

# CGRP-antibodies, topiramate and botulinum toxin type A in episodic and chronic migraine: A systematic review and meta-analysis

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## Abstract

**Background:** The approval of monoclonal antibodies for prevention of migraine has revolutionized treatment for patients. Oral preventatives are still considered first line treatments as head-to-head trials comparing them with antibodies are lacking.

**Methods:** The main purpose of this study was to provide a comparative overview of the efficacy of three commonly prescribed migraine preventative medication classes. For this systematic review and meta-analysis, we searched the databases CENTRAL, EMBASE, and MEDLINE until 20 March 2020. We included RCTs reporting the 50% response rates for topiramate, Botulinum Toxin Type A and monoclonal antibodies against CGRP(r). Studies were excluded if response rates were not reported, treatment allocation was unclear, or if study quality was insufficient. Primary outcome measure were the 50% response rates. The pooled odds ratios with 95% confidence intervals were calculated with the random effects model. The study was registered at PROSPERO (CRD42020222880).

**Findings:** We identified 6552 reports. Thirty-two were eligible for our review. Studies assessing monoclonal antibodies included 13,302 patients and yielded pooled odds ratios for the 50% response rate of 2.30 (CI: 2.11–2.50). Topiramate had an overall effect estimate of 2.70 (CI: 1.97–3.69) with 1989 included patients and Botulinum Toxin Type A achieved 1.28 (CI: 0.98–1.67) with 2472 patients included.

**Interpretation:** Topiramate, botulinum toxin type A and monoclonal antibodies showed higher odds ratios in achieving a 50% response rate compared to placebo. Topiramate numerically demonstrated the greatest effect size but also the highest drop-out rate.

## Keywords

Migraine disorders, prevention, treatment, efficacy, responder rate, outcome

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## Introduction

Migraine is a frequent and highly debilitating disorder ranking second regarding years lived with disability (1). Recognizing the high prevalence of more than 12% and the fact that it peaks in the most productive years of life has sparked an increasing interest in medical and pharmaceutical research for this disease (2–4). For many patients, the abortive treatment of the acute attack with simple analgesics or triptans is insufficient to taper the burden of the disease, as these medications are ineffective in at least 30% of attacks, may be poorly

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tolerated, and may even worsen the migraine if over-used. Besides ineffective acute medication, physicians' decision to start preventive therapy is based on attack frequency, headache days, severity of attacks, and impact on the patient's quality of life. Thus, more than a third of the patients qualify for prophylactic treatment (5–9).

The desired outcome of preventative treatments for migraine is a reduction in monthly migraine days (MMD) or migraine frequency, as well as the reduction of the severity of migraine attacks. These outcomes have first been observed with pharmacological compounds that have been initially developed for other indications than migraine. The adherence to these oral preventive anti-migraine treatments is still somewhat disappointing: They are ineffective in 40–50% of patients and this, together with poor tolerance due to side effects, explains why over 60% of chronic migraine sufferers abandon them after 2 months (10). There is thus a real need for better-performing and especially better-tolerated treatments (11). Neurologists, headache specialists and patients eagerly awaited the approval of human monoclonal antibodies (mABs) targeting calcitonin gene-related peptide (CGRP) or its receptor (CGRP<sub>r</sub>). They were developed specifically for migraine prevention and demonstrated good efficacy and low adverse reaction rates in various clinical trials (12). However, major drawbacks in the therapy with mABs in migraine prevention are the lack of long-term data and the costs that render them a second- or third-line option in many countries to date. Therefore, it is necessary to evaluate the risk- and cost-benefit ratio for each individual patient before initiating therapy. The efficacy of pharmacological agents is vital information needed to assess this ratio. A common measurement to assess efficacy is the response rates. The 50% response rate depicts the percentage of patients with a reduction of mean monthly migraines of at least 50% compared to baseline. In this systematic review and meta-analysis, we evaluated the efficacy as expressed with the 50% response rate for topiramate (TPM), botulinum toxin type A (BoNTA), and CGRP pathway monoclonal antibodies (mABs).

## Methods

The aim of this review was to provide a comparison between monoclonal antibodies targeting the CGRP pathway and the already established therapeutic means, TPM and BoNTA, using a meta-analysis. TPM and BoNTA were selected for this review as they are usually administered to a collective of patients that qualifies for treatment with monoclonal antibodies.

## Literature search

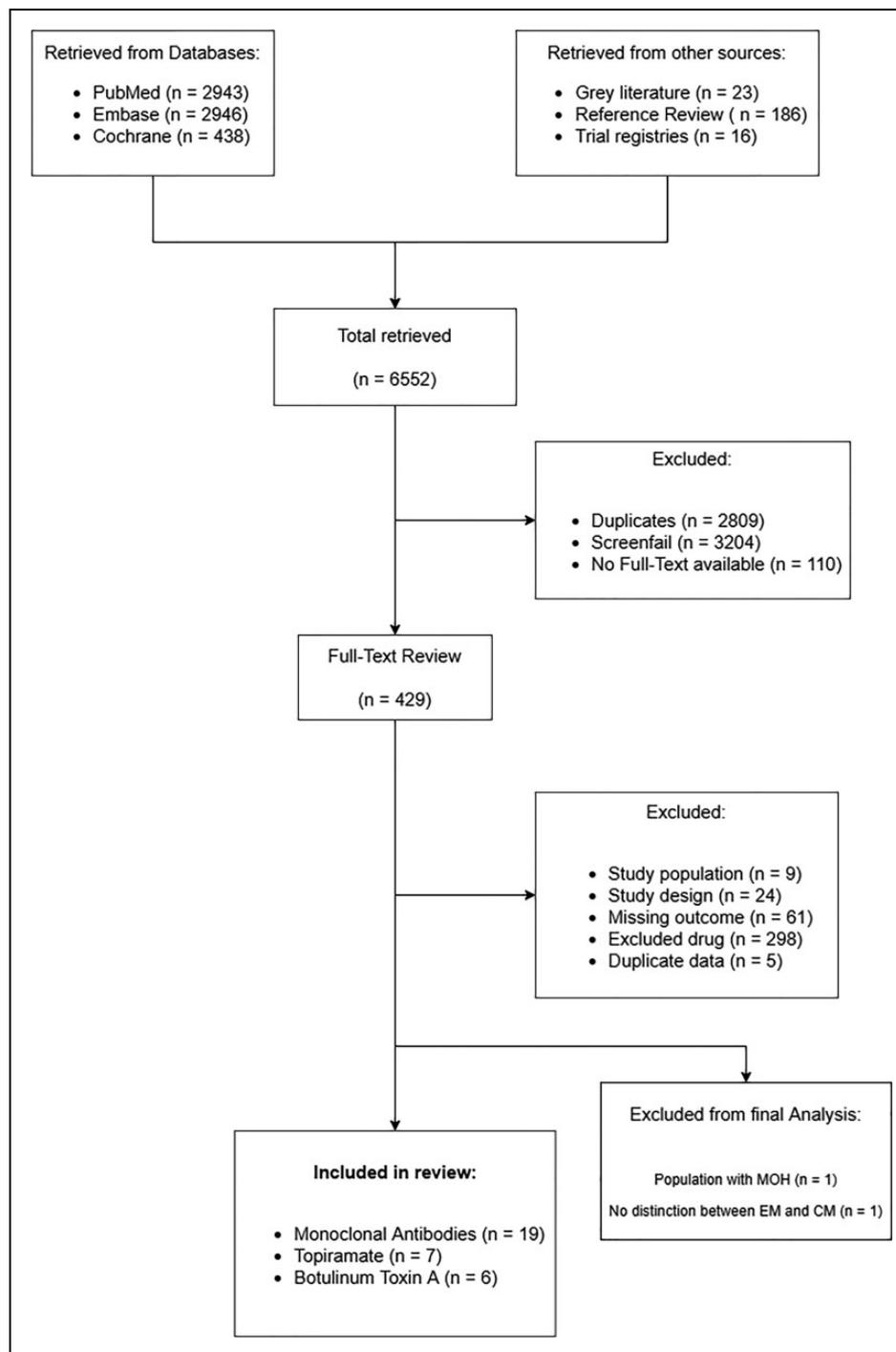
This review was conducted in adherence with the recommendations of the Preferred Reporting Items for Systematic Reviews and Meta Analyses (PRISMA) statement (13). We performed a systematic search of the Cochrane Controlled Trials Register (CENTRAL), EMBASE, and MEDLINE. The search strategy was established to include published clinical trials assessing the efficacy of preventative treatments for migraines. Language was restricted to English or German, and reference lists of retrieved studies or other meta-analyses were searched manually. In order not to omit any relevant data, the pharmacological agents were not restricted to mABs, TPM and BoNTA. Relevant studies were searched through 20 May 2020. Our search strategy comprised four concepts defining disorder, application, intervention, and outcome. We used free text terms as well as controlled vocabulary terms (MeSH).

The detailed search strategy and keywords are included in the supplemental material.

**Study selection.** Two researchers screened the titles and abstracts of the candidate studies individually for inclusion and exclusion criteria. Duplicate studies were excluded from data extraction. For study selection flow, see Figure 1.

For eligibility, trials had to be placebo-controlled and randomized. The defined diseases studied were episodic and chronic migraine according to the criteria valid at the time of conducting the trial (e.g. ICHD criteria) (14,15). The eligible pharmacologic interventions were TPM, BoNTA and mABs targeting CGRP for preventative migraine treatment. For this review, we included all available dosing regimens, regardless of the formal approval for the respective pharmacological agent. Studies were required to report response rates (the proportion of subjects reporting a reduction in migraine attack frequency or mean migraine days of 50%, 75% and/or 100%) and the number of subjects in each intervention group. As secondary outcome variables, we collected reduction in migraine days or headache days. Outcome variables reported as least square means were included and denoted as such.

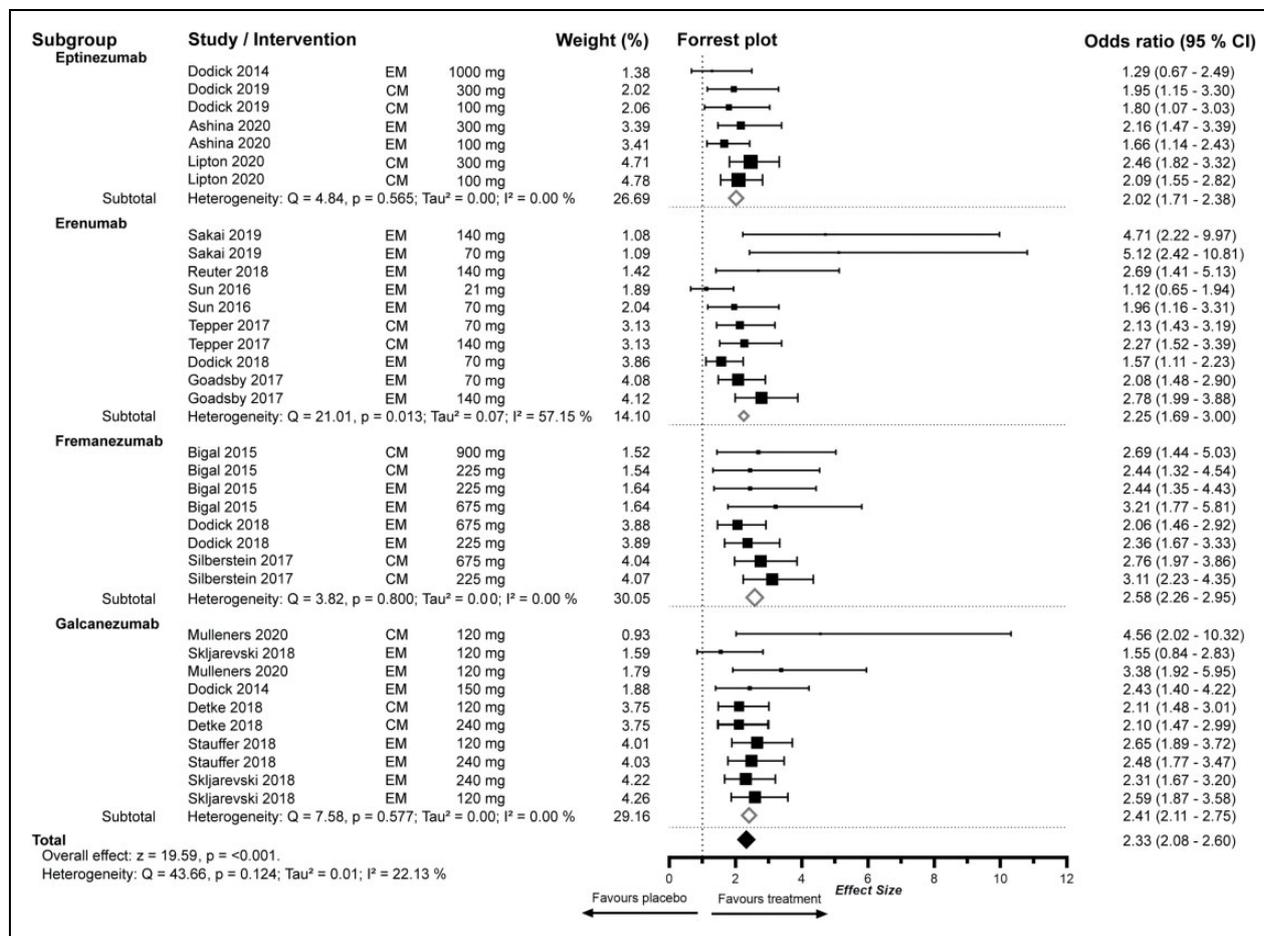
We included placebo-controlled RCTs of sufficient quality reporting the 50% response rates for mABs against CGRP<sub>r</sub>, TPM, and BoNTA. Studies were excluded if response rates were not reported, treatment allocation was unclear, or if study quality was insufficient. Therefore, we applied the JADAD score, the most widely used tool to assess the methodological quality of a clinical trial. JADAD allocates a score between zero (low quality) and five (high quality) to



**Figure 1.** Flow diagram of study selection process. The database search yielded more than 6000 results. Of these, 2812 duplicates were identified. All drug regimens have been considered for initial full-text review to include studies using mABs, TPM or BoNTA as comparators.

trials; we excluded studies with a JADAD score below 3 (16). Furthermore, we excluded studies assessing other headaches than migraine or migraine variants (i.e. menstrual migraine, status migrainosus, etc). Trials regarding any other species than human were not included.

**Data extraction.** Two investigators extracted the data independently. Information extracted comprised full title, authors, publication date, study population, interventions and duration of intervention, baseline data, outcomes, and potential source of bias. Risk of bias of all included studies was assessed using the

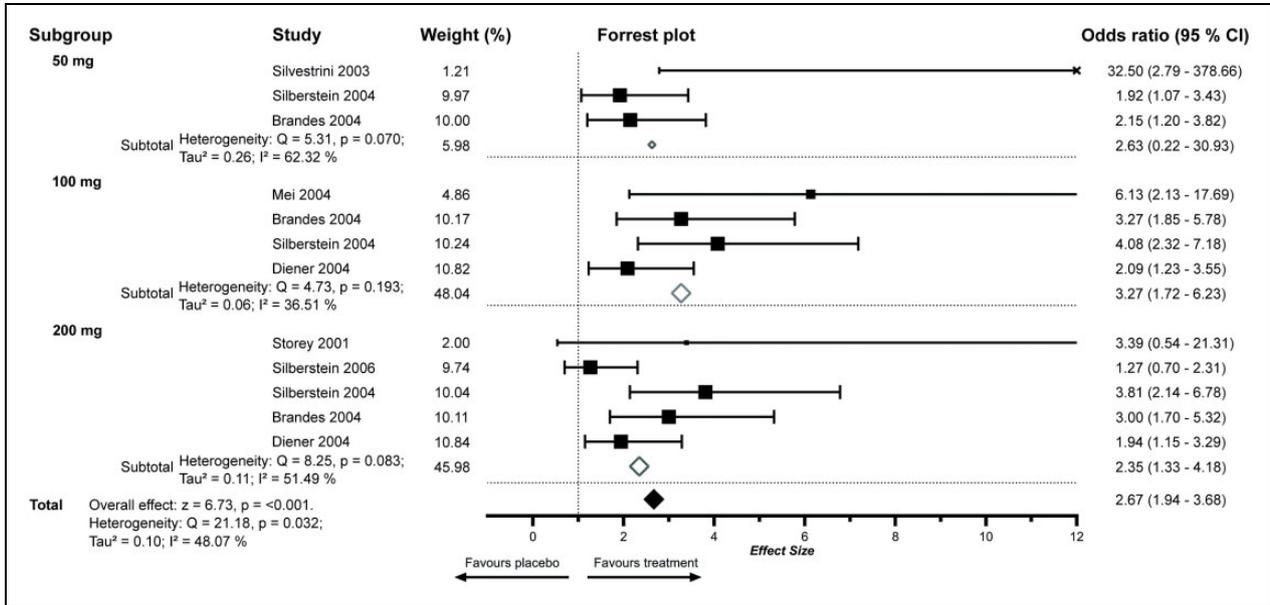


**Figure 2.** Meta-analysis of 50% response rates of mABs for the prevention of migraine. The random effects model depicts the odds ratios (OR) of individual studies and dosing regimens regarding our primary endpoint of 50% response rate compared to placebo. Studies are ordered by weight. Weighting was performed with the inverse variance method. Bigger boxes indicate higher weighting. The model's confidence level was defined as 95%. Subgroup analysis was performed for the respective monoclonal antibody. Total effect size was calculated with consideration of the weighting of the respective subgroups in comparison to the total effect size presented in Figure 5 with weighting applied regarding to episodic or chronic migraine. The x-axis is presented as standard decimal plot. The study by Mulleners et al. 2020<sup>39</sup> evaluated Galcanezumab for chronic and episodic migraine.

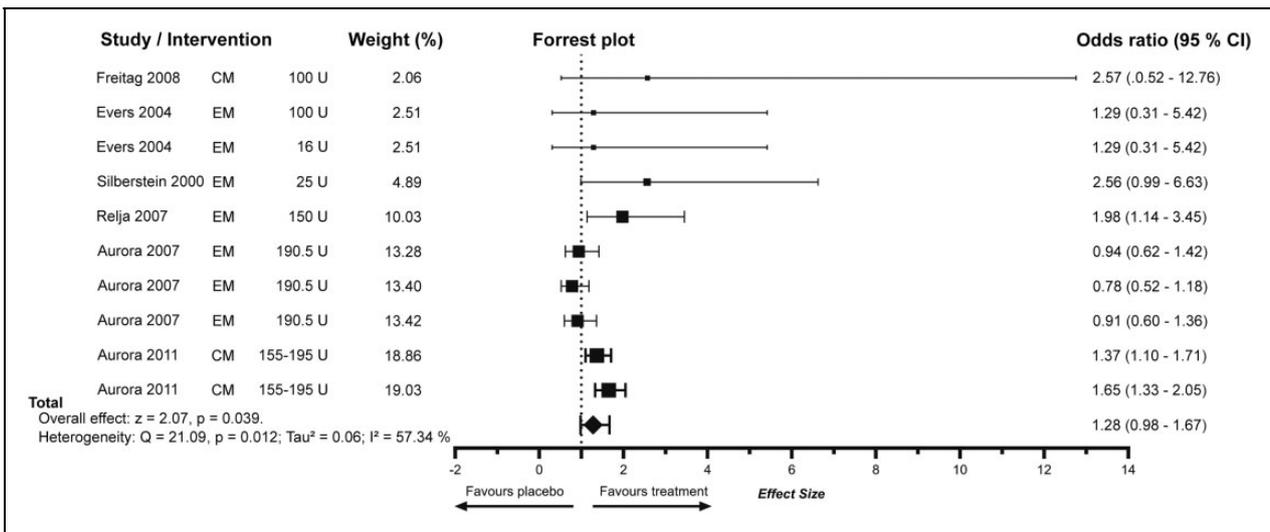
Cochrane collaboration tool (17). Both individual patient-level data and summary estimates were extracted where available. The extracted data was entered in a purpose-built database and consolidated for relevant analyses by the lead investigator. For the primary outcome measurement, we compared the 50% response rates (RR50) of included studies. We chose the RR50 since a 50% response to any preventative migraine medication is used to assess efficacy in clinical practice and required as outcome by regulatory agencies.

**Statistical analysis.** Duplicates were identified and removed using the citation manager Mendeley® (Mendeley Ltd.). Furthermore, studies reporting the same dataset were identified manually. If the dataset comprised the whole information needed

for our analyses, we selected the earlier report. If data were distributed between multiple reports, a master case was created encompassing all necessary data. Aggregated study data were transferred to Excel and meta-analyses were performed using MetaEssentials and GraphPad Prism 8 (GraphPad Software, San Diego, US) (18). The primary outcome was defined as the 50% response rate, comprising reductions in mean monthly migraine days (90.0%), mean monthly headache days (5.0%), and mean monthly headache hours (5.0%). Odds ratios for 50% response rates were selected as effect measures. We chose to use odds ratios as the effect measure because it is a conservative, robust measure, therefore minimizing discrepancies in study designs (inclusion criteria, length of treatment, length of observation, etc). Heterogeneity across studies was



**Figure 3.** Meta-Analysis of 50% response rates of TPM separated by dosing regimens. The x-axis is presented as standard decimal plot. Box sizes indicate weighting. OR outside of the selected interval is marked with (x). The study by Silvestrini et al. 2003<sup>49</sup> was the sole study evaluating TPM for chronic migraine that fulfilled our inclusion criteria. The sample size was comparatively low (n = 28), additionally only one subject in the placebo group reached a 50% response. TPM in the recommended doses of 100 or 200 mg was superior to placebo regarding the 50% response rate.



**Figure 4.** Meta-analysis of 50% response rates of BoNTA. Studies are in ascending order of respective weight. Box sizes indicate weighting. The x-axis is presented as standard decimal plot.

assessed using the  $I^2$  statistics (19). Odds ratios for achieving 50% response rates were pooled across studies using random effects meta-analyses (20). Because of considerable heterogeneity ( $I^2 > 50\%$ ) in the different analyses, summarized ORs from the random effects model were chosen and reported as final results. Effect sizes were graphically displayed using forest plots.

Studies were weighted by calculating the inverse variance of their effect estimates. We determined the baseline migraine days (where available) as a moderator variable to perform a meta-regression analysis. Funnel plots that allow visual interpretation regarding publication bias were generated. In case of suspected publication bias, missing study data were imputed into these plots to facilitate the

interpretation of whether a publication bias was likely to exist.

For mABs, we performed a subgroup analysis of the different available agents and further divided the results in studies evaluating episodic or chronic migraine. For TPM and BoNTA, subgroups were defined for episodic and chronic migraine only.

**Role of the funding source.** There was no funding source for this study.

## Results

The database and trial registry search yielded 6552 results (2943 MedLine, 438 Cochrane Library, 2946 Embase). After removing duplicates, letters, case reports and studies where full text could not be retrieved, 429 studies were identified as eligible for full review. By restricting the results to studies on mABs, TPM and BoNTA, we obtained 131 studies. Of these, 32 randomized, placebo-controlled trials reporting responder rates finally fulfilled our inclusion criteria. Both studies investigating episodic and chronic migraine were included. Study characteristics are summarized in Tables 1–3. Main reasons for exclusion of retrieved studies was failure to report response rates, investigation of excluded treatments or a JADAD score below 3. One study of mABs assessing patients with episodic and chronic migraine had to be excluded from the analysis as the 50% response rate was not reported individually for these groups. Another study with a mixed episodic and chronic migraine population reported data separately and was assigned to the respective subgroups.

Mean patient age across all included studies varied between 21.6 to 46.2. Total summarized study population was 17,763 participants with 74.9% investigated in trials evaluating mABs, 11.2% in TPM trials and 13.9% in BoNTA studies. The mean percentages of participants using concomitant preventative medication during the respective studies varied from 0.0% to 52.5%. Studies allowing concomitant preventive migraine medication did not consistently report drug, dosing or treatment duration but required the patients to be on a stable regime prior to and during the study. Studies not allowing concomitant prophylaxis required an adequate wash-out period prior to participation. The mean overall adverse-event rate and drop-out rate ranged from 21.4% to 90% and 0.0% to 62.6% respectively. The corresponding rates for the respective treatment arms are presented in Tables 1–3.

The primary outcome measures in mABs studies comprised reduction in mean monthly migraine days (90.0%), mean monthly headache days (5.0%), and mean monthly headache hours (5.0%). TPM studies

assessed mean monthly migraine frequency (71.43%), mean monthly headache frequency (14.29%) and mean monthly headache days (14.29%). The most common primary outcome measurements in BoNTA studies were mean monthly migraine frequency (66.67%), mean monthly headache frequency (16.67%) and mean monthly headache days (16.67%). All included studies applied a parallel-arm study design with placebo as control. Date of publication ranged from 2014 to 2020 for mABs, 2003 to 2006 for TPM and 2000 to 2011 for BoNTA.

## Efficacy

Each included study reached their primary endpoint and showed superiority compared to placebo regarding efficacy.

**Monoclonal antibodies.** All included studies investigating mABs for the prevention of episodic migraine had higher OR for achieving 50% response compared to placebo. Three studies with antibodies for the prevention of episodic migraine demonstrated a lower bound of the confidence interval below the threshold of 1 and hence were statistically not significant. All studies assessing mABs for chronic migraine showed significant higher efficacy regarding RR50 compared to placebo. The combined effect size regarding the 50% response rate for mABs in the preventative treatment of episodic and chronic migraine was 2.26 (CI 1.98–2.58) and 2.34 (CI 2.13–2.56) respectively.

In the subgroup analysis of the four available monoclonal antibodies for the prevention of episodic migraine, all drugs showed a higher OR in achieving 50% response rate compared to placebo. Eptinezumab demonstrated the lowest effect size, with only two studies fulfilling our inclusion criteria, while erenumab, fremanezumab and galcanezumab demonstrated similar effect sizes. For the prevention of chronic migraine, all antibodies yielded comparable ORs and were at least twice as effective as placebo (Figure 2).

**Topiramate.** Topiramate for the prevention of episodic migraine was evaluated in doses ranging from 50 mg to 200 mg per day. Two studies of 200 mg TPM did not show a significant positive effect in achieving 50% response compared to placebo. The combined effect size for all TPM studies was 2.70 (CI: 1.97–3.69). Only one study evaluating TPM for chronic migraine met our inclusion criteria. When separated by episodic or chronic migraine, TPM showed ORs of 2.57 (CI: 1.95–3.40) and 22.68 (CI: 0.06–8366.11) respectively. The different dosing regimens of topiramate were analysed separately and showed an OR of 3.27 (CI: 1.72–6.23) for 100 mg,

**Table 1.** Overview of included studies assessing monoclonal antibodies for migraine prevention. All studies were blinded and used placebo as comparator. For the dropout rate, we considered overall dropouts (including the placebo group) to capture study design related withdrawals. Unless otherwise noted, drop-out rate resembles withdrawal for any reason. Studies marked with “\*” report subjects terminating due to treatment-emergent adverse events. Unless stated otherwise, adverse-event rates are the percentage of subjects in the treatment group reporting adverse events.

Monoclonal antibodies												
Study	Drug (doses)	Study design (allocation)	Sample size	Population	Primary endpoint	Duration (DBTP)	Baseline frequency	Concurrent prevention (%)	AE-Rate (%)	Dropouts (%)	Age, years (SD or range)	
Ashina 2020 (23)	Eptinezumab (30, 100, 300)	Parallel (1:1:1)	888	EM	Efficacy	12 weeks	8.6 MD	0	59.7	3.5	39.8 (± 11.4)	
Dodick 2014 (24)	Eptinezumab (1000)	Parallel (1:1)	163	EM	Safety	One Dose	8.6 MD	0	57.0	4.3*	38.8 (± 10.2)	
Dodick 2019 (25)	Eptinezumab (10, 30, 100, 300)	Parallel (1:1:1:1)	616	CM	Efficacy	12 weeks	16.5 MD	34.9	56.0	2.0	36.6 (± 12.1)	
Lipton 2020 (26)	Eptinezumab (100, 300)	Parallel (1:1)	1072	CM	Efficacy	12 weeks	16.1 MD	44.7	47.8	1.0	40.5 (± 11.2)	
Dodick 2018 (27)	Erenumab (70)	Parallel+OLE (1:1)	577	EM	Efficacy (75-% Risk Reduction)	12 weeks (28 weeks OLE)	8.3 MD	6.1	48.4	1.1	42.0 (± 11.5)	
Goadsby 2017 (28)	Erenumab (70, 140)	Parallel (1:1)	955	EM	Efficacy	28 weeks	8.3 MD	2.8	56.4	2.3	40.9 (± 11.2)	
Reuter 2018 (29)	Erenumab (140)	Parallel (1:1)	246	EM	Efficacy	12 weeks	9.3 MD	0	54.5	2.4*	44.4 (± 10.6)	
Sakai 2019 (30)	Erenumab (28, 70, 140)	Parallel (2:1:2:2)	475	EM	Efficacy	12 weeks	7.8 MD	9.2	66.8	2.5	44.3 (n.a)	
Sun 2016 (31)	Erenumab (7, 21, 70)	Parallel (3:2:2:2)	483	EM	Efficacy	12 weeks	8.7 MD	0	51.7	3.6*	41.1 (± 10.8)	
Tepper 2017 (32)	Erenumab (140, 70)	Parallel (3:2:2)	667	CM	Efficacy	12 weeks	18.0 MD	0	45.5	3.5*	42.1 (± 11.2)	
Bigal 2015 (33)	Fremanezumab (675/225, 900)	Parallel (1:1)	264	CM	Efficacy	12 weeks	161.9 HH	39.7	50.5	1.1	40.7 (± 12.0)	
Bigal 2015 (34)	Fremanezumab (675, 225)	Parallel (1:1)	295	EM	Efficacy	12 weeks	11.4 MD	29.3	52.5	9.1*	41.2 (± 12.2)	
Dodick 2018 (35)	Fremanezumab (225, 675)	Parallel (1:1)	875	EM	Efficacy	12 weeks	9.1 MD	20.8	62.4	1.7	41.8 (± 12.0)	
Ferrari 2019 <sup>†</sup> (36)	Fremanezumab (675, 225)	Parallel (1:1)	838	EM + CM	Efficacy	12 weeks (12 weeks OLE)	14.2 MD	0	50.0	1.0	46.2 (± 11.1)	
Silberstein 2017 (37)	Fremanezumab (675, 675/225)	Parallel (1:1)	1130	CM	Efficacy	12 weeks	13.1 HD	21.0	70.5	1.7	41.3 (± 12.1)	
Detke 2018 (38)	Galcanezumab (240/120, 240)	Parallel+OLE (2:1:1)	1113	CM	Efficacy	12 weeks (36 weeks OLE)	19.4 MD	15.0	57.5	0.9	40.8 (± 12.1)	
Mulleners 2020 (39)	Galcanezumab (120)	Parallel (1:1)	462	EM + CM	Efficacy	12 weeks	13.2 MD	0	51.0	2.4*	45.8 (± 11.8)	
Skjajevski 2018 (40)	Galcanezumab (240, 120)	Parallel (1:1:2)	915	EM	Efficacy	24 weeks	9.1 MD	0	68.3	13.4*	41.7 (± 11.1)	

(continued)

Table 1. Continued.

Monoclonal antibodies											
Study	Drug (doses)	Study design (allocation)	Sample size	Population	Primary endpoint	Duration (DBTP)	Baseline frequency	Concurrent prevention (%)	AE-Rate (%)	Dropouts (%)	Age, years (SD or range)
Skjarevski 2018 (41)	Galcanezumab (5, 50, 120, 300)	Parallel (2:1:1:1:1)	410	EM	Efficacy	12 weeks	6.7 MD	0	51.3	8.5*	40.0 (±12.0)
Strauffer 2018 (42)	Galcanezumab (240,120)	Parallel (2:1:1)	858	EM	Efficacy	24 weeks	9.1 MD	0	66.6	17.8*	40.4 (±11.6)
Total			13,302					11.18	56.2	5.1	41.5 (±2.2)

†Excluded from final analysis because 50% response rate was not reported individually for the episodic or chronic migraine group.

DBTP: double-blind treatment phase; OLE: open-label extension; MD: mean migraine days; HD: mean headache days; HH: mean headache hours; CM: chronic migraine; EM: episodic migraine. Baseline frequency is given in numbers and the respective primary outcome measure of the studies.

2.35 (CI: 1.33–4.18) for 200 mg and 2.63 (CI: 0.22–30.93) for 50 mg (Figure 3).

**Botulinum toxin type A.** Studies assessing the efficacy of BoNTA were more heterogeneous. The dosing ranged from 16 Units to 225 Units of BoNTA. The injection sites and respective units across them were different in each study. The response regarding RR50 was similar in four of the studies for BoNTA and placebo, yet overall BoNTA was more favourable. Overall, the combined effect size was 1.36 (CI 1.00–1.86) for BoNTA when weighting was performed with consideration to episodic and chronic migraine. Analysing all BoNTA studies together, the combined effect size was 1.28 (CI: 0.98–1.67). In accordance with the approval for the use of BoNTA in migraine prevention, BoNTA for chronic migraine showed positive results with an OR of 1.51 (CI 1.10–2.09). For episodic migraine, the OR of BoNTA achieving RR50 was not significant (OR 1.14; CI 0.76–1.70) (Figure 4).

### Study heterogeneity

Study heterogeneity ( $I^2$ ) was 22.1% for mABs, 48.1% for TPM and 57.3% for BoNTA when not analysed separately for episodic and chronic migraine. To rule out migraine frequency to be a predictor of response to treatment, we performed a regression analysis for each treatment regime. After dividing data into studies assessing episodic or chronic migraine, we found no significant association of effect size with baseline migraine/headache days or migraine/headache frequency ( $R^2$ : 6.42% TPM; 35.36% BoNTA; 3.48% mABs).

### Risk of bias

To test for publication bias an Egger's regression test was performed. The  $p$ -values for testing 0 intercept revealed low significant results for topiramate ( $p=0.042$ ) and no significant results for BoNTA ( $p=0.414$ ) or mABs ( $p=0.528$  chronic migraine;  $p=0.383$  episodic migraine). See funnel plots for visualization (Figure 5).

### Discussion

Our evaluation confirmed the efficacy of mABs and TPM in the prevention of episodic and chronic migraine, as well as the efficacy of BoNTA in the prevention of chronic migraine. Utilizing the 50% response rate as a clinically relevant effect marker and authority required benchmark, enables decision-making. The RR50 has been assessed more consistently in recent studies, which led to a higher inclusion of studies evaluating mABs. Clinical trials assessing beta-blockers or antidepressants for the prevention of

**Table 2.** Overview of included studies assessing topiramate for migraine prevention. All studies were blinded and used placebo as comparator. For the dropout rate we considered overall dropouts (including placebo group) to capture study design-related withdrawals. Unless otherwise noted, dropout rate resembles withdrawal for any reason. Studies marked with “\*§” report subjects terminating due to treatment-emergent adverse events. Unless stated otherwise, adverse event rates are the percentage of subjects in the treatment group reporting adverse events.

Study	Drug (doses)	Study design (allocation)	Sample size	Population	Primary endpoint	Duration (DBTP)	Baseline frequency	Concurrent prevention (%)	AE rate (%)	Dropouts (%)	Age, years (SD or range)
Brandes 2004 (43)	TPM (50, 100, 200)	Parallel (1:1:1:1)	483	EM	Efficacy	18 weeks	5.5 MF	0	n.a†	44.1*	38.9 (±12.3)
Diener 2004 (44)	TPM (100, 200, PRO) ‡	Parallel (1:1:1:1)	575	EM	Efficacy	18 weeks	5.1 MF	0	36.0§	62.6*	40.9 (±10.9)
Mei 2004 (45)	TPM (100)	Parallel (1:1)	115	EM	Efficacy	12 weeks	5.5 MF	0	30.4	16.5	39.2 (±11.5)
Mei 2006¶(46)	TPM (100)	Parallel (2:3)	50	CM	Efficacy	12 weeks	23.9 HD	0	n.a	30.0	45.9 (±8.7)
Silberstein 2004 (47)	TPM (50, 100, 200)	Parallel (1:1:1:1)	487	EM	Efficacy	18 weeks	5.5 MF	0	n.a	43.5*	40.4 (±11.4)
Silberstein 2006 (48)	TPM (200)	Parallel (2:1)	211	EM	Efficacy	12 weeks	4.9 MF	0	90.0	26.5*	40.5 (±11.1)
Silvestrini 2003 (49)	TPM (50)	Parallel (1:1)	28	CM	Efficacy	8 weeks	20.0 HF	0	21.4	3.6	43.5 (34-58)
Storey 2001 (50)	TPM (200)	Parallel (1:1)	40	EM	Efficacy	20 weeks	4.8 MF	52.5	n.a†	12.5	38.2 (19-62)
Total			1949					6.56	44.5	29.9	40.9 (±2.4)

†No overall AE rate reported. This study reported adverse events that were commonly associated with topiramate and occurred in 10% or more of the patients. Most common AE was paraesthesia.

‡Propranolol was used as active comparator in addition to placebo.

§This study reported treatment-limiting adverse events. No overall AE rate reported.

¶Excluded from final analysis as the population consisted of migraine patients with medication overuse headache.

DBTP: double-blind treatment phase; OLE: open-label extension; MD: mean migraine days; HD: mean headache days; MF: mean migraine frequency; HF: mean headache frequency; HH: mean headache hours; CM: chronic migraine; EM: episodic migraine; PRO: propranolol; n.a.: not available/not reported. Baseline frequency is given in numbers and the respective primary outcome measure of the studies.

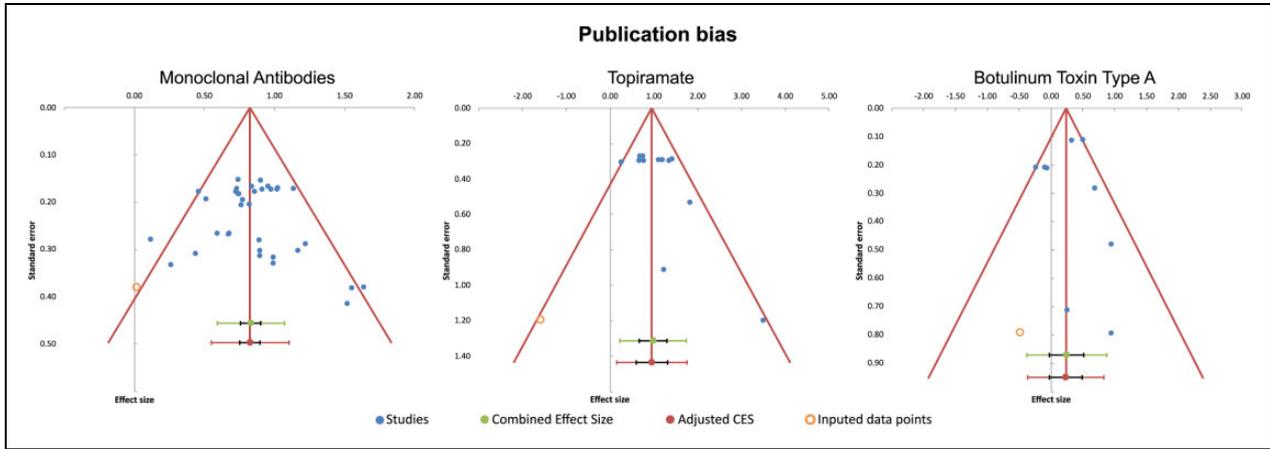
**Table 3.** Overview of included studies assessing botulinum toxin type A for migraine prevention. All studies were blinded and used placebo as comparator. For the dropout rate, we considered overall dropouts (including placebo group) to capture study design-related withdrawals. Unless otherwise noted, dropout rate resembles withdrawal for any reason. Studies marked with “\*” report subjects terminating due to treatment-emergent adverse events. Unless stated otherwise, adverse-event rates are the percentage of subjects in the treatment group reporting adverse events.

Botulinum Toxin Type A											
Study	Drug (doses)	Study design (Allocation)	Sample size	Population	Primary endpoint	Duration (DBTP)	Baseline frequency	Concurrent prevention (%)	AE rate (%)	Dropouts (%)	Age, years (SD or range)
Aurora 2007 (51)	BoNTA (110–260U)	Parallel (1:1) †	369	EM	Efficacy	26 weeks	6.5 MF	38.2	60.4	1.9	21.6 (±11.6)
Aurora 2011 (52)	BoNTA (155–195U)	Parallel (1:1) +OLE	1384	CM	Efficacy	24 weeks (32 weeks OLE)	19.9 HD	0	62.4	2.6	41.3 (±10.6)
Evers 2004 (53)	BoNTA (16U, 100U)	Parallel (1:1)	60	EM	Efficacy	12 weeks	3.8 MF	30.0	36.7	0	38.0 (±11.0)
Freitag 2008 (54)	BoNTA (100U)	Parallel (1:1)	41	CM	Efficacy	16 weeks	14.2 MD	n.a	n.a	12.2	42.2 (19–64)
Relja 2007 (55)	BoNTA (225U, 150U, 75U)	Parallel (1:1:1) †	495	EM	Efficacy	38 weeks	4.1 MF	0	77.2	2.8	43.2 (±10.3)
Silberstein 2000 (56)	BoNTA (25U, 75U)	Parallel (1:1)	123	EM	Efficacy	12 weeks	5.0 MF	n.a	50.0 ‡	0.8*	44.0 (22–63)
Total			2472					17.1	57.3	3.4	38.4 (±7.7)

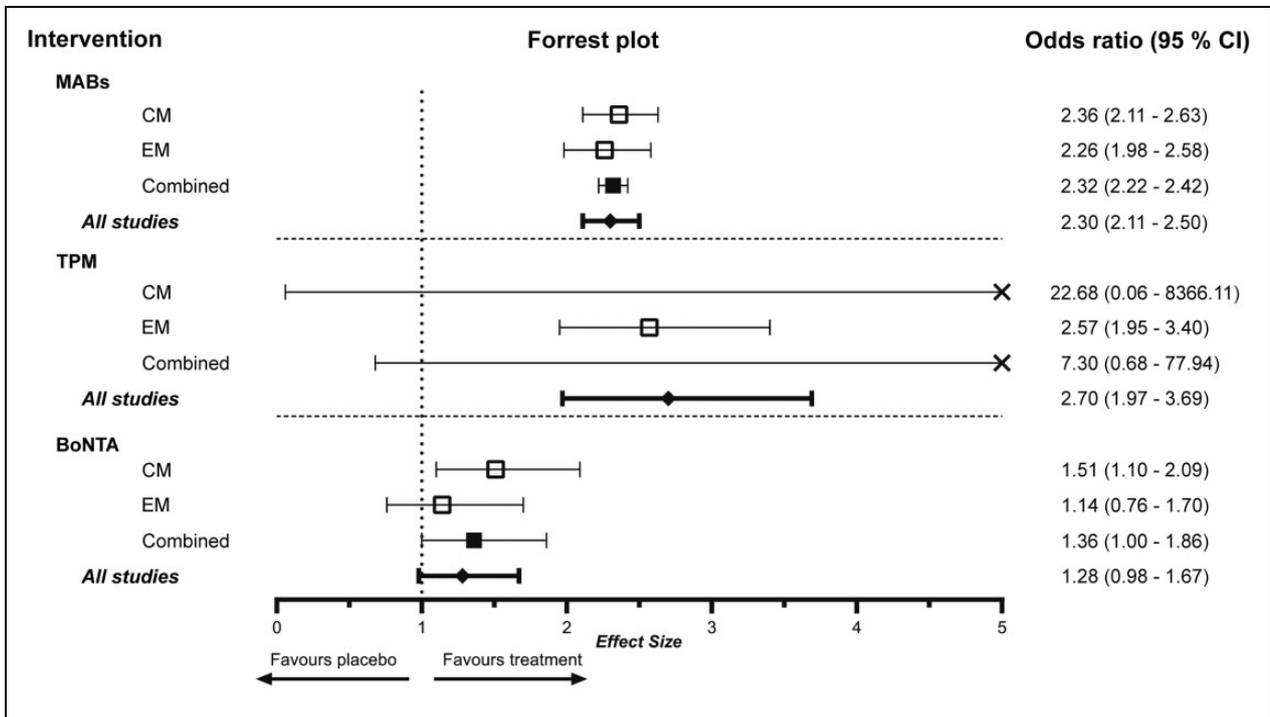
†Patients were stratified into placebo responders and placebo non-responders.

‡No overall AE rate reported. Adverse events were reported in 50% in the 75U group and 24% in the vehicle (placebo) group.

DBTP: double-blind treatment phase; OLE: open-label extension; MD: mean migraine days; HD: mean headache days; MF: mean migraine frequency; HF: mean headache frequency; HH: mean headache hours; CM: chronic migraine; EM: episodic migraine; PRO: propranolol. Baseline frequency is given in numbers and the respective primary outcome measure of the studies.



**Figure 5.** Funnel-plot of studies addressing mABs, TPM and BoNTA for the prevention of migraine. (a) Results for mABs. There were fewer studies with higher standard error showing little or no benefit regarding 50% response rate leading to slight asymmetry in the funnel plot. Overall, published studies were consistently positive. (b) Results for TPM. No studies were published with a negative outcome regarding the 50% response rate. Data is skewed by the study of Silvestrini et al. 2003<sup>49</sup> with a Logs Odds Ratio of 3.48. This study showed an unexpected low placebo response. (c) Results for BoNTA. There were fewer studies published with a negative outcome regarding the 50% response rate compared to placebo. Studies with a lower standard error were published equally independent of outcome.



**Figure 6.** Subgroup-analysis of mABs, TPM and BoNTA for the prevention of episodic and chronic migraine. X-axis is depicted as standard decimal plot. Box size indicates weighting. All available antibodies showed overall superiority regarding the 50% response rate compared to placebo. The overall effect size of TPM for the prevention of migraine compared to placebo was the highest in our analysis. Robust data exist for TPM in the prevention of episodic migraine. When weighting studies according to episodic and chronic migraine the combined effect size was not significantly superior compared to placebo. This effect is caused by the abundance of large, randomized controlled studies evaluating TPM for chronic migraine and thus yielding a broad CI. Corresponding to international and national recommendations, BoNTA showed superiority in the prevention of chronic migraine regarding 50% response rate. Data to support its use in the prevention of episodic migraine is scarce and not consistent. The combined effect size of all studies when weighting regarding episodic or chronic migraine still results in a favourable outcome for BoNTA of an OR of 1.36 (CI: 1.00–1.86).

migraine scarcely report 50% response rates and were therefore not considered for this review.

Direct comparisons of mABs, TPM and BoNTA have not been published to date, which is partially due to the difficulty of blinding in such a study. A comparison of studies in a meta-analysis has several limitations, such as different study durations or definitions of adverse events. Furthermore, the available studies also tend to use different outcome measures such as headache or migraine days or attack frequency. The RR50 can be used as a surrogate comparator between studies, as it is an artificial variable independent of the underlying efficacy measurement (i.e. frequencies). The utilization of odds ratios furthermore reduces variations emerging due to variable placebo rates.

In the prevention of episodic migraine, two antibody studies, Dodick 2014 and Skljarevski 2018 showed an exceptionally high placebo response, rendering their comparison inconclusive. Dodick et al. suggest the high placebo response might be due to the intravenous mode of administration of eptinezumab. The dose-finding study of erenumab by Sun 2016 also yielded no significant effect for the subtherapeutic dose of 21 mg. For the prevention of chronic migraine, all included mAB studies were favourable compared to placebo. We could find no significant difference between the respective antibodies regarding the RR50. As most of these studies were carried out in a similar fashion and comparable populations, the main source of uncertainty as expressed with broad confidence intervals is most likely a difference in sample size. No relevant publication bias was detected.

The studies by Silvestrini 2003 and Storey 2001 had the lowest sample size and were weighted  $\leq 2.0\%$  for calculating the combined effect size of all TPM studies. The distinctively broad CI for TPM in chronic migraine is mainly due to the low sample size in studies investigating TPM for chronic migraine. We recommend interpreting this finding with caution. The study by Silberstein 2006 evaluating the efficacy of TPM 200 mg/d compared to placebo was inconclusive. The authors report no significant superiority of TPM in the reduction of monthly migraine frequency when analysed in a per-protocol ANCOVA (analysis of covariance). In a *post-hoc* intention to treat analysis, however, topiramate was significantly more effective than placebo.

Both TPM 100 mg and 200 mg per day were shown to be effective in achieving 50% reduction. Only one study on TPM for the prevention of chronic migraine fulfilled our inclusion criteria. This study had a small sample size of 28 patients and used a low dose of 50 mg per day. Thus, the results need to be interpreted with

caution but TPM can be assumed to be effective in chronic migraine.

For BoNTA, only two studies demonstrated significant efficacy in achieving a 50% response rate. Relja 2007 evaluated BoNTA for the prevention of episodic migraine. Although not reaching the primary endpoint, the BoNTA group had a higher 50% response rate. Aurora 2011 introduced the PREEMPT protocol, which is the recommended use of BoNTA for the treatment of chronic migraine. The methods employed varied considerably within the included BoNTA studies. An interpretation of this data must therefore be made with caution (Figure 6).

The rate of concomitant preventive medication was lowest in the TPM group. This is not surprising, as in clinical practice patients only rarely receive concurrent daily oral medications for the prevention of migraines. Topiramate studies had reported a significant lower mean adverse event rate compared to mABs ( $p \leq 0.001$ ) or BoNTA ( $p = 0.005$ ). Interestingly, mean dropout rate was also significantly higher in topiramate (mABs:  $p \leq 0.001$ ; BoNTA:  $p = 0.005$ ). A potential explanation for these lower mean adverse event rates in TPM is a variable definition of adverse events, as several studies reported only treatment-emergent adverse events rather than overall adverse events. Although the CONSORT statement has been introduced as early as 1996, the approach to performing studies for the prevention of migraines has changed over the years (21). The introduction of electronic devices to record data as well as the inclusion of outcome variables not directly assessing efficacy is a more recent development. Due to the chronological dispersion of the included studies, a moderate heterogeneity of reporting in study design and outcomes must be assumed. This variance might be an explanation for relatively high reported adverse events in studies of mABs compared to TPM.

The effect size of reported response rates was highest for TPM and lowest for BoNTA. In a clinically practical view, one must assume that the new targeted therapies for migraine prevention are not more effective but considerably better tolerated than oral preventatives, at least in a placebo-controlled study setting. Although newer therapies have already been proven safe in long-term safety studies, TPM and BoNTA have been utilized for 2 decades enabling observation of seldom adverse reactions. Thus, long-term tolerability and late-onset effects of mABs still need evaluation. A factor in favour of mABs and BoNTA is the frequency of administration; while available oral preventative medications are administered daily, mABs require injection only monthly or quarterly, like BoNTA, accounting for a rather good treatment adherence.

Study heterogeneity was low for mABs but moderate for TPM and BoNTA, and not attributed to baseline headache or migraine frequency alone or publication bias. For better comparability, adherence to standard protocols of performing and reporting clinical trials is desirable. For a reliable direct comparison of preventative treatments in migraine head-to-head studies need to be conducted, such as the unpublished HER-MES study (22).

## Conclusion

New targeted therapies are considered a milestone for the treatment of migraines. A positive mean treatment

effect can be easily measured by a 50% response rate. In this review, we compared three treatment regimens that are commonly used in clinical practice – monoclonal CGRP antibodies, topiramate and botulinum toxin type A. In general, all treatments show higher ORs in achieving a 50% response compared to placebo. Topiramate demonstrated the greatest effect size but also the highest drop-out rate. This might indicate that new therapies are not more effective but more tolerable. A comparison of different treatment regimes, particularly from different decades, must be carried out with caution and requires head-to-head studies in the future.

## Clinical implications

- Efficacy, expressed as 50% response rate, is highest in topiramate.
- The lower dropout rate in monoclonal antibodies against CGRP indicates better tolerability.
- Patients tolerating adequate doses of oral preventative treatments might achieve a greater reduction in migraine headaches.

## Contributors

FF planned the study and developed the search algorithm, and also carried out article review and data extraction as well as statistical analysis and drafted and wrote the manuscript. HU planned and carried out statistical analysis and revised figures and the manuscript. VS carried out article review and data extraction and revised the manuscript. GB planned the study and wrote the manuscript and supervised the data extraction process and resolved disagreements at the study selection level.

## Glossary

CENTRAL: Cochrane Controlled Trials Register  
 RCT: randomized controlled trial  
 CI: confidence interval  
 MMD: mean monthly migraine days  
 AB(s): monoclonal antibody(ies)  
 CGRP: calcitonin gene-related peptide  
 CGRP<sub>r</sub>: calcitonin gene-related peptide receptor  
 TPM: topiramate  
 BoNTA: botulinum toxin type A  
 MeSH: medical subject headings  
 RR50: 50% response rate  
 FDA: Food and Drug Administration  
 EMA: European Medicines Agency  
 ICHD: International Classification of Headache Disorders  
 OR: odds ratio  
 ANCOVA: analysis of co-variance  
 CONSORT: Consolidated Standards of Reporting Trials

## Search Algorithm

(((((migraine[Text Word]) OR episodic migraine[Text Word]) OR chronic migraine[Text Word]) OR migraine with aura[Text Word]) OR migraine without aura[Text Word]) OR migrain\*[Text Word]) OR cephalgi\*[Text Word]) OR migraine\*[Text Word]) OR cephalalgi\*[Text Word]) OR migraine disorders[MeSH Terms]) AND (((((((((((((((((((((((preventive therapy[Text Word]) OR prophylaxis[Text Word]) OR treatment[Text Word]) OR therapies[Title/Abstract]) OR prevention[Text Word]) OR prophylactic[Text Word]) OR preventive treatment[Text Word]) OR preventative treatment[Text Word]) OR pharmacologic[Title/Abstract]) OR prevent\*[Text Word]) OR drug\*[Text Word]) OR preventative\*[Title/Abstract]) OR therapy[Title/Abstract]) OR effective[Title/Abstract]) OR frequency\*[Title/Abstract]) OR reduction[Title/Abstract]) OR reduces[Title/Abstract]) OR reduced[Title/Abstract]) OR attack\*[Title/Abstract]) OR month\*[Text Word]) OR therapeutic[Title/Abstract]) OR effectively[Title/Abstract]) OR effect[Title/Abstract]) OR (Prevention and Control[MeSH Terms]) OR Drug Therapy[MeSH Terms]) OR Treatment Outcome[MeSH Terms]) OR Therapeutic Use[MeSH Subheading]) OR monthly[Text Word]) OR outcome\*[Text Word])) AND (((((((((((((((((((((((beta-blocker[Text Word]) OR topiramate[Text Word]) OR anticonvu\*[Text Word]) OR antiepilep\*[Text Word]) OR topira\*[Text Word]) OR valproate[Text Word]) OR valpro\*[Text Word]) OR candesartan[Text Word]) OR candesart\*[Text Word]) OR onabotulinum[Text Word]) OR botox[Text Word]) OR onabotulinum\*[Text Word]) OR erenumab[Text Word]) OR CGRP[Text Word]) OR anti-CGRP[Text Word]) OR Calcitonin Gene-Related\*[Text Word]) OR gepants[Text Word]) OR \*gepant[Text Word]) OR Valproic Acid[MeSH



Continued.

Concept 1	Search #	Concept 2	Search #	Concept 3	Search #	Concept 4
	#28	attack*[Title/ Abstract]	#57	*gepant[Text Word]	#102	trial*[Text Word]
	#29	month*[Text Word]	#58	Valproic Acid [MeSH Terms]	#103	control*[Text Word]
	#30	therapeutic[Title/ Abstract]	#59	Botulinum Toxins, Type A[MeSH Terms]	#104	efficacy*[Text Word]
	#31	effectively[Title/ Abstract]	#60	Amitriptyline [MeSH Terms]	#105	compare*[Text Word]
	#32	effect[Title/ Abstract]	#61	fremanezumab [Supplementary Concept]	#106	Clinical Trials as Topic[MeSH Terms]
	#33	Prevention and Control[MeSH Terms]	#62	TEV-48125[Text Word]	#107	*blind*[Text Word]
	#34	Drug Therapy [MeSH Terms]	#63	galcanezumab [Supplementary Concept]	#108	Multicenter Study [Publication Type]
	#35	Treatment Outcome [MeSH Terms]	#64	eptinezumab [Supplementary Concept]	#109	Clinical Studies as Topic[MeSH Terms]
	#36	Therapeutic Use [MeSH Subheading]	#65	telcagepant [Supplementary Concept]	#110	Cross-Over Studies [MeSH Terms]
	#37	monthly[Text Word]	#66	Propranolol[MeSH Terms]	#111	Clinical Trial [Publication Type]
	#38	outcome*[Text Word]	#67	Metoprolol[MeSH Terms]	#112	Drug Evaluation [MeSH Terms]
	#39	preventative treat- ment[Text Word]	#68	Nebivolol[MeSH Terms]	#113	Preliminary Data [MeSH Terms]
			#69	Adrenergic Beta- Antagonists [MeSH Terms]	#114	pivot*[Text Word]
			#70	Bisoprolol[MeSH Terms]	#115	Review Literature as Topic[MeSH Terms]
			#71	Flunarizine[MeSH Terms]	#116	Systematic Review [Publication Type]
			#72	Verapamil[MeSH Terms]	#117	Review[Publication Type]
			#73	Anticonvulsants [MeSH Terms]		
			#74	Calcitonin Gene- Related Peptide [MeSH Terms]		
			#75	Receptors, Calcitonin Gene- Related Peptide [MeSH Terms]		
			#76	atogepant[Text Word]		

(continued)

Continued.

Concept 1	Search #	Concept 2	Search #	Concept 3	Search #	Concept 4
			#77	rimegepant[Text Word]		
			#78	Pituitary Adenylate Cyclase-Activating Polypeptide [MeSH Terms]		
			#79	PACAP*[Text Word]		
			#80	AMG334[Text Word]		
			#81	PAC1 [Text Word]		
			#82	filorexant[Text Word]		
			#83	orexin[Text Word]		
			#84	LBR-101[Text Word]		

[Text Word]) OR Clinical Trials as Topic[MeSH Terms]) OR \*blind\*[Text Word]) OR Multicenter Study[Publication Type]) OR Clinical Studies as Topic[MeSH Terms]) OR cross-over studies[MeSH Terms]) OR clinical trial [Publication Type]) OR drug evaluation[MeSH Terms]) OR preliminary data[MeSH Terms]) OR pivot\*[Text Word]) OR Review Literature as Topic[MeSH Terms]) OR Systematic Review[Publication Type]) OR Review[Publication Type])  
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