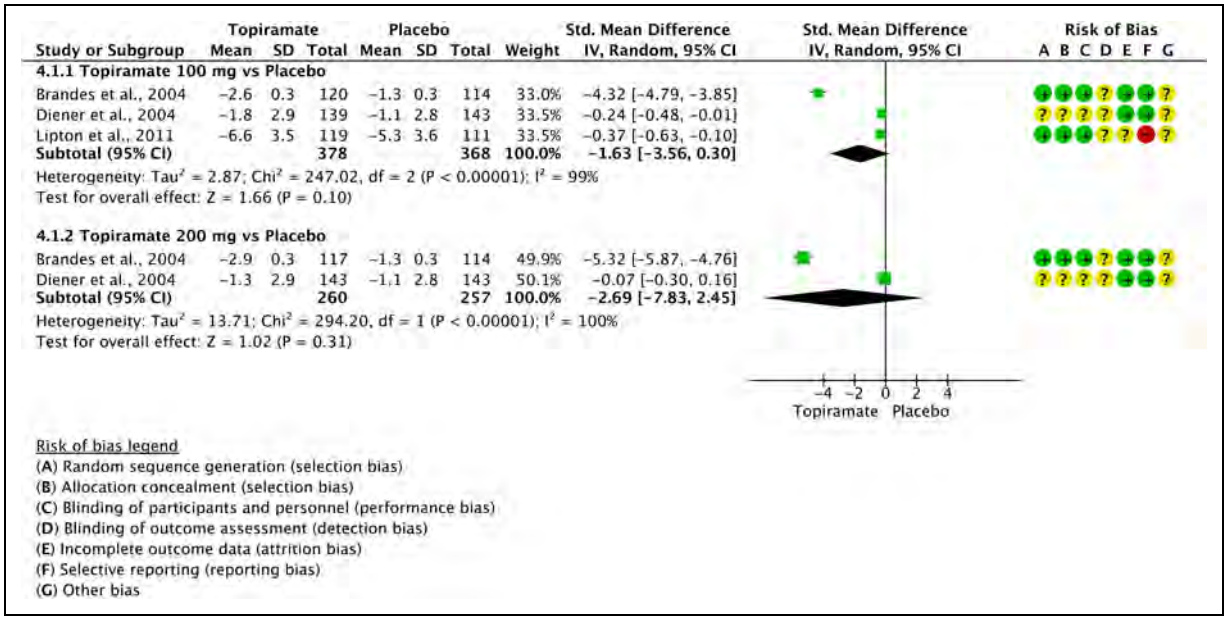


Figure 4.2.4. Forest plot showing the comparison between oral topiramate (100 or 200 mg) and placebo for the outcome change in monthly migraine days in patients with episodic migraine.

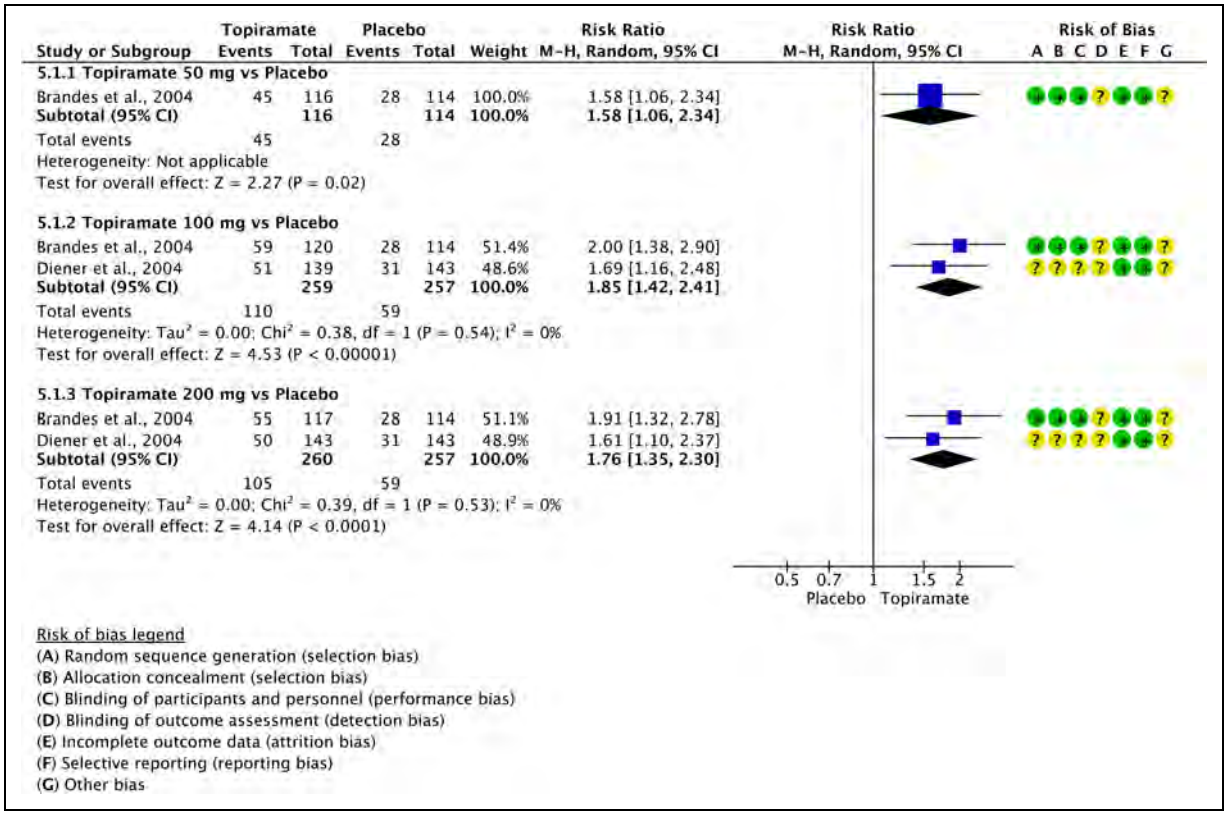


Figure 4.2.5. Forest plot showing the comparison between oral topiramate (50, 100 or 200 mg) and placebo for the outcome ≥50% response rate in patients with episodic migraine.

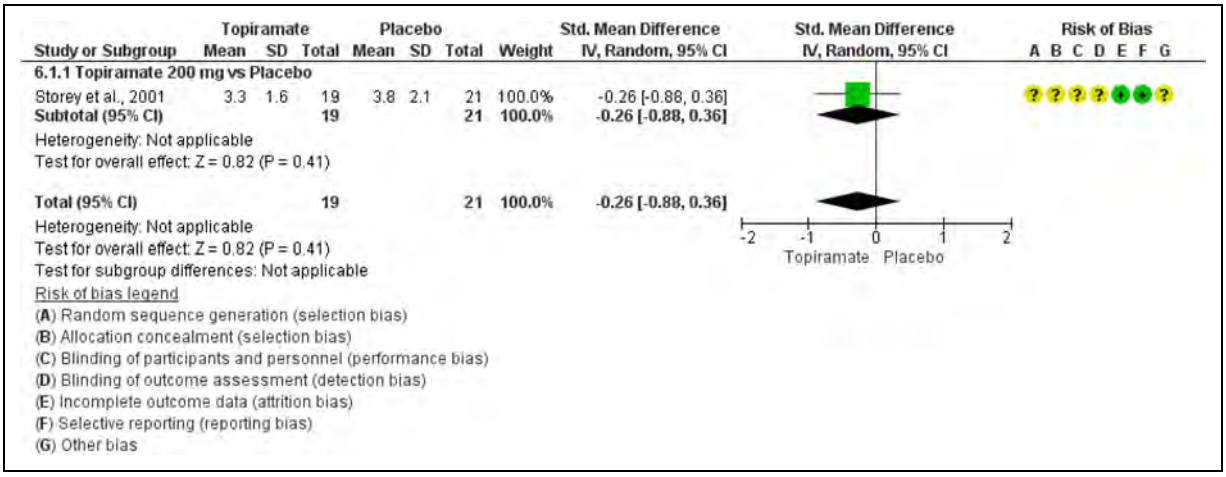


Figure 4.2.6. Forest plot showing the comparison between oral topiramate 200 mg and placebo for the outcome persisting monthly migraine days in patients with episodic migraine.

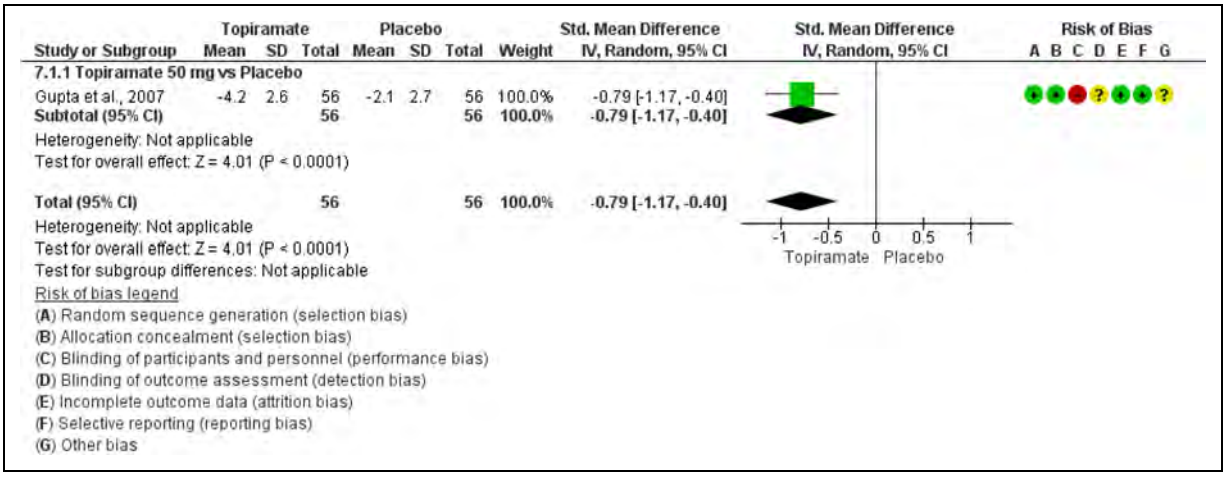


Figure 4.2.7. Forest plot showing the comparison between oral topiramate 50 mg and placebo for the outcome change in monthly migraine days in patients with episodic migraine.

blood pressure and heart rate before reaching a full dose. Monitoring heart rate and blood pressure is advisable when prescribing candesartan (749).

Topic: Selection of candidates for migraine prevention with candesartan. Suggestion: Candesartan should be considered as an option for the prevention of migraine in subjects with uncontrolled hypertension.

Rationale: The efficacy of candesartan was shown in a single RCT in a small population of participants (738). Therefore, the evidence for candesartan use is less robust than that of other migraine preventive agents and previous reviews suggest that candesartan should not be used as a first choice for migraine prevention (749,750). In the experts' opinion, given the established efficacy of candesartan in decreasing blood pressure (755), candesartan should be considered an option for migraine prevention especially in subjects with hypertension.

4.5 Botulinum toxin

Introduction. The clinical observation that in some people onabotulinumtoxinA injected for cosmetic purposes appeared to alleviate headache led to the hypothesis that the drug may be a useful preventive treatment for migraine (756). The mechanism of action of onabotulinumtoxinA in migraine subjects is still not fully understood (757). However, sensory effects of onabotulinumtoxinA in migraine are supported by many findings. Indeed, onabotulinumtoxinA is thought to achieve its therapeutic effect through blocking activation of unmyelinated meningeal nociceptors by cortical spreading depression (758). Moreover, onabotulinumtoxinA inhibits

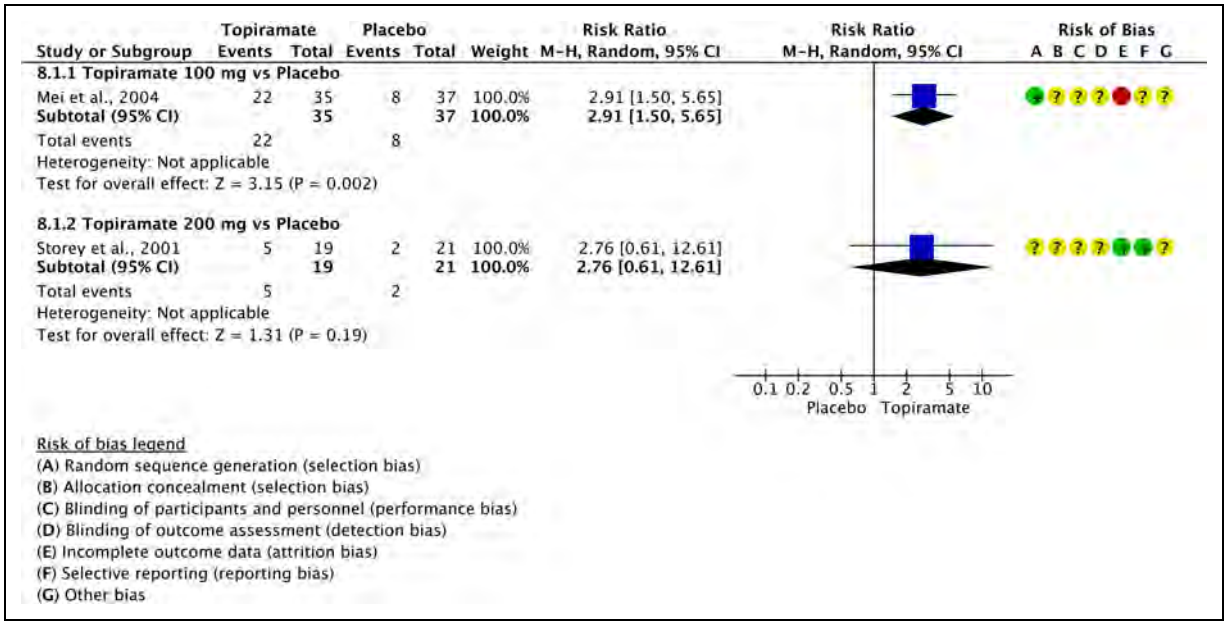


Figure 4.2.8. Forest plot showing the comparison between oral topiramate (100 or 200 mg) and placebo for the outcome ≥50% response rate in patients with episodic migraine.

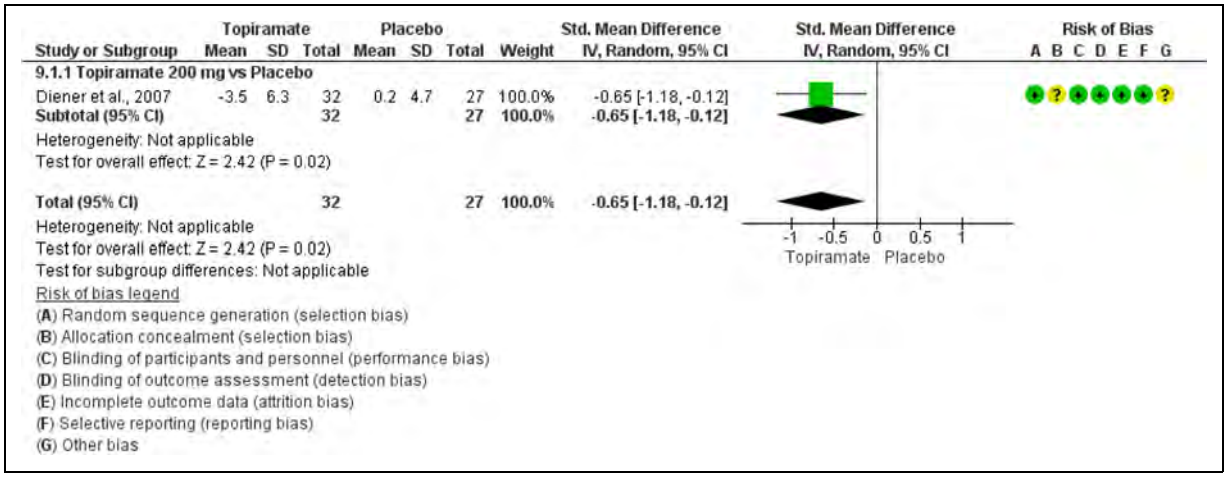


Figure 4.2.9. Forest plot showing the comparison between oral topiramate 200 mg and placebo for the outcome change in monthly migraine days in patients with chronic migraine.

the release of CGRP, substance P and other neuropeptides that are deeply involved in migraine pathophysiology (759). More recently, onabotulinumtoxinA was also found to alter inflammatory gene expression and immune cells in chronic headache subjects (760). Since 2010, onabotulinumtoxinA has been approved in many countries for the prevention of chronic migraine based on two large RCTs (761,762). The recommended reconstituted dose is 155 to 195 units, administered intramuscularly as 0.1 mL (five units) injections to between 31 and 39 sites in the head and neck.

In 2018, a consensus statement from the European Headache Federation recommended onabotulinumtoxinA as an effective and well-tolerated treatment of CM (763). Indeed, in the same year, Cochrane analyses reported that onabotulinumtoxinA may reduce the number of migraine days per month by two days compared with placebo treatment. Conversely, it was uncertain whether this treatment

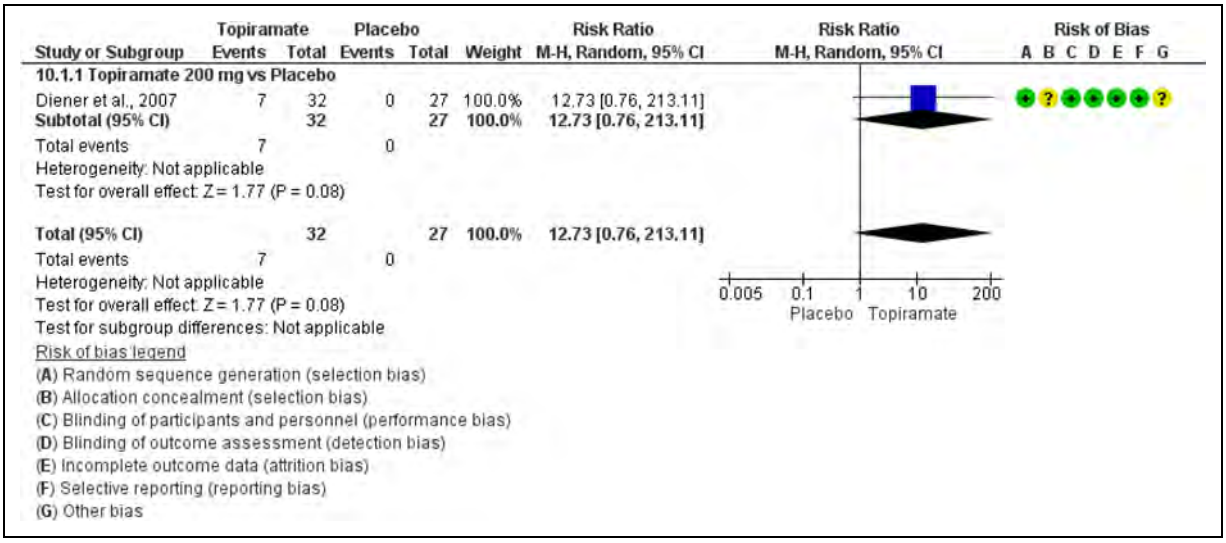


Figure 4.2.10. Forest plot showing the comparison between oral topiramate 200 mg and placebo for the outcome ≥50% response rate in patients with chronic migraine.

is effective for people with episodic migraine (764). Since Cochrane analyses, RCTs and real-world evidence have expanded the evidence and knowledge for this treatment.

Section-specific methods. This section followed the general procedure to develop this guideline. In general, for the guideline, we excluded dose-finding dosages that were not marketed for each of the considered drugs. In the case of botulinum toxin, given the peculiarities and the possibility to customize dosages we included all doses adopted by the selected studies.

Search strings for the guideline on botulinum toxin for systematic review/meta-analysis and for additional RCTs are reported in Online Appendix 4.5.1.

Results. Overall, we retrieved 1108 references from searching for systematic reviews and meta-analyses. After duplicate removal and screening stages, we included 1087 references.

Finally, we included one systematic review and meta-analysis as source of randomized controlled trials (RCTs) (764). After analyzing full texts of these RCTs, we included 13 of them in the quantitative synthesis (663,761,762,765–774) (Figure 4.5.1).

Overall, we retrieved 1336 references from searching for RCTs and after removing duplicates we had 1185 references to analyze. However, considering the most recent included systematic review/meta-analysis on the topic, the analysis of additional RCTs was performed for papers published since 31 August 2020 (275 references). From the literature search updates performed in May 2023 and November 2023, we retrieved 211 references and examined 205 of them after removing duplicates. We finally included no additional RCTs (Figure 4.5.2).

Overall, 13 studies were included in the quantitative synthesis (meta-analyses) to develop the evidence-based guideline. Among these, 11 reported a comparison between an active drug and placebo and are presented in this section, while the remaining two reported head-to-head comparisons and were included in Section 4.8. Four studies practiced the PREEMPT injection protocol; different protocols are reported in Table 4.5.1.

OnabotulinumtoxinA. **PICO 4.5.1.** In subjects with episodic migraine, is onabotulinumtoxinA superior to placebo for migraine prevention (outcomes: change in monthly migraine/headache days, persisting monthly migraine/headache days, ≥ 50% responder rate)?

Main evidence. None.

Additional evidence. We found three RCTs comparing onabotulinumtoxinA to placebo (761,769,773) in subjects with episodic migraine that did not meet the pre-defined criteria to be included in main evidence. Risk of bias of included studies was serious and the quality of evidence was considered very low (Figures 4.5.3 and 4.5.4).

One of the RCTs compared onabotulinumtoxinA 100 UI with placebo (769). This study did not show significant benefit from onabotulinumtoxinA over placebo in the change in monthly migraine days (Figure 4.5.3) or in ≥50% response rate (Figure 4.5.4).

One of the RCTs compared onabotulinumtoxinA 150 UI and 255 UI with placebo (773). Overall, this study did not show any benefit from onabotulinumtoxinA treatment in the change in monthly migraine days (Figure 4.5.3) but

Table 4.2.2. GRADE evidence profile table of oral topiramate versus placebo in patients with chronic migraine

Certainty assessment							№ of patients		Effect			
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Topiramate	Placebo	Relative (95% CI)	Absolute (95% CI)	Quality	Importance
Change in monthly migraine days – Topiramate 200 mg oral vs Placebo												
1	RCT	Not serious	Not applicable[a]	Not serious	Serious[b]	None	32	27	-	SMD **0.6 lower** (1.1 lower to 0.1 lower)	⊕⊖⊖⊖ **Low**	Critical
≥50% responder rate – Topiramate 200 mg oral vs Placebo												
1	RCT	Not serious	Not applicable[a]	Not serious	Serious[b]	None	7/32 (21.9%)	0/27 (0.0%)	**RR 12.73** (0.76 to 213.11)	**0 fewer per 1.000** (from 0 fewer to 0 fewer)	⊕⊖⊖⊖ **Low**	Critical

[a]Only one trial; [b]Small sample size (<50 patients per group).

showed a significant increase in ≥50% response rate in patients treated with onabotulinumtoxinA (Figure 4.5.4).

One additional RCT did not show any benefit from onabotulinumtoxinA treatment (761) in the change of monthly migraine days associated with onabotulinumtoxinA use (Figure 4.5.3). This study did not address ≥50% response rate. In this study, all patients were initially treated with placebo and classified as "placebo responders" and "placebo non responders". Afterwards, all patients were randomized to receive onabotulinumtoxinA (from 110 to 260 UI) or placebo and results were provided separately.

Evidence-based recommendation for PICO 4.5.1

In subjects with episodic migraine, we suggest against onabotulinumtoxinA (100 to 255 UI) for migraine prevention.
Level of evidence: Very low (⊕⊖⊖⊖)
Strength of recommendation: Weak (↓)

PICO 4.5.2. In subjects with chronic migraine, is onabotulinumtoxinA superior to placebo for migraine prevention (outcomes: persisting in monthly migraine day, change in monthly migraine days, ≥ 50% responder rate)?

Main evidence. We found three RCTs comparing onabotulinumtoxinA to placebo (761,762,772) in subjects with chronic migraine that met the criteria to be included in main evidence.

Two RCTs (761,762) considered the outcome change in monthly headache days. Their pooled analysis showed a significant mean reduction in monthly headache days in subjects who were treated with onabotulinumtoxinA (Figure 4.5.5). The quality of evidence for the outcome was considered high (Table 4.5.2).

Only one study (772), which provided a patient-level pooled analysis of two RCTs, considered the outcome ≥50% response rate. This study showed a significantly increased probability of ≥50% response rate in subjects treated with onabotulinumtoxinA as compared to those treated with placebo (Figure 4.5.6). The quality of evidence for the outcome ≥50% response rate was considered high (Table 4.5.2).

Additional evidence. We found four additional RCTs comparing onabotulinumtoxinA to placebo (767,770,771,774) in subjects with chronic migraine that did not meet all the pre-defined criteria to be included in main evidence. Overall risk of bias was considered not serious, and the quality of evidence was considered low (Figures 4.5.7 and 4.5.8).

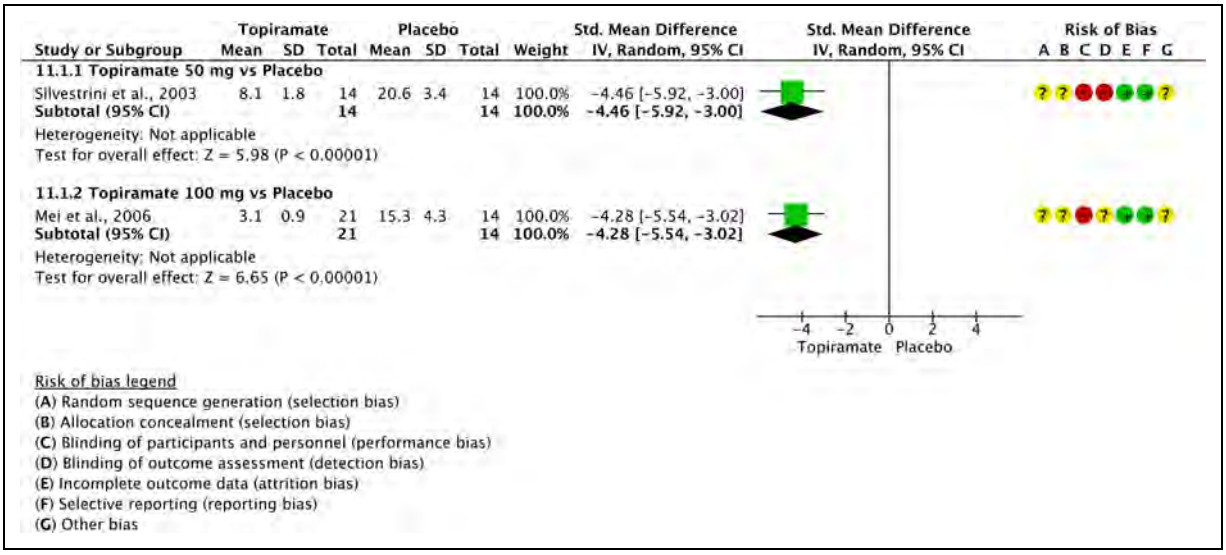


Figure 4.2.11. Forest plot showing the comparison between oral topiramate (50 and 100 mg) and placebo for the outcome persisting monthly migraine days in patients with chronic migraine.

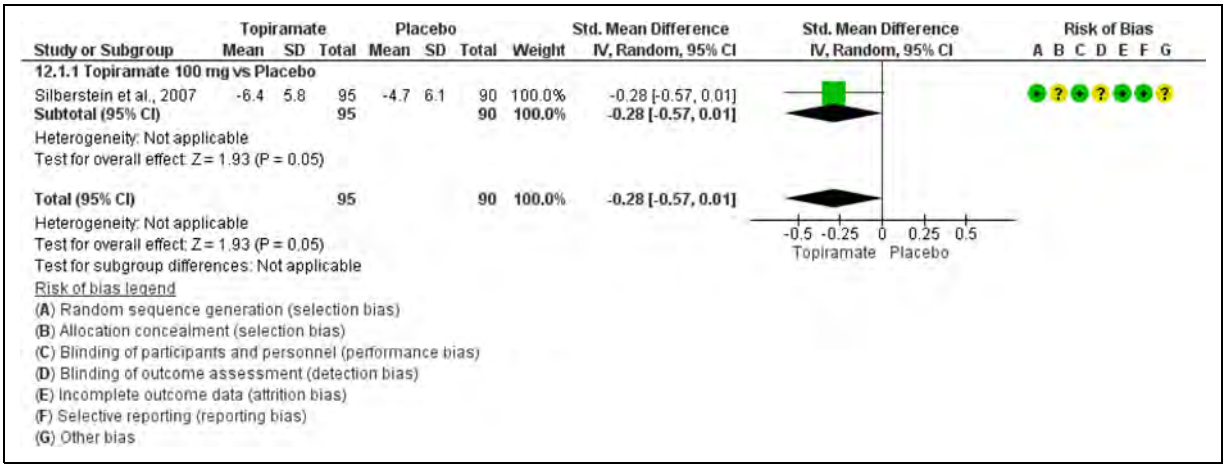


Figure 4.2.12. Forest plot showing the comparison between oral topiramate 100 mg and placebo for the outcome change in monthly migraine days in patients with chronic migraine.

Two RCTs compared onabotulinumtoxinA 100 UI with placebo (771,774). Overall, those studies did not show a significant reduction in monthly migraine days in subjects treated with onabotulinumtoxinA as compared to those treated with placebo (Figure 4.5.7). One additional RCT (767) compared onabotulinumtoxinA 155–195 UI with placebo. This RCT showed a marginally non-significant reduction in monthly migraine days in subjects treated with onabotulinumtoxinA as compared to those treated with placebo (Figure 4.5.7). However, this study had a small sample size which could have been inadequate to detect significant differences.

One additional RCT (770) reported for onabotulinumtoxinA 100 UI the outcome ≥50% response rate and results did not show a significant increased probability of ≥50% response in subjects treated with onabotulinumtoxinA 100 UI as compared to those treated with placebo (Figure 4.5.8).

Evidence-based recommendation for PICO 4.5.2

In subjects with chronic migraine, we recommend intramuscular onabotulinumtoxinA (155–195 UI quarterly administered according to the PREEMPT injection paradigm) for migraine prevention.
Quality of evidence: High (⊕⊕⊕⊕)
Strength of recommendation: Strong (↑↑)

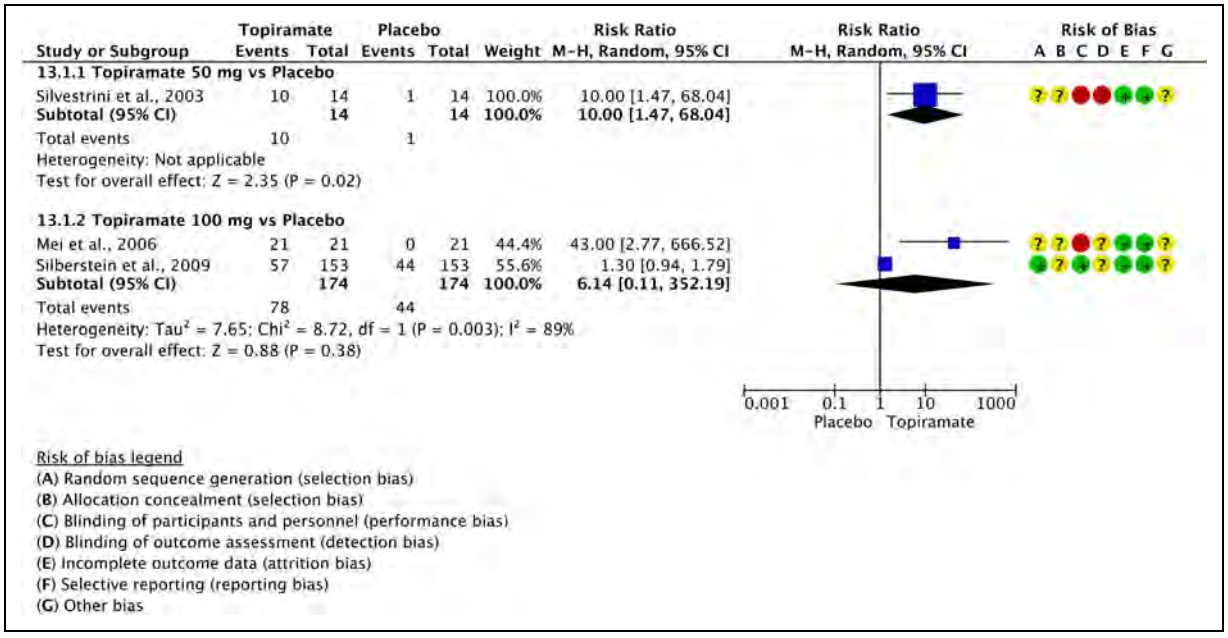


Figure 4.2.13. Forest plot showing the comparison between oral topiramate (50 and 100 mg) and placebo for the outcome ≥50% response rate in patients with chronic migraine.

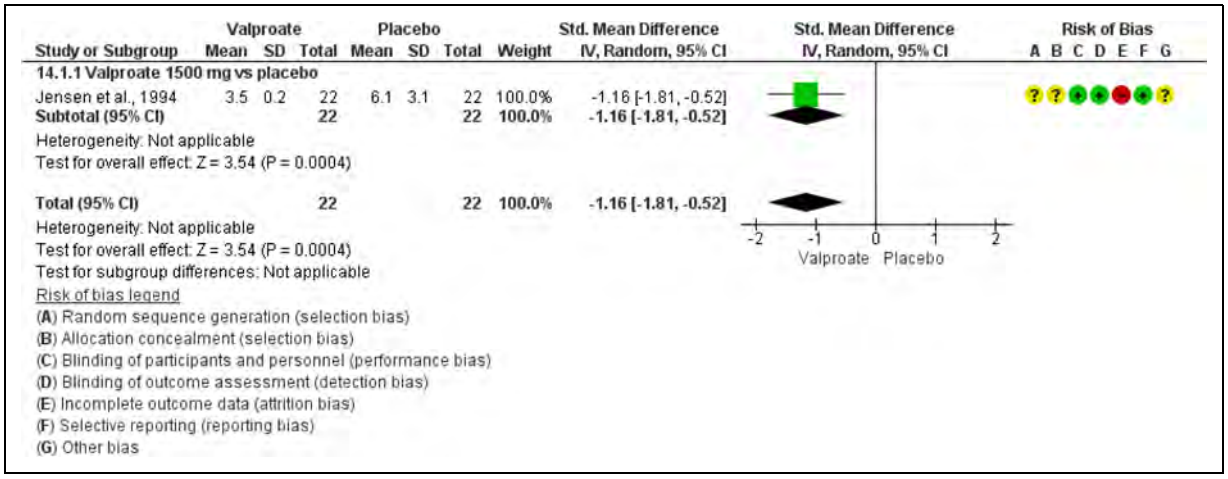


Figure 4.2.14. Forest plot showing the comparison between oral valproate 1500 mg and placebo for the outcome change in monthly migraine days in patients with episodic migraine.

Safety and tolerability of onabotulinumtoxinA. Warnings and contraindications: Pregnancy and breast-feeding women were not included in trials. Safety was shown in infants breast-fed by lactating women treated with onabotulinumtoxinA for chronic migraine (663). Safety in pregnant women exposed to onabotulinumtoxinA was similar to the general population in a study (775). However, there is not sufficient data to recommend onabotulinumtoxinA in nursing and pregnant women. OnabotulinumtoxinA should be avoided in subjects with coexisting myasthenia gravis and other myasthenic syndromes, in agreement with the International Consensus Guidance for management of myasthenia (776). OnabotulinumtoxinA can weaken neuromuscular transmission and worsen possible adverse effects or unmask a subclinical disease of the neuromuscular junction. However, optimizing treatment for myasthenia gravis or using ultrasound-guided or electromyography-guided

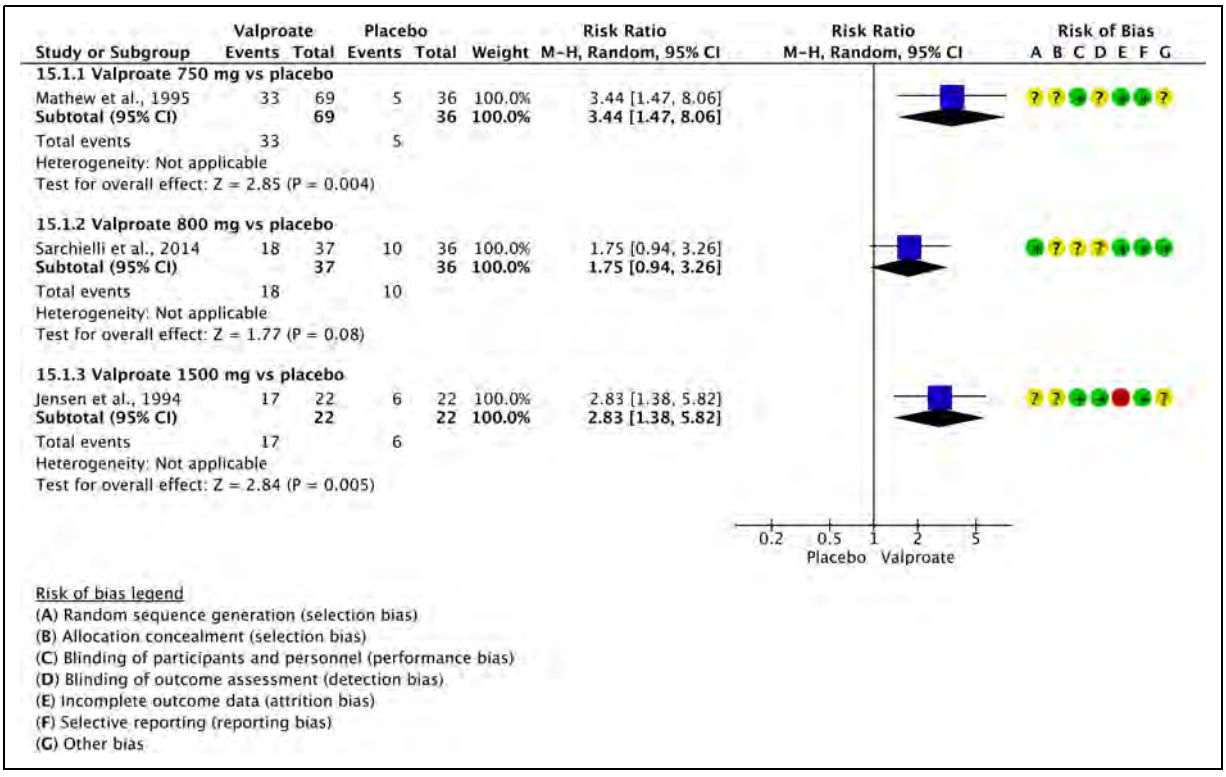


Figure 4.2.15. Forest plot showing the comparison between oral valproate (750, 800 or 1500 mg) and placebo for the outcome ≥50% response rate in patients with episodic migraine.

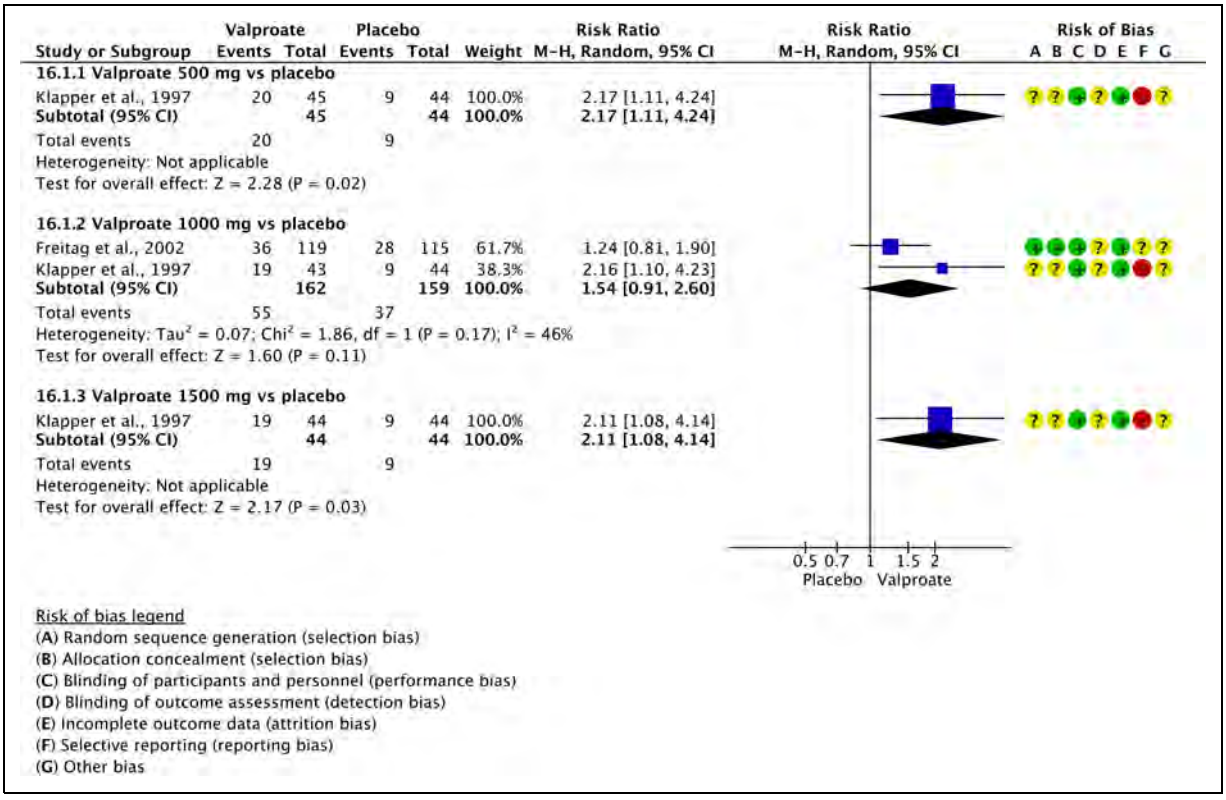


Figure 4.2.16. Forest plot showing the comparison between valproate (500, 1000 or 1500 mg) and placebo for the outcome ≥50% response rate in patients with migraine (no distinction between episodic and chronic).

Table 4.2.3. GRADE evidence profile for oral valproate versus placebo in patients with migraine

Certainty assessment							№ of patients		Effect			
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Valproate	Placebo	Relative (95% CI)	Absolute (95% CI)	Quality	Importance
≥50% responder rate – Valproate 500 mg oral vs Placebo												
1	RCT	Serious	Not applicable[a]	Not serious	Serious[b]	None	20/45 (44.4%)	9/44 (20.5%)	**RR 2.17** (1.11 to 4.24)	**239 more per 1.000** (from 23 more to 663 more)	⊕⊖⊖⊖ **Very low**	Critical
≥50% responder rate – Valproate 1000 mg oral vs Placebo												
2	RCTs	Serious	Not serious	Not serious	Serious[c]	None	55/162 (34.0%)	37/159 (23.3%)	**RR 1.54** (0.91 to 2.60)	**126 more per 1.000** (from 21 fewer to 372 more)	⊕⊖⊖⊖ **Very low**	Critical
≥50% responder rate – Valproate 1500 mg oral vs Placebo												
1	RCT	Very serious	Not applicable[a]	Not serious	Serious[b]	None	19/44 (43.2%)	9/44 (20.5%)	**RR 2.11** (1.08 to 4.14)	**227 more per 1.000** (from 16 more to 642 more)	⊕⊖⊖⊖ **Very low**	Critical

[a]only one trial; [b]Small sample size (<50 per group); [c]confidence interval crossing the threshold for clinical decision.

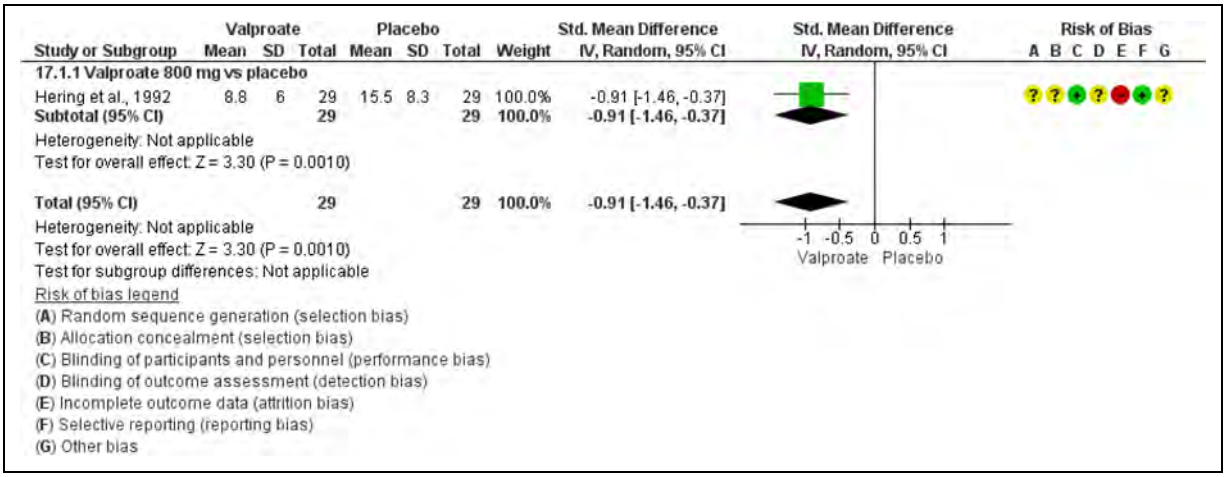


Figure 4.2.17. Forest plot showing the comparison between oral valproate 800 mg and placebo for the outcome persisting monthly migraine days in patients with migraine (no distinction between episodic and chronic).

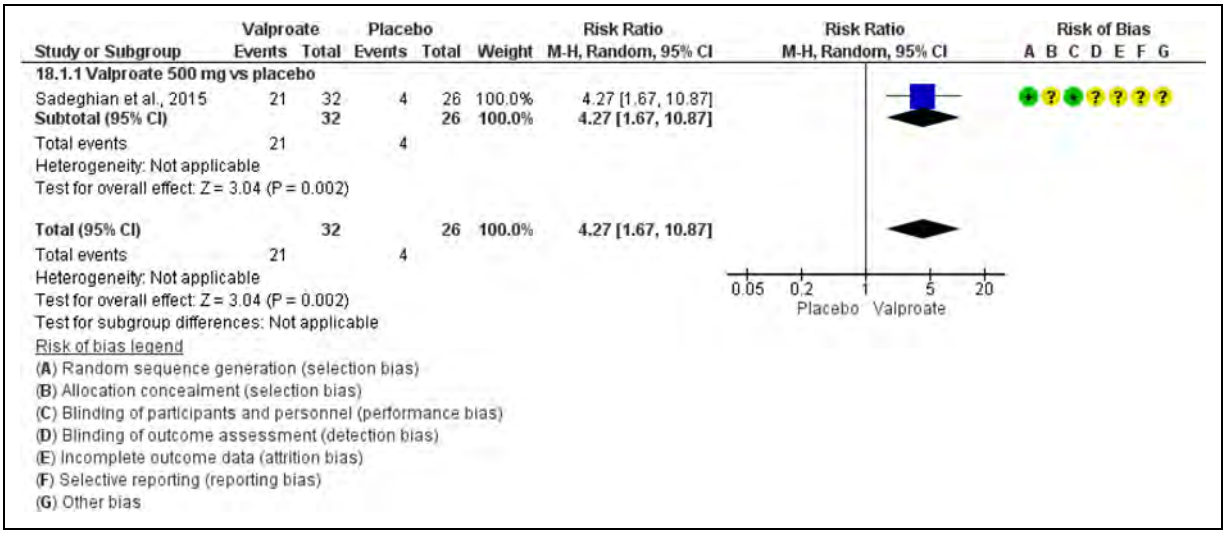


Figure 4.2.18. Forest plot showing the comparison between oral valproate 500 mg and placebo for the outcome ≥50% response rate in patients with migraine (no distinction between episodic and chronic).

onabotulinumtoxinA injection and dose modification can greatly help reduce unwanted side effects (777). Nevertheless, caution is advised and onabotulinumtoxinA should be either avoided or used sparingly if there is no therapeutic alternative (778).

Serious safety concerns: No significant safety concerns were found in the available studies.

Tolerability: Most adverse events reported by subjects were mild or moderate in severity and resolved without sequelae. Most common adverse events were neck pain and muscles weakness related to the site of injection. Treatment-related adverse events were consistent with the known tolerability profile of onabotulinumtoxinA, and no new emerging safety findings were observed. Some subjects may experience pain during the injection.

AbobotulinumtoxinA

PICO 4.5.3. In subjects with episodic migraine, is abobotulinumtoxinA superior to placebo for the prevention of migraine (outcomes: persisting monthly migraine days, change in monthly migraine days, ≥ 50% responder rate)?

Main evidence. None.

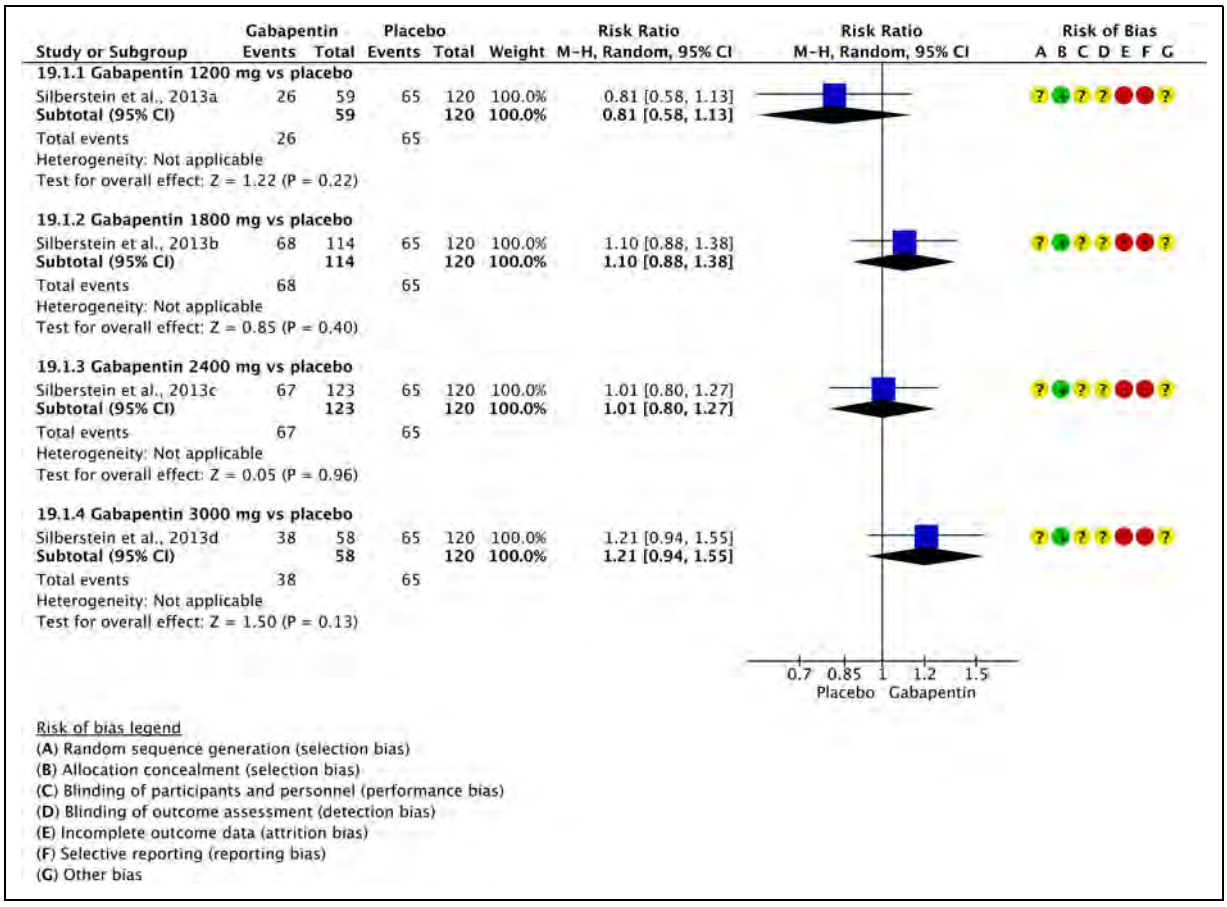


Figure 4.2.19. Forest plot showing the comparison between oral gabapentin (1200–3000 mg) and placebo for the outcome ≥50% response rate in patients with episodic migraine.

Additional evidence. We found one RCT comparing abobotulinumtoxinA with placebo (768) that did not meet all the pre-defined criteria to be included in the main evidence. The study reported an overall serious risk of bias, and the quality of evidence was downgraded to very low (Figure 4.5.9).

Evidence-based recommendation for PICO 4.5.3

In subjects with episodic migraine, we suggest against intramuscular abobotulinumtoxinA (120 UI or 240 UI) for migraine prevention.
Quality of evidence: Very low (⊕⊖⊖⊖)
Strength of recommendation: Weak (↓)

Overall, this study did not show any benefit from abobotulinumtoxinA 120 or 240 UI in the outcome persisting monthly migraine days (Figure 4.5.9). Data showed a non-significant trend toward benefit from abobotulinumtoxinA 120 UI and 240 UI when considering ≥50% response rate (Figure 4.5.10). The pooled analysis of the two different doses indicated a significant benefit from abobotulinumtoxinA considering this same outcome (768).

Evidence-based guideline summary

We found studies on onabotulinumtoxinA and abobotulinumtoxinA to be included for deriving evidence-based recommendations for this guideline. No studies on other toxins met eligibility criteria. For onabotulinumtoxinA, evidence covered episodic migraine and chronic migraine. No studies were included for any migraine. For abobotulinumtoxinA, evidence covered episodic migraine. No studies were included for any migraine or chronic migraine.

There is high quality of evidence to recommend the use of onabotulinumtoxinA for chronic migraine prevention while there is low quality of evidence indicating lack of benefits

Table 4.2.4. GRADE evidence profile table of gabapentin versus placebo in patients with episodic migraine

Certainty assessment							№ of patients		Effect			
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Gabapentin	Placebo	Relative (95% CI)	Absolute (95% CI)	Quality	Importance
≥50% responder rate – Gabapentin 1200 mg oral vs Placebo												
1	RCT	Very serious	Not applicable[a]	Not serious	Not serious	None	26/59 (44.1%)	65/120 (54.2%)	**RR 0.81** (0.58 to 1.13)	**103 fewer per 1.000** (from 228 fewer to 70 more)	⊕⊖⊖⊖ **Very low**	Critical
≥50% responder rate – Gabapentin 1800 mg oral vs Placebo												
1	RCT	Very serious	Not applicable[a]	Not serious	Not serious	None	68/114 (59.6%)	65/120 (54.2%)	**RR 1.10** (0.88 to 1.38)	**54 more per 1.000** (from 65 fewer to 206 more)	⊕⊖⊖⊖ **Very low**	Critical
≥50% responder rate – Gabapentin 2400 mg oral vs Placebo												
1	RCT	Very serious	Not applicable[a]	Not serious	Not serious	None	67/123 (54.5%)	65/120 (54.2%)	**RR 1.01** (0.80 to 1.27)	**5 more per 1.000** (from 108 fewer to 146 more)	⊕⊖⊖⊖ **Very low**	Critical
≥50% responder rate – Gabapentin 3000 mg oral vs Placebo												
1	RCT	Very serious	Not applicable[a]	Not serious	Not serious	None	38/58 (65.5%)	65/120 (54.2%)	**RR 1.21** (0.94 to 1.55)	**114 more per 1.000** (from 33 fewer to 298 more)	⊕⊖⊖⊖ **Very low**	Critical

[a]Only one trial.

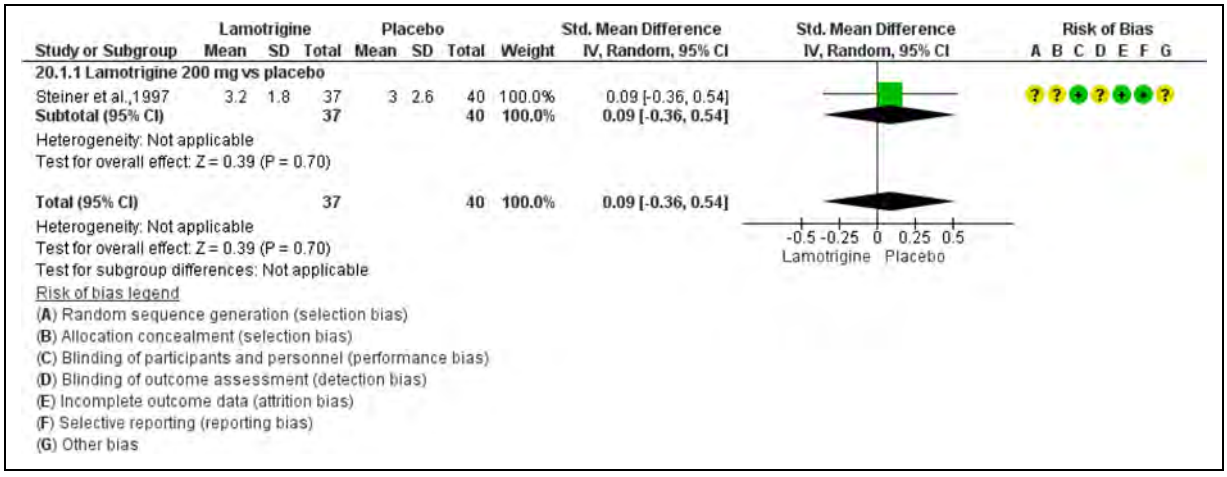


Figure 4.2.20. Forest plot showing the comparison between oral lamotrigine 200 mg and placebo for the outcome persisting monthly migraine days in patients with episodic migraine.

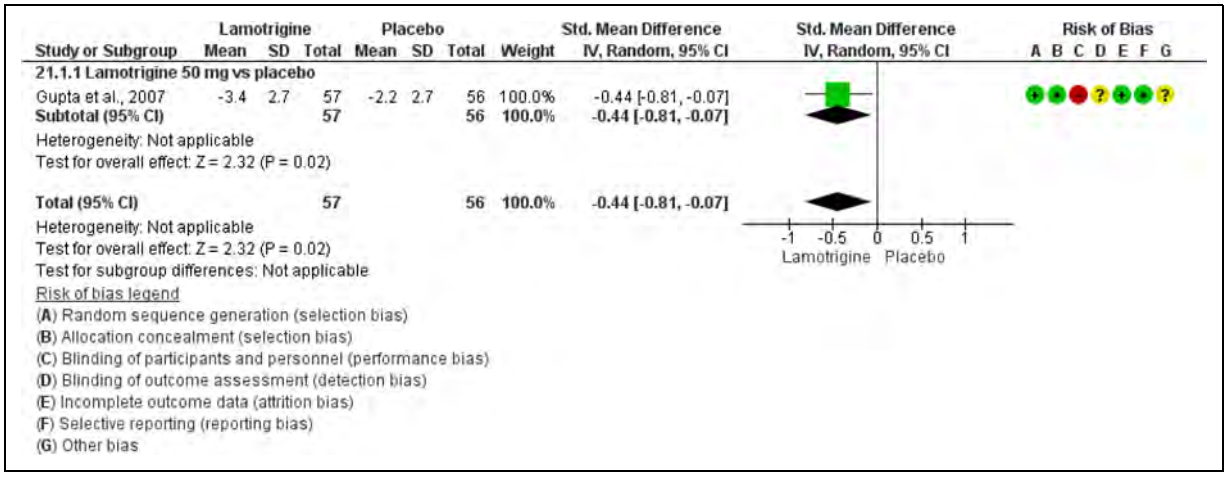


Figure 4.2.21. Forest plot showing the comparison between oral lamotrigine 50 mg and placebo for the outcome change in monthly migraine days in patients with episodic migraine.

from onabotulinumtoxinA and abobotulinumtoxinA for episodic migraine prevention. (Figure 4.5.11).

Expert-based opinion

Topic: OnabotulinumtoxinA titration. Suggestion: When starting onabotulinumtoxinA in individuals with chronic migraine, we suggest 155 units.

Rationale: According to the two largest pivotal RCTs (761,762) and real-world data (779) the recommended dose of OnabotulinumtoxinA is 155 UI administered regularly every three months.

Topic: OnabotulinumtoxinA dosing. Suggestion: In individuals with chronic migraine with less than 50% response after the first injection, we suggest increasing the dose to 195 units.

Rationale: A large two-year real-world prospective study evidenced effectiveness of increasing the dose of onabotulinumtoxinA from 155 to 195 U (780). Together with other real-life experiences (2,781), all clinical evidence suggests that after the first injection of onabotulinumtoxinA 155 U, the dose should be increased to 195 U in subjects who are low or non-responders and in patients who are suboptimal responders.

Topic: First evaluation of effectiveness of onabotulinumtoxinA. Suggestion: We suggest that the effectiveness of onabotulinumtoxinA be assessed after at least six months equivalent to two administrations of the drug.

Rationale: A pooled analysis of the PREEMPT trials showed that 49.3% of subjects treated with onabotulinumtoxinA had a $\geq$ 50% reduction in headache-

Table 4.2.5. GRADE evidence profile of oral lamotrigine versus placebo in patients with episodic migraine

Certainty assessment							№ of patients		Effect			
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Lamotrigine	Placebo	Relative (95% CI)	Absolute (95% CI)	Quality	Importance
Persisting monthly migraine days – Lamotrigine 200 mg oral vs Placebo												
1	RCT	Serious	Not applicable[a]	Not serious	Serious[b]	None	37	40	-	SMD **0.1 higher** (0.4 lower to 0.5 higher)	⊕⊖⊖⊖ **Very Low**	Critical
Change in monthly migraine days – Lamotrigine 50 mg oral vs Placebo												
1	RCT	Very serious	Not applicable[a]	Not serious	Not serious	None	57	56	-	SMD **0.4 lower** (0.8 lower to 0.1 lower)	⊕⊖⊖⊖ **Very Low**	Critical

[a]Only one trial; [b]Small sample size (<50 patients per group).

day frequency during the first treatment cycle, with 11.3% and 10.3% of patients first responding during the second and third cycle, respectively (782). A pooled patient-level analysis of real-world data showed that a relevant proportion of patients not responding to the first onabotulinumtoxinA responded to the second cycle, while patients who did not respond to the first two cycles were unlikely to respond to a third cycle (783). Although some other real-world data suggest that some patients might start having benefit from onabotulinumtoxinA even after the fourth administration (784), the availability of other preventive treatments for migraine suggests that clinicians should not wait for one year of treatment with onabotulinumtoxinA before changing treatments.

Topic: Administration scheme other than PREEMPT.
Suggestion: We suggest against administration schemes other than PREEMPT.

Rationale: Although administration protocols different from the PREEMPT studies were proposed (Table 4.5.2) and new injection schemes are under study (785), there is no sufficient evidence to suggest administration paradigms other than PREEMPT. An open-label RCT compared a new scheme of abobotulinumtoxinA injection following cranial sutures with incobotulinumtoxinA administered in a similar way to the PREEMPT paradigm (786). Both study groups obtained a benefit, but none of the two interventions was compared with placebo, which prevents the assessment of efficacy.

4.6 Gepants for migraine prevention

Introduction. Gepants are oral preventives for the treatment of migraine that act as competitive antagonists of the CGRP receptor (787). Gepants are highly selective for the canonical CGRP receptor (CLR/RAMP1), with poor affinity for other members of the CGRP receptor-family (788). This is due to their binding site between the CLR and the RAMP1 components of the canonical CGRP receptor (789). Their great affinity for this receptor is confirmed by an inhibition constant (Ki) in the nanomolar range (790). Multiple preclinical studies demonstrate the action of gepants on the trigeminovascular system. Firstly, they reduce CGRP-mediated meningeal vasodilation (791). Furthermore, gepants suppress activation of trigeminal Aδ and, partially, of C-fibers (792). As gepants cross the blood brain barrier (BBB) to a miniscule degree (523), some authors speculate that they may provide central effects (793).

The first generation of gepants, telcagepant and olcegepant, were developed in the early 2000s as acute treatments for migraine, but their development was interrupted due to liver toxicity (526). However, after the anti-CGRP monoclonal antibodies demonstrated efficacy for prevention, gepant development was resumed. The second generation of gepants were chemically modified from the first and did

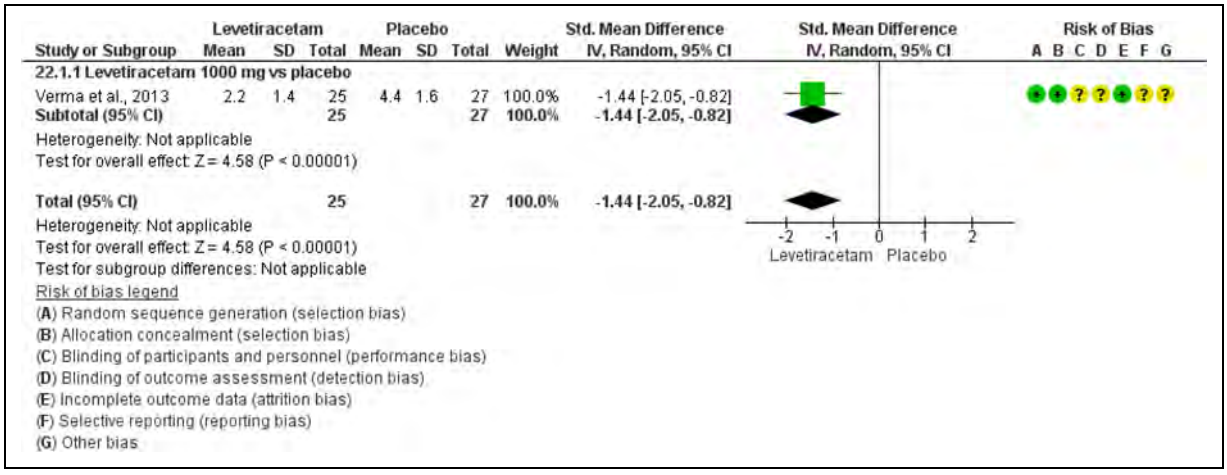


Figure 4.2.22. Forest plot showing the comparison between oral levetiracetam 1000 mg and placebo for the outcome persisting monthly migraine days in patients with episodic migraine.

not show hepatotoxicity. Among these, atogepant was specifically developed for migraine prevention, whilst rimegepant was first explored for acute and subsequently for preventive treatment (794). Indeed, the favorable safety profile of the gepants, including the intriguing possibility that gepants may not induce MOH, led to their use also as preventive treatment (794). Nowadays, atogepant is marketed at doses of 10 mg, 30 mg and 60 mg and rimegepant at the dose of 75 mg.

Section-specific methods. This section followed the general procedure to develop this guideline. However, there was only one literature update performed in November 2023, without that performed in May 2023 (see also Section 3.8).

Search strings for the guideline on gepants (preventive treatment) for systematic review/meta-analysis and for additional RCTs are reported in Online Appendix 4.6.1.

Results. Overall, we retrieved 139 references from searching for systematic reviews and meta-analyses. After duplicate removal and selection phases, we included two systematic reviews and meta-analyses (795,796) as sources of randomized controlled trials (RCTs) (Figure 4.6.1).

After analyzing full texts of these RCTs, we included two of them in the quantitative synthesis (797,798) (Figure 4.6.2).

Overall, we retrieved 299 references from searching for RCTs. After removing duplicates, 245 references remained for analysis; three RCTs were finally included (543,797,798). From the literature search update performed in November 2023, we retrieved 136 references and 121 were examined after removing duplicates. Three further studies were included from this search (799–801) (Figure 4.6.2).

Overall, five studies were included to develop the evidence-based guideline as they reported a comparison between an active drug and placebo and are presented in this Section. One RCT reported a head-to-head comparison and was included in Section 4.8.

Atogepant. **PICO 4.6.1.** In subjects with episodic migraine, is atogepant superior to placebo in migraine prevention (outcomes: change in monthly migraine days, persisting monthly migraine days, ≥50% responder rate)?

Main evidence. We found three RCTs (797–799) comparing oral atogepant to placebo in subjects with episodic migraine that met the criteria to be included in main evidence.

The pooled analysis showed benefits of oral atogepant 10, 30 and 60 mg daily over placebo considering the outcomes of change in monthly migraine days (Figure 4.6.3) and ≥50% responder rate (Figure 4.6.4) (797,798). The quality of evidence for both outcomes was considered high (Table 4.6.1).

Additional evidence. None.

Evidence-based recommendation for PICO 4.6.1

In subjects with episodic migraine, we recommend oral atogepant 60 mg daily for migraine prevention.
Quality of evidence: High (⊕⊕⊕⊕).
Strength of the recommendation: Strong (↑↑)
[NOTE: In Europe and in the USA atogepant is approved only in the 60 mg dose (802); therefore, the recommendation applies to commercial doses only].

PICO 4.6.2. In subjects with chronic migraine, is atogepant superior to placebo in migraine prevention (outcomes:

Table 4.2.6. GRADE evidence profile of oral levetiracetam versus placebo in episodic migraine prevention

Certainty assessment								№ of patients		Effect		
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations		Levetiracetam	Placebo	Relative (95% CI)	Absolute (95% CI)	Quality	Importance
Persisting monthly migraine days – Levetiracetam 1000 mg oral vs Placebo													
1	RCT	Serious[a]	Not applicable[b]	Not serious	Serious[c]	Only one outcome; very selective setting		25	27	-	SMD **1.4 lower** (2.1 lower to 0.8 lower)	⊕⊖⊖⊖ **Very Low**	Critical

[a]Relevant risk of bias detected in available RCTs; [b]only one trial; [c]Small sample size.

change in monthly migraine days, persisting monthly migraine days, ≥ 50% responder rate)?

Main evidence. We found one RCT comparing oral atogepant to placebo (800) in subjects with chronic migraine that met the criteria to be included in main evidence.

The pooled analysis showed benefits of oral atogepant 30 twice a day and 60 mg daily over placebo considering the outcomes of change in monthly migraine days (Figure 4.6.5) and of ≥50% responder rate (Figure 4.6.6) (800). The quality of evidence was considered high (Table 4.6.2).

Evidence-based recommendation for PICO 4.6.2

In subjects with chronic migraine, we recommend oral atogepant 60 mg daily for migraine prevention.
Quality of evidence: High (⊕⊕⊕⊕).
Strength of the recommendation: Strong (↑↑)
[NOTE: In Europe and in the USA atogepant is approved only in the 60 mg dose (802); therefore, the recommendation applies to commercial doses only].

Safety and tolerability of atogepant. Warnings and contraindications: Atogepant should not be used in subjects allergic to it. Moreover, it should not be used in pregnant or breastfeeding women, as well as in pediatric patients, since atogepant has not been tested on these populations in RCTs. These prohibitions are corroborated with data from animals, according to which atogepant may induce fetal malformations and it can even pass in the milk of breastfeeding rats (802). Geriatric patients were excluded from RCTs, so there is not enough data to clarify risks of this drug in patients older than 65 years of age. Considering the previous concerns about the liver toxicity that emerged with the first generation of gepants, atogepant should not be administered in patients with impaired liver function. Since the renal route of administration plays a minor role in atogepant elimination, this drug may be also prescribed in patients with severe renal impairment with multiple preventive treatment failure. However, a dose adjustment is warranted in patients with severe renal impairment or with an end-stage renal disease (803).

Serious safety concerns: To this day, no serious safety concerns have emerged.

Tolerability: From the published RCTs the most frequent AEs (emerged in more than the 2% of the patients) were nausea, somnolence, constipation, and decreased appetite (800).

Rimegepant. **PICO 4.6.3**. In patients with any migraine (no distinction between episodic and chronic), is rimegepant superior to placebo in migraine prevention (outcomes:

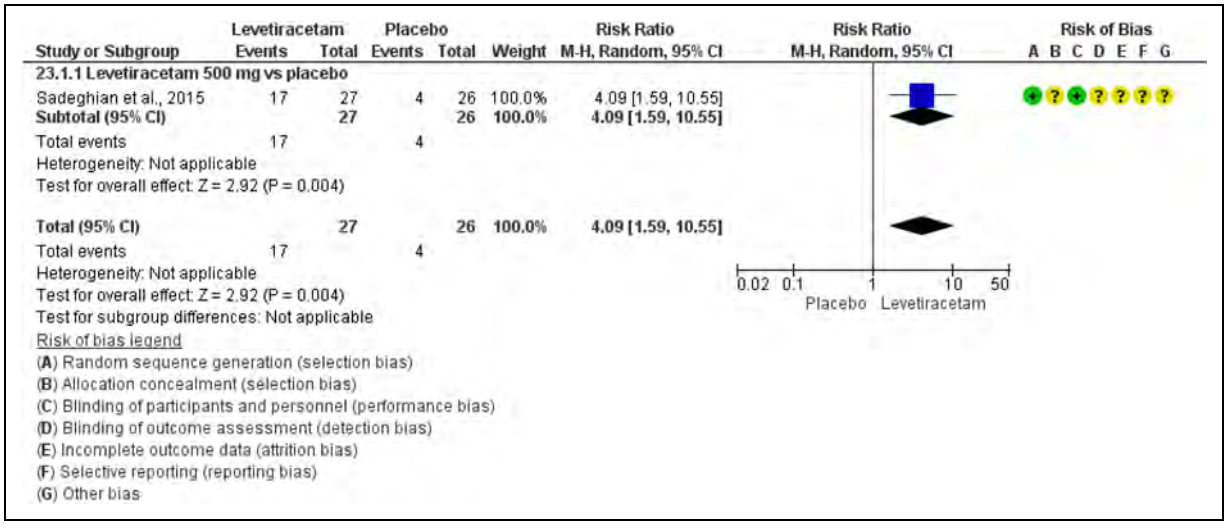


Figure 4.2.23. Forest plot showing the comparison between oral levetiracetam 500 mg and placebo for the outcome ≥50% response rate in patients with migraine (no distinction between episodic and chronic).

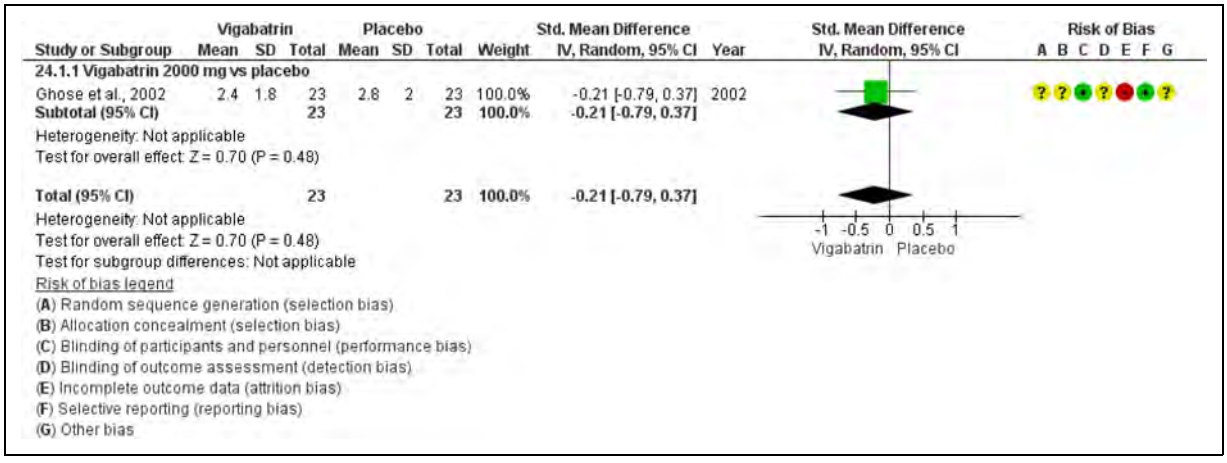


Figure 4.2.24. Forest plot showing the comparison between oral vigabatrin 2000 mg and placebo for the outcome persisting monthly migraine days in patients with migraine (no distinction between episodic and chronic).

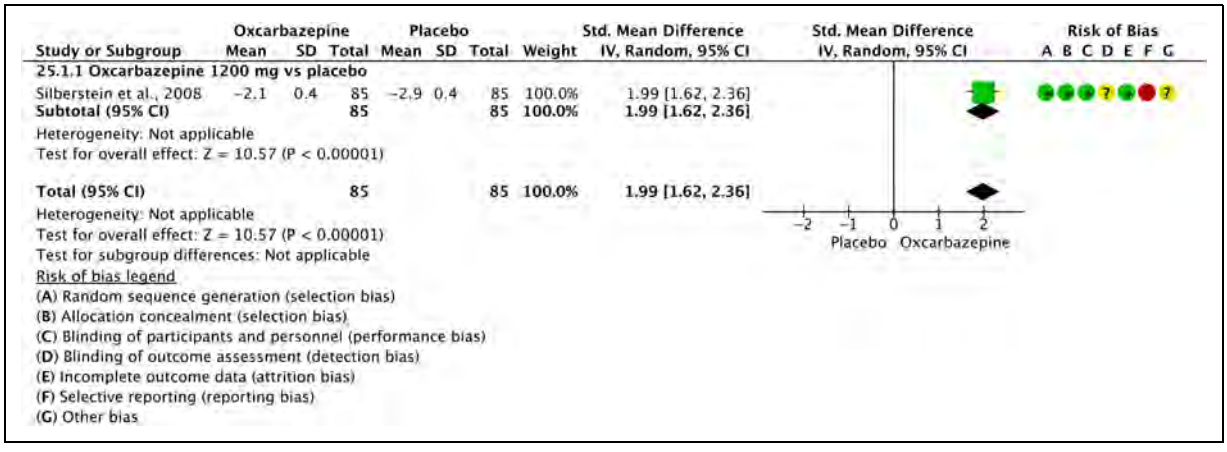


Figure 4.2.25. Forest plot showing the comparison between oral oral oxcarbazepine 1200 mg and placebo for the outcome change in monthly migraine days in patients with migraine (no distinction between episodic and chronic).

Table 4.2.7. GRADE evidence profile for oral oxcarbazepine versus placebo in patients with any migraine (no distinction between episodic and chronic)

Certainty assessment							№ of patients		Effect			
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Oxcarbazepine	Placebo	Relative (95% CI)	Absolute (95% CI)	Quality	Importance
Change in monthly migraine days – Oxcarbazepine 1200 mg oral vs Placebo												
1	RCT	Very serious	Not applicable[a]	Not serious	Not serious	None	85	85	-	SMD **2.0 higher** (1.6 higher to 2.4 higher)	⊕⊖⊖⊖ **Very low**	Critical
≥50% responder rate – Oxcarbazepine 1200 mg oral vs Placebo												
1	RCT	Very serious	Not applicable[a]	Not serious	Not serious	None	28/85 (32.9%)	31/85 (36.5%)	**RR 0.90** (0.60 to 1.37)	**36 fewer per 1.000** (from 146 fewer to 135 more)	⊕⊖⊖⊖ **Very low**	Critical

[a]Only one trial.

change in monthly migraine days, persisting monthly migraine days, ≥ 50% responder rate)?

Main evidence. We found one RCT comparing oral rimegepant to placebo (543) in subjects with migraine (between four and 18 monthly migraine days at baseline) that met the pre-defined criteria to be included in main evidence.

The RCT showed benefits of oral rimegepant 75 mg every other day over placebo considering the outcomes change in monthly migraine days (Figure 4.6.7) and ≥50% response rate (Figure 4.6.8) (543). The quality of evidence for both outcomes was considered moderate (Table 4.6.3) due to the availability of only one RCT.

Additional evidence. None.

Evidence-based recommendation for PICO 4.6.3

In subjects with migraine (between four and 18 monthly migraine days), we recommend oral rimegepant 75 mg every other day for migraine prevention.
Quality of evidence: Moderate (⊕⊕⊕⊖)
Strength of the recommendation: Strong (↑↑)

[NOTE: Current approvals of rimegepant only include subjects with episodic migraine (552), which represent most subjects treated in the available RCT.]

Safety and tolerability of rimegepant

Warnings and contraindications: Rimegepant should not be used in subjects with hypersensitivity reaction to it or to one of its excipients. Serious hypersensitivity reactions have been registered, even after several days from the administration of rimegepant (543). Rimegepant should not be used during pregnancy or lactation, since these categories were excluded from the RCT. Similarly, subjects aged <18 or >65 years have no RCT data. Rimegepant is mainly metabolized by the CYP3A4 and is a substrate of the P-gp and the BCRP efflux transporters. Hence, rimegepant should not be co-administered with strong inhibitors of the CYP3A4 – which might increase the risk for AEs – or with strong inducers of the CYP3A4 – which might decrease its efficacy (552). Additionally, rimegepant should not be used in patients with severe liver or renal impairment as those conditions might interfere with the metabolism of the drug (549).

Serious safety concerns: To this day, no serious safety concerns have emerged. All the serious AEs registered were considered unrelated to rimegepant (543).

Tolerability: from the published RCTs the most frequent AEs (emerged in more than 2% of the patients) were nasopharyngitis, nausea, urinary tract infection and upper respiratory tract infections (543).

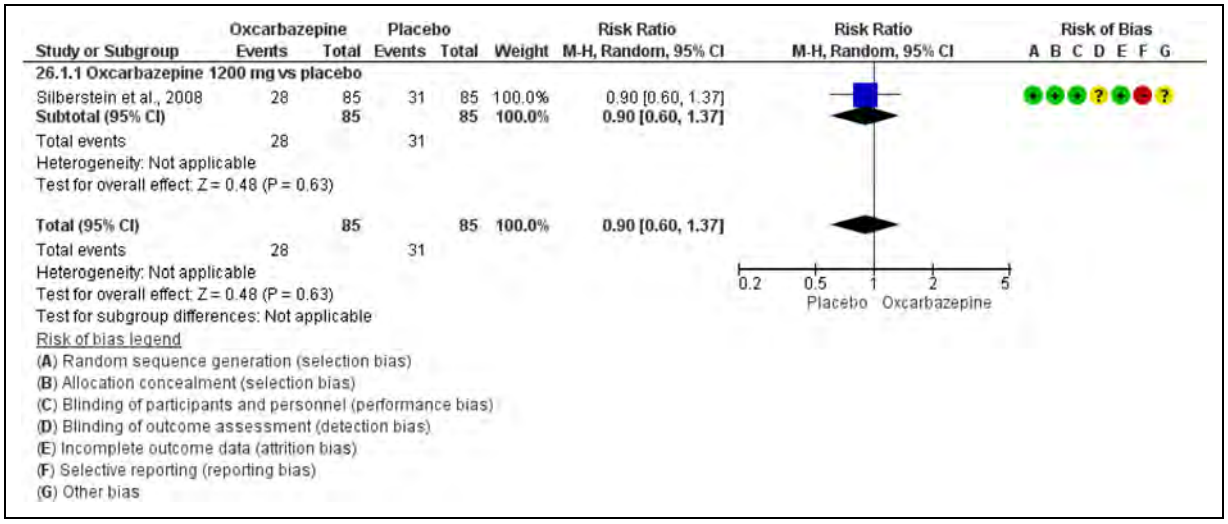


Figure 4.2.26. Forest plot showing the comparison between oral oxcarbazepine 1200 mg and placebo for the outcome ≥50% response rate in patients with migraine (no distinction between episodic and chronic).

Evidence-based guideline summary

We found five studies meeting eligibility criteria to be included as main evidence in this guideline on atogepant and rimegepant in migraine prevention. This study class is still under investigation in clinical trials and new results are expected that may change the present guideline. There is evidence to recommend the use of atogepant and rimegepant for episodic migraine prevention (Figure 4.6.9). No studies are currently available specifically for chronic migraine.

Expert-based opinion

Optimization of atogepant use

Topic: Which patients should currently receive limited or no treatment with gepants?. Suggestion: Gepants should be used with caution in subjects with vascular disease, severe constipation, inflammatory bowel disease, chronic obstructive pulmonary disease, or Raynaud's phenomenon.

Rationale: CGRP has numerous biological functions and is a particularly potent vasodilator in reduced perfusion and ischemia (804). In addition, CGRP receptors are also found, for example, in the intestine, in the endothelium of the bronchi and in the skin (804). For purely pathophysiological reasons, there are therefore a number of diseases in which both the monoclonal antibodies against CGRP and the gepants should only be used with great restraint or caution. The new migraine drugs are currently contraindicated in pregnant women, children, and adolescents.

4.7 ***Monoclonal antibodies targeting the CGRP pathway***

Introduction. Four monoclonal antibodies against the CGRP pathway (anti-CGRP mAbs) are currently available on several markets (805). One (erenumab) is directed against the CGRP receptor (R) (anti-CGRP/R mAb) and three (eptinezumab, galcanezumab and fremanezumab) are against the ligand (L) (anti-CGRP/L mAbs). RCTs and real-world studies demonstrated similar efficacy and tolerability of all these new drugs in chronic and episodic migraine, regardless of the presence of medication overuse and various previous treatment failures (804–806). Furthermore, anti-CGRP mAbs demonstrated a very favorable AE profile, with reported AEs slightly superior to the placebo group (807). The introduction of the anti-CGRP mAbs, which are disease-specific and mechanism-based treatments for the prevention of migraine, substantially improved patients' management even if raising costs. Providing evidence-based clinical guidance on the use of the CGRP mAbs is of paramount importance to optimize the use of highly effective although currently costly treatments.

Section-specific methods. This section followed the general procedure to develop this guideline.

Search strings for the guideline on monoclonal antibodies targeting the CGRP pathway for systematic review/meta-analysis and for additional RCTs are reported in Online Appendix 4.7.1.

Results. Overall, we retrieved 1308 references from searching for systematic reviews and meta-analyses. After duplicate removal and screening stages, we included 11 systematic reviews and meta-analyses (618,808–817) that were considered as sources of randomized controlled trials (RCTs). From the 11 systematic reviews and meta-analyses 19 RCTs were included in the quantitative synthesis (818–836) (Figure 4.7.1).

Drug	Any migraine	Episodic migraine	Chronic migraine
Topiramate 50 mg	⊖⊖⊖⊖ -	⊕⊕⊖⊖ ↑	⊕⊖⊖⊖ ↑
Topiramate 100 mg	⊖⊖⊖⊖ -	⊕⊕⊕⊖ ↑↑	⊕⊖⊖⊖ ↑
Topiramate 200 mg	⊖⊖⊖⊖ -	⊕⊕⊕⊖ ↑↑	⊕⊕⊖⊖ ↑
Valproate 500 mg	⊕⊖⊖⊖ ↑	⊖⊖⊖⊖ -	⊖⊖⊖⊖ -
Valproate 750 mg	⊖⊖⊖⊖ -	⊕⊖⊖⊖ ↑	⊖⊖⊖⊖ -
Valproate 800 mg	⊖⊖⊖⊖ -	⊖⊖⊖⊖ -	⊖⊖⊖⊖ -
Valproate 1000 mg*	⊕⊖⊖⊖ ↑	⊖⊖⊖⊖ -	⊖⊖⊖⊖ -
Valproate 1500 mg	⊕⊖⊖⊖ ↑	⊖⊖⊖⊖ -	⊖⊖⊖⊖ -
Gabapentin (1200-3000 mg)	⊖⊖⊖⊖ -	⊕⊖⊖⊖ ↓	⊖⊖⊖⊖ -
Lamotrigine 50 mg	⊖⊖⊖⊖ -	⊕⊖⊖⊖ ↑	⊖⊖⊖⊖ -
Levetiracetam 1000 mg	⊖⊖⊖⊖ -	⊕⊖⊖⊖ ↑	⊖⊖⊖⊖ -
Vigabatrin	⊕⊖⊖⊖ ↓	⊖⊖⊖⊖ -	⊖⊖⊖⊖ -
Oxcarbazepine	⊕⊖⊖⊖ ↓	⊖⊖⊖⊖ -	⊖⊖⊖⊖ -

Quality of selected evidence	
⊕⊕⊕⊕	high
⊕⊕⊕⊖	moderate
⊕⊕⊖⊖	low
⊕⊖⊖⊖	very low
⊖⊖⊖⊖	none
Strength of the recommendation	
↑↑	strong in favor
↑	weak in favor
↓	weak against
↓↓	strong against
-	none

Figure 4.2.27. Summary of evidence-based recommendations on anti-seizure medication for migraine prevention.
*The weak recommendation in favor of oral valproate 1000 mg for patients with any migraine derives from the fact that the 500 mg and 1500 mg doses are superior to placebo and the results from the 1000 mg dose are imprecise. The quality of evidence is very low for all dosages.

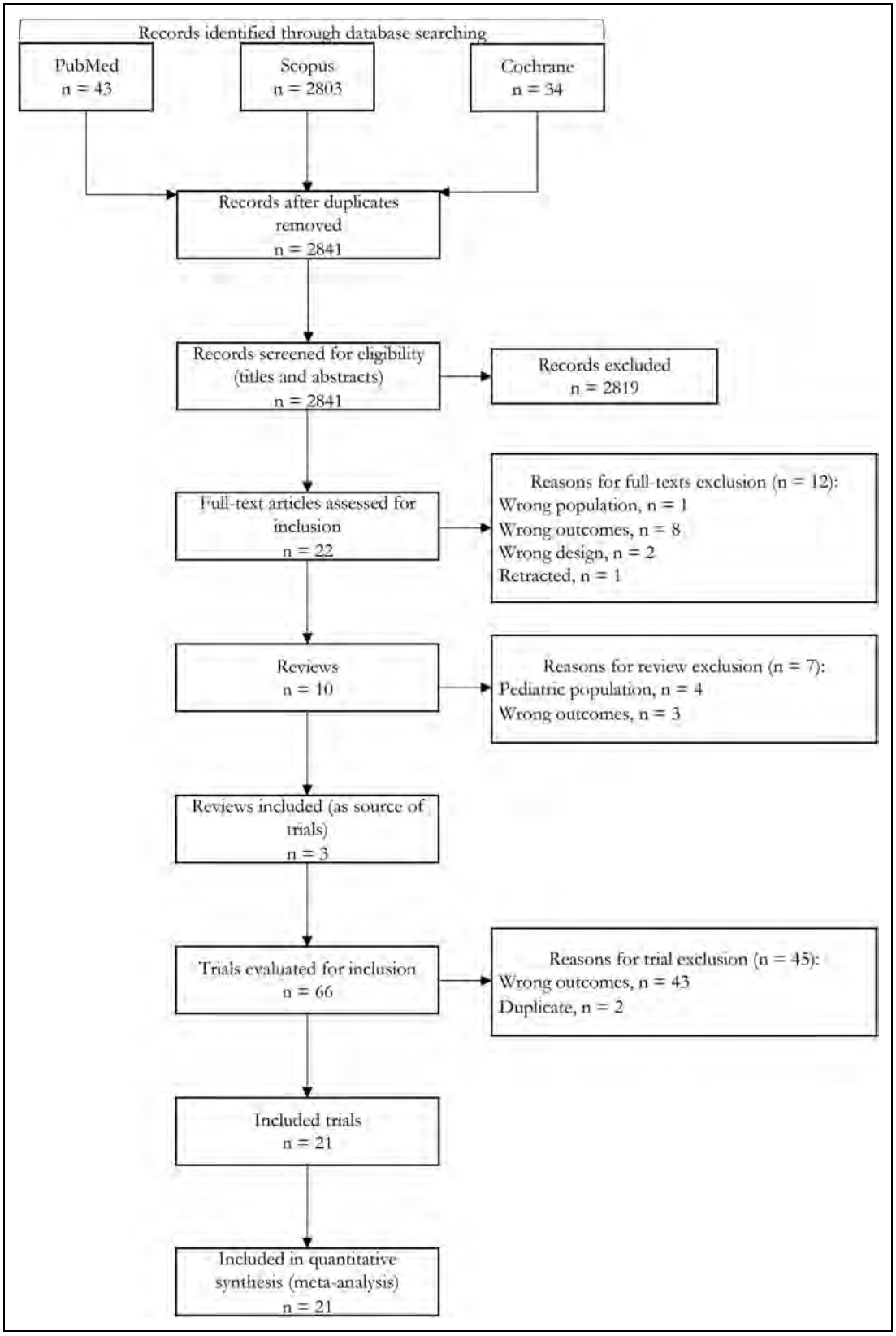


Figure 4.3.1. Meta-analysis selection flow chart - beta blockers.

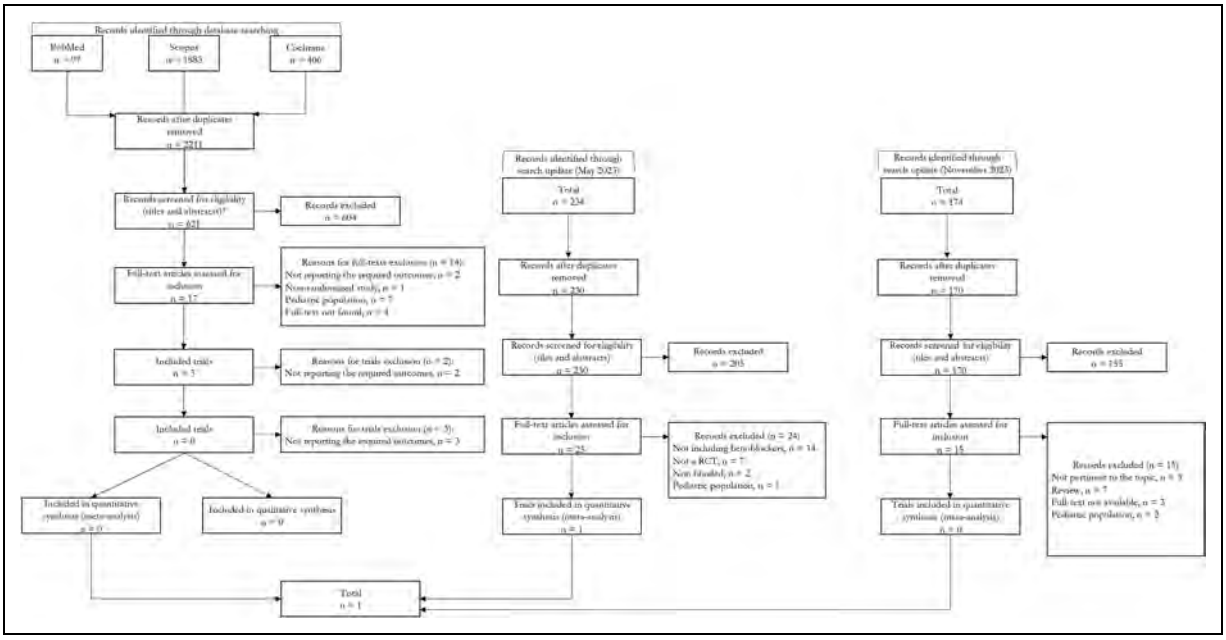


Figure 4.3.2. RCTs selection flow chart - beta blockers.
*trials published since August 2018 were screened.

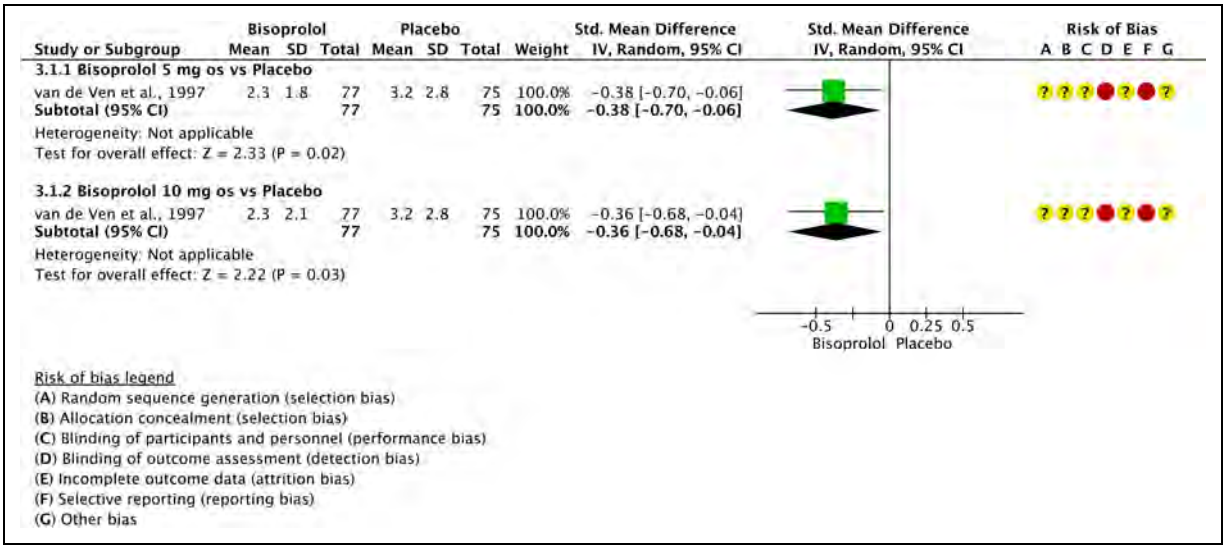


Figure 4.3.3. Forest plot showing the comparison between oral bisoprolol 5 or 10 mg and placebo for the outcome persisting monthly migraine days in patients with migraine (no distinction between episodic and chronic).

More recent papers, published since October 2020 and not reported in the reviews and meta-analyses, were searched. We retrieved 2762 references from which, after removing duplicates, five RCTs were selected and analyzed (837–841). From the literature search update performed in May and November 2023, three further RCTs were included (842–844) (Figure 4.7.2).

Overall, 26 studies were included in the quantitative synthesis to develop the evidence-based guideline (meta-analyses) and are presented in this Section. One RCT reported a head-to-head comparison and was presented in Section 4.8.

Eptinezumab. **PICO 4.7.1.** In subjects with episodic migraine, is eptinezumab superior to placebo for migraine prevention (outcomes: persisting monthly migraine days, change in monthly migraine days, $\geq 50\%$ responder rate)?

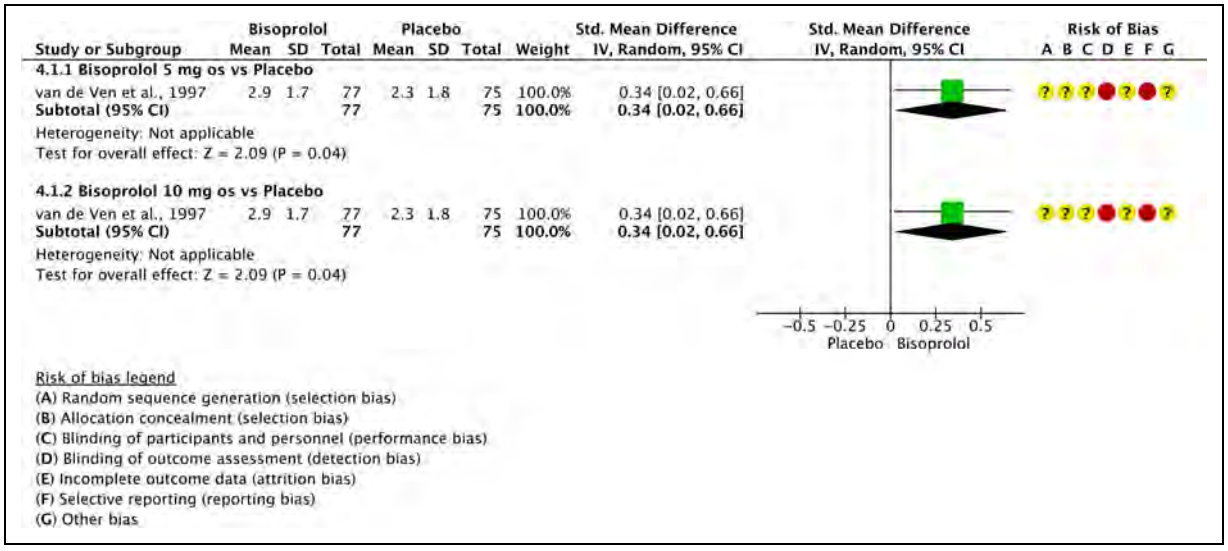


Figure 4.3.4. Forest plot showing the comparison between oral bisoprolol 5 or 10 mg and placebo for the outcome change in monthly migraine days in patients with migraine (no distinction between episodic and chronic).

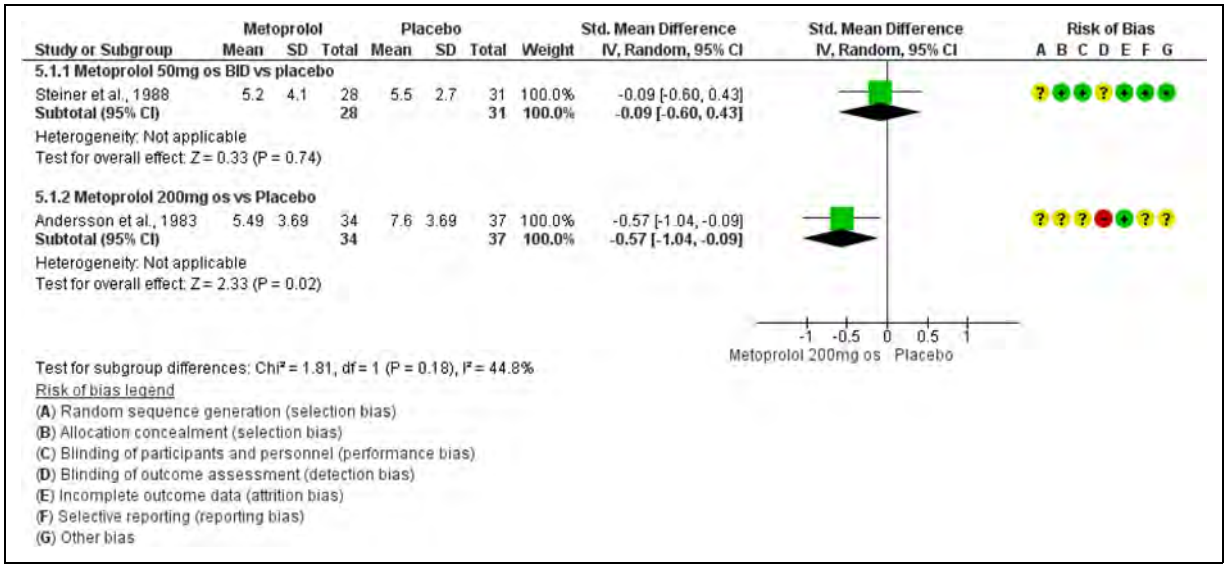


Figure 4.3.5. Forest plot showing the comparison between oral metoprolol (50 mg BID or 200 mg) and placebo for the outcome persisting monthly migraine days in patients with migraine (no distinction between episodic and chronic).

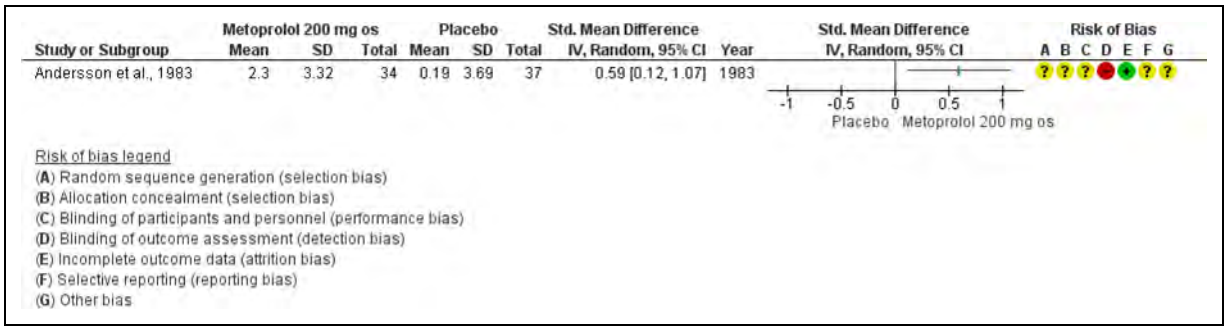


Figure 4.3.6. Forest plot showing the comparison between oral metoprolol 200 mg and placebo for the outcome change in monthly migraine days in patients with any migraine (no distinction between episodic and chronic).

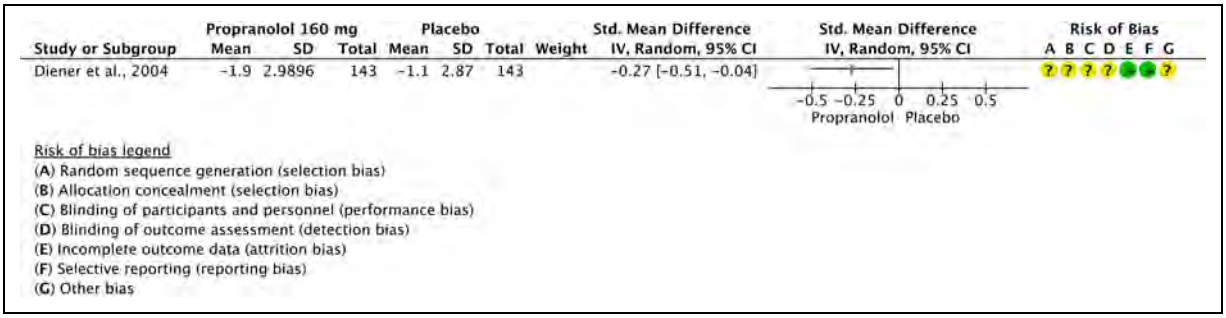


Figure 4.3.7. Forest plot showing the comparison between oral propranolol 160 mg daily and placebo for the outcome change in monthly migraine days in patients with episodic migraine.

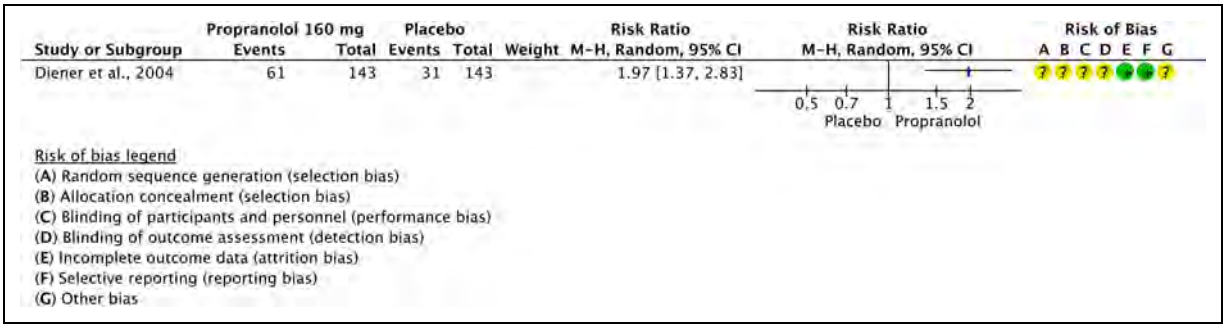


Figure 4.3.8. Forest plot showing the comparison between oral propranolol 160 mg daily and placebo for the outcome ≥50% responder rate in patients with episodic migraine.

Main evidence. We found one RCT comparing eptinezumab to placebo in subjects with episodic migraine (818) that met the criteria to be included in the main evidence.

The RCT showed a significant improvement in subjects treated with intravenous (IV) eptinezumab 100 and 300 mg quarterly over placebo considering the outcomes of change in monthly migraine days (Figure 4.7.3) and ≥50% response rate (Figure 4.7.4). The quality of evidence for both outcomes was considered moderate (Table 4.7.1).

Additional evidence. None.

Evidence-based recommendation for PICO 4.7.1

In subjects with episodic migraine, we recommend IV eptinezumab 100 or 300 mg quarterly for migraine prevention.
Quality of evidence: Moderate (⊕⊕⊕⊖)
Strength of the recommendation: Strong (↑↑)

PICO 4.7.2. In subjects with chronic migraine, is eptinezumab superior to placebo for migraine prevention (outcomes: persisting monthly migraine days, change in monthly migraine days, ≥ 50% responder rate)?

Main evidence. We found two RCTs comparing eptinezumab to placebo in subjects with chronic migraine (823,827) that met the criteria to be included in the main evidence.

The pooled analysis showed a significant improvement in subjects treated with IV eptinezumab 100 and 300 mg quarterly over placebo considering the outcomes of change in monthly migraine days (Figure 4.7.5) and ≥50% responder rate (Figure 4.7.6). The quality of evidence for both outcomes was considered high (Table 4.7.2).

Additional evidence. None.

Evidence-based recommendation for PICO 4.7.2

In subjects with chronic migraine, we recommend intravenous eptinezumab 100 or 300 mg quarterly for migraine prevention.
Quality of evidence: High (⊕⊕⊕⊕)
Strength of the recommendation: Strong (↑↑)

PICO 4.7.3. In subjects with any migraine (no distinction between episodic and chronic), is eptinezumab superior to placebo for migraine prevention (outcomes: persisting

Table 4.3.1. GRADE evidence profile for oral propranolol 160 mg versus placebo in patients with episodic migraine

Certainty assessment							№ of patients		Effect			
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Propranolol	Placebo	Relative (95% CI)	Absolute (95% CI)	Quality	Importance
Change in monthly migraine days – Propranolol 160 mg oral vs Placebo												
1	RCT	Serious	Not applicable[a]	Not serious	Not serious	None	143	143	-	SMD **0.3 lower** (0.5 lower to 0.0 lower)	⊕⊕⊖⊖ **Low**	Critical
≥50% responder rate – Propranolol 160 mg oral vs Placebo												
1	RCT	Serious	Not applicable[a]	Not serious	Not serious	None	61/143 (42.7%)	31/143 (21.7%)	**RR 1.97** (1.37 to 2.83)	**210 more per 1.000** (from 80 more to 397 more)	⊕⊕⊖⊖ **Low**	Critical

[a]Only one trial.

monthly migraine days, change in monthly migraine days, ≥ 50% responder rate)?

Main evidence. We found one RCT comparing eptinezumab to placebo in subjects with migraine (no distinction between episodic and chronic) (843) that met the criteria to be included in the main evidence. This study only included subjects with previous failure to at least 2–4 classes of migraine preventatives.

The RCT showed a significant improvement in patients treated with IV eptinezumab 100 and 300 mg quarterly over placebo considering the outcomes of change in monthly migraine days (Figure 4.7.7) and ≥50% responder rate (Figure 4.7.8). The quality of evidence for both outcomes was considered moderate (Table 4.7.3).

Additional evidence. None.

Evidence-based recommendation for PICO 4.7.3

In subjects with migraine (no distinction between episodic and chronic), we recommend intravenous eptinezumab 100 or 300 mg quarterly for migraine prevention.
Quality of evidence: Moderate (⊕⊕⊕⊖)
Strength of the recommendation: Strong (↑↑)

Erenumab. **PICO 4.7.4.** In subjects with episodic migraine, is erenumab superior to placebo for migraine prevention (outcomes: persisting monthly migraine days, change in monthly migraine days, ≥ 50% responder rate)?

Main evidence. We found six RCTs comparing erenumab to placebo in subjects with episodic migraine (822,826,831,835,840,841) that met the criteria to be included in the main evidence.

The pooled analysis showed a significant improvement in subjects treated with subcutaneous (SC) erenumab 70 and 140 mg monthly over placebo considering the outcomes of change in monthly migraine days (Figure 4.7.9) and ≥50% response rate (Figure 4.7.10). The quality of evidence for both outcomes was considered high (Table 4.7.4). Analyses were pooled for 12-week and 24-week outcomes.

Additional evidence. None.

Evidence-based recommendation for PICO 4.7.4

In subjects with episodic migraine, we recommend subcutaneous erenumab 70 or 140 mg monthly for migraine prevention.
Quality of evidence: High (⊕⊕⊕⊕)
Strength of the recommendation: Strong (↑↑)

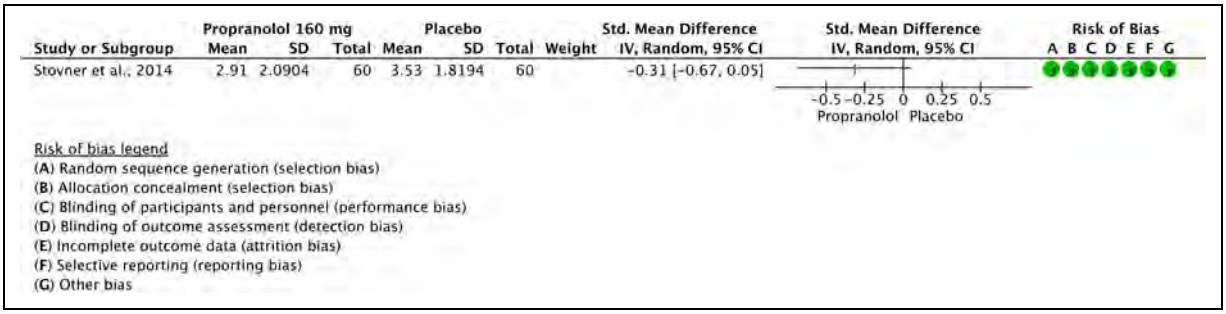


Figure 4.3.9. Forest plot showing the comparison between oral propranolol 160 mg daily and placebo for the outcome persisting monthly migraine days in patients with any migraine (no distinction between episodic and chronic).

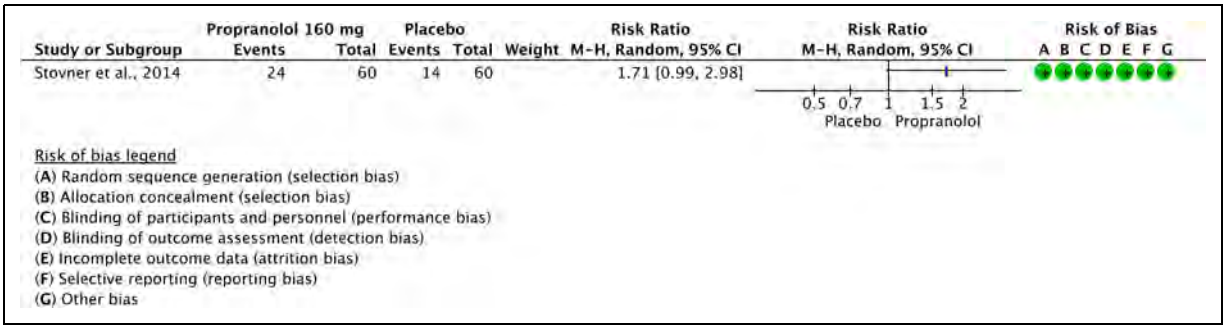


Figure 4.3.10. Forest plot showing the comparison between oral propranolol 160 mg daily and placebo for the outcome ≥50% responder rate in patients with any migraine (no distinction between episodic and chronic).

PICO 4.7.5. In subjects with chronic migraine, is erenumab superior to placebo for migraine prevention (outcomes: persisting monthly migraine days, change in monthly headache days, ≥ 50% responder rate)?

Main evidence. We found two RCTs comparing erenumab to placebo in subjects with chronic migraine (836,840) that met the criteria to be included in the main evidence.

The pooled analysis showed benefits of SC erenumab 70 and 140 mg monthly over placebo considering the outcomes of change in monthly headache days (Figure 4.7.11) and ≥50% response rate (Figure 4.7.12). The quality of evidence for the outcome of monthly headache days was considered high for erenumab 70 mg and moderate for erenumab 140 mg; the quality of evidence for ≥50% response rate was considered moderate for both 70 and 140 mg doses (Table 4.7.5). Analyses were pooled for 12-week and 24-week outcomes.

Additional evidence. None.

Evidence-based recommendation for PICO 4.7.5

In subjects with chronic migraine, we recommend subcutaneous erenumab 70 or 140 mg monthly for migraine prevention.
Quality of evidence: Moderate (⊕⊕⊕⊖)
Strength of the recommendation: Strong (↑↑)

Fremanezumab. **PICO 4.7.6.** In subjects with episodic migraine, is fremanezumab superior to placebo for migraine prevention (outcomes: persisting monthly migraine days, change in monthly headache days, ≥ 50% responder rate)?

Main evidence. We found four RCTs comparing fremanezumab to placebo in subjects with episodic migraine (819,824,825,838) that met the criteria to be included in the main evidence.

The pooled analysis showed benefits of subcutaneous fremanezumab 225 mg monthly and 675 mg quarterly over placebo considering the outcomes of change in monthly migraine days (Figure 4.7.13) and ≥50% response rate (Figure 4.7.14). The quality of evidence for both outcomes was considered high (Table 4.7.6).

Additional evidence. None.

Table 4.3.2. GRADE evidence profile for oral propranolol 160 mg versus placebo in patients with any migraine (no distinction between episodic and chronic)

Certainty assessment							№ of patients		Effect			
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Propranolol	Placebo	Relative (95% CI)	Absolute (95% CI)	Quality	Importance
Persisting monthly migraine days – Propranolol 160 mg oral vs Placebo												
1	RCT	Not serious	Not applicable[a]	Not serious	Not serious	None	60	60	-	SMD **0.3 lower** (0.7 lower to 0.0 higher)	⊕⊕⊕⊖ **Moderate**	Critical
≥50% responder rate – Propranolol 160 mg oral vs Placebo												
1	RCT	Not serious	Not applicable[a]	Not serious	Not serious	None	24/60 (40.0%)	14/60 (23.3%)	**RR 1.71** (0.99 to 2.98)	**166 more per 1.000** (from 2 fewer to 462 more)	⊕⊕⊕⊖ **Moderate**	Critical

[a]Only one trial.

Evidence-based recommendation for PICO 4.7.6

In subjects with episodic migraine, we recommend subcutaneous fremanezumab 225 mg monthly or 675 mg quarterly for migraine prevention.
Quality of evidence: High (⊕⊕⊕⊕)
Strength of the recommendation: Strong (↑↑)

PICO 4.7.7. In subjects with chronic migraine, is fremanezumab superior to placebo for migraine prevention (outcomes: persisting monthly migraine days, change in monthly headache days, ≥ 50% responder rate)?

Main evidence. We found four RCTs comparing fremanezumab to placebo in subjects with chronic migraine (820,825,832,839) that met the criteria to be included in the main evidence.

The pooled analysis showed benefits of subcutaneous fremanezumab 225 mg monthly (with 675 mg loading dose) and 675 mg quarterly mg over placebo considering the outcomes change in monthly headache days (Figure 4.7.15) and ≥50% response rate (Figure 4.7.16). The quality of evidence for both outcomes was high for fremanezumab 675 mg quarterly. For both outcomes related to fremanezumab 225 mg monthly the quality of evidence was downgraded to moderate since in RCTs the intervention also included a loading dose of 675 mg that is not approved for clinical use (Table 4.7.7). However, it should be noted that the loading dose was deemed not necessary by regulatory agencies as not influencing the efficacy of the drug or its onset of effect.

Additional evidence. None.

Evidence-based recommendations for PICO 4.7.7

1) In subjects with chronic migraine, we recommend subcutaneous fremanezumab 225 mg monthly for migraine prevention.

Quality of evidence: Moderate (⊕⊕⊕⊖)
Strength of the recommendation: Strong (↑↑)

2) In subjects with chronic migraine, we recommend subcutaneous fremanezumab 675 mg quarterly for migraine prevention.

Quality of evidence: High (⊕⊕⊕⊕)
Strength of the recommendation: Strong (↑↑)

Galcanezumab. **PICO 4.7.8.** In subjects with episodic migraine, is galcanezumab superior to placebo for migraine

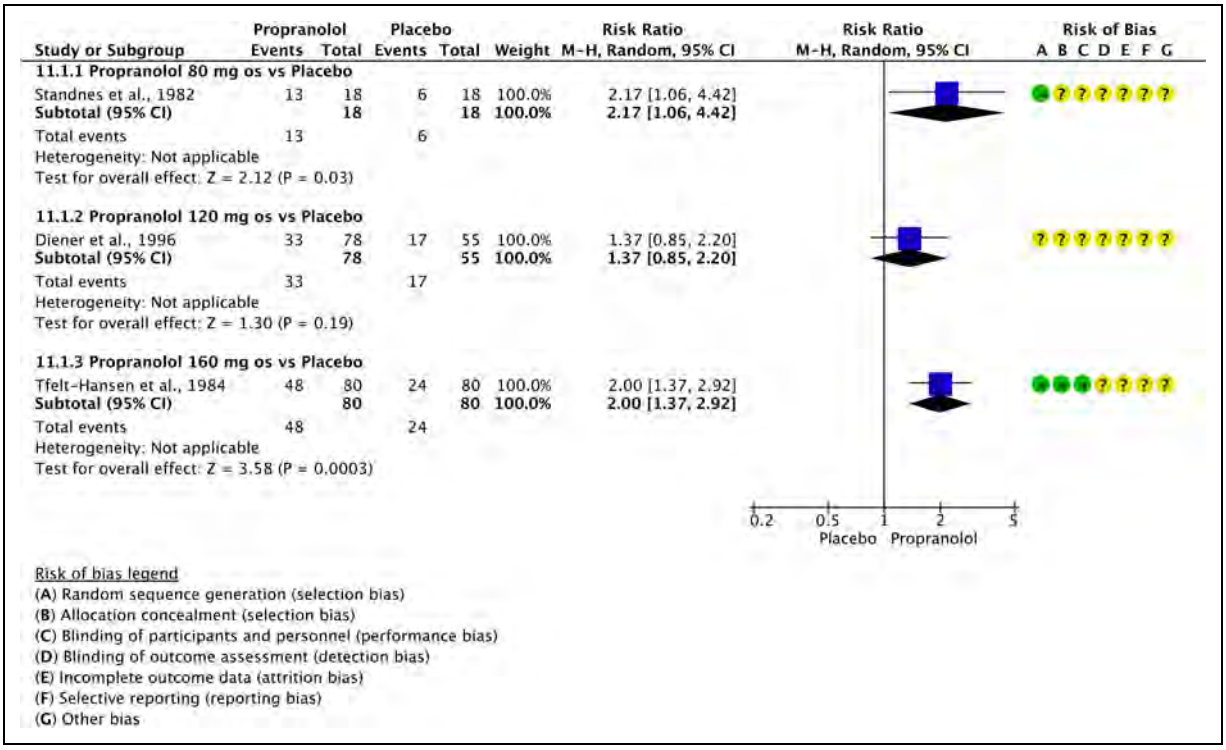


Figure 4.3.11. Forest plot showing the comparison between oral propranolol and placebo for the outcome ≥50% responder rate in patients with any migraine (no distinction between episodic and chronic).

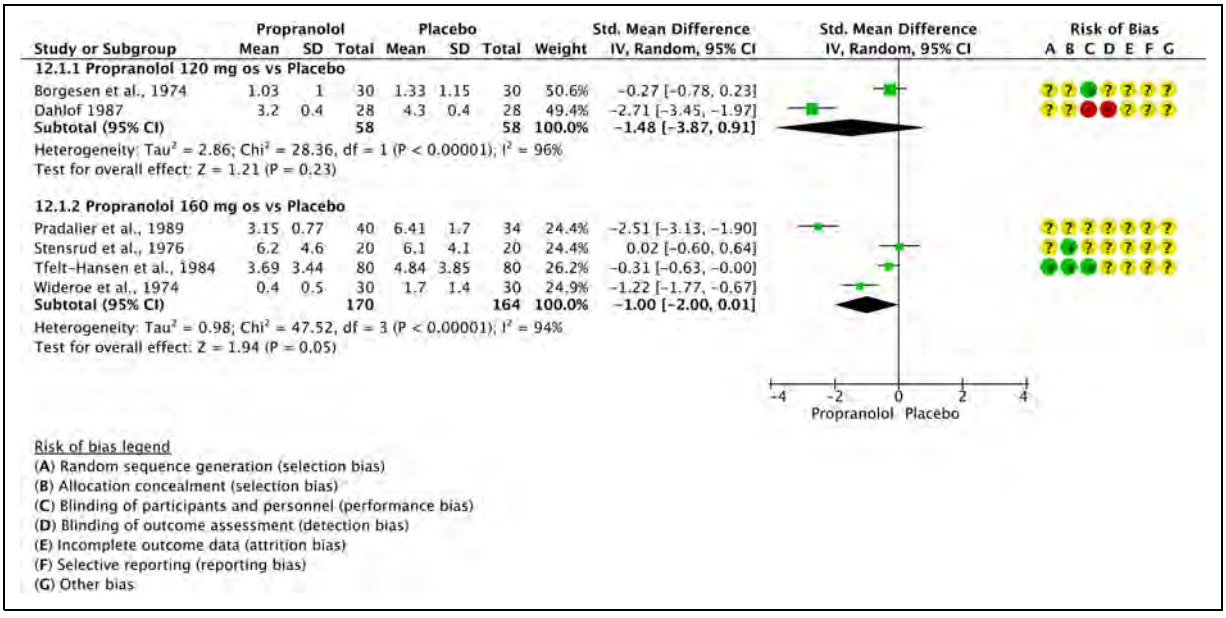
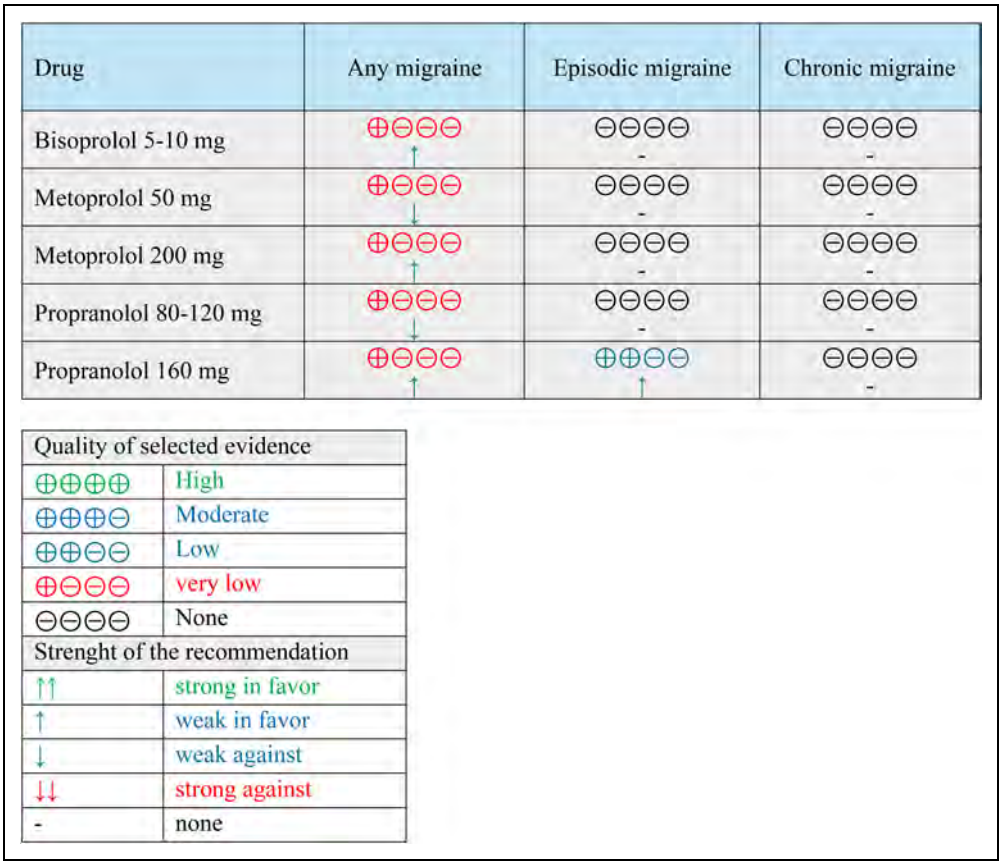


Figure 4.3.12. Forest plot showing the comparison between oral propranolol and placebo for the outcome persisting monthly migraine attacks in patients with any migraine (no distinction between episodic and chronic).



Drug	Any migraine	Episodic migraine	Chronic migraine
Bisoprolol 5-10 mg	⊕⊖⊖⊖ ↑	⊖⊖⊖⊖ -	⊖⊖⊖⊖ -
Metoprolol 50 mg	⊕⊖⊖⊖ ↓	⊖⊖⊖⊖ -	⊖⊖⊖⊖ -
Metoprolol 200 mg	⊕⊖⊖⊖ ↑	⊖⊖⊖⊖ -	⊖⊖⊖⊖ -
Propranolol 80-120 mg	⊕⊖⊖⊖ ↓	⊖⊖⊖⊖ -	⊖⊖⊖⊖ -
Propranolol 160 mg	⊕⊖⊖⊖ ↑	⊕⊕⊖⊖ ↑	⊖⊖⊖⊖ -

Quality of selected evidence	
⊕⊕⊕⊕	High
⊕⊕⊕⊖	Moderate
⊕⊕⊖⊖	Low
⊕⊖⊖⊖	very low
⊖⊖⊖⊖	None
Strenght of the recommendation	
↑↑	strong in favor
↑	weak in favor
↓	weak against
↓↓	strong against
-	none

Figure 4.3.13. Summary of evidence-based recommendations on beta-blockers for migraine prevention.

prevention (outcomes: persisting monthly migraine days, change in monthly migraine days, ≥ 50% responder rate)?

Main evidence. We found five RCTs comparing galcanezumab to placebo in subjects with episodic migraine (828,830,833,834,844) that met the criteria to be included in the main evidence.

The pooled analysis showed benefits of SC galcanezumab 120 mg monthly (with 240 mg loading dose at the first administration) over placebo considering the outcomes of change in monthly headache days (Figure 4.7.17) and ≥50% responder rate (Figure 4.7.18). The quality of evidence for both outcomes was considered high (Table 4.7.8). Analyses were pooled for three-month and six-month outcomes.

Additional evidence. None.

Evidence-based recommendation for PICO 4.7.8

In subjects with episodic migraine, we recommend subcutaneous galcanezumab 120 mg monthly (with 240 mg loading dose at the first administration) for migraine prevention.
Quality of evidence: High (⊕⊕⊕⊕)
Strength of the recommendation: Strong (↑↑)

PICO 4.7.9. In subjects with chronic migraine, is galcanezumab superior to placebo for migraine prevention (outcomes: persisting monthly migraine days, change in monthly headache days, ≥ 50% responder rate)?

Main evidence. We found two RCTs comparing galcanezumab to placebo in subjects with chronic migraine (821,828) that met the criteria to be included in the main evidence.

The pooled analysis showed benefits of subcutaneous galcanezumab 120 mg monthly (with 240 mg loading dose at the first administration) over placebo considering the outcomes change in monthly headache days (Figure 4.7.19) and ≥50% response rate (Figure 4.7.20). The quality of evidence for both outcomes was considered high (Table 4.7.9).

Additional evidence. None.

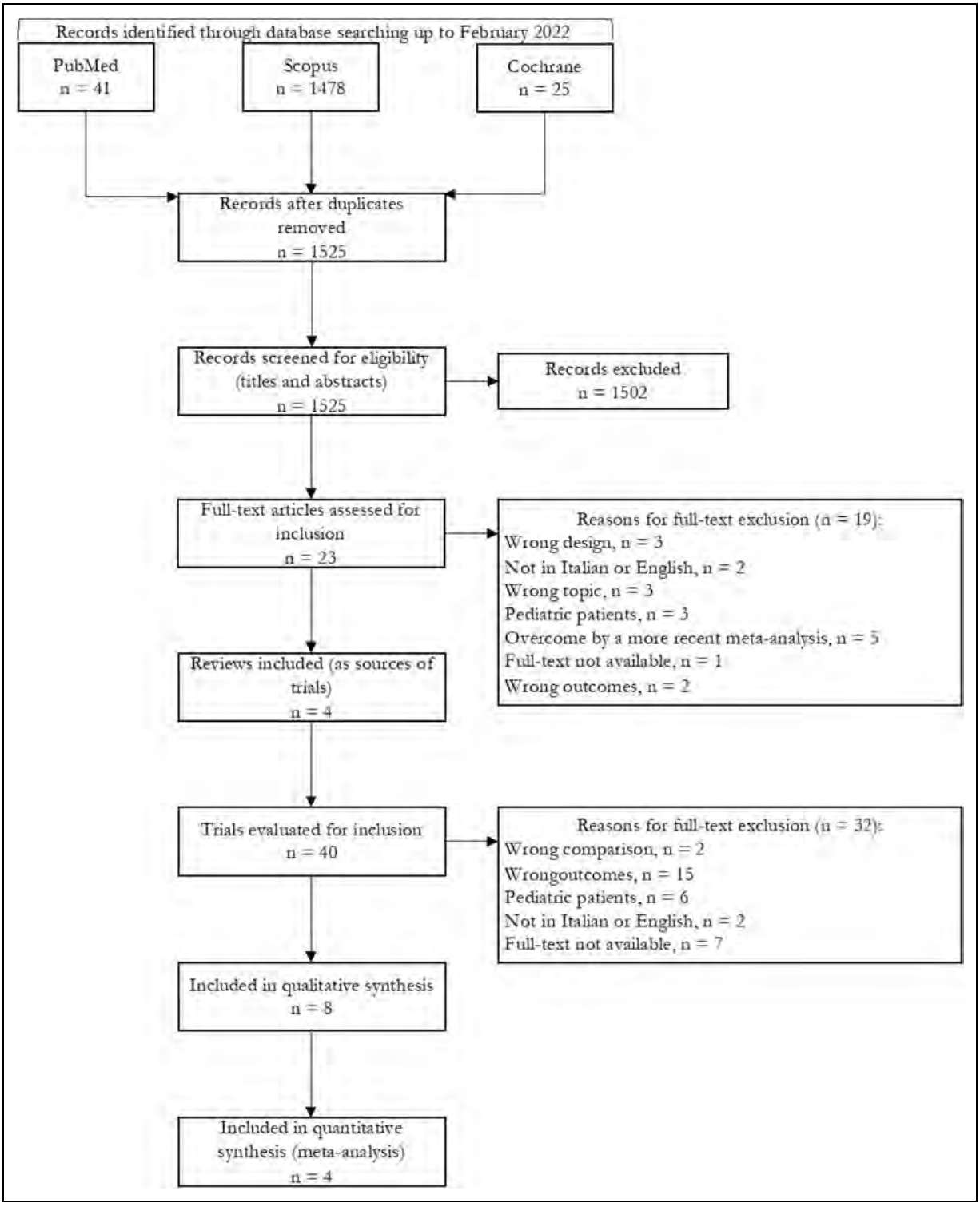


Figure 4.4.1. Meta-analysis selection flow chart - calcium channel blockers and blood pressure-lowering medications.

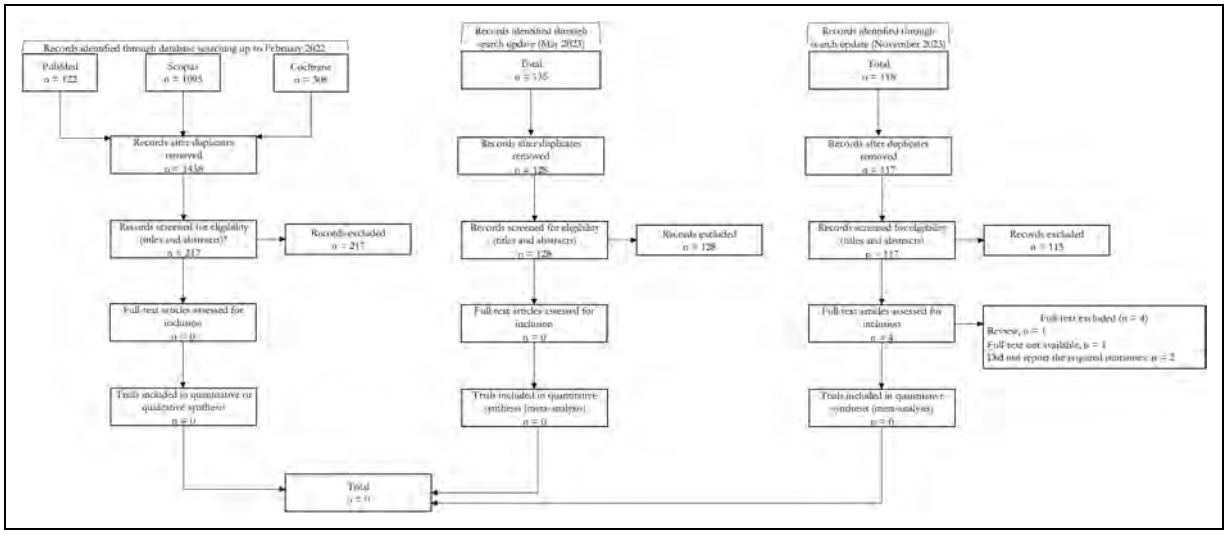


Figure 4.4.2. RCT selection flow chart - calcium channel blockers and blood pressure-lowering medications.

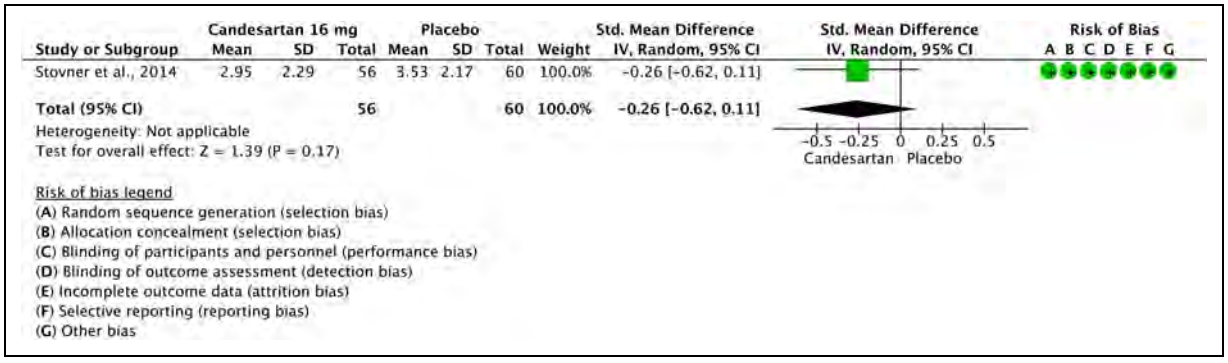


Figure 4.4.3. Forest plot showing the comparison between oral candesartan 16 mg and placebo for the outcome change in monthly migraine days in patients with migraine (no distinction between episodic and chronic).

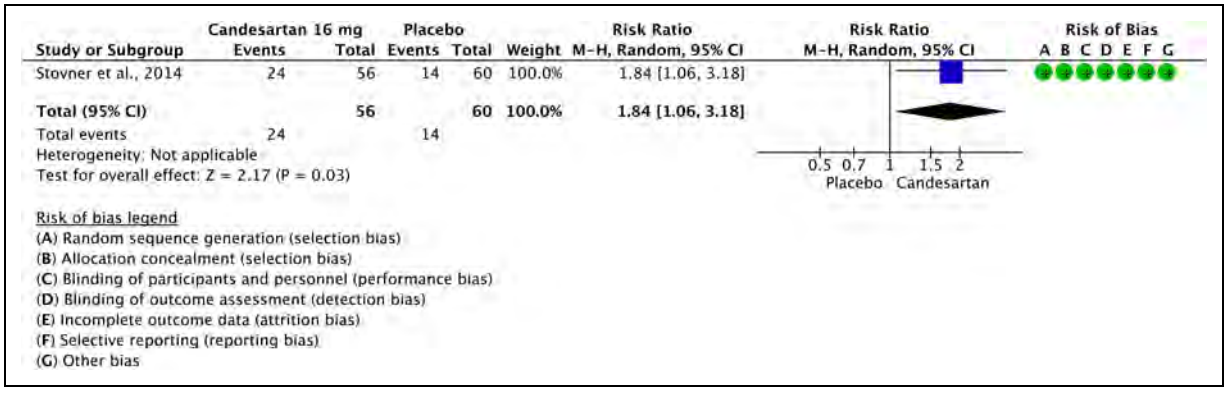


Figure 4.4.4. Forest plot showing the comparison between oral candesartan 16 mg and placebo for the outcome ≥50% response rate in patients with migraine (no distinction between episodic and chronic).

Table 4.4.1. GRADE evidence profile table for oral candesartan 16 mg versus placebo in patients with migraine (no distinction between episodic and chronic)

Certainty assessment							№ of patients		Effect			
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Candesartan 16 mg	Placebo	Relative (95% CI)	Absolute (95% CI)	Quality	Importance
Monthly migraine days - Candesartan 16 mg oral vs Placebo												
1	RCTs	Not serious	Not applicable[a]	Not serious	Not serious	Serious[b]	56	60	**SMD 0.3 lower** (from 0.6 lower to 0.1 higher)	-	⊕⊕⊖⊖ Low	Critical
≥50% responder rate - Candesartan 16 mg oral vs Placebo												
1	RCTs	Not serious	Not applicable[a]	Not serious	Not serious	Serious[b]	24/56 (42.9%)	14/60 (23.3%)	**RR 1.84** (1.06 to 3.18)	**42 more per 1000** (from 3 more to 109 more)*	⊕⊕⊖⊖ Low	Critical

[a]Only one trial; [b]Inconsistency of findings in the same study.

Evidence-based recommendation for PICO 4.7.9

In subjects with chronic migraine, we recommend subcutaneous galcanezumab 120 mg monthly (with 240 mg loading dose at the first administration) for migraine prevention.
Quality of evidence: High (⊕⊕⊕⊕)
Strength of the recommendation: Strong (↑↑)

Safety and tolerability of anti-CGRP monoclonal antibodies. Warnings and contraindications: Anti-CGRP mAbs should not be used in pregnant or nursing women, as these populations are not included in RCTs, and preclinical data indicate that erenumab could cross the placenta (845,846).

Serious safety concerns: No serious safety concerns have emerged for anti-CGRP mAbs. RCTs and real-world evidence did not show any relevant vascular risk or association with vascular events in subjects treated with anti-CGRP mAbs (805,807). However, subjects enrolled in these studies were at low vascular risk, with no cardiovascular or cerebrovascular disease and without prior major vascular events. Considering that CGRP is one of the most potent vasodilators in mammals (804), and some preclinical evidence showed that blockade of the CGRP pathway worsened ischemic stroke (847), caution is needed in subjects with elevated risk or history of cardio- and cerebral-vascular events (848).

Tolerability: Results from RCTs and observational real-world studies have shown a favorable safety and tolerability profile for all the anti-CGRP mAbs even with a long follow-up (805–807). The use of the anti-CGRP/R mAbs erenumab was associated with hypertension and severe constipation, that led to an FDA label change (849,850). Due to CGRP regulation of gastrointestinal motility, mild constipation – usually not leading to treatment discontinuation – was reported with anti-CGRP/L mAbs (851). Thus, subjects need to be closely monitored for these events and caution might be necessary in patients with a history of constipation. Caution should be necessary also in patients with Raynaud's phenomenon (852,853).

Evidence-based guideline summary

We found 25 studies that met eligibility criteria to be included in the main evidence on CGRP mAbs in migraine prevention. There is evidence to recommend the use of CGRP mAbs for episodic and chronic migraine prevention (Figure 4.7.21).

Expert based opinion

Topic: Eptinezumab dosing and titration. Suggestion: We suggest starting with eptinezumab 100 mg quarterly dose

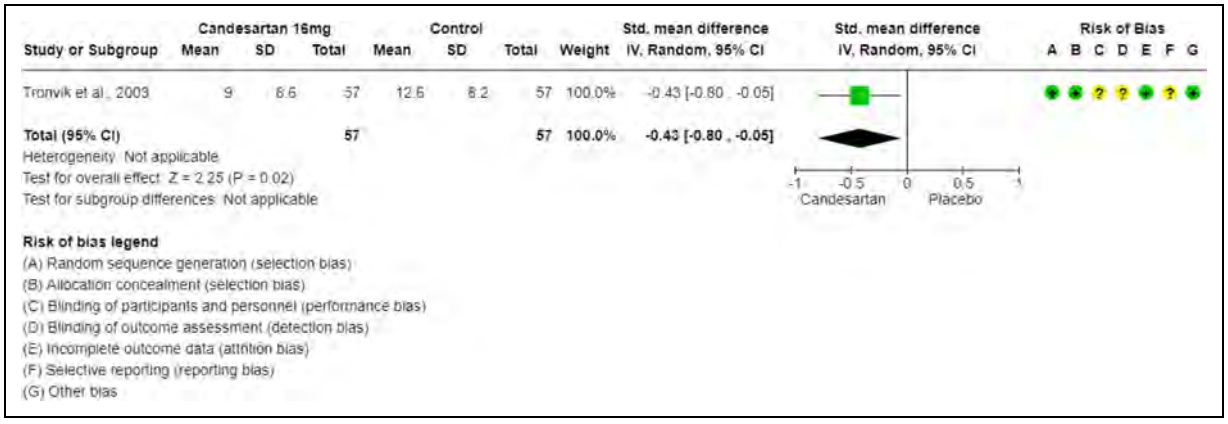


Figure 4.4.5. Forest plot showing the comparison between oral candesartan 16 mg os and placebo for the outcome persisting monthly migraine days in patients with episodic migraine.

and increasing it to 300 mg in cases of insufficient effectiveness.

Rationale: The recommended dose of eptinezumab is 100 mg infused every three months. Although 300 mg every three months may be helpful for some patients without increasing any safety or tolerability concerns, the advantages of the higher dose (300 mg) do not clearly emerge from RCTs (818,843) and real-world evidence studies are not available yet. The definition of "insufficient effectiveness" is also controversial. A 30% response rate could be considered a satisfactory response at least in subjects with chronic migraine (854), even if a 30% or 50% response rate could be associated with a substantial residual disability (855).

Topic: Erenumab dosing and titration. Suggestion: We suggest starting with erenumab 140 mg monthly dose.

Rationale: RCTs and real-world data provided evidence for a higher efficacy of erenumab 140 mg compared with 70 mg in several migraine-related variables, regardless of disease type – episodic or chronic migraine –, presence of medication overuse, or multiple prior treatment failures (856). Overall, the efficacy of the two erenumab doses indicates that administration of erenumab 140 mg provides superior benefits compared with erenumab 70 mg. The incidence of AEs for both dosages were similar.

Topic: Fremanezumab administration. Suggestion: We suggest, when starting fremanezumab, to choose between quarterly and monthly administration according to patients' preference.

Rationale: Analysis of data from the fremanezumab long-term study in subjects with episodic or chronic migraine confirmed that there was no evidence of a wearing-off effect toward the end of dosing intervals with either quarterly or monthly dosing (857). No increase in the mean number of weekly migraine days between the first two weeks and last two weeks of quarterly or monthly dosing intervals was observed with benefit maintained through the 15 months of treatment. In principle, the quarterly dose with fremanezumab could improve adherence to treatment and reduce the number of months of drug administration. No difference in tolerability was shown between quarterly and monthly doses.

Topic: Intravenous versus subcutaneous administration. Suggestion: In subjects eligible for anti-CGRP mAbs, we suggest the intravenous formulation in those who may have more benefit from the drug administration in a healthcare setting or those asking for faster relief of severe headache. The intravenous administration can also be selected based on patients' or clinicians' preference.

Rationale: Eptinezumab is dosed as a 30-min intravenous infusion and requires administration in a healthcare facility and more time for supervised administration, thus raising direct and indirect costs. On the other hand, intravenous eptinezumab provides 100% bioavailability that warrants a rapid beneficial effect. One study demonstrated the effect of the drug even on ongoing attacks (858). Finally, many patients might prefer mAb administration in a healthcare setting instead of a self-administered autoinjector.

Topic: Switch in real life studies. Suggestion: In subjects who do not have an adequate response to a first anti-CGRP mAb, we suggest switching to a second anti-CGRP mAb.

Rationale: A proportion (20–30%) of treated patients discontinued anti-CGRP mAbs treatment due to lack of efficacy, defined according to different variables. In these patients, switching between anti-CGRP mAbs could be an option, considering differences in the target (receptor vs. ligand), structure and pharmacokinetic properties. No

Table 4.4.2. GRADE evidence profile table for candesartan 16 mg os versus placebo in episodic migraine

Certainty assessment							№ of patients		Effect			
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Candesartan 16 mg	Placebo	Relative (95% CI)	Absolute (95% CI)	Quality	Importance
Persisting monthly migraine days - Candesartan 16 mg vs placebo												
1	RCTs	Not serious	Not applicabe[a]	Not serious	Not serious	None	57	57	**SMD 0.4 lower** (from 0.8 lower to 0.1 lower)	-	⊕⊕⊕⊖ Moderate	Critical

[a]Only one trial.

Table 4.4.3. GRADE evidence profile table for oral lisinopril 20 mg versus placebo in patients with episodic migraine

Certainty assessment							№ of patients		Effect			
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Lisinopril 20 mg	Placebo	Relative (95% CI)	Absolute (95% CI)	Quality	Importance
Monthly migraine days – Lisinopril 20 mg oral vs Placebo												
1	RCTs	Not serious	Not applicable[a]	Not seriuos	Not serious	Serious[b]	55	55	**SMD 0.4 lower** (from 0.8 lower to 0.1 lower)	-	⊕⊕⊖⊖ Low	Critical

[a]Only one trial; [b]Only one outcome.

Table 4.4.4. GRADE evidence profile table for oral telmisartan 80 mg versus placebo in episodic migraine

Certainty assessment							№ of patients		Effect			
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Telmisartan 80 mg	Placebo	Relative (95% CI)	Absolute (95% CI)	Quality	Importance
Monthly migraine days – Telmisartan 80 mg oral vs Placebo												
1	RCTs	Very serious	Not applicable[a]	Not serious	Serious[b]	None	40	44	**SMD 0.1 lower** (from 0.6 lower to 0.3 higher)	-	⊕⊖⊖⊖ Very Low	Critical
≥50% responder rate – Telmisartan 80 mg oral vs Placebo												
1	RCTs	Very serious	Not applicable[a]	Not serious	Serious[b]	None	16/40 (40.0%)	11/44 (25.0%)	**RR 1.60 (95% CI 0.85 to 3.03)**	**30 more per 1000** (from 8 fewer to 102 more)	⊕⊖⊖⊖ Very Low	Critical

[a]Only one trial; [b]Low numbers of patients (<50 per group).

RCTs designed to assess the effect of the anti-CGRP mAb switch in non-responders, have been performed so far. Initial real-world evidence, including observational studies (859–861) and case series (862–864), have suggested that switching between anti-CGRP mAbs might be a successful option in some patients, who previously tried without effectiveness one anti-CGRP mAb. After three or six months of ineffective treatment, a switch may be performed in selected patients, considering clinical and patient pragmatic treatment goals.

Topic: First evaluation of effectiveness. Suggestion: In subjects prescribed with an anti-CGRP mAb, we suggest the first evaluation of effectiveness after a minimum of three to six months of treatment.

Rationale: The choice of appropriate time points for the evaluation and decision of treatment continuation seems to have a major impact on patient treatment and cost optimization. Response to treatment should be multi-assessed with different migraine-related variables, preferably not limited to migraine/headache days, and including patients' reported outcomes. Although a three-month treatment seems sufficient to achieve a clinical benefit in the majority of patients (865–874), it cannot be excluded that additional benefit could be achieved after an additional three-month course of treatment, as real-world studies have shown further improvement from three to six months (806). Therefore, a six-month follow up could be a better option to assess effectiveness. However, in patients with none or very poor improvement in most migraine-related variables at three-months, a delayed onset of effectiveness may be unlikely.

Topic: In which patients should monoclonal antibodies targeting the CGRP pathway be used with caution?. Suggestion: Monoclonal antibodies targeting the CGRP pathway should be used with caution in patients with vascular disease, severe constipation, inflammatory bowel disease, chronic obstructive pulmonary disease, or Raynaud's phenomenon.

Rationale: As stated in Section 4.6 on gepants, CGRP has numerous biological functions and can be found in several apparatuses, including the gastrointestinal tract, the endothelium of the bronchi, and the skin (804). For purely pathophysiological reasons, there are therefore several diseases in which monoclonal antibodies targeting the CGRP pathway – as well as gepants – should be used with caution (Table 4.7.10). The new migraine drugs are also contraindicated in pregnant women, children, and adolescents.

4.8 Head-to-head comparisons – Preventive treatments

Introduction. A systematic examination of head-to-head comparisons of migraine preventive drugs might guide

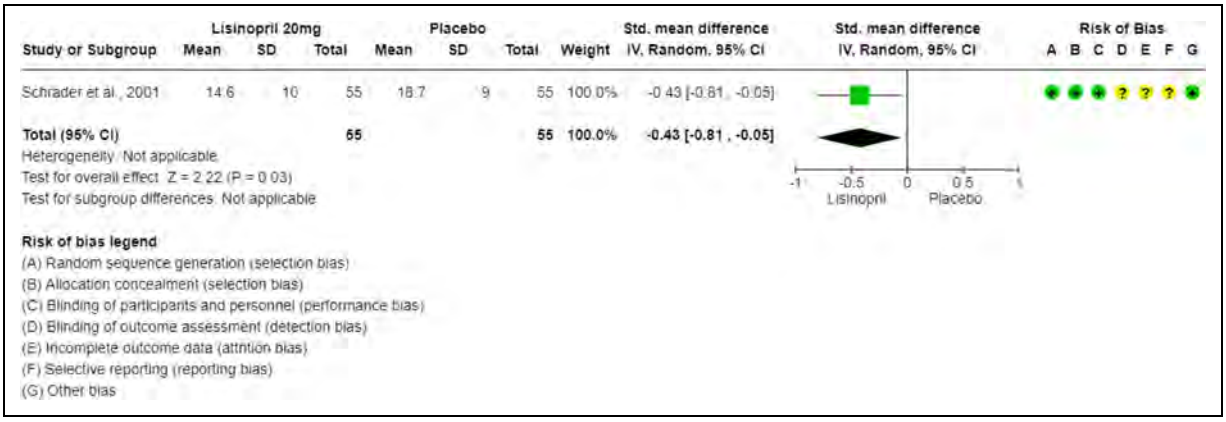


Figure 4.4.6. Forest plot showing the comparison between oral lisinopril 20 mg and placebo for the outcome persisting monthly migraine days in patients with episodic migraine.

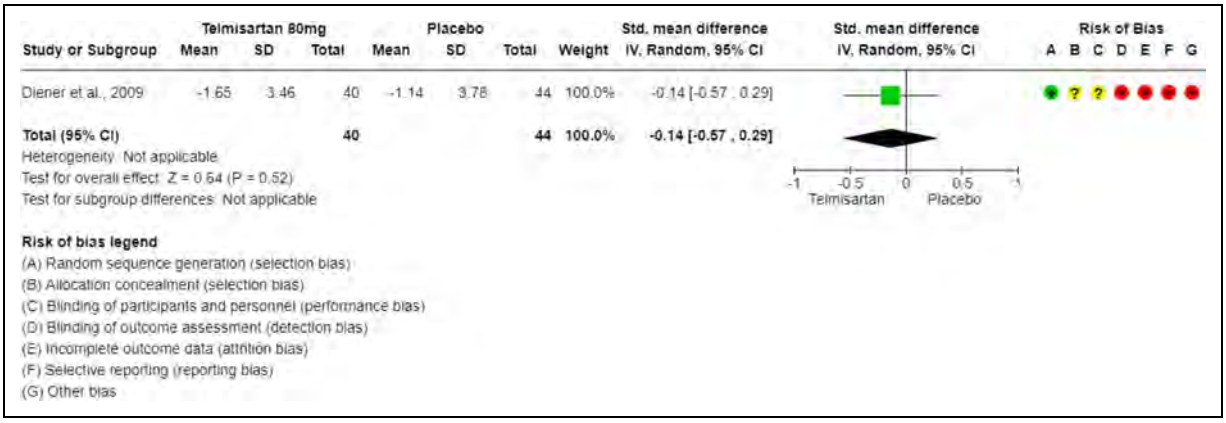


Figure 4.4.7. Forest plot showing the comparison between oral telmisartan 80 mg and placebo for the outcome change in monthly migraine days in patients with episodic migraine.

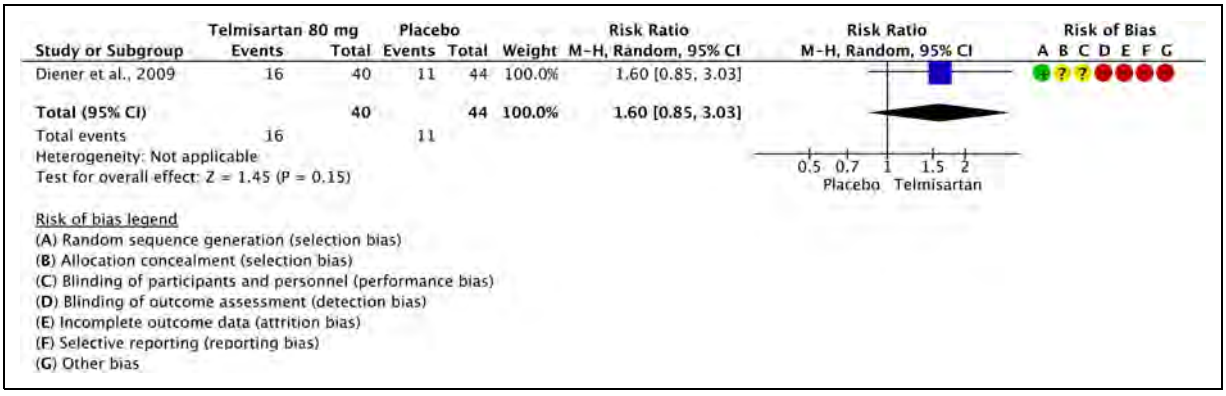


Figure 4.4.8. Forest plot showing the comparison between oral telmisartan 80 mg and placebo for the outcome ≥50% response rate in patients with episodic migraine.

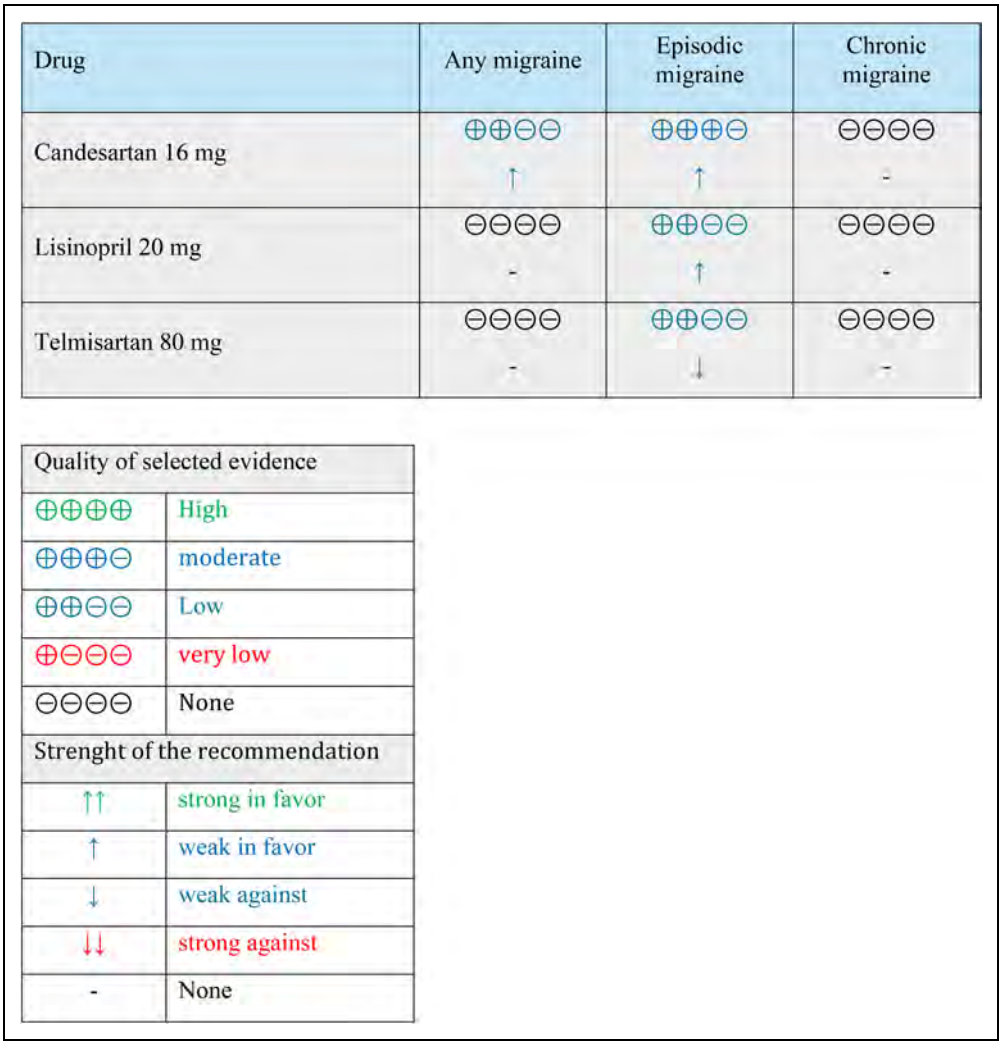


Figure 4.4.9. Summary of evidence-based recommendations on antihypertensives for migraine prevention.

Table 4.4.5. Main efficacy data for flunarizine versus placebo; data are taken from a systematic review (725)

RCT	Sample size (N)	Flunarizine dose (mg)	Treatment duration (weeks)	Reduction in headache frequency	Reduction in headache duration	Reduction in headache severity
Louis 1981 (758)	58	10	12	at least one attack at 3rd month: 17.2% flunarizine vs 55.2% placebo, $p = 0.006$	No difference	No difference
Sørensen 1986 (759)	29	10	16	reduction in number of attacks at 4th month: 50% flunarizine vs 15% placebo, $p = 0.02$	No difference	No difference
Freitag 1991 (760)	101	10	16	Number of migraine attacks from baseline to the end: −50% flunarizine vs −39.9% placebo, $p = 0.018$	No difference	No difference
Frenken 1984 (761)	35	10	12	Significant reduction in flunarizine arm; $p = 0.029$ at 1st month	Significant (p value not reported)	No difference
Mendenopoulos 1985 (762)	20	10	12–16	50% reduction in attacks after 3 months in flunarizine arm; $p = 0.033$	Significant reduction in flunarizine arm: p=0.037	Significant reduction in flunarizine arm: p=0.006

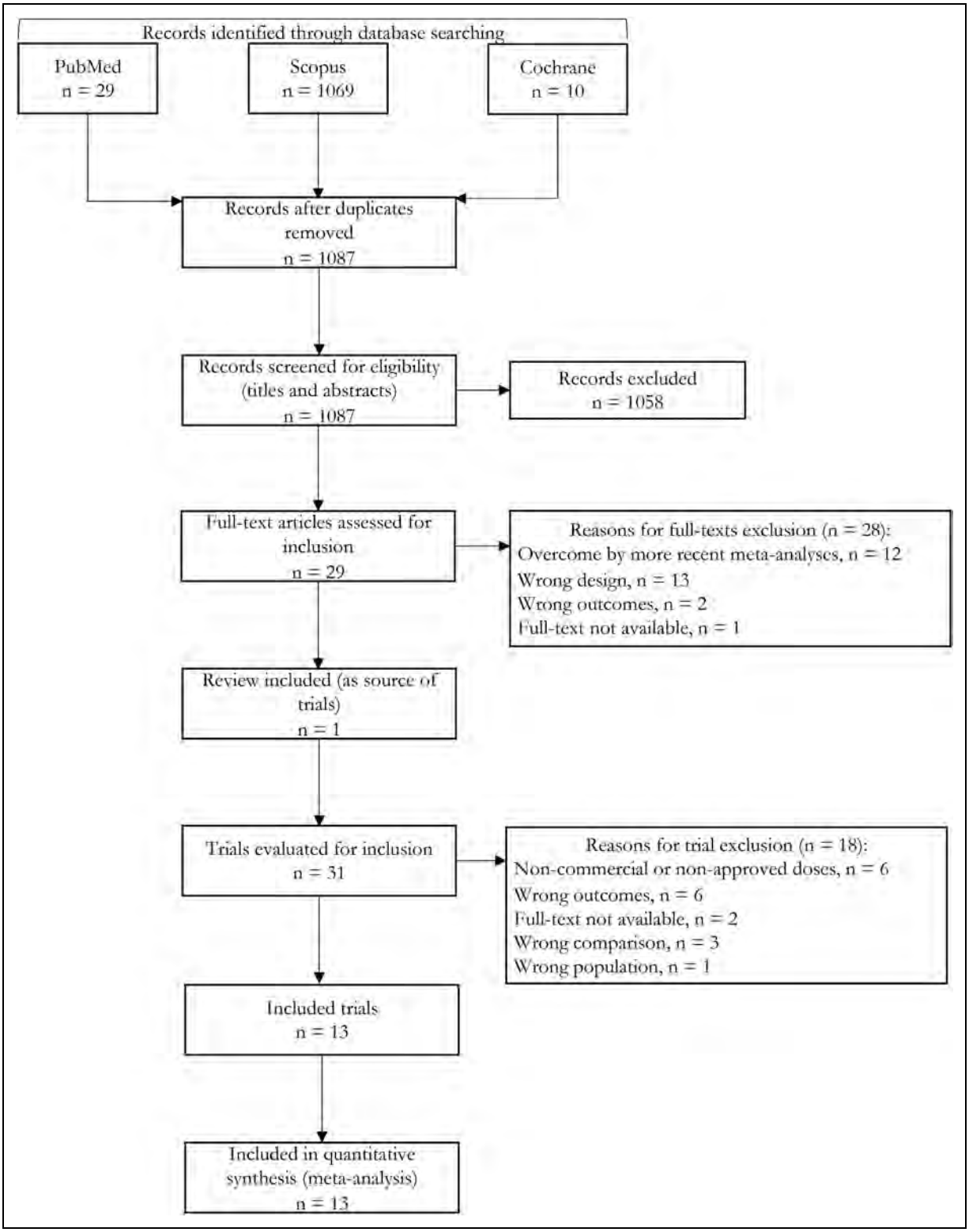


Figure 4.5.1. Meta-analysis selection flow chart - botulinum toxin.

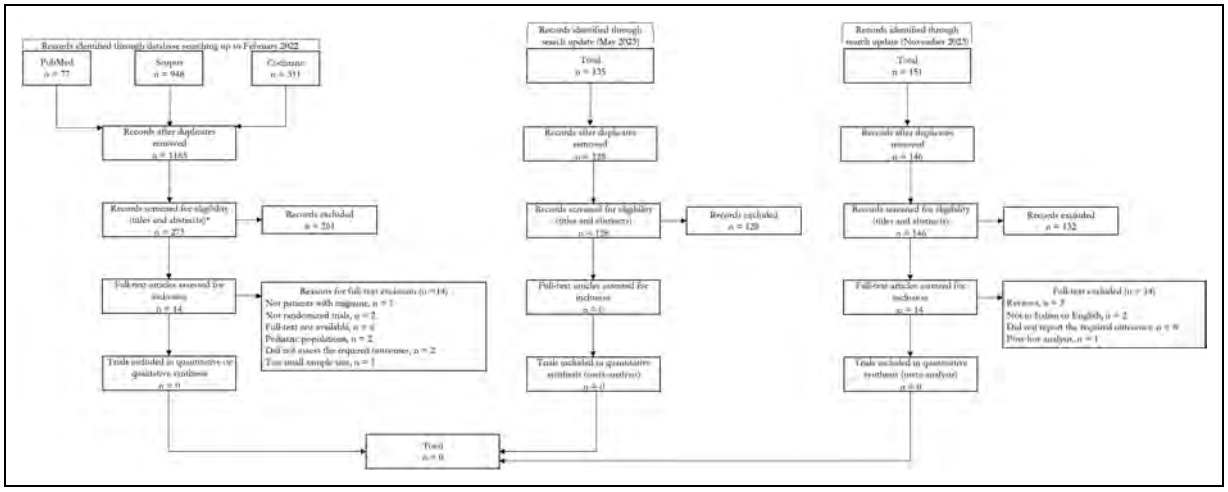


Figure 4.5.2. RCTs selection flow-chart.
*trials published since 31 August 2020 were screened.

Table 4.5.1. Protocol of onabotulinumtoxinA injections in the included studies.
*PREEMPT: 31 fixed sites of injection (Corrugator 10 U, Procerus 5 U, Frontalis 20 U, Temporalis 40 U, Occipitalis 30 U, Cervical/paraspinal 20 U, Trapezius 30 U) + 8 sites of injection with follow the pain approach (40 U)

RCT	Type of migraine	Protocol
Aurora, 2007 (765)	Episodic migraine	Frontal/glabellar 40 U, Occipitalis 20 U, Temporalis 40 U, Trapezius 60 U, Semispinalis 20 U, Splenius capitis 20 U (Total 200 U)
Aurora, 2010 (761)	Chronic migraine	PREEMPT*
Cady, 2014 (767)	Chronic migraine	PREEMPT*
Chankrachang, 2011a (768)	Any migraine	Frontal region, temporal region. Occipital region (Total 120 U)
Chankrachang, 2011b (768)	Any migraine	Frontal region, temporal region. Occipital region (Total 240 U)
Diener, 2010 (771)	Chronic migraine	PREEMPT*
Evers, 2004 (769)	Episodic migraine	M. frontalis 8 U, M. temporalis 8 U, M. sternocleidomastoideus 20 U, M. trapezius 24 U, M. splenius capitis 20 U, M. semispinalis 20 U (Total 100 U)
Freitag, 2008 (770)	Chronic migraine	Glabella 20 U, Temporal 20 U, Frontal 10 U, Suboccipital 30 U, Trapezius 20 U (Total 100 U)
Hollanda, 2014 (771)	Chronic migraine	Right frontal 6–12 U, Left frontal 6–12 U, Right temporal 8–16 U, Left temporal 8–16 U, Right occipital 10–20 U, Left occipital 10–20 U
Lipton, 2016 (772)	Chronic migraine	PREEMPT*
Relja, 2007a (773)	Episodic migraine	M. frontalis 20 U, M. corrugator 10 U, M. temporalis 20 U, M. trapezius 40 U, M. splenius capitis 20 U, M. semispinalis 20 U, M suboccipital 20 U (Total 150 U)
Relja, 2007b (773)	Episodic migraine	M. frontalis 30 U, M. corrugator 15 U, M. temporalis 30 U, M. trapezius 60 U, M. splenius capitis 30 U, M. semispinalis 30 U, M suboccipital 30 U (Total 225 U)
Sandrini, 2011 (774)	Chronic migraine	M. frontalis, M. corrugator, M. temporalis, M. cervical paraspinal, M. trapezius (Total 100 U)

the decision for the choice of those drugs and for their combination. When choosing a single drug for migraine prevention, it would be reasonable to select a drug that is more effective than others. On the other hand, when choosing a combination of migraine preventive drugs, it is reasonable to combine medications that have a better tolerability profile. Head-to-head comparisons of preventive drugs are also important to simplify migraine treatment by establishing the best sequence of preventive drugs to try in each patient.

In the present section, we reported all head-to-head comparisons between different migraine preventive drugs for which RCTs are available. Both efficacy and safety information were discussed.

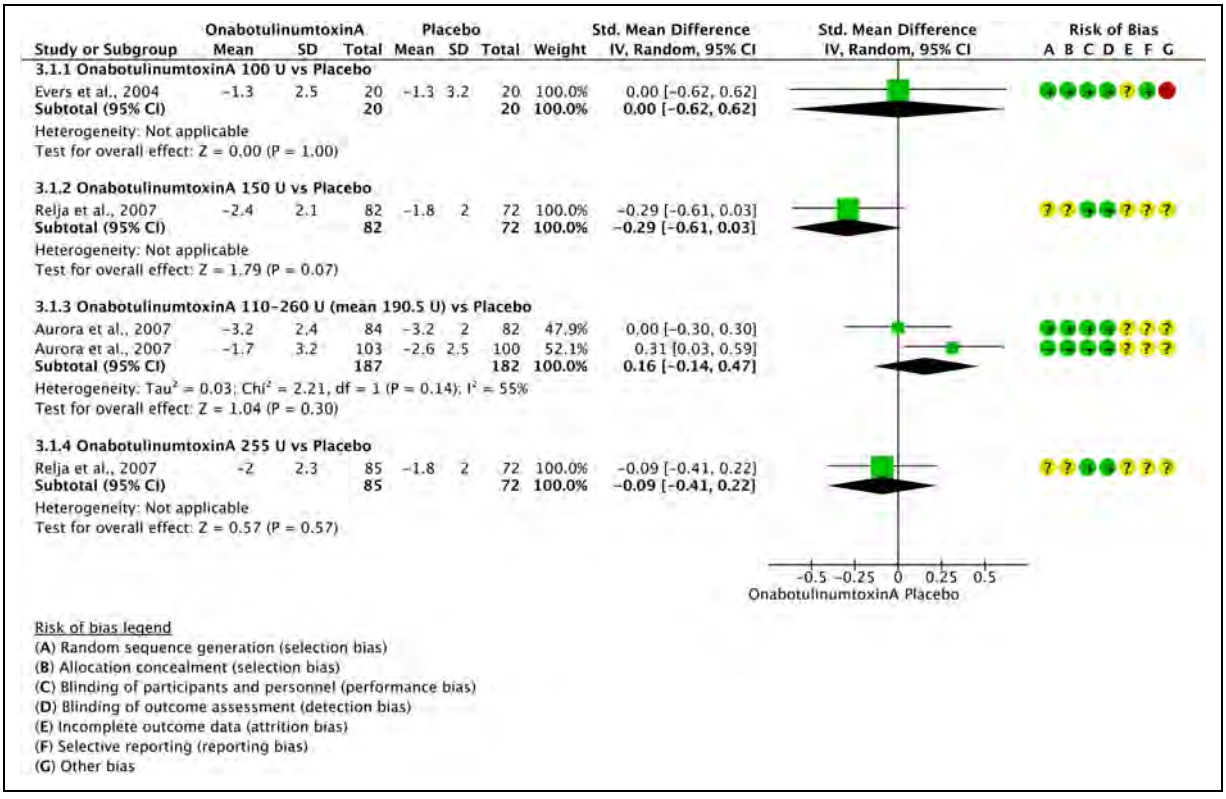


Figure 4.5.3. Forest plot showing the comparison between intramuscular onabotulinumtoxinA and placebo for the outcome change in monthly migraine days in patients with episodic migraine. *The study by Aurora* et al., *2007 included the two populations of "placebo non responders" and "placebo responders".*

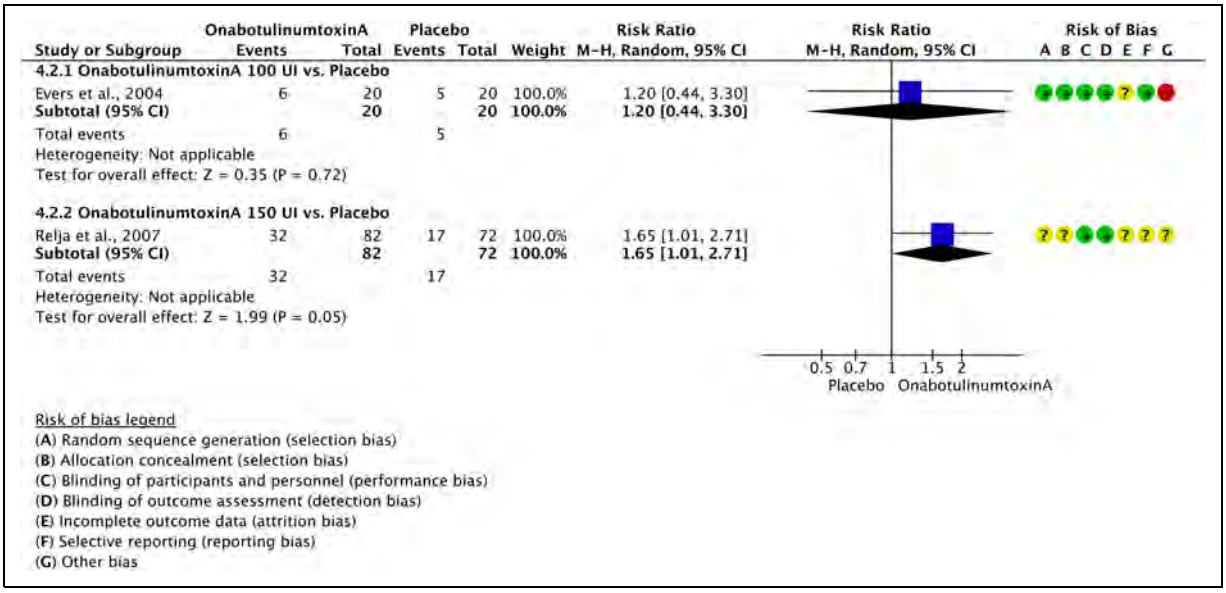


Figure 4.5.4. Forest plot showing the comparison between intramuscular onabotulinumtoxinA and placebo for the outcome ≥50% response rate in patients with episodic migraine.

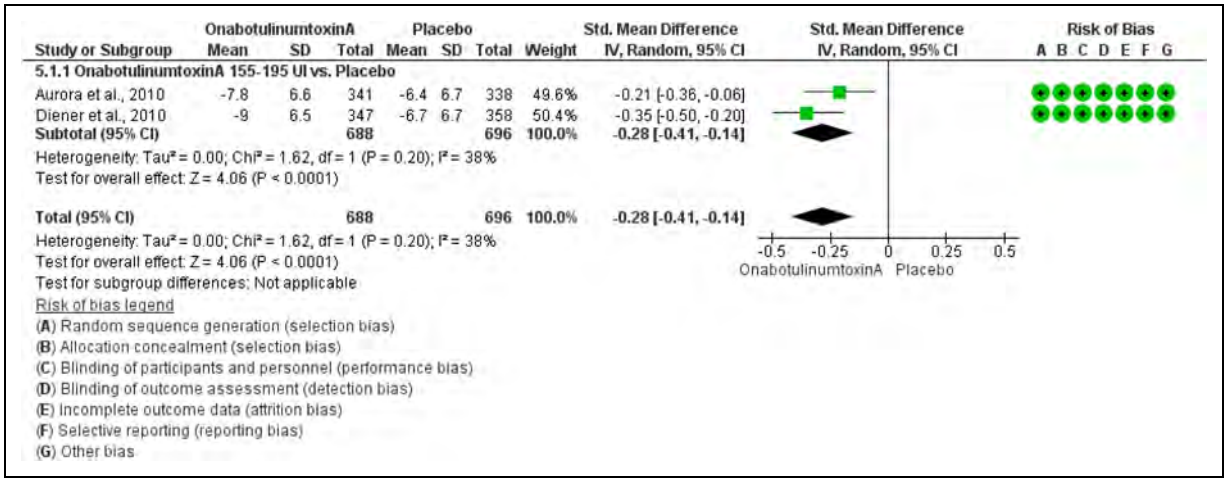


Figure 4.5.5. Forest plot showing the comparison between intramuscular onabotulinumtoxinA and placebo for the outcome change in monthly headache days in patients with chronic migraine.

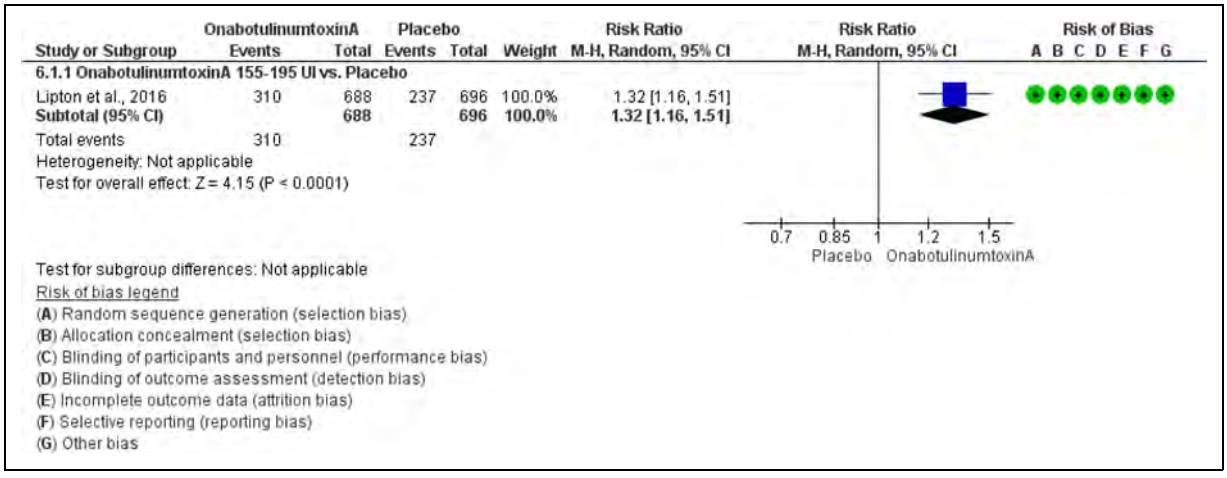


Figure 4.5.6. Forest plot showing the comparison between intramuscular onabotulinumtoxinA and placebo for the outcome ≥50% response rate in patients with chronic migraine.

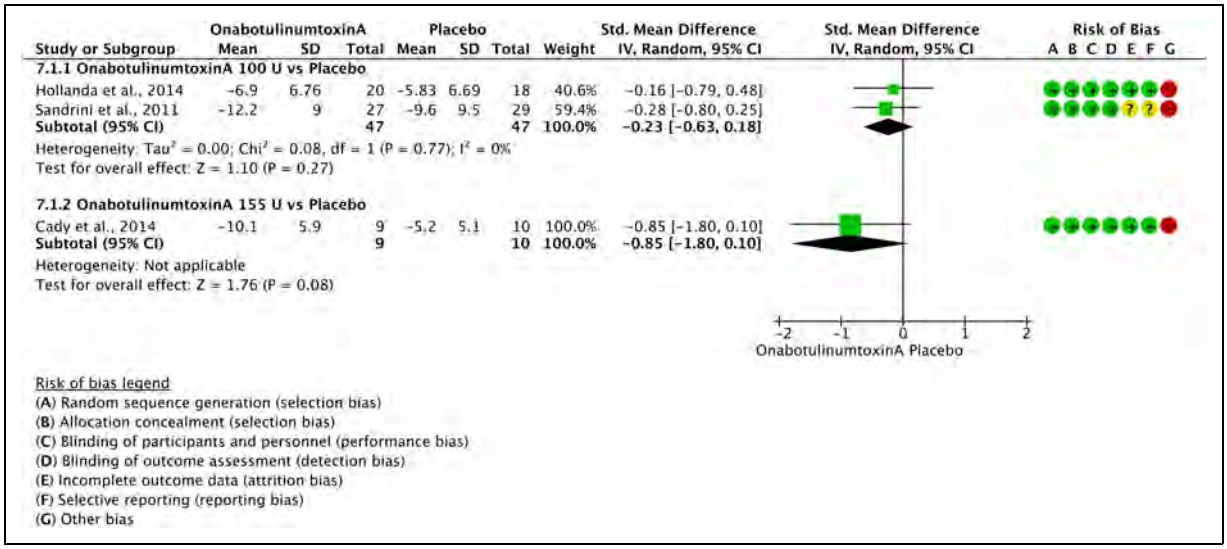


Figure 4.5.7. Forest plot showing the comparison between intramuscular onabotulinumtoxinA and placebo for the outcome change in monthly headache days in patients with chronic migraine.

Table 4.5.2. GRADE evidence profile table for intramuscular onabotulinumtoxinA versus placebo in patients with chronic migraine

Certainty assessment							№ of patients		Effect			
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	OnabotulinumtoxinA	Placebo	Relative (95% CI)	Absolute (95% CI)	Quality	Importance
Change in monthly headache days - OnabotulinumtoxinA 155–195 UI intramuscular vs. Placebo												
2	RCTs	Not serious	Not serious	Not serious	Not serious	None	688	696	-	SMD **0.3 lower** (0.4 lower to 0.1 lower)	⊕⊕⊕⊕ High	Critical
≥50% responder rate - OnabotulinumtoxinA 155–195 UI intramuscular vs. Placebo												
1	RCT	Not serious	Not serious	Not serious	Not serious	None	310/688 (45.1%)	237/696 (34.1%)	**RR 1.32** (1.16 to 1.51)	**109 more per 1000** (from 54 more to 174 more)	⊕⊕⊕⊕ High[a]	Critical

[a]Although only one study was available, it reported a patient-level pooled analysis of two RCTs.

Section-specific methods. All RCTs included in this section were retrieved from the search strings of the other sections dedicated to RCTs of the respective migraine preventive drugs. We considered only PICOs including at least one drug as intervention or comparator that has an independent comparison against placebo.

At first, we collected all the head-to-head RCTs retrieved from the literature search. Duplicates were removed as an initial step. All the remaining RCTs were grouped by prioritizing injectables (CGRP-mAbs, onabotulinumtoxinA), followed by oral drugs. All RCTs were considered only once, even if eligible for more than one comparison. Comparisons were structured to be read in either direction, without the concept of a main intervention and its comparator. The terms "intervention" and "comparator" were replaced by "Drug 1" and "Drug 2" in the PICO structure (Table 4.8.1).

RCTs were included in the main evidence if they met all the following criteria:

- A hypothesis of non-inferiority or superiority of one drug over the other was clearly stated
- The study sample size was justified.

All trials not meeting those criteria were excluded from the main evidence and considered for additional evidence.

Figure 4.8.1 reports the results of the literature search. Table 4.8.1 reports the PICO question structure of the present section.

It is important to note that PICO questions referring to the present section were structured after the literature search, as there were no expected results prior to the search.

PICO 4.8.1.In subjects with any migraine (no distinction between episodic and chronic migraine), are erenumab and topiramate equivalent for migraine prevention (outcomes: change in monthly headache/migraine days, persisting monthly headache/migraine days, 50% response rate)?

Main evidence. We found one RCT comparing erenumab to topiramate in subjects with any migraine that met the criteria to be included in the main evidence (836). The risk of bias was low (Figures 4.8.2 and 4.8.3).

The RCT showed benefits of SC erenumab 70 mg or 140 mg quarterly over oral topiramate up to 100 mg daily considering the endpoints change in monthly headache days (Figure 4.8.2) and ≥50% response rate (Figure 4.8.3). The quality of evidence for both outcomes was considered low (Table 4.8.2) as the RCT was designed to address tolerability and not efficacy as primary endpoint.

Additional evidence. None.

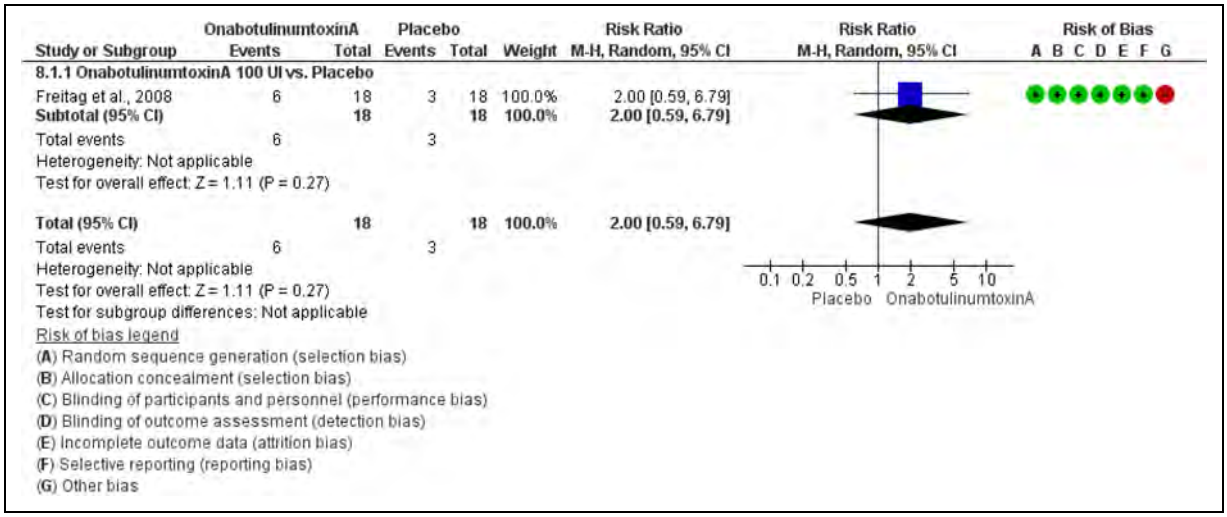


Figure 4.5.8. Forest plot showing the comparison between intramuscular onabotulinumtoxinA and placebo for the outcome ≥50% response rate in patients with chronic migraine.

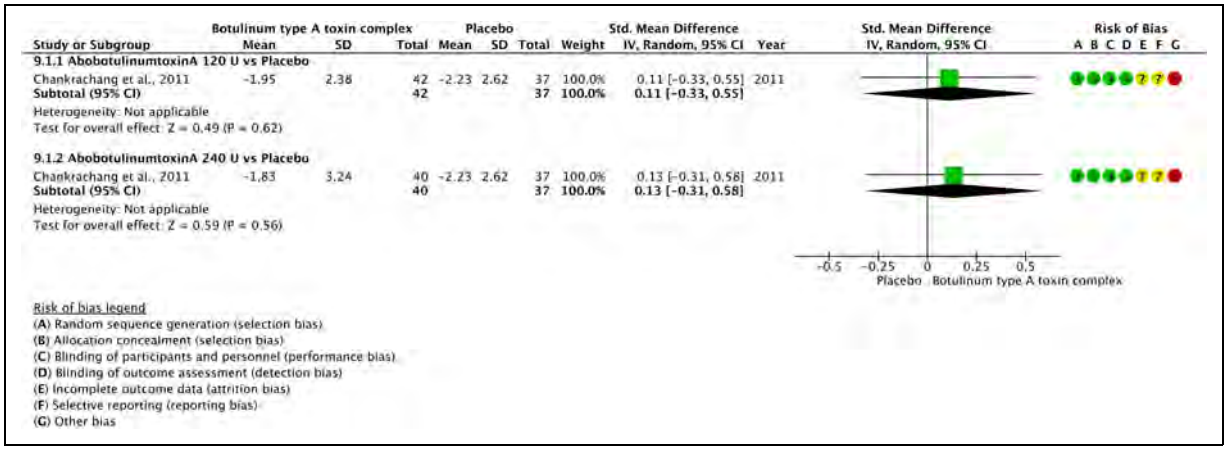


Figure 4.5.9. Forest plot showing the comparison between intramuscular abobotulinumtoxinA and placebo for the outcome change in monthly migraine days in patients with episodic migraine.

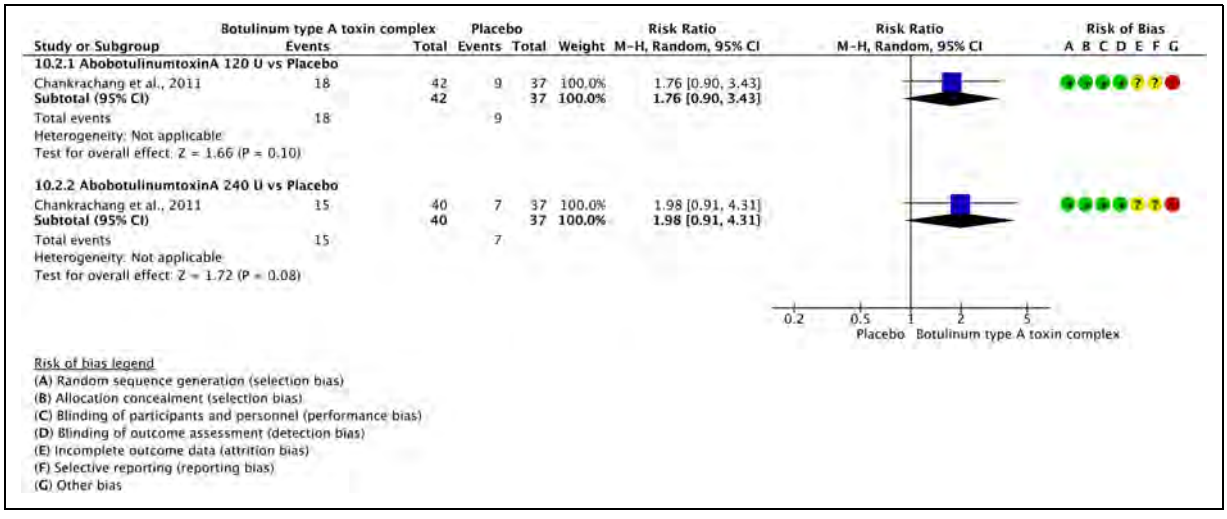


Figure 4.5.10. Forest plot showing the comparison between intramuscular abobotulinumtoxinA and placebo for the outcome ≥50% response rate in patients with episodic migraine.

Drug	Any migraine	Episodic migraine	Chronic migraine
OnabotulinumtoxinA (100 UI to 255 UI)*	⊖⊖⊖⊖ -	⊕⊖⊖⊖ ↓	⊕⊕⊕⊕ ↑↑
AbobotulinumtoxinA (120 UI or 240 UI)	⊖⊖⊖⊖ -	⊕⊖⊖⊖ ↓	⊖⊖⊖⊖ -

Quality of selected evidence	
⊕⊕⊕⊕	High
⊕⊕⊕⊖	Moderate
⊕⊕⊖⊖	Low
⊕⊖⊖⊖	Very low
⊖⊖⊖⊖	None
Strength of the recommendation	
↑↑	strong in favor
↑	weak in favor
↓	weak against
↓↓	strong against
-	none

Figure 4.5.11. Summary of evidence-based recommendations on botulinum toxin for migraine prevention.
*155-195 UI for patients with chronic migraine.

Evidence-based recommendation for PICO 4.8.1

In subjects with any migraine (no distinction between episodic and chronic), we recommend subcutaneous erenumab 70 mg or 140 mg monthly over oral topiramate up to 100 mg daily for migraine prevention.
Quality of evidence: Low (⊕⊕⊖⊖)
Strength of the recommendation: Strong (↑↑)

Safety and tolerability of erenumab compared with topiramate. In the only head-to-head RCT (HER-MES) of a monoclonal antibody acting on the CGRP pathway, erenumab was more effective than topiramate for migraine prevention (837). The primary endpoint of HER-MES was tolerability, which was met as erenumab showed a far higher tolerability than topiramate. For those reasons, monoclonal antibodies acting on the CGRP pathway could be preferable to oral migraine preventive treatments.

PICO 4.8.2. In subjects with chronic migraine, are onabotulinumtoxinA and topiramate equivalent for migraine prevention (outcomes: change in monthly headache/migraine days, persisting monthly headache/migraine days, 50% responder rate)?

Main evidence. None.

Additional evidence. We found two RCTs comparing onabotulinumtoxinA with topiramate in subjects with chronic migraine (662,663). Overall, the risk of bias of included studies was high (Figure 4.8.3).

The meta-analysis of RCTs did not show any benefit of onabotulinumtoxinA (100–200 units) over topiramate up to 100 mg daily for ≥50% response (Figure 4.8.4). The quality of evidence for the outcome was considered very low as the RCTs had a serious risk for indirectness and imprecision. Indirectness was due to the lower dose of onabotulinumtoxinA used in the RCTs – 100–200 IUs – compared with clinical practice – 155–195 IU. Imprecision was due to the low number of participants in each RCT. No recommendation was issued due to the low numbers of participants (<50 in each group).

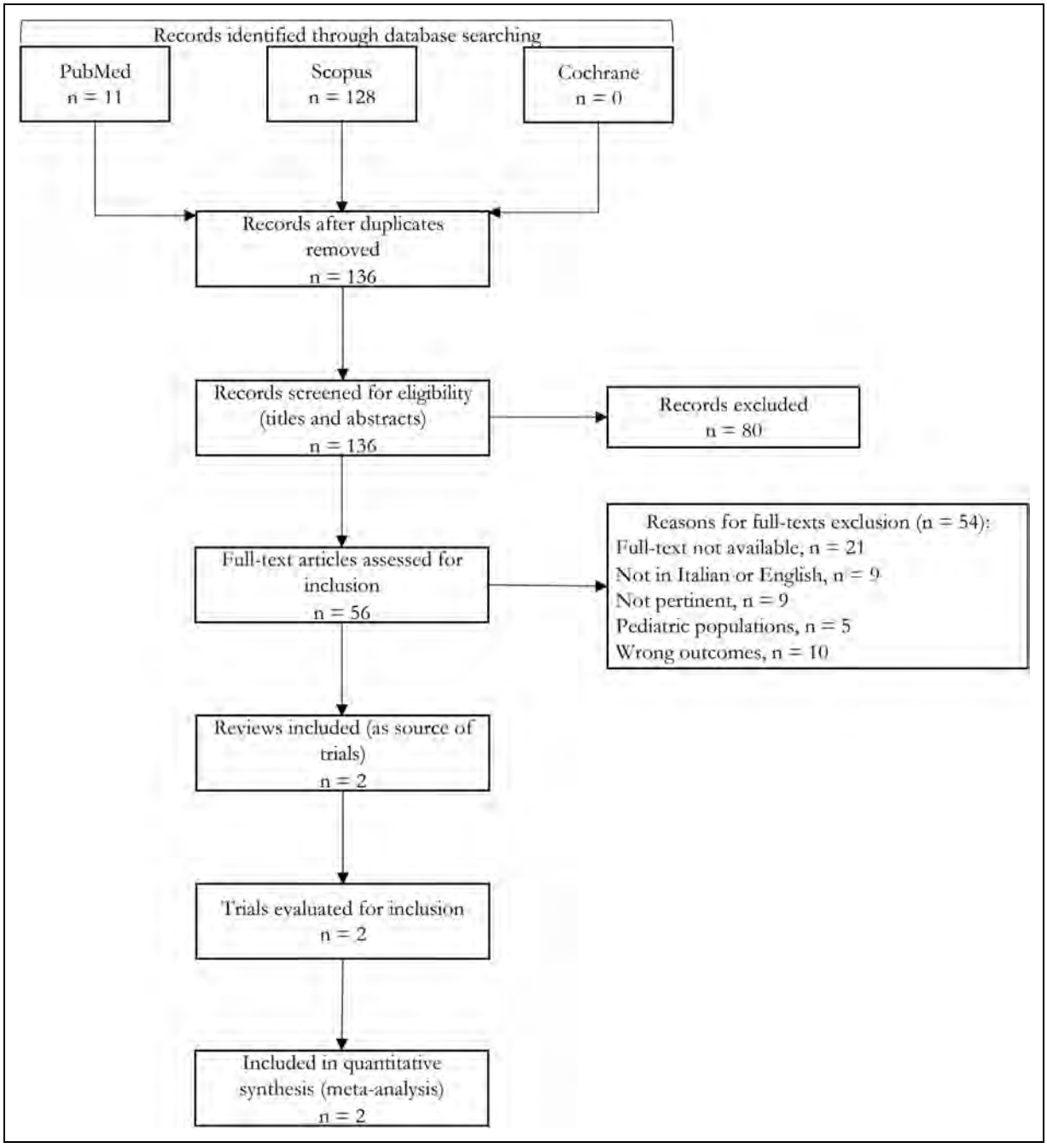


Figure 4.6.1. Meta-analysis selection flow chart - gepants for migraine prevention.

Evidence-based recommendation for PICO 4.8.2

None.
Quality of evidence: -
Strength of the recommendation: -

Safety and tolerability of onabotulinumtoxinA over topiramate. According to the available evidence, the efficacy profile of onabotulinumtoxinA is comparable to that of topiramate. However, the two drugs might have a different tolerability profile. Topiramate is an anticonvulsant medication that crosses the blood-brain barrier, while onabotulinumtoxinA is applied locally and has no systemic effects. Therefore, it is expected that onabotulinumtoxinA has a better tolerability profile than topiramate. Surprisingly, the RCTs included in this guideline did not find any difference in adverse events between onabotulinumtoxinA and topiramate.

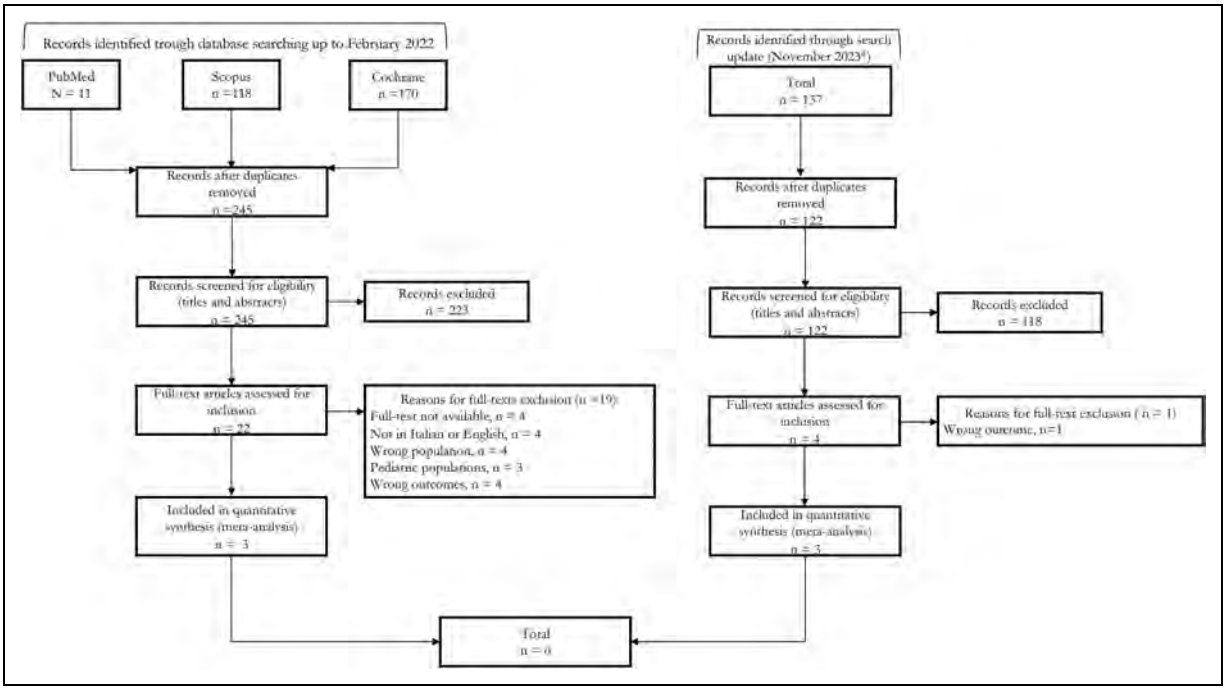


Figure 4.6.2. Flow chart of article selection - gepants for migraine prevention.
*search was updated by the Authors directly in November 2023.

PICO 4.8.3. In subjects with any migraine (no distinction between episodic and chronic), are onabotulinumtoxinA and valproate equivalent in migraine prevention (outcomes: change in monthly headache days, persisting monthly headache/migraine days, ≥ 50% responder rate)?

Evidence-based recommendation for PICO 4.8.3

None.
Quality of evidence: -
Strength of the recommendation: -

Main evidence. None.

Additional evidence. We found one RCT comparing onabotulinumtoxinA (100 UI) with valproate (250 mg bid) in subjects with any migraine (766). The risk of bias was high (Figure 4.8.5).

The RCT did not show any benefit of onabotulinumtoxinA over valproate for the outcome of change in monthly migraine days (Figure 4.8.5). The quality of evidence for the outcome was considered very low as the RCT had a serious risk for indirectness and imprecision. Indirectness was due to the lower dose of onabotulinumtoxinA compared with clinical practice, i.e., 100 IU instead of 155–195 IU. Imprecision was due to the low number of participants in the RCT. It should also be noted that 100 IU of onabotulinumtoxinA is a dosage that did not prove superior to placebo (see Section 4.5). No recommendation was issued due to the low numbers of participants (<50 in each group).

Safety and tolerability of onabotulinumtoxinA over valproate. According to the available evidence, the efficacy profile of onabotulinumtoxinA is comparable to that of valproate. However, onabotulinumtoxinA was better tolerated compared with valproate, with less adverse events and less dropouts due to adverse events. Although this result suggests that onabotulinumtoxinA might be more tolerable than valproate with similar efficacy, and thus generally preferable to valproate, we should also note that the evidence comes from a single RCT on few patients and with a lower dose of onabotulinumtoxinA compared with current clinical practice. Additionally, the RCT was performed in subjects with either episodic or chronic migraine, while the current indication of onabotulinumtoxinA is chronic migraine only.

PICO 4.8.4. In subjects with chronic migraine, are onabotulinumtoxinA and amitriptyline equivalent in migraine prevention (outcomes: change in monthly headache/migraine days, persisting monthly headache/migraine days, ≥ 50% responder rate)?

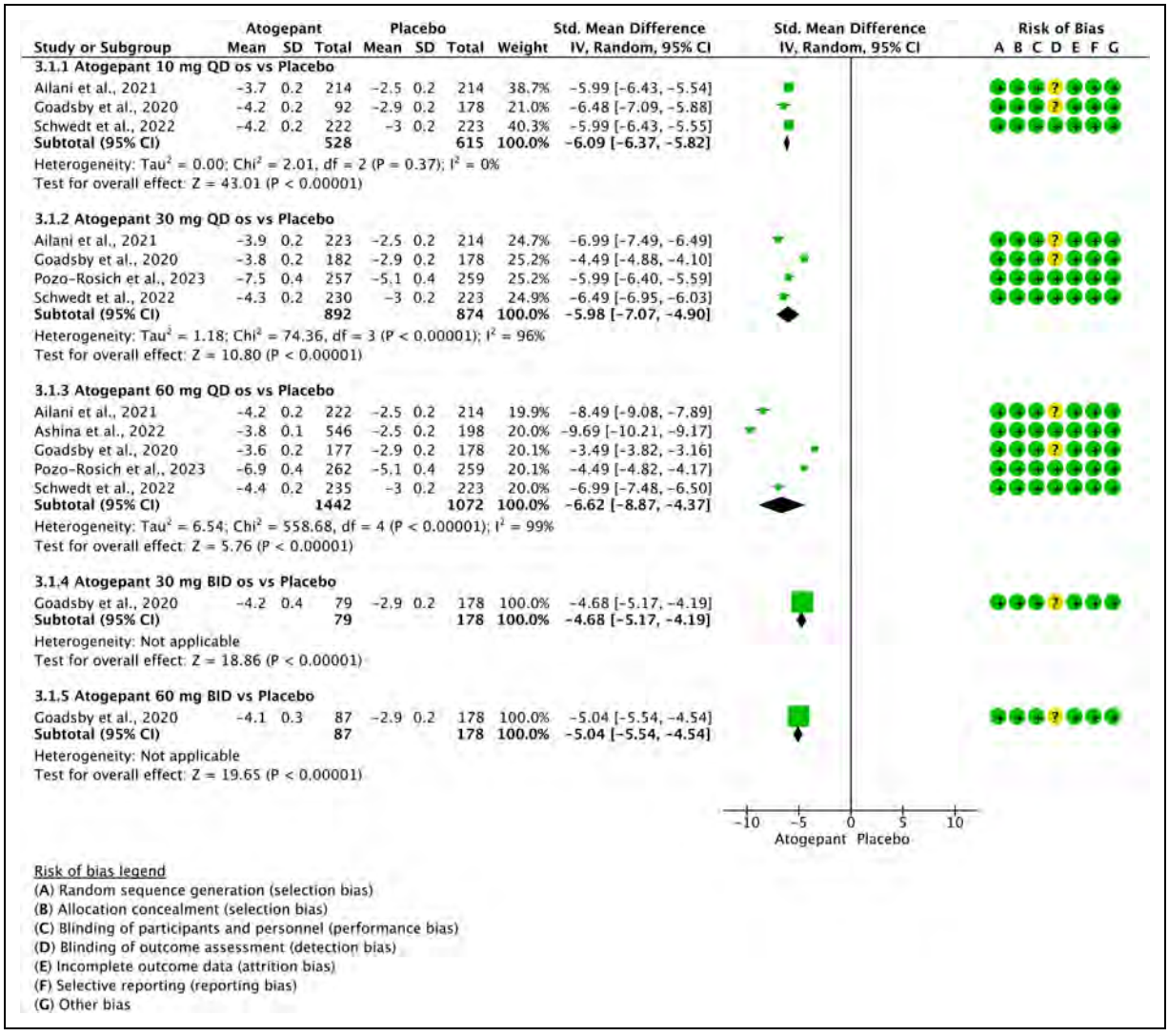


Figure 4.6.3. Forest plot showing the comparison between oral atogepant and placebo for the outcome change in monthly migraine days in episodic migraine.

Main evidence. None.

Additional evidence. We found one RCT comparing onabotulinumtoxinA (250 UI) to amitriptyline (25–50 mg daily) in subjects with chronic migraine (590). The RCT did not meet the quality criteria (Figure 4.8.6) as it lacked a clear superiority or non-inferiority hypothesis and a sample size estimate.

The RCT did not show differences between onabotulinumtoxinA and amitriptyline considering the outcome of ≥50% responder rate (Figure 4.8.6). The quality of evidence was considered very low due to the availability of only one RCT and the high risk of bias. Imprecision was also a concern as onabotulinumtoxinA was used in the RCT at higher doses than those used in clinical practice (250 U vs 155–195 U). No recommendation was issued due to the low numbers of participants (<50 in each group).

Evidence-based recommendation for PICO 4.8.4

None.
Quality of evidence: -
Strength of recommendation: -

Safety and tolerability of onabotulinumtoxinA over amitriptyline. According to the available evidence, the efficacy profile of onabotulinumtoxinA is comparable to that of amitriptyline. We should note that the dosage of onabotulinumtoxinA used in the trial (250 IU) was higher than the maximum dosage used in clinical practice (195 IU).

PICO 4.8.5. In subjects with episodic migraine, are topiramate and valproate equivalent in migraine prevention (outcomes: monthly headache/migraine days, persisting monthly headache/migraine days, ≥ 50% responder rate)?

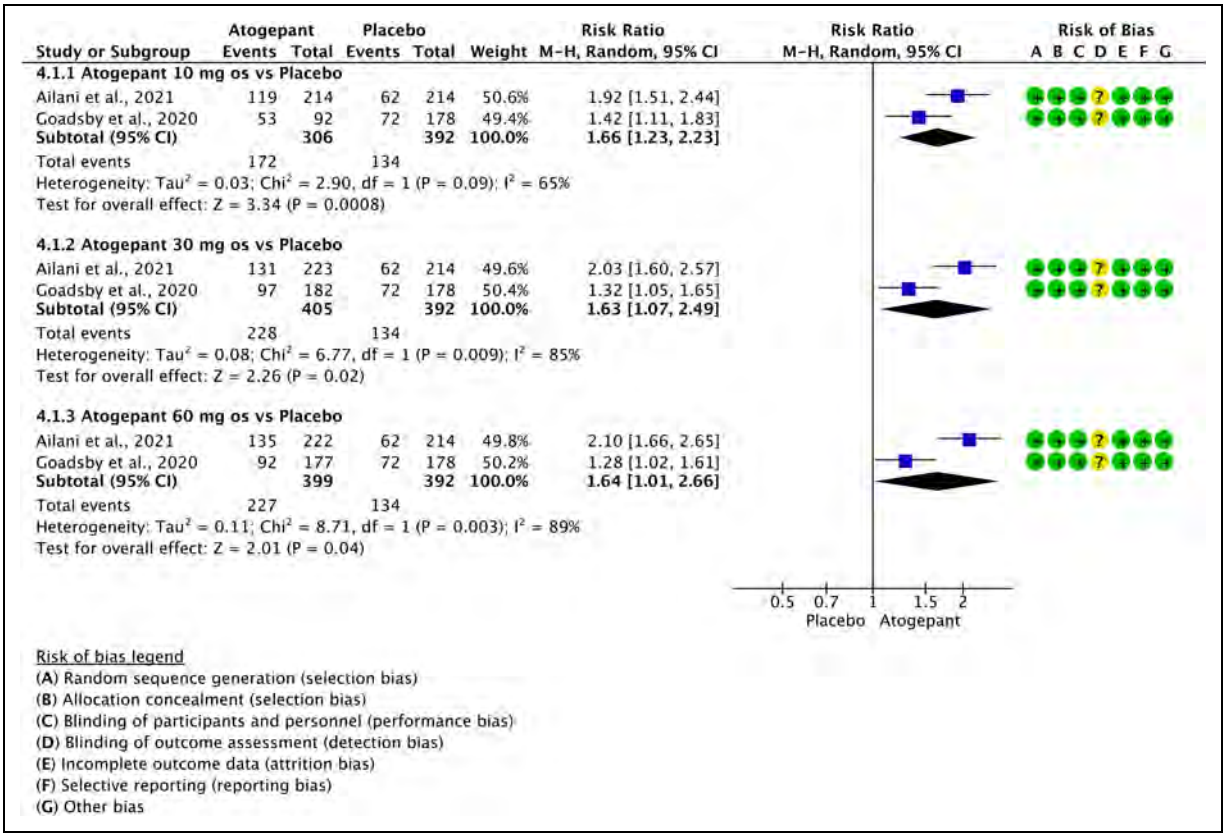


Figure 4.6.4. Forest plot showing the comparison between oral atogepant and placebo for the outcome ≥50% response rate in patients with episodic migraine.

Main evidence. None.

Additional evidence. We found one RCT comparing topiramate (50 mg daily) to valproate (400 mg daily) in subjects with episodic migraine (654) that did not meet the criteria to be included in the main evidence due to the absence of a pre-specified sample size calculation. The risk of bias of the RCT was high (Figures 4.8.7 and 4.8.8).

The RCT showed no benefit of topiramate over valproate considering the outcomes of monthly headache days (Figure 4.8.7) and ≥50% responder rate (Figure 4.8.8). The quality of evidence for both outcomes was considered very low due to the low number of subjects and high risk of bias. Additionally, both drugs were used at lower doses than those tested against placebo. No recommendation was issued due to the low numbers of participants (<50 in each group).

Evidence-based recommendation for PICO 4.8.5

None.
Quality of evidence: -
Strength of the recommendation: -

Safety and tolerability of topiramate compared with valproate. In the head-to-head RCT of topiramate versus valproate for episodic migraine, drug dosages and number of participants were low. Therefore, tolerability considerations are as difficult to draw as those on efficacy. In the included RCT, topiramate and valproate users reported comparable proportions of adverse events (64.3% vs 78.6%, respectively), even if they were different in quality; weight loss occurred in the topiramate group and weight gain in the valproate group.

PICO 4.8.6. In subjects with chronic migraine, are topiramate and valproate equivalent for migraine prevention (outcomes: monthly migraine/headache days, persisting monthly migraine/headache days, ≥ 50% responder rate)?

Main evidence. None.

Additional evidence. We found one RCT comparing topiramate (75 mg daily) to valproate (750 mg daily) in subjects with chronic migraine (644) that did not meet the criteria to be included in the main evidence due to the absence of a pre-specified sample size calculation. The risk of bias of the RCT was high (Figures 4.8.9 and 4.8.10).

The RCT did not show any difference between topiramate and valproate considering the endpoints persisting monthly headache days (Figure 4.8.9) and ≥50% responder rate

Table 4.6.1. GRADE evidence profile table of oral atogepant versus placebo in episodic migraine

Certainty assessment							№ of patients		Effect			
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Atogepant	Placebo	Relative (95% CI)	Absolute (95% CI)	Quality	Importance
Change in monthly migraine days - Atogepant 10 mg QD oral vs Placebo												
3	RCTs	Not serious	Not serious	Not serious	Not serious	None	528	615	-	SMD **6.1 lower** (6.4 lower to 5.8 lower)	⊕⊕⊕⊕ High	Critical
Change in monthly migraine days - Atogepant 30 mg QD oral vs Placebo												
3	RCTs	Not serious	Not serious	Not serious	Not serious	None	635	615	-	SMD **6.0 lower** (7.1 lower to 4.9 lower)	⊕⊕⊕⊕ High	Critical
Change in monthly migraine days - Atogepant 60 mg QD oral vs Placebo												
4	RCTs	Not serious	Not serious	Not serious	Not serious	None	1180	813	-	SMD **6.6 lower** (8.9 lower to 4.4 lower)	⊕⊕⊕⊕ High	Critical
Change in monthly migraine days - Atogepant 30 mg QD oral vs Placebo												
1	RCTs	Not applicable[a]	Not serious	Not serious	Not serious	None	79	178	-	**SMD 4.7 lowe** (5.2 lower to 4.2 lower)	⊕⊕⊕⊖ Moderate	Critical
Change in monthly migraine days - Atogepant 60 mg QD oral vs Placebo												
1	RCTs	Not applicable[a]	Not serious	Not serious	Not serious	None	87	178	-	**SMD 5.0 lower** (5.5 lower to 4.5 lower)	⊕⊕⊕⊖ Moderate	Critical
≥50% responder rate - Atogepant 10 mg QD oral vs Placebo												
2	RCTs	Not serious	Not serious	Not serious	Not serious	None	172/306 (56.2%)	134/392 (34.2%)	**RR 1.66** (1.23 to 2.23)	**226 more per 1.000** (from 79 more to 420 more)	⊕⊕⊕⊕ High	Critical
≥50% responder rate - Atogepant 30 mg QD oral vs Placebo												
2	RCTs	Not serious	Not serious	Not serious	Not serious	None	228/405 (56.3%)	134/392 (34.2%)	**RR 1.63** (1.07 to 2.49)	**215 more per 1.000** (from 24 more to 509 more)	⊕⊕⊕⊕ High	Critical
≥50% responder rate - Atogepant 60 mg QD oral vs Placebo												
2	RCTs	Not serious	Not serious	Not serious	Not serious	None	227/399 (56.9%)	134/392 (34.2%)	**RR 1.64** (1.01 to 2.66)	**219 more per 1.000** (from 3 more to 567 more)	⊕⊕⊕⊕ High	Critical

[a]Only one trial.

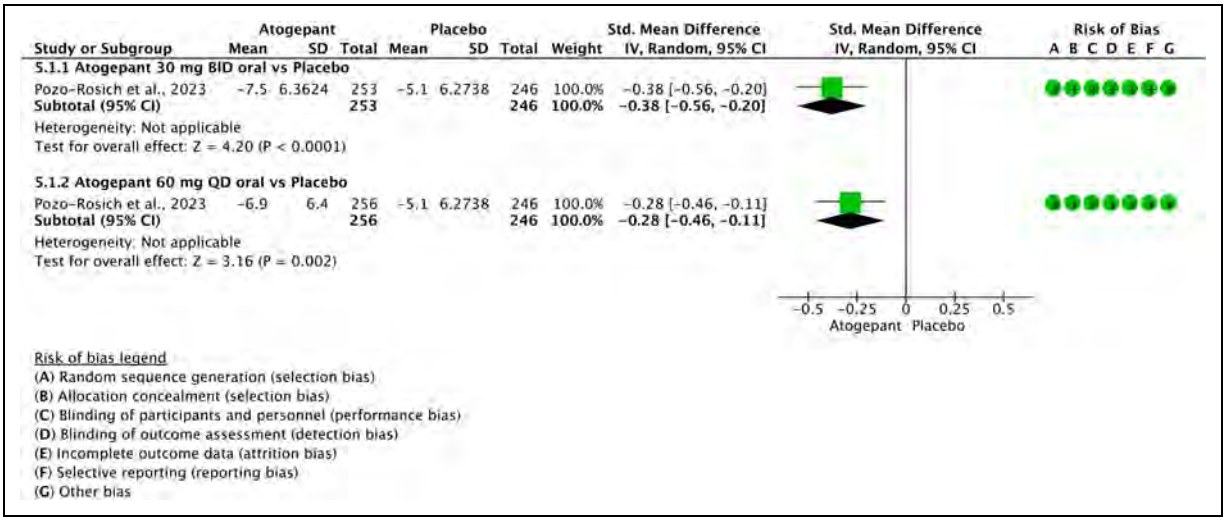


Figure 4.6.5. Forest plot showing the comparison between oral atogepant and placebo for the outcome change in monthly migraine days in patients with chronic migraine.

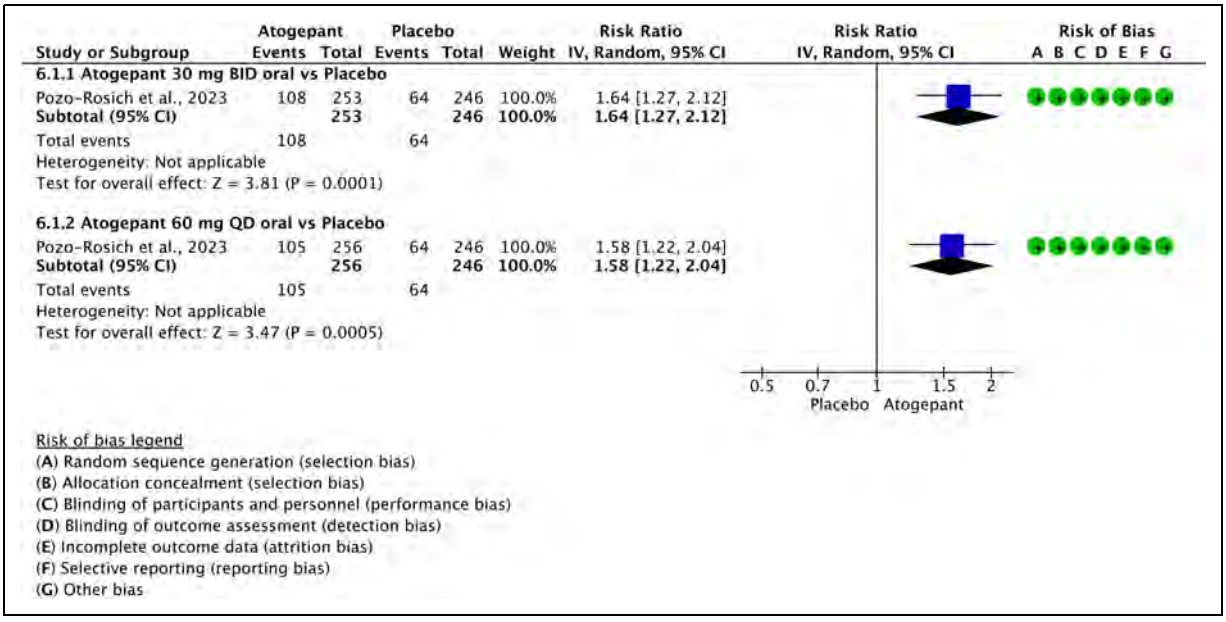


Figure 4.6.6. Forest plot showing the comparison between oral atogepant and placebo for the outcome ≥50% responder rate in patients with chronic migraine.

(Figure 4.8.10). The quality of evidence for both outcomes was considered very low due to the low number of subjects and high risk of bias. No recommendation was issued due to the low numbers of participants (<50 in each group).

Evidence-based recommendation for PICO 4.8.6

None.
Quality of evidence: -
Strength of the recommendation: -

Safety and tolerability of topiramate compared with valproate. In the head-to-head RCT of topiramate over valproate for chronic migraine, safety and tolerability were not specifically assessed. The number of dropouts was similar in both the topiramate and valproate groups (three subjects each); however, this is not enough evidence to conclude on a similar tolerability profile between the two drugs. Besides, the two drugs have different adverse event profiles, which should be considered in clinical practice for treatment choice.

Table 4.6.2. GRADE evidence profile table of oral atogepant versus placebo in chronic migraine

Certainty assessment							№ of patients		Effect			
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Atogepant	Placebo	Relative (95% CI)	Absolute (95% CI)	Quality	Importance
Change in monthly migraine days - Atogepant 30 mg twice daily oral vs Placebo												
1	RCT	Not serious	Not applicable[a]	Not serious	Not serious	None	253	246	-	SMD **0.4 lower** (0.6 lower to 5.59 lower)	⊕⊕⊕⊕ High[b]	Critical
Change in monthly migraine days - Atogepant 60 mg oral vs Placebo												
1	RCT	Not serious	Not applicable[a]	Not serious	Not serious	None	256	246	-	SMD **0.3 lower** (0.5 lower to 0.1 lower)	⊕⊕⊕⊕ High[b]	Critical

[a]Only one trial; [b]Upgraded because of a very low risk of bias.

PICO 4.8.7. In subjects with any migraine (no distinction between episodic and chronic), are topiramate and valproate equivalent for migraine prevention (outcomes: change in monthly headache/migraine days, persisting monthly headache/migraine days, ≥ 50% responder rate)?

Main evidence. None.

Additional evidence. We found one RCT comparing topiramate (50 mg daily) to valproate (400 mg daily) in subjects with any migraine (no distinction between episodic and chronic) (652) that did not meet the criteria to be included in the main evidence due to the absence of a pre-specified sample size calculation. The risk of bias of the RCT was high (Figure 4.8.11).

The RCT showed a slight benefit of topiramate over valproate considering the endpoint change in monthly headache days (Figure 4.8.11). The quality of evidence for the outcome was considered very low due to the low number of subjects and high risk of bias. A further concern is that topiramate and valproate were both used at lower doses than those tested in placebo-controlled trials. No recommendation was issued due to the low numbers of participants (<50 in each group).

Evidence-based recommendation for PICO 4.8.7

None.
Quality of evidence: -
Strength of the recommendation: -

Safety and tolerability of topiramate compared with valproate. In the head-to-head RCT of topiramate over valproate for migraine (no distinction between episodic and chronic), safety and tolerability were comparable between the two drugs with a different profile of adverse events. Notably, no dropouts were recorded in any of the two groups. It is likely that valproate and topiramate had a low proportion of adverse events because of the low doses used in the RCT.

PICO 4.8.8. In subjects with episodic migraine, are topiramate and propranolol equivalent for migraine prevention (outcomes: change in monthly headache days, persisting monthly headache/migraine days, ≥ 50% responder rate)?

Main evidence. We found one RCT comparing topiramate (100 mg or 200 mg daily) to propranolol (160 mg daily) in subjects with episodic migraine (628) that met the criteria to be included in the main evidence. The risk of bias of the RCT was low (Figures 4.8.12 and 4.8.13).

The RCT showed no difference between topiramate and propranolol considering the endpoints change in monthly headache days (Figure 4.8.12) and ≥50% responder (Figure 4.8.13). The quality of evidence for both outcomes was considered moderate (Table 4.8.3) due to the availability of only one

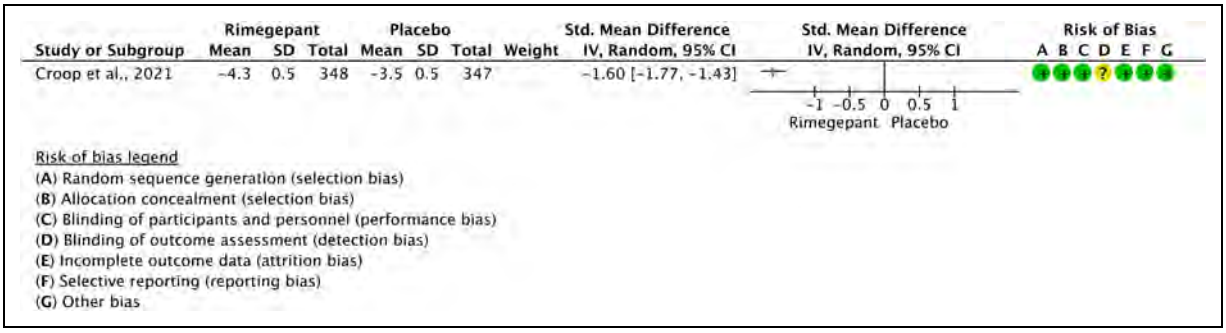


Figure 4.6.7. Forest plot showing the comparison between oral rimegepant 75 mg and placebo for the outcome change in monthly migraine days in any migraine (no distinction between episodic and chronic).

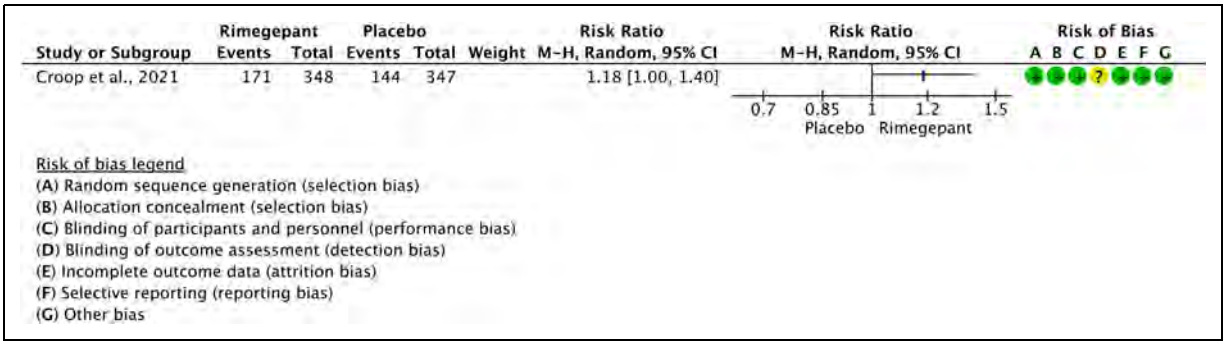


Figure 4.6.8. Forest plot showing the comparison between oral rimegepant 75 mg and placebo for the outcome ≥50% response rate in patients with any migraine (no distinction between episodic and chronic).

RCT. Nevertheless, the RCT included a placebo group together with active groups, which increases the reliability of findings.

Additional evidence. None.

Evidence-based recommendation for PICO 4.8.8

In subjects with episodic migraine, we suggest either oral topiramate 100 mg or 200 mg daily or oral propranolol 160 mg daily as equivalent options for migraine prevention.
Quality of evidence: Low (⊕⊕⊖⊖)
Strength of the recommendation: =

Safety and tolerability of topiramate compared with valproate. In the head-to-head RCT of topiramate over propranolol for chronic migraine, adverse events leading to treatment limitation or discontinuation were more frequent in the topiramate 200 mg group (44%) compared with the topiramate 100 mg group (28%) and the propranolol 160 mg group (20%). Therefore, based on safety data, it could be reasonable to treat subjects with a 100 mg daily dose of topiramate rather than the 200 mg daily dose, which could not give any efficacy advantage while increasing the probability of tolerability issues.

PICO 4.8.9. In subjects with chronic migraine, are topiramate and propranolol equivalent for migraine prevention (outcome: change in monthly headache/migraine days, persisting monthly headache/migraine days, ≥ 50% responder rate)?

Main evidence. We found one RCT comparing oral topiramate (100 mg daily) with oral propranolol (160 mg daily) in subjects with chronic migraine (656) that met the criteria to be included in the main evidence. The risk of bias of the RCT was low (Figure 4.8.14).

The RCT showed no benefit of topiramate over propranolol considering the outcome change in monthly headache days (Figure 4.8.14). The quality of evidence for the outcome was considered moderate (Table 4.8.4) due to the availability of only one RCT.

Additional evidence. None.

Table 4.6.3. GRADE evidence profile table for oral rimegepant versus placebo in migraine

Certainty assessment							№ of patients		Effect			
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Rimegepant	Placebo	Relative (95% CI)	Absolute (95% CI)	Quality	Importance
Change in monthly migraine days - Rimegepant 75 mg oral vs Placebo												
1	RCT	Not serious	Not applicable[a]	Not serious	Not serious	None	348	347	-	MD **1.6 lower** (1.77 lower to 1.43 lower)	⊕⊕⊕⊖ Moderate	Critical
≥50% responder rate - Rimegepant 75 mg oral vs Placebo												
1	RCT	Not serious	Not applicable[a]	Not serious	Not serious	None	171/348 (49.1%)	144/347 (41.5%)	**RR 1.18** (1.00 to 1.40)	**75 more per 1.000** (from 0 fewer to 166 more)	⊕⊕⊕⊖ Moderate	Critical

[a]Only one trial.

Evidence-based recommendation for PICO 4.8.9

In subjects with chronic migraine, based on efficacy data, we suggest oral topiramate 100 mg daily and oral propranolol 160 mg daily as equivalent options for migraine prevention.
Quality of evidence: Moderate (⊕⊕⊕⊖)
Strength of the recommendation: Weak (=)

Safety and tolerability of topiramate compared with propranolol. In the head-to-head RCT of topiramate over propranolol for chronic migraine, the safety profile was comparable between the two drugs, even if the kind of adverse events was different between the two drugs. Literature suggests that the choice between topiramate and propranolol be done according to safety more than to efficacy data.

PICO 4.8.10. In subjects with any migraine (no distinction between episodic and chronic), are topiramate and propranolol equivalent for migraine prevention (outcome: change in monthly headache/migraine days, persisting monthly headache/migraine days, ≥ 50% responder rate)?

Main evidence. We found one RCT comparing topiramate (50 mg daily) with propranolol (80 mg daily) in subjects with migraine (no distinction between episodic and chronic) (649) that met the criteria to be included in the main evidence. The risk of bias of the RCT was considered moderate (Figure 4.8.15) due to low numbers.

The RCT showed a benefit of topiramate over propranolol considering the outcome change in monthly headache days (Figure 4.8.15). The quality of evidence for the outcome was considered moderate (Table 4.8.5) due to the availability of only one RCT.

Additional evidence. None.

Evidence-based recommendation for PICO 4.8.10

In subjects with any migraine (no distinction between episodic and chronic), we suggest oral topiramate 50 mg daily over oral propranolol 80 mg daily for migraine prevention.
Quality of evidence: Very low (⊕⊖⊖⊖)
Strength of the recommendation: Weak (↑)

Safety and tolerability of topiramate compared with propranolol. In the head-to-head RCT of topiramate versus propranolol for migraine (no distinction between episodic and chronic), the safety profile was comparable between the two drugs. It should be noted that both drugs were

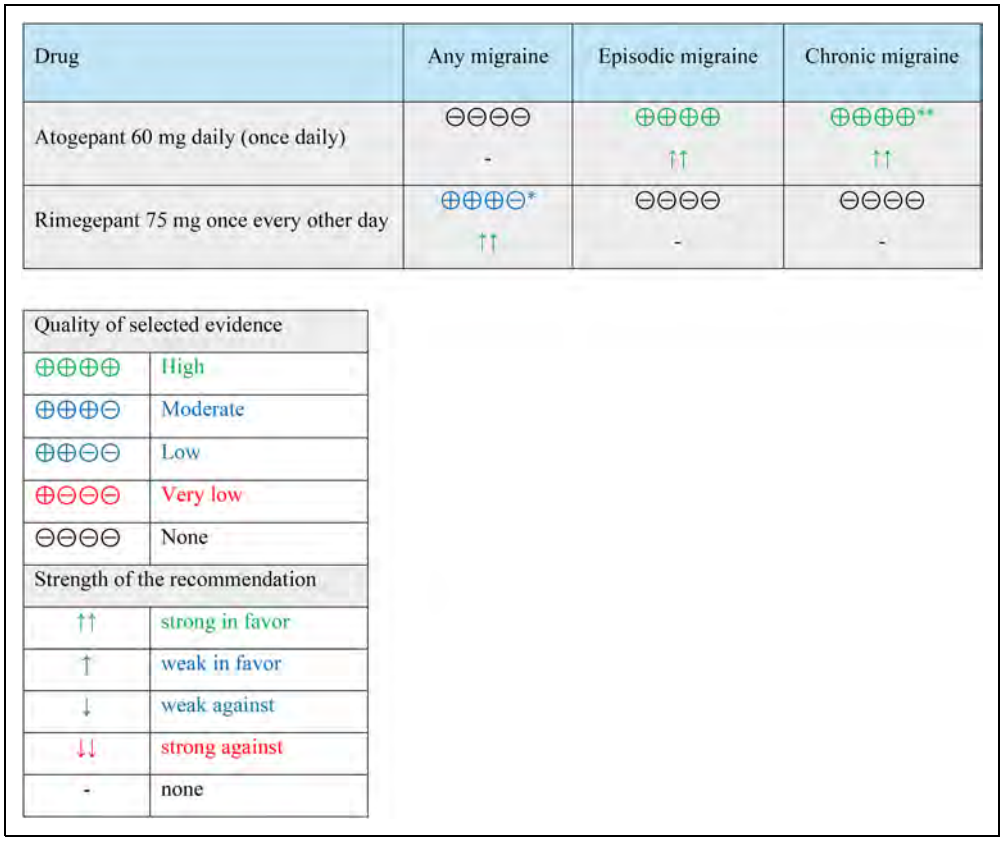


Figure 4.6.9. Summary of evidence-based recommendations on gepants for migraine prevention.
*patients with 4- 18 monthly migraine days.
**Only 30 mg twice a day or 60 mg daily.

Table 4.6.4. Patients in whom gepants should be used with care

Acute ischemic stroke, TIA	Disruption of the blood-brain barrier, e.g., traumatic brain injury, meningitis
Subarachnoid hemorrhage	Wound healing
Acute coronary syndrome	Inflammatory bowel disease
Angina pectoris	COPD
Severe constipation	Raynaud's phenomenon

used in lower doses if compared with those of placebo controlled RCTs.

PICO 4.8.11. In subjects with any migraine (no distinction between episodic and chronic), are topiramate and amitriptyline equivalent for migraine prevention (outcomes: change in monthly headache/migraine days, persisting monthly headache/migraine days, ≥ 50% responder rate)?

Main evidence. We found one RCT comparing topiramate (50 mg daily) with amitriptyline (recommended dose 25–100 mg daily) in subjects with migraine (596) that met the criteria to be included in the main evidence. The risk of bias of the RCT was low (Figure 4.8.16).

The RCT showed that topiramate up to 100 mg daily was at least as effective as amitriptyline 100 mg daily considering the outcome of ≥50% responder rate (Figure 4.8.16). The quality of evidence for the outcome was considered moderate (Table 4.8.6) due to the availability of only one RCT.

Additional evidence. None.

Evidence-based recommendation for PICO 4.8.11

In subjects with any migraine (no distinction between episodic and chronic), based on efficacy data, we suggest oral topiramate (100–200 mg daily) and oral amitriptyline (25–150 mg daily) as equivalent options for migraine prevention.
Quality of evidence: Low (⊕⊕⊖⊖)
Strength of the recommendation: =

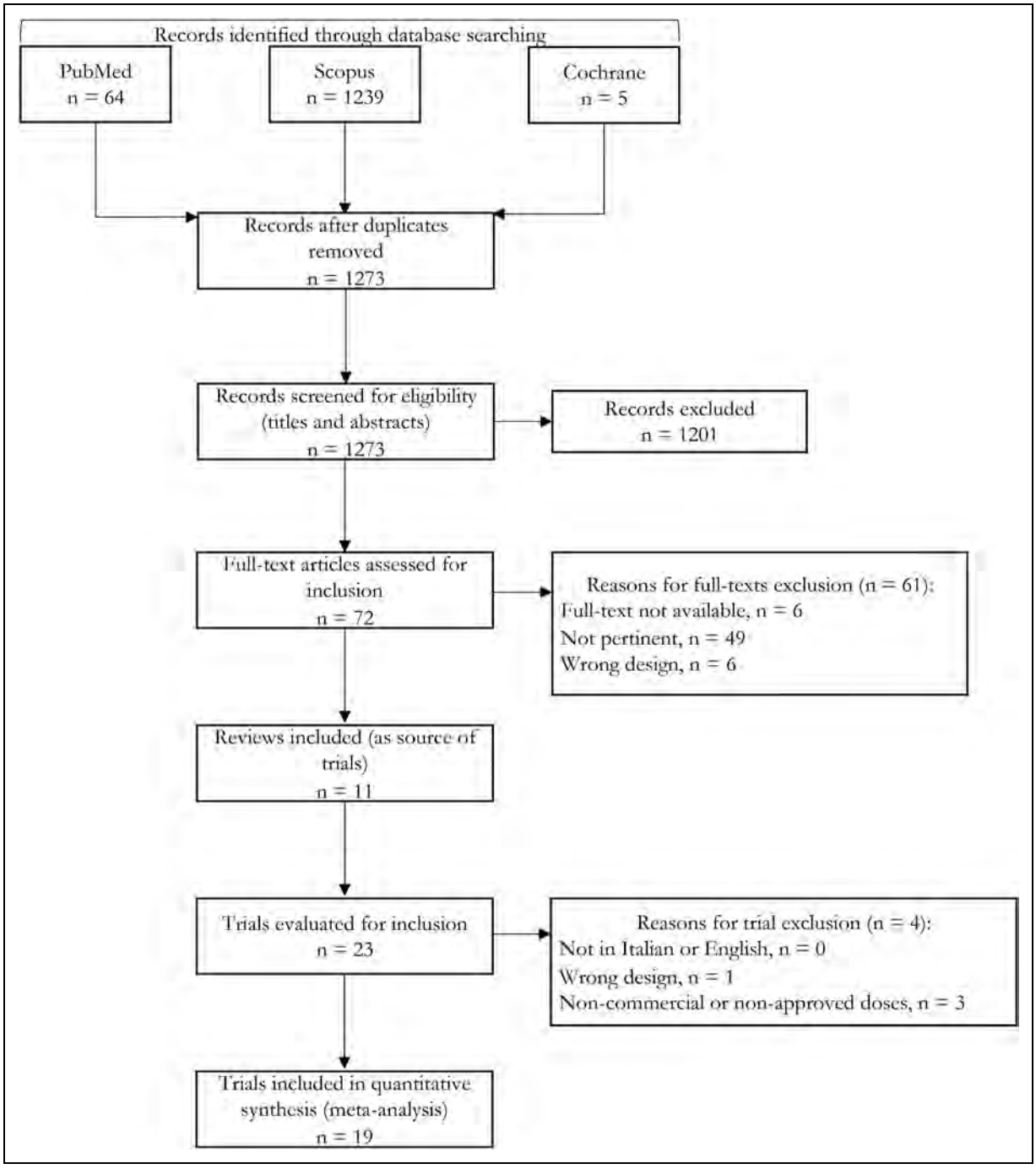


Figure 4.7.1. Meta-analysis selection flow chart - monoclonal antibodies targeting the CGRP pathway.

PICO 4.8.12. In subjects with episodic migraine, are topiramate and amitriptyline equivalent for migraine prevention (outcomes: change in monthly headache/migraine days, persisting monthly headache/migraine days, ≥ 50% responder rate)?

Main evidence. None.

Additional evidence. We found one RCT comparing topiramate (up to 200 mg daily) with amitriptyline (up to 150 mg daily) in subjects with episodic migraine (589) that did not meet the criteria to be included in the main evidence as it did not pre-specify a sample size calculation. The risk of bias of the RCT was serious (Figure 4.8.17).

The RCT showed that topiramate was at least as effective as amitriptyline considering the outcome of monthly

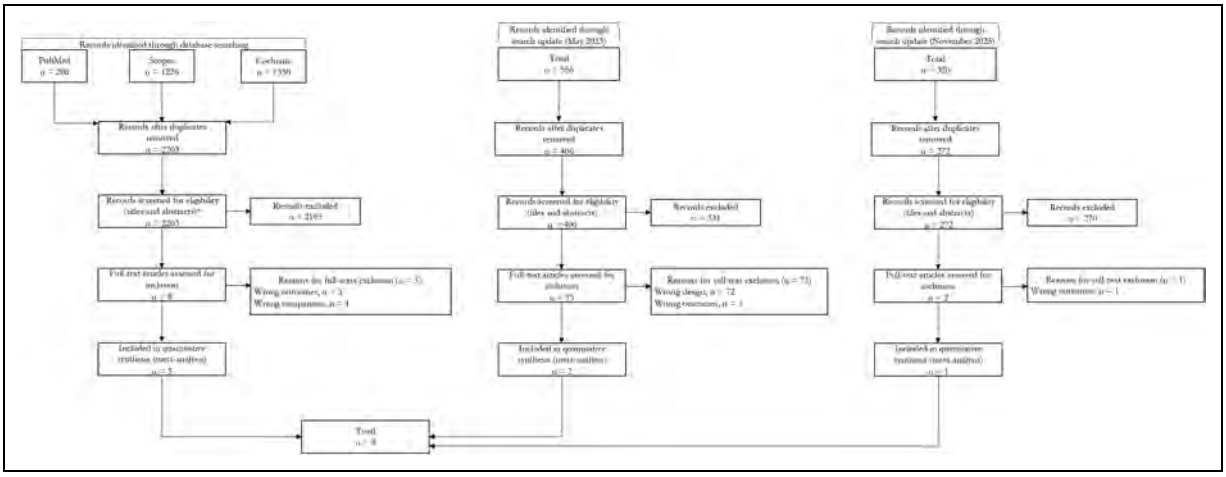


Figure 4.7.2. RCTs selection flow chart - monoclonal antibodies targeting the CGRP pathway.
*trials published since October 2020 were screened.

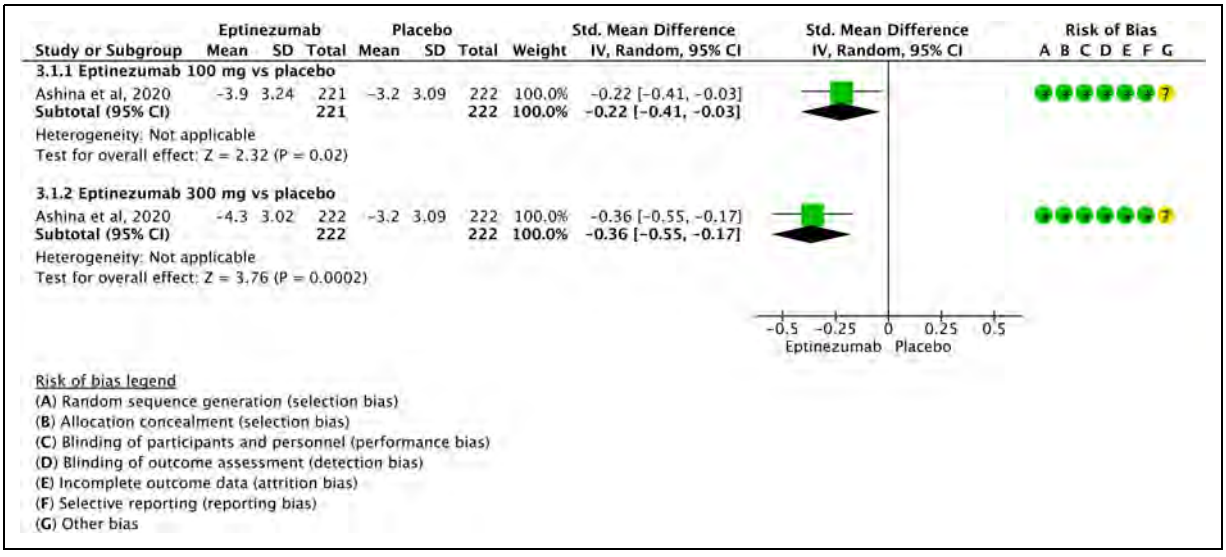


Figure 4.7.3. Forest plot showing the comparison between intravenous eptinezumab (100 or 300 mg quarterly) and placebo for the outcome change in monthly migraine days in patients with episodic migraine at 12 weeks.

headache days (Figure 4.8.17). The quality of evidence for the outcome was considered very low due to the availability of only one RCT.

Evidence-based recommendation for PICO 4.8.12

In subjects with episodic migraine, we suggest oral topiramate (200 mg daily) and oral amitriptyline (150 mg daily) as equivalent options for migraine prevention.
Quality of evidence: Very low (⊕⊖⊖⊖)
Strength of the recommendation: =

Safety and tolerability of topiramate compared with amitriptyline. In the head-to-head RCTs of topiramate versus amitriptyline for migraine (no distinction between episodic and chronic), the safety profile was comparable between the two drugs.

PICO 4.8.13. In subjects with any migraine (no distinction between episodic and chronic), are topiramate and flunarizine equivalent for migraine prevention (outcomes: change in monthly headache/migraine days, persisting monthly headache/migraine days, ≥ 50% responder rate)?

Main evidence. None.

Additional evidence. We found one RCT comparing topiramate (100 mg daily) with flunarizine (5 mg daily) and a combination of the two drugs in subjects with migraine (634) that did not meet the criteria to be included in the main evidence due to the lack of sample size calculation. The risk of bias of the RCT was high (Figure 4.8.18). For

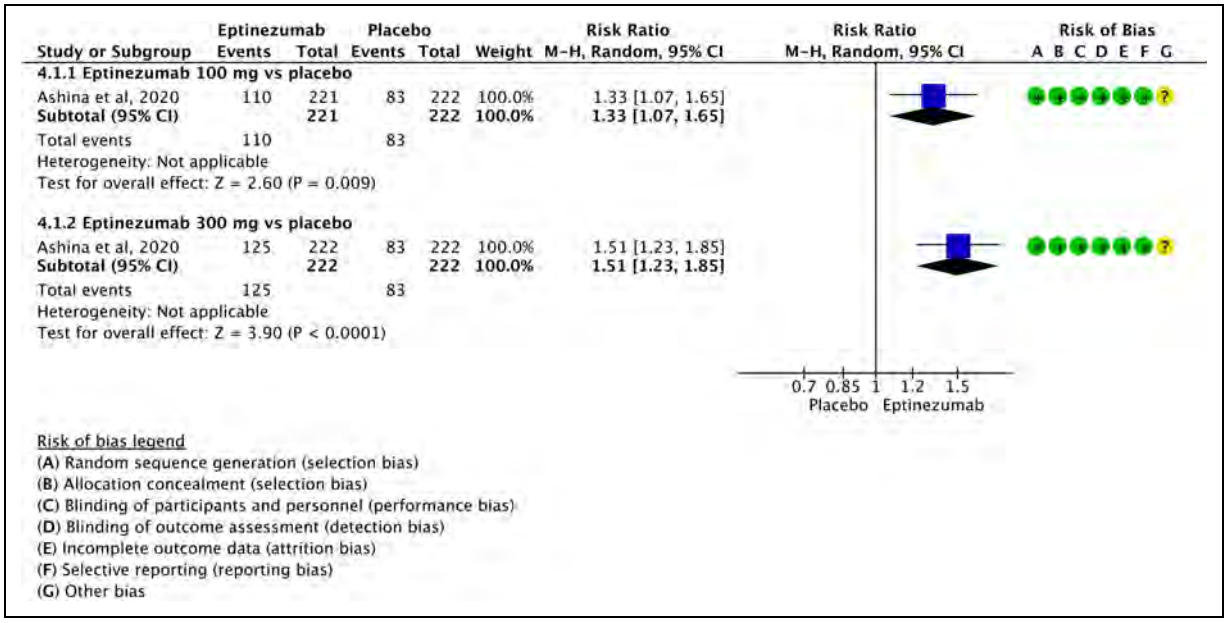


Figure 4.7.4. Forest plot showing the comparison between intravenous eptinezumab (100 and 300 mg quarterly) and placebo for the outcome ≥50% response rate in patients with episodic migraine at 12 weeks.

the present analysis, we considered the topiramate and flunarizine arm and discarded the arm of combination treatment.

The RCT did not show any difference between topiramate up to 100 mg daily and flunarizine 5 mg daily considering the outcome of ≥50% response rate (Figure 4.8.18). No recommendation was issued due to the low numbers of participants (<50 in each group).

Evidence-based recommendation for PICO 4.8.13

None.
Quality of evidence: -
Strength of the recommendation: -

Safety and tolerability of topiramate compared with flunarizine. In the head-to-head RCTs of topiramate over flunarizine for migraine, adverse events leading to treatment limitation or discontinuation were comparable between the two groups, in the absence of dropouts. However, the high risk of bias of the included RCT did not allow to draw conclusions on potential safety differences.

PICO 4.8.14. In subjects with any migraine (no distinction between episodic and chronic), are topiramate and lamotrigine equivalent for migraine prevention (outcomes: change in monthly headache/migraine days, persisting monthly headache/migraine days, ≥ 50% responder rate)?

Main evidence. We found one RCT comparing topiramate (50 mg daily) with lamotrigine (50 mg daily) in subjects with migraine (638) that met the criteria to be included in the main evidence. The risk of bias of the RCT was high (Figures 4.8.19 and 4.8.20).

The RCT did not show any difference between topiramate 50 mg daily and lamotrigine 50 mg daily considering the outcomes of change in monthly headache days (Figure 4.8.19) and ≥50% responder rate (Figure 4.8.20). The quality of evidence for both outcomes was considered low (Table 4.8.7) due to the availability of only one RCT and the high risk of bias. Nevertheless, the RCT included a placebo group together with active groups, which increases the reliability of findings.

Additional evidence. None.

Evidence-based recommendation for PICO 4.8.14

In subjects with any migraine (no distinction between episodic and chronic), we suggest oral topiramate 50 mg daily and oral lamotrigine 50 mg daily as equivalent options for migraine prevention.
Quality of evidence: Very low (⊕⊖⊖⊖)
Strength of the recommendation: =

Safety and tolerability of topiramate vs lamotrigine. Although numerically higher (15% vs 10%), the rate of adverse events in patients treated with topiramate 50 mg did not significantly differ from that of patients treated with lamotrigine 50 mg daily. Notably, the two doses of both drugs were lower than those used in comparable RCTs and lower than those commonly used in clinical practice.

Table 4.7.1. GRADE evidence profile table for intravenous eptinezumab versus placebo in episodic migraine

Certainty assessment							№ of patients		Effect			
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Eptinezumab	Placebo	Relative (95% CI)	Absolute (95% CI)	Quality	Importance
Change in monthly migraine days - Eptinezumab 100 mg intravenous vs Placebo												
1	RCT	Not serious	Not applicable[a]	Not serious	Not Serious	None	221	222	-	SMD **0.2 lower** (0.4 lower to 0.0 lower)	⊕⊕⊕⊖ Moderate	Critical
Change in monthly migraine days - Eptinezumab 300 mg intravenous vs Placebo												
1	RCT	Not serious	Not applicable[a]	Not serious	Not Serious	None	222	222	-	SMD **0.4 lower** (0.6 lower to 0.2 lower)	⊕⊕⊕⊖ Moderate	Critical
≥50% responder rate - Eptinezumab 100 mg intravenous vs Placebo												
1	RCT	Not serious	Not applicable[a]	Not serious	Not Serious	None	110/221 (49.8%)	83/222 (37.4%)	**RR 1.33** (1.07 to 1.65)	**123 more per 1.000** (from 26 more to 243 more)	⊕⊕⊕⊖ Moderate	Critical
≥50% responder rate - Eptinezumab 300 mg intravenous vs Placebo												
1	RCT	Not serious	Not applicable[a]	Not serious	Not Serious	None	125/222 (56.3%)	83/222 (37.4%)	**RR 1.51** (1.23 to 1.85)	**191 more per 1.000** (from 86 more to 318 more)	⊕⊕⊕⊖ Moderate	Critical

[a]Only one trial.

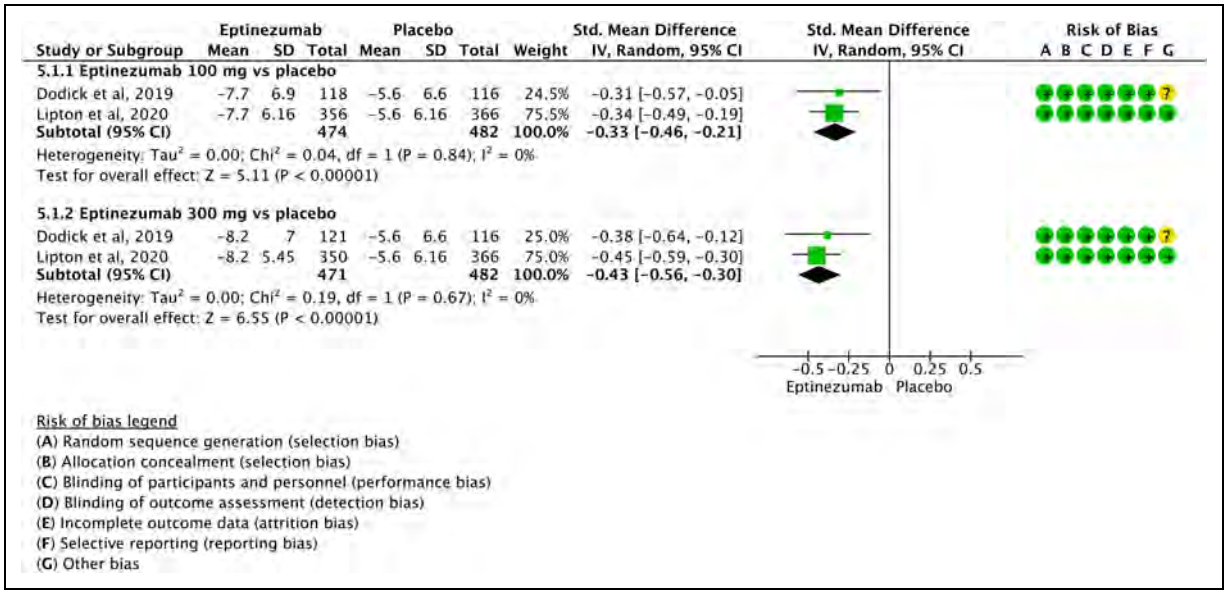


Figure 4.7.5. Forest plot showing the comparison between intravenous eptinezumab (100 or 300 mg quarterly) and placebo for the outcome change in monthly migraine days in patients with chronic migraine at 12 weeks.

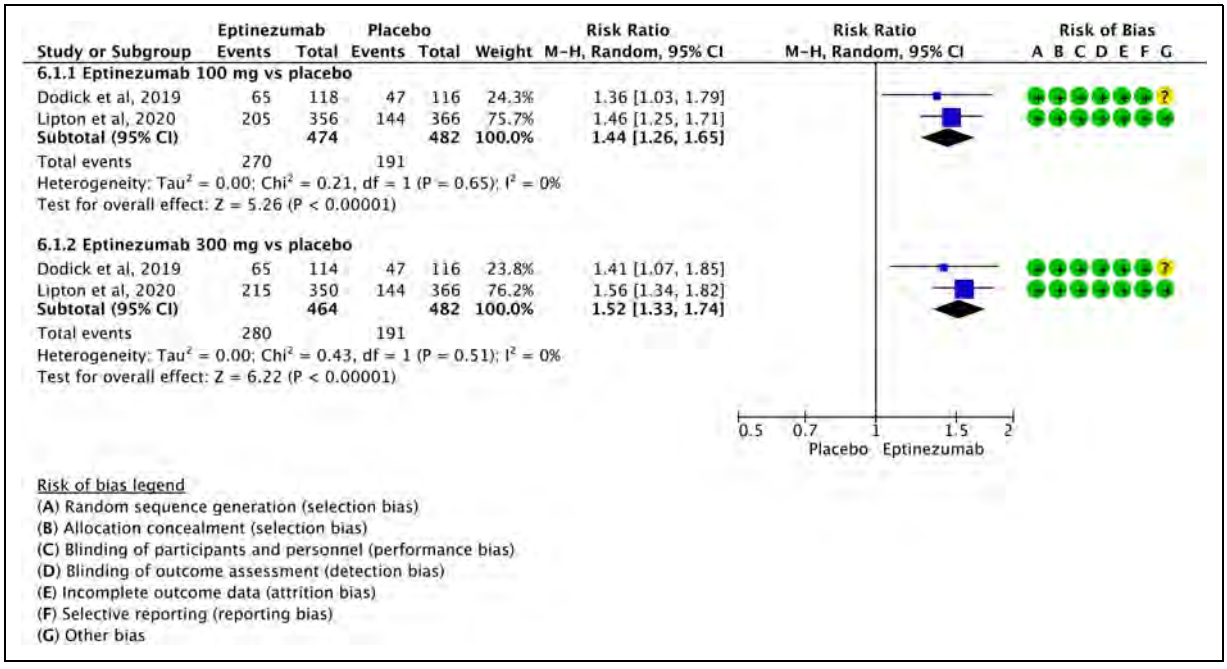


Figure 4.7.6. Forest plot showing the comparison between intravenous eptinezumab (100 or 300 mg quarterly) and placebo for the outcome ≥50% response rate in patients with chronic migraine at 12 weeks.

PICO 4.8.15. In subjects with episodic migraine, are topiramate and zonisamide equivalent for migraine prevention (outcomes: change in monthly headache/migraine days, persisting monthly headache/migraine days, ≥ 50% responder rate)?

Main evidence. None.

Additional evidence. We found one RCT comparing topiramate 100 mg daily to zonisamide 200 mg daily in subjects with episodic migraine (624). This RCT did not meet the quality criteria for main evidence and therefore the quality of evidence was considered low.

The study did not show differences between topiramate up to 100 mg daily and zonisamide up to 200 mg daily

Table 4.7.2. GRADE evidence profile table for intravenous eptinezumab versus placebo in chronic migraine

Certainty assessment							№ of patients		Effect			
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Eptinezumab	Placebo	Relative (95% CI)	Absolute (95% CI)	Quality	Importance
Change in monthly migraine days - Eptinezumab 100 mg intravenous vs Placebo												
2	RCTs	Not serious	Not serious	Not serious	Not serious	None	474	482	-	SMD **0.3 lower** (0.5 lower to 0.2 lower)	⊕⊕⊕⊕ High	Critical
Change in monthly migraine days - Eptinezumab 300 mg intravenous vs Placebo												
2	RCTs	Not serious	Not serious	Not serious	Not serious	None	471	482	-	SMD **0.4 lower** (0.6 lower to 0.3 lower)	⊕⊕⊕⊕ High	Critical
≥50% responder rate - Eptinezumab 100 mg intravenous vs Placebo												
2	RCTs	Not serious	Not serious	Not serious	Not serious	None	270/474 (57.0%)	191/482 (39.6%)	**RR 1.44** (1.26 to 1.65)	**174 more per 1.000** (from 103 more to 258 more)	⊕⊕⊕⊕ High	Critical
≥50% responder rate - Eptinezumab 300 mg intravenous vs Placebo												
2	RCTs	Not serious	Not serious	Not serious	Not serious	None	280/464 (60.3%)	191/482 (39.6%)	**RR 1.52** (1.33 to 1.74)	**206 more per 1.000** (from 131 more to 293 more)	⊕⊕⊕⊕ High	Critical

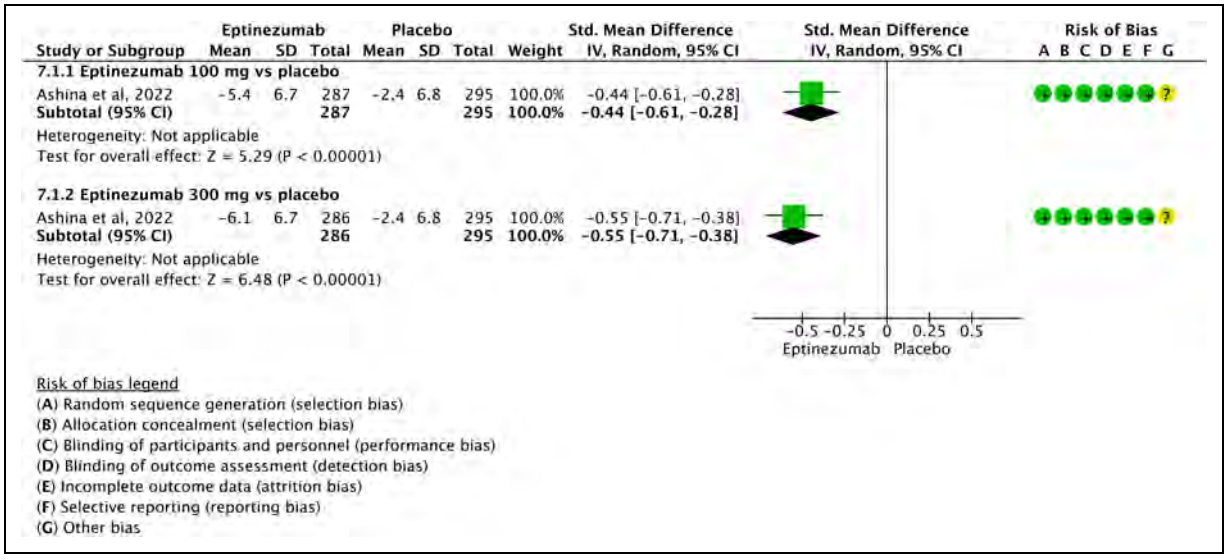


Figure 4.7.7. Forest plot showing the comparison between intravenous eptinezumab (100 or 300 mg quarterly) and placebo for the outcome change in monthly migraine days in patients with any migraine (no distinction between episodic and chronic) at 24 weeks.

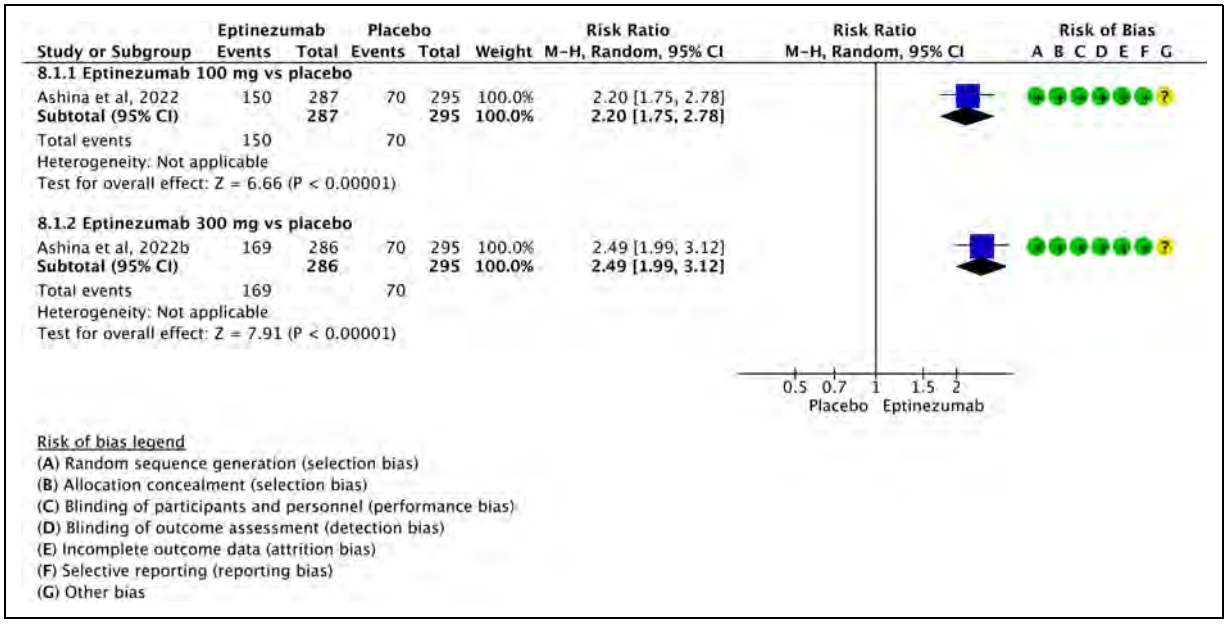


Figure 4.7.8. Forest plot showing the comparison between intravenous eptinezumab (100 or 300 mg quarterly) and placebo for the outcome ≥50% response rate in patients with any migraine (no distinction between episodic and chronic) at 24 weeks.

considering the outcomes of persisting monthly headache days (Figure 4.8.21) and ≥50% responder rate (Figure 4.8.22). The quality of evidence for both outcomes was considered very low due to the availability of only one RCT and the high risk of bias. No recommendation was issued due to the low numbers of participants (<50 per group).

Evidence-based recommendation for PICO 4.8.15

None.
Quality of evidence: -
Strength of recommendation: -

Table 4.7.3. GRADE evidence profile table for intravenous eptinezumab versus placebo in patients with migraine (no distinction between episodic and chronic)

Certainty assessment							№ of patients		Effect			
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Eptinezumab	Placebo	Relative (95% CI)	Absolute (95% CI)	Quality	Importance
Change in monthly migraine days - Eptinezumab 100 mg intravenous vs Placebo												
1	RCT	Not serious	Not applicable[a]	Not serious	Not serious	None	287	295	-	SMD **0.4 lower** (0.6 lower to 0.3 lower)	⊕⊕⊕⊖ Moderate	Critical
Change in monthly migraine days - Eptinezumab 300 mg intravenous vs Placebo												
1	RCT	Not serious	Not applicable[a]	Not serious	Not serious	None	286	295	-	SMD **0.6 lower** (0.7 lower to 0.4 lower)	⊕⊕⊕⊖ Moderate	Critical
≥50% responder rate - Eptinezumab 100 mg intravenous vs Placebo												
1	RCT	Not serious	Not applicable[a]	Not serious	Not serious	None	150/287 (52.3%)	70/295 (23.7%)	**RR 2.20** (1.75 to 2.78)	**285 more per 1.000** (from 178 more to 422 more)	⊕⊕⊕⊖ Moderate	Critical
≥50% responder rate - Eptinezumab 300 mg intravenous vs Placebo												
1	RCT	Not serious	Not applicable[a]	Not serious	Not serious	None	169/286 (59.1%)	70/295 (23.7%)	**RR 2.49** (1.99 to 3.12)	**354 more per 1.000** (from 235 more to 503 more)	⊕⊕⊕⊖ Moderate	Critical

[a]Only one trial.

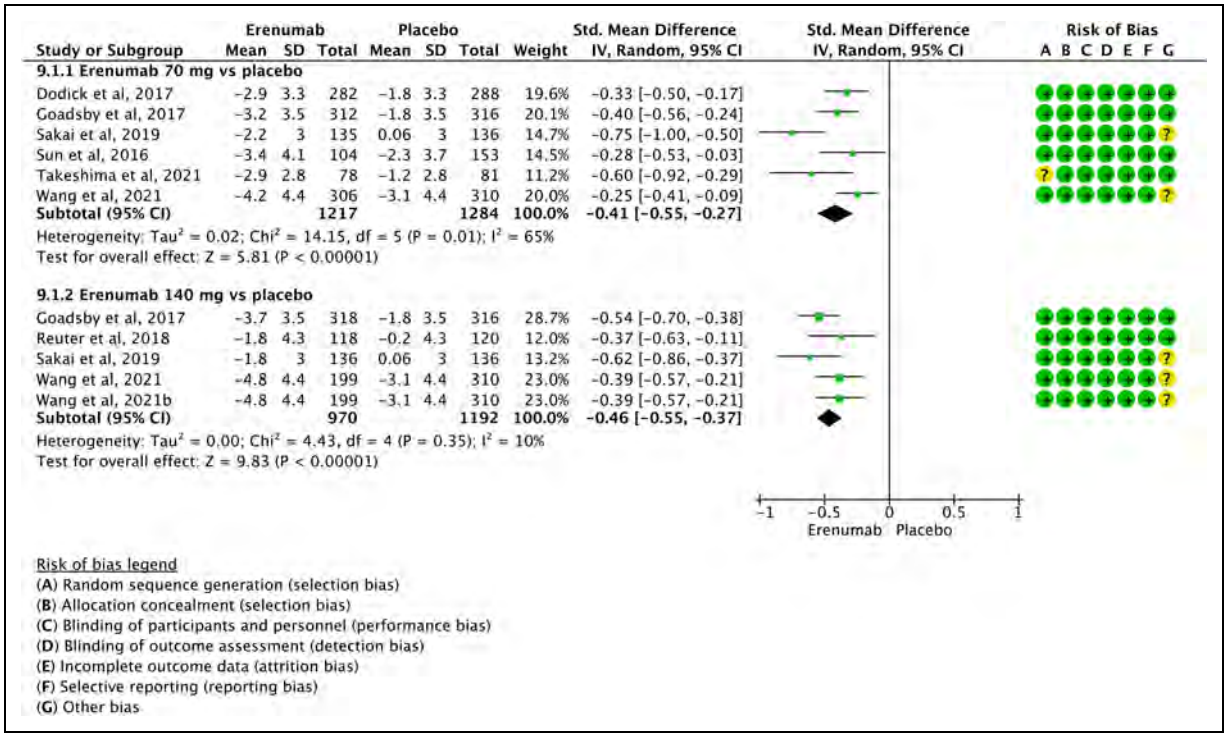


Figure 4.7.9. Forest plot showing the comparison between subcutaneous erenumab (70 or 140 mg every 4 weeks) and placebo for the outcome change in monthly migraine days in patients with episodic migraine at 12 or 24 weeks.

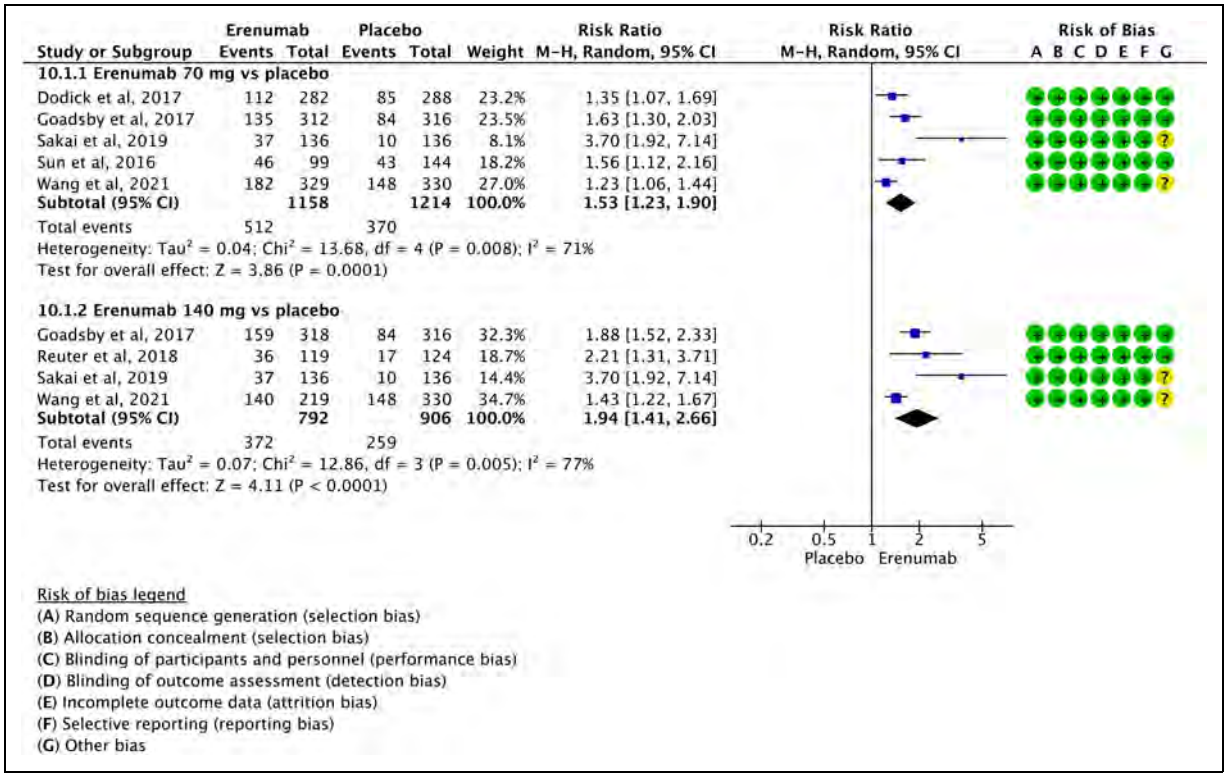


Figure 4.7.10. Forest plot showing the comparison between subcutaneous erenumab (70 or 140 mg every four weeks) and placebo for the outcome ≥50% response rate in patients with episodic migraine at 12 or 24 weeks.

Table 4.7.4. GRADE evidence profile table for subcutaneous erenumab versus placebo in patients with episodic migraine

Certainty assessment							№ of patients		Effect			
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Erenumab	Placebo	Relative (95% CI)	Absolute (95% CI)	Quality	Importance
Change in monthly migraine days - Erenumab 70 mg subcutaneous vs Placebo												
6	RCTs	Not serious	Not serious	Not serious	Not serious	None	1217	1284	-	SMD **0.4 lower** (0.6 lower to 0.3 lower)	⊕⊕⊕⊕ High	Critical
Change in monthly migraine days - Erenumab 140 mg subcutaneous vs Placebo												
5	RCTs	Not serious	Not serious	Not serious	Not serious	None	970	1192	-	SMD **0.5 lower** (0.6 lower to 0.4 lower)	⊕⊕⊕⊕ High	Critical
≥50% responder rate - Erenumab 70 mg subcutaneous vs Placebo												
5	RCTs	Not serious	Not serious	Not serious	Not serious	None	512/1158 (44.4%)	370/1214 (30.5%)	**RR 1.53** (1.23 to 1.90)	**162 more per 1.000** (from 70 more to 274 more)	⊕⊕⊕⊕ High	Critical
≥50% responder rate - Erenumab 140 mg subcutaneous vs Placebo												
4	RCTs	Not serious	Not serious	Not serious	Not serious	None	372/792 (47.0%)	259/906 (28.6%)	**RR 1.94** (1.41 to 2.66)	**269 more per 1.000** (from 117 more to 475 more)	⊕⊕⊕⊕ High	Critical

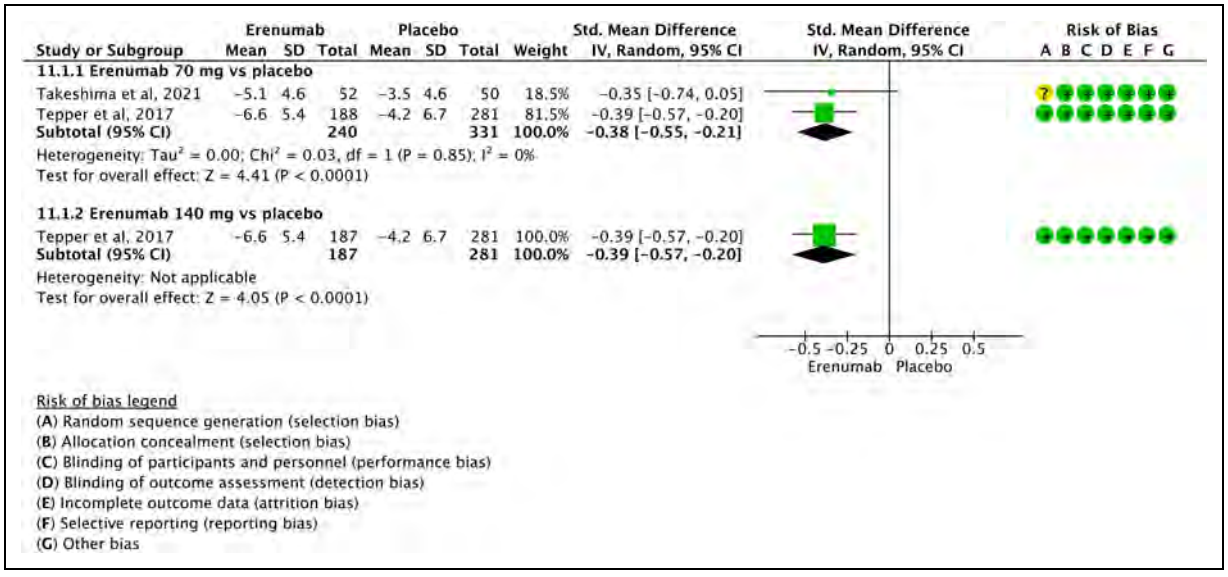


Figure 4.7.11. Forest plot showing the comparison between subcutaneous erenumab (70 or 140 mg every 4 weeks) and placebo for the outcome change in monthly migraine days in patients with chronic migraine at 12 or 24 weeks.

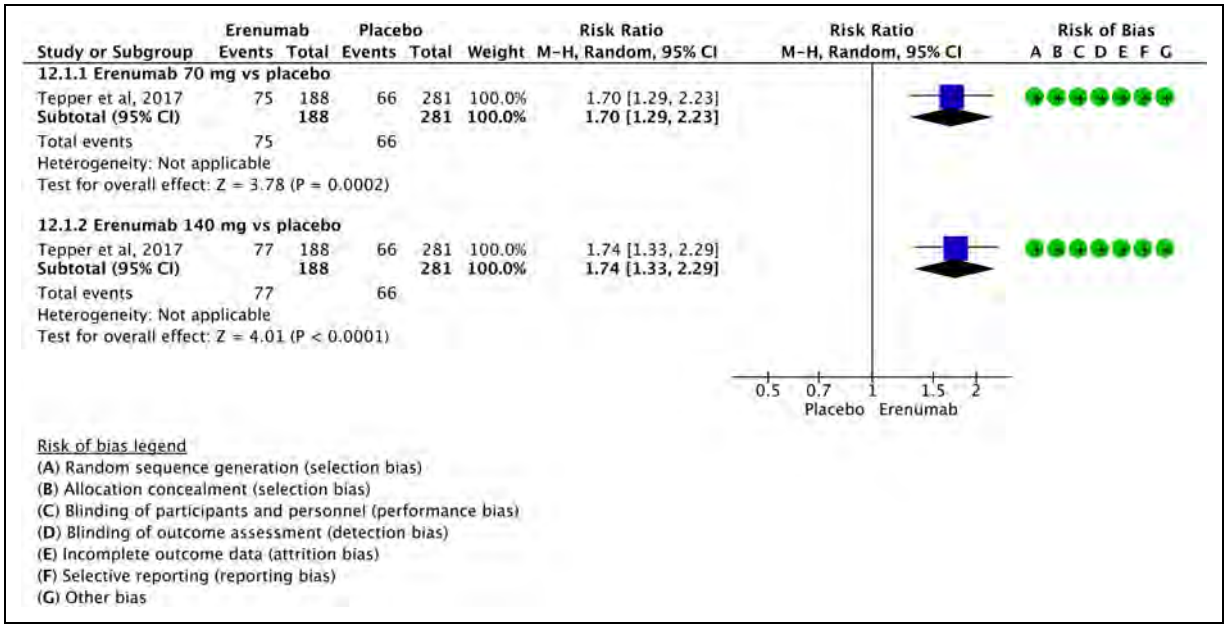


Figure 4.7.12. Forest plot showing the comparison between subcutaneous erenumab (70 or 140 mg every 4 weeks) and placebo for the outcome ≥50% response rate in patients with chronic migraine at 12 weeks.

Safety and tolerability of topiramate compared with zonisamide. The RCT comparing topiramate with zonisamide did not find differences in the safety of the two drugs. It should be noted that the evidence base for topiramate is much larger than that of zonisamide, which does not have a placebo-controlled trial for migraine prevention.

PICO 4.8.16. In subjects with episodic migraine, are valproate and cinnarizine equivalent for migraine prevention (outcomes: change in monthly headache/migraine days, persisting monthly headache/migraine days, ≥ 50% responder rate)?

Main evidence. None.

Table 4.7.5. GRADE evidence profile table for subcutaneous erenumab versus placebo in patients with chronic migraine

Certainty assessment							№ of patients		Effect			
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Erenumab	Placebo	Relative (95% CI)	Absolute (95% CI)	Quality	Importance
Change in monthly migraine days - Erenumab 70 mg subcutaneous vs Placebo												
2	RCTs	Not serious	Not serious	Not serious	Not serious	None	240	331	-	SMD **0.4 lower** (0.6 lower to 0.2 lower)	⊕⊕⊕⊕ High	Critical
Change in monthly migraine days - Erenumab 140 mg subcutaneous vs Placebo												
1	RCT	Not serious	Not applicable[a]	Not serious	Not serious	None	187	281	-	SMD **0.4 lower** (0.6 lower to 0.2 lower)	⊕⊕⊕⊖ Moderate	Critical
≥50% responder rate - Erenumab 70 mg subcutaneous vs Placebo												
1	RCT	Not serious	Not applicable[a]	Not serious	Not serious	None	75/188 (39.9%)	66/281 (23.5%)	**RR 1.70** (1.29 to 2.23)	**164 more per 1.000** (from 68 more to 289 more)	⊕⊕⊕⊖ Moderate	Critical
≥50% responder rate - Erenumab 140 mg subcutaneous vs Placebo												
1	RCT	Not serious	Not applicable[a]	Not serious	Not serious	None	77/187 (41.0%)	66/281 (23.5%)	**RR 1.74** (1.33 to 2.29)	**174 more per 1.000** (from 78 more to 303 more)	⊕⊕⊕⊖ Moderate	Critical

[a]Only one trial.

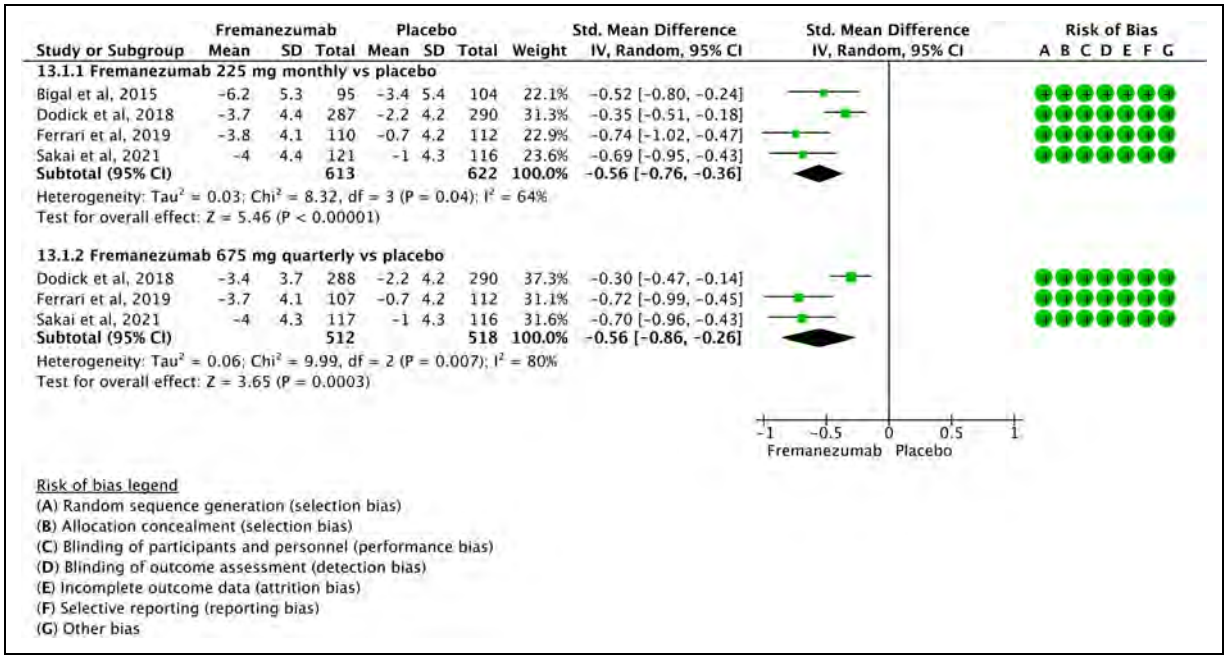


Figure 4.7.13. Forest plot showing the comparison between subcutaneous fremanezumab (225 mg monthly or 675 mg quarterly) and placebo for the outcome change in monthly migraine days in patients with episodic migraine at 12 weeks.

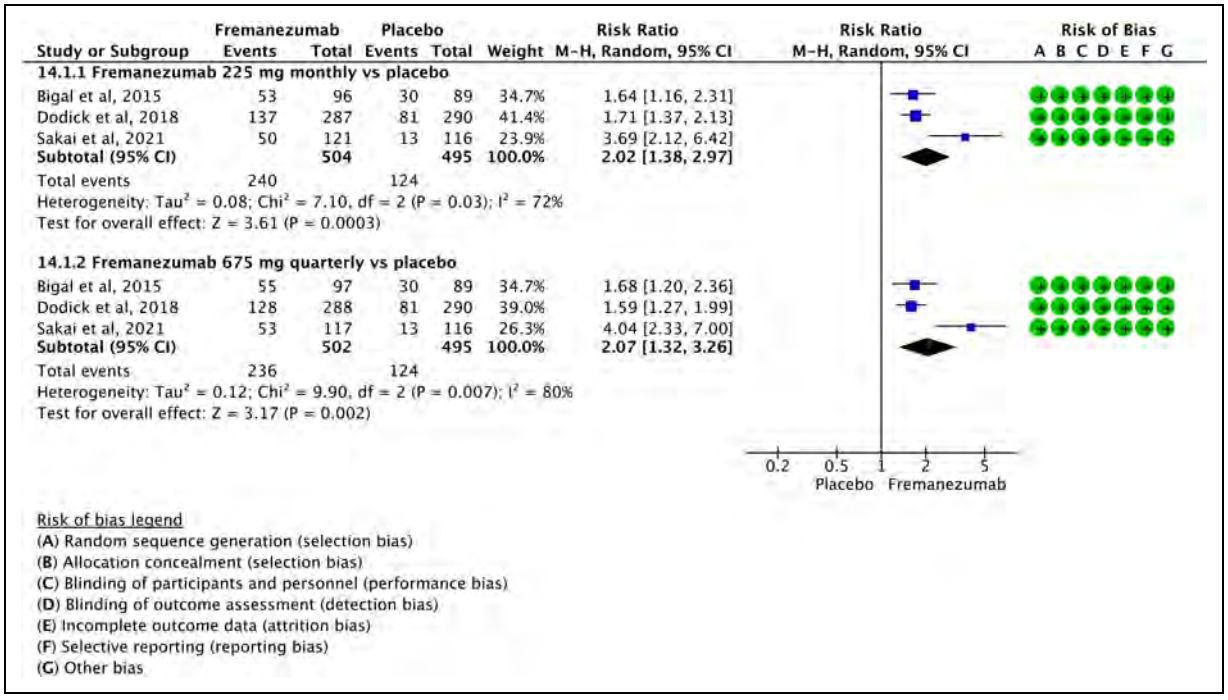


Figure 4.7.14. Forest plot showing the comparison between subcutaneous fremanezumab (225 mg monthly or 675 mg quarterly) and placebo for the outcome ≥50% response rate in patients with episodic migraine at 12 weeks.

Table 4.7.6. GRADE evidence profile table for fremanezumab versus placebo in episodic migraine

Certainty assessment							№ of patients		Effect			
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Fremanezumab	Placebo	Relative (95% CI)	Absolute (95% CI)	Quality	Importance
Change in monthly migraine days - Fremanezumab 225 mg monthly subcutaneous vs Placebo												
4	RCTs	Not serious	Not serious	Not serious	Not serious	None	613	622	-	SMD **0.6 lower** (0.8 lower to 0.4 lower)	⊕⊕⊕⊕ High	Critical
Change in monthly migraine days - Fremanezumab 675 mg quarterly subcutaneous vs Placebo												
3	RCTs	Not serious	Not serious	Not serious	Not serious	None	512	518	-	SMD **0.6 lower** (0.9 lower to 0.3 lower)	⊕⊕⊕⊕ High	Critical
≥50% responder rate - Fremanezumab 225 mg monthly subcutaneous vs Placebo												
3	RCTs	Not serious	Not serious	Not serious	Not serious	None	240/504 (47.6%)	124/495 (25.1%)	**RR 2.02** (1.38 to 2.97)	**256 more per 1.000** (from 95 more to 493 more)	⊕⊕⊕⊕ High	Critical
≥50% responder rate - Fremanezumab 675 mg quarterly subcutaneous vs Placebo												
3	RCTs	Not serious	Not serious	Not serious	Not serious	None	236/502 (47.0%)	124/495 (25.1%)	**RR 2.07** (1.32 to 3.26)	**336 more per 1.000** (from 7 less to 1000 more)	⊕⊕⊕⊕ High	Critical

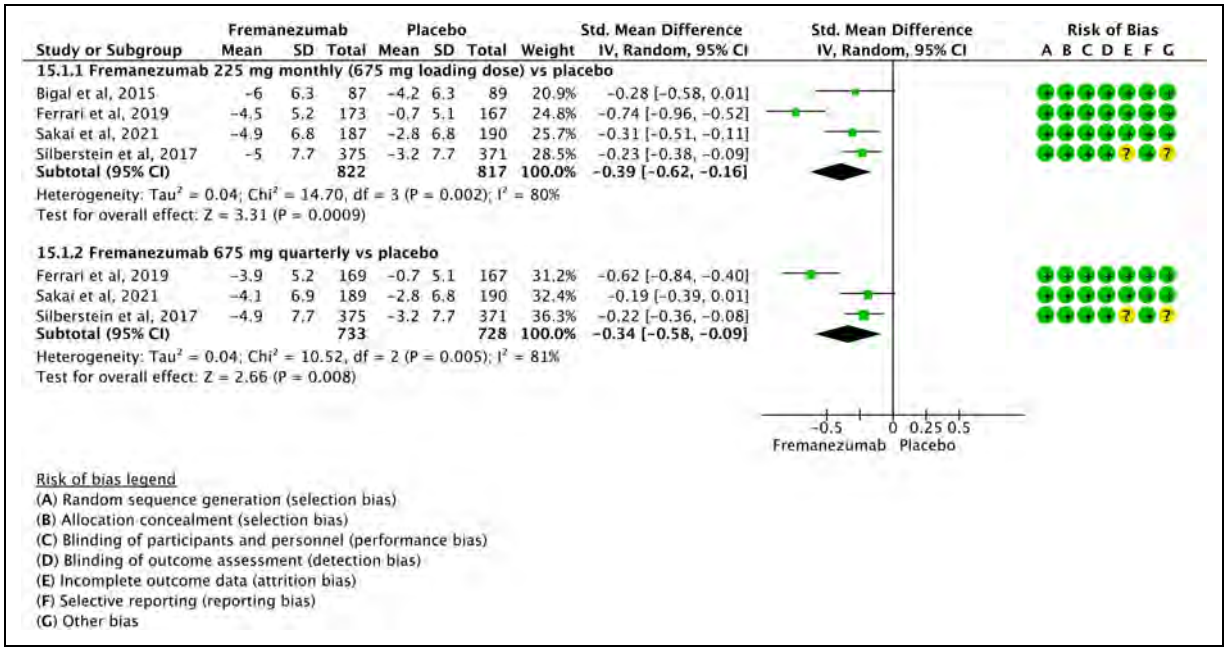


Figure 4.7.15. Forest plot showing the comparison between subcutaneous fremanezumab (225 mg monthly plus 675 mg loading dose or 675 mg quarterly) and placebo for the outcome change in monthly migraine days in patients with chronic migraine at 12 weeks.

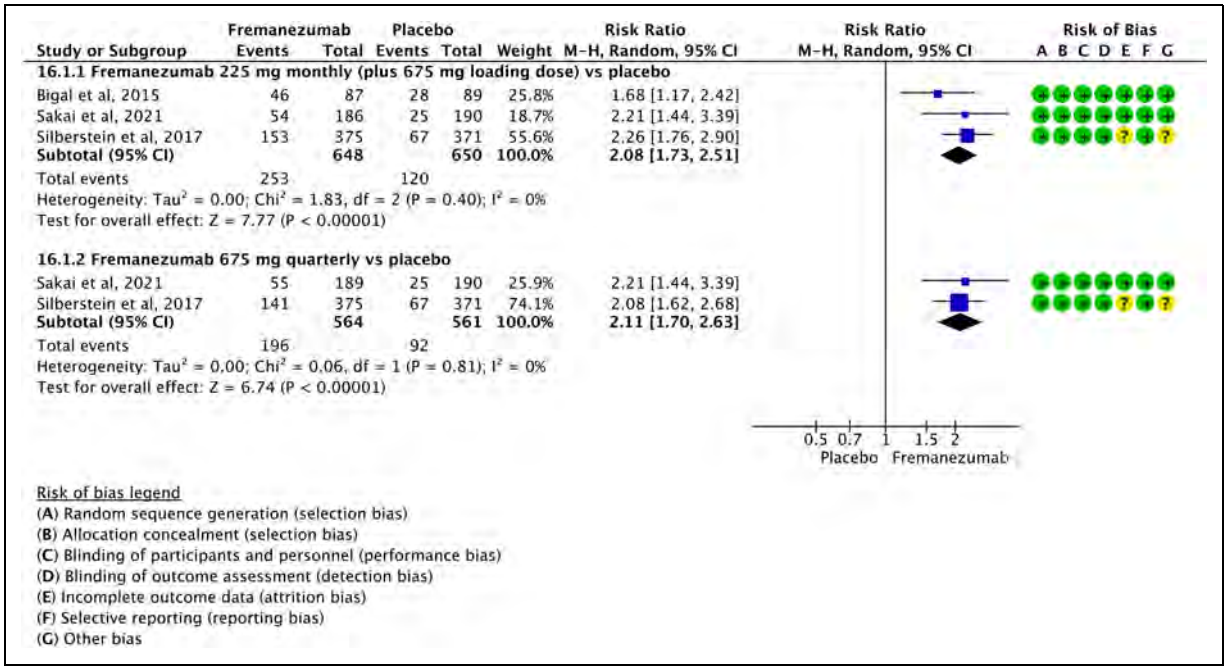


Figure 4.7.16. Forest plot showing the comparison between subcutaneous fremanezumab (225 mg monthly plus 675 mg loading dose or 675 mg quarterly) and placebo for the outcome ≥50% response rate in patients with chronic migraine at 12 weeks.

Table 4.7.7. GRADE evidence profile table for subcutaneous fremanezumab versus placebo in patients with chronic migraine

Certainty assessment							№ of patients		Effect			
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Fremanezumab	Placebo	Relative (95% CI)	Absolute (95% CI)	Quality	Importance
Change in monthly migraine days - Fremanezumab 225 mg monthly (675 mg loading dose) subcutaneous vs Placebo												
4	RCTs	Not serious	Not serious	Not serious	Not serious	Serious[a]	822	817	-	SMD **0.4 lower** (0.6 lower to 0.2 lower)	⊕⊕⊕⊖ Moderate	Critical
Change in monthly migraine days - Fremanezumab 675 mg quarterly subcutaneous vs Placebo												
3	RCTs	Not serious	Not serious	Not serious	Not serious	None	733	728	-	SMD **0.3 lower** (0.6 lower to 0.1 lower)	⊕⊕⊕⊕ High	Critical
≥50% responder rate - Fremanezumab 225 mg monthly (plus 675 mg loading dose) subcutaneous vs Placebo												
3	RCTs	Not serious	Not serious	Not serious	Not serious	Serious[a]	253/648 (39.0%)	120/650 (18.5%)	**RR 2.08** (1.73 to 2.51)	**199 more per 1.000** (from 135 more to 279 more)	⊕⊕⊕⊖ Moderate	Critical
≥50% responder rate - Fremanezumab 675 mg quarterly subcutaneous vs Placebo												
2	RCTs	Not serious	Not serious	Not serious	Not serious	None	196/564 (34.8%)	92/561 (16.4%)	**RR 2.11** (1.70 to 2.63)	**182 more per 1.000** (from 115 more to 267 more)	⊕⊕⊕⊕ High	Critical

[a]RTC used a 675 mg loading dose not approved for clinical practice.

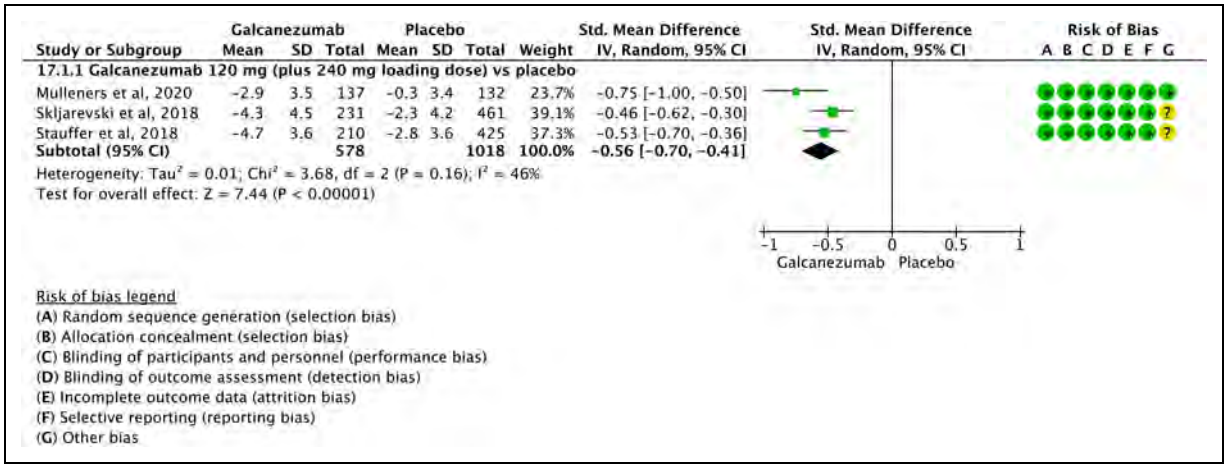


Figure 4.7.17. Forest plot showing the comparison between subcutaneous galcanezumab (120 mg monthly plus 240 mg loading dose) and placebo for the outcome change in monthly headache/migraine days in patients with episodic migraine at 3 or 6 months.

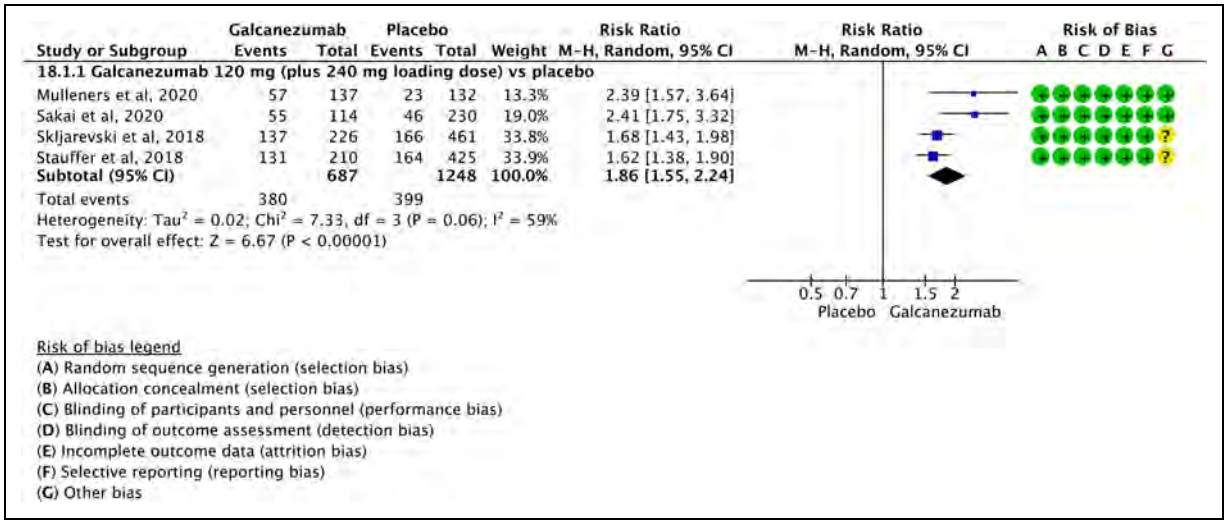


Figure 4.7.18. Forest plot showing the comparison between galcanezumab (120 mg monthly plus 240 mg loading dose) and placebo for the outcome ≥50% responder rate in patients with episodic migraine at 3 or 6 months.

Additional evidence. We found two RCTs comparing valproate to cinnarizine in subjects with episodic migraine (648,655). Those RCTs did not meet the predefined quality criteria (Figures 4.8.23 and 4.8.24) and for this reason the quality of evidence was considered very low.

The studies did not show differences between valproate (400 mg or 600 mg daily) and cinnarizine (50 mg or 75 mg daily) considering the outcome of persisting monthly headache days (Figure 4.8.23), nor between valproate 600 mg daily and cinnarizine 75 mg daily considering the outcome and ≥50% responder rate (Figure 4.8.24).

Evidence-based recommendation for PICO 4.8.16

In subjects with episodic migraine, we suggest oral valproate (400 or 600 mg daily) and oral cinnarizine (50 or 75 mg daily) as equivalent options for migraine prevention.
Quality of evidence: very low (⊕⊖⊖⊖).
Strength of recommendation: =.

Safety and tolerability of valproate compared with cinnarizine. The tolerability of valproate and cinnarizine was

Table 4.7.8. GRADE evidence profile table for subcutaneous galcanezumab versus placebo in patients with episodic migraine

Certainty assessment							№ of patients		Effect			
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Galcanezumab	Placebo	Relative (95% CI)	Absolute (95% CI)	Quality	Importance
Change in monthly migraine days - Galcanezumab 120 mg (plus 240 mg loading dose) subcutaneous vs Placebo												
3	RCTs	Low	Not serious	Not serious	Not serious	None	578	1018	-	SMD **0.6 lower** (0.7 lower to 0.4 lower)	⊕⊕⊕⊕ High	Critical
≥50% responder rate - Galcanezumab 120 mg (plus 240 mg loading dose) subcutaneous vs Placebo												
4	RCTs	Low	Not serious	Not serious	Not serious	None	380/687 (%)	399/1248 (%)	**RR 1.86** (1.55 to 2.24)	**275 more per 1.000** (from 176 more to 396 more)	⊕⊕⊕⊕ High	Critical

comparable in the RCT. However, cinnarizine does not have a RCT with a comparison against placebo. Therefore, the evidence base for use in clinical practice is higher for valproate than for cinnarizine.

PICO 4.8.17. In subjects with episodic migraine, are valproate and amitriptyline equivalent for migraine prevention (outcomes: change in monthly headache/migraine days, persisting monthly headache/migraine days, ≥ 50% responder rate)?

Main evidence. None.

Additional evidence. We found one RCT comparing valproate to amitriptyline in subjects with episodic migraine (600). The RCT did not meet the pre-defined quality criteria (Figure 4.8.25) and for this reason the quality of evidence was considered very low.

The study did not show differences between valproate 1000 mg daily and amitriptyline 100 mg daily considering the outcome of persisting monthly headache days (Figure 4.8.25). The quality of evidence for monthly headache days was considered very low due to the availability of only one RCT and the high risk of bias. No recommendation was issued due to the low numbers of participants (<50 in each group).

Evidence-based recommendation for PICO 4.8.17

None.
Quality of evidence: -
Strength of recommendation: -

Safety and tolerability of valproate compared with amitriptyline. In the RCT comparing valproate with amitriptyline, there was no difference in safety between the two drugs. However, the low number of patients reduces the reliability of safety considerations.

PICO 4.8.18. In subjects with any migraine (no distinction between episodic and chronic), are amitriptyline and venlafaxine equivalent for migraine prevention (outcomes: change in monthly headache/migraine days, persisting monthly headache/migraine days, ≥ 50% responder rate)?

Main evidence. None.

Additional evidence. We found one RCT comparing amitriptyline (75 mg daily) to venlafaxine (150 mg daily) in subjects with migraine (588). The RCT did not meet the quality criteria for main evidence (Figure 4.8.26) and for this reason the quality of evidence was considered low.

The study did not show differences between amitriptyline and venlafaxine considering the outcome of persisting monthly headache days (Figure 4.8.26). The quality of evidence was considered low due to the availability of only one RCT.

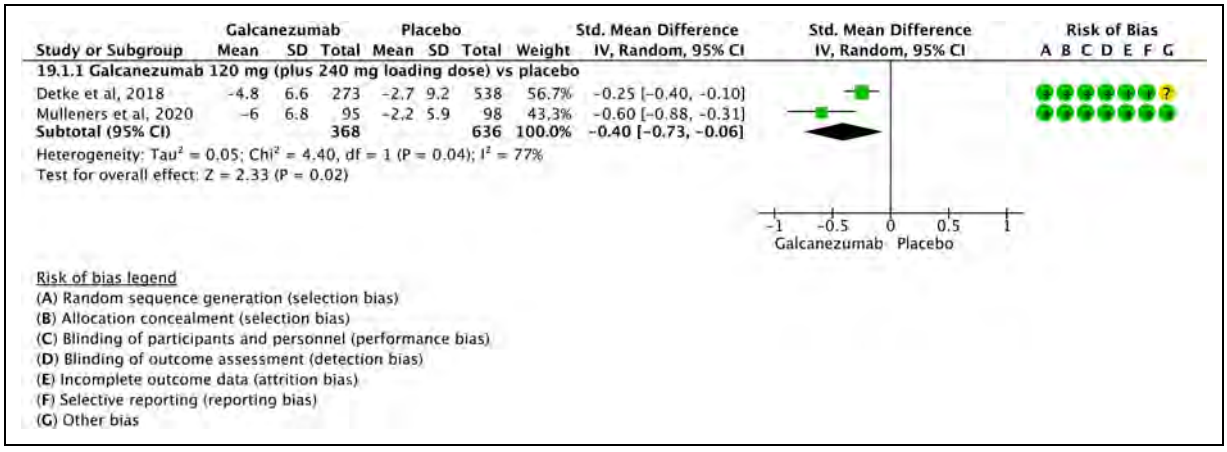


Figure 4.7.19. Forest plot showing the comparison between subcutaneous galcanezumab (120 mg monthly plus 240 mg loading dose) and placebo for the outcome change in monthly headache/migraine days in patients with chronic migraine at 3 months.

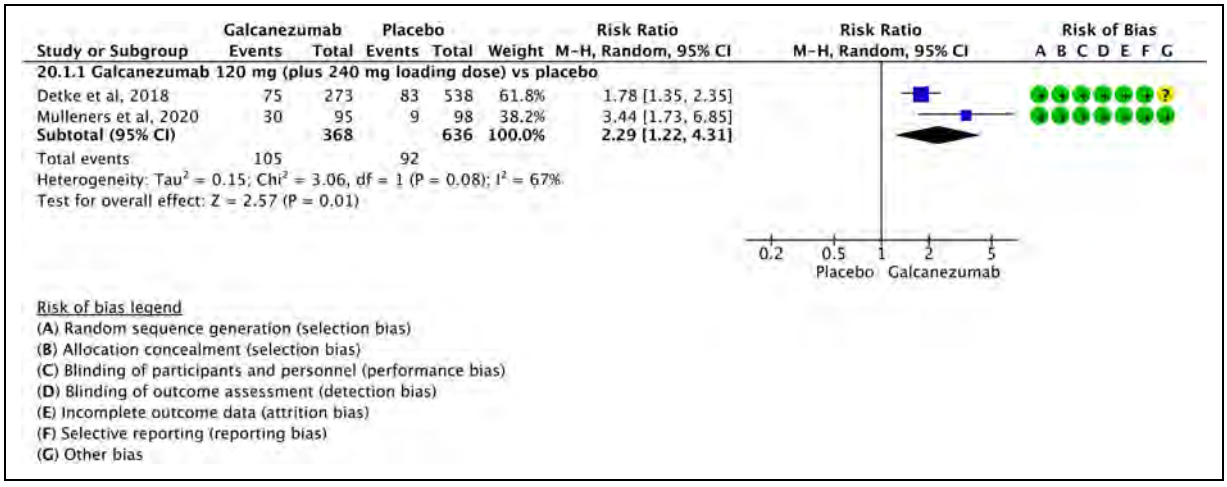


Figure 4.7.20. Forest plot showing the comparison between subcutaneous galcanezumab (120 mg monthly plus 240 mg loading dose) and placebo for the outcome ≥50% response rate in patients with chronic migraine at 3 months.

An additional RCT compared amitriptyline at a daily oral dosage of 25 mg and venlafaxine at a daily oral dose of 37.5 mg (875). The RCT could not be included in quantitative analyses as it did not contain the outcomes considered for quantitative analyses. The RCT showed no difference in efficacy between amitriptyline and venlafaxine in decreasing the number of monthly headache attacks. Conversely, amitriptyline showed a worse tolerability profile, as the adverse drug reactions in the amitriptyline group exceeded those of the venlafaxine group.

Evidence-based recommendation for PICO 4.8.18

In subjects with any migraine (no distinction between episodic and chronic) we suggest oral amitriptyline 75 mg daily and oral venlafaxine 150 mg daily as equivalent options for migraine prevention.
Quality of evidence: Very low (⊕⊖⊖⊖)
Strength of recommendation: Weak (=)

Safety and tolerability of amitriptyline compared with venlafaxine. Safety and tolerability of the two drugs were comparable in the only available head-to-head RCT. The evidence base for placebo-controlled RCTs is higher for amitriptyline than for venlafaxine. However, venlafaxine has a better antidepressant profile than amitriptyline.

Table 4.7.9. GRADE evidence profile table for subcutaneous galcanezumab versus placebo in patients with chronic migraine

Certainty assessment							№ of patients		Effect			
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Galcanezumab	Placebo	Relative (95% CI)	Absolute (95% CI)	Quality	Importance
Change in monthly migraine days - Galcanezumab 120 mg (plus 240 mg loading dose) subcutaneous vs Placebo												
2	RCTs	Not serious	Not serious	Not serious	Not serious	None	368	636	-	SMD **0.4 lower** (0.7 lower to 0.1 lower)	⊕⊕⊕⊕ High	Critical
≥50% responder rate - Galcanezumab 120 mg (plus 240 mg loading dose) subcutaneous vs Placebo												
2	RCTs	Not serious	Not serious	Not serious	Not serious	None	105/368 (28.5%)	92/636 (14.5%)	**RR 2.29** (1.22 to 4.31)	**187 more per 1.000** (from 32 more to 479 more)	⊕⊕⊕⊕ High	Critical

Therefore, in patients with depressive comorbidities venlafaxine could be a suitable option.

PICO 4.8.19. In subjects with any migraine (no distinction between episodic and chronic), are amitriptyline and citalopram equivalent for migraine prevention (outcomes: change in monthly headache/migraine days, persisting monthly headache/migraine days, ≥ 50% responder rate)?

Main evidence. None.

Additional evidence. We found one RCT comparing amitriptyline (50 mg daily) to citalopram (20 mg daily) in subjects with migraine (591). The RCT did not meet the pre-defined quality criteria (Figure 4.8.27) and for this reason the quality of evidence was considered low.

The study did showed the superiority of amytriptiline over citalopram considering the outcome of persisting monthly headache days (Figure 4.8.27). The quality of evidence was considered low due to the availability of only one RCT. It should also be noted that citalopram was not tested against placebo for migraine prevention. No recommendation was issued due to low numbers of participants (<50 per group).

Evidence-based recommendation for PICO 4.8.19

None.
Quality of evidence: -
Strength of recommendation: -

PICO 4.8.20. In subjects with any migraine (no distinction between episodic and chronic), are venlafaxine and nortriptyline plus propranolol equivalent for migraine prevention (outcome: change in monthly headache/migraine days, persisting monthly headache/migraine days, ≥ 50% responder rate)?

Main evidence. None.

Additional evidence. We found one RCT comparing venlafaxine (37.5 mg daily) to nortriptyline (25 mg daily) plus propranolol (40 mg daily) in subjects with migraine (601). The RCT did not meet the pre-defined quality criteria (Figure 4.8.28) and for this reason the quality of evidence was considered low.

The study did not show differences between venlafaxine and nortriptyline plus propranolol considering the outcome of persisting monthly headache days (Figure 4.8.28). The quality of evidence was considered very low due to the availability of only one RCT and to the high risk of bias. No recommendation was issued due to the low number of participants (<50 per group).

Drug	Any migraine	Episodic migraine	Chronic migraine
Eptinezumab 100 mg quarterly	⊕⊕⊕⊖ ↑↑	⊕⊕⊕⊖ ↑↑	⊕⊕⊕⊕ ↑↑
Eptinezumab 300 mg quarterly	⊕⊕⊕⊖ ↑↑	⊕⊕⊕⊖ ↑↑	⊕⊕⊕⊕ ↑↑
Erenumab 70 mg monthly	⊖⊖⊖⊖ -	⊕⊕⊕⊕ ↑↑	⊕⊕⊕⊖ ↑↑
Erenumab 140 mg monthly	⊖⊖⊖⊖ -	⊕⊕⊕⊕ ↑↑	⊕⊕⊕⊖ ↑↑
Fremanezumab 225 mg monthly	⊖⊖⊖⊖ -	⊕⊕⊕⊕ ↑↑	⊕⊕⊕⊖ ↑↑
Fremanezumab 675 mg quarterly	⊖⊖⊖⊖ -	⊕⊕⊕⊕ ↑↑	⊕⊕⊕⊕ ↑↑
Galcanezumab 120 mg* monthly	⊖⊖⊖⊖ -	⊕⊕⊕⊕ ↑↑	⊕⊕⊕⊕ ↑↑

Quality of selected evidence	
⊕⊕⊕⊕	high
⊕⊕⊕⊖	moderate
⊕⊕⊖⊖	low
⊕⊖⊖⊖	very low
⊖⊖⊖⊖	none
Strenght of the recommendation	
↑↑	strong in favor
↑	weak in favor
↓	weak against
↓↓	strong against
-	none

Figure 4.7.21. Summary of evidence-based recommendations on CGRP mAbs for migraine prevention.
*240 mg loading dose.

Evidence-based recommendation for PICO 4.8.20

None.
Quality of evidence: -
Strength of recommendation: -

PICO 4.8.21. In subjects with any migraine (no distinction between episodic and chronic), are propranolol and candesartan equivalent for migraine prevention (outcomes: change in monthly headache/migraine days, persisting monthly headache/migraine days, ≥ 50% responder rate)?

Main evidence. We found one RCT comparing propranolol (160 mg daily) to candesartan (16 mg daily) for migraine prevention (709). The RCT met the quality criteria for main evidence (Figure 4.8.30) and had a low risk of bias.

The study did not show differences between propranolol and candesartan considering the outcomes of persisting monthly headache days (Figure 4.8.29) and ≥50% responder rate (Figure 4.8.30). The quality of evidence was considered moderate (Table 4.8.8) due to the availability of only one RCT.

Additional evidence. None.

Table 4.7.10. Conditions in whom monoclonal antibodies targeting the CGRP pathway should be used with caution

Acute ischemic stroke, TIA	Disruption of the blood-brain barrier, e.g., traumatic brain injury, meningitis
Subarachnoid hemorrhage	Wound healing
Acute coronary syndrome	Inflammatory bowel disease
Angina pectoris	Chronic obstructive pulmonary disease
Severe constipation	Raynaud's phenomenon

Evidence-based recommendation for PICO 4.8.21

In subjects with any migraine (no distinction between episodic and chronic), we suggest oral propranolol (160 mg daily) and candesartan (16 mg daily) as equivalent options for migraine prevention.
Quality of evidence: Moderate (⊕⊕⊕⊖)
Strength of recommendation: Weak (=)

PICO 4.8.22. In subjects with any migraine (no distinction between episodic and chronic), are propranolol and nortriptyline equivalent for migraine prevention (outcomes: change in monthly headache/migraine days, persisting monthly headache/migraine days, ≥ 50% responder rate)?

Main evidence. None.

Additional evidence. We found one RCT comparing propranolol (80 mg daily) to nortriptyline (40 mg daily) for migraine prevention (705). The RCT did not meet the predefined quality criteria (Figure 4.8.32) due to the lack of a pre-specified sample size calculation and had a high risk of bias.

The study did not show differences between propranolol and nortriptyline considering the outcome ≥50% responder

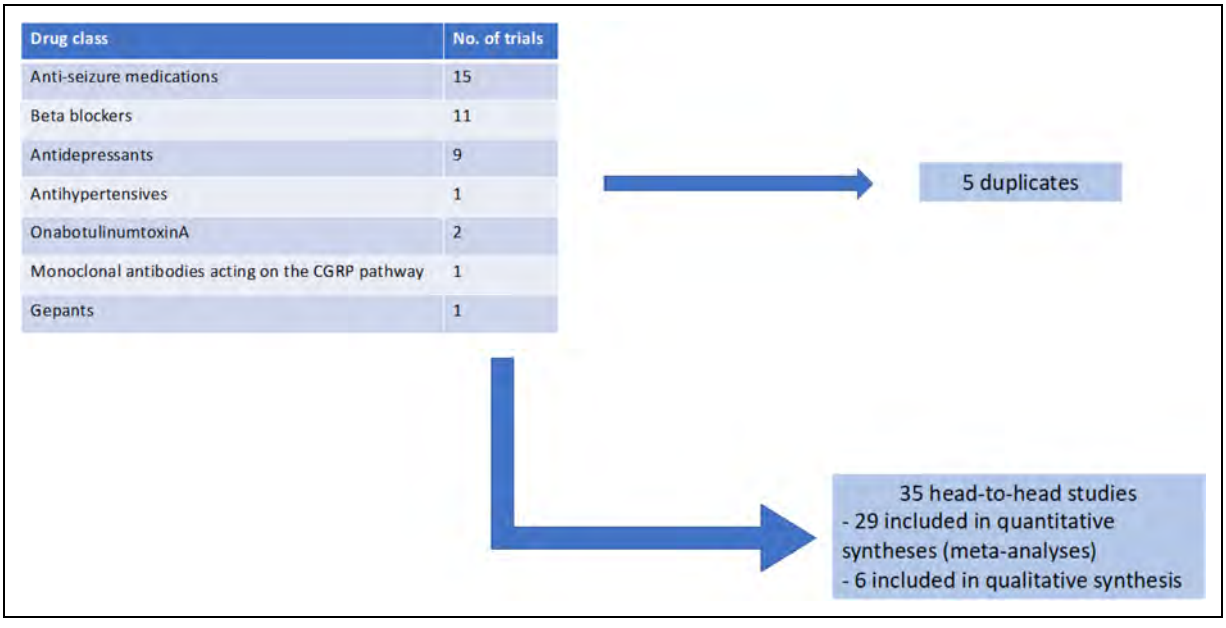


Figure 4.8.1. Flow chart of study selection.

Table 4.8.1. PICO structure of randomized controlled trials included in the present chapter

Question	Reference	Migraine type (Population)	Drug 1	Drug 2	Outcomes
1	(836)	Any	Erenumab (70mg or 140mg monthly)	Topiramate (up to 100mg daily)	Change in monthly headache days, ≥50% responder rate
2	(662)	Chronic	OnabotulinumtoxinA (200 IU quarterly)	Topiramate (up to 100mg daily)	≥50% responder rate
	(663)	Chronic	OnabotulinumtoxinA (100 IU quarterly)	Topiramate (up to 100mg daily)	≥50% responder rate
3	(766)	Any	OnabotulinumtoxinA (100 IU quarterly)	Valproate (500mg daily)	Change in monthly migraine days
4	(590)	Chronic	OnabotulinumtoxinA (250 IU quarterly)	Amitriptyline (25–50 mg daily)	≥50% responder rate
5	(659)	Episodic	Topiramate (50 mg daily)	Valproate (400 mg daily)	Persisting monthly headache days, ≥50% responder rate
6	(880)	Chronic	Topiramate (75 mg daily)	Valproate (750 mg daily)	Change in monthly headache days, ≥50% responder rate
7	(657)	Any	Topiramate (50 mg daily)	Valproate (400 mg daily)	Change in monthly headache days
8	(633)	Episodic	Topiramate (100 mg or 200 mg daily)	Propranolol (160 mg daily)	Change in monthly headache days, ≥50% responder rate
9	(661)	Chronic	Topiramate (100 mg daily)	Propranolol (160 mg daily)	Change in monthly headache days
10	(654)	Any	Topiramate (50 mg daily)	Propranolol (80 mg daily)	Change in monthly headache days
11	(881)	Any	Topiramate (50 mg daily)	Amitriptyline (25–100 mg daily)	≥50% responder rate
12	(590)	Episodic	Topiramate (up to 200 mg daily)	Amitriptyline (up to 150 mg daily)	Persisting monthly headache days
13	(639)	Any	Topiramate (100 mg daily)	Flunarizine (5 mg daily)	Persisting monthly headache days, ≥50% responder rate
14	(644)	Any	Topiramate (50 mg daily)	Lamotrigine (50 mg daily)	Persisting monthly headache days, ≥50% responder rate
15	(628)	Episodic	Topiramate (100 mg daily)	Zonisamide (200 mg daily)	Persisting monthly headache days, ≥50% responder rate
16	(653)	Any	Valproate (400 mg daily)	Cinnarizine (50 mg daily)	Change in monthly headache days, ≥50% responder rate
	(660)	Any	Valproate (600 mg daily)	Cinnarizine (75 mg daily)	Change in monthly headache days, ≥50% responder rate
17	(882)	Any	Valproate (1000 mg daily)	Amitriptyline (100 mg daily)	Persisting monthly headache days
18	(587)	Any	Amitriptyline (75 mg daily)	Venlafaxine (150 mg daily)	Persisting monthly headache days
	(883)	Any	Amitriptyline (25 mg daily)	Venlafaxine (37,5 mg daily)	Persisting monthly headache days
19	(593)	Any	Amitriptyline (50 mg daily)	Citalopram (20 mg daily)	Persisting monthly headache days
20	(884)	Any	Venlafaxine (37.5 mg daily)	Nortriptyline (25 mg daily) + Propranolol (40 mg daily)	Persisting monthly headache days
21	(715)	Any	Propranolol (160 mg daily)	Candesartan (16 mg daily)	Persisting monthly headache days, ≥50% responder rate
22	(711)	Any/Chronic	Propranolol (80 mg daily)	Nortriptyline (40 mg daily)	≥50% responder rate
23	(885)	Any	Metoprolol (200 mg daily)	Flunarizine (10 mg daily)	Change in monthly migraine days
24	(886)	Any	Metoprolol (200 mg daily)	Acetylsalicylic acid (300 mg daily)	Persisting monthly headache

(continued)

Table 4.8.1. (continued)

Question	Reference	Migraine type (Population)	Drug 1	Drug 2	Outcomes
					days, change in monthly headache days
25	(701)	Any	Propranolol (180 mg daily)	Nifedipine (90 mg daily)	Persisting monthly headache days
26	(841)	Any	Galcanezumab (120 mg monthly)	Rimegepant (75 mg eeey other day)	Change in monthly migraine days, ≥50% responder rate
Expert-based opinion	(876)	Any	Valproate (1000–2000 mg daily)	Propranolol (60–240 mg daily)	≥50% responder rate
	(704)	Any	Propranolol (160 mg daily)	Flunarizine (5 or 10 mg daily)	Persisting monthly headache days, ≥50% responder rate
	(702)	Any	Propranolol (40 mg daily)	Flunarizine (10 mg daily)	Persisting monthly headache days, change in monthly headache days
	(706)	Any	Propranolol (160 mg daily)	Flunarizine (10 mg daily)	Persisting monthly headache days, change in monthly headache days
	(877)	Any	Propranolol (60 mg daily)	Flunarizine (10 mg daily)	Persisting monthly headache days
	(707)	Any	Propranolol (80 mg daily)	Timolol (20 mg daily)	-

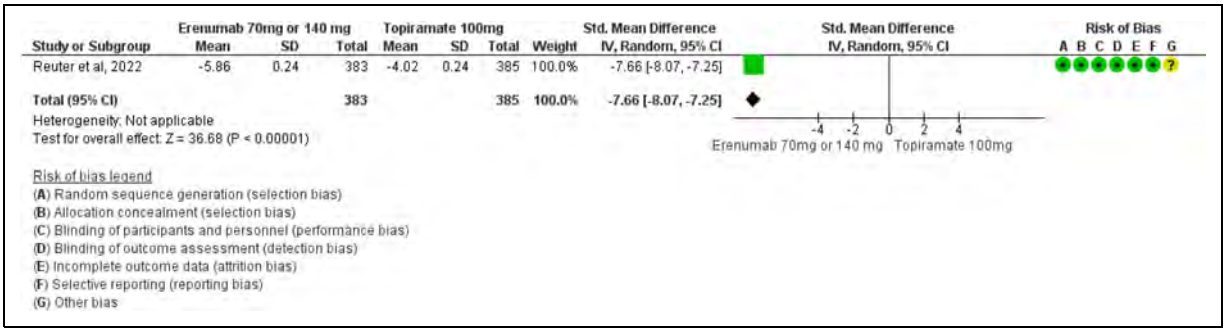


Figure 4.8.2. Forest plot showing the comparison between subcutaneous erenumab (70 mg or 140 mg monthly) and oral topiramate (up to 100 mg daily) for the outcome change in monthly headache days in patients with any migraine (no distinction between episodic and chronic).

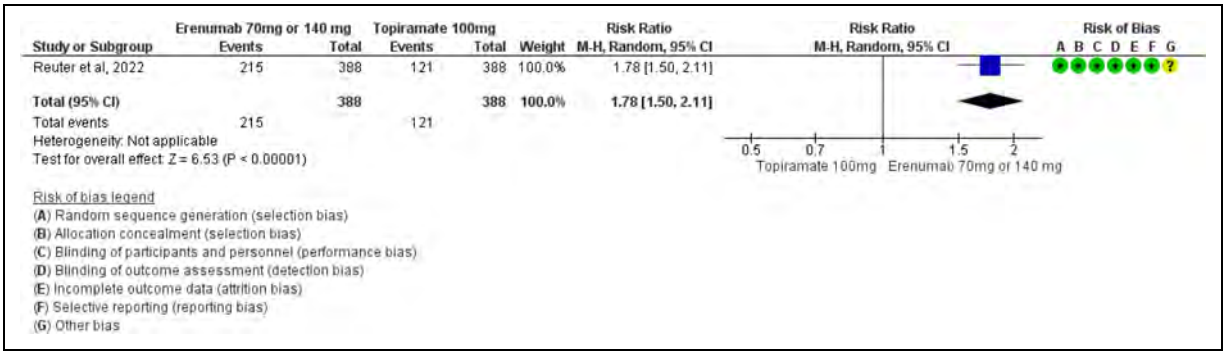


Figure 4.8.3. Forest plot showing the comparison between subcutaneous erenumab (70 mg or 140 mg monthly) and oral topiramate (up to 100 mg daily) for the outcome ≥50% response rate in patients with any migraine (no distinction between episodic and chronic).

Table 4.8.2. GRADE evidence profile table for subcutaneous erenumab versus oral topiramate in any migraine (no distinction between episodic and chronic)

Certainty assessment							№ of patients		Effect			
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Erenumab	Topiramate	Relative (95% CI)	Absolute (95% CI)	Quality	Importance
Change in monthly migraine days - Erenumab 70 or 140 mg subcutaneous vs Topiramate 100 mg oral												
1	RCT	Not serious	Not applicable[a]	Serious[b]	Not serious	None	383	385	-	SMD **7.7 lower** (8.1 lower to 7.3 lower)	⊕⊕⊖⊖ Low	Critical
≥50% responder rate - Erenumab 70 or 140 mg subcutaneous vs Topiramate 100 mg oral												
1	RCT	Not serious	Not applicable[a]	Serious[b]	Not serious	None	215/388 (55.4%)	121/388 (31.2%)	**RR 1.78** (1.50 to 2.11)	**243 more per 1.000** (from 156 more to 346 more)	⊕⊕⊖⊖ Low	Critical

[a]Only one trial; [b]Primary outcome of the trial was tolerability and not efficacy.

rate (Figure 4.8.31). The quality of evidence was considered very low due to the availability of only one RCT and the high risk of bias. It should be mentioned that nortriptyline does not have any placebo-controlled RCT. No recommendation was issued due to the low numbers of participants (<50 per group).

Evidence-based recommendation for PICO 4.8.22

None.

Quality of evidence: -

Strength of recommendation: -

PICO 4.8.23. In subjects with any migraine (no distinction between episodic and chronic), are metoprolol and flunarizine equivalent for migraine prevention (outcomes: change in monthly headache/migraine days, ≥ 50% responder rate)?

Main evidence. We found one RCT comparing metoprolol (200 mg daily) with flunarizine (10 mg daily) in subjects with migraine (876). The risk of bias was unclear (Figure 4.8.32).

The RCT showed superiority of flunarizine over metoprolol for the outcome change in monthly migraine days (Figure 4.8.32). The quality of evidence for the outcome was considered low as there was only one available RCT with low numbers and an unclear risk of bias.

Additional evidence. None.

Evidence-based recommendation for PICO 4.8.23

In subjects with any migraine (no distinction between episodic and chronic), we suggest oral flunarizine (10 mg daily) over oral metoprolol (200 mg daily) for migraine prevention.

Quality of evidence: Low (⊕⊕⊖⊖).

Strength of the recommendation: Weak (↑)

PICO 4.8.24. In subjects with any migraine (no distinction between episodic and chronic), are metoprolol and acetylsalicylic acid equivalent for migraine prevention (outcomes: change in monthly headache/migraine days, persisting monthly headache/migraine days, ≥ 50% responder rate)?

Main evidence. None.

Additional evidence. We found one RCT comparing oral metoprolol (80 mg daily) to oral acetylsalicylic acid (300 mg daily) for migraine prevention (699). The RCT did not meet the quality criteria for main evidence due to the lack of a sample size calculation and had a high risk of bias.

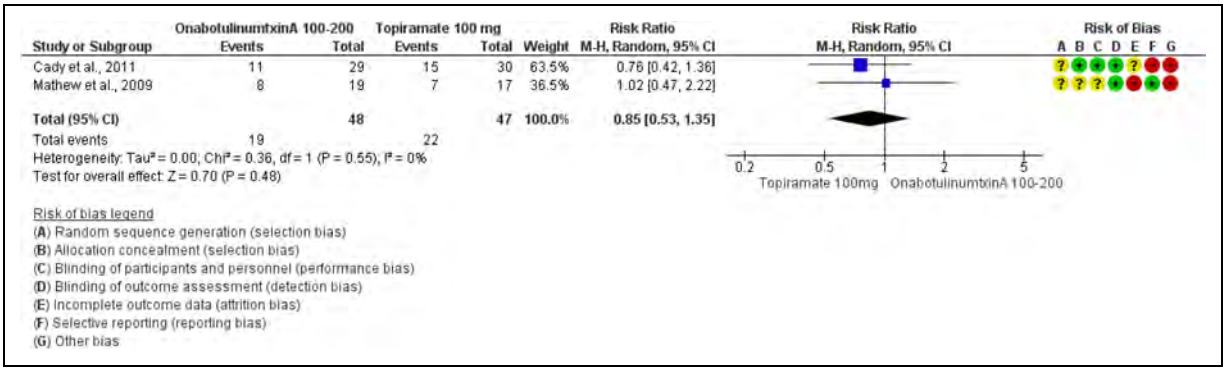


Figure 4.8.4. Forest plot showing the comparison between intramuscular onabotulinumtoxinA (100–200 units) and oral topiramate (up to 100 mg daily) for the outcome ≥50% response rate in patients with chronic migraine.

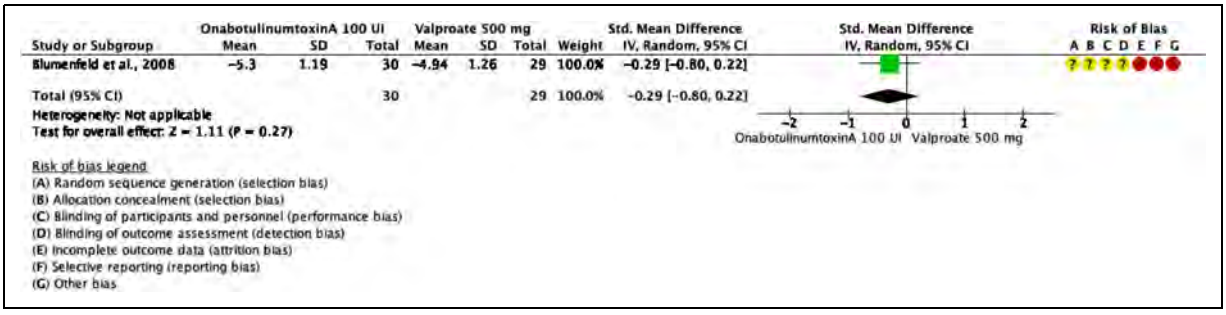


Figure 4.8.5. Forest plot showing the comparison between intramuscular onabotulinumtoxinA (100 units) and oral valproate (250 mg bid) for the outcome change in monthly migraine days in patients with any migraine (no distinction between episodic and chronic).

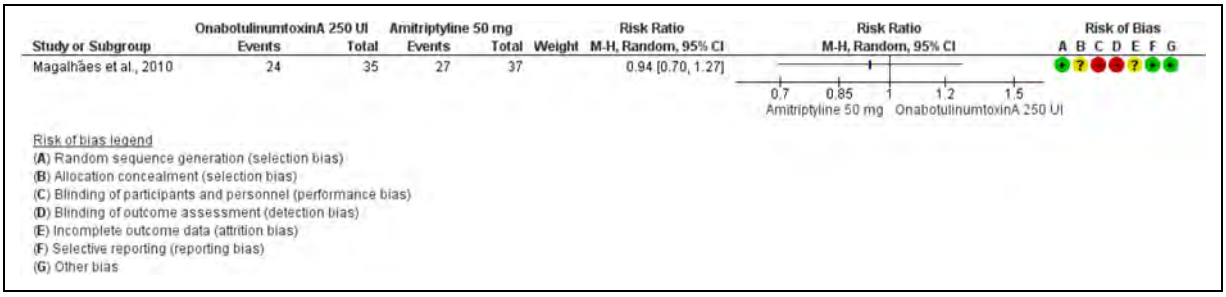


Figure 4.8.6. Forest plot showing the comparison between intramuscular onabotulinumtoxinA (250 U quarterly) and oral amitriptyline (25–50 mg daily) for the outcome ≥50% response rate in patients with chronic migraine.

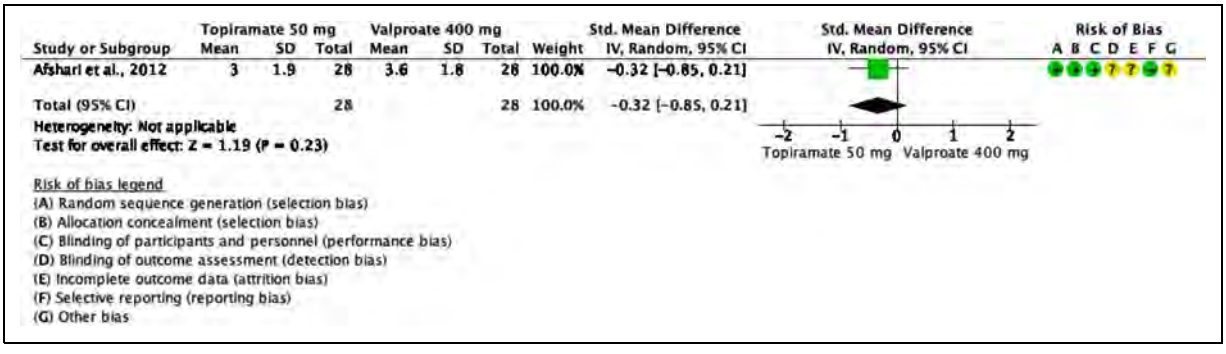


Figure 4.8.7. Forest plot showing the comparison between oral topiramate 50 mg daily and oral valproate 400 mg daily for the outcome persisting monthly headache days in patients with episodic migraine.

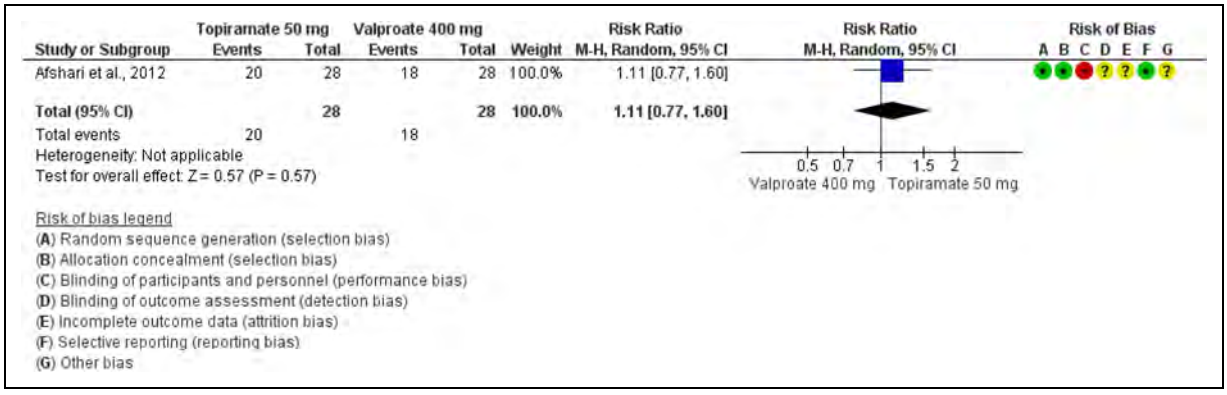


Figure 4.8.8. Forest plot showing the comparison between oral topiramate 50 mg daily and oral valproate 400 mg daily for the outcome ≥50% response rate in patients with episodic migraine.

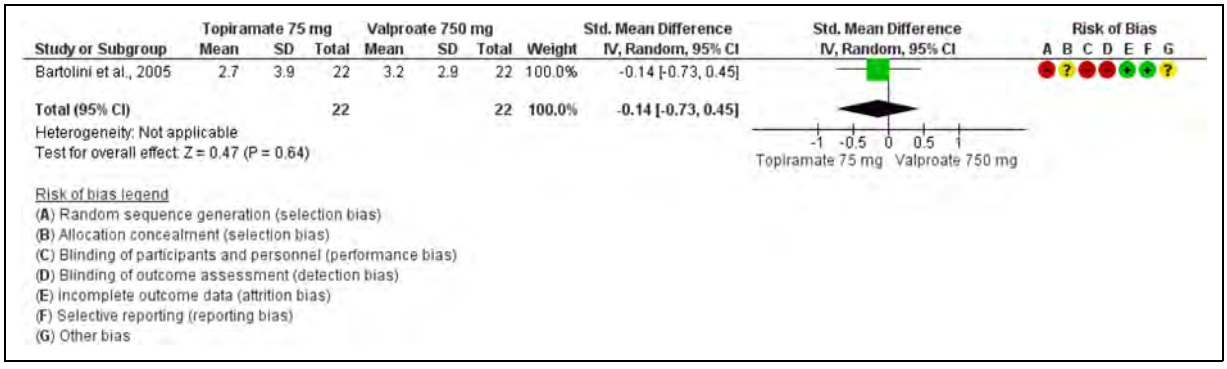


Figure 4.8.9. Forest plot showing the comparison between oral topiramate 75 mg daily and oral valproate 750 mg daily for the outcome persisting monthly headache days in patients with chronic migraine.

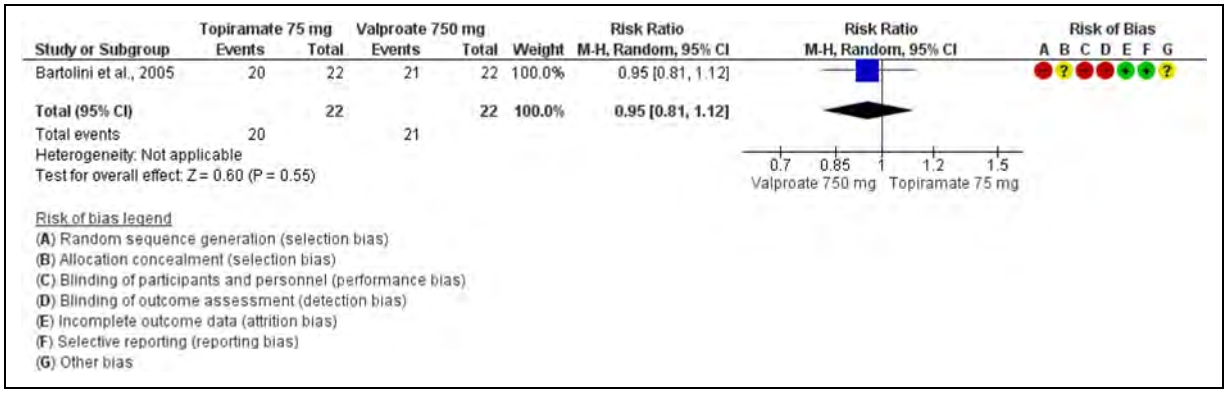


Figure 4.8.10. Forest plot showing the comparison between oral topiramate 75 mg daily and oral valproate 750 mg daily for the outcome ≥50% response rate in patients with chronic migraine.

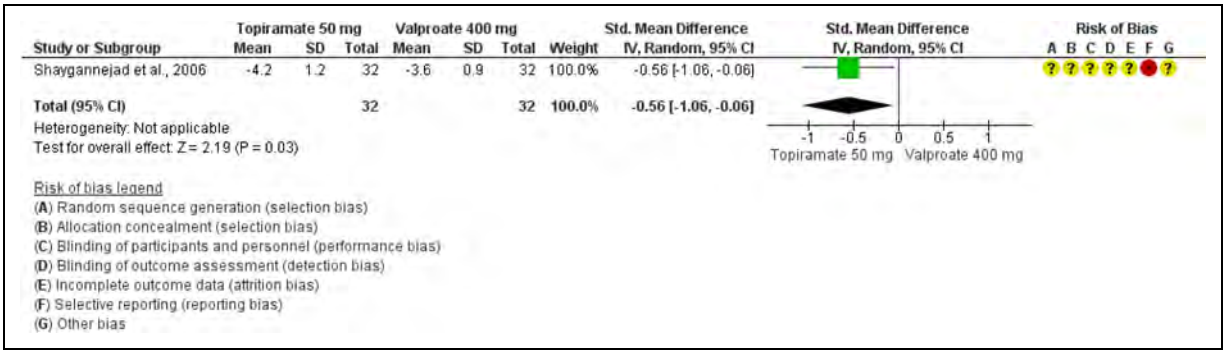


Figure 4.8.11. Forest plot showing the comparison between oral topiramate 50 mg daily and oral valproate 400 mg daily for the outcome change in monthly headache days in patients with any migraine (no distinction between episodic and chronic).

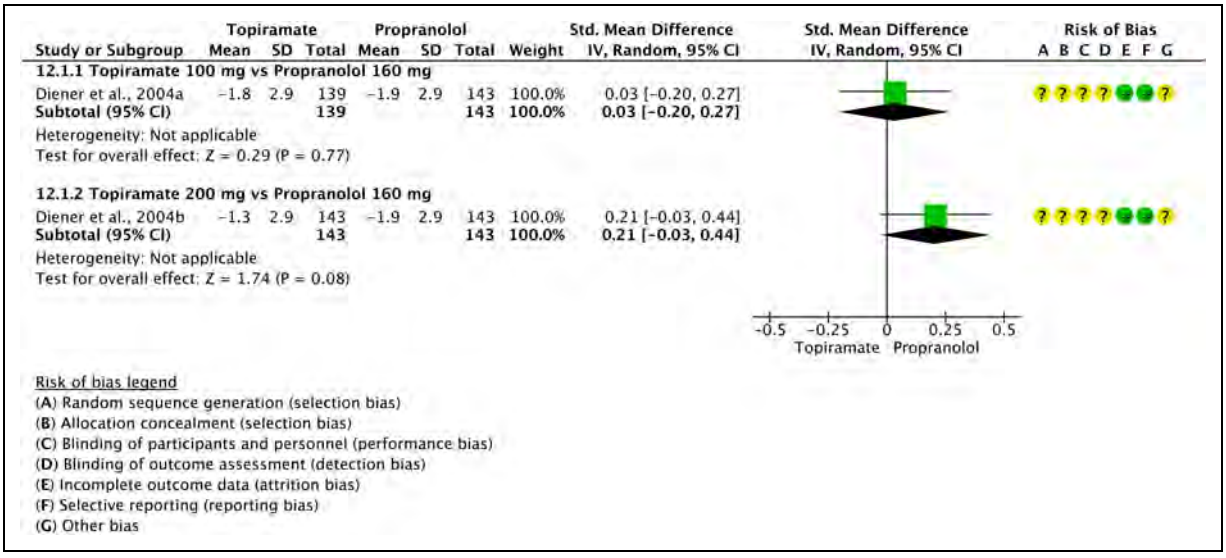


Figure 4.8.12. Forest plot showing the comparison between oral topiramate 100 mg or 200 mg daily and oral propranolol 160 mg daily for the outcome change in monthly headache days in patients with episodic migraine.

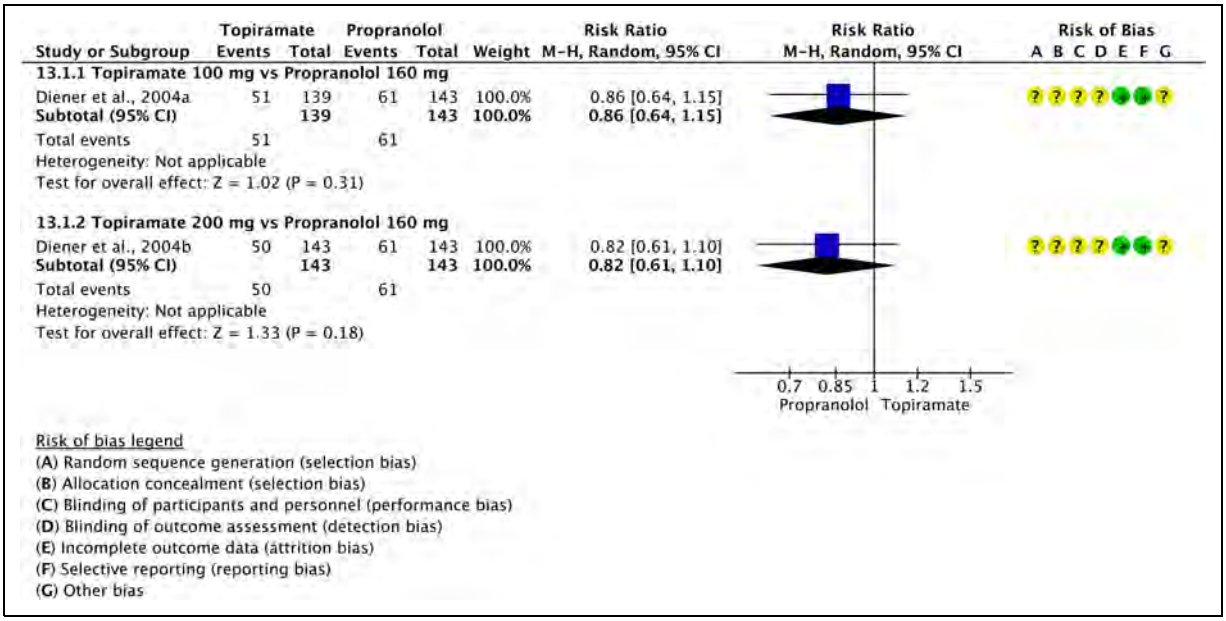


Figure 4.8.13. Forest plot showing the comparison between oral topiramate 100 mg or 200 mg daily and oral propranolol 160 mg daily for the outcome ≥50% response rate in patients with episodic migraine.

Table 4.8.3. GRADE evidence profile table for oral topiramate 100mg or 200mg daily vs oral propranolol 160mg daily in patients with episodic migraine

Certainty assessment							№ of patients		Effect			
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Topiramate	Propranolol	Relative (95% CI)	Absolute (95% CI)	Quality	Importance
Change in monthly headache days - Topiramate 100mg oral vs Propranolol 160mg oral												
1	RCT	Serious	Not applicable[a]	Not serious	Not serious	None	139	143	-	SMD **0.0 higher** (0.2 lower to 0.3 higher)	⊕⊕⊖⊖ Low	Critical
≥50% responder rate - Topiramate 100mg oral vs Propranolol 160mg oral												
1	RCT	Serious	Not applicable[a]	Not serious	Not serious	None	139	143	**RR 0.86** (0.64 to 1.15)	**12 more per 1.000** (from 46 less to 29 more)	⊕⊕⊖⊖ Low	Critical
Change in monthly headache days - Topiramate 200mg oral vs Propranolol 160mg oral												
1	RCT	Serious	Not applicable[a]	Not serious	Not serious	None	143	143	-	**SMD 0.2 higher** (0.0 lower to 0.4 higher)	⊕⊕⊖⊖ Low	Critical
≥50% responder rate - Topiramate 200mg oral vs Propranolol 160mg oral												
1	RCT	Serious	Not applicable[a]	Not serious	Not serious	None	143	143	**RR 0.82** (0.61 to 1.10)	**43 less per 1.000** (from 93 less to 24 more)	⊕⊕⊖⊖ Low	Critical

[a]Only one trial.

Table 4.8.4. GRADE evidence profile table for oral topiramate 100 mg daily vs oral propranolol 160mg daily in patients with chronic migraine

Certainty assessment							№ of patients		Effect			
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Topiramate	Valproate	Relative (95% CI)	Absolute (95% CI)	Quality	Importance
Change in monthly headache days - Topiramate 100mg oral vs Propranolol 160mg oral												
1	RCT	Not serious	Not applicable[a]	Not serious	Not serious	None	93	82	-	SMD **0.2 higher** (0.1 lower to 0.5 higher)	⊕⊕⊕⊖ Moderate	Critical

[a]Only one trial.

Table 4.8.5. GRADE evidence profile table for oral topiramate 50mg daily vs oral propranolol 80mg daily in patients with any migraine (no distinction between episodic and chronic)

Certainty assessment							№ of patients		Effect			
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Topiramate	Valproate	Relative (95% CI)	Absolute (95% CI)	Quality	Importance
Change in monthly headache days - Topiramate 50mg oral vs Propranolol 80mg oral												
1	RCT	Serious	Not applicable[a]	Not serious	Serious[b]	None	30	30	-	SMD **0.6 lower** (1.1 lower to 0.0 lower)	⊕⊕⊖⊖ Low	Critical

[a]Only one trial; [b]low numbers of patients (<50 per group).

Table 4.8.6. GRADE evidence profile table for oral topiramate 100 mg daily vs oral amitriptyline up to 100 mg daily in patients with any migraine (no distinction between episodic and chronic)

Certainty assessment							№ of patients		Effect			
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Topiramate	Amitriptyline	Relative (95% CI)	Absolute (95% CI)	Quality	Importance
≥50% responder rate - Topiramate 100mg oral vs Amitriptyline 25–100mg oral												
1	RCT	Serious	Not applicable[a]	Not serious	Not serious	None	73	95	**RR 0.83** (0.67 to 1.03)	**41 less per 1.000** (from 79 less to 7 more)	⊕⊕⊖⊖ Low	Critical

[a]Only one trial.

Table 4.8.7. GRADE evidence profile table for oral topiramate 50mg daily vs oral lamotrigine 50mg daily in patients with any migraine (no distinction between episodic and chronic)

Certainty assessment							№ of patients		Effect			
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Topiramate	Lamotrigine	Relative (95% CI)	Absolute (95% CI)	Quality	Importance
Monthly headache days - Topiramate 50mg oral vs Lamotrigine 50mg oral												
1	RCT	Very serious	Not applicable[a]	Not serious	Not serious	None	56	57	-	SMD **0.3 lower** (0.6 lower to 0.1 higher)	⊕⊖⊖⊖ Very low	Critical
≥50% responder rate - Topiramate 100mg oral vs Lamotrigine 50mg oral												
1	RCT	Very serious	Not applicable[a]	Not serious	Not serious	None	35/56 (62.5%)	26/57 (45.6%)	**RR 1.37** (0.97 to 1.94)	**138 more per 1.000** (from 11 less to 351 more)	⊕⊖⊖⊖ Very low	Critical

[a]Only one trial.

Table 4.8.8. GRADE evidence profile table for oral propranolol 160 mg daily vs oral candesartan 16 mg daily in patients with any migraine (no distinction between episodic and chronic)

Certainty assessment							№ of patients		Effect			
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Candesartan	Propranolol	Relative (95% CI)	Absolute (95% CI)	Quality	Importance
Change in monthly headache days – Propranolol 160 mg oral vs Candesartan 16 mg oral												
1	RCT	Not serious	Not applicable[a]	Not serious	Not serious	None	56	60	-	**SMD 0.0 higher** (0.4 lower to 0.4 higher)	⊕⊕⊕⊖ Moderate	Critical
≥50% responder rate - Propranolol 160 mg oral vs Candesartan 16mg oral												
1	RCT	Not serious	Not applicable[a]	Not serious	Not serious	None	24/56 (42.9%)	24/60 (40.0%)	**RR 1.07** (0.69 to 1.65)	**26 more per 1.000** (from 116 less to 243 more)	⊕⊕⊕⊖ Moderate	Critical

[a]Only one trial.

Table 4.8.9. GRADE evidence profile table for oral metoprolol 200 mg daily versus oral flunarizine 10 mg daily in patients with any migraine (no distinction between episodic and chronic)

Certainty assessment							№ of patients		Effect			
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Metoprolol	Flunarizine	Relative (95% CI)	Absolute (95% CI)	Quality	Importance
Change in monthly migraine days – Metoprolol 200 mg oral vs Flunarizine 10 mg oral												
1	RCTs	Serious	Not applicable[a]	Not serious	Not serious	None	69	58	-	**SMD 2.9 higher** (2.4 higher to 3.4 higher)	⊕⊕⊖⊖ Low	Critical

[a]Only one trial.

Table 4.8.10. GRADE evidence profile table for subcutaneous galcanezumab (120 mg monthly with 240 mg loading dose) vs oral rimegepant dispersible tablets (75 mg every other day) in patients with any migraine (no distinction between episodic and chronic)

Certainty assessment							№ of patients		Effect				
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Galcanezumab	Rimegepant	Relative (95% CI)	Absolute (95% CI)	Quality	Importance
Change in monthly headache days – Galcanezumab 120 mg monthly subcutaneous vs Rimegepant 75 mg every other day oral												
1	RCT	Not serious	Not applicable[a]	Not serious	Not serious	None	269	284	-	**SMD 0.2 lower** (0.3 lower to 0.0 higher)	⊕⊕⊕⊖ Moderate	Critical
≥50% responder rate - Galcanezumab 120 mg monthly subcutaneous vs Rimegepant 75 mg every other day oral												
1	RCT	Not serious	Not applicable[a]	Not serious	Not serious	None	167/269 (62.1%)	173/284 (60.9%)	**RR 1.02** (0.89 to 1.16)	**12 more per 1.000** (from 67 less to 97 more)	⊕⊕⊕⊖ Moderate	Critical

[a]Only one trial.

The study showed superiority of metoprolol over acetylsalicylic acid for the outcomes of persisting monthly headache days (Figure 4.8.33) and change in monthly headache days (Figure 4.8.34). The quality of evidence was considered very low due to the availability of only one RCT and the high risk of bias.

Additional evidence. None.

Evidence-based recommendation for PICO 4.8.24

In subjects with any migraine (no distinction between episodic and chronic), we suggest oral metoprolol (200 mg daily) over oral acetylsalicylic acid (300 mg daily) for migraine prevention.
Quality of evidence: Very low (⊕⊖⊖⊖)
Strength of the recommendation: Weak (↑)

PICO 4.8.25. In subjects with any migraine (no distinction between episodic and chronic), are propranolol and nifedipine equivalent for migraine prevention (outcomes: change in monthly headache/migraine days, persisting monthly headache/migraine days, ≥ 50% responder rate)?

Main evidence. None.

Additional evidence. We found one RCT comparing oral propranolol (60 mg three times per day - TID) to nifedipine (30 mg three times per day - TID) for migraine prevention (701). The RCT did not meet the criteria for main evidence (Figure 4.8.35) due to the lack of a pre-specified sample size calculation and had a high risk of bias.

The study showed not significant difference between the two drugs for the outcome of persisting monthly headache days (Figure 4.8.35). The quality of evidence was considered very low due to the availability of only one RCT and the high risk of bias. No recommendation was issued due to the low numbers of participants (<50 per group).

Evidence-based recommendation for PICO 4.8.25

None.
Quality of evidence: -
Strength of recommendation: -

PICO 4.8.26. In subjects with episodic migraine, are galcanezumab and rimegepant equivalent for migraine prevention (outcomes: change in monthly headache/migraine days, persisting monthly headache/migraine days, ≥ 50% responder rate)?

Main evidence. We found one RCT comparing subcutaneous galcanezumab 120 mg monthly (with 240 mg loading dose) with oral rimegepant 75 mg (dispersible tablets) every

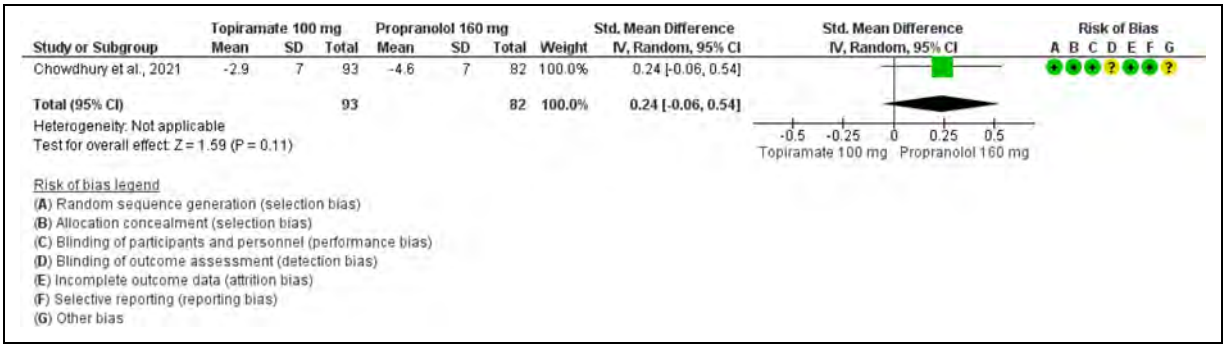


Figure 4.8.14. Forest plot showing the comparison between oral topiramate 100 mg daily and oral propranolol 160 mg daily for the outcome change in monthly headache days in patients with chronic migraine.

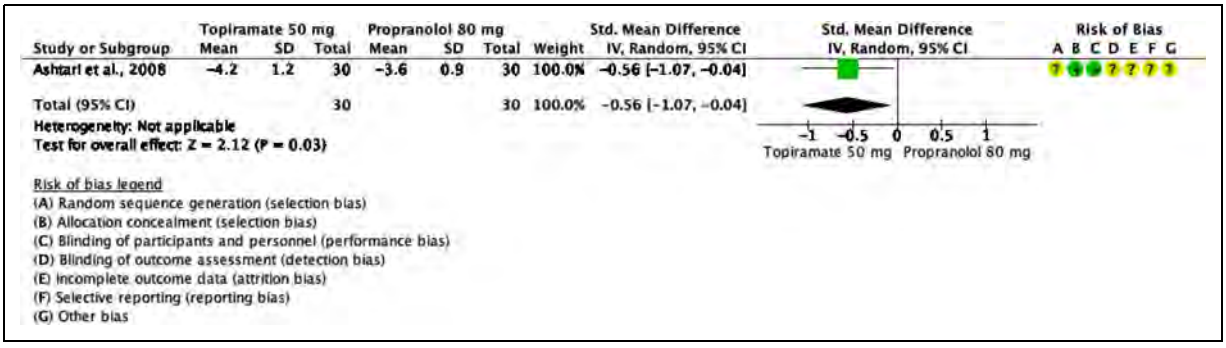


Figure 4.8.15. Forest plot showing the comparison between oral topiramate 50 mg daily and oral propranolol 80 mg daily for the outcome change in monthly headache days in patients with any migraine (no distinction between episodic and chronic).

other day (842) that met the criteria for main evidence. The risk of bias was considered low. The RCT showed no difference between galcanezumab and rimegepant considering the outcome of change in monthly migraine days (Figure 4.8.36) and ≥50% response rate (Figure 4.8.37). The quality of evidence was considered moderate (Table 4.8.25) due to the availability of only one RCT.

Additional evidence. None.

Evidence-based recommendation for PICO 4.8.26

In subjects with episodic migraine, we recommend subcutaneous galcanezumab (120 mg monthly with 240 mg loading dose) and oral rimegepant dispersible tablets (75 mg every other day) as equivalent options for migraine prevention.
Quality of evidence: Moderate (⊕⊕⊕⊖)
Strength of recommendation: Strong (=)

Safety and tolerability of galcanezumab compared with rimegepant. Both galcanezumab and rimegepant act on the CGRP pathway, the former as a ligand and the latter as a receptor antagonist. The safety profile of both drugs is excellent due to their specific mechanism of action. Both drugs should be used with caution in patients with previous vascular events, Raynaud's phenomenon, severe constipation, and bowel disease (see Sections 4.6 and 4.7). Given the equivalent efficacy of the two drugs, patients' preference and attitude toward the route of administration (oral or subcutaneous) is important. The oral route might be preferable for patients who do not manage injections, while the subcutaneous route could be preferable in those with poor compliance to oral medications.

Summary of evidence for head-to-head comparison trials of preventive treatments

Figure 4.8.38 shows the summary of evidence for comparisons reported in the present section.

Expert-based opinion

Topic: Other head-to-head comparisons between preventive treatments. Suggestion 1: In subjects with any migraine (no distinction between episodic and chronic), valproate

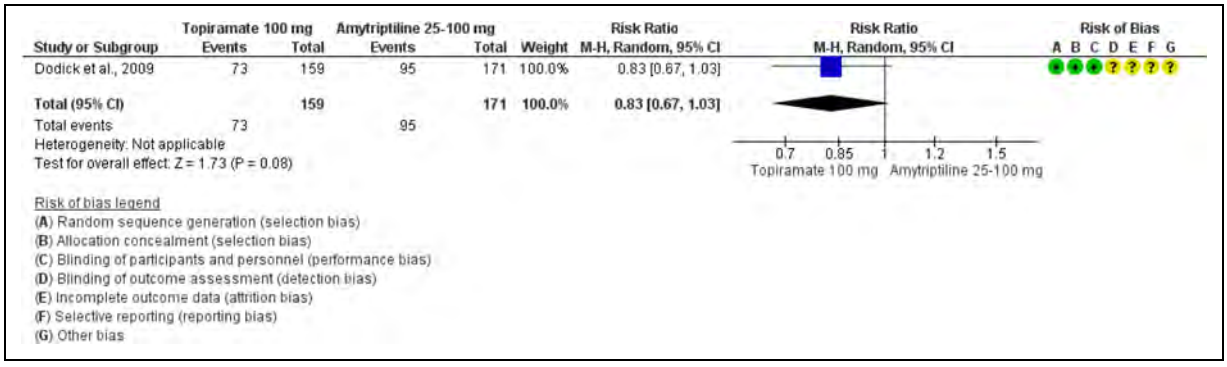


Figure 4.8.16. Forest plot showing the comparison between oral topiramate 100 mg daily and oral amitriptyline 25–100 mg daily for the outcome ≥50% response rate in patients with any migraine (no distinction between episodic and chronic).

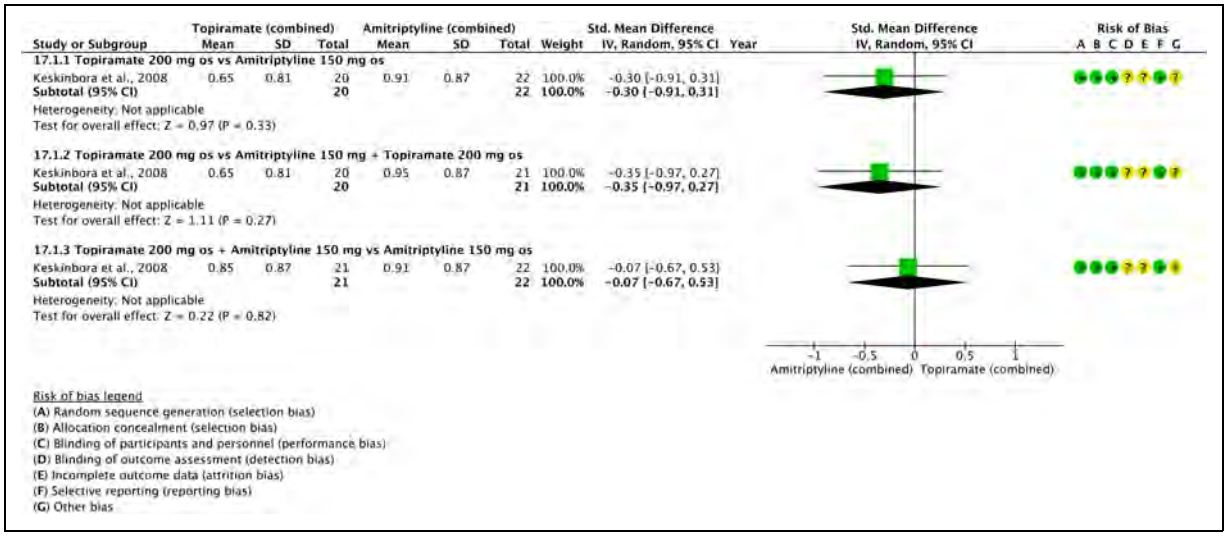


Figure 4.8.17. Forest plot showing the comparison between oral topiramate 200 mg daily and oral amitriptyline 150 mg daily for the outcome monthly headache days in patients with episodic migraine.

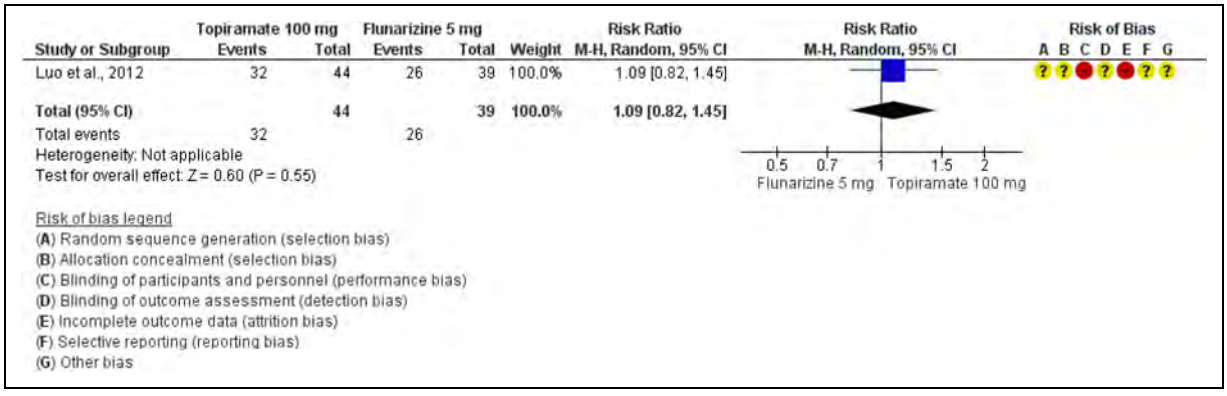


Figure 4.8.18. Forest plot showing the comparison between oral topiramate 100 mg and oral flunarizine 5 mg daily for the outcome 50% response rate in patients with any migraine (no distinction between episodic and chronic).

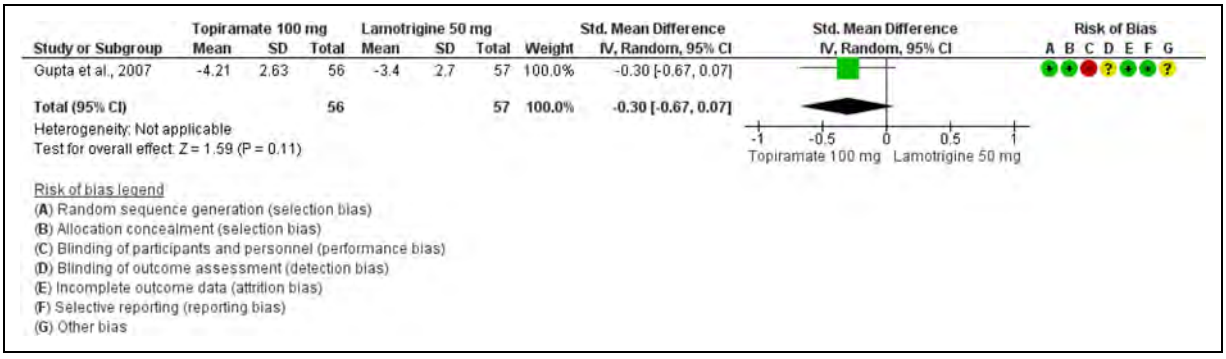


Figure 4.8.19. Forest plot showing the comparison between oral topiramate 50 mg and oral lamotrigine 50 mg daily for the outcome change in monthly headache days in patients with any migraine (no distinction between episodic and chronic).

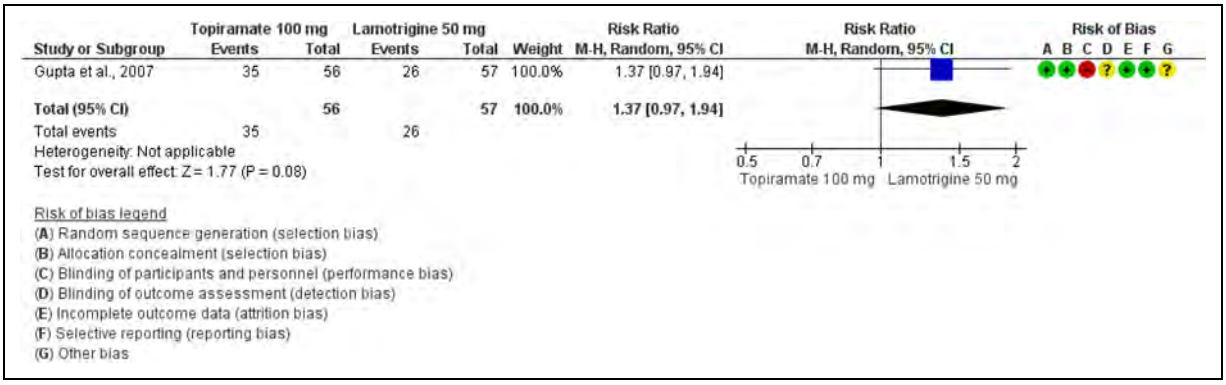


Figure 4.8.20. Forest plot showing the comparison between oral topiramate 50 mg and oral lamotrigine 50 mg daily for the outcome ≥50% response rate in patients with any migraine (no distinction between episodic and chronic).

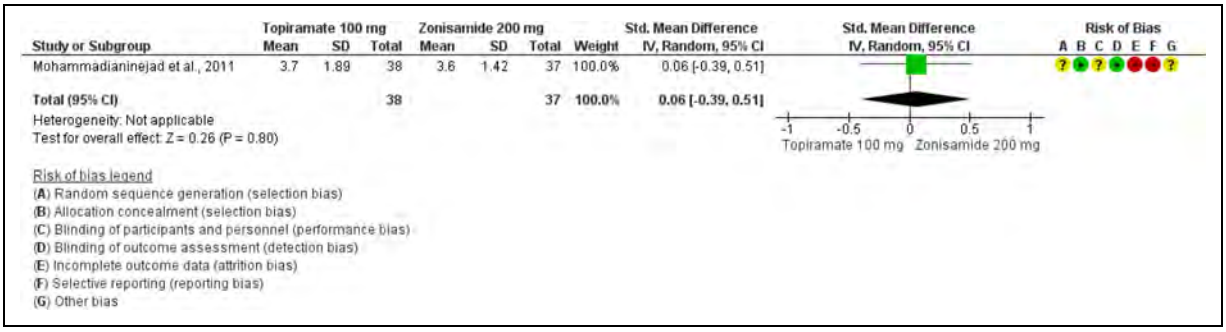


Figure 4.8.21. Forest plot showing the comparison between oral topiramate 100 mg and oral zonisamide 200 mg daily for the outcome persisting monthly headache days in patients with episodic migraine.

and propranolol might be equivalent for migraine prevention.

Rationale 1: We found one RCT comparing valproate (1000–2000 mg daily) to propranolol (60–180 mg daily) in subjects with migraine (877). The RCT was single-blinded and did not meet the pre-defined quality criteria and for this reason the quality of evidence was considered very low. The RCT included 32 subjects, 15 randomized to divalproex and 17 to propranolol, followed-up for 12 weeks. No difference was found between the two drugs

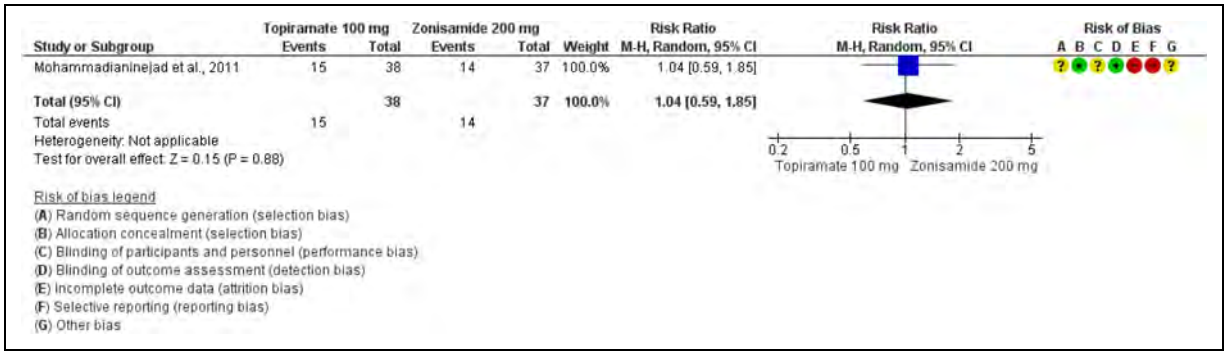


Figure 4.8.22. Forest plot showing the comparison between oral topiramate 100 mg and oral zonisamide 200 mg daily for the outcome ≥50% response rate in patients with episodic migraine.

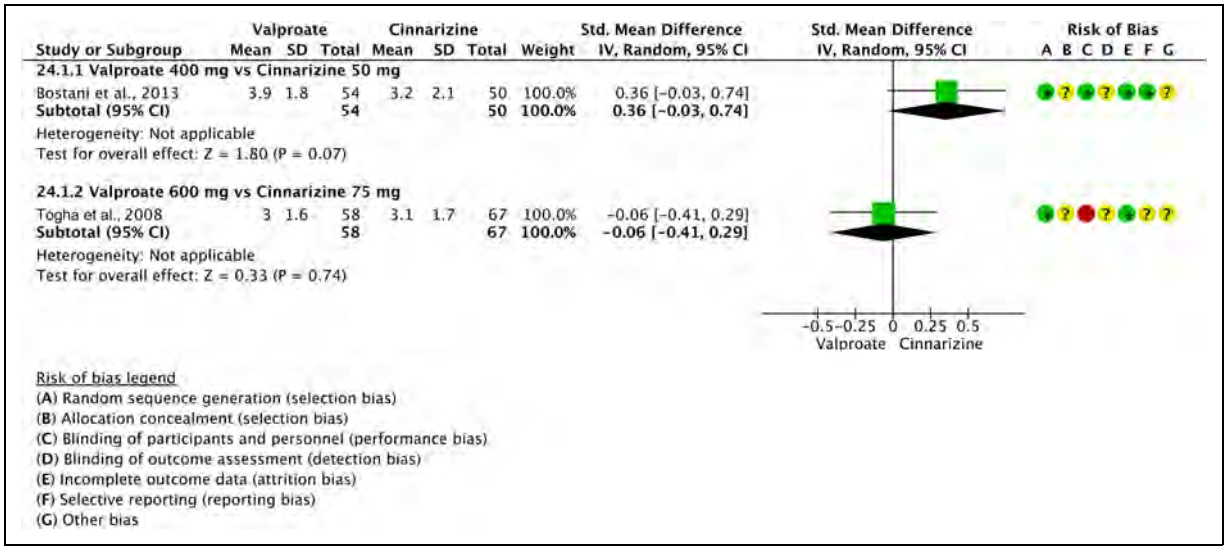


Figure 4.8.23. Forest plot showing the comparison between oral valproate (400 or 600 mg daily) and oral cinnarizine (50 or 75 mg daily) for the outcome persisting monthly headache days in patients with episodic migraine.

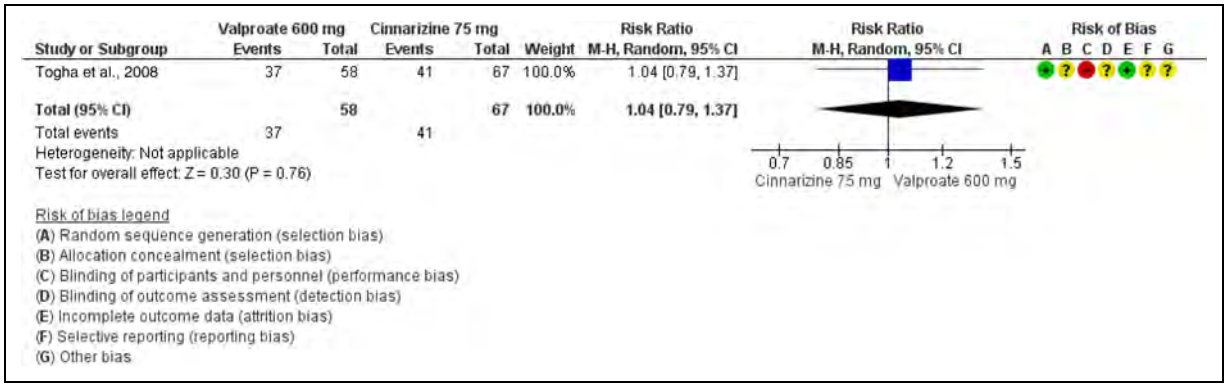


Figure 4.8.24. Forest plot showing the comparison between oral valproate (600 mg daily) and oral cinnarizine (75 mg daily) for the outcome ≥50% response rate in patients with episodic migraine.

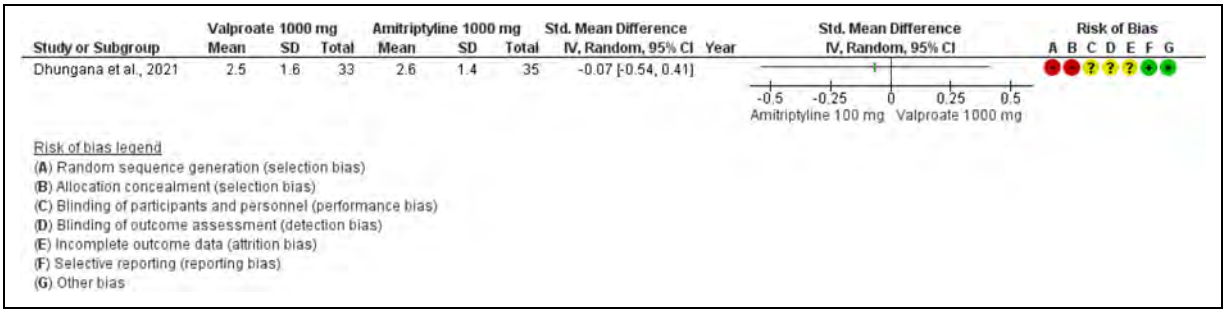


Figure 4.8.25. Forest plot showing the comparison between valproate (1000 mg daily) and amitriptyline (100 mg daily) for the outcome persisting monthly headache days in patients with episodic migraine.

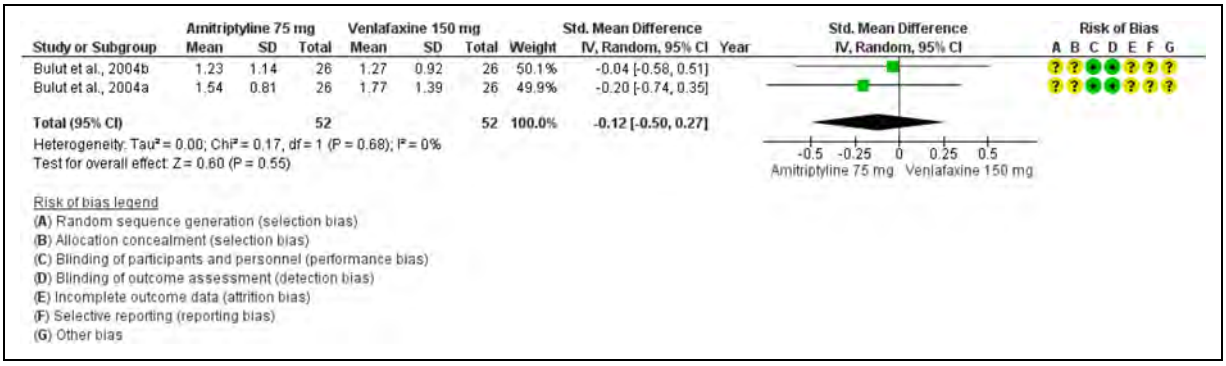


Figure 4.8.26. Forest plot showing the comparison between oral amitriptyline 75 mg daily and oral venlafaxine 150 mg daily for the outcome persisting monthly headache days in patients with migraine (no distinction between episodic and chronic).

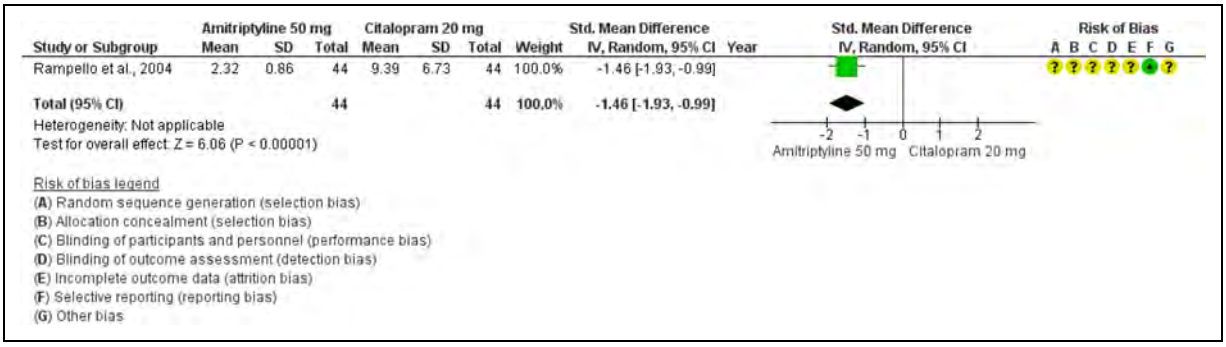


Figure 4.8.27. Forest plot showing the comparison between oral amitriptyline 50 mg daily and oral citalopram 20 mg daily for the outcome persisting monthly headache days in patients with any migraine (no distinction between episodic and chronic).

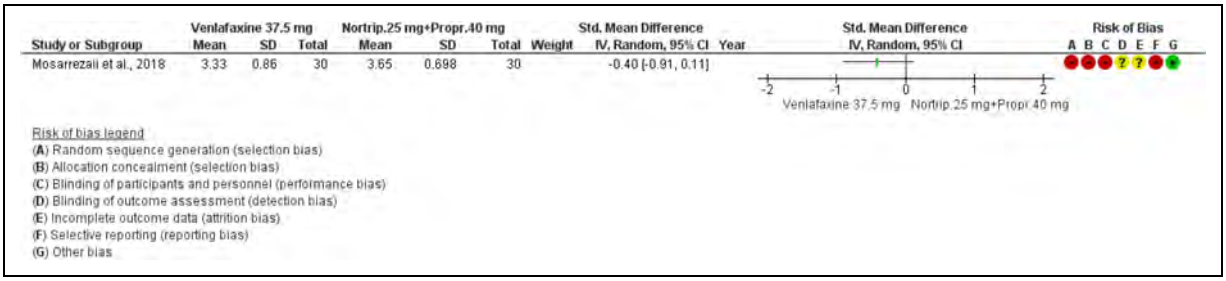


Figure 4.8.28. Forest plot showing the comparison between oral venlafaxine 37.5 mg daily and oral nortriptyline 25 mg daily plus propranolol 40 mg daily for the outcome persisting monthly headache days in patients with any migraine (no distinction between episodic and chronic).

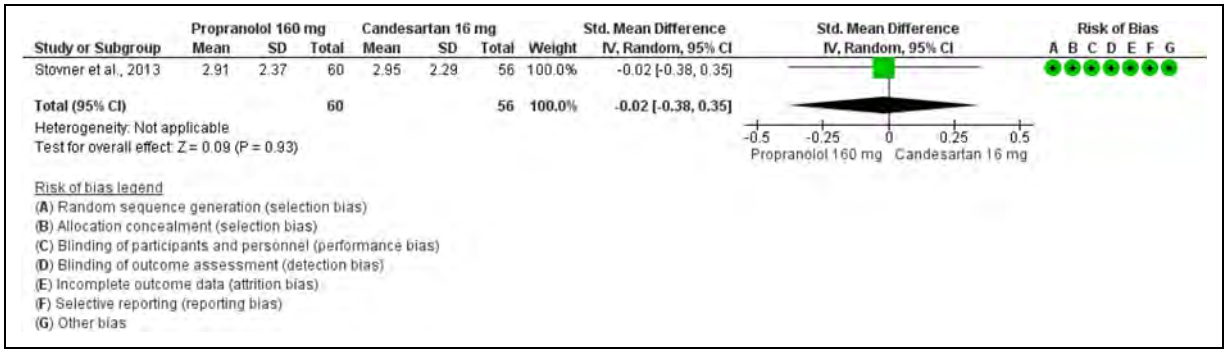


Figure 4.8.29. Forest plot showing the comparison between oral propranolol 160 mg daily and oral candesartan 16 mg daily for the outcome persisting monthly headache days in patients with any migraine (no distinction between episodic and chronic).

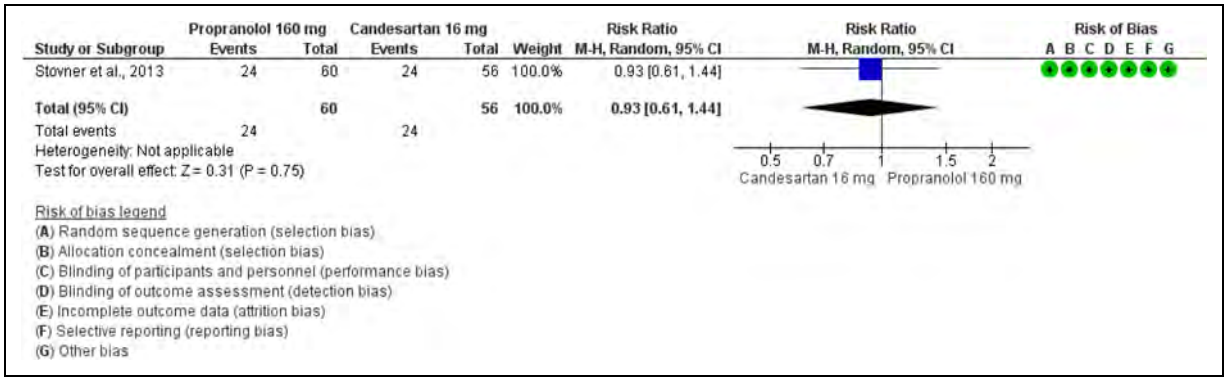


Figure 4.8.30. Forest plot showing the comparison between oral propranolol 160 mg daily and oral candesartan 16 mg daily for the outcome ≥50% response rate in patients with any migraine (no distinction between episodic and chronic).

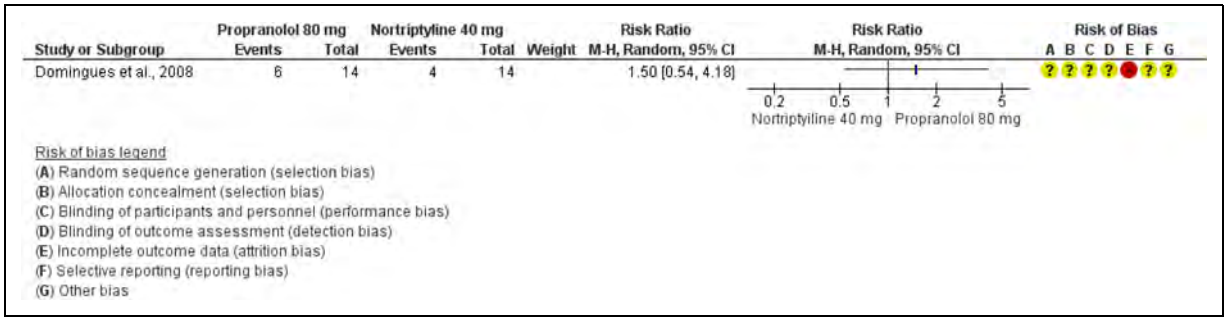


Figure 4.8.31. Forest plot showing the comparison between propranolol 80 mg daily and nortriptyline 40 mg daily for the outcome ≥50% response rate in patients with any migraine (no distinction between episodic and chronic).

considering change in monthly migraine days and ≥50% response rate.

Suggestion 2: In subjects with episodic migraine, propranolol and flunarizine might be equivalent for migraine prevention.

Rationale 2: We found one RCT comparing propranolol (160 mg daily) to flunarizine (5–10 mg daily) in subjects with episodic migraine (704). The RCT met the quality criteria, but did not measure the requested efficacy parameters, as it assessed migraine attacks instead of migraine days.

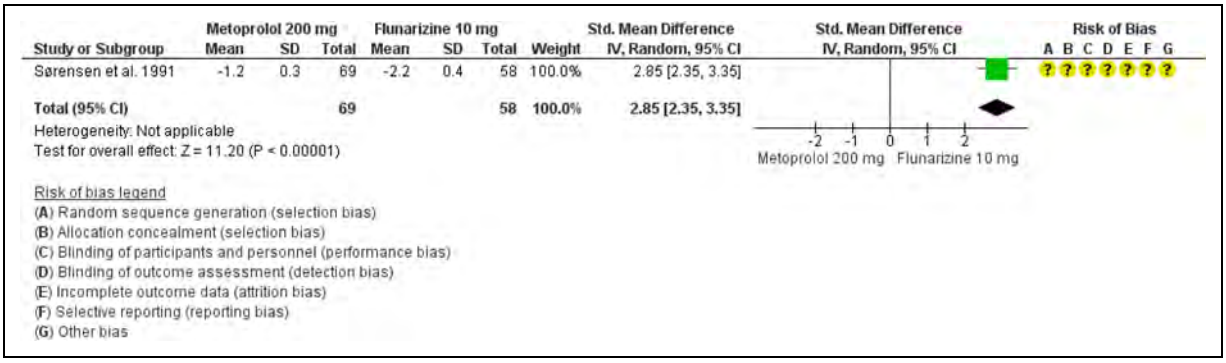


Figure 4.8.32. Forest plot showing the comparison between oral metoprolol 200 mg daily and oral flunarizine 10 mg daily for the outcome change in monthly migraine days in patients with any migraine (no distinction between episodic and chronic).

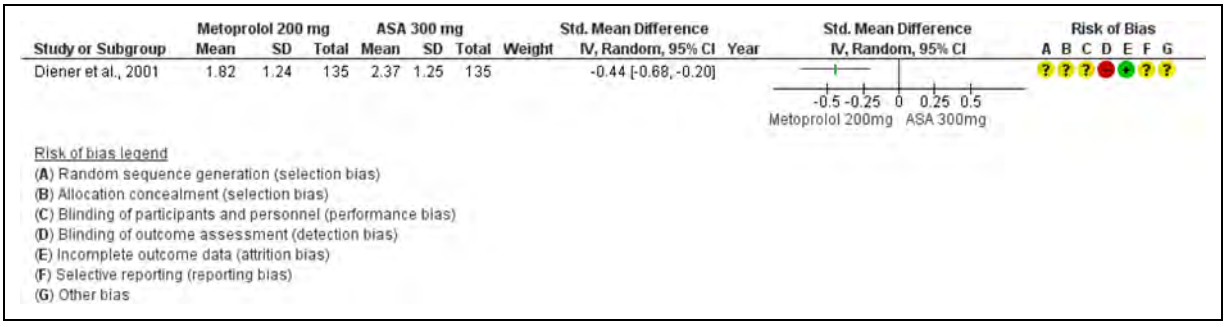


Figure 4.8.33. Forest plot showing the comparison between oral metoprolol 200 mg daily and oral acetylsalicylic acid 300 mg daily for the outcome persisting monthly headache days in patients with any migraine (no distinction between episodic and chronic).

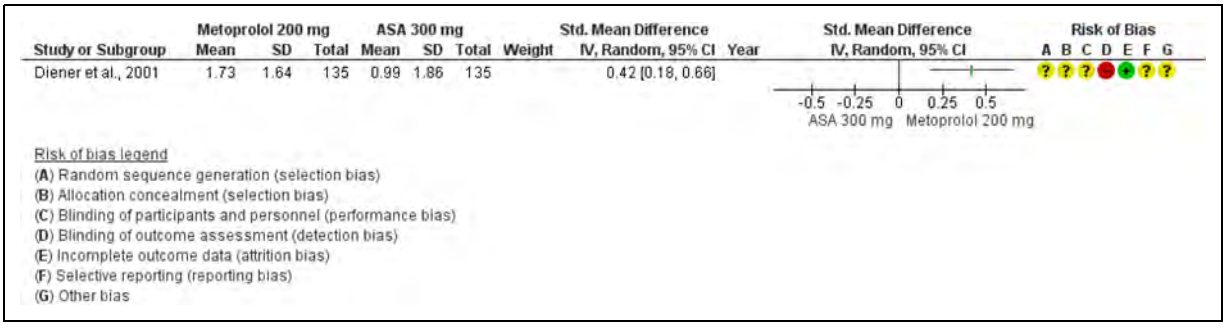


Figure 4.8.34. Forest plot showing the comparison between oral metoprolol 200 mg daily and oral acetylsalicylic acid 300 mg daily for the outcome change in monthly headache days in patients with any migraine (no distinction between episodic and chronic).

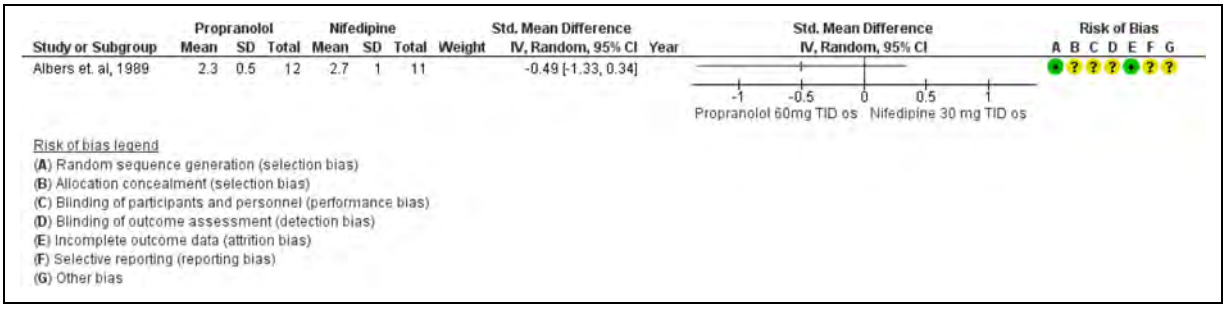


Figure 4.8.35. Forest plot showing the comparison between oral propranolol 60 mg three times per day and oral nifedipine 30 mg three times per day for the outcome persisting monthly headache days in patients with any migraine (no distinction between episodic and chronic).

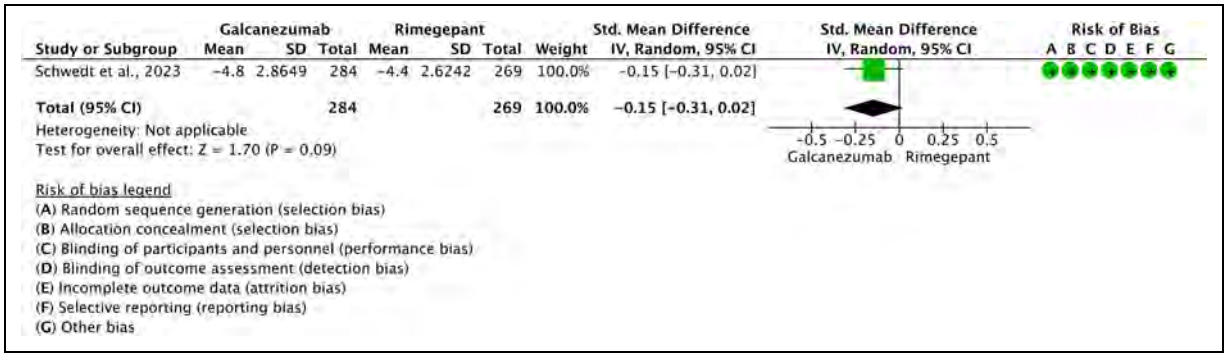


Figure 4.8.36. Forest plot showing the comparison between subcutaneous galcanezumab (120 mg monthly with 240 mg loading dose) and oral rimegepant dispersible tablet (75 mg every other day) for the outcome change in monthly migraine days in patients with any migraine (no distinction between episodic and chronic).

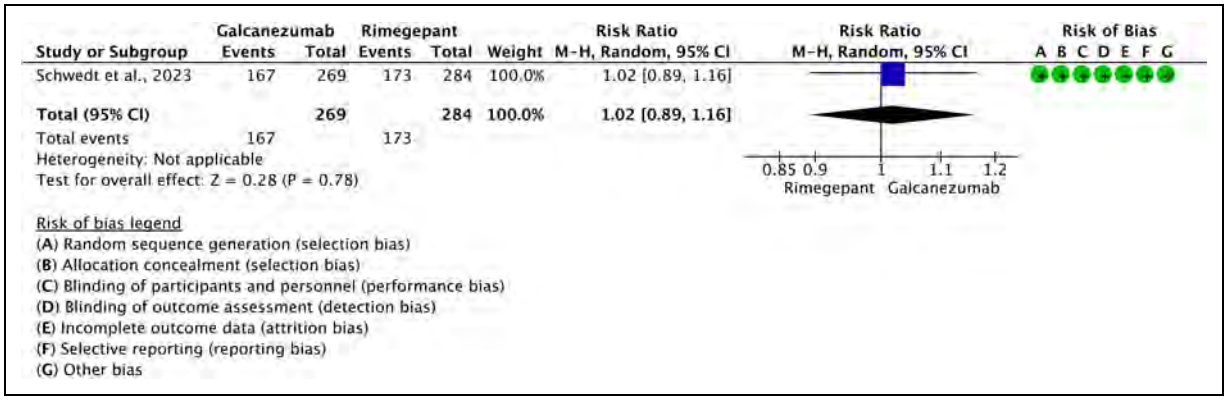


Figure 4.8.37. Forest plot showing the comparison between subcutaneous galcanezumab (120 mg monthly with 240 mg loading dose) and oral Rimegepant dispersible tablet (75 mg every other day) for the outcome ≥50% response rate in patients with episodic migraine.

The RCT randomized 808 subjects with episodic migraine to flunarizine 5 mg daily (n = 263), flunarizine 10 mg daily (n = 275) or propranolol 160 mg daily (n = 270). Mean (95% confidence interval) monthly migraine attacks decreased from 3.1 (2.3–3.9) to 2.0 (1.8–2.2) in the flunarizine 5 mg group, from 3.0 (2.1–3.8) to 1.9 (1.7–2.1) in the flunarizine 10 mg group, and from 3.0 (2.9–3.2) to 1.9 (1.7–2.0) in the propranolol 160 mg group. All decreases were statistically significant. Proportions of responders – defined as ≥50% decrease in migraine attacks from run-in to follow-up – were 36% for flunarizine 5 mg, 44% for flunarizine 10 mg, and 44% for propranolol 160 mg. The study did not show differences between propranolol and flunarizine. Adverse events occurred in 47.7% of subjects in the flunarizine 5 mg group, 35.8% in the flunarizine 10 mg group, and 40.0% in the propranolol 160 mg group; proportions were comparable.

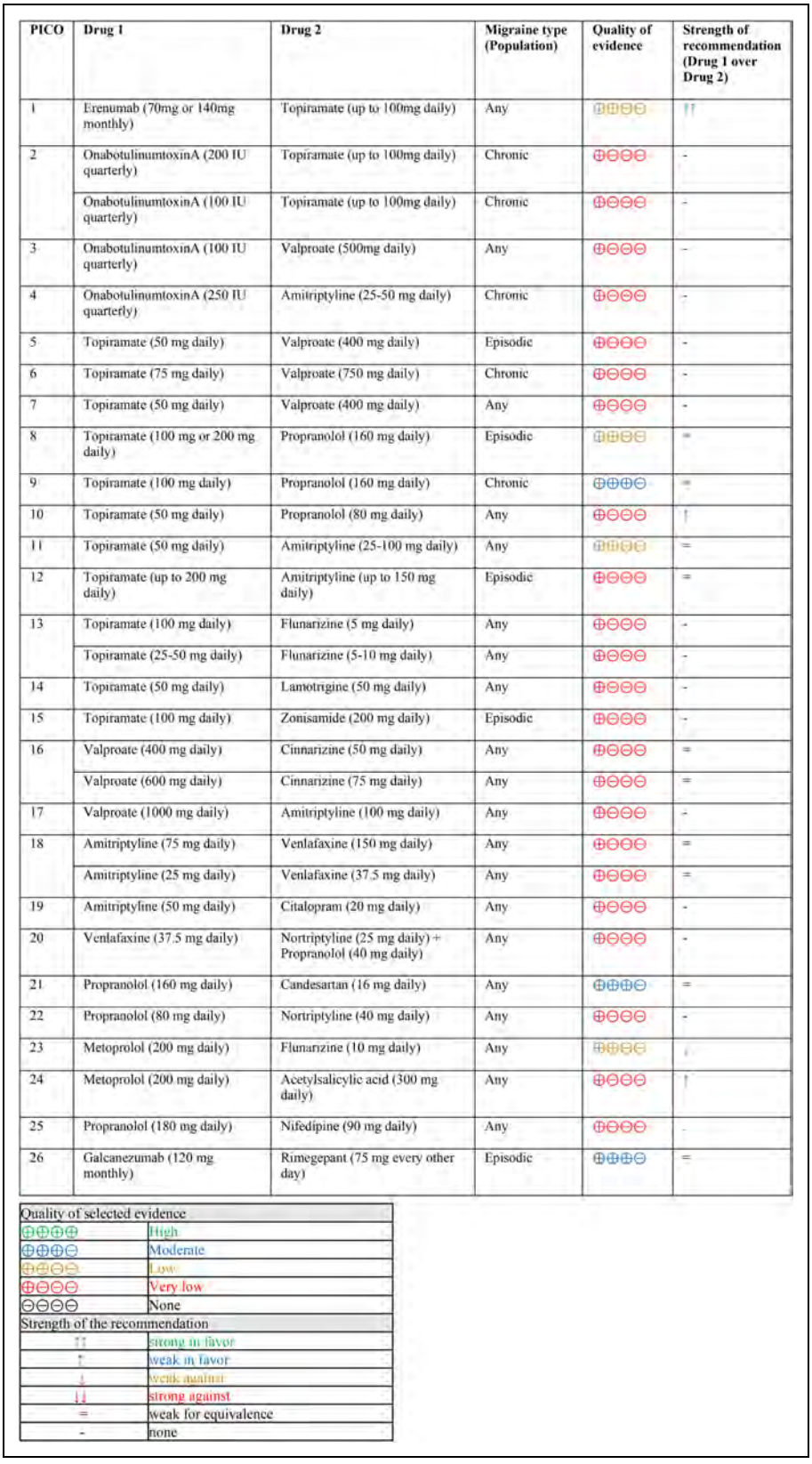
Suggestion 3: In subjects with any migraine (no distinction between episodic and chronic), propranolol and flunarizine might be equivalent for migraine prevention.

Rationale 3: We found three RCTs comparing propranolol with flunarizine in subjects with migraine (702,706,878). None of those studies considered the efficacy outcomes of the present guidelines; therefore, they were excluded from the evidence base. The first RCT (706) compared flunarizine 10 mg daily with propranolol 40 mg daily, while the second (878) compared flunarizine 10 mg daily with propranolol 80 mg BID and the third (702) compared flunarizine 10 mg daily with propranolol 60 mg daily and with a combination of the two drugs. All three RCTs showed similar efficacy between the two drugs.

Suggestion 5: In subjects with any migraine (no distinction between episodic and chronic), propranolol and timolol might be equivalent for migraine prevention.

Rationale 5: We found one RCT comparing propranolol (80 mg daily) to timolol (20 mg daily) for migraine prevention (707). The RCT did not meet the quality criteria due to the lack of a pre-specified sample size calculation and had a high risk of bias. The study did not assess the outcomes included in the present guidelines; it showed that migraine attacks decreased significantly from baseline to follow-up in both groups.

Topic: Which is the best sequence of oral preventive treatments for migraine?. Suggestion: There is no definite treatment sequence.



PICO	Drug 1	Drug 2	Migraine type (Population)	Quality of evidence	Strength of recommendation (Drug 1 over Drug 2)
1	Erenumab (70mg or 140mg monthly)	Topiramate (up to 100mg daily)	Any	⊕⊖⊖⊖	↑↑
2	OnabotulinumtoxinA (200 IU quarterly)	Topiramate (up to 100mg daily)	Chronic	⊕⊖⊖⊖	-
	OnabotulinumtoxinA (100 IU quarterly)	Topiramate (up to 100mg daily)	Chronic	⊕⊖⊖⊖	-
3	OnabotulinumtoxinA (100 IU quarterly)	Valproate (500mg daily)	Any	⊕⊖⊖⊖	-
4	OnabotulinumtoxinA (250 IU quarterly)	Amitriptyline (25-50 mg daily)	Chronic	⊕⊖⊖⊖	-
5	Topiramate (50 mg daily)	Valproate (400 mg daily)	Episodic	⊕⊖⊖⊖	-
6	Topiramate (75 mg daily)	Valproate (750 mg daily)	Chronic	⊕⊖⊖⊖	-
7	Topiramate (50 mg daily)	Valproate (400 mg daily)	Any	⊕⊖⊖⊖	-
8	Topiramate (100 mg or 200 mg daily)	Propranolol (160 mg daily)	Episodic	⊕⊕⊖⊖	=
9	Topiramate (100 mg daily)	Propranolol (160 mg daily)	Chronic	⊕⊕⊕⊖	=
10	Topiramate (50 mg daily)	Propranolol (80 mg daily)	Any	⊕⊖⊖⊖	↑
11	Topiramate (50 mg daily)	Amitriptyline (25-100 mg daily)	Any	⊕⊕⊖⊖	=
12	Topiramate (up to 200 mg daily)	Amitriptyline (up to 150 mg daily)	Episodic	⊕⊖⊖⊖	=
13	Topiramate (100 mg daily)	Flunarizine (5 mg daily)	Any	⊕⊖⊖⊖	-
	Topiramate (25-50 mg daily)	Flunarizine (5-10 mg daily)	Any	⊕⊖⊖⊖	-
14	Topiramate (50 mg daily)	Lamotrigine (50 mg daily)	Any	⊕⊖⊖⊖	-
15	Topiramate (100 mg daily)	Zonisamide (200 mg daily)	Episodic	⊕⊖⊖⊖	-
16	Valproate (400 mg daily)	Cinnarizine (50 mg daily)	Any	⊕⊖⊖⊖	=
	Valproate (600 mg daily)	Cinnarizine (75 mg daily)	Any	⊕⊖⊖⊖	=
17	Valproate (1000 mg daily)	Amitriptyline (100 mg daily)	Any	⊕⊖⊖⊖	-
18	Amitriptyline (75 mg daily)	Venlafaxine (150 mg daily)	Any	⊕⊖⊖⊖	=
	Amitriptyline (25 mg daily)	Venlafaxine (37.5 mg daily)	Any	⊕⊖⊖⊖	=
19	Amitriptyline (50 mg daily)	Citalopram (20 mg daily)	Any	⊕⊖⊖⊖	-
20	Venlafaxine (37.5 mg daily)	Nortriptyline (25 mg daily) + Propranolol (40 mg daily)	Any	⊕⊖⊖⊖	-
21	Propranolol (160 mg daily)	Candesartan (16 mg daily)	Any	⊕⊕⊕⊖	=
22	Propranolol (80 mg daily)	Nortriptyline (40 mg daily)	Any	⊕⊖⊖⊖	-
23	Metoprolol (200 mg daily)	Flunarizine (10 mg daily)	Any	⊕⊕⊖⊖	↓
24	Metoprolol (200 mg daily)	Acetylsalicylic acid (300 mg daily)	Any	⊕⊖⊖⊖	↑
25	Propranolol (180 mg daily)	Nifedipine (90 mg daily)	Any	⊕⊖⊖⊖	-
26	Galcanezumab (120 mg monthly)	Rimegepant (75 mg every other day)	Episodic	⊕⊕⊕⊖	=

Quality of selected evidence	
⊕⊕⊕⊕	High
⊕⊕⊕⊖	Moderate
⊕⊕⊖⊖	Low
⊕⊖⊖⊖	Very low
⊖⊖⊖⊖	None
Strength of the recommendation	
↑↑	strong in favor
↑	weak in favor
↓	weak against
↓↓	strong against
=	weak for equivalence
-	none

Figure 4.8.38. Summary of evidence for head-to-head comparisons of preventive treatments.

Rationale: Most head-to-head comparisons are either neutral or inconclusive due to low numbers.

Topic: When choosing an oral preventive treatment for migraine, should clinicians prioritize efficacy or safety?. Suggestion: Safety should be prioritized.

Rationale: Treatments did not differ in efficacy or overall tolerability; however, they showed different adverse events. Therefore, it is reasonable to consider the possible adverse events of each patient.

Topic: When combining more than one oral preventive treatment for migraine, should dose of individual drugs be reduced?. Suggestion: It is reasonable to combine drugs with the minimal effective dose.

Rationale: Oral treatments were tested in many different dosages. Minimal effective doses could be associated with less adverse events.

Topic: When combining more than one oral preventive treatment for migraine, which safety elements should be considered?. Suggestion: It is reasonable to combine drugs with different tolerability profiles.

Rationale: Head-to-head comparisons allowed the comparison of different tolerability profiles. Drugs with very different or complementary adverse event profiles are safer to combine. For example, amitriptyline causes weight gain while topiramate can cause weight loss. It is more reasonable to combine those two drugs than two different drugs both causing weight gain.

Acknowledgements

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References

1. Diener HC, Tassorelli C, Dodick DW, et al. Guidelines of the international headache society for controlled trials of acute treatment of migraine attacks in adults: fourth edition. *Cephalalgia* 2019; 39: 687–710.
2. Tassorelli C, Diener HC, Dodick DW, et al. Guidelines of the international headache society for controlled trials of preventive treatment of chronic migraine in adults. *Cephalalgia* 2018; 38: 815–832.
3. Diener HC, Tassorelli C, Dodick DW, et al. Guidelines of the international headache society for controlled trials of preventive treatment of migraine attacks in episodic migraine in adults. *Cephalalgia* 2020; 40: 1026–1044.
4. Higgins JPT, Chandler J, Cumpston M, et al. *Cochrane handbook for systematic reviews of interventions version 6.3*, www.training.cochrane.org/handbook. (2022, accessed Jan 15, 2023)
5. Pollock M, Becker LA, Pieper D, et al. Chapter V: Overviews of reviews. In: Higgins JPT, Thomas J, Chandler J, et al (eds) *Cochrane handbook for systematic reviews of interventions version 6.3*, www.training.cochrane.org/handbook. (2022, accessed Jan 15, 2023)
6. Page MJ, McKenzie JE, Bossuyt PM, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. *BMJ* 2021; 372: n71.
7. Headache Classification Committee of the International Headache Society (IHS). The International Classification of Headache Disorders, 3rd edition. *Cephalalgia* 2018; 38: 1–211.
8. Balshem H, Helfand M, Schunemann HJ, et al. GRADE Guidelines: 3. Rating the quality of evidence. *J Clin Epidemiol* 2011; 64: 401–406.
9. Guyatt GH, Oxman AD, Kunz R, et al. GRADE Guidelines 6. Rating the quality of evidence–imprecision. *J Clin Epidemiol* 2011; 64: 1283–1293.
10. Grosser T, Smith E and Fitzgerald GA. Anti-inflammatory, antipyretic, and analgesic agents; pharmacotherapy of gout. In: Brunton LL, Chabner BA and Knollmann BC (eds). *Goodman & Gilman's: The pharmacological basis of therapeutics, 12e*. New York, NY: McGraw-Hill, 2015.
11. Noor N, LaChute C, Root M, et al. A Comprehensive Review of Celecoxib Oral Solution for the Acute Treatment of Migraine, https://healthpsychologyresearch.openmedicalpublishing.org/article/34265-a-comprehensive-review-of-celecoxib-oral-solution-for-the-acute-treatment-of-migraine. (accessed Jan 15, 2023)
12. Schain AJ, Melo-Carrillo A, Ashina S, et al. Celecoxib reduces cortical spreading depression-induced macrophage activation and dilatation of dural but not pial arteries in rodents: implications for mechanism of action in terminating migraine attacks. *Pain* 2020; 161: 1019–1026.
13. Lucas S. The pharmacology of indomethacin. *Headache* 2016; 56: 436–446.
14. Forderreuther S and Straube A. Indomethacin reduces CSF pressure in intracranial hypertension. *Neurology* 2000; 55: 1043–1045.
15. Sarchielli P, Granella F, Prudenzano MP, et al. Italian Guidelines for primary headaches: 2012 revised version. *J Headache Pain* 2012; 13(Suppl 2): S31–70.
16. Pringsheim T, Davenport WJ, Marmura MJ, et al. How to apply the AHS evidence assessment of the acute treatment of migraine in adults to your patient with migraine. *Headache* 2016; 56: 1194–1200.
17. Ashina M. Migraine. *N Engl J Med* 2020; 383: 1866–1876.
18. Ailani J, Burch RC and Robbins MS. Board of directors of the American headache S. The American headache society consensus statement: update on integrating new migraine treatments into clinical practice. *Headache* 2021; 61: 1021–1039.
19. Law S, Derry S and Moore RA. Naproxen with or without an antiemetic for acute migraine headaches in adults. *Cochrane Database Syst Rev* 2013; 2013: CD009455.
20. Law S, Derry S and Moore RA. Sumatriptan plus naproxen for the treatment of acute migraine attacks in adults. *Cochrane Database Syst Rev* 2016; 4: CD008541.
21. Kirthi V, Derry S and Moore RA. Aspirin with or without an antiemetic for acute migraine headaches in adults. *Cochrane Database Syst Rev* 2013: CD008041.
22. Derry S, Rabbie R and Moore RA. Diclofenac with or without an antiemetic for acute migraine headaches in adults. *Cochrane Database Syst Rev* 2013: CD008783.
23. Rabbie R, Derry S and Moore RA. Ibuprofen with or without an antiemetic for acute migraine headaches in adults. *Cochrane Database Syst Rev* 2013: CD008039.
24. VanderPluym JH, Halker Singh RB, Urtecho M, et al. Acute treatments for episodic migraine in adults: a systematic review and meta-analysis. *JAMA* 2021; 325: 2357–2369.
25. Yang B, Xu Z, Chen L, et al. The efficacy of dexketoprofen for migraine attack: a meta-analysis of randomized controlled studies. *Medicine (Balt)* 2019; 98: e17734.
26. Boureau F, Joubert JM, Lasserre V, et al. Double-blind comparison of an Acetaminophen 400 mg-codeine 25 mg combination versus aspirin 1000 mg and placebo in acute migraine attack. *Cephalalgia* 1994; 14: 156–161.
27. Brandes JL, Kudrow D, Stark SR, et al. Sumatriptan-naproxen for acute treatment of migraine: a randomized trial. *JAMA* 2007; 297: 1443–1454.
28. Codispoti JR, Prior MJ, Fu M, et al. Efficacy of nonprescription doses of ibuprofen for treating migraine headache. a randomized controlled trial. *Headache* 2001; 41: 665–679.
29. Diener HC, Eikermann A, Gessner U, et al. Efficacy of 1,000 mg effervescent acetylsalicylic acid and sumatriptan in treating associated migraine symptoms. *Eur Neurol* 2004; 52: 50–56.
30. Diener HC, Bussone G, de Liano H, et al. Placebo-controlled comparison of effervescent acetylsalicylic acid, sumatriptan

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31. Diener HC, Montagna P, Gacs G, et al. Efficacy and tolerability of diclofenac potassium sachets in migraine: a randomized, double-blind, cross-over study in comparison with diclofenac potassium tablets and placebo. *Cephalalgia* 2006; 26: 537–547.
32. Kellstein DE, Lipton RB, Geetha R, et al. Evaluation of a novel solubilized formulation of ibuprofen in the treatment of migraine headache: a randomized, double-blind, placebo-controlled, dose-ranging study. *Cephalalgia* 2000; 20: 233–243.
33. Lange R, Schwarz JA and Hohn M. Acetylsalicylic acid effervescent 1000 mg (aspirin) in acute migraine attacks; a multicentre, randomized, double-blind, single-dose, placebo-controlled parallel group study. *Cephalalgia* 2000; 20: 663–667.
34. Lipton RB, Goldstein J, Baggish JS, et al. Aspirin is efficacious for the treatment of acute migraine. *Headache* 2005; 45: 283–292.
35. Lipton RB, Grosberg B, Singer RP, et al. Efficacy and tolerability of a new powdered formulation of diclofenac potassium for oral solution for the acute treatment of migraine: results from the international migraine pain assessment clinical trial (IMPACT). *Cephalalgia* 2010; 30: 1336–1345.
36. MacGregor EA, Dowson A and Davies PT. Mouth-dispersible aspirin in the treatment of migraine: a placebo-controlled study. *Headache* 2002; 42: 249–255.
37. Misra UK, Jose M and Kalita J. Rofecoxib versus ibuprofen for acute treatment of migraine: a randomised placebo controlled trial. *Postgrad Med J* 2004; 80: 720–723.
38. Misra UK, Kalita J and Yadav RK. Rizatriptan vs. Ibuprofen in migraine: a randomised placebo-controlled trial. *J Headache Pain* 2007; 8: 175–179.
39. Saper J, Dahlof C, So Y, et al. Rofecoxib in the acute treatment of migraine: a randomized controlled clinical trial. *Headache* 2006; 46: 264–275.
40. Wentz AL, Jimenez TB, Dixon RM, et al. A double-blind, randomized, placebo-controlled, single-dose study of the cyclooxygenase-2 inhibitor, GW406381, as a treatment for acute migraine. *Eur J Neurol* 2008; 15: 420–427.
41. Smith TR, Sunshine A, Stark SR, et al. Sumatriptan and naproxen sodium for the acute treatment of migraine. *Headache* 2005; 45: 983–991.
42. Mainardi F, Maggioni F, Pezzola D, et al. Dexketoprofen trometamol in the acute treatment of migraine attack: a phase II, randomized, double-blind, crossover, placebo-controlled, dose optimization study. *J Pain* 2014; 15: 388–394.
43. Lipton RB, Munjal S, Brand-Schieber E, et al. Efficacy, tolerability, and safety of DFN-15 (celecoxib oral solution, 25 mg/mL) in the acute treatment of episodic migraine: a randomized, double-blind, placebo-controlled study. *Headache*. 2020; 60: 58–70.
44. Rao AS, Gelaye B, Kurth T, et al. A randomized trial of ketorolac vs. Sumatripan vs. Placebo nasal spray (KSPN) for acute migraine. *Headache* 2016; 56: 331–340.
45. Geppetti P, De Cesaris F, Benemei S, et al. Self-administered subcutaneous diclofenac sodium in acute migraine attack: a randomized, double-blind, placebo-controlled dose-finding pilot study. *Cephalalgia* 2022; 42: 1058–1070.
46. Arif H and Aggarwal S. *Salicylic Acid (Aspirin)*. Treasure Island (FL): StatPearls, 2024.
47. Aithal GP. Diclofenac-induced liver injury: a paradigm of idiosyncratic drug toxicity. *Expert Opin Drug Saf* 2004; 3: 519–523.
48. Mount M and Toltzis P. 50 Years ago in the journal of pediatrics: aspirin and reye syndrome. *J Pediatr* 2020; 222: 192.
49. Schmidt M, Sorensen HT and Pedersen L. Diclofenac use and cardiovascular risks: series of nationwide cohort studies. *BMJ* 2018; 362: k3426.
50. Schmidt M, Sorensen HT and Pedersen L. Cardiovascular risks of diclofenac versus other older COX-2 inhibitors (meloxicam and etodolac) and newer COX-2 inhibitors (celecoxib and etoricoxib): a series of nationwide emulated trials. *Drug Saf* 2022; 45: 983–994.
51. Minhas D, Nidhaan A and Husni ME. Recommendations for the use of nonsteroidal anti-inflammatory drugs and cardiovascular disease risk: decades later, any new lessons learned? *Rheum Dis Clin North Am* 2023; 49: 179–191.
52. Schjerning AM, McGettigan P and Gislason G. Cardiovascular effects and safety of (non-aspirin) NSAIDs. *Nat Rev Cardiol* 2020; 17: 574–584.
53. Cohen B and Preuss CV. *Celecoxib*. Treasure Island (FL): StatPearls, 2024.
54. Strom BL, Schinnar R, Apter AJ, et al. Absence of cross-reactivity between sulfonamide antibiotics and sulfonamide nonantibiotics. *N Engl J Med* 2003; 349: 1628–1635.
55. Pardutz A and Schoenen J. NSAIDs in the acute treatment of migraine: a review of clinical and experimental data. *Pharmaceuticals (Basel)* 2010; 3: 1966–1987.
56. Summ O, Andreou AP, Akerman S, et al. Differential actions of indomethacin: clinical relevance in headache. *Pain* 2021; 162: 591–599.
57. Macone AE and Perloff MD. Triptans and migraine: advances in use, administration, formulation, and development. *Expert Opin Pharmacother* 2017; 18: 387–397.
58. Cameron C, Kelly S, Hsieh SC, et al. Triptans in the acute treatment of migraine: a systematic review and network meta-analysis. *Headache* 2015; 55(Suppl 4): 221–235.
59. Ferrari MD, Goadsby PJ, Roon KI, et al. Triptans (serotonin, 5-HT1B/1D agonists) in migraine: detailed results and methods of a meta-analysis of 53 trials. *Cephalalgia* 2002; 22: 633–658.
60. Humphrey PP, Feniuk W, Perren MJ, et al. Serotonin and migraine. *Ann N Y Acad Sci* 1990; 600: 587–598; discussion 598–600.
61. Moskowitz MA and Cutrer FM. SUMATRIPTAN: a receptor-targeted treatment for migraine. *Annu Rev Med* 1993; 44: 145–54.
62. Buzzi MG, Moskowitz MA, Peroutka SJ, et al. Further characterization of the putative 5-HT receptor which mediates blockade of neurogenic plasma extravasation in rat dura mater. *Br J Pharmacol* 1991; 103: 1421–1428.
63. Burstein R, Collins B and Jakubowski M. Defeating migraine pain with triptans: a race against the development of cutaneous allodynia. *Ann Neurol* 2004; 55: 19–26.

64. Burstein R and Jakubowski M. Analgesic triptan action in an animal model of intracranial pain: a race against the development of central sensitization. *Ann Neurol* 2004; 55: 27–36.
65. Levy D, Jakubowski M and Burstein R. Disruption of communication between peripheral and central trigeminovascular neurons mediates the antimigraine action of 5HT 1B/1D receptor agonists. *Proc Natl Acad Sci U S A* 2004; 101: 4274–4279.
66. Jhee SS, Shiovitz T, Crawford AW, et al. Pharmacokinetics and pharmacodynamics of the triptan antimigraine agents: a comparative review. *Clin Pharmacokinet* 2001; 40: 189–205.
67. Chen LC and Ashcroft DM. Meta-analysis examining the efficacy and safety of almotriptan in the acute treatment of migraine. *Headache* 2007; 47: 1169–1177.
68. McCormack PL and Keating GM. Eletriptan: a review of its use in the acute treatment of migraine. *Drugs* 2006; 66: 1129–1149.
69. Capi M, Curto M, Lionetto L, et al. Eletriptan in the management of acute migraine: an update on the evidence for efficacy, safety, and consistent response. *Ther Adv Neurol Disord* 2016; 9: 414–423.
70. Poolsup N, Leelasangaluk V, Jittangtrong J, et al. Efficacy and tolerability of frovatriptan in acute migraine treatment: systematic review of randomized controlled trials. *J Clin Pharm Ther* 2005; 30: 521–532.
71. MacGregor EA. A review of frovatriptan for the treatment of menstrual migraine. *Int J Womens Health* 2014; 6: 523–535.
72. Evers S, Savi L, Omboni S, et al. Efficacy of frovatriptan as compared to other triptans in migraine with aura. *J Headache Pain* 2015; 16: 514.
73. Ashcroft DM and Millson D. Naratriptan for the treatment of acute migraine: meta-analysis of randomised controlled trials. *Pharmacoepidemiol Drug Saf* 2004; 13: 73–82.
74. Ferrari MD, Loder E, McCarroll KA, et al. Meta-analysis of rizatriptan efficacy in randomized controlled clinical trials. *Cephalalgia* 2001; 21: 129–136.
75. Hargreaves RJ, Lines CR, Rapoport AM, et al. Ten years of rizatriptan: from development to clinical science and future directions. *Headache* 2009; 49(Suppl 1): S3–20.
76. McCrory DC and Gray RN. Oral sumatriptan for acute migraine. *Cochrane Database Syst Rev* 2003: CD002915.
77. Menshawy A, Ahmed H, Ismail A, et al. Intranasal sumatriptan for acute migraine attacks: a systematic review and meta-analysis. *Neurol Sci* 2018; 39: 31–44.
78. Derry CJ, Derry S and Moore RA. Sumatriptan (all routes of administration) for acute migraine attacks in adults - overview of cochrane reviews. *Cochrane Database Syst Rev* 2014: CD009108.
79. Bird S, Derry S and Moore RA. Zolmitriptan for acute migraine attacks in adults. *Cochrane Database Syst Rev* 2014: CD008616.
80. Chen LC and Ashcroft DM. Meta-analysis of the efficacy and safety of zolmitriptan in the acute treatment of migraine. *Headache* 2008; 48: 236–247.
81. Ferrari MD, Roon KI, Lipton RB, et al. Oral triptans (serotonin 5-HT(1B/1D) agonists) in acute migraine treatment: a meta-analysis of 53 trials. *Lancet* 2001; 358: 1668–1675.
82. Pascual J, Mateos V, Roig C, et al. Marketed oral triptans in the acute treatment of migraine: a systematic review on efficacy and tolerability. *Headache* 2007; 47: 1152–1168.
83. Sanford M. Frovatriptan: a review of its use in the acute treatment of migraine. *CNS Drugs* 2012; 26: 791–811.
84. Richer L, Billinghurst L, Linsdell MA, et al. Drugs for the acute treatment of migraine in children and adolescents. *Cochrane Database Syst Rev* 2016; 4: CD005220.
85. Thorlund K, Mills EJ, Wu P, et al. Comparative efficacy of triptans for the abortive treatment of migraine: a multiple treatment comparison meta-analysis. *Cephalalgia* 2014; 34: 258–267.
86. Xu H, Han W, Wang J, et al. Network meta-analysis of migraine disorder treatment by NSAIDs and triptans. *J Headache Pain* 2016; 17: 113.
87. Dahlof C, Tfelt-Hansen P, Massiou H, et al. Dose finding, placebo-controlled study of oral almotriptan in the acute treatment of migraine. *Neurology* 2001; 57: 1811–1817.
88. Diener HC. Efficacy of almotriptan 12.5 mg in achieving migraine-related composite endpoints: a double-blind, randomized, placebo-controlled study in patients controlled study in patients with previous poor response to sumatriptan 50 mg. *Curr Med Res Opin* 2005; 21: 1603–1610.
89. Goadsby PJ, Zanchin G, Geraud G, et al. Early vs. Non-early intervention in acute migraine-'Act when mild (AwM)'. A double-blind, placebo-controlled trial of almotriptan. *Cephalalgia* 2008; 28: 383–391.
90. Mathew NT, Finlayson G, Smith TR, et al. Early intervention with almotriptan: results of the AEGIS trial (AXERT early migraine intervention study). *Headache* 2007; 47: 189–198.
91. Pascual J, Falk RM, Piessens F, et al. Consistent efficacy and tolerability of almotriptan in the acute treatment of multiple migraine attacks: results of a large, randomized, double-blind, placebo-controlled study. *Cephalalgia* 2000; 20: 588–596.
92. Eletriptan Steering Committee in J. Efficacy and safety of eletriptan 20 mg, 40 mg and 80 mg in Japanese migraineurs. *Cephalalgia* 2002; 22: 416–423.
93. Goadsby PJ, Ferrari MD, Olesen J, et al. Eletriptan in acute migraine: a double-blind, placebo-controlled comparison to sumatriptan. Eletriptan steering committee. *Neurology* 2000; 54: 156–163.
94. Sheftell F, Ryan R, Pitman V, et al. Efficacy, safety, and tolerability of oral eletriptan for treatment of acute migraine: a multicenter, double-blind, placebo-controlled study conducted in the United States. *Headache* 2003; 43: 202–213.
95. Brandes JL, Kudrow D, Cady R, et al. Eletriptan in the early treatment of acute migraine: influence of pain intensity and time of dosing. *Cephalalgia* 2005; 25: 735–742.
96. Garcia-Ramos G, MacGregor EA, Hilliard B, et al. Comparative efficacy of eletriptan vs. Naratriptan in the acute treatment of migraine. *Cephalalgia* 2003; 23: 869–876.
97. Mathew NT, Schoenen J, Winner P, et al. Comparative efficacy of eletriptan 40 mg versus sumatriptan 100 mg. *Headache* 2003; 43: 214–222.
98. Sandrini G, Farkkila M, Burgess G, et al. Eletriptan vs sumatriptan: a double-blind, placebo-controlled, multiple migraine attack study. *Neurology* 2002; 59: 1210–1217.
99. Stark R, Dahlof C, Haughie S, et al. Efficacy, safety and tolerability of oral eletriptan in the acute treatment of migraine:

results of a phase III, multicentre, placebo-controlled study across three attacks. *Cephalalgia* 2002; 22: 23–32.
100. Steiner TJ, Diener HC, MacGregor EA, et al. Comparative efficacy of eletriptan and zolmitriptan in the acute treatment of migraine. *Cephalalgia* 2003; 23: 942–952.
101. Farkkila M, Olesen J, Dahlof C, et al. Eletriptan for the treatment of migraine in patients with previous poor response or tolerance to oral sumatriptan. *Cephalalgia* 2003; 23: 463–471.
102. Cady R, Elkind A, Goldstein J, et al. Randomized, placebo-controlled comparison of early use of frovatriptan in a migraine attack versus dosing after the headache has become moderate or severe. *Curr Med Res Opin* 2004; 20: 1465–1472.
103. Goldstein J, Keywood C and Study G. Frovatriptan for the acute treatment of migraine: a dose-finding study. *Headache* 2002; 42: 41–48.
104. Moon HS, Chu MK, Park JW, et al. Frovatriptan is effective and well tolerated in Korean migraineurs: a double-blind, randomized, placebo-controlled trial. *J Clin Neurol* 2010; 6: 27–32.
105. Rapoport A, Ryan R, Goldstein J, et al. Dose range-finding studies with frovatriptan in the acute treatment of migraine. *Headache* 2002; 42(Suppl 2): S74–83.
106. Oliva A. Clinical review of NDA – Frovatriptan, https://www.accessdata.fda.gov/drugsatfda_docs/nda/2001/21-006_Frova_medr_P1.pdf. (accessed Jan 15, 2023)
107. Bomhof M, Paz J, Legg N, et al. Comparison of rizatriptan 10 mg vs. Naratriptan 2.5 mg in migraine. *Eur Neurol* 1999; 42: 173–179.
108. Dahlof C, Hogenhuis L, Olesen J, et al. Early clinical experience with subcutaneous naratriptan in the acute treatment of migraine: a dose-ranging study. *Eur J Neurol* 1998; 5: 469–477.
109. Havanka H, Dahlof C, Pop PH, et al. Efficacy of naratriptan tablets in the acute treatment of migraine: a dose-ranging study. Naratriptan S2WB2004 study group. *Clin Ther* 2000; 22: 970–980.
110. Stark S, Spierings EL, McNeal S, et al. Naratriptan efficacy in migraineurs who respond poorly to oral sumatriptan. *Headache* 2000; 40: 513–520.
111. Gijsman H, Kramer MS, Sargent J, et al. Double-blind, placebo-controlled, dose-finding study of rizatriptan (MK-462) in the acute treatment of migraine. *Cephalalgia* 1997; 17: 647–651.
112. Goldstein J, Ryan R, Jiang K, et al. Crossover comparison of rizatriptan 5 mg and 10 mg versus sumatriptan 25 mg and 50 mg in migraine. Rizatriptan protocol 046 study group. *Headache* 1998; 38: 737–747.
113. Teall J, Tuchman M, Cutler N, et al. Rizatriptan (MAXALT) for the acute treatment of migraine and migraine recurrence. A placebo-controlled, outpatient study. Rizatriptan 022 study group. *Headache* 1998; 38: 281–287.
114. Tfelt-Hansen P, Teall J, Rodriguez F, et al. Oral rizatriptan versus oral sumatriptan: a direct comparative study in the acute treatment of migraine. Rizatriptan 030 study group. *Headache* 1998; 38: 748–755.
115. Ahrens SP, Farmer MV, Williams DL, et al. Efficacy and safety of rizatriptan wafer for the acute treatment of migraine. Rizatriptan wafer protocol 049 study group. *Cephalalgia* 1999; 19: 525–530.
116. Barbanti P, Fofi L, Dall'Armi V, et al. Rizatriptan in migraineurs with unilateral cranial autonomic symptoms: a double-blind trial. *J Headache Pain* 2012; 13: 407–414.
117. Cady R, Martin V, Mauskop A, et al. Efficacy of rizatriptan 10 mg administered early in a migraine attack. *Headache* 2006; 46: 914–924.
118. Freitag F, Diamond M, Diamond S, et al. Efficacy and tolerability of coadministration of rizatriptan and Acetaminophen vs rizatriptan or Acetaminophen alone for acute migraine treatment. *Headache* 2008; 48: 921–930.
119. Kramer MS, Matzura-Wolfe D, Polis A, et al. A placebo-controlled crossover study of rizatriptan in the treatment of multiple migraine attacks. Rizatriptan multiple attack study group. *Neurology* 1998; 51: 773–781.
120. Pascual J, Vega P, Diener HC, et al. Comparison of rizatriptan 10 mg vs. Zolmitriptan 2.5 mg in the acute treatment of migraine. Rizatriptan-zolmitriptan study group. *Cephalalgia* 2000; 20: 455–461.
121. Visser WH, Terwindt GM, Reines SA, et al. Rizatriptan vs sumatriptan in the acute treatment of migraine. A placebo-controlled, dose-ranging study. Dutch/US rizatriptan study group. *Arch Neurol* 1996; 53: 1132–1137.
122. Sheftell FD, Dahlof CG, Brandes JL, et al. Two replicate randomized, double-blind, placebo-controlled trials of the time to onset of pain relief in the acute treatment of migraine with a fast-disintegrating/rapid-release formulation of sumatriptan tablets. *Clin Ther* 2005; 27: 407–417.
123. Tfelt-Hansen P, Bach FW, Daugaard D, et al. Treatment with sumatriptan 50 mg in the mild phase of migraine attacks in patients with infrequent attacks: a randomised, double-blind, placebo-controlled study. *J Headache Pain* 2006; 7: 389–394.
124. Winner P, Mannix LK, Putnam DG, et al. Pain-free results with sumatriptan taken at the first sign of migraine pain: 2 randomized, double-blind, placebo-controlled studies. *Mayo Clin Proc* 2003; 78: 1214–1222.
125. Myllyla VV, Havanka H, Herrala L, et al. Tolfenamic acid rapid release versus sumatriptan in the acute treatment of migraine: comparable effect in a double-blind, randomized, controlled, parallel-group study. *Headache* 1998; 38: 201–207.
126. Nappi G, Sicuteri F, Byrne M, et al. Oral sumatriptan compared with placebo in the acute treatment of migraine. *J Neurol* 1994; 241: 138–144.
127. Evaluation of a multiple-dose regimen of oral sumatriptan for the acute treatment of migraine. The oral sumatriptan international multiple-dose study group. *Eur Neurol* 1991; 31: 306–313.
128. Wang SJ, Fuh JL and Wu ZA. Intranasal sumatriptan study with high placebo response in Taiwanese patients with migraine. *J Chin Med Assoc* 2007; 70: 39–46.
129. Bousser MG, D'Allens H and Richard A. Efficacy of subcutaneous sumatriptan in the acute treatment of early-morning migraine: a placebo-controlled trial. Early-morning migraine sumatriptan study group. *J Intern Med* 1993; 234: 211–6.
130. Diener HC, Tfelt-Hansen P, de Beukelaar F, et al. The efficacy and safety of sc alniditan vs. Sc sumatriptan in the acute treatment of migraine: a randomized, double-blind, placebo-controlled trial. *Cephalalgia* 2001; 21: 672–9.
131. Diener HC. Efficacy and safety of intravenous acetylsalicylic acid lysinate compared to subcutaneous sumatriptan and

parenteral placebo in the acute treatment of migraine. A double-blind, double-dummy, randomized, multicenter, parallel group study. The ASASUMAMIG study group. *Cephalalgia* 1999; 19: 581–588; discussion 42.
132. Winner P, Adelman J, Aurora S, et al. Efficacy and tolerability of sumatriptan injection for the treatment of morning migraine: two multicenter, prospective, randomized, double-blind, controlled studies in adults. *Clin Ther* 2006; 28: 1582–1591.
133. Lipton RB, Munjal S, Brand-Schieber E, et al. DFN-02 (Sumatriptan 10 mg with a permeation enhancer) nasal spray vs placebo in the acute treatment of migraine: a double-blind, placebo-controlled study. *Headache* 2018; 58: 676–687.
134. Henry P and d'Allens H. Subcutaneous sumatriptan in the acute treatment of migraine in patients using dihydroergotamine as prophylaxis. French migraine network Bordeaux-Lyon-Grenoble. *Headache* 1993; 33: 432–435.
135. Diamond S, Elkind A, Jackson RT, et al. Multiple-attack efficacy and tolerability of sumatriptan nasal spray in the treatment of migraine. *Arch Fam Med* 1998; 7: 234–240.
136. Salonen R, Ashford E, Dahlof C, et al. Intranasal sumatriptan for the acute treatment of migraine. International intranasal sumatriptan study group. *J Neurol* 1994; 241: 463–469.
137. Bussone G, Manzoni GC, Cortelli P, et al. Efficacy and tolerability of sumatriptan in the treatment of multiple migraine attacks. *Neurol Sci* 2000; 21: 272–278.
138. Jelinski SE, Becker WJ, Christie SN, et al. Pain free efficacy of sumatriptan in the early treatment of migraine. *Can J Neurol Sci* 2006; 33: 73–79.
139. Mathew NT, Dexter J, Couch J, et al. Dose ranging efficacy and safety of subcutaneous sumatriptan in the acute treatment of migraine. US sumatriptan research group. *Arch Neurol* 1992; 49: 1271–1276.
140. Mushet GR, Cady RK, Baker CC, et al. Efficacy and tolerability of subcutaneous sumatriptan administered using the IMITREX STATdose system. *Clin Ther* 1996; 18: 687–699.
141. Kaniecki R, Ruoff G, Smith T, et al. Prevalence of migraine and response to sumatriptan in patients self-reporting tension/stress headache. *Curr Med Res Opin* 2006; 22: 1535–1544.
142. Patten JP. Clinical experience with oral sumatriptan: a placebo-controlled, dose-ranging study. Oral sumatriptan dose-defining study group. *J Neurol* 1991; 238(Suppl 1): S62–5.
143. Gross ML, Kay J, Turner AM, et al. Sumatriptan in acute migraine using a novel cartridge system self-injector. United Kingdom study group. *Headache* 1994; 34: 559–563.
144. Jensen K, Tfelt-Hansen P, Hansen EW, et al. Introduction of a novel self-injector for sumatriptan. A controlled clinical trial in general practice. *Cephalalgia* 1995; 15: 423–429.
145. Russell MB, Holm-Thomsen OE, Rishoj Nielsen M, et al. A randomized double-blind placebo-controlled crossover study of subcutaneous sumatriptan in general practice. *Cephalalgia* 1994; 14: 291–296.
146. Carpay J, Schoenen J, Ahmad F, et al. Efficacy and tolerability of sumatriptan tablets in a fast-disintegrating, rapid-release formulation for the acute treatment of migraine: results of a multicenter, randomized, placebo-controlled study. *Clin Ther* 2004; 26: 214–223.
147. Landy S, Savani N, Shackelford S, et al. Efficacy and tolerability of sumatriptan tablets administered during the mild-pain phase of menstrually associated migraine. *Int J Clin Pract* 2004; 58: 913–919.
148. Savani N, Pfaffenrath V, Rice L, et al. Efficacy, tolerability, and patient satisfaction with 50- and 100-mg sumatriptan tablets in those initially dissatisfied with the efficacy of 50-mg sumatriptan tablets. *Clin Ther* 2001; 23: 260–271.
149. Tepper SJ, Cady R, Dodick D, et al. Oral sumatriptan for the acute treatment of probable migraine: first randomized, controlled study. *Headache* 2006; 46: 115–124.
150. Dowson AJ, MacGregor EA, Purdy RA, et al. Zolmitriptan orally disintegrating tablet is effective in the acute treatment of migraine. *Cephalalgia* 2002; 22: 101–106.
151. Sakai F, Iwata M, Tashiro K, et al. Zolmitriptan is effective and well tolerated in Japanese patients with migraine: a dose-response study. *Cephalalgia* 2002; 22: 376–383.
152. Solomon GD, Cady RK, Klapper JA, et al. Clinical efficacy and tolerability of 2.5 mg zolmitriptan for the acute treatment of migraine. The 042 clinical trial study group. *Neurology* 1997; 49: 1219–1225.
153. Spierings EL, Rapoport AM, Dodick DW, et al. Acute treatment of migraine with zolmitriptan 5 mg orally disintegrating tablet. *CNS Drugs* 2004; 18: 1133–1141.
154. Tepper SJ, Donnan GA, Dowson AJ, et al. A long-term study to maximise migraine relief with zolmitriptan. *Curr Med Res Opin* 1999; 15: 254–271.
155. Loder E, Freitag FG, Adelman J, et al. Pain-free rates with zolmitriptan 2.5 mg ODT in the acute treatment of migraine: results of a large double-blind placebo- controlled trial. *Curr Med Res Opin* 2005; 21: 381–389.
156. Rapoport AM, Ramadan NM, Adelman JU, et al. Optimizing the dose of zolmitriptan (zomig, 311C90) for the acute treatment of migraine. A multicenter, double-blind, placebo-controlled, dose range-finding study. The 017 clinical trial study group. *Neurology* 1997; 49: 1210–1218.
157. Charlesworth BR, Dowson AJ, Purdy A, et al. Speed of onset and efficacy of zolmitriptan nasal spray in the acute treatment of migraine: a randomised, double-blind, placebo-controlled, dose-ranging study versus zolmitriptan tablet. *CNS Drugs* 2003; 17: 653-667.
158. Gawel M, Aschoff J, May A, et al. Zolmitriptan 5 mg nasal spray: efficacy and onset of action in the acute treatment of migraine–results from phase 1 of the REALIZE study. *Headache* 2005; 45: 7–16.
159. Barbanti P, Carpay JA, Kwong WJ, et al. Effects of a fast disintegrating/rapid release oral formulation of sumatriptan on functional ability in patients with migraine. *Curr Med Res Opin* 2004; 20: 2021–2029.
160. Bartolini M, Giamberardino MA, Lisotto C, et al. A double-blind, randomized, multicenter, Italian study of frovatriptan versus almotriptan for the acute treatment of migraine. *J Headache Pain* 2011; 12: 361–368.
161. Cady RC, Ryan R, Jhingran P, et al. Sumatriptan injection reduces productivity loss during a migraine attack: results of a double-blind, placebo-controlled trial. *Arch Intern Med* 1998; 158: 1013–1018.

162. Cady RK, Martin VT, Geraud G, et al. Rizatriptan 10-mg ODT for early treatment of migraine and impact of migraine education on treatment response. *Headache* 2009; 49: 687–696.
163. Cady RK, McAllister PJ, Spierings EL, et al. A randomized, double-blind, placebo-controlled study of breath powered nasal delivery of sumatriptan powder (AVP-825) in the treatment of acute migraine (the TARGET study). *Headache* 2015; 55: 88–100.
164. Dahlof C, Diener HC, Goadsby PJ, et al. Zolmitriptan, a 5-HT1B/1D receptor agonist for the acute oral treatment of migraine: a multicentre, dose-range finding study. *Eur J Neurol* 1998; 5: 535–543.
165. Dahlof CG, Hauge AW and Olesen J. Efficacy and safety of tonabersat, a gap-junction modulator, in the acute treatment of migraine: a double-blind, parallel-group, randomized study. *Cephalalgia* 2009; 29(Suppl 2): 7–16.
166. Di Monda V, Nicolodi M, Aloisio A, et al. Efficacy of a fixed combination of indomethacin, prochlorperazine, and caffeine versus sumatriptan in acute treatment of multiple migraine attacks: a multicenter, randomized, crossover trial. *Headache* 2003; 43: 835–844.
167. Diener HC, Jansen JP, Reches A, et al. Efficacy, tolerability and safety of oral eletriptan and ergotamine plus caffeine (cafergot) in the acute treatment of migraine: a multicentre, randomised, double-blind, placebo-controlled comparison. *Eur Neurol* 2002; 47: 99–107.
168. Diener HC, Gendolla A, Gebert I, et al. Almotriptan in migraine patients who respond poorly to oral sumatriptan: a double-blind, randomized trial. *Headache* 2005; 45: 874–882.
169. Diener HC, Barbanti P, Dahlof C, et al. BI 44370 TA, an oral CGRP antagonist for the treatment of acute migraine attacks: results from a phase II study. *Cephalalgia* 2011; 31: 573–584.
170. Dodick DW. Almotriptan increases sustained pain-free outcomes in acute migraine: results from three controlled clinical trials. *Headache* 2002; 42: 21–27.
171. Dodick D, Brandes J, Elkind A, et al. Speed of onset, efficacy and tolerability of zolmitriptan nasal spray in the acute treatment of migraine: a randomised, double-blind, placebo-controlled study. *CNS Drugs* 2005; 19: 125–136.
172. Dowson AJ, Massiou H, Lainez JM, et al. Almotriptan is an effective and well-tolerated treatment for migraine pain: results of a randomized, double-blind, placebo-controlled clinical trial. *Cephalalgia* 2002; 22: 453–461.
173. Dowson AJ, Massiou H, Lainez JM, et al. Almotriptan improves response rates when treatment is within 1 hour of migraine onset. *Headache* 2004; 44: 318–322.
174. Friedman BW, Solorzano C, Esses D, et al. Treating headache recurrence after emergency department discharge: a randomized controlled trial of naproxen versus sumatriptan. *Ann Emerg Med* 2010; 56: 7–17.
175. Gallagher RM, Dennish G, Spierings EL, et al. A comparative trial of zolmitriptan and sumatriptan for the acute oral treatment of migraine. *Headache* 2000; 40: 119–128.
176. Geraud G, Olesen J, Pfaffenrath V, et al. Comparison of the efficacy of zolmitriptan and sumatriptan: issues in migraine trial design. *Cephalalgia* 2000; 20: 30–38.
177. Geraud G, Compagnon A and Rossi A. Zolmitriptan versus a combination of acetylsalicylic acid and metoclopramide in the acute oral treatment of migraine: a double-blind, randomised, three-attack study. *Eur Neurol* 2002; 47: 88–98.
178. Goadsby PJ, Massiou H, Pascual J, et al. Almotriptan and zolmitriptan in the acute treatment of migraine. *Acta Neurol Scand* 2007; 115: 34–40.
179. Gruffyd-Jones K, Kies B, Middleton A, et al. Zolmitriptan versus sumatriptan for the acute oral treatment of migraine: a randomized, double-blind, international study. *Eur J Neurol* 2001; 8: 237–245.
180. Ho TW, Ferrari MD, Dodick DW, et al. Efficacy and tolerability of MK-0974 (telcagepant), a new oral antagonist of calcitonin gene-related peptide receptor, compared with zolmitriptan for acute migraine: a randomised, placebo-controlled, parallel-treatment trial. *Lancet* 2008; 372: 2115–2123.
181. Ho TW, Mannix LK, Fan X, et al. Randomized controlled trial of an oral CGRP receptor antagonist, MK-0974, in acute treatment of migraine. *Neurology* 2008; 70: 1304–1312.
182. Ishkanian G, Blumenthal H, Webster CJ, et al. Efficacy of sumatriptan tablets in migraineurs self-described or physician-diagnosed as having sinus headache: a randomized, double-blind, placebo-controlled study. *Clin Ther* 2007; 29: 99–109.
183. Klassen A, Elkind A, Asgharnejad M, et al. Naratriptan is effective and well tolerated in the acute treatment of migraine. Results of a double-blind, placebo-controlled, parallel-group study. Naratriptan S2WA3001 study group. *Headache* 1997; 37: 640–645.
184. Kolodny A, Polis A, Battisti WP, et al. Rizatriptan protocol 052 study G. Comparison of rizatriptan 5 mg and 10 mg tablets and sumatriptan 25 mg and 50 mg tablets. *Cephalalgia* 2004; 24: 540–546.
185. Kudrow D, Thomas HM, Ruoff G, et al. Valdecoxib for treatment of a single, acute, moderate to severe migraine headache. *Headache* 2005; 45: 1151–1162.
186. Lipton RB, Dodick DW, Adelman JU, et al. Consistency of response to sumatriptan/naproxen sodium in a placebo-controlled, crossover study. *Cephalalgia* 2009; 29: 826–836.
187. A study to compare oral sumatriptan with oral aspirin plus oral metoclopramide in the acute treatment of migraine. The oral sumatriptan and aspirin plus metoclopramide comparative study group. *Eur Neurol* 1992; 32: 177–184.
188. Ryan R, Geraud G, Goldstein J, et al. Clinical efficacy of frovatriptan: placebo-controlled studies. *Headache* 2002; 42(Suppl 2): S84–92.
189. Sandrini G, Cerbo R, Del Bene E, et al. Efficacy of dosing and re-dosing of two oral fixed combinations of indomethacin, prochlorperazine and caffeine compared with oral sumatriptan in the acute treatment of multiple migraine attacks: a double-blind, double-dummy, randomised, parallel group, multicentre study. *Int J Clin Pract* 2007; 61: 1256–1269.
190. Savi L, Omboni S, Lisotto C, et al. A double-blind, randomized, multicenter, Italian study of frovatriptan versus rizatriptan for the acute treatment of migraine. *J Headache Pain* 2011; 12: 219–226.

191. Schulman EA. Transdermal sumatriptan for acute treatment of migraineurs with baseline nausea. *Headache* 2012; 52: 204–212.
192. Schulman EA, Cady RK, Henry D, et al. Effectiveness of sumatriptan in reducing productivity loss due to migraine: results of a randomized, double-blind, placebo-controlled clinical trial. *Mayo Clin Proc* 2000; 75: 782–789.
193. Spierings EL, Gomez-Mancilla B, Grosz DE, et al. Oral almotriptan vs. Oral sumatriptan in the abortive treatment of migraine: a double-blind, randomized, parallel-group, optimum-dose comparison. *Arch Neurol* 2001; 58: 944–950.
194. Tfelt-Hansen P, Henry P, Mulder LJ, et al. The effectiveness of combined oral lysine acetylsalicylate and metoclopramide compared with oral sumatriptan for migraine. *Lancet* 1995; 346: 923–926.
195. Sunshine A, Mulhern SA, Olson N, et al. Comparative sensitivity of stopwatch methodology and conventional pain assessment measures for detecting early response to triptans in migraine: results of a randomized, open-label pilot study. *Clin Ther* 2006; 28: 1107–1115.
196. Self-treatment of acute migraine with subcutaneous sumatriptan using an auto-injector device. The sumatriptan auto-injector study group. *Eur Neurol* 1991; 31: 323–331.
197. Touchon J, Bertin L, Pilgrim AJ, et al. A comparison of subcutaneous sumatriptan and dihydroergotamine nasal spray in the acute treatment of migraine. *Neurology* 1996; 47: 361–365.
198. Sumatriptan–an oral dose-defining study. The oral sumatriptan dose-defining study group. *Eur Neurol* 1991; 31: 300–305.
199. Cutler N, Mushet GR, Davis R, et al. Oral sumatriptan for the acute treatment of migraine: evaluation of three dosage strengths. *Neurology* 1995; 45: S5–9.
200. Tullo V, Allais G, Ferrari MD, et al. Frovatriptan versus zolmitriptan for the acute treatment of migraine: a double-blind, randomized, multicenter, Italian study. *Neurol Sci* 2010; 31(Suppl 1): S51–4.
201. Freitag F, Taylor FR, Hamid MA, et al. Elimination of migraine-associated nausea in patients treated with rizatriptan orally disintegrating tablet (ODT): a randomized, double-blind, placebo-controlled study. *Headache* 2008; 48: 368–377.
202. Sargent J, Kirchner JR, Davis R, et al. Oral sumatriptan is effective and well tolerated for the acute treatment of migraine: results of a multicenter study. *Neurology* 1995; 45: S10–4.
203. Negro A, Koverech A and Martelletti P. Serotonin receptor agonists in the acute treatment of migraine: a review on their therapeutic potential. *J Pain Res* 2018; 11: 515–526.
204. Edvinsson L, Uddman E, Wackenfors A, et al. Triptan-induced contractile (5-HT1B receptor) responses in human cerebral and coronary arteries: relationship to clinical effect. *Clin Sci (Lond)* 2005; 109: 335–342.
205. Zebenholzer K, Gall W, Gleiss A, et al. Triptans and vascular comorbidity in persons over fifty: findings from a nationwide insurance database - A cohort study. *Headache* 2022; 62: 604–612.
206. Roberto G, Raschi E, Piccinni C, et al. Adverse cardiovascular events associated with triptans and ergotamines for treatment of migraine: systematic review of observational studies. *Cephalalgia* 2015; 35: 118–131.
207. Diener HC. The risks or lack thereof of migraine treatments in vascular disease. *Headache* 2020; 60: 649–653.
208. Cooper W, Doty EG, Hochstetler H, et al. The current state of acute treatment for migraine in adults in the United States. *Postgrad Med* 2020; 132: 581–589.
209. Thorlund K, Toor K, Wu P, et al. Comparative tolerability of treatments for acute migraine: a network meta-analysis. *Cephalalgia* 2017; 37: 965–978.
210. Dodick DW, Martin VT, Smith T, et al. Cardiovascular tolerability and safety of triptans: a review of clinical data. *Headache* 2004; 44(Suppl 1): S20–30.
211. Dodick DW and Martin V. Triptans and CNS side-effects: pharmacokinetic and metabolic mechanisms. *Cephalalgia* 2004; 24: 417–424.
212. Valade D. Early treatment of acute migraine: new evidence of benefits. *Cephalalgia* 2009; 29(Suppl 3): 15–21.
213. Lainez M. Clinical benefits of early triptan therapy for migraine. *Cephalalgia* 2004; 24(Suppl 2): 24–30.
214. Lanteri-Minet M, Mick G and Allaf B. Early dosing and efficacy of triptans in acute migraine treatment: the TEMPO study. *Cephalalgia* 2012; 32: 226–235.
215. Freitag F, Smith T, Mathew N, et al. Effect of early intervention with almotriptan vs placebo on migraine-associated functional disability: results from the AEGIS trial. *Headache* 2008; 48: 341–354.
216. Bernstein C and Burstein R. Sensitization of the trigeminovascular pathway: perspective and implications to migraine pathophysiology. *J Clin Neurol* 2012; 8: 89–99.
217. Lipton RB, Munjal S, Buse DC, et al. Allodynia is associated with initial and sustained response to acute migraine treatment: results from the American migraine prevalence and prevention study. *Headache* 2017; 57: 1026–1040.
218. Klapper J, Mathew N and Nett R. Triptans in the treatment of basilar migraine and migraine with prolonged aura. *Headache* 2001; 41: 981–984.
219. Artto V, Nissila M, Wessman M, et al. Treatment of hemiplegic migraine with triptans. *Eur J Neurol* 2007; 14: 1053–1056.
220. Hansen JM and Charles A. Differences in treatment response between migraine with aura and migraine without aura: lessons from clinical practice and RCTs. *J Headache Pain* 2019; 20: 96.
221. Bates D, Ashford E, Dawson R, et al. Subcutaneous sumatriptan during the migraine aura. Sumatriptan aura study group. *Neurology* 1994; 44: 1587–1592.
222. Olesen J, Diener HC, Schoenen J, et al. No effect of eletriptan administration during the aura phase of migraine. *Eur J Neurol* 2004; 11: 671–677.
223. Klapper J, Lucas C, Rosjo O, et al., group Zs. Benefits of treating highly disabled migraine patients with zolmitriptan while pain is mild. *Cephalalgia* 2004; 24: 918–924.
224. Mathew PG, Krel R, Buddhdev B, et al. A retrospective analysis of triptan and dhe use for basilar and hemiplegic migraine. *Headache* 2016; 56: 841–848.
225. Aurora SK, Papapetropoulos S, Kori SH, et al. Gastric stasis in migraineurs: etiology, characteristics, and clinical and therapeutic implications. *Cephalalgia* 2013; 33: 408–415.
226. Arca KN, Cai J, Wang F, et al. Migraine and gastroparesis. *Curr Neurol Neurosci Rep* 2022; 22: 813–821.

227. Kassem AA. Formulation approaches of triptans for management of migraine. *Curr Drug Deliv* 2016; 13: 882–898.
228. Gladstone JP and Gawel M. Newer formulations of the triptans: advances in migraine management. *Drugs* 2003; 63: 2285–2305.
229. Lainez MJ, Garcia-Casado A and Gascon F. Optimal management of severe nausea and vomiting in migraine: improving patient outcomes. *Patient Relat Outcome Meas* 2013; 4: 61–73.
230. Martin V, Hoekman J, Aurora SK, et al. Nasal delivery of acute medications for migraine: the upper versus lower nasal space. *J Clin Med* 2021; 10: 2468.
231. Moore JC and Miner JR. Subcutaneous delivery of sumatriptan in the treatment of migraine and primary headache. *Patient Prefer Adherence* 2012; 6: 27–37.
232. Ferrari MD, James MH, Bates D, et al. Oral sumatriptan: effect of a second dose, and incidence and treatment of headache recurrences. *Cephalalgia* 1994; 14: 330–338.
233. De Felice M, Ossipov MH, Wang R, et al. Triptan-induced latent sensitization: a possible basis for medication overuse headache. *Ann Neurol* 2010; 67: 325–337.
234. Geraud G, Keywood C and Senard JM. Migraine headache recurrence: relationship to clinical, pharmacological, and pharmacokinetic properties of triptans. *Headache* 2003; 43: 376–388.
235. Sacco S, Lampl C, Amin FM, et al. European headache federation (EHF) consensus on the definition of effective treatment of a migraine attack and of triptan failure. *J Headache Pain* 2022; 23: 133.
236. Dahlof CG. Infrequent or non-response to oral sumatriptan does not predict response to other triptans–review of four trials. *Cephalalgia* 2006; 26: 98–106.
237. Yang CP, Liang CS, Chang CM, et al. Comparison of new pharmacologic agents with triptans for treatment of migraine: a systematic review and meta-analysis. *JAMA Netw Open* 2021; 4: e2128544.
238. Bigal ME, Serrano D, Buse D, et al. Acute migraine medications and evolution from episodic to chronic migraine: a longitudinal population-based study. *Headache* 2008; 48: 1157–1168.
239. Ferrari A, Tiraferri I, Neri L, et al. Why pharmacokinetic differences among oral triptans have little clinical importance: a comment. *J Headache Pain* 2011; 12: 5–12.
240. Goldberg MR, Sciberras D, De Smet M, et al. Influence of beta-adrenoceptor antagonists on the pharmacokinetics of rizatriptan, a 5-HT1B/1D agonist: differential effects of propranolol, nadolol and metoprolol. *Br J Clin Pharmacol* 2001; 52: 69–76.
241. Reddy DS. The pathophysiological and pharmacological basis of current drug treatment of migraine headache. *Expert Rev Clin Pharmacol* 2013; 6: 271–288.
242. Fleishaker JC, Ryan KK, Jansat JM, et al. Effect of MAO-A inhibition on the pharmacokinetics of almotriptan, an antimigraine agent in humans. *Br J Clin Pharmacol* 2001; 51: 437–441.
243. Gillman PK. Triptans, serotonin agonists, and serotonin syndrome (serotonin toxicity): a review. *Headache* 2010; 50: 264–272.
244. Evans RW, Tepper SJ, Shapiro RE, et al. The FDA alert on serotonin syndrome with use of triptans combined with selective serotonin reuptake inhibitors or selective serotonin-norepinephrine reuptake inhibitors: American headache society position paper. *Headache* 2010; 50: 1089–1099.
245. McEnroe JD and Fleishaker JC. Clinical pharmacokinetics of almotriptan, a serotonin 5-HT(1B/1D) receptor agonist for the treatment of migraine. *Clin Pharmacokinet* 2005; 44: 237–246.
246. Dixon R, French S, Kemp J, et al. The metabolism of zolmitriptan: effects of an inducer and an inhibitor of cytochrome p450 on its pharmacokinetics in healthy volunteers. *Clin Drug Investig* 1998; 15: 515–522.
247. Maasumi K, Tepper SJ and Kriegler JS. Menstrual migraine and treatment options: review. *Headache* 2017; 57: 194–208.
248. Hu Y, Guan X, Fan L, et al. Triptans in prevention of menstrual migraine: a systematic review with meta-analysis. *J Headache Pain* 2013; 14: 7.
249. Burch R. Epidemiology and treatment of menstrual migraine and migraine during pregnancy and lactation: a narrative review. *Headache* 2020; 60: 200–216.
250. Marchenko A, Etwel F, Olutunfese O, et al. Pregnancy outcome following prenatal exposure to triptan medications: a meta-analysis. *Headache* 2015; 55: 490–501.
251. Spielmann K, Kayser A, Beck E, et al. Pregnancy outcome after anti-migraine triptan use: a prospective observational cohort study. *Cephalalgia* 2018; 38: 1081–1092.
252. American Academy of Pediatrics Committee on D. Transfer of drugs and other chemicals into human milk. *Pediatrics* 2001; 108: 776–789.
253. Hutchinson S, Marmura MJ, Calhoun A, et al. Use of common migraine treatments in breast-feeding women: a summary of recommendations. *Headache* 2013; 53: 614–627.
254. Stern JI, Datta S, Chiang CC, et al. Narrative review of migraine management in patients with renal or hepatic disease. *Headache* 2023; 63: 9–24.
255. Ong JJY and De Felice M. Migraine treatment: current acute medications and their potential mechanisms of action. *Neurotherapeutics* 2018; 15: 274–290.
256. Prescott LF. Paracetamol: past, present, and future. *Am J Ther* 2000; 7: 143–147.
257. McGill MR and Hinson JA. The development and hepatotoxicity of Acetaminophen: reviewing over a century of progress. *Drug Metab Rev* 2020; 52: 472–500.
258. Ghanem CI, Perez MJ, Manautou JE, et al. Acetaminophen From liver to brain: new insights into drug pharmacological action and toxicity. *Pharmacol Res* 2016; 109: 119–131.
259. Zafeiri A, Raja EA, Mitchell RT, et al. Maternal over-the-counter analgesics use during pregnancy and adverse perinatal outcomes: cohort study of 151 141 singleton pregnancies. *BMJ Open* 2022; 12: e048092.
260. Tadokoro-Cuccaro R, Fisher BG, Thankamony A, et al. Maternal paracetamol intake during pregnancy-impacts on offspring reproductive development. *Front Toxicol* 2022; 4: 884704.
261. Bauer AZ, Swan SH, Kriebel D, et al. Paracetamol use during pregnancy - a call for precautionary action. *Nat Rev Endocrinol* 2021; 17: 757–766.
262. Patel R, Sushko K, van den Anker J, et al. Long-Term safety of prenatal and neonatal exposure to paracetamol:

a systematic review. *Int J Environ Res Public Health* 2022; 19.
263. Hogestatt ED, Jonsson BA, Ermund A, et al. Conversion of Acetaminophen to the bioactive N-acylphenolamine AM404 via fatty acid amide hydrolase-dependent arachidonic acid conjugation in the nervous system. *J Biol Chem* 2005; 280: 31405–31412.
264. Derry S and Moore RA. Paracetamol (Acetaminophen) with or without an antiemetic for acute migraine headaches in adults. *Cochrane Database Syst Rev* 2013: CD008040.
265. Przybyla GW, Szychowski KA and Gminski J. Paracetamol - an old drug with new mechanisms of action. *Clin Exp Pharmacol Physiol* 2020; 48: 3–19.
266. Prior MJ, Codispoti JR and Fu M. A randomized, placebo-controlled trial of Acetaminophen for treatment of migraine headache. *Headache* 2010; 50: 819–833.
267. Lipton RB, Baggish JS, Stewart WF, et al. Efficacy and safety of Acetaminophen in the treatment of migraine: results of a randomized, double-blind, placebo-controlled, population-based study. *Arch Intern Med* 2000; 160: 3486–3492.
268. Phillpotts S, Tash E and Sen S. Glucose-6-phosphate dehydrogenase deficiency: an unusual cause of acute jaundice after paracetamol overdose. *Eur J Haematol* 2014; 93: 446–448.
269. Watkins PB, Kaplowitz N, Slattery JT, et al. Aminotransferase elevations in healthy adults receiving 4 grams of Acetaminophen daily: a randomized controlled trial. *JAMA* 2006; 296: 87–93.
270. Bauer AZ, Kriebel D, Herbert MR, et al. Prenatal paracetamol exposure and child neurodevelopment: a review. *Horm Behav* 2018; 101: 125–147.
271. Kristensen DM, Mazaud-Guittot S, Gaudriault P, et al. Analgesic use - prevalence, biomonitoring and endocrine and reproductive effects. *Nat Rev Endocrinol* 2016; 12: 381–393.
272. Craig DG, Bates CM, Davidson JS, et al. Overdose pattern and outcome in paracetamol-induced acute severe hepatotoxicity. *Br J Clin Pharmacol* 2011; 71: 273–282.
273. Bigal ME and Lipton RB. Excessive acute migraine medication use and migraine progression. *Neurology* 2008; 71: 1821–1828.
274. Westergaard ML, Lau CJ, Allesoe K, et al. Monitoring chronic headache and medication-overuse headache prevalence in Denmark. *Cephalalgia* 2020; 40: 6–18.
275. Goadsby PJ, Lipton RB and Ferrari MD. Migraine–current understanding and treatment. *N Engl J Med* 2002; 346: 257–270.
276. Watkins LR, Milligan ED and Maier SF. Glial proinflammatory cytokines mediate exaggerated pain states: implications for clinical pain. *Adv Exp Med Biol* 2003; 521: 1–21.
277. Burstein R. Deconstructing migraine headache into peripheral and central sensitization. *Pain* 2001; 89: 107–110.
278. Burstein R, Cutrer MF and Yarnitsky D. The development of cutaneous allodynia during a migraine attack clinical evidence for the sequential recruitment of spinal and supraspinal nociceptive neurons in migraine. *Brain* 2000; 123(Pt 8): 1703–1709.
279. Burstein R, Yarnitsky D, Goor-Aryeh I, et al. An association between migraine and cutaneous allodynia. *Ann Neurol* 2000; 47: 614–624.
280. Goadsby PJ. Current concepts of the pathophysiology of migraine. *Neurol Clin* 1997; 15: 27–42.
281. Krymchantowski AV and Jevoux Cda C. The experience of combining agents, specially triptans and non steroidal anti-inflammatory drugs, for the acute treatment of migraine - a review. *Recent Pat CNS Drug Discov* 2007; 2: 141–144.
282. Blumenfeld A, Gennings C and Cady R. Pharmacological synergy: the next frontier on therapeutic advancement for migraine. *Headache* 2012; 52: 636–647.
283. Haag G, Diener HC, May A, et al. Self-medication of migraine and tension-type headache: summary of the evidence-based recommendations of the deutsche migrane und kopfschmerzgesellschaft (DMKG), the deutsche gesellschaft fur neurologie (DGN), the osterreichische kopfschmerzgesellschaft (OKSG) and the schweizerische kopfwehgesellschaft (SKG). *J Headache Pain* 2011; 12: 201–217.
284. Straube A, Aicher B, Fiebich BL, et al. Combined analgesics in (headache) pain therapy: shotgun approach or precise multi-target therapeutics? *BMC Neurol* 2011; 11: 43.
285. Wilkinson M. Editorial: the treatment of acute migraine attacks. *Headache* 1976; 15: 291–292.
286. Dalessio DJ. Aspirin prophylaxis for migraine. *JAMA* 1990; 264: 1721.
287. Buzzi MG, Sakas DE and Moskowitz MA. Indomethacin and acetylsalicylic acid block neurogenic plasma protein extravasation in rat dura mater. *Eur J Pharmacol* 1989; 165: 251–258.
288. Catania A, Arnold J, Macaluso A, et al. Inhibition of acute inflammation in the periphery by central action of salicylates. *Proc Natl Acad Sci U S A* 1991; 88: 8544–8547.
289. Chen AC and Chapman CR. Aspirin analgesia evaluated by event-related potentials in man: possible central action in brain. *Exp Brain Res* 1980; 39: 359–364.
290. Gobel H, Ernst M, Jeschke J, et al. Acetylsalicylic acid activates antinociceptive brain-stem reflex activity in headache patients and in healthy subjects. *Pain* 1992; 48: 187–195.
291. Raffa RB, Stone Jr DJ and Tallarida RJ. Discovery of "self-synergistic" spinal/supraspinal antinociception produced by Acetaminophen (paracetamol). *J Pharmacol Exp Ther* 2000; 295: 291–294.
292. Ghelardini C, Galeotti N and Bartolini A. Caffeine induces central cholinergic analgesia. *Naunyn Schmiedebergs Arch Pharmacol* 1997; 356: 590–595.
293. Baratloo A, Rouhipour A, Forouzanfar MM, et al. The role of caffeine in pain management: a brief literature review. *Anesth Pain Med* 2016; 6: e33193.
294. Yancey JR and Dattoli G. Caffeine as an analgesic adjuvant for acute pain in adults. *Am Fam Physician* 2013; 87: 11.
295. Lipton RB, Diener HC, Robbins MS, et al. Caffeine in the management of patients with headache. *J Headache Pain* 2017; 18: 107.
296. Boppana SH, Peterson M, Du AL, et al. Caffeine: what is its role in pain medicine? *Cureus* 2022; 14: e25603.
297. Fiebich BL, Lieb K, Hull M, et al. Effects of caffeine and paracetamol alone or in combination with acetylsalicylic acid on prostaglandin E(2) synthesis in rat microglial cells. *Neuropharmacology* 2000; 39: 2205–2213.
298. Miners JO. Drug interactions involving aspirin (acetylsalicylic acid) and salicylic acid. *Clin Pharmacokinet* 1989; 17: 327–44.

299. Isola S, Hussain A, Dua A, et al. *Metoclopramide*. Treasure Island (FL): StatPearls, 2023.
300. Chabriat H, Joire JE, Danchot J, et al. Combined oral lysine acetylsalicylate and metoclopramide in the acute treatment of migraine: a multicentre double-blind placebo-controlled study. *Cephalalgia* 1994; 14: 297–300.
301. Azzopardi TD and Brooks NA. Oral metoclopramide as an adjunct to analgesics for the outpatient treatment of acute migraine. *Ann Pharmacother* 2008; 42: 397–402.
302. Friedman BW, Corbo J, Lipton RB, et al. A trial of metoclopramide vs sumatriptan for the emergency department treatment of migraines. *Neurology* 2005; 64: 463–468.
303. Friedman BW, Mulvey L, Esses D, et al. Metoclopramide for acute migraine: a dose-finding randomized clinical trial. *Ann Emerg Med* 2011; 57: 475–82 e1.
304. Colman I, Brown MD, Innes GD, et al. Parenteral metoclopramide for acute migraine: meta-analysis of randomised controlled trials. *BMJ* 2004; 329: 1369–1373.
305. Oldman AD, Smith LA, McQuay HJ, et al. Pharmacological treatments for acute migraine: quantitative systematic review. *Pain* 2002; 97: 247–257.
306. Snow V, Weiss K, Wall EM, et al. American Academy of Family P, American College of Physicians-American Society of Internal M. Pharmacologic management of acute attacks of migraine and prevention of migraine headache. *Ann Intern Med* 2002; 137: 840–849.
307. Adams NJ, Plane MB, Fleming MF, et al. Opioids and the treatment of chronic pain in a primary care sample. *J Pain Symptom Manage* 2001; 22: 791–796.
308. Raffa RB, Friderichs E, Reimann W, et al. Opioid and nonopioid components independently contribute to the mechanism of action of tramadol, an 'atypical' opioid analgesic. *J Pharmacol Exp Ther* 1992; 260: 275–285.
309. Ngo M and Tadi P. *Ergotamine/Caffeine*. Treasure Island (FL): StatPearls, 2023.
310. Tfelt-Hansen P, Saxena PR, Dahlof C, et al. Ergotamine in the acute treatment of migraine: a review and European consensus. *Brain* 2000; 123(Pt 1): 9–18.
311. Silberstein SD. The pharmacology of ergotamine and dihydroergotamine. *Headache* 1997; 37(Suppl 1): S15–25.
312. Berde B, Cerletti A, Dengler HJ, et al. *Studies of the Interaction Between Ergot Alkaloids and Xanthine Derivatives*. London: William Heinemann Medical Books, 1970.
313. Jakubowski M, Levy D, Goor-Aryeh I, et al. Terminating migraine with allodynia and ongoing central sensitization using parenteral administration of COX1/COX2 inhibitors. *Headache* 2005; 45: 850–861.
314. Burstein R, Jakubowski M and Levy D. Naproxen suppresses sensitization in central trigeminovascular neurons. *Neurology* 2006; 66.
315. Jakubowski M, Levy D, Kainz V, et al. Sensitization of central trigeminovascular neurons: blockade by intravenous naproxen infusion. *Neuroscience* 2007; 148: 573–583.
316. Yang LP. Sumatriptan/naproxen sodium: a review of its use in adult patients with migraine. *Drugs* 2013; 73: 1339–1355.
317. Syed YY. Sumatriptan/naproxen sodium: a review in migraine. *Drugs* 2016; 76: 111–121.
318. Anneken K, Evers S and Husstedt IW. Efficacy of fixed combinations of acetylsalicyclic acid, Acetaminophen and caffeine in the treatment of idiopathic headache: a review. *Eur J Neurol* 2010; 17: 534–e25.
319. Ashkenazi A and Silberstein S. Menstrual migraine: a review of hormonal causes, prophylaxis and treatment. *Expert Opin Pharmacother* 2007; 8: 1605–1613.
320. Becker WJ. Acute migraine treatment in adults. *Headache* 2015; 55: 778–793.
321. Kirthi V, Derry S, Moore RA, et al. Aspirin with or without an antiemetic for acute migraine headaches in adults. *Cochrane Database Syst Rev* 2010: CD008041.
322. Fox AW. Efficacy, end points and eventualities: sumatriptan/naproxen versus butalbital/paracetamol/caffeine in the treatment of migraine. *Expert Rev Clin Pharmacol* 2012; 5: 513–516.
323. Fernandez S, Knopf MA, Bjork SK, et al. Bone marrow-derived macrophages express functional CGRP receptors and respond to CGRP by increasing transcription of c-fos and IL-6 mRNA. *Cell Immunol* 2001; 209: 140–148.
324. Loder E. Fixed drug combinations for the acute treatment of migraine : place in therapy. *CNS Drugs* 2005; 19: 769–784.
325. Peck J, Urits I, Zeien J, et al. A comprehensive review of over-the-counter treatment for chronic migraine headaches. *Curr Pain Headache Rep* 2020; 24: 19.
326. Buse DC, Loder EW, Gorman JA, et al. Sex differences in the prevalence, symptoms, and associated features of migraine, probable migraine and other severe headache: results of the American migraine prevalence and prevention (AMPP) study. *Headache* 2013; 53: 1278–1299.
327. Silberstein S, McDonald SA, Goldstein J, et al. Sumatriptan/naproxen sodium for the acute treatment of probable migraine without aura: a randomized study. *Cephalalgia* 2014; 34: 268–279.
328. Tajti J, Majlath Z, Szok D, et al. Drug safety in acute migraine treatment. *Expert Opin Drug Saf* 2015; 14: 891–909.
329. Worthington I, Pringsheim T, Gawel MJ, et al. Canadian Headache society guideline: acute drug therapy for migraine headache. *Can J Neurol Sci* 2013; 40: S1–S80.
330. Asadollahi S, Heidari K, Vafaee R, et al. Promethazine plus sumatriptan in the treatment of migraine: a randomized clinical trial. *Headache* 2014; 54: 94–108.
331. Christie S, Gobel H, Mateos V, et al., Rizatriptan-Ergotamine/Caffeine Preference Study G. Crossover comparison of efficacy and preference for rizatriptan 10 mg versus ergotamine/caffeine in migraine. *Eur Neurol* 2003; 49: 20–29.
332. Derosier F, Sheftell F, Silberstein S, et al. Sumatriptan-naproxen and butalbital: a double-blind, placebo-controlled crossover study. *Headache* 2012; 52: 530–543.
333. Dowson A, Ball K and Haworth D. Comparison of a fixed combination of domperidone and paracetamol (domperamol) with sumatriptan 50 mg in moderate to severe migraine: a randomised UK primary care study. *Curr Med Res Opin* 2000; 16: 190–197.
334. Freitag FG, Cady R, DiSerio F, et al. Comparative study of a combination of isometheptene mucate, dichloralphenazone with Acetaminophen and sumatriptan succinate in the treatment of migraine. *Headache* 2001; 41: 391–398.
335. Goldstein J, Silberstein SD, Saper JR, et al. Acetaminophen, aspirin, and caffeine versus sumatriptan succinate in the

early treatment of migraine: results from the ASSET trial. *Headache* 2005; 45: 973–982.
336. Goldstein J, Hoffman HD, Armellino JJ, et al. Treatment of severe, disabling migraine attacks in an over-the-counter population of migraine sufferers: results from three randomized, placebo-controlled studies of the combination of Acetaminophen, aspirin, and caffeine. *Cephalalgia* 1999; 19: 684–691.
337. Goldstein J, Gawel MJ, Winner P, et al. Comparison of butorphanol nasal spray and fiorinal with codeine in the treatment of migraine. *Headache* 1998; 38: 516–522.
338. Krymchantowski AV, Filho PF and Bigal ME. Rizatriptan vs. Rizatriptan plus trimebutine for the acute treatment of migraine: a double-blind, randomized, cross-over, placebo-controlled study. *Cephalalgia* 2006; 26: 871–874.
339. Le Jeunne C, Gomez JP, Pradalier A, et al. Comparative efficacy and safety of calcium carbasalate plus metoclopramide versus ergotamine tartrate plus caffeine in the treatment of acute migraine attacks. *Eur Neurol* 1999; 41: 37–43.
340. Lipton RB, Stewart WF, Ryan Jr RE, et al. Efficacy and safety of Acetaminophen, aspirin, and caffeine in alleviating migraine headache pain: three double-blind, randomized, placebo-controlled trials. *Arch Neurol* 1998; 55: 210–217.
341. Mathew NT, Landy S, Stark S, et al. Fixed-dose sumatriptan and naproxen in poor responders to triptans with a short half-life. *Headache* 2009; 49: 971–982.
342. Miljkovic S, Smajlovic D, Tiric Campara M, et al. The first comparative double-blind trial on efficacy and safety of ergotamine based five-component combination and sumatriptan in migraine without aura. *Hippokratia* 2018; 22: 17–22.
343. Pradalier A, Guerard des Lauriers A, Scheck F, et al. [Calcium carbasalate-metoclopramide combination versus dihydroergotamine in the treatment of migraine attacks]. *Pathol Biol (Paris)* 1995; 43: 806–813.
344. Schoenen J, De Klippel N, Giurgea S, et al. Almotriptan and its combination with aceclofenac for migraine attacks: a study of efficacy and the influence of auto-evaluated brush allodynia. *Cephalalgia* 2008; 28: 1095–1105.
345. Schulman EA and Dermott KF. Sumatriptan plus metoclopramide in triptan-nonresponsive migraineurs. *Headache* 2003; 43: 729–733.
346. Silberstein SD, Mannix LK, Goldstein J, et al. Multimechanistic (sumatriptan-naproxen) early intervention for the acute treatment of migraine. *Neurology* 2008; 71: 114–121.
347. Silberstein SD, Freitag FG, Rozen TD, et al. Tramadol/Acetaminophen for the treatment of acute migraine pain: findings of a randomized, placebo-controlled trial. *Headache* 2005; 45: 1317–1327.
348. Silberstein SD, Armellino JJ, Hoffman HD, et al. Treatment of menstruation-associated migraine with the nonprescription combination of Acetaminophen, aspirin, and caffeine: results from three randomized, placebo-controlled studies. *Clin Ther* 1999; 21: 475–491.
349. A randomized, double-blind comparison of sumatriptan and cafergot in the acute treatment of migraine. The multinational oral sumatriptan and cafergot comparative study group. *Eur Neurol* 1991; 31: 314–322.
350. Goldstein J, Silberstein SD, Saper JR, et al. Acetaminophen, aspirin, and caffeine in combination versus ibuprofen for acute migraine: results from a multicenter, double-blind, randomized, parallel-group, single-dose, placebo-controlled study. *Headache* 2006; 46: 444–453.
351. Sostres C and Lanas A. Gastrointestinal effects of aspirin. *Nat Rev Gastroenterol Hepatol* 2011; 8: 385–394.
352. Zheng SL and Roddick AJ. Association of aspirin use for primary prevention with cardiovascular events and bleeding events: a systematic review and meta-analysis. *JAMA* 2019; 321: 277–287.
353. van der Woude FJ, Heinemann LA, Graf H, et al. Analgesics use and ESRD in younger age: a case-control study. *BMC Nephrol* 2007; 8: 15.
354. McLaughlin JK, Lipworth L, Chow WH, et al. Analgesic use and chronic renal failure: a critical review of the epidemiologic literature. *Kidney Int* 1998; 54: 679–686.
355. Jozwiak-Bebenista M and Nowak JZ. Paracetamol: mechanism of action, applications and safety concern. *Acta Pol Pharm* 2014; 71: 11–23.
356. Nowaczewska M, Wicinski M and Kazmierczak W. The ambiguous role of caffeine in migraine headache: from trigger to treatment. *Nutrients* 2020; 12: 2259.
357. Grimes JD, Hassan MN and Preston DN. Adverse neurologic effects of metoclopramide. *Can Med Assoc J* 1982; 126: 23–25.
358. Al-Saffar A, Lennernas H and Hellstrom PM. Gastroparesis, metoclopramide, and tardive dyskinesia: risk revisited. *Neurogastroenterol Motil* 2019; 31: e13617.
359. Svendsen K, Wood M, Olsson E, et al. Reported time to onset of neurological adverse drug reactions among different age and gender groups using metoclopramide: an analysis of the global database vigibase(R). *Eur J Clin Pharmacol* 2018; 74: 627–636.
360. Miller LG and Jankovic J. Metoclopramide-induced movement disorders. Clinical findings with a review of the literature. *Arch Intern Med* 1989; 149: 2486–2492.
361. Preuss CV, Kalava A and King KC. *Prescription of Controlled Substances: Benefits and Risks*. Treasure Island (FL): StatPearls, 2023.
362. Vadivelu N, Kai AM, Kodumudi V, et al. The opioid crisis: a comprehensive overview. *Curr Pain Headache Rep* 2018; 22: 16.
363. Dhillon S. Tramadol/paracetamol fixed-dose combination: a review of its use in the management of moderate to severe pain. *Clin Drug Investig* 2010; 30: 711–738.
364. Beakley BD, Kaye AM and Kaye AD. Tramadol, pharmacology, Side effects, and serotonin syndrome: a review. *Pain Physician* 2015; 18: 395–400.
365. Lundqvist C, Gossop M, Russell MB, et al. Severity of analgesic dependence and medication-overuse headache. *J Addict Med* 2019; 13: 346–353.
366. Dydyk AM, Jain NK and Gupta M. *Opioid Use Disorder*. Treasure Island (FL): StatPearls, 2023.
367. Mazer M and Perrone J. Acetaminophen-induced nephrotoxicity: pathophysiology, clinical manifestations, and management. *J Med Toxicol* 2008; 4: 2–6.
368. McCrae JC, Morrison EE, MacIntyre IM, et al. Long-term adverse effects of paracetamol - a review. *Br J Clin Pharmacol* 2018; 84: 2218–2230.
369. Peechakara BV, Tharp JG and Gupta M. *Codeine*. Treasure Island (FL): StatPearls, 2023.

370. Brutzkus JC, Shahrokhi M and Varacallo M. *Naproxen*. Treasure Island (FL): StatPearls, 2023.
371. Brar Y, Hosseini SA and Saadabadi A. *Sumatriptan*. Treasure Island (FL): StatPearls, 2023.
372. Tepper SJ and Millson D. Safety profile of the triptans. *Expert Opin Drug Saf* 2003; 2: 123–132.
373. Gerriets V, Anderson J and Nappe TM. *Acetaminophen*. Treasure Island (FL): StatPearls, 2023.
374. Meyler WJ. Side effects of ergotamine. *Cephalalgia* 1996; 16: 5–10.
375. Wooltorton E. Risk of stroke, gangrene from ergot drug interactions. *CMAJ* 2003; 168: 1015.
376. Glazer G, Myers KA and Davies ER. Ergot poisoning. *Postgrad Med J* 1966; 42: 562–8.
377. Skowronski GA, Tronson MD and Parkin WG. Successful treatment of ergotamine poisoning with sodium nitroprusside. *Med J Aust* 1979; 2: 8–9.
378. Antonaci F, Ghiotto N, Wu S, et al. Recent advances in migraine therapy. *Springerplus* 2016; 5: 637.
379. Lipton RB. Ergotamine tartrate and dihydroergotamine mesylate: safety profiles. *Headache* 1997; 37(Suppl 1): S33–41.
380. Health NIo. FIORICET- butalbital, acetaminophen, and caffeine capsule, https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=c018be7d-f7b8-45e2-97b8-8e7a71740657. (accessed Jan 15, 2023)
381. Rubin A and Winter Jr L. A double-blind randomized study of an aspirin/caffeine combination versus Acetaminophen/aspirin combination versus Acetaminophen versus placebo in patients with moderate to severe post-partum pain. *J Int Med Res* 1984; 12: 338–345.
382. Marmura MJ, Silberstein SD and Schwedt TJ. The acute treatment of migraine in adults: the American headache society evidence assessment of migraine pharmacotherapies. *Headache* 2015; 55: 3–20.
383. Goldstein J, Hagen M and Gold M. Results of a multicenter, double-blind, randomized, parallel-group, placebo-controlled, single-dose study comparing the fixed combination of Acetaminophen, acetylsalicylic acid, and caffeine with ibuprofen for acute treatment of patients with severe migraine. *Cephalalgia* 2014; 34: 1070–1078.
384. Derry CJ, Derry S and Moore RA. Sumatriptan (oral route of administration) for acute migraine attacks in adults. *Cochrane Database Syst Rev* 2012: CD008615.
385. Aurora SK, Barrodale PM, McDonald SA, et al. Revisiting the efficacy of sumatriptan therapy during the aura phase of migraine. *Headache* 2009; 49: 1001–1004.
386. Limmroth V, Katsarava Z, Fritsche G, et al. Features of medication overuse headache following overuse of different acute headache drugs. *Neurology* 2002; 59: 1011–1014.
387. Kristoffersen ES and Lundqvist C. Medication-overuse headache: a review. *J Pain Res* 2014; 7: 367–378.
388. Gibbins AK, Wood PJ and Spark MJ. Managing inappropriate use of non-prescription combination analgesics containing codeine: a modified Delphi study. *Res Social Adm Pharm* 2017; 13: 369–377.
389. Le H, Tfelt-Hansen P, Skytthe A, et al. Increase in self-reported migraine prevalence in the Danish adult population: a prospective longitudinal population-based study. *BMJ Open* 2012; 2: e000962.
390. Kelley NE and Tepper DE. Rescue therapy for acute migraine, part 3: opioids, NSAIDs, steroids, and post-discharge medications. *Headache* 2012; 52: 467–482.
391. Grazzi L, Grignani E, D'Amico D, et al. Is medication overuse drug specific or not? Data from a review of published literature and from an original study on Italian MOH patients. *Curr Pain Headache Rep* 2018; 22: 71.
392. Schnitzer T. The new analgesic combination tramadol/Acetaminophen. *Eur J Anaesthesiol Suppl* 2003; 28: 13–17.
393. Schug SA. Combination analgesia in 2005 - a rational approach: focus on paracetamol-tramadol. *Clin Rheumatol* 2006; 25(Suppl 1): S16–21.
394. Smith HS. Potential analgesic mechanisms of Acetaminophen. *Pain Physician* 2009; 12: 269–280.
395. Castaneda-Hernandez G, Castillo-Mendez MS, Lopez-Munoz FJ, et al. Potentiation by caffeine of the analgesic effect of aspirin in the pain-induced functional impairment model in the rat. *Can J Physiol Pharmacol* 1994; 72: 1127–1131.
396. Tukker JJ, Sitsen JM and Gusdorf CF. Bioavailability of paracetamol after oral administration to healthy volunteers. Influence of caffeine on rate and extent of absorption. *Pharm Weekbl Sci* 1986; 8: 239–243.
397. Renner B, Clarke G, Grattan T, et al. Caffeine accelerates absorption and enhances the analgesic effect of Acetaminophen. *J Clin Pharmacol* 2007; 47: 715–726.
398. Yoovathaworn KC, Sriwatanakul K and Thithapandha A. Influence of caffeine on aspirin pharmacokinetics. *Eur J Drug Metab Pharmacokinet* 1986; 11: 71–76.
399. Weiser T and Weigmann H. Effect of caffeine on the bioavailability and pharmacokinetics of an acetylsalicylic acid-paracetamol combination: results of a phase I study. *Adv Ther* 2019; 36: 597–607.
400. Bhandari M, Bhandari A and Bhandari A. Recent updates on codeine. *Pharm Methods* 2011; 2: 3–8.
401. Mattia C and Coluzzi F. A look inside the association codeine-paracetamol: clinical pharmacology supports analgesic efficacy. *Eur Rev Med Pharmacol Sci* 2015; 19: 507–516.
402. Somogyi A, Bochner F and Chen ZR. Lack of effect of paracetamol on the pharmacokinetics and metabolism of codeine in man. *Eur J Clin Pharmacol* 1991; 41: 379–382.
403. Sonne J, Poulsen HE, Loft S, et al. Therapeutic doses of codeine have no effect on Acetaminophen clearance or metabolism. *Eur J Clin Pharmacol* 1988; 35: 109–111.
404. Leppert W. CYP2D6 In the metabolism of opioids for mild to moderate pain. *Pharmacology* 2011; 87: 274–285.
405. Kirchheiner J, Schmidt H, Tzvetkov M, et al. Pharmacokinetics of codeine and its metabolite morphine in ultra-rapid metabolizers due to CYP2D6 duplication. *Pharmacogenomics J* 2007; 7: 257–265.
406. Samer CF, Lorenzini KI, Rollason V, et al. Applications of CYP450 testing in the clinical setting. *Mol Diagn Ther* 2013; 17: 165–84.
407. Grond S and Sablotzki A. Clinical pharmacology of tramadol. *Clin Pharmacokinet* 2004; 43: 879–923.
408. Mattia C, Coluzzi F, Sarzi Puttini P, et al. Paracetamol/tramadol association: the easy solution for mild-moderate pain. *Minerva Med* 2008; 99: 369–390.

409. Tallarida RJ and Raffa RB. Testing for synergism over a range of fixed ratio drug combinations: replacing the isobologram. *Life Sci* 1996; 58: PL 23–8.
410. Filitz J, Ihmsen H, Gunther W, et al. Supra-additive effects of tramadol and Acetaminophen in a human pain model. *Pain* 2008; 136: 262–270.
411. Miotto K, Cho AK, Khalil MA, et al. Trends in tramadol: pharmacology, metabolism, and misuse. *Anesth Analg* 2017; 124: 44–51.
412. Liao S, Li X and Larson K. Population pharmacokinetics of tramadol and Acetaminophen given orally as a single dose combination tablet in healthy volunteers. *Clin Ther* 1999; 65: 122.
413. Health NIo. Ultracet: 37.5 mg tramadol hydrochloride/ 325 mg acetaminophen tablets, https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=750e7372-022b-454e-86c4-e4b325fb9f42. (accessed Jan 15, 2023)
414. Moron Merchante I, Pergolizzi Jr JV, van de Laar M, et al. Tramadol/paracetamol fixed-dose combination for chronic pain management in family practice: a clinical review. *ISRN Family Med* 2013: 638469.
415. Dolgorukova A, Osipchuk AV, Murzina AA, et al. The influence of metoclopramide on trigeminovascular nociception: possible anti-migraine mechanism of action. *Neuroscience* 2020; 425: 123–133.
416. Webb D, Buss DC, Fifield R, et al. The plasma protein binding of metoclopramide in health and renal disease. *Br J Clin Pharmacol* 1986; 21: 334–336.
417. Bateman DN. Clinical pharmacokinetics of metoclopramide. *Clin Pharmacokinet* 1983; 8: 523–529.
418. Volans GN. The effect of metoclopramide on the absorption of effervescent aspirin in migraine. *Br J Clin Pharmacol* 1975; 2: 57–63.
419. Tokola RA, Kangasniemi P, Neuvonen PJ, et al. Tolfenamic acid, metoclopramide, caffeine and their combinations in the treatment of migraine attacks. *Cephalalgia* 1984; 4: 253–263.
420. Duggan KC, Walters MJ, Musee J, et al. Molecular basis for cyclooxygenase inhibition by the non-steroidal anti-inflammatory drug naproxen. *J Biol Chem* 2010; 285: 34950–34959.
421. Vause CV and Durham PL. Identification of cytokines and signaling proteins differentially regulated by sumatriptan/naproxen. *Headache* 2012; 52: 80–89.
422. Berges A, Robertson J, Upward J, et al. Pharmacokinetics, safety, and tolerability following the administration of a single dose of a combination tablet containing sumatriptan and naproxen sodium in adolescent patients with migraine and in healthy adult volunteers. *Clin Pharmacol Drug Dev* 2012; 1: 85–92.
423. Administration FaD. Treximet® (sumatriptan/naproxen sodium): US Prescribing Information, https://www.accessdata.fda.gov/drugsatfda_docs/label/2016/021926s013lbl.pdf. (accessed Jan 15, 2023)
424. Hargreaves RJ. Pharmacology and potential mechanisms of action of rizatriptan. *Cephalalgia* 2000; 20(Suppl 1): 2–9.
425. Silberstein SD and McCrory DC. Ergotamine and dihydroergotamine: history, pharmacology, and efficacy. *Headache* 2003; 43: 144–166.
426. Fischer MA and Jan A. *Medication-Overuse Headache*. Treasure Island (FL): StatPearls, 2023.
427. Anderson JR, Drehsen G and Pitman IH. Effect of caffeine on ergotamine absorption from rat small intestine. *J Pharm Sci* 1981; 70: 651–657.
428. Johnson AG, Seidemann P and Day RO. NSAID-related adverse drug interactions with clinical relevance. An update. *Int J Clin Pharmacol Ther* 1994; 32: 509–532.
429. Rajah SM, Penny AF, Crow MJ, et al. The interaction of varying doses of dipyridamole and acetyl salicylic acid on the inhibition of platelet functions and their effect on bleeding time. *Br J Clin Pharmacol* 1979; 8: 483–489.
430. Johnson AG, Seideman P and Day RO. Adverse drug interactions with nonsteroidal anti-inflammatory drugs (NSAIDs). recognition, management and avoidance. *Drug Saf* 1993; 8: 99–127.
431. Brouwers JR and de Smet PA. Pharmacokinetic-pharmacodynamic drug interactions with nonsteroidal anti-inflammatory drugs. *Clin Pharmacokinet* 1994; 27: 462–485.
432. Goulden KJ, Dooley JM, Camfield PR, et al. Clinical valproate toxicity induced by acetylsalicylic acid. *Neurology* 1987; 37: 1392–1394.
433. Verbeeck RK. Pharmacokinetic drug interactions with nonsteroidal anti-inflammatory drugs. *Clin Pharmacokinet* 1990; 19: 44–66.
434. Jain A, McMahon FG, Slattery JT, et al. Effect of naproxen on the steady-state serum concentration and anticoagulant activity of warfarin. *Clin Pharmacol Ther* 1979; 25: 61–66.
435. Chen MM and Lee CS. Cimetidine–Acetaminophen interaction in humans. *J Clin Pharmacol* 1985; 25: 227–229.
436. Parikh S, Dillon LC and Scharf SL. Hepatotoxicity possibly due to paracetamol with carbamazepine. *Intern Med J* 2004; 34: 441–442.
437. Dimova S and Stoytchev T. Influence of rifampicin on the toxicity and the analgesic effect of Acetaminophen. *Eur J Drug Metab Pharmacokinet* 1994; 19: 311–317.
438. Kostrubsky SE, Sinclair JF, Strom SC, et al. Phenobarbital and phenytoin increased Acetaminophen hepatotoxicity due to inhibition of UDP-glucuronosyltransferases in cultured human hepatocytes. *Toxicol Sci* 2005; 87: 146–155.
439. Faber MS, Jetter A and Fuhr U. Assessment of CYP1A2 activity in clinical practice: why, how, and when? *Basic Clin Pharmacol Toxicol* 2005; 97: 125–134.
440. Jeppesen U, Loft S, Poulsen HE, et al. A fluvoxamine-caffeine interaction study. *Pharmacogenetics* 1996; 6: 213–222.
441. Haller CA, Jacob 3rd P and Benowitz NL. Enhanced stimulant and metabolic effects of combined ephedrine and caffeine. *Clin Pharmacol Ther* 2004; 75: 259–273.
442. Kamerman PR, Becker N and Fick LG. Interactions between metoclopramide and morphine: enhanced antinociception and motor dysfunction in rats. *Clin Exp Pharmacol Physiol* 2007; 34: 106–112.
443. Mazhar F, Akram S, Haider N, et al. Overlapping of serotonin syndrome with neuroleptic malignant syndrome due to linezolid-fluoxetine and olanzapine-metoclopramide interactions: a case report of two serious adverse drug effects caused by medication reconciliation failure on hospital admission. *Case Rep Med* 2016: 7128909.
444. Harada T, Hirosawa T, Morinaga K, et al. Metoclopramide-induced serotonin syndrome. *Intern Med* 2017; 56: 737–739.

445. Fisher AA and Davis MW. Serotonin syndrome caused by selective serotonin reuptake-inhibitors-metoclopramide interaction. *Ann Pharmacother* 2002; 36: 67–71.
446. Albibi R and McCallum RW. Metoclopramide: pharmacology and clinical application. *Ann Intern Med* 1983; 98: 86–95.
447. Johnson BF, Bustrack JA, Urbach DR, et al. Effect of metoclopramide on digoxin absorption from tablets and capsules. *Clin Pharmacol Ther* 1984; 36: 724–730.
448. Morricone L, Murari M, Bombonato M, et al. Effect of acute administration of metoclopramide on insulin secretion in man. *Acta Diabetol Lat* 1990; 27: 53–57.
449. Heiskanen T and Kalso E. Non-analgesic effects of opioids: interactions between opioids and other drugs. *Curr Pharm Des* 2012; 18: 6079–6089.
450. Boostani R and Derakhshan S. Tramadol induced seizure: a 3-year study. *Caspian J Intern Med* 2012; 3: 484–487.
451. Dumo PA and Kielbasa LA. Successful anticoagulation and continuation of tramadol therapy in the setting of a tramadol-warfarin interaction. *Pharmacotherapy* 2006; 26: 1654–1657.
452. Sabbe JR, Sims PJ and Sims MH. Tramadol-warfarin interaction. *Pharmacotherapy* 1998; 18: 871–873.
453. Eadie MJ. Clinically significant drug interactions with agents specific for migraine attacks. *CNS Drugs* 2001; 15: 105–118.
454. Oberhardt F and Fox AW. Oral sumatriptan and almotriptan–delimiting the MAOI effect. *Headache* 2012; 52: 765–772.
455. Van Haarst AD, Van Gerven JM, Cohen AF, et al. The effects of moclobemide on the pharmacokinetics of the 5-HT1B/1D agonist rizatriptan in healthy volunteers. *Br J Clin Pharmacol* 1999; 48: 190–196.
456. Gardner DM and Lynd LD. Sumatriptan contraindications and the serotonin syndrome. *Ann Pharmacother* 1998; 32: 33–38.
457. Goldberg MR, Lowry RC, Musson DG, et al. Lack of pharmacokinetic and pharmacodynamic interaction between rizatriptan and paroxetine. *J Clin Pharmacol* 1999; 39: 192–199.
458. Dresser GK, Spence JD and Bailey DG. Pharmacokinetic-pharmacodynamic consequences and clinical relevance of cytochrome P450 3A4 inhibition. *Clin Pharmacokinet* 2000; 38: 41–57.
459. Gandy W. Dihydroergotamine interaction with propranolol. *Ann Emerg Med* 1990; 19: 221.
460. Amundsen S, Nordeng H, Nezvalova-Henriksen K, et al. Pharmacological treatment of migraine during pregnancy and breastfeeding. *Nat Rev Neurol* 2015; 11: 209–219.
461. Bloor M and Paech M. Nonsteroidal anti-inflammatory drugs during pregnancy and the initiation of lactation. *Anesth Analg* 2013; 116: 1063–1075.
462. James JE. Maternal caffeine consumption and pregnancy outcomes: a narrative review with implications for advice to mothers and mothers-to-be. *BMJ Evid Based Med* 2021; 26: 114–115.
463. Lacroix I, Hurault-Delarue C, Viard D, et al. Use of triptans during pregnancy? With caution!. *Therapie* 2021; 76: 477–478.
464. Soldin OP, Dahlin J and O'Mara DM. Triptans in pregnancy. *Ther Drug Monit* 2008; 30: 5–9.
465. Banhidy F, Acs N, Puho E, et al. Ergotamine treatment during pregnancy and a higher rate of low birthweight and preterm birth. *Br J Clin Pharmacol* 2007; 64: 510–516.
466. Hughes HE and Goldstein DA. Birth defects following maternal exposure to ergotamine, beta blockers, and caffeine. *J Med Genet* 1988; 25: 396–399.
467. Acetaminophen. *Drugs and lactation database (LactMed(R))*. Bethesda (MD), 2006.
468. Codeine. *Drugs and lactation database (LactMed(R))*. Bethesda (MD), 2006.
469. Amundsen S, Nordeng H, Fuskevag OM, et al. Transfer of triptans into human breast milk and estimation of infant drug exposure through breastfeeding. *Basic Clin Pharmacol Toxicol* 2021; 128: 795–804.
470. Jolivet A, Robyn C, Huraux-Rendu C, et al. [Effect of ergot alkaloid derivatives on milk secretion in the immediate postpartum period]. *J Gynecol Obstet Biol Reprod (Paris)* 1978; 7: 129–134.
471. Organization WH. Breastfeeding and maternal medication - Recommendations for drugs in the eleventh WHO model list of essential drug, https://www.who.int/publications/i/item/55732. (accessed Jan 15, 2023)
472. Pham PC, Khaing K, Sievers TM, et al. 2017 Update on pain management in patients with chronic kidney disease. *Clin Kidney J* 2017; 10: 688–697.
473. Kanchanasurakit S, Arsu A, Siriplabpla W, et al. Acetaminophen Use and risk of renal impairment: a systematic review and meta-analysis. *Kidney Res Clin Pract* 2020; 39: 81–92.
474. Foundation NK. Pain Medicines (Analgesics), https://www.kidney.org/atoz/content/painmeds_analgesics. (accessed Jan 15, 2023)
475. Murphy EJ. Acute pain management pharmacology for the patient with concurrent renal or hepatic disease. *Anaesth Intensive Care* 2005; 33: 311–322.
476. Mercadante S and Arcuri E. Opioids and renal function. *J Pain* 2004; 5: 2–19.
477. Lund J. Prolonged renal impairment after chronic ergotamine intoxication. *Nephrol Dial Transplant* 1992; 7: 879–880.
478. Williams M and Coulson J. Isolated paracetamol-induced acute kidney injury: a systematic review. *Acute Med* 2022; 21: 96–103.
479. Fulton JA, Kahn J, Nelson LS, et al. Renal infarction during the use of rizatriptan and zolmitriptan: two case reports. *Clin Toxicol (Phila)* 2006; 44: 177–180.
480. Akhigbe RE, Ajayi LO, Adelakun AA, et al. Codeine-induced hepatic injury is via oxido-inflammatory damage and caspase-3-mediated apoptosis. *Mol Biol Rep* 2020; 47: 9521–9530.
481. Tramadol. *Livertox: clinical and research information on drug-induced liver injury*. Bethesda (MD), 2012.
482. Prescott LF. Hepatotoxicity of mild analgesics. *Br J Clin Pharmacol* 1980; 10(Suppl 2): 373S–9S.
483. Laster J and Satoskar R. Aspirin-Induced acute liver injury. *ACG Case Rep J* 2014; 2: 48–49.
484. Serotonin Receptor Agonists (Triptans). *Livertox: clinical and research information on drug-induced liver injury*. Bethesda (MD), 2012.
485. Fard JK, Hamzeiy H, Sattari M, et al. Triazole rizatriptan induces liver toxicity through lysosomal/mitochondrial dysfunction. *Drug Res (Stuttg)* 2016; 66: 470–478.
486. Hendren G, Aponte-Feliciano A and Kovac A. Safety and efficacy of commonly used antiemetics. *Expert Opin Drug Metab Toxicol* 2015; 11: 1753–1767.

487. Tek DS, McClellan DS, Olshaker JS, et al. A prospective, double-blind study of metoclopramide hydrochloride for the control of migraine in the emergency department. *Ann Emerg Med* 1990; 19: 1083–1087.
488. Tfelt-Hansen P, Olesen J, Aebelholt-Krabbe A, et al. A double blind study of metoclopramide in the treatment of migraine attacks. *J Neurol Neurosurg Psychiatry* 1980; 43: 369–371.
489. Sharma S, Prasad A, Nehru R, et al. Efficacy and tolerability of prochlorperazine buccal tablets in treatment of acute migraine. *Headache* 2002; 42: 896–902.
490. Iserson KV. Parenteral chlorpromazine treatment of migraine. *Ann Emerg Med* 1983; 12: 756–758.
491. Waelkens J. Domperidone in the prevention of complete classical migraine. *Br Med J (Clin Res Ed)* 1982; 284: 944.
492. *Goodman & Gilman's Pharmacological Basis of Therapeutics. 14th ed.* McGraw-Hill, 2023.
493. National Academies of Sciences E, and Medicine; Health and Medicine Division; Board on Health Care Services; Committee on Evidence-Based Clinical Practice Guidelines for Prescribing Opioids for Acute Pain. Framing Opioid Prescribing Guidelines, https://www.ncbi.nlm.nih.gov/books/NBK554977/. (accessed Jan 15, 2023)
494. Brat GA, Agniel D, Beam A, et al. Postsurgical prescriptions for opioid naive patients and association with overdose and misuse: retrospective cohort study. *BMJ* 2018; 360: j5790.
495. DeWeerdt S. Tracing the US opioid crisis to its roots. *Nature* 2019; 573: S10–S2.
496. Busse JW, Craigie S, Juurlink DN, et al. Guideline for opioid therapy and chronic noncancer pain. *CMAJ* 2017; 189: E659–E66.
497. Dowell D, Ragan KR, Jones CM, et al. CDC Clinical practice guideline for prescribing opioids for pain - United States, 2022. *MMWR Recomm Rep* 2022; 71: 1–95.
498. Nadeau SE, Wu JK and Lawhern RA. Opioids and chronic pain: an analytic review of the clinical evidence. *Front Pain Res (Lausanne)* 2021; 2: 721357.
499. Lipton RB, Nicholson RA, Reed ML, et al. Diagnosis, consultation, treatment, and impact of migraine in the US: results of the OVERCOME (US) study. *Headache* 2022; 62: 122–140.
500. Rosner B, Neicun J, Yang JC, et al. Opioid prescription patterns in Germany and the global opioid epidemic: systematic review of available evidence. *PLoS One* 2019; 14: e0221153.
501. Ballantyne JC. Avoiding opioid analgesics for treatment of chronic low back pain. *JAMA* 2016; 315: 2459–2460.
502. Hauser W, Morlion B, Vowles KE, et al. European* clinical practice recommendations on opioids for chronic noncancer pain - part 1: role of opioids in the management of chronic noncancer pain. *Eur J Pain* 2021; 25: 949–968.
503. Hoffert MJ, Couch JR, Diamond S, et al. Transnasal butorphanol in the treatment of acute migraine. *Headache* 1995; 35: 65–69.
504. Nelson DL, Phebus LA, Johnson KW, et al. Preclinical pharmacological profile of the selective 5-HT1F receptor agonist lasmiditan. *Cephalalgia* 2010; 30: 1159–1169.
505. Labastida-Ramirez A, Rubio-Beltran E, Haanes KA, et al. Lasmiditan inhibits calcitonin gene-related peptide release in the rodent trigeminovascular system. *Pain* 2020; 161: 1092–1099.
506. Ramadan NM, Skljarevski V, Phebus LA, et al. 5-HT1F Receptor agonists in acute migraine treatment: a hypothesis. *Cephalalgia* 2003; 23: 776–785.
507. Hou M, Xing H, Li C, et al. Short-term efficacy and safety of lasmiditan, a novel 5-HT(1F) receptor agonist, for the acute treatment of migraine: a systematic review and meta-analysis. *J Headache Pain* 2020; 21: 66.
508. Beauchene JK and Levien TL. Lasmiditan: acute migraine treatment without vasoconstriction. A review. *J Pharm Technol* 2021; 37: 244–253.
509. Clemow DB, Johnson KW, Hochstetler HM, et al. Lasmiditan mechanism of action - review of a selective 5-HT(1F) agonist. *J Headache Pain* 2020; 21: 71.
510. Rubio-Beltran E, Labastida-Ramirez A, Haanes KA, et al. Characterization of binding, functional activity, and contractile responses of the selective 5-HT(1F) receptor agonist lasmiditan. *Br J Pharmacol* 2019; 176: 4681–4695.
511. Shapiro RE, Hochstetler HM, Dennehy EB, et al. Lasmiditan for acute treatment of migraine in patients with cardiovascular risk factors: post-hoc analysis of pooled results from 2 randomized, double-blind, placebo-controlled, phase 3 trials. *J Headache Pain* 2019; 20: 90.
512. Yang Y, Sun Y, Gao B, et al. Lasmiditan for acute treatment of migraine in adults: a systematic review and meta-analysis of randomized controlled trials. *CNS Drugs* 2020; 34: 1015–1024.
513. Zhu H, Tang Y, Zhou T, et al. The efficacy of lasmiditan for the treatment of migraine: a meta-analysis of randomized controlled studies. *Clin Neuropharmacol* 2020; 43: 191–195.
514. Gu P, Chen C, Wu Q, et al. The effect and safety of 5-HT(1F) receptor agonist lasmiditan on migraine: a systematic review and meta-analysis. *Biomed Res Int* 2021; 2021: 6663591.
515. Maiti R, Mishra A, Puliappadamb HM, et al. Efficacy and safety of lasmiditan for acute treatment of migraine in adults: a meta-analysis. *J Clin Pharmacol* 2021; 61: 1534–44.
516. Ashina M, Reuter U, Smith T, et al. Randomized, controlled trial of lasmiditan over four migraine attacks: findings from the CENTURION study. *Cephalalgia* 2021; 41: 294–304.
517. Farkkila M, Diener HC, Geraud G, et al. Efficacy and tolerability of lasmiditan, an oral 5-HT(1F) receptor agonist, for the acute treatment of migraine: a phase 2 randomised, placebo-controlled, parallel-group, dose-ranging study. *Lancet Neurol* 2012; 11: 405–13.
518. Goadsby PJ, Wietecha LA, Dennehy EB, et al. Phase 3 randomized, placebo-controlled, double-blind study of lasmiditan for acute treatment of migraine. *Brain* 2019; 142: 1894–1904.
519. Kuca B, Silberstein SD, Wietecha L, et al. Lasmiditan is an effective acute treatment for migraine: a phase 3 randomized study. *Neurology* 2018; 91: e2222–e32.
520. Sakai F, Takeshima T, Homma G, et al. Phase 2 randomized placebo-controlled study of lasmiditan for the acute treatment of migraine in Japanese patients. *Headache* 2021; 61: 755–765.

521. Ahmed Z, Martin V, Buchanan A, et al. Tolerability of lasmiditan in elderly patients with migraine (1814). *Neurology* 2021; 96: 1814.
522. Pearlman EM, Wilbraham D, Dennehy EB, et al. Effects of lasmiditan on simulated driving performance: results of two randomized, blinded, crossover studies with placebo and active controls. *Hum Psychopharmacol* 2020; 35: e2732.
523. Edvinsson L. CGRP Receptor antagonists and antibodies against CGRP and its receptor in migraine treatment. *Br J Clin Pharmacol* 2015; 80: 193–199.
524. Altamura C, Brunelli N, Marcosano M, et al. Gepants - a long way to cure: a narrative review. *Neurol Sci* 2022; 43: 5697–5708.
525. Inc PLDP. ZAVZPRET - Zavegepant nasal spray, https://labeling.pfizer.com/ShowLabeling.aspx?id=19471#section-8.1. (accessed Jan 15, 2023)
526. Moreno-Ajona D, Villar-Martinez MD and Goadsby PJ. New generation gepants: migraine acute and preventive medications. *J Clin Med* 2022; 11: 1656.
527. Zhang Z, Shu Y, Diao Y, et al. Calcitonin gene-related peptide receptor antagonist ubrogepant for the treatment of acute migraine: a meta-analysis. *Medicine (Balt)* 2021; 100: e24741.
528. Yang Y, Chen M, Sun Y, et al. Safety and efficacy of ubrogepant for the acute treatment of episodic migraine: a meta-analysis of randomized clinical trials. *CNS Drugs* 2020; 34: 463–471.
529. Pak K, Kim J, Lee GH, et al. Effectiveness of calcitonin gene-related peptide receptor antagonists for migraine treatment: a meta-analysis. *Eur Neurol* 2022; 85: 195–201.
530. Nedd M, Garland S, Falk N, et al. Ubrogepant: an oral calcitonin gene-related peptide (CGRP) receptor antagonist for abortive migraine treatment. *Ann Pharmacother* 2022; 56: 346–351.
531. Ha DK, Kim MJ, Han N, et al. Comparative efficacy of oral calcitonin-gene-related peptide antagonists for the treatment of acute migraine: updated meta-analysis. *Clin Drug Investig* 2021; 41: 119–132.
532. Gao B, Yang Y, Wang Z, et al. Efficacy and safety of rimegepant for the acute treatment of migraine: evidence from randomized controlled trials. *Front Pharmacol* 2019; 10: 1577.
533. Croop R, Goadsby PJ, Stock DA, et al. Efficacy, safety, and tolerability of rimegepant orally disintegrating tablet for the acute treatment of migraine: a randomised, phase 3, double-blind, placebo-controlled trial. *Lancet* 2019; 394: 737–745.
534. Lipton RB, Conway CM, Stock EG, et al. Efficacy, safety, and tolerability of rimegepant 75 mg, an oral CGRP receptor antagonist, for the acute treatment of migraine: results from a phase 3, double-blind, randomized, placebo-controlled trial, study 301. *Headache* 2018; 20: 1226–1227.
535. Lipton RB, Croop R, Stock EG, et al. Rimegepant, an oral calcitonin gene-related peptide receptor antagonist, for migraine. *N Engl J Med* 2019; 381: 142–149.
536. Marcus R, Goadsby PJ, Dodick D, et al. BMS-927711 for the acute treatment of migraine: a double-blind, randomized, placebo controlled, dose-ranging trial. *Cephalalgia* 2014; 34: 114–125.
537. Dodick DW, Lipton RB, Ailani J, et al. Ubrogepant for the treatment of migraine. *N Engl J Med* 2019; 381: 2230–2241.
538. Voss T, Lipton RB, Dodick DW, et al. A phase IIb randomized, double-blind, placebo-controlled trial of ubrogepant for the acute treatment of migraine. *Cephalalgia* 2016; 36: 887–898.
539. Lipton RB, Dodick DW, Ailani J, et al. Effect of ubrogepant vs placebo on pain and the most bothersome associated symptom in the acute treatment of migraine: the ACHIEVE II randomized clinical trial. *JAMA* 2019; 322: 1887–1898.
540. Yu S, Kim BK, Guo A, et al. Safety and efficacy of rimegepant orally disintegrating tablet for the acute treatment of migraine in China and South Korea: a phase 3, double-blind, randomised, placebo-controlled trial. *Lancet Neurol* 2023; 22: 476–484.
541. Croop R, Madonia J, Stock DA, et al. Zavegepant nasal spray for the acute treatment of migraine: a phase 2/3 double-blind, randomized, placebo-controlled, dose-ranging trial. *Headache* 2022; 62: 1153–1163.
542. Lipton RB, Croop R, Stock DA, et al. Safety, tolerability, and efficacy of zavegepant 10 mg nasal spray for the acute treatment of migraine in the USA: a phase 3, double-blind, randomised, placebo-controlled multicentre trial. *Lancet Neurol* 2023; 22: 209–217.
543. Croop R, Lipton RB, Kudrow D, et al. Oral rimegepant for preventive treatment of migraine: a phase 2/3, randomised, double-blind, placebo-controlled trial. *Lancet* 2021; 397: 51–60.
544. Croop R, Ivans A, Stock D, et al. A phase 1 study to evaluate the bioequivalence of oral tablet and orally dissolving tablet formulations of rimegepant, a small molecule CGRP receptor antagonist [abstract MTIS2018-170]. *Cephalalgia* 2018; 38: 142–143.
545. Goadsby PJ, Blumenfeld AM, Lipton RB, et al. Time course of efficacy of ubrogepant for the acute treatment of migraine: clinical implications. *Cephalalgia* 2021; 41: 546–560.
546. Hutchinson S, Dodick DW, Treppendahl C, et al. Ubrogepant for the acute treatment of migraine: pooled efficacy, safety, and tolerability from the ACHIEVE I and ACHIEVE II phase 3 randomized trials. *Neurol Ther* 2021; 10: 235–249.
547. Goadsby PJ, Tepper SJ, Watkins PB, et al. Safety and tolerability of ubrogepant following intermittent, high-frequency dosing: randomized, placebo-controlled trial in healthy adults. *Cephalalgia* 2019; 39: 1753–1761.
548. Bhardwaj R, Collins JL, Stringfellow J, et al. P-Glycoprotein and breast cancer resistance protein transporter inhibition by cyclosporine and quinidine on the pharmacokinetics of oral rimegepant in healthy subjects. *Clin Pharmacol Drug Dev* 2022; 11: 889–897.
549. Szkutnik-Fiedler D. Pharmacokinetics, pharmacodynamics and drug-drug interactions of new anti-migraine drugs-lasmiditan, gepants, and calcitonin-gene-related peptide (CGRP) receptor monoclonal antibodies. *Pharmaceutics* 2020; 12.
550. Scott LJ. Ubrogepant: first approval. *Drugs* 2020; 80: 323–328.
551. Baker TE, Croop R, Kamen L, et al. Human milk and plasma pharmacokinetics of single-dose rimegepant 75 mg in healthy lactating women. *Breastfeed Med* 2022; 17: 277–282.

552. Scott LJ. Rimegepant: first approval. *Drugs* 2020; 80: 741–746.
553. Dhillon S. Zavegepant: first approval. *Drugs* 2023; 83: 825–831.
554. Labs P. ZAVZPRET (zavegepant) nasal spray: US prescribing information, https://zavzpret.pfizerpro.com/. (accessed Jan 15, 2023)
555. Ailani J, Lipton RB, Hutchinson S, et al. Long-Term safety evaluation of ubrogepant for the acute treatment of migraine: phase 3, randomized, 52-week extension trial. *Headache* 2020; 60: 141–152.
556. Dodick DW, Goadsby PJ, Schwedt TJ, et al. Ubrogepant for the treatment of migraine attacks during the prodrome: a phase 3, multicentre, randomised, double-blind, placebo-controlled, crossover trial in the USA. *Lancet* 2023; 402: 2307–2316.
557. Jakate A, Blumenfeld AM, Boinpally R, et al. Pharmacokinetics and safety of ubrogepant when coadministered with calcitonin gene-related peptide-targeted monoclonal antibody migraine preventives in participants with migraine: a randomized phase 1b drug-drug interaction study. *Headache* 2021; 61: 642–652.
558. Misra M, Sharma T, Kalra J, et al. Comparative efficacy and tolerability of sumatriptan, ergotamine, naproxen and rizatriptan in moderate to severe acute attack of migraine. *JK Science* 2010; 12: 175–179.
559. Tullo V, Valguarnera F, Barbanti P, et al. Comparison of frovatriptan plus dexketoprofen (25 mg or 37.5 mg) with frovatriptan alone in the treatment of migraine attacks with or without aura: a randomized study. *Cephalalgia* 2014; 34: 434–445.
560. Diener HC, Pfaffenrath V, Pageler L, et al. The fixed combination of acetylsalicylic acid, paracetamol and caffeine is more effective than single substances and dual combination for the treatment of headache: a multicentre, randomized, double-blind, single-dose, placebo-controlled parallel group study. *Cephalalgia* 2005; 25: 776–787.
561. Burch R. Antidepressants for preventive treatment of migraine. *Curr Treat Options Neurol* 2019; 21: 18.
562. Lopez-Munoz F and Alamo C. Monoaminergic neurotransmission: the history of the discovery of antidepressants from 1950s until today. *Curr Pharm Des* 2009; 15: 1563–1586.
563. Marks DM, Shah MJ, Patkar AA, et al. Serotonin-norepinephrine reuptake inhibitors for pain control: premise and promise. *Curr Neuropharmacol* 2009; 7: 331–336.
564. Gillman PK. Tricyclic antidepressant pharmacology and therapeutic drug interactions updated. *Br J Pharmacol* 2007; 151: 737–748.
565. Sprenger T, Viana M and Tassorelli C. Current prophylactic medications for migraine and their potential mechanisms of action. *Neurotherapeutics* 2018; 15: 313–323.
566. Edinoff AN, Akuly HA, Hanna TA, et al. Selective serotonin reuptake inhibitors and adverse effects: a narrative review. *Neurol Int* 2021; 13: 387–401.
567. Lambert O and Bourin M. SNRIs: mechanism of action and clinical features. *Expert Rev Neurother* 2002; 2: 849–858.
568. Fanelli D, Weller G and Liu H. New serotonin-norepinephrine reuptake inhibitors and their anesthetic and analgesic considerations. *Neurol Int* 2021; 13: 497–509.
569. Deen M, Christensen CE, Hougaard A, et al. Serotonergic mechanisms in the migraine brain - a systematic review. *Cephalalgia* 2017; 37: 251–264.
570. Hirschberg S, Li Y, Randall A, et al. Functional dichotomy in spinal- vs prefrontal-projecting locus coeruleus modules splits descending noradrenergic analgesia from ascending aversion and anxiety in rats. *Elife* 2017; 6: e29808.
571. Ferrari MD, Odink J, Tapparelli C, et al. Serotonin metabolism in migraine. *Neurology* 1989; 39: 1239–1242.
572. Hamel E. Serotonin and migraine: biology and clinical implications. *Cephalalgia* 2007; 27: 1293–1300.
573. Sicuteri F, Testi A and Anselmi B. Biochemical investigations in headache: increase in the hydroxyindoleacetic acid excretion during migraine attacks. *Int Arch Allergy App Immunol* 1961; 19: 55–58.
574. Brighina F, Cosentino G and Fierro B. Is lack of habituation a biomarker of migraine? A critical perspective. *J Headache Pain* 2015; 16: A13.
575. Judit A, Sandor PS and Schoenen J. Habituation of visual and intensity dependence of auditory evoked cortical potentials tends to normalize just before and during the migraine attack. *Cephalalgia* 2000; 20: 714–719.
576. Ozkul Y and Bozlar S. Effects of fluoxetine on habituation of pattern reversal visually evoked potentials in migraine prophylaxis. *Headache* 2002; 42: 582–587.
577. Gray AM, Pache DM and Sewell RD. Do alpha2-adrenoceptors play an integral role in the antinociceptive mechanism of action of antidepressant compounds? *Eur J Pharmacol* 1999; 378: 161–168.
578. Goadsby PJ and Duckworth JW. Low frequency stimulation of the locus coeruleus reduces regional cerebral blood flow in the spinalized cat. *Brain Res* 1989; 476: 71–77.
579. Afridi SK, Giffin NJ, Kaube H, et al. A positron emission tomographic study in spontaneous migraine. *Arch Neurol* 2005; 62: 1270–1275.
580. Schulte LH and May A. The migraine generator revisited: continuous scanning of the migraine cycle over 30 days and three spontaneous attacks. *Brain* 2016; 139: 1987–1993.
581. Weiller C, May A, Limmroth V, et al. Brain stem activation in spontaneous human migraine attacks. *Nat Med* 1995; 1: 658–660.
582. Banzi R, Cusi C, Randazzo C, et al. Selective serotonin reuptake inhibitors (SSRIs) and serotonin-norepinephrine reuptake inhibitors (SNRIs) for the prevention of migraine in adults. *Cochrane Database Syst Rev* 2015; 4: CD002919.
583. Ducros A, de Gaalon S, Roos C, et al. Revised guidelines of the French headache society for the diagnosis and management of migraine in adults. Part 2: pharmacological treatment. *Rev Neurol (Paris)* 2021; 177: 734–752.
584. Jackson JL, Shimeall W, Sessums L, et al. Tricyclic antidepressants and headaches: systematic review and meta-analysis. *BMJ* 2010; 341: c5222.
585. Leite Pacheco R, de Oliveira Cruz Latorraca C, Adriano Leal Freitas da Costa A, et al. Melatonin for preventing primary headache: a systematic review. *Int J Clin Pract* 2018; 72: e13203.
586. Wang F, Wang J, Cao Y, et al. Serotonin-norepinephrine reuptake inhibitors for the prevention of migraine and

vestibular migraine: a systematic review and meta-analysis. *Reg Anesth Pain Med* 2020; 45: 323–330.
587. Xu XM, Yang C, Liu Y, et al. Efficacy and feasibility of antidepressants for the prevention of migraine in adults: a meta-analysis. *Eur J Neurol* 2017; 24: 1022–1031.
588. Bulut S, Berilgen MS, Baran A, et al. Venlafaxine versus amitriptyline in the prophylactic treatment of migraine: randomized, double-blind, crossover study. *Clin Neurol Neurosurg* 2004; 107: 44–48.
589. Keskinbora K and Aydinli I. A double-blind randomized controlled trial of topiramate and amitriptyline either alone or in combination for the prevention of migraine. *Clin Neurol Neurosurg* 2008; 110: 979–984.
590. Magalhaes E, Menezes C, Cardeal M, et al. Botulinum toxin type A versus amitriptyline for the treatment of chronic daily migraine. *Clin Neurol Neurosurg* 2010; 112: 463–466.
591. Rampello L, Alvano A, Chiechio S, et al. Evaluation of the prophylactic efficacy of amitriptyline and citalopram, alone or in combination, in patients with comorbidity of depression, migraine, and tension-type headache. *Neuropsychobiology* 2004; 50: 322–328.
592. Couch JR, Amitriptyline Versus Placebo Study G. Amitriptyline in the prophylactic treatment of migraine and chronic daily headache. *Headache* 2011; 51: 33–51.
593. Couch JR and Hassanein RS. Amitriptyline in migraine prophylaxis. *Arch Neurol* 1979; 36: 695–699.
594. Kisler LB, Weissman-Fogel I, Coghill RC, et al. Individualization of migraine prevention: a randomized controlled trial of psychophysical-based prediction of duloxetine efficacy. *Clin J Pain* 2019; 35: 753–765.
595. Goncalves AL, Martini Ferreira A, Ribeiro RT, et al. Randomised clinical trial comparing melatonin 3 mg, amitriptyline 25 mg and placebo for migraine prevention. *J Neurol Neurosurg Psychiatry* 2016; 87: 1127–1132.
596. Dodick DW, Freitag F, Banks J, et al. Topiramate versus amitriptyline in migraine prevention: a 26-week, multicenter, randomized, double-blind, double-dummy, parallel-group noninferiority trial in adult migraineurs. *Clin Ther* 2009; 31: 542–559.
597. Ozyalcin SN, Talu GK, Kiziltan E, et al. The efficacy and safety of venlafaxine in the prophylaxis of migraine. *Headache* 2005; 45: 144–152.
598. Steiner TJ, Ahmed F, Findley LJ, et al. S-fluoxetine in the prophylaxis of migraine: a phase II double-blind randomized placebo-controlled study. *Cephalalgia* 1998; 18: 283–286.
599. Tarlaci S. Escitalopram and venlafaxine for the prophylaxis of migraine headache without mood disorders. *Clin Neuropharmacol* 2009; 32: 254–258.
600. Dhungana S, Sharma P, Pant SB, et al. A comparison between amitriptyline and divalproex in prophylactic treatment of episodic migraine: an open label study from Nepal. *Neurology Asia* 2021; 26: 107–112.
601. Mosarrezaii A. Comparing the effect of venlafaxine and the combination of nortriptyline and propranolol in the prevention of migraine. *Asian J Pharmaceutics* 2018; 12: S571–S5.
602. Stahl SM. *Prescriber's Guide: Stahl's Essential Psychopharmacology*. Cambridge University Press, 2020.
603. Gentile S. Tricyclic antidepressants in pregnancy and puerperium. *Expert Opin Drug Saf* 2014; 13: 207–225.
604. Berard A, Zhao JP and Sheehy O. Antidepressant use during pregnancy and the risk of major congenital malformations in a cohort of depressed pregnant women: an updated analysis of the Quebec pregnancy cohort. *BMJ Open* 2017; 7: e013372.
605. Irimia P, Garrido-Cumbrera M, Santos-Lasaosa S, et al. Impact of monthly headache days on anxiety, depression and disability in migraine patients: results from the Spanish atlas. *Sci Rep* 2021; 11: 8286.
606. Doyle Strauss L, Weizenbaum E, Loder EW, et al. Amitriptyline dose and treatment outcomes in specialty headache practice: a retrospective cohort study. *Headache* 2016; 56: 1626–1634.
607. Ziegler DK, Hurwitz A, Hassanein RS, et al. Migraine prophylaxis. A comparison of propranolol and amitriptyline. *Arch Neurol* 1987; 44: 486–489.
608. Evers S, Afra J, Frese A, et al. EFNS Guideline on the drug treatment of migraine–revised report of an EFNS task force. *Eur J Neurol* 2009; 16: 968–981.
609. Loder E, Burch R and Rizzoli P. The 2012 AHS/AAN guidelines for prevention of episodic migraine: a summary and comparison with other recent clinical practice guidelines. *Headache* 2012; 52: 930–945.
610. Silberstein SD. Preventive migraine treatment. *Continuum (Minneap Minn)* 2015; 21: 973–989.
611. Hayasaka Y, Purgato M, Magni LR, et al. Dose equivalents of antidepressants: evidence-based recommendations from randomized controlled trials. *J Affect Disord* 2015; 180: 179–184.
612. Loscher W and Klein P. The pharmacology and clinical efficacy of antiseizure medications: from bromide salts to cenobamate and beyond. *CNS Drugs* 2021; 35: 935–963.
613. Kanner AM and Bicchi MM. Antiseizure medications for adults with epilepsy: a review. *JAMA* 2022; 327: 1269–1281.
614. Johannessen Landmark C. Antiepileptic drugs in non-epilepsy disorders: relations between mechanisms of action and clinical efficacy. *CNS Drugs* 2008; 22: 27–47.
615. Rogawski MA and Loscher W. The neurobiology of antiepileptic drugs for the treatment of nonepileptic conditions. *Nat Med* 2004; 10: 685–692.
616. Rollo E, Romozzi M, Vollono C, et al. Antiseizure medications for the prophylaxis of migraine during the anti- CGRP drugs era. *Curr Neuropharmacol* 2023; 21: 1767–1785.
617. Cui XY, Sun SM, Liu J, et al. The efficacy and safety of valproate medications for migraine in adults: a meta-analysis. *Eur Rev Med Pharmacol Sci* 2020; 24: 5734–5741.
618. Frank F, Ulmer H, Sidoroff V, et al. CGRP-antibodies, topiramate and botulinum toxin type A in episodic and chronic migraine: a systematic review and meta-analysis. *Cephalalgia* 2021; 41: 1222–1239.
619. Linde M, Mulleners WM, Chronicle EP, et al. Antiepileptics other than gabapentin, pregabalin, topiramate, and valproate for the prophylaxis of episodic migraine in adults. *Cochrane Database Syst Rev* 2013: CD010608.
620. Linde M, Mulleners WM, Chronicle EP, et al. Valproate (valproic acid or sodium valproate or a combination of the two) for the prophylaxis of episodic migraine in adults. *Cochrane Database Syst Rev* 2013: CD010611.
621. Linde M, Mulleners WM, Chronicle EP, et al. Gabapentin or pregabalin for the prophylaxis of episodic migraine in adults. *Cochrane Database Syst Rev* 2013: CD010609.

622. Linde M, Mulleners WM, Chronicle EP, et al. Topiramate for the prophylaxis of episodic migraine in adults. *Cochrane Database Syst Rev* 2013: CD010610.
623. Yen PH, Kuan YC, Tam KW, et al. Efficacy of levetiracetam for migraine prophylaxis: a systematic review and meta-analysis. *J Formos Med Assoc* 2021; 120: 755–64.
624. Mohammadianinejad SE, Abbasi V, Sajedi SA, et al. Zonisamide versus topiramate in migraine prophylaxis: a double-blind randomized clinical trial. *Clin Neuropharmacol* 2011; 34: 174–177.
625. Lipton RB, Silberstein S, Dodick D, et al. Topiramate intervention to prevent transformation of episodic migraine: the topiramate INTREPID study. *Cephalalgia* 2011; 31: 18–30.
626. Silvestrini M, Bartolini M, Coccia M, et al. Topiramate in the treatment of chronic migraine. *Cephalalgia* 2003; 23: 820–824.
627. Mei D, Capuano A, Vollono C, et al. Topiramate in migraine prophylaxis: a randomised double-blind versus placebo study. *Neurol Sci* 2004; 25: 245–250.
628. Diener HC, Tfelt-Hansen P, Dahlof C, et al. Topiramate in migraine prophylaxis–results from a placebo-controlled trial with propranolol as an active control. *J Neurol* 2004; 251: 943–950.
629. Storey JR, Calder CS, Hart DE, et al. Topiramate in migraine prevention: a double-blind, placebo-controlled study. *Headache* 2001; 41: 968–975.
630. Brandes JL, Saper JR, Diamond M, et al. Topiramate for migraine prevention: a randomized controlled trial. *JAMA* 2004; 291: 965–973.
631. Hering R and Kuritzky A. Sodium valproate in the prophylactic treatment of migraine: a double-blind study versus placebo. *Cephalalgia* 1992; 12: 81–84.
632. Sarchielli P, Messina P, Cupini LM, et al. Sodium valproate in migraine without aura and medication overuse headache: a randomized controlled trial. *Eur Neuropsychopharmacol* 2014; 24: 1289–1297.
633. Jensen R, Brinck T and Olesen J. Sodium valproate has a prophylactic effect in migraine without aura: a triple-blind, placebo-controlled crossover study. *Neurology* 1994; 44: 647–651.
634. Luo N, Di W, Zhang A, et al. A randomized, one-year clinical trial comparing the efficacy of topiramate, flunarizine, and a combination of flunarizine and topiramate in migraine prophylaxis. *Pain Med* 2012; 13: 80–86.
635. Silberstein S, Goode-Sellers S, Twomey C, et al. Randomized, double-blind, placebo-controlled, phase II trial of gabapentin enacarbil for migraine prophylaxis. *Cephalalgia* 2013; 33: 101–111.
636. Freitag FG, Collins SD, Carlson HA, et al. A randomized trial of divalproex sodium extended-release tablets in migraine prophylaxis. *Neurology* 2002; 58: 1652–1659.
637. Silberstein S, Saper J, Berenson F, et al. Oxcarbazepine in migraine headache: a double-blind, randomized, placebo-controlled study. *Neurology* 2008; 70: 548–555.
638. Gupta P, Singh S, Goyal V, et al. Low-dose topiramate versus lamotrigine in migraine prophylaxis (the lotolamp study). *Headache* 2007; 47: 402–412.
639. Mathew NT, Saper JR, Silberstein SD, et al. Migraine prophylaxis with divalproex. *Arch Neurol* 1995; 52: 281–286.
640. Verma A, Srivastava D, Kumar A, et al. Levetiracetam in migraine prophylaxis: a randomized placebo-controlled study in a rural medical institute in northern India. *Clin Neuropharmacol* 2013; 36: 193–197.
641. Steiner TJ, Findley LJ and Yuen AW. Lamotrigine versus placebo in the prophylaxis of migraine with and without aura. *Cephalalgia* 1997; 17: 109–112.
642. Silberstein SD, Loder E, Forde G, et al. The impact of migraine on daily activities: effect of topiramate compared with placebo. *Curr Med Res Opin* 2006; 22: 1021–1029.
643. Cady RK, Mathew N, Diener HC, et al. Evaluation of carisbamate for the treatment of migraine in a randomized, double-blind trial. *Headache* 2009; 49: 216–226.
644. Bartolini M, Silvestrini M, Taffi R, et al. Efficacy of topiramate and valproate in chronic migraine. *Clin Neuropharmacol* 2005; 28: 277–279.
645. Silberstein SD, Hulihan J, Karim MR, et al. Efficacy and tolerability of topiramate 200 mg/d in the prevention of migraine with/without aura in adults: a randomized, placebo-controlled, double-blind, 12-week pilot study. *Clin Ther* 2006; 28: 1002–1011.
646. Vahedi K, Taupin P, Djomby R, et al. Efficacy and tolerability of Acetazolamide in migraine prophylaxis: a randomised placebo-controlled trial. *J Neurol* 2002; 249: 206–211.
647. Silberstein SD, Lipton RB, Dodick DW, et al. Efficacy and safety of topiramate for the treatment of chronic migraine: a randomized, double-blind, placebo-controlled trial. *Headache* 2007; 47: 170–180.
648. Bostani A, Rajabi A, Moradian N, et al. The effects of cinnarizine versus sodium valproate in migraine prophylaxis. *Int J Neurosci* 2013; 123: 487–493.
649. Ashtari F, Shaygannejad V and Akbari M. A double-blind, randomized trial of low-dose topiramate vs propranolol in migraine prophylaxis. *Acta Neurol Scand* 2008; 118: 301–305.
650. Ghose K, Niven BE and Berry D. A double-blind crossover comparison of the effects of vigabatrin with placebo in the prevention of migraine headache. *J Headache Pain* 2002; 3: 79–85.
651. Klapper J. Divalproex sodium in migraine prophylaxis: a dose-controlled study. *Cephalalgia* 1997; 17: 103–108.
652. Shaygannejad V, Janghorbani M, Ghorbani A, et al. Comparison of the effect of topiramate and sodium valporate in migraine prevention: a randomized blinded crossover study. *Headache* 2006; 46: 642–648.
653. Sadeghian H and Motiei-Langroudi R. Comparison of levetiracetam and sodium valproate in migraine prophylaxis: a randomized placebo-controlled study. *Ann Indian Acad Neurol* 2015; 18: 45–48.
654. Afshari D, Rafizadeh S and Rezaei M. A comparative study of the effects of low-dose topiramate versus sodium valproate in migraine prophylaxis. *Int J Neurosci* 2012; 122: 60–68.
655. Togha M, Rahmat Jirde M, Nilavari K, et al. Cinnarizine in refractory migraine prophylaxis: efficacy and tolerability. A comparison with sodium valproate. *J Headache Pain* 2008; 9: 77–82.
656. Chowdhury D, Bansal L, Duggal A, et al. TOP-PRO study: a randomized double-blind controlled trial of topiramate versus propranolol for prevention of chronic migraine. *Cephalalgia* 2022; 42: 396–408.

657. Karimi N, Razian A and Heidari M. The efficacy of magnesium oxide and sodium valproate in prevention of migraine headache: a randomized, controlled, double-blind, crossover study. *Acta Neurol Belg* 2021; 121: 167–173.
658. Khani S, Hejazi SA, Yaghoubi M, et al. Comparative study of magnesium, sodium valproate, and concurrent magnesium-sodium valproate therapy in the prevention of migraine headaches: a randomized controlled double-blind trial. *J Headache Pain* 2021; 22: 21.
659. Silberstein S, Lipton R, Dodick D, et al. Topiramate treatment of chronic migraine: a randomized, placebo-controlled trial of quality of life and other efficacy measures. *Headache* 2009; 49: 1153–1162.
660. Diener HC, Bussone G, Van Oene JC, et al. Topiramate reduces headache days in chronic migraine: a randomized, double-blind, placebo-controlled study. *Cephalalgia* 2007; 27: 814–823.
661. Mei D, Ferraro D, Zelano G, et al. Topiramate and triptans revert chronic migraine with medication overuse to episodic migraine. *Clin Neuropharmacol* 2006; 29: 269–75.
662. Cady RK, Schreiber CP, Porter JA, et al. A multi-center double-blind pilot comparison of onabotulinumtoxinA and topiramate for the prophylactic treatment of chronic migraine. *Headache* 2011; 51: 21–32.
663. Mathew NT and Jaffri SF. A double-blind comparison of onabotulinumtoxina (BOTOX) and topiramate (TOPAMAX) for the prophylactic treatment of chronic migraine: a pilot study. *Headache* 2009; 49: 1466–78.
664. Silberstein SD, Neto W, Schmitt J, et al. Topiramate in migraine prevention: results of a large controlled trial. *Arch Neurol* 2004; 61: 490–495.
665. Ferrari A, Tiraferri I, Neri L, et al. Clinical pharmacology of topiramate in migraine prevention. *Expert Opin Drug Metab Toxicol* 2011; 7: 1169–1181.
666. Bagnato F and Good J. The use of antiepileptics in migraine prophylaxis. *Headache* 2016; 56: 603–615.
667. Shank RP, Gardocki JF, Streeter AJ, et al. An overview of the preclinical aspects of topiramate: pharmacology, pharmacokinetics, and mechanism of action. *Epilepsia* 2000; 41: 3–9.
668. Mirza NS, Alfirevic A, Jorgensen A, et al. Metabolic acidosis with topiramate and zonisamide: an assessment of its severity and predictors. *Pharmacogenet Genomics* 2011; 21: 297–302.
669. Maalouf NM, Langston JP, Van Ness PC, et al. Nephrolithiasis in topiramate users. *Urol Res* 2011; 39: 303–307.
670. Luykx J, Mason M, Ferrari MD, et al. Are migraineurs at increased risk of adverse drug responses? A meta-analytic comparison of topiramate-related adverse drug reactions in epilepsy and migraine. *Clin Pharmacol Ther* 2009; 85: 283–288.
671. Hu C, Zhang Y and Tan G. Advances in topiramate as prophylactic treatment for migraine. *Brain Behav* 2021; 11: e2290.
672. Minton GC, Miller AD, Bookstaver PB, et al. Topiramate: safety and efficacy of its use in the prevention and treatment of migraine. *J Cent Nerv Syst Dis* 2011; 3: 155–168.
673. Parikh S, Goldstein A, Karaa A, et al. Patient care standards for primary mitochondrial disease: a consensus statement from the mitochondrial medicine society. *Genet Med* 2017; 10:10.1038/gim.2017.107.
674. Vatzaki E, Straus S, Dogne JM, et al. Latest clinical recommendations on valproate use for migraine prophylaxis in women of childbearing age: overview from European medicines agency and European headache federation. *J Headache Pain* 2018; 19: 68.
675. Agency EM. Valproate and related substances, https://www.ema.europa.eu/en/medicines/human/referrals/valproate-related-substances-0. (accessed Jan 15, 2023)
676. Ashina S, Terwindt GM, Steiner TJ, et al. Medication overuse headache. *Nat Rev Dis Primers* 2023; 9: 5.
677. Verrotti A, Scaparrotta A, Agostinelli S, et al. Topiramate-induced weight loss: a review. *Epilepsy Res* 2011; 95: 189–199.
678. Marmura MJ and Kumpinsky AS. Refining the benefit/risk profile of anti-epileptic drugs in headache disorders. *CNS Drugs* 2018; 32: 735–746.
679. Bjork MH, Zoega H, Leinonen MK, et al. Association of prenatal exposure to antiseizure medication with risk of autism and intellectual disability. *JAMA Neurol* 2022; 79: 672–681.
680. Wells-Gatnik W and Martelletti P. Antiseizure medications as migraine preventatives: a call for action for a teratogenic and neurodevelopmental risk removal. *Expert Opin Drug Saf* 2023; 22: 777–781.
681. Lampl C, MaassenVanDenBrink A, Deligianni CI, et al. The comparative effectiveness of migraine preventive drugs: a systematic review and network meta-analysis. *J Headache Pain* 2023; 24: 56.
682. Cologno D, d'Onofrio F, Castriota O, et al. Basilar-type migraine patients responsive to lamotrigine: a 5-year follow-up. *Neurol Sci* 2013; 34(Suppl 1): S165–6.
683. Pelzer N, Stam AH, Carpay JA, et al. Familial hemiplegic migraine treated by sodium valproate and lamotrigine. *Cephalalgia* 2014; 34: 708–711.
684. Wang XQ, Xiong J, Xu WH, et al. Risk of a lamotrigine-related skin rash: current meta-analysis and postmarketing cohort analysis. *Seizure* 2015; 25: 52–61.
685. Ogrodowczyk M, Dettlaff K and Jelinska A. Beta-Blockers: current state of knowledge and perspectives. *Mini Rev Med Chem* 2016; 16: 40–54.
686. Holroyd KA, Penzien DB and Cordingley GE. Propranolol in the management of recurrent migraine: a meta-analytic review. *Headache* 1991; 31: 333–340.
687. Jackson JL, Cogbill E, Santana-Davila R, et al. A comparative effectiveness meta-analysis of drugs for the prophylaxis of migraine headache. *PLoS One* 2015; 10: e0130733.
688. Jackson JL, Kuriyama A, Kuwatsuka Y, et al. Beta-blockers for the prevention of headache in adults, a systematic review and meta-analysis. *PLoS One* 2019; 14: e0212785.
689. Silberstein SD, Holland S, Freitag F, et al. Evidence-based guideline update: pharmacologic treatment for episodic migraine prevention in adults: report of the quality standards subcommittee of the American academy of neurology and the American headache society. *Neurology* 2012; 78: 1337–1345.

690. Behan PO and Reid M. Propranolol in the treatment of migraine. *Practitioner* 1980; 224: 201–203.
691. Borgesen SE, Nielsen JL and Moller CE. Prophylactic treatment of migraine with propranolol. A clinical trial. *Acta Neurol Scand* 1974; 50: 651–656.
692. Diamond S and Medina JL. Double blind study of propranolol for migraine prophylaxis. *Headache* 1976; 16: 24–27.
693. Forssman B, Henriksson KG, Johannsson V, et al. Propranolol for migraine prophylaxis. *Headache* 1976; 16: 238–245.
694. Malvea BP, Gwon N and Graham JR. Propranolol prophylaxis of migraine. *Headache* 1973; 12: 163–167.
695. Weber RB and Reinmuth OM. The treatment of migraine with propranolol. *Neurology* 1972; 22: 366–369.
696. Wideroe TE and Vigander T. Propranolol in the treatment of migraine. *Br Med J* 1974; 2: 699–701.
697. Stensrud P and Sjaastad O. Short-term clinical trial of phopranolol in racemic form (inderal), D-propranolol and placebo in migraine. *Acta Neurol Scand* 1976; 53: 229–232.
698. Marichal-Cancino BA, Gonzalez-Hernandez A, Guerrero-Alba R, et al. A critical review of the neurovascular nature of migraine and the main mechanisms of action of prophylactic antimigraine medications. *Expert Rev Neurother* 2021; 21: 1035–1050.
699. Diener HC, Hartung E, Chrubasik J, et al. A comparative study of oral acetylsalicyclic acid and metoprolol for the prophylactic treatment of migraine. A randomized, controlled, double-blind, parallel group phase III study. *Cephalalgia* 2001; 21: 120–128.
700. Holroyd KA and Penzien DB. Pharmacological versus nonpharmacological prophylaxis of recurrent migraine headache: a meta-analytic review of clinical trials. *Pain* 1990; 42: 1–13.
701. Albers GW, Simon LT, Hamik A, et al. Nifedipine versus propranolol for the initial prophylaxis of migraine. *Headache* 1989; 29: 215–218.
702. Bordini CA, Arruda MA, Ciciarelli MC, et al. Propranolol vs flunarizine vs flunarizine plus propranolol in migraine without aura prophylaxis. A double-blind trial. *Arq Neuropsiquiatr* 1997; 55: 536–541.
703. Andersson PG, Dahl S, Hansen JH, et al. Prophylactic treatment of classical and non-classical migraine with metoprolol–a comparison with placebo. *Cephalalgia* 1983; 3: 207–212.
704. Diener HC, Matias-Guiu J, Hartung E, et al. Efficacy and tolerability in migraine prophylaxis of flunarizine in reduced doses: a comparison with propranolol 160 mg daily. *Cephalalgia* 2002; 22: 209–221.
705. Domingues RB, Silva AL, Domingues SA, et al. A double-blind randomized controlled trial of low doses of propranolol, nortriptyline, and the combination of propranolol and nortriptyline for the preventive treatment of migraine. *Arq Neuropsiquiatr* 2009; 67: 973–977.
706. Lucking CH, Oestreich W, Schmidt R, et al. Flunarizine vs. Propranolol in the prophylaxis of migraine: two double-blind comparative studies in more than 400 patients. *Cephalalgia* 1988; 8(Suppl 8): 21–26.
707. Standnes B. The prophylactic effect of timolol versus propranolol and placebo in common migraine: beta-blockers in migraine. *Cephalalgia* 1982; 2: 165–170.
708. Steiner TJ, Joseph R, Hedman C, et al. Metoprolol in the prophylaxis of migraine: parallel-groups comparison with placebo and dose-ranging follow-up. *Headache* 1988; 28: 15–23.
709. Stovner LJ, Linde M, Gravdahl GB, et al. A comparative study of candesartan versus propranolol for migraine prophylaxis: a randomised, triple-blind, placebo-controlled, double cross-over study. *Cephalalgia* 2014; 34: 523–532.
710. van de Ven LL, Franke CL and Koehler PJ. Prophylactic treatment of migraine with bisoprolol: a placebo-controlled study. *Cephalalgia* 1997; 17: 596–599.
711. Kjaersgård Rasmussen MJ, Holt Larsen B, Borg L, et al. Tolfenamic acid versus propranolol in the prophylactic treatment of migraine. *Acta Neurol Scand* 1994; 89: 446–450.
712. Diener HC, Foh M, Iaccarino C, et al. Cyclandelate in the prophylaxis of migraine: a randomized, parallel, double-blind study in comparison with placebo and propranolol. The study group. *Cephalalgia* 1996; 16: 441–447.
713. Tfelt-Hansen P, Standnes B, Kangasneimi P, et al. Timolol vs propranolol vs placebo in common migraine prophylaxis: a double-blind multicenter trial. *Acta Neurol Scand* 1984; 69: 1–8.
714. Pradalier A, Serratrice G, Collard M, et al. Long-acting propranolol in migraine prophylaxis: results of a double-blind, placebo-controlled study. *Cephalalgia* 1989; 9: 247–253.
715. Dahlöf CG. No clearcut longterm prophylactic effect of one month of treatment with propranolol in migraineurs. *Cephalalgia* 1987; 7: 459–460.
716. Chua AL, Mehla S and Orlova YY. Drug safety in episodic migraine management in adults. Part 2: preventive treatments. *Curr Pain Headache Rep* 2022; 26: 493–504.
717. Kaeser HE. Drug-induced myasthenic syndromes. *Acta Neurol Scand Suppl* 1984; 100: 39–47.
718. Linde K and Rossnagel K. Propranolol for migraine prophylaxis. *Cochrane Database Syst Rev* 2004: CD003225.
719. Ljung O. Metoprolol in migraine. *Cephalalgia* 1981; 1: 142.
720. Francis MV, Singh S, Goyal V, et al. Flunarizine: a review of its role in migraine prophylaxis. *Int J Res Med Sci* 2022; 8: 786–793.
721. Stubberud A, Flaaen NM, McCrory DC, et al. Flunarizine as prophylaxis for episodic migraine: a systematic review with meta-analysis. *Pain* 2019; 160: 762–772.
722. Deligianni CI, Sacco S, Ekizoglu E, et al. European headache federation (EHF) critical re-appraisal and meta-analysis of oral drugs in migraine prevention-part 2: flunarizine. *J Headache Pain* 2023; 24: 128.
723. Bisol LW, Brunstein MG, Ottoni GL, et al. Is flunarizine a long-acting oral atypical antipsychotic? A randomized clinical trial versus haloperidol for the treatment of schizophrenia. *J Clin Psychiatry* 2008; 69: 1572–1579.
724. Shimazawa M, Hara H, Watano T, et al. Effects of Ca2 + channel blockers on cortical hypoperfusion and expression of c-fos-like immunoreactivity after cortical spreading depression in rats. *Br J Pharmacol* 1995; 115: 1359–1368.
725. Li F, Qiu E, Dong Z, et al. Protection of flunarizine on cerebral mitochondria injury induced by cortical spreading

depression under hypoxic conditions. *J Headache Pain* 2011; 12: 47–53.
726. Yang T and Xu C. Physiology and pathophysiology of the intrarenal renin-angiotensin system: an update. *J Am Soc Nephrol* 2017; 28: 1040–1049.
727. Hall A, Busse LW and Ostermann M. Angiotensin in critical care. *Crit Care* 2018; 22: 69.
728. Probstfield JL and O'Brien KD. Progression of cardiovascular damage: the role of renin-angiotensin system blockade. *Am J Cardiol* 2010; 105: 10A–20A.
729. Unger T and Stoppelhaar M. Rationale for double renin-angiotensin-aldosterone system blockade. *Am J Cardiol* 2007; 100: 25J–31J.
730. Tronvik E, Stovner LJ, Schrader H, et al. Involvement of the renin-angiotensin system in migraine. *J Hypertens Suppl* 2006; 24: S139–43.
731. Ripa P, Ornello R, Pistoia F, et al. The renin-angiotensin system: a possible contributor to migraine pathogenesis and prophylaxis. *Expert Rev Neurother* 2014; 14: 1043–1055.
732. Horasanli B, Atac FB, Coven I, et al. Angiotensin I-converting enzyme gene (I/D) polymorphism in patients with migraine. *Headache* 2013; 53: 161–164.
733. Kowa H, Fusayasu E, Ijiri T, et al. Association of the insertion/deletion polymorphism of the angiotensin I-converting enzyme gene in patients of migraine with aura. *Neurosci Lett* 2005; 374: 129–131.
734. Paterna S, Di Pasquale P, D'Angelo A, et al. Angiotensin-converting enzyme gene deletion polymorphism determines an increase in frequency of migraine attacks in patients suffering from migraine without aura. *Eur Neurol* 2000; 43: 133–136.
735. Dorosch T, Ganzer CA, Lin M, et al. Efficacy of angiotensin-converting enzyme inhibitors and angiotensin receptor blockers in the preventative treatment of episodic migraine in adults. *Curr Pain Headache Rep* 2019; 23: 85.
736. Diener HC, Gendolla A, Feuersenger A, et al. Telmisartan in migraine prophylaxis: a randomized, placebo-controlled trial. *Cephalalgia* 2009; 29: 921–927.
737. Reuter U, Chiarugi A, Bolay H, et al. Nuclear factor-kappaB as a molecular target for migraine therapy. *Ann Neurol* 2002; 51: 507–516.
738. Tronvik E, Stovner LJ, Helde G, et al. Prophylactic treatment of migraine with an angiotensin II receptor blocker: a randomized controlled trial. *JAMA* 2003; 289: 65–69.
739. Schrader H, Stovner LJ, Helde G, et al. Prophylactic treatment of migraine with angiotensin converting enzyme inhibitor (lisinopril): randomised, placebo controlled, cross-over study. *BMJ* 2001; 322: 19–22.
740. Lugaresi A, Montagna P, Gallassi R, et al. Extrapyramidal syndrome and depression induced by flunarizine. *Eur Neurol* 1988; 28: 208–211.
741. Berilgen MS, Bulut S, Gonen M, et al. Comparison of the effects of amitriptyline and flunarizine on weight gain and serum leptin, C peptide and insulin levels when used as migraine preventive treatment. *Cephalalgia* 2005; 25: 1048–1053.
742. Brown NJ, Ray WA, Snowden M, et al. Black Americans have an increased rate of angiotensin converting enzyme inhibitor-associated angioedema. *Clin Pharmacol Ther* 1996; 60: 8–13.
743. Quan A. Fetopathy associated with exposure to angiotensin converting enzyme inhibitors and angiotensin receptor antagonists. *Early Hum Dev* 2006; 82: 23–28.
744. Kuenzli A, Bucher HC, Anand I, et al. Meta-analysis of combined therapy with angiotensin receptor antagonists versus ACE inhibitors alone in patients with heart failure. *PLoS One* 2010; 5: e9946.
745. Rousaud Baron F, Garcia JM, Camps EM, et al. ACE Inhibitors and anaphylactoid reactions to high-flux membrane dialysis (AN69): clinical aspects. *Nephron* 1992; 60: 487.
746. Tunon-de-Lara JM, Villanueva P, Marcos M, et al. ACE Inhibitors and anaphylactoid reactions during venom immunotherapy. *Lancet* 1992; 340: 908.
747. Al-Rifaie A, Khan MA, Ali A, et al. Lisinopril-Induced liver injury: an unusual presentation and literature review. *Eur J Case Rep Intern Med* 2020; 7: 001600.
748. Na Takuathung M, Sakuludomkan W, Khatsri R, et al. Adverse effects of angiotensin-converting enzyme inhibitors in humans: a systematic review and meta-analysis of 378 randomized controlled trials. *Int J Environ Res Public Health* 2022; 19: 10.3390/ijerph19148373
749. Rau JC and Dodick DW. Other preventive anti-migraine treatments: ACE inhibitors, ARBs, calcium channel blockers, serotonin antagonists, and NMDA receptor antagonists. *Curr Treat Options Neurol* 2019; 21: 17.
750. Halker RB, Starling AJ, Vargas BB, et al. ACE And ARB agents in the prophylactic therapy of migraine-how effective are they? *Curr Treat Options Neurol* 2016; 18: 15.
751. Holmes B, Brogden RN, Heel RC, et al. Flunarizine. A review of its pharmacodynamic and pharmacokinetic properties and therapeutic use. *Drugs* 1984; 27: 6–44.
752. Amery WK, Caers LI and Aerts TJ. Flunarizine, a calcium entry blocker in migraine prophylaxis. *Headache* 1985; 25: 249–254.
753. Pringsheim T, Davenport W, Mackie G, et al. Canadian Headache society guideline for migraine prophylaxis. *Can J Neurol Sci* 2012; 39: S1–59.
754. Togha M, Martami F, Abdollahi M, et al. Cinnarizine as an alternative recommendation for migraine prophylaxis: a narrative review. *Expert Rev Neurother* 2020; 20: 943–951.
755. Carey RM, Moran AE and Whelton PK. Treatment of hypertension: a review. *JAMA* 2022; 328: 1849–1861.
756. Binder WJ, Brin MF, Blitzer A, et al. Botulinum toxin type A (BOTOX) for treatment of migraine headaches: an open-label study. *Otolaryngol Head Neck Surg* 2000; 123: 669–676.
757. Burstein R, Blumenfeld AM, Silberstein SD, et al. Mechanism of action of OnabotulinumtoxinA in chronic migraine: a narrative review. *Headache* 2020; 60: 1259–1272.
758. Burstein R, Zhang X, Levy D, et al. Selective inhibition of meningeal nociceptors by botulinum neurotoxin type A: therapeutic implications for migraine and other pains. *Cephalalgia* 2014; 34: 853–869.
759. Cernuda-Morollon E, Ramon C, Martinez-Camblor P, et al. Onabotulinumtoxina decreases interictal CGRP plasma

levels in patients with chronic migraine. *Pain* 2015; 156: 820–824.
760. Gfrerer L, Xu W, Austen W, et al. Onabotulinumtoxina alters inflammatory gene expression and immune cells in chronic headache patients. *Brain* 2022; 145: 2436–2449.
761. Aurora SK, Dodick DW, Turkel CC, et al. Onabotulinumtoxina for treatment of chronic migraine: results from the double-blind, randomized, placebo-controlled phase of the PREEMPT 1 trial. *Cephalalgia* 2010; 30: 793–803.
762. Diener HC, Dodick DW, Aurora SK, et al. Onabotulinumtoxina for treatment of chronic migraine: results from the double-blind, randomized, placebo-controlled phase of the PREEMPT 2 trial. *Cephalalgia* 2010; 30: 804–814.
763. Bendtsen L, Sacco S, Ashina M, et al. Guideline on the use of onabotulinumtoxinA in chronic migraine: a consensus statement from the European headache federation. *J Headache Pain* 2018; 19: 91.
764. Herd CP, Tomlinson CL, Rick C, et al. Botulinum toxins for the prevention of migraine in adults. *Cochrane Database Syst Rev* 2018; 6: CD011616.
765. Aurora SK, Gawel M, Brandes JL, et al., Group BNAEMS. Botulinum toxin type a prophylactic treatment of episodic migraine: a randomized, double-blind, placebo-controlled exploratory study. *Headache* 2007; 47: 486–499.
766. Blumenfeld AM, Schim JD and Chippendale TJ. Botulinum toxin type A and divalproex sodium for prophylactic treatment of episodic or chronic migraine. *Headache* 2008; 48: 210–220.
767. Cady R, Turner I, Dexter K, et al. An exploratory study of salivary calcitonin gene-related peptide levels relative to acute interventions and preventative treatment with onabotulinumtoxinA in chronic migraine. *Headache* 2014; 54: 269–277.
768. Chankrachang S, Arayawichanont A, Poungvarin N, et al. Prophylactic botulinum type A toxin complex (dysport(R)) for migraine without aura. *Headache* 2011; 51: 52–63.
769. Evers S, Vollmer-Haase J, Schwaag S, et al. Botulinum toxin A in the prophylactic treatment of migraine–a randomized, double-blind, placebo-controlled study. *Cephalalgia* 2004; 24: 838–843.
770. Freitag FG, Diamond S, Diamond M, et al. Botulinum toxin type A in the treatment of chronic migraine without medication overuse. *Headache* 2008; 48: 201–209.
771. Hollanda L, Monteiro L and Melo A. Botulinum toxin type a for cephalic cutaneous allodynia in chronic migraine: a randomized, double-blinded, placebo-controlled trial. *Neurol Int* 2014; 6: 5133.
772. Lipton RB, Rosen NL, Ailani J, et al. Onabotulinumtoxina improves quality of life and reduces impact of chronic migraine over one year of treatment: pooled results from the PREEMPT randomized clinical trial program. *Cephalalgia* 2016; 36: 899–908.
773. Relja M, Poole AC, Schoenen J, et al., European Bo NTAHSG. A multicentre, double-blind, randomized, placebo-controlled, parallel group study of multiple treatments of botulinum toxin type A (BoNTA) for the prophylaxis of episodic migraine headaches. *Cephalalgia* 2007; 27: 492–503.
774. Sandrini G, Perrotta A, Tassorelli C, et al. Botulinum toxin type-A in the prophylactic treatment of medication-overuse headache: a multicenter, double-blind, randomized, placebo-controlled, parallel group study. *J Headache Pain* 2011; 12: 427–433.
775. Development NIoCHaH. OnabotulinumtoxinA. Drugs and Lactation Database (LactMed®) https://www.ncbi.nlm.nih.gov/books/NBK501922/ (accessed Feb 14, 2023).
776. Brin MF, Kirby RS, Slavotinek A, et al. Pregnancy outcomes following exposure to onabotulinumtoxinA. *Pharmacoepidemiol Drug Saf* 2016; 25: 179–187.
777. Narayanaswami P, Sanders DB, Wolfe G, et al. International consensus guidance for management of myasthenia Gravis: 2020 update. *Neurology* 2021; 96: 114–122.
778. Ma Q, Ran H, Ou C, et al. Is myasthenia gravis a contraindication for botulinum toxin? *J Clin Neurosci* 2022; 95: 44–47.
779. Lanteri-Minet M, Ducros A, Francois C, et al. Effectiveness of onabotulinumtoxinA (BOTOX(R)) for the preventive treatment of chronic migraine: a meta-analysis on 10 years of real-world data. *Cephalalgia* 2022; 42: 1543–1564.
780. Negro A, Curto M, Lionetto L, et al. A two years open-label prospective study of OnabotulinumtoxinA 195 U in medication overuse headache: a real-world experience. *J Headache Pain* 2015; 17: 1.
781. Sacco S, Russo A, Geppetti P, et al. What is changing in chronic migraine treatment? An algorithm for onabotulinumtoxinA treatment by the Italian chronic migraine group. *Expert Rev Neurother* 2020; 20: 1275–1286.
782. Silberstein SD, Dodick DW, Aurora SK, et al. Per cent of patients with chronic migraine who responded per onabotulinumtoxinA treatment cycle: PREEMPT. *J Neurol Neurosurg Psychiatry* 2015; 86: 996–1001.
783. Ornello R, Ahmed F, Negro A, et al. Early management of OnabotulinumtoxinA treatment in chronic migraine: insights from a real-life European multicenter study. *Pain Ther* 2021; 10: 637–650.
784. Vernieri F, Paolucci M, Altamura C, et al. Onabotulinumtoxin-A in chronic migraine: should timing and definition of non-responder Status be revised? Suggestions from a real-life Italian multicenter experience. *Headache* 2019; 59: 1300–1309.
785. Stovner LJ, Hagen K, Tronvik E, et al. Followthesutures: piloting a new way to administer onabotulinumtoxinA for chronic migraine. *Cephalalgia* 2022; 42: 590–597.
786. Hemasian H, Abedini F, Arab A, et al. A novel technique of botulinum toxin injection around skull sutures for chronic migraine: a randomized controlled clinical trial. *J Res Med Sci* 2022; 27: 85.
787. Salvatore CA, Moore EL, Calamari A, et al. Pharmacological properties of MK-3207, a potent and orally active calcitonin gene-related peptide receptor antagonist. *J Pharmacol Exp Ther* 2010; 333: 152–160.
788. Leung L, Liao S and Wu C. To probe the binding interactions between two FDA approved migraine drugs (ubrogepant and rimegepant) and calcitonin-gene related peptide receptor (CGRPR) using molecular dynamics simulations. *ACS Chem Neurosci* 2021; 12: 2629–2642.
789. Rist B, Entzeroth M and Beck-Sickinger AG. From micromolar to nanomolar affinity: a systematic approach to

identify the binding site of CGRP at the human calcitonin gene-related peptide 1 receptor. *J Med Chem* 1998; 41: 117–123.
790. Labruijere S, Ibrahimi K, Chan KY, et al. Discovery techniques for calcitonin gene-related peptide receptor antagonists for potential antimigraine therapies. *Expert Opin Drug Discov* 2013; 8: 1309–1323.
791. Rubio-Beltran E, Chan KY, Danser AJ, et al. Characterisation of the calcitonin gene-related peptide receptor antagonists ubrogepant and atogepant in human isolated coronary, cerebral and middle meningeal arteries. *Cephalalgia* 2020; 40: 357–366.
792. Strassman AM, Melo-Carrillo A, Houle TT, et al. Atogepant - an orally-administered CGRP antagonist - attenuates activation of meningeal nociceptors by CSD. *Cephalalgia* 2022; 42: 933–943.
793. Edvinsson L and Warfvinge K. Recognizing the role of CGRP and CGRP receptors in migraine and its treatment. *Cephalalgia* 2019; 39: 366–373.
794. Lo Castro F, Guerzoni S and Pellesi L. Safety and risk of medication overuse headache in lasmiditan and second-generation gepants: a rapid review. *Drug Healthc Patient Saf* 2021; 13: 233–240.
795. Tao X, Yan Z, Meng J, et al. The efficacy and safety of atogepant for the prophylactic treatment of migraine: evidence from randomized controlled trials. *J Headache Pain* 2022; 23: 19.
796. Capi M, De Angelis V, De Bernardini D, et al. CGRP Receptor antagonists and 5-HT1F receptor agonist in the treatment of migraine. *J Clin Med* 2021; 10: 1429.
797. Goadsby PJ, Dodick DW, Ailani J, et al. Safety, tolerability, and efficacy of orally administered atogepant for the prevention of episodic migraine in adults: a double-blind, randomised phase 2b/3 trial. *Lancet Neurol* 2020; 19: 727–737.
798. Ailani J, Lipton RB, Goadsby PJ, et al. Atogepant for the preventive treatment of migraine. *N Engl J Med* 2021; 385: 695–706.
799. Schwedt TJ, Lipton RB, Ailani J, et al. Time course of efficacy of atogepant for the preventive treatment of migraine: results from the randomized, double-blind ADVANCE trial. *Cephalalgia* 2022; 42: 3–11.
800. Pozo-Rosich P, Ailani J, Ashina M, et al. Atogepant for the preventive treatment of chronic migraine (PROGRESS): a randomised, double-blind, placebo-controlled, phase 3 trial. *Lancet* 2023; 402: 775–785.
801. Ashina M, Tepper SJ, Reuter U, et al. Once-daily oral atogepant for the long-term preventive treatment of migraine: findings from a multicenter, randomized, open-label, phase 3 trial. *Headache* 2023; 63: 79–88.
802. Deeks ED. Atogepant: first approval. *Drugs* 2022; 82: 65–70.
803. Corporation A. Qulipta (atogepant). Product information.
804. Russo AF and Hay DL. CGRP Physiology, pharmacology, and therapeutic targets: migraine and beyond. *Physiol Rev* 2023; 103: 1565–1644.
805. Al-Hassany L, Goadsby PJ, Danser AHJ, et al. Calcitonin gene-related peptide-targeting drugs for migraine: how pharmacology might inform treatment decisions. *Lancet Neurol* 2022; 21: 284–294.
806. Pavelic AR, Wober C, Riederer F, et al. Monoclonal antibodies against calcitonin gene-related peptide for migraine prophylaxis: a systematic review of real-world data. *Cells* 2022; 12.
807. Drellia K, Kokoti L, Deligianni CI, et al. Anti-CGRP monoclonal antibodies for migraine prevention: a systematic review and likelihood to help or harm analysis. *Cephalalgia* 2021; 41: 851–864.
808. Abu-Zaid A, AlBatati SK, AlHossan AM, et al. Galcanezumab for the management of migraine: a systematic review and meta-analysis of randomized placebo-controlled trials. *Cureus* 2020; 12: e11621.
809. Alasad YW and Asha MZ. Monoclonal antibodies as a preventive therapy for migraine: a meta-analysis. *Clin Neurol Neurosurg* 2020; 195: 105900.
810. Deng H, Li GG, Nie H, et al. Efficacy and safety of calcitonin-gene-related peptide binding monoclonal antibodies for the preventive treatment of episodic migraine - an updated systematic review and meta-analysis. *BMC Neurol* 2020; 20: 57.
811. Forbes RB, McCarron M and Cardwell CR. Efficacy and contextual (placebo) effects of CGRP antibodies for migraine: systematic review and meta-analysis. *Headache* 2020; 60: 1542–1557.
812. Gao B, Lu Q, Wan R, et al. Monthly versus quarterly fremanezumab for the prevention of migraine: a systemic review and meta-analysis from randomized controlled trials. *Naunyn Schmiedebergs Arch Pharmacol* 2021; 394: 819–828.
813. Gao B, Sun N, Yang Y, et al. Safety and efficacy of fremanezumab for the prevention of migraine: a meta-analysis from randomized controlled trials. *Front Neurol* 2020; 11: 435.
814. Lattanzi S, Brigo F, Trinka E, et al. Erenumab for preventive treatment of migraine: a systematic review and meta-analysis of efficacy and safety. *Drugs* 2019; 79: 417–431.
815. Yan Z, Xue T, Chen S, et al. Different dosage regimens of eptinezumab for the treatment of migraine: a meta-analysis from randomized controlled trials. *J Headache Pain* 2021; 22: 10.
816. Zhao X, Xu X and Li Q. Correction to: efficacy and safety of galcanezumab for preventive treatment of migraine: a systematic review and meta-analysis. *J Neurol* 2021; 268: 2377–2378.
817. Zhao X, Xu X and Li Q. Efficacy and safety of galcanezumab for preventive treatment of migraine: a systematic review and meta-analysis. *J Neurol* 2021; 268: 2364–2376.
818. Ashina M, Saper J, Cady R, et al. Eptinezumab in episodic migraine: a randomized, double-blind, placebo-controlled study (PROMISE-1). *Cephalalgia* 2020; 40: 241–254.
819. Bigal ME, Dodick DW, Rapoport AM, et al. Safety, tolerability, and efficacy of TEV-48125 for preventive treatment of high-frequency episodic migraine: a multicentre, randomised, double-blind, placebo-controlled, phase 2b study. *Lancet Neurol* 2015; 14: 1081–1090.
820. Bigal ME, Edvinsson L, Rapoport AM, et al. Safety, tolerability, and efficacy of TEV-48125 for preventive treatment of chronic migraine: a multicentre, randomised, double-blind, placebo-controlled, phase 2b study. *Lancet Neurol* 2015; 14: 1091–1100.
821. Detke HC, Goadsby PJ, Wang S, et al. Galcanezumab in chronic migraine: the randomized, double-blind, placebo-controlled REGAIN study. *Neurology* 2018; 91: e2211–e21.

822. Dodick DW, Ashina M, Brandes JL, et al. ARISE: a phase 3 randomized trial of erenumab for episodic migraine. *Cephalalgia* 2018; 38: 1026–1037.
823. Dodick DW, Lipton RB, Silberstein S, et al. Eptinezumab for prevention of chronic migraine: a randomized phase 2b clinical trial. *Cephalalgia* 2019; 39: 1075–1085.
824. Dodick DW, Silberstein SD, Bigal ME, et al. Effect of fremanezumab compared with placebo for prevention of episodic migraine: a randomized clinical trial. *JAMA* 2018; 319: 1999–2008.
825. Ferrari MD, Diener HC, Ning X, et al. Fremanezumab versus placebo for migraine prevention in patients with documented failure to up to four migraine preventive medication classes (FOCUS): a randomised, double-blind, placebo-controlled, phase 3b trial. *Lancet* 2019; 394: 1030–1040.
826. Goadsby PJ, Reuter U, Hallstrom Y, et al. A controlled trial of erenumab for episodic migraine. *N Engl J Med* 2017; 377: 2123–2132.
827. Lipton RB, Goadsby PJ, Smith J, et al. Efficacy and safety of eptinezumab in patients with chronic migraine: PROMISE-2. *Neurology* 2020; 94: e1365–e77.
828. Mulleners WM, Kim BK, Lainez MJA, et al. Safety and efficacy of galcanezumab in patients for whom previous migraine preventive medication from two to four categories had failed (CONQUER): a multicentre, randomised, double-blind, placebo-controlled, phase 3b trial. *Lancet Neurol* 2020; 19: 814–825.
829. Reuter U, Goadsby PJ, Lanteri-Minet M, et al. Efficacy and tolerability of erenumab in patients with episodic migraine in whom two-to-four previous preventive treatments were unsuccessful: a randomised, double-blind, placebo-controlled, phase 3b study. *Lancet* 2018; 392: 2280–2287.
830. Sakai F, Ozeki A and Skljarevski V. Efficacy and safety of galcanezumab for prevention of migraine headache in Japanese patients with episodic migraine: a phase 2 randomized controlled clinical trial. *Cephalalgia Rep* 2020; 3.
831. Sakai F, Takeshima T, Tatsuoka Y, et al. A randomized phase 2 study of erenumab for the prevention of episodic migraine in Japanese adults. *Headache* 2019; 59: 1731–1742.
832. Silberstein SD, Dodick DW, Bigal ME, et al. Fremanezumab for the preventive treatment of chronic migraine. *N Engl J Med* 2017; 377: 2113–2122.
833. Skljarevski V, Matharu M, Millen BA, et al. Efficacy and safety of galcanezumab for the prevention of episodic migraine: results of the EVOLVE-2 phase 3 randomized controlled clinical trial. *Cephalalgia* 2018; 38: 1442–1454.
834. Stauffer VL, Dodick DW, Zhang Q, et al. Evaluation of galcanezumab for the prevention of episodic migraine: the EVOLVE-1 randomized clinical trial. *JAMA Neurol* 2018; 75: 1080–1088.
835. Sun H, Dodick DW, Silberstein S, et al. Safety and efficacy of AMG 334 for prevention of episodic migraine: a randomised, double-blind, placebo-controlled, phase 2 trial. *Lancet Neurol* 2016; 15: 382–390.
836. Tepper S, Ashina M, Reuter U, et al. Safety and efficacy of erenumab for preventive treatment of chronic migraine: a randomised, double-blind, placebo-controlled phase 2 trial. *Lancet Neurol* 2017; 16: 425–434.
837. Reuter U, Ehrlich M, Gendolla A, et al. Erenumab versus topiramate for the prevention of migraine - a randomised, double-blind, active-controlled phase 4 trial. *Cephalalgia* 2022; 42: 108–118.
838. Sakai F, Suzuki N, Kim BK, et al. Efficacy and safety of fremanezumab for episodic migraine prevention: multicenter, randomized, double-blind, placebo-controlled, parallel-group trial in Japanese and Korean patients. *Headache* 2021; 61: 1102–1111.
839. Sakai F, Suzuki N, Kim BK, et al. Efficacy and safety of fremanezumab for chronic migraine prevention: multicenter, randomized, double-blind, placebo-controlled, parallel-group trial in Japanese and Korean patients. *Headache* 2021; 61: 1092–1101.
840. Takeshima T, Sakai F, Hirata K, et al. Erenumab treatment for migraine prevention in Japanese patients: efficacy and safety results from a phase 3, randomized, double-blind, placebo-controlled study. *Headache* 2021; 61: 927–935.
841. Wang SJ, Roxas Jr AA, Saravia B, et al. Randomised, controlled trial of erenumab for the prevention of episodic migraine in patients from Asia, the Middle East, and Latin America: the EMPOwER study. *Cephalalgia* 2021; 41: 1285–1297.
842. Schwedt TJ, Myers Oakes TM, Martinez JM, et al. Comparing the efficacy and safety of galcanezumab versus rimegepant for prevention of episodic migraine: results from a randomized, controlled clinical trial. *Neurol Ther* 2024; 13: 85–105.
843. Ashina M, Lanteri-Minet M, Pozo-Rosich P, et al. Safety and efficacy of eptinezumab for migraine prevention in patients with two-to-four previous preventive treatment failures (DELIVER): a multi-arm, randomised, double-blind, placebo-controlled, phase 3b trial. *Lancet Neurol* 2022; 21: 597–607.
844. Hu B, Li G, Li X, et al. Galcanezumab in episodic migraine: the phase 3, randomized, double-blind, placebo-controlled PERSIST study. *J Headache Pain* 2022; 23: 90.
845. Bussiere JL, Davies R, Dean C, et al. Nonclinical safety evaluation of erenumab, a CGRP receptor inhibitor for the prevention of migraine. *Regul Toxicol Pharmacol* 2019; 106: 224–238.
846. Noseda R, Bedussi F, Gobbi C, et al. Safety profile of erenumab, galcanezumab and fremanezumab in pregnancy and lactation: analysis of the WHO pharmacovigilance database. *Cephalalgia* 2021; 41: 789–798.
847. Mulder IA, Li M, de Vries T, et al. Anti-migraine calcitonin gene-related peptide receptor antagonists worsen cerebral ischemic outcome in mice. *Ann Neurol* 2020; 88: 771–784.
848. MaassenVanDenBrink A, Meijer J, Villalon CM, et al. Wiping out CGRP: potential cardiovascular risks. *Trends Pharmacol Sci* 2016; 37: 779–788.
849. Dodick DW, Tepper SJ, Ailani J, et al. Risk of hypertension in erenumab-treated patients with migraine: analyses of clinical trial and postmarketing data. *Headache* 2021; 61: 1411–1420.
850. Ashina M, Kudrow D, Reuter U, et al. Long-term tolerability and nonvascular safety of erenumab, a novel calcitonin gene-related peptide receptor antagonist for prevention of migraine: a pooled analysis of four placebo-controlled trials with long-term extensions. *Cephalalgia* 2019; 39: 1798–1808.

851. Ailani J, Kaiser EA, Mathew PG, et al. Role of calcitonin gene-related peptide on the gastrointestinal symptoms of migraine-clinical considerations: a narrative review. *Neurology* 2022; 99: 841–853.
852. Breen ID, Brumfiel CM, Patel MH, et al. Evaluation of the safety of calcitonin gene-related peptide antagonists for migraine treatment among adults with raynaud phenomenon. *JAMA Netw Open* 2021; 4: e217934.
853. Evans RW. Raynaud's phenomenon associated with calcitonin gene-related peptide monoclonal antibody antagonists. *Headache* 2019; 59: 1360–1364.
854. Khalil M, Zafar HW, Quarshie V, et al. Prospective analysis of the use of OnabotulinumtoxinA (BOTOX) in the treatment of chronic migraine; real-life data in 254 patients from hull. *U.K. J Headache Pain* 2014; 15: 54.
855. Ornello R, Baraldi C, Guerzoni S, et al. Comparing the relative and absolute effect of erenumab: is a 50% response enough? Results from the ESTEEMen study. *J Headache Pain* 2022; 23: 38.
856. Tepper SJ, Sheikh HU, Dougherty CO, et al. Erenumab dosage for migraine prevention: an evidence-based narrative review with recommendations. *Headache* 2022; 62: 420–435.
857. Blumenfeld AM, Stevanovic DM, Ortega M, et al. No "wearing-off effect" seen in quarterly or monthly dosing of fremanezumab: subanalysis of a randomized long-term study. *Headache* 2020; 60: 2431–2443.
858. Winner PK, McAllister P, Chakhava G, et al. Effects of intravenous eptinezumab vs placebo on headache pain and most bothersome symptom when initiated during a migraine attack: a randomized clinical trial. *JAMA* 2021; 325: 2348–2356.
859. Iannone LF, Burgalassi A, Vigani G, et al. Switching anti-CGRP(R) monoclonal antibodies in multi-assessed non-responder patients and implications for ineffectiveness criteria: a retrospective cohort study. *Cephalalgia* 2023; 43: 10.1177/03331024231160519.
860. Kaltseis K, Filippi V, Frank F, et al. Monoclonal antibodies against CGRP (R): non-responders and switchers: real world data from an Austrian case series. *BMC Neurol* 2023; 23: 174.
861. Overeem LH, Lange KS, Fitzek MP, et al. Effect of switching to erenumab in non-responders to a CGRP ligand antibody treatment in migraine: a real-world cohort study. *Front Neurol* 2023; 14: 1154420.
862. Briceno-Casado MDP, Gil-Sierra MD and De-La-Calle-Riaguas B. Switching of monoclonal antibodies against calcitonin gene-related peptide in chronic migraine in clinical practice: a case series. *Eur J Hosp Pharm* 2023; 30: e19.
863. Fresan Restituto D, Lacalle Fabo E and Martin Bujanda M. Salvage therapy for patients who do not respond to the first anti-CGRP monoclonal antibody: a new chance for patients with migraine? *Neurol Persp* 2022; 2: 102–104.
864. Patier Ruiz I, Sánchez-Rubio Ferrández J, Cárcamo Fonfría A, et al. Early experiences in switching between monoclonal antibodies in patients with nonresponsive migraine in Spain: a case series. *Eur Neurol* 2021; 85: 132–135.
865. Winner PK, Spierings ELH, Yeung PP, et al. Early onset of efficacy with fremanezumab for the preventive treatment of chronic migraine. *Headache* 2019; 59: 1743–1752.
866. Tepper SJ, Lucas S, Ashina M, et al. Timing and durability of response to erenumab in patients with chronic migraine. *Headache* 2021; 61: 1255–1263.
867. Takeshima T, Nakai M, Shibasaki Y, et al. Early onset of efficacy with fremanezumab in patients with episodic and chronic migraine: subanalysis of two phase 2b/3 trials in Japanese and Korean patients. *J Headache Pain* 2022; 23: 24.
868. Schwedt TJ, Kuruppu DK, Dong Y, et al. Early onset of effect following galcanezumab treatment in patients with previous preventive medication failures. *J Headache Pain* 2021; 22: 15.
869. Schwedt T, Reuter U, Tepper S, et al. Early onset of efficacy with erenumab in patients with episodic and chronic migraine. *J Headache Pain* 2018; 19: 92.
870. McAllister PJ, Turner I, Reuter U, et al. Timing and durability of response to erenumab in patients with episodic migraine. *Headache* 2021; 61: 1553–1561.
871. Kuruppu DK, North JM, Kovacik AJ, et al. Onset, maintenance, and cessation of effect of galcanezumab for prevention of migraine: a narrative review of three randomized placebo-controlled trials. *Adv Ther* 2021; 38: 1614–1626.
872. Igarashi H, Shibata M, Ozeki A, et al. Early onset and maintenance effect of galcanezumab in Japanese patients with episodic migraine. *J Pain Res* 2021; 14: 3555–3564.
873. Goadsby PJ, Dodick DW, Martinez JM, et al. Onset of efficacy and duration of response of galcanezumab for the prevention of episodic migraine: a post-hoc analysis. *J Neurol Neurosurg Psychiatry* 2019; 90: 939–944.
874. Detke HC, Millen BA, Zhang Q, et al. Rapid onset of effect of galcanezumab for the prevention of episodic migraine: analysis of the EVOLVE studies. *Headache* 2020; 60: 348–359.
875. Hedayat M, Nazarbaghi S, Heidari M, et al. Venlafaxine can reduce the migraine attacks as well as amitriptyline: a noninferiority randomized trial. *Clin Neurol Neurosurg* 2022; 214: 107151.
876. Sorensen PS, Larsen BH, Rasmussen MJ, et al. Flunarizine versus metoprolol in migraine prophylaxis: a double-blind, randomized parallel group study of efficacy and tolerability. *Headache* 1991; 31: 650–657.
877. Kaniecki RG. A comparison of divalproex with propranolol and placebo for the prophylaxis of migraine without aura. *Arch Neurol* 1997; 54: 1141–1145.
878. Gawel MJ, Kreeft J, Nelson RF, et al. Comparison of the efficacy and safety of flunarizine to propranolol in the prophylaxis of migraine. *Can J Neurol Sci* 1992; 19: 340–345.