Systematic Review and Meta-Analysis

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Different routes of administration in chronic migraine prevention lead to different placebo responses: a meta-analysis

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Abstract

Placebo response is a powerful determinant of health outcomes in several disorders. Meta-analysis of clinical trials in pain conditions shows that it can contribute up to 75% of the overall treatment effect. Placebo response deriving from different routes of administration is poorly understood in primary headaches' pharmacological prevention. Thus, this meta-analysis aims to analyze how different routes of administration affect the placebo response in chronic migraine (CM). We conducted a meta-analysis with 7 randomized, double-blind, placebo-controlled clinical trials, with 5672 patients older than 18 years who suffer from CM without associated comorbidities. We compared those who received a placebo-administered agent for the preventive treatment of CM subcutaneous, endovenous, or oral against those who received multiple head injections. The primary outcome was reduction in the number of days with migraine in the month assessed at 12, 16, and 24 weeks of treatment compared with baseline. Our study shows that placebo responses were greater when botulinum toxin was applied to the head, followed by intravenous injection of the anti-calcitonin gene-related peptide monoclonal antibody eptinezumab. Oral topiramate and subcutaneous monoclonal showed no difference, being inferior to head injection. Administration route affects placebo responses in CM preventive treatment. Elucidating the underlying mechanisms that mediate a placebo response in migraine treatment is beneficial to clinical practice and drug development, especially when comparing drugs with different routes of administration, with the effect of application to the head being superior to the other routes in this study. In our study the placebo response accounted for approximately 75% of the therapeutic gain in the treatment of CM.

Keywords: Chronic migraine, Placebo response, Randomized clinical trials

1. Introduction

Chronic migraine (CM) is a debilitating neurological condition, estimated to affect 2% of the world population.[29] It is defined as a headache occurring on 15 or more days/month for more than 3 months.[9] Chronic migraine therapeutic approach is more complex than episodic migraine.[8,16,17] Comorbid conditions are common, particularly psychiatric and sleep disorders,[22,28] with significant reduction in quality of life[35] and frequent analgesic use. Patients often need a multifactorial approach, adding pharmacological treatments to nonpharmacological options.

Placebo response is a powerful determinant of health outcomes in several disorders and may directly interfere with tolerance and efficacy of pharmacological therapy.[1,2] High-evidence studies have demonstrated the importance of placebo and nocebo effects, with symptom relief in conditions such as pain, depression, Parkinson disease, hypertension, arthritis, migraine, cancer, and asthma.[20] This result reaches 75% of the overall treatment in conditions such as fibromyalgia[37] and osteoarthritis.[38] In the management of acute headache, these results ranged between 21% and 30% of remission with placebo.[25,26,30]

In a consensus of experts in placebo and nocebo,[13] the importance of differentiating between the placebo effect and the placebo response[14] was emphasized. The placebo response includes all health changes that result after the application of an inactive treatment, whereas the placebo effect refers to changes specifically attributable to the placebo mechanism, including patient's expectation, genetics, disease severity, patient–physician relationship, environmental circumstances, and external factors such as the route of administration and treatment aggressiveness.[24]

Previous studies show that different routes of administration and placebo procedures result in different outcomes. Intra-articular and topical placebo had a significantly greater response than oral placebo in osteoarthritis.[5] Pain threshold was not different in an experiment comparing placebo pills, sham acupuncture, and cue conditioning.[21] In high-altitude headache, placebo oxygen inhaled through a mask was superior to placebo aspirin pills.[6]

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In migraine, subcutaneous placebo was superior to the oral route,[9,26] another meta-analysis showed greater effect with intranasal route,[30] and finally sham acupuncture surgery and sham surgery had more pronounced reduction of migraine frequency than oral placebos.[27]

Such studies corroborate the hypothesis that a good part of the clinical treatment of migraine might be due to nonspecific effects and that the size of such effects might differ between different routes of administration. Therefore, we aim to answer the question: Do different routes of administration have different placebo effects in migraine?

Chronic migraine is a good model for studying placebo response. It is a well-defined disease, affects a large population, and a great number of clinical trials have been performed. We aimed to estimate the difference between placebo response in application on specific areas in the head and neck (botulinum toxin[3,4,12]) vs administered orally (topiramate),[33] intravenous (eptinezumab),[23,31] and subcutaneous (erenumab,[36] galcanezumab,[11,15] and fremanezumab[7,32]) in CM preventive treatment, by collecting data from completed randomized double-blind placebo-controlled trials in adults. This knowledge would benefit both clinical practice and drug development.

2. Methods

We conducted a meta-analysis in accordance with the PRISMA protocol and registered the protocol a priori on the International Prospective Register for Systematic Reviews (PROSPERO) (CRD42020139049).

2.1. Search strategy

A systematic search of the literature before January 2021 was performed, we follow the methods recommended by the Cochrane to minimise publication bias.

We searched on PubMed, Clinical Trials, UpToDate, Cochrane Reviews, The International Clinical Trials Register Platform (www.who.int/ictrp), and MEDLINE (www.ncbi.nlm.nih.gov/pubmed) for randomized, double-blind, placebo-controlled trials of CM preventive treatment. Meeting abstracts were hand searched, looking for articles presented in the main headache congresses (see full strategy in online supplementary file 1, available at http://links.lww.com/PAIN/B407).

Two authors (D.B.S. and M.F.P.) independently extracted and agreed on data from included trials using a standard pro forma. Trials without peer-reviewed publications were excluded. Trials could be published in any language in any publication status. Observational, quasi-randomized, and nonrandomized studies were excluded.

2.2. Selection criteria

We included randomized, double-blind, placebo-controlled trials in CM preventive treatment which reported change in monthly migraine days (MMD) at 12, 16, and 24 weeks as an outcome measure, compared with baseline (**Table 1**). As the primary outcome, we analyzed placebo responses in different routes of application. As a secondary outcome, we synthesized the results of the intervention with medications vs the placebo response. Finally, we analyzed the result of the effect size of the intervention of different drugs.

Patients had to be at least 18 years old, without a secondary disease, and without previous refractory treatment. All studies had to follow the International Classification of Headache Disorders, third edition. Patients with other comorbidities (anxiety, depression, attention deficit and hyperactivity disorder, or obsessive compulsive disorder) were excluded to reduce confounders in the analysis.

Table 1

Description of PICO components of systematic review.

P	Men and women older than 18 years who suffer from chronic migraine (more than 15 migraine episodes per month from 3 months) without associated comorbidities
I	Placebo-administered agent for preventive treatment of chronic migraine
C	Placebo agent administered according to the PREEMPT protocol
O	Reduction in the number of days with migraine in the month accessed at 12, 16, or 24 weeks of treatment compared with baseline

We used interventions that are common in clinical practice for the treatment of CM by evaluating the placebo response of the different routes of application. Among the treatments, we have found oral topiramate, monoclonal antibodies (MAbs) applied subcutaneously, intravenous eptinezumab, and botulinum toxin type A injected in the forehead according to the PREEMPT protocol; the description of the studies is summarized in **Table 2**. Our study compared the different response of placebo with the application of placebo on the head.

2.3. Quality assessment

Two reviewers (D.B.S. and M.F.P.) assessed eligible materials independently using Cochrane risk of bias methods. Publications were assessed on their method of randomization, blinding and concealment of allocation, the number of participants lost to follow-up, evidence of selective reporting, and study size. We did not use funnel plots because of the small number of studies included in the individual meta-analyses and the true heterogeneity in the trial design (dose, different drugs, and different routes of application).

All included studies underwent the ethics committee analysis, ensuring the safety of patients included in the study, with minimal risk of intervention for patients. The Grading of Recommendations Assessment, Development and Evaluation (GRADE) tables were created for each comparison; this process involves assessment of the risk of publication bias for each outcome measure (**Figs. 1 and 2**).

2.4. Data extraction

We independently extracted data in an Excel and entered trials into RevMan twice, cross-checking for consistency. The data were collected manually from the articles and submitted in the Review Manager to create the forest plot.

In the analysis of the data, we used articles comparing placebo groups and intervention groups to reduce the number of episodes of migraine in 12, 16, and 24 weeks, where $P < 0.05$ was observed and a 95% confidence interval [CI] power of 80%. The articles should contain (1) SD or SEM and means of the groups, (2) well-specified sample space, and (3) well-researched survey participants with information on loss of follow-up and initial characteristics of the groups, all of which should be included in

Table 2

Characteristics included studies.

Studies	Year	Country	Population	Participant	Method	Intervention	Results
PREEMPT1	2010	North America sites	Men or women aged 18-65 years with a history of CM meeting the diagnostic criteria listed in ICHD-II, with the exception of complicated migraine (hemiplegic migraine, basilar-type migraine, ophthalmoplegic migraine, and migrainous infarction) were eligible.	Onabotulinumtoxin A (n 341) Mean age 41.2 Placebo (n 332) Mean age 42.1	24-week, double-blind, parallel group, placebo-controlled phase.	Subjects were randomized (1:1) to injections every 12 weeks of onabotulinumtoxin A (155-195 U) or placebo (2 cycles)	The study showed a greater reduction in MHDs in the intervention group (−7.6 onabotulinumtoxinA vs −6.1 placebo $P=$ 0.002, 95% CI −1.5 (−2.6 to 0.59))
PREEMPT2	2010	66 Global sites (50 North America and 16 European)	Men or women aged 18-65 years with a history of CM meeting the diagnostic criteria listed in ICHD-II, with the exception of complicated migraine (hemiplegic migraine, basilar type migraine, ophthalmoplegic migraine, migraineurs infarction) were eligible	Onabotulinumtoxin A (n 347) Mean age 41 Placebo (n 358) Mean age 40.9	24-week, phase 3, double-blind, parallel group, placebo-controlled phase.	Subjects were randomized (1:1) to injections every 12 weeks of onabotulinumtoxin A (155-195 U) or placebo (2 cycles)	The study showed a greater reduction in MHDs in the intervention group (−8.7 days onabotulinumtoxinA vs −6.3 placebo, $P<$ 0.01, 95% CI −2.4 (−3.31 to −1.36))
Epitnezumab (PROMISE-2)	2020	128 sites in 13 countries (USA, Spain, Ukraine, Russia, United Kingdom, Republic of Georgia, Hungary, Italy, Slovakia, Germany, Czech Republic, Denmark, and Belgium)	Adults 18-65 years, with a diagnosis of CM at or before 50 years of age were eligible for participation if they had a history of CM for ≥12 months before screening and experienced ≥ 15 to ≤ 26 headache days and ≥ 8 migraine during the 28-day screening period.	Eptinezumab 100 mg (n 356) Mean age 41.0 Epitinezumab 300 mg (n 350) Mean age 41.0 Placebo (n 366) Mean age 39.6	Phase 3, multicenter, randomized double-blind, parallel group, placebo-controlled phase. The primary endpoint was change from baseline in MMDs over wk 1 to 12	Subjects were randomized to receive eptinezumab 100, 300 mg, or placebo (1:1:1) administered on day 0 and week 12.	Epitinezumab 100 and 300 mg was associated with significant reductions in MMDs across weeks 1 to 12 compared with placebo (placebo −5.6, 100 mg −7.7, $P<$ 0.01 vs placebo; 300 mg − 8.2, $P<$ 0.01 vs placebo)
Erenumab	2017	69 headache and clinical research centers in North America (Canada and USA) and Europe (Czech Republic, Denmark, Finland, Germany, Norway, Poland, Sweden, and United Kingdom)	Men or women aged 18-65 years with a history of CM (with or without aura). Patient had to have migraine for 15 or more days per month, or 8 or more of those days were migraine days	Erenumab 70 mg (n 191) Mean age 41.4 Erenumab 140 mg (n 190) Mean age 42.9 Placebo (n 286) Mean age 42.1	Phase 2, multicenter, randomized double-blind, parallel group, placebo-controlled phase. The primary endpoint was change from baseline in MMDs over weeks 1 to 12	Patients were randomly assigned (3:2:2) to subcutaneous placebo, erenumab 70 mg, or erenumab 140 mg	Erenumab 70 and 140 mg reduce MMDs vs placebo (both doses −6.6 days vs placebo −4.2 days, difference −2.5, $P<$ 0.01, 95% CI (−3.5 to −1.4)
Galcanezumab (REGAIN)	2018	116 headache and clinical research in 12 countries (Argentina, Canada, Czech Republic, Germany, Israel, Italy, Mexico, the Netherlands, Spain, Taiwan, United Kingdom, and USA)	Adults 18-65 years with CM meeting the diagnostic criteria listed in ICHD-II. The continuation or start of any additional migraine preventive treatment was not permitted	Galcanezumab 120 mg (n 278) Mean age 39.6 Galcanezumab 240 mg (n 277) Mean age 41.05 Placebo (n 555) Mean age 41.5	Phase 3, multicenter, randomized double-blind, parallel group, placebo-controlled phase with 12 weeks.	Randomized in a 1:1:2 ratio received a subcutaneous injection of galcanezumab 120 mg/month (after an initial loan of 240 mg) or 240 mg/month or placebo	Both galcanezumab groups demonstrated a greater reduction in MHDs compared with placebo ($P<$ 0.001; placebo −2.7; galcanezumab 120 mg −4.8; 240 mg −4.6)
Fremanezumab	2017	132 sites in 9 countries	Adults 18-70 years with CM meeting the diagnostic criteria listed in ICHD-II.	Fremanezumab quarterly (n 376) Mean age 42.0 Fremanezumab monthly (n 379) Mean age 40.6 Placebo (n 375) Mean age 41.4	Randomized double-blind, placebo-controlled phase with a screening visit, a 28-day preintervention period and a 12-week intervention period	Randomized in a ratio 1:1:1 to receive fremanezumab quarterly (a single dose 675 mg at baseline and placebo at week 4 and 8), fremanezumab monthly (625 mg at baseline and 225 mg at week 4 and 8) or matching placebo	There was a reduction in the average number of monthly MHDs with fremanezumab quarterly (4.9 days) and fremanezumab monthly (5.0) superior than with placebo (3.2) ($P>$ 0.001 in both comparisons)

(*continued on next page*)

Table 2 (*continued*)

Studies	Year	Country	Population	Participant	Method	Intervention	Results
Topiramate	2007	46 U.S. sites	Adults 18-65 years with 15 or more headache days per month, at least half of those were migraine/migrainous headaches	Topiramate 100 mg (153) Mean age 37.8 Placebo (n 153) Mean age 38.6	Randomized double-blind, placebo-controlled, multicenter study with 16 weeks of treatment	Randomized 1:1 to receive topiramate 100 mg or placebo. An initial dose of topiramate 25 mg/d was titulated upward in weekly increments of 25 mg/d to a maximum 100 mg/d (or to the maximum tolerated dose)	Topiramate treatment results in a statistically significant mean reduction of migraine and reduction of MHDs relative to baseline (topiramate −5.6 vs placebo −4.1; $P = 0.032$)

CI, confidence interval; CM, chronic migraine.

the diagnosis of CM. For each trial we recorded the year of completion, number of participants, change in monthly migraine days (MMD), and SD of change in MMD. The deviation of the mean was converted to SD, which was used in the forest plot. We adhered as far as possible to the PRISMA guidelines. We attempted to contact authors and obtain missing data.

2.5. Statistical analysis

We submitted data in Review Manager, where the difference in absolute reduction of migraine episodes was analyzed by a forest plot. Heterogeneity was present in doses, routes of administration, and participant populations, and we use a random-effects model for the analysis. RevMan implements a version of random-effects meta-analysis that is described by DerSimonian and Laird[10]

3. Results

3.1. Description of included studies

Thousand four hundred forty-seven articles were found in the first search, of which 51 were selected for full reading and only 7 articles were selected for statistical analysis (**Fig. 3**). The included studies are summarized in **Table 3**. The studies included in the analysis were 7 hazards: 3 referring to anti-calcitonin gene-related peptide (CGRP) MAbs subcutaneous application (erenumab 70 and 140 mg, galcanezumab 120 and 240 mg, and fremanezumab monthly and quarterly), 1 referring to intravenous monoclonal (eptinezumab 100 mg and 300 mg), 1 referring article topiramate by mouth, and 2 articles refer to the PREEMPT study (Botox application on 12 points on the head) being used as a standard for comparison. All are randomized controlled trials in which both groups were similar before the outcome, with similar predictors, such as age, disease status, ethnicity, socioeconomic factors, and presence of comorbidities. Groups were analyzed by the administration route compared with the PREEMPT study. In total, the population attached to the study was 5672 patients.

The population of the studies had a predominance of female, White ethnicity, and average age around 40 years, with a minority with the use of previous medication and a minority with failure to 2 preventive drugs or more.

3.2. Placebo response of different routes of administration

Placebo response of the PREEMPT study (application of botulinum toxin type A to the head) is superior to the subcutaneous route and oral route with a mean reduction in migraine episodes in the month of −6.20 (**Fig. 4**). Regarding the intravenous route, it was nonsuperior to epitnezumab, both at 12 and 24 weeks, with a mean difference compared with head injection of −0.32 (adjusted HR −0.3, 95% CI −0.1.03 to 0.38, $P < 0.001$). Subcutaneous MAbs together showed a reduction of −2.84 compared with botulinum toxin type A application (adjusted hazard ratio [HR] −2.84, 95% CI −3.70 to −1.97, $P < 0.001$). Among the CGRP MAbs, erenumab showed a better placebo response, with a reduction of −4.2 days with headache at baseline and with a difference in Botox placebo at a mean of 2

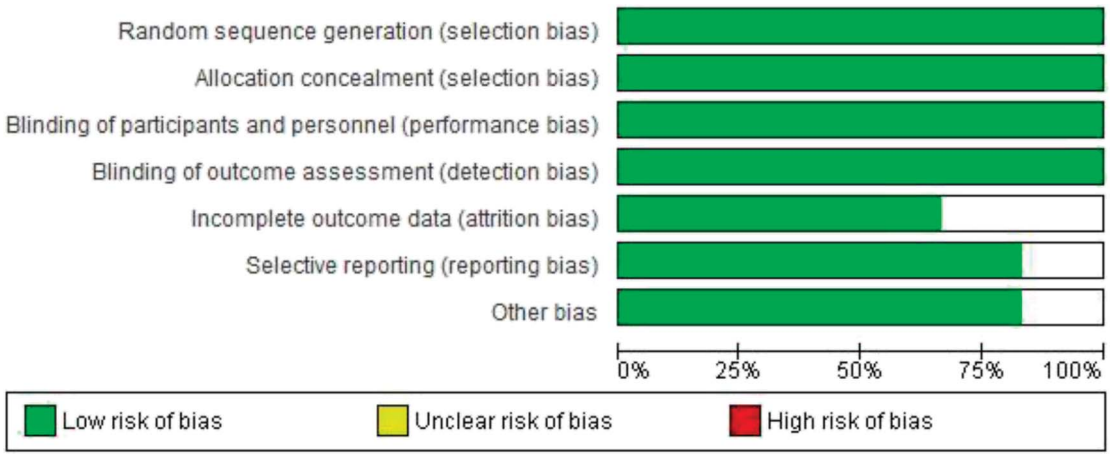

Figure 1. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.

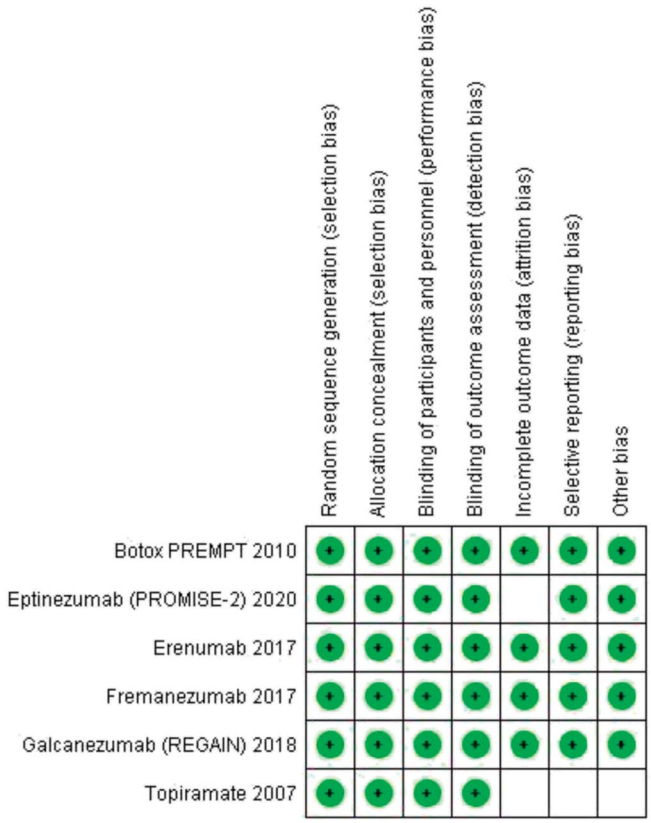

Figure 2. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.

days (adjusted HR −1.5, 95% CI [LC, confidence limit] −0.94 to −3.07, $P < 0.001$). Oral topiramate had a range of −4.7 (adjusted HR 1.5, 95% CI −0.30 to −2.71, $P < 0.001$) compared with the PREEMPT study.

3.3. Effectiveness vs placebo

The results in **Figure 5** show that although the placebo response was good, all interventions are superior, showing a greater reduction in the number of migraine episodes in the month. Eptinezumab showed a reduction of −2.33 compared with placebo (adjusted HR -2.33, 95% CI [LC] −3.13 to −1.53, $P < 0.001$). Botulinum toxin application was also superior, with an average reduction of −8.15, compared with its placebo reduction of −1.95 (adjusted HR −1.95, 95% CI [LC] −3.41 to −0.49, $P < 0.001$). The added monoclonals showed a reduction of −2.05 compared with placebo (95% CI [LC] −2.69 to −1.41, $P < 0.001$), with erenumab having the lowest mean reduction of −2.40 compared with subcutaneous placebo. Topiramate was also shown to be superior to the placebo effect, with a reduction of −1.70 (adjusted HR −1.70, 95% CI [LC] −3.03 to −0.37, $P < 0.001$).

3.4. Effectiveness of different medications

Figure 6 shows the analysis of the effect of medications (monoclonal and topiramate) compared with the therapeutic application of Botox to the head according to the PREEMPT protocol; we noticed that Botox was superior to monoclonal subcutaneous (erenumab, fremanezumab, and galcanezumab). In comparison with epitnezumab, PREEMPT was equivalent, with a tendency to have a greater effect as the dosage is increased and the therapy duration is longer. Compared with epinezumab 100mg at 12 weeks, PREEMPT had an average reduction of 0.45. In the dosage of 300 mg at 24 weeks, it had an average reduction of −8.8, compared with PREEMPT at −0.65 days (adjusted HR -0.65, 95% CI [LC]−2.13 to 0.84, $P < 0.001$). Erenumab was equivalent in relation to the other subcutaneous (SC) monoclonal, however, without dose interference in the result. Fremanezumab applied monthly or quarterly proved to be equivalent, with 3.15 and 3.25 days of difference in relation to Botox. Galcanezumab 120 mg was equal to the dosage of 240 mg. Topiramate had an average reduction of −6.4, with an average difference of 1.75 days compared with PREEMPT (adjusted HR 1.75, 95% CI [LC] 0.18 to 3.33, $P < 0.001$).

4. Discussion

Our study shows that placebo responses were greater when botulinum toxin type A was applied to the head, followed by intravenous injection of an anti-CGRP monoclonal antibody eptinezumab. Oral topiramate and subcutaneous MAbs had no difference, being inferior to head injection. Therapeutic gains across the 4 administration routes did not vary as much as the placebo responses.

One difficulty of the study was to isolate the placebo effect because there are no studies comparing the placebo response and nonintervention. In a study of patients with severe cognitive impairment in 2017,[19] the authors investigated the effect of the drug in open-label studies, with a 100% chance of receiving treatment, vs the drug and placebo in randomized

Table 3

Baseline and duration of Included studies.

Trials	Year	Phase	Duration (wk)	Baseline monthly migraine days placebo	Baseline monthly migraine days intervention
PREEMPT 1	2010	Phase 3	24	19.1 (4.1)	19.1 (4.0)
PREEMPT 2	2010	Phase 3	24	18.7 (4.1)	19.2 (3.9)
Eptinezumab (Promise-2)	2020	Phase 3	12, 24	16.2 (4.6)	16.1 (4.6)//16.1 (4.8)
Erenumab	2017	Phase 2	12	18.2 (4.7)	17.9 (4.4)//17.8 (4.7)
Galcanezumab (REGAIN)	2018	Phase 3	12	19.6 (4.6)	19.4 (4.3)//19.2 (4.6)
Fremanezumab	2017	Phase 3	12	16.2 (4.9)	16 (5.2)//16.4 (5.2)
Topiramate	2007	Phase 3	16	15.1 (5.8)	15.2 (6.4)

Data are mean (SD). In the intervention, we have the baseline in the different doses of medications. Epitnezumab 10//300 mg. Erenumab 70//140 mg. Galcanezumab 120//240 mg. Fremanezumab monthly//quarterly.

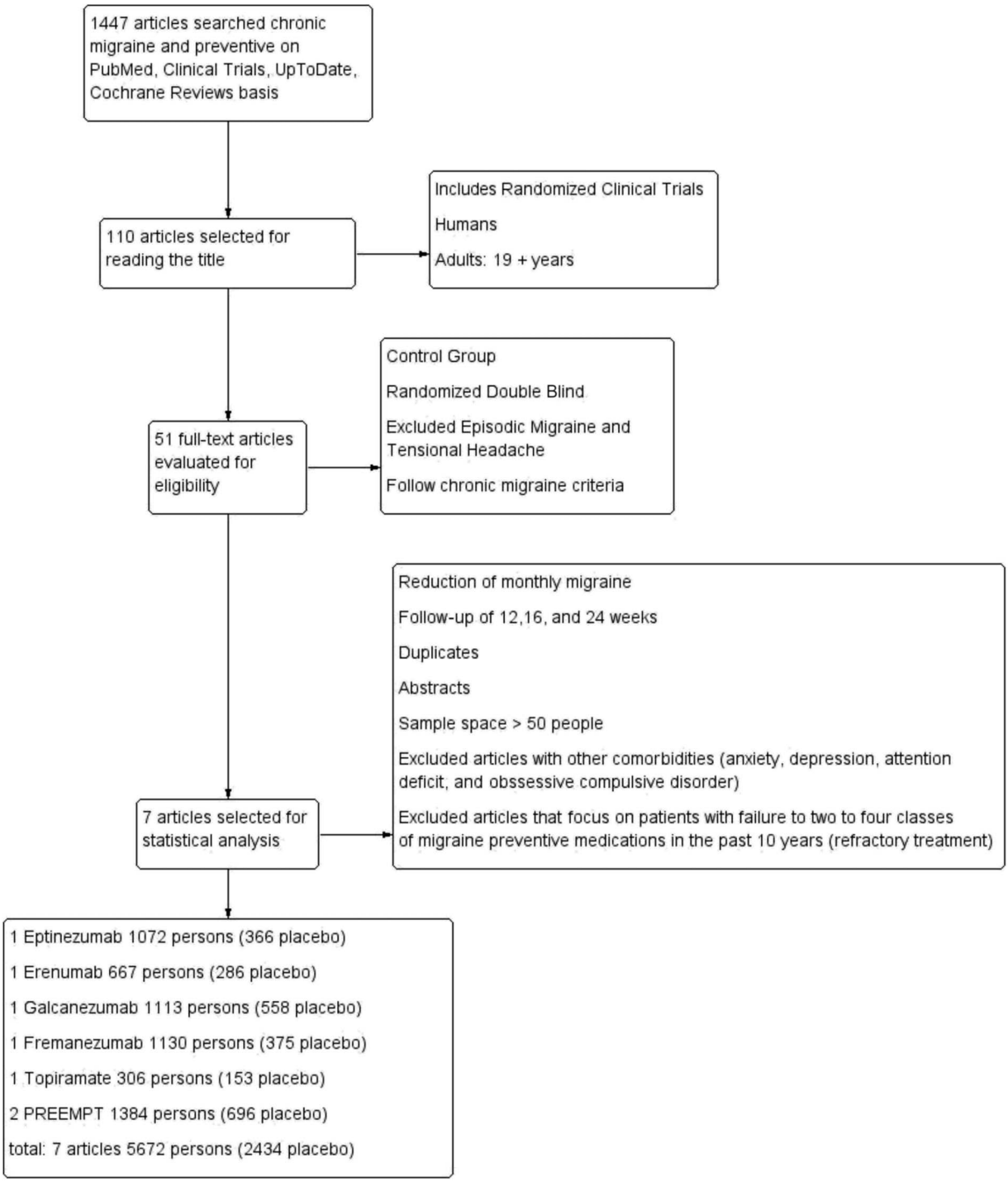

Figure 3. Inclusion and exclusion criteria.

clinical trials, with a 50% chance of receiving the drug. The results revealed higher effect sizes in studies with 100% likelihood of getting an active drug, compared with both the drug and placebo arm of placebo-controlled trials. Thus, the genuine placebo effect was proven, not explainable by natural history or regression toward the mean, among patients intellectually disabled. Therefore, although our study evaluated the placebo response, the methodology of the studies was kept constant, all of which were double-blinded randomized clinical trials, with the natural history being kept constant. Thus, the differences in the placebo response found reflect a difference in the placebo effect.

It is well known in pain literature that placebo analgesia is greater when comparing an injected vs oral administered therapy. A meta-analysis of acute migraine treatment trials comparing placebo effects of subcutaneous vs oral sumatriptan showed 32.4% response in the subcutaneous vs 25.7% in oral.[9] In our study, we found no difference between the oral route and the subcutaneous route, going against this hypothesis. Our study showed botulinum toxin treatment was superior to oral

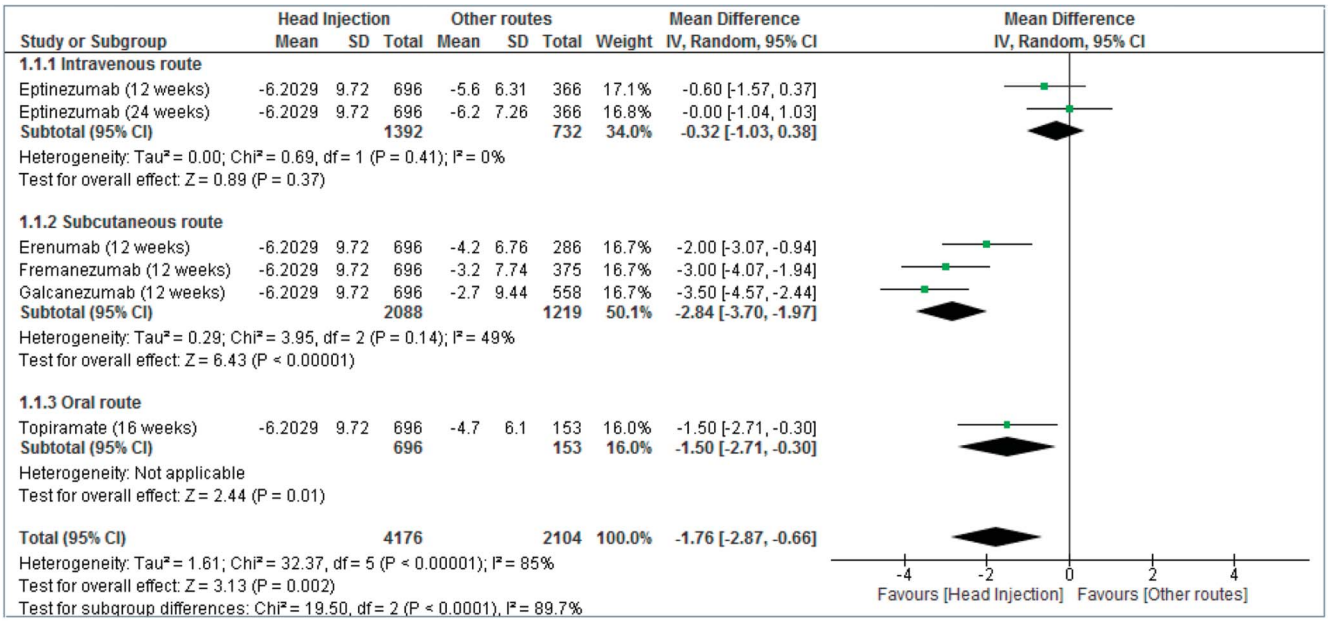

Figure 4. Placebo responses across different routes of administration at 12,16 or 24 weeks in migraine monthly days compared to botulinum toxin type A by the PREEMPT protocol at 24 weeks.

topiramate placebo rates in CM prophylaxis, but not subcutaneous treatment with anti-CGRP MAbs.

Some limitations of the study have to be taken into account in the analysis. Although all trials protocol methodology followed the same endpoint (number of migraine days per month), the time frame was slightly different (12, 16, or 24 weeks after treatment compared with baseline), and in the intravenous application, the effect tended to be greater at 24 weeks compared with 12 weeks, so time may interfere with the equivalence of the oral route (16 weeks) in relation to the subcutaneous route (12 weeks). In addition, PREEMPT at 24 weeks had a longer time compared with other routes of administration.

Another limitation in the comparison between the placebos response and the effects of the medications is the fact that the studies start from baselines different from the number of days with migraine, although they all fit the criteria for CM. In **Figure 4**, we can see that the patients in the PREEMPT and galcanezumab studies had more episodes per month than the other studies, which may have contributed to a greater reduction in the PREEMPT group. However, there is no statistical difference between the baseline of the head injection placebo groups and the subcutaneous ones (adjusted HR −0.89, 95% CI [LC] −2.90 to 1.13, $P < 0.001$); however, in relation to epitinezumab (EV), there is a difference of −2.69 days with migraine (adjusted

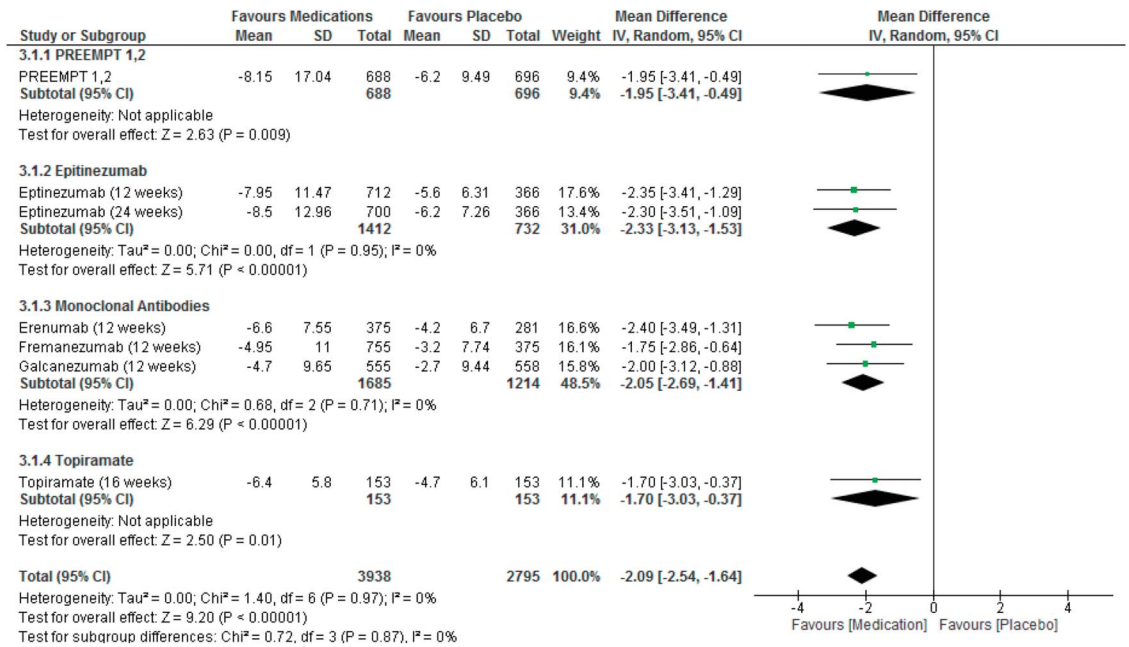

Figure 5. Therapeutic gain among the four administration routes.

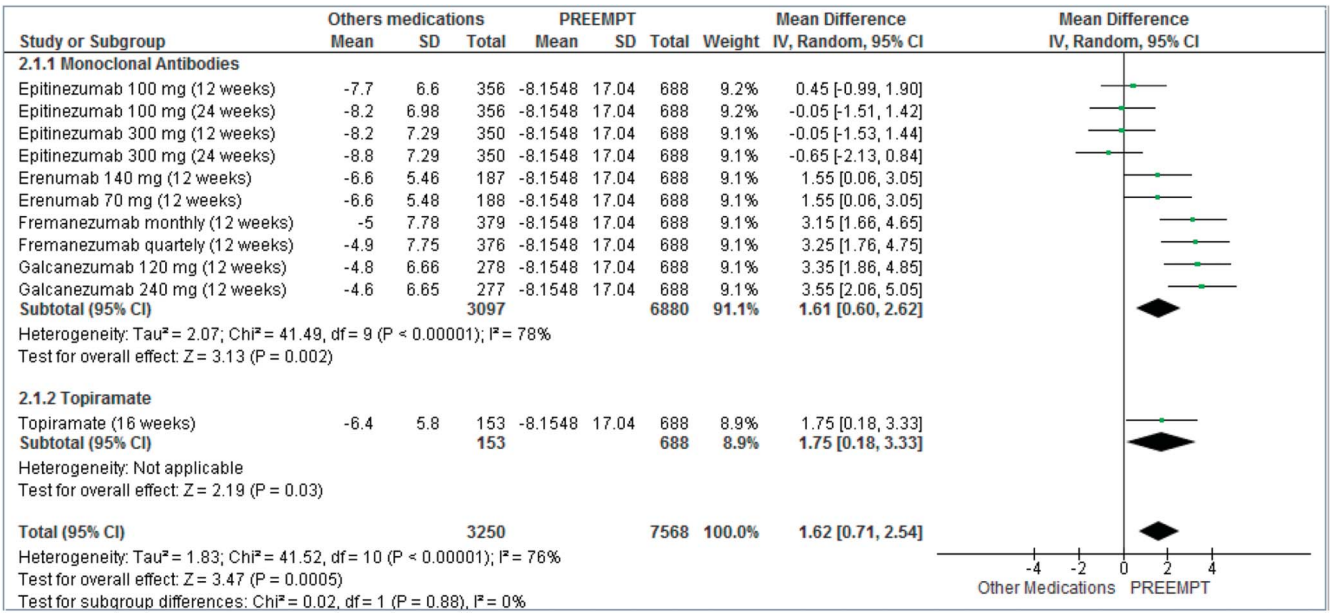

Figure 6. Comparison between Effects of Medicines on the reduction in the number of migraine episodes in the month compared to the botox applied to the head by the PREEMPT protocol at 24 weeks.

HR -2.69, 95% CI [LC] −3.25 to −2.13, $P < 0.001$) and compared with oral placebo −3.79 days (adjusted HR -3.79, 95% CI [LC] −4.76 to −2.82, $P < 0.001$), and these differences in the baseline should be weighted in the interpretation of the results in **Figure 4**. However, as the baselines of the PREEMPT group (head injection) are equivalent to the monoclonal groups (subcutaneous), there is superiority in head injection route in relation to SC.

Other differences that may have a share in the result; the trials had 10 years difference, topiramate in 2007 and MAbs after 2017. In 2007, limited therapies were available for CM, therefore more expectation could be present in patients. Topiramate trial recruited patients from 56 sites in the United States, whereas trials with MAbs recruited patients from Europe too.

The methods of administration can interfere with the placebo response. In the PREEMPT study, 31 injections were applied, fixed-site, fixed-dose, intramuscular (IM) injections across 7 specific head/neck muscle areas (corrugator, procerus, frontalis, temporalis, occipitalis, cervical paraspinal, and trapezius). Injections were administered IM using a sterile 30-gauge, 0.5-inch needle and 0.1 mL of placebo injected at each site. In eptinezumab, 100 mL of 0.9% saline, EV, was applied to the placebo group over a period of 30 minutes.

In relation to the monoclonal ones, we see in **Figure 4** that there is no statistical difference between the SC groups; however, we notice a trend of greater reduction in the placebo of erenumab in relation to galcanezumab, although both have the same route of administration. The application methods were similar, both studies are double-blind and randomized. Several factors interfere with the placebo results, among them the trial phase. Studies in earlier phases may lead to higher expectation from both patients and clinicians due to its novelty, perhaps this explains the difference between the groups.

Intravenous injection could be considered as a stronger suggestion for efficacy to patients; however, its placebo response was equivalent with BoNTA in CM prophylaxis at 12 weeks and 24 weeks. It is interesting to note the increase in the intravenous placebo with the dose increase, bringing an idea of amplification of the placebo. Several other factors are implied in BoNTA administration: (1) 31 injections of the PREEMPT protocol may be perceived with greater invasiveness than the intravenous injection, (2) the known higher cost of BoNTA, (3) although aesthetic protocol is different, an additional cosmetic gain may be perceived by patients in BoNTA therapy, and (4) the authority and enthusiasm of physicians and research staff.[34]

Placebo response in BoNTA could be affected by the result in forehead wrinkle improvement in the treatment group. The meta-analysis,[27] which showed the superiority of sham acupuncture surgery and sham surgery over oral placebo, questions whether the placebo effect of head injection vs botulin toxin would not be inferior because the side effect of muscle relaxation would lead to the unblinding of the patients and physicians, decreasing the placebo effect. Despite this fact having an impact on the placebo response, in our study we saw the superiority of the placebo response through head injection in relation to other routes of administration, going contrary to this thought. In addition if patients observe wrinkles persist, they may assume that they enter the placebo group decreasing their expectation to treatment; therefore, placebo rates in trials could be even higher. Same principle applies for topiramate trials when paresthesias may be experienced, known to affect 50% of patients.

It is interesting to note that, although the placebo response was analyzed, administration of higher impact (botulinum toxin type A on the head) reduced migraine frequency by −6.20 episodes per month (adjusted HR −1.5, 95% CI [CL] −6.17 to- 6.23, $P < 0.001$), which in clinical practice shows that a patient with CM with 15 episodes per month may have up to 40% reduction in episodes per month.

In addition, therapeutic gain of the medications compared with the placebo response averaged 2 days, so we analyzed that this therapeutic gain should be analyzed with other variables, which are not in the scope of this article, as adverse effects of these medications compared with the placebo, costs associated with medications, so that with other studies we can evaluate the therapeutic gain with greater robustness. We concluded through this analysis that much of the effect of drugs in the treatment of migraine is still due to the high placebo response, which contributes about 75% of the therapeutic gain.

5. Conclusion

Administration route affects placebo responses in CM preventive treatment. Elucidating the underlying mechanisms that mediate placebo response in migraine treatment is beneficial to clinical practice and drug development, especially when comparing drugs with different routes of administration.

Conflict of interest statement

The author D.B. Swerts received a scientific initiation scholarship from the Brasile association. The remaining authors have no conflicts of interest to declare.

Appendix A. Supplemental digital content

Supplemental digital content associated with this article can be found online at http://links.lww.com/PAIN/B407.

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