Neurotherapeutics (2021) 18:2639–2650
https://doi.org/10.1007/s13311-021-01128-0

ORIGINAL ARTICLE

Comparative Effectiveness and Tolerability of the Pharmacology of Monoclonal Antibodies Targeting the Calcitonin Gene-Related Peptide and Its Receptor for the Prevention of Chronic Migraine: a Network Meta-analysis of Randomized Controlled Trials

Chun-Pai Yang[1,2] · Bing-Yan Zeng[3,14] · Ching-Mao Chang[4,5,6] · Po-Hsuan Shih[6,7] · Cheng-Chia Yang[8] · Ping-Tao Tseng[9,10,11] · Shuu-Jiun Wang[5,12,13]

Accepted: 16 September 2021 / Published online: 27 September 2021

Abstract

Monoclonal antibodies (mAbs) acting on the calcitonin gene-related peptide (CGRP) or on its receptor are new therapeutic biologics to prevent chronic migraine (CM). Four mAbs acting on the CGRP or on its receptor are new therapeutic biologics to prevent CM. The aim of current network meta-analysis (NMA) was to compare the efficacy and acceptability of CGRP mAbs with onabotulinumtoxinA or topiramate for CM. We included randomized controlled trials (RCTs) examining CGRP mAbs and onabotulinumtoxinA or topiramate in patients with CM. All network meta-analytic procedures were conducted using the frequentist model. The primary outcomes were changes in the monthly migraine days and the 50% response rate. The safety was evaluated with acceptability (i.e., drop-out rate) and rate of any adverse event. This NMA of thirteen RCTs, which, in total, consisted of 5634 participants, demonstrated that a single 300 mg of eptinezumab (mean difference = −2.60 days, 95% confidence intervals (95% CIs) = −4.43 to −0.77 compared with placebo) demonstrated the best improvement in monthly migraine days among all interventions. In addition, 675 mg fremanezumab in the first month followed by 225 mg in the second and third months (odds ratio (OR) = 2.96, 95% CIs = 2.20 to 3.97 compared to placebo) was associated with the best response rate among all the interventions. Monthly 140 mg erenumab (MD = −2.50 days, 95% CIs = −3.83 to −1.17 compared with placebo) was the best choice for reducing the number of acute migraine-specific medication use days. The safety analysis revealed that loading dose of 240 mg galcanezumab and monthly 240 mg (OR = 0.43, 95% CIs = 0.22 to 0.84) was associated with the lowest drop-out rate; loading dose fremanezumab 675 mg and monthly 675 mg (OR = 1.44, 95% CIs = 1.10 to 1.89), loading dose of 240 mg galcanezumab and monthly 120 mg (OR = 1.37, 95% CIs = 1.02 to 1.84), and single dose of fremanezumab 675 mg (OR = 1.35, 95% CIs = 1.00 to 1.83) were associated with significantly higher rates of AEs than the placebo/control groups. Our NMA indicated that all four CGRP mAbs demonstrated excellent safety, acceptability, and efficacy profiles compared to the traditional prophylaxis for CM. However, because there are several limitations, the findings of the current NMA should be taken into consideration with caution.

Keywords Chronic migraine · Prevention · Prophylaxis · Calcitonin gene-related peptide · Network meta-analysis

Abbreviations

Onabot	OnabotulinumtoxinA
CGRP	Calcitonin gene-related peptide
CI	Confidence interval
Ep300STAT	Eptinezumab 300 mg STAT
Ep100STAT	Eptinezumab 100 mg STAT
Ep10STAT	Eptinezumab 10 mg STAT
Ep30STAT	Eptinezumab 30 mg STAT
Er140QM	Erenumab 140 mg monthly
Er70QM	Erenumab 70 mg monthly
ES	Effect size
F675STAT675QM	Fremanezumab 675 mg monthly with loading dose with 675 mg at baseline

Chun-Pai Yang contributed as the first author.

✉ Ping-Tao Tseng
ducktseng@gmail.com

✉ Shuu-Jiun Wang
sjwang@vghtpe.gov.tw

Extended author information available on the last page of the article

F675STAT	Single dose of fremanezumab 675-mg group
F900QM	Monthly fremanezumab 900-mg group
G240STAT120QM	Galcanezumab 120 mg monthly with loading dose with 240 mg at baseline
G240STAT240QM	Galcanezumab 240 mg monthly with loading dose with 240 mg at baseline
mAB	Monoclonal antibody
MD	Mean difference
NMA	Network meta-analysis
OR	Odds ratio
Pla	Placebo/control
RCT	Randomized controlled trial
SUCRA	Surface under the cumulative ranking curve
Topiramate	Oral topiramate treatment

Introduction

Chronic migraine (CM) affects approximately 1.4 to 2.2% of the general population [1, 2]. It is the most prevalent type of headache in tertiary clinics and presents a clinical treatment challenge [3]. According to the third edition of the International Classification of Headache Disorders (ICHD-3), CM is characterized by experiencing a headache at least 15 days per month, of which at least 8 headache days per month meet the criteria for migraine or respond to migraine-specific treatment (CM, A1.3) [4]. These patients are often burdened with substantial disability, comorbidities, significant reduction in health-related quality of life, and high healthcare costs [1, 5].

Other than the already enormous burden, patients with CM have substantial unmet needs, especially when medication overuse worsened their conditions. Despite that many patients respond to conventional prophylactics, current preventive treatments are still insufficient to a considerable amount of patients due to contradictions, poor acceptability, or a long latency to efficacy [6, 7]. Only one-third of patients with CM receive preventive treatments, less than 20% of whom adhere to labeled or off-labeled preventive treatments after one year [6, 8, 9]. Poor adherence can lead to the worsening of the disorder. Furthermore, many prophylactic drugs used to prevent episodic migraine (EM) are frequently used to treat CM despite a lack of evidence in patients with CM. OnabotulinumtoxinA and topiramate are class I drugs with level A evidence for CM, while other oral preventive agents are considered with lower evidence levels [7]. However, the considerable side effects of topiramate and the invasiveness with a relatively high cost, at least in regions where its fees, are not covered by general health insurance plans of onabotulinumtoxinA precluding their widespread use for CM [10–12].

Currently, the four monoclonal antibodies (mAbs) available that act on the calcitonin gene-related peptide (CGRP) pathway and represent a mechanism-based and disease-specific class for migraine prevention are erenumab, eptinezumab, fremanezumab, and galcanezumab, of which erenumab targets the CGRP receptor and eptinezumab and fremanezumab, and galcanezumab target the CGRP peptide [9, 13]. Considering migraine pathophysiology, CGRP mAbs are migraine-specific, whereas all other available preventive drugs were developed for indications other than migraine and have an unclear mechanism of action. CGRP mAbs have demonstrated efficacy and acceptability with minimal side effects for the preventive treatment of CM in either phase 2 or phase 3 randomized, placebo-controlled trials [12]. Nevertheless, uncertainties remain regarding the effectiveness and safety of CGRP inhibitors compared with existing preventive therapies. Thus, the aim of the current study was to perform a systematic review and network meta-analysis (NMA) to clarify the precise benefits of CGRP mAbs in migraine prevention compared with existing preventive therapies in CM. Clinicians will benefit from this comprehensive review of clinical evidence, and the outcomes of this NMA will provide a guide for further studies.

Methods

The detailed description of method had been listed in eTable 1. In brief, the current NMA followed the PRISMA guidelines (eTable 2) [14] with keywords of (migraine OR chronic migraine OR aura) AND (anti-CGRP receptor monoclonal antibodies OR erenumab OR anti-calcitonin gene-related peptide monoclonal antibodies OR galcanezumab OR fremanezumab OR eptinezumab) AND (random OR randomized OR randomized) (eTable 9) and followed a priori defined unpublished protocol (appendix: study protocol), which was designed according to the previous meta-analyses and network meta-analyses [15–24, 23–27]. We only included published RCTs investigating prophylactic effect of CGRP in patients with CM. To increase the reliability of the current NMA, we included patients diagnosed with CM based on the ICHD system. To provide additional clinical information, we also included trials investigating the efficacy of topiramate or onabotulinumtoxinA in patients with CM to serve as active controls [7]. To be specific, our comparisons were focused between topiramate, onabotulinumtoxinA, and CGRP mAbs. The inclusion criteria applied in the current NMA included (1) published RCTs with either placebo-controlled or active-controlled designs, (2) human study, (3) investigated CGRP interventions applied in patients

with CM, and (4) patients diagnosed with CM based on the ICHD. The exclusion criteria included (1) not a clinical trial, (2) not an RCT, (3) no target outcome (i.e., response rate or change in monthly migraine days), (4) no inclusion of patients with CM, and (5) not reporting CGRP, topiramate, or onabotulinumtoxinA interventions. The primary outcomes were the change in monthly migraine days and response rate [12]. The secondary outcomes included the change in monthly days with acute migraine-specific abortive medications and acceptability. The acceptability was defined as drop-out rate and rate of adverse events (AEs) [7, 28]. To be specific, the drop-out was defined as leaving study before the end of the trial due to any reason. Based on frequentist model, the current NMA, under the hypotheses of similarity and transitivity, was performed using STATA (version 16.0; StataCorp Statistics/Data Analysis, StataCorp LLC, College Station, TX, USA) with the mvmeta command [29]. The indirect evidence between two active treatment arms could be derived from the comparisons to placebo. For continuous outcome, we calculated the mean difference (MD) with 95% confidence intervals (95% CIs). For categorical data, we calculated the summary odds ratio (OR) with 95% CIs. To provide clinical applications, we calculated the surface under the cumulative ranking curve (SUCRA) to rate the relative ranking probabilities between the preventive effects of all treatments for the target outcomes [30]. To improve the reading of the current NMA, we abbreviate the treatment arms following the rationale below: the first character was the regimen (i.e., Ep = eptinezumab, Er = erenumab, F = fremanezumab, and G = galcanezumab), the numbers were dosage, and the final characters were frequency (i.e., STAT = single use, QM = monthly).

Results

In Fig. 1, 329 articles were excluded because of unrelated topics after screening according to their titles and abstracts. After the initial screening procedure, forty-three articles were considered for full-text review. Thirty articles were excluded for various reasons (see Fig. 1 and eTable 3). Finally, thirteen articles were included in the current study (Table 1) [10, 11, 31–41]. The whole geometric distribution of the treatment arms is provided in Fig. 2A, B.

Characteristics of the Included Studies

A total of 5634 participants (mean age = 40.7 (ranging from 35.7 to 48.5) years old, mean female proportion = 85.8% (ranging from 71.4% to 91.5%)) were included with different health conditions, such as concomitant use of prophylactic medications, headache medication overuse, or failure of prior preventive therapies. The duration of CGRP interventions ranged from 4 to 49 weeks (mean duration = 19.3 weeks). The investigated pharmacologic

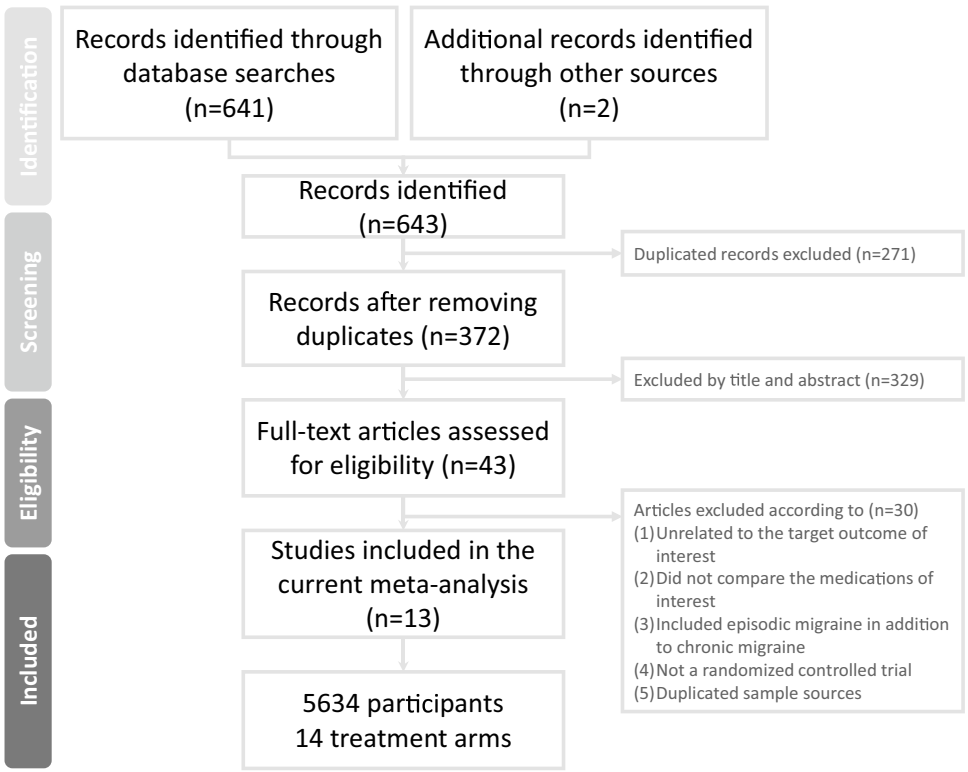
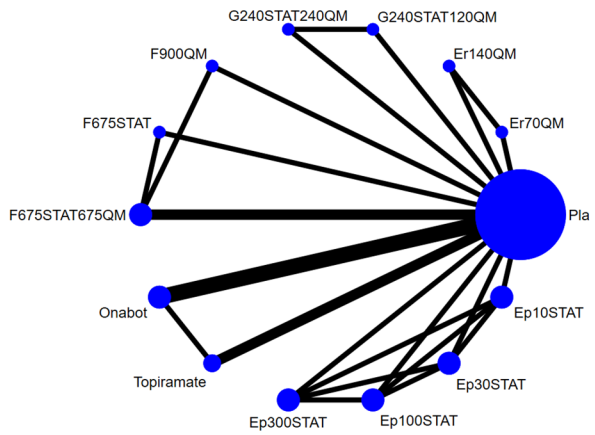
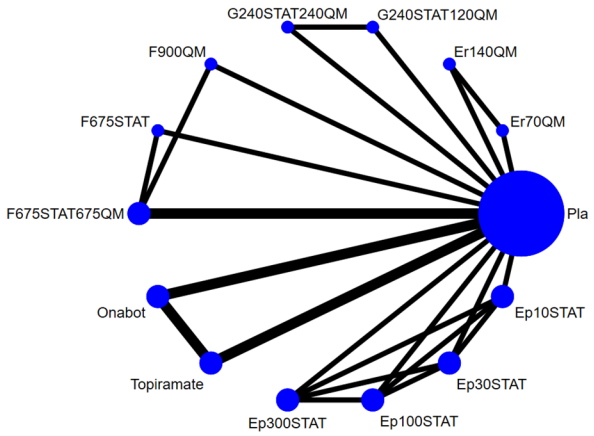


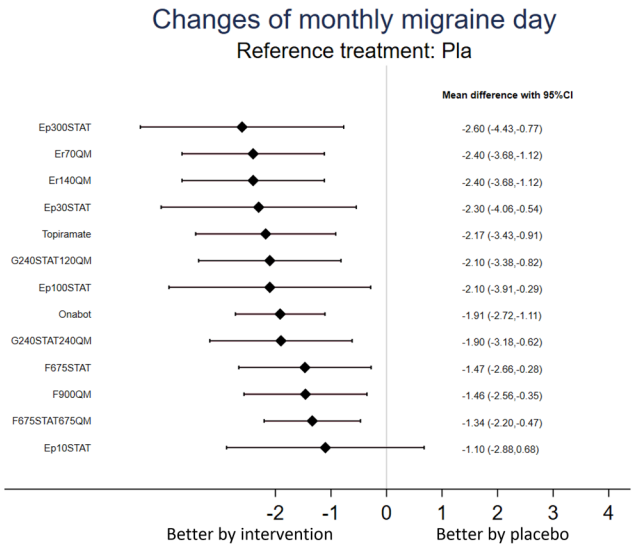
Fig. 1 Flowchart of the current network meta-analysis



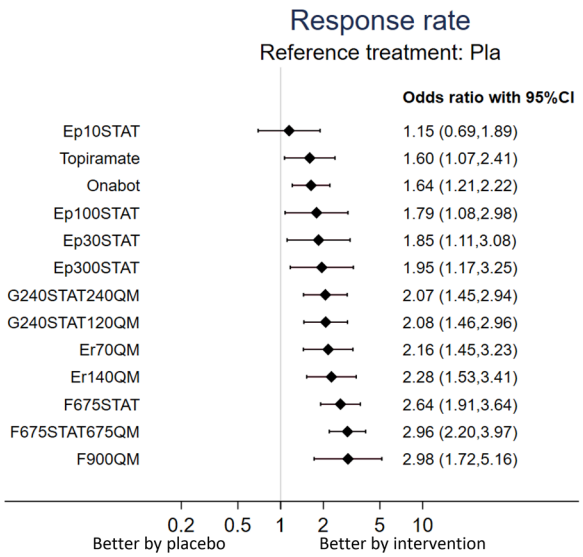
A Network structure of the NMA for changes in monthly migraine days



B Network structure of the NMA for 50% response rate



C Forest plot of the NMA for the changes in monthly migraine days



D Forest plot of the NMA for response rate

Fig. 2 The result of current network meta-analysis: **A** network structure of the primary outcome: the change in monthly migraine days and **B** network structure of the primary outcome: the 50% response rate. The lines between nodes represent direct comparisons in various trials, and the size of each circle is proportional to the size of the population involved in each specific treatment; **C** forest plot of the result of primary outcome: change in monthly migraine days; and **D** forest plot of the result of primary outcome: the 50% response rate. In panels **A** and **B**, the thickness of the lines is proportional to the number of trials connected to the network. In panel **C**, when the effect size was less than zero, the specified treatment was associated with improvements in the change in monthly migraine days compared with placebo/control. In panel **D**, when the effect size was more than one, the specified treatment was associated with a higher 50% response rate than placebo/control

interventions included eptinezumab (1 study), erenumab (1 study), fremanezumab (2 studies), galcanezumab (1 study), onabotulinumtoxinA (6 studies), and topiramate (4 studies).

Primary Outcome: Change in Monthly Migraine Days

Eleven articles with fourteen individual treatment arms were included in the current NMA. In the NMA, all the interventions were associated with significantly greater reductions of monthly migraine days than the placebo/control, except for a single dose of 10 mg eptinezumab (Ep10STAT) (MD = − 1.10 days, 95% CIs = − 2.88 to 0.68) (Table 2 and Fig. 2C). According to the SUCRA, a single dose of 300 mg eptinezumab (Ep300STAT) (MD = − 2.60 days, 95% CIs = − 4.43 to − 0.77 compared with placebo) was associated with the best improvement in monthly migraine days among all the interventions, followed by monthly doses of 70 mg erenumab (Er70QM) (MD = − 2.40 days, 95% CIs = − 3.68 to − 1.12 compared to placebo) and monthly doses of 140 mg erenumab (Er140QM) (MD = − 2.40 days, 95% CIs = − 3.68 to − 1.12 compared with placebo) (eTable 4A).

Table 1 The characteristics of the enrolled trials for current prophylaxis of chronic migraine

Study	Traditional Mx	Subject	Age range (years)	Diagnostic criteria	Concomitant Mx (% of using)	Select by previous preventive failure (n. of drugs/categories)	Administration route/treatment duration
Silberstein, 2007	Topiramate	328	18–65	ICHD-2	Not allowed	≥ 2	4 weeks titration and 12 weeks maintenance
Diener, 2007	Topiramate	59	18–65	ICHD-2	Not allowed (unless stable for 3 months)	Prior history of topiramate, other anti-convulsant or carbonic anhydrase inhibitors	Titration during 12 weeks and remained stable during the last 4 weeks
Aurora, 2010 (PREEMPT 1)	OnabotulinumtoxinA	679	18–65	ICHD-2, revised[b]	Not allowed	Not mentioned	Subcutaneous every 12 weeks for 24 weeks
Dinner, 2010 (PREEMPT 2)	OnabotulinumtoxinA	705	18–65	ICHD-2, revised[b]	Not allowed	Not mentioned	Subcutaneous every 12 weeks for 24 weeks
Freitag, 2007	OnabotulinumtoxinA	41	18–65	Silberstein & Lipton	Not allowed (unless stable for 60 days)	Prior use of botulinum toxin	Subcutaneous at the end of baseline
Cady 2011	OnabotulinumtoxinA Topiramate	59	18–65	ICHD-2, revised[b]	Not allowed	Prior history of topiramate or onabotulinumtoxinA use	A single intravenous dose for 12 weeks
Mathew 2009	OnabotulinumtoxinA Topiramate	90	18–65	Silberstein & Lipton	Not allowed	Prior history of topiramate use	A single intravenous dose for 12 weeks
Tepper, 2017	Erenumab (AMG334)	667	18–65	ICHD-3β	Not allowed	> 3	Subcutaneous every 4 weeks for 12 weeks
Bigal, 2015	Fremanezumab (TEV-48,125)	264	18–65	ICHD-3β	40%	> 3	Subcutaneous 675 mg in the first month and 225 mg in the second and third month[a] subcutaneous 900 mg for 3 months
Silberstein, 2017 (HALO CM)	Fremanezumab (TEV-48,125)	1130	18–70	ICHD-3β	20%	≥ 2	Subcutaneous 225 mg monthly for 12 weeks subcutaneous 675 mg quarterly for 12 weeks
Detke, 2018 (REGAIN 2018)	Galcanezumab (LY2951742)	1117	18–65	ICHD-3β	14%	> 2	Subcutaneous 120 mg (with 240 mg loading dose) monthly for 12 weeks subcutaneous 240 mg monthly for 12 weeks
Dodick, 2019	Eptinezumab (ALD403)	616	18–55	ICHD-3β	35%	Not mentioned	A single intravenous dose for 12 weeks

CGRP calcitonin gene-related peptide, *ICHD* International Classification of Headache Disorders, *Mx* medication, *onabotulinumtoxinA* onabotulinumtoxinA injection

[a]One month is 28 days

[b]ICHD-2 2006 revised

Table 2 League table of the primary outcome: changes in monthly migraine days

Ep300STAT			−0.30 (−1.99, 1.39)			−0.50 (−2.25, 1.25)					−1.50 (−3.21, 0.21)	*** −2.60 (− 4.31, − 0.89)**
−0.20 (−2.43, 2.03)	Er70QM	0.00 (−1.11, 1.11)										*** −2.40 (− 3.51, − 1.29)**
−0.20 (−2.43, 2.03)	0.00 (−1.28, 1.28)	Er140QM										*** −2.40 (− 3.51, − 1.29)**
−0.30 (−2.10, 1.50)	−0.10 (−2.27, 2.07)	−0.10 (−2.27, 2.07)	Ep30STAT			−0.20 (−1.87, 1.47)					−1.20 (−2.83, 0.43)	*** −2.30 (− 3.94, − 0.67)**
−0.43 (−2.65, 1.80)	−0.23 (−2.02, 1.57)	−0.23 (−2.02, 1.57)	−0.13 (−2.29, 2.04)	Topiramate				−0.60 (−3.74, 2.54)				*** −2.30 (− 4.10, − 0.50)**
−0.50 (−2.73, 1.73)	−0.30 (−2.11, 1.51)	−0.30 (−2.11, 1.51)	−0.20 (−2.37, 1.97)	−0.07 (−1.87, 1.72)	G240STAT 120QM		−0.20 (−1.31, 0.91)					*** −2.10 (− 3.21, − 0.99)**
−0.50 (−2.36, 1.36)	−0.30 (−2.52, 1.92)	−0.30 (−2.52, 1.92)	−0.20 (−1.99, 1.59)	−0.07 (−2.28, 2.14)	−0.00 (−2.22, 2.22)	Ep100STAT					−1.00 (−2.69, 0.69)	*** −2.10 (− 3.80, − 0.40)**
−0.70 (−2.93, 1.53)	−0.50 (−2.31, 1.31)	−0.50 (−2.31, 1.31)	−0.40 (−2.57, 1.77)	−0.27 (−2.07, 1.52)	−0.20 (−1.48, 1.08)	−0.20 (−2.42, 2.02)	G240STAT 240QM					*** −1.90 (− 3.01, − 0.79)**
−0.69 (−2.69, 1.31)	−0.49 (−2.00, 1.03)	−0.49 (−2.00, 1.03)	−0.39 (−2.32, 1.55)	−0.26 (−1.67, 1.15)	−0.19 (−1.70, 1.33)	−0.19 (−2.17, 1.80)	0.01 (−1.50, 1.53)	Onabot				*** −1.96 (− 2.90,, − 1.02)**
−1.13 (−3.32, 1.05)	−0.93 (−2.68, 0.82)	−0.93 (−2.68, 0.82)	−0.83 (−2.95, 1.29)	−0.71 (−2.43, 1.02)	−0.63 (−2.38, 1.12)	−0.63 (−2.80, 1.54)	−0.43 (−2.18, 1.32)	−0.45 (− 1.88, 0.99)	F675STAT		0.10 (−1.01, 1.21)	*** −1.70 (− 2.81, − 0.59)**
−1.14 (−3.28, 1.00)	−0.94 (−2.63, 0.75)	−0.94 (−2.63, 0.75)	−0.84 (−2.92, 1.23)	−0.72 (−2.39, 0.95)	−0.64 (−2ww.33, 1.05)	−0.64 (−2.77, 1.48)	−0.44 (−2.13, 1.25)	−0.46 (−1.82, 0.91)	−0.01 (−1.52, 1.50)	F900QM	0.32 (−0.67, 1.31)	*** −1.27 (− 2.25, − 0.29)**
−1.26 (−3.29, 0.76)	−1.06 (−2.61, 0.48)	−1.06 (−2.61, 0.48)	−0.96 (−2.92, 0.99)	−0.84 (−2.36, 0.68)	−0.76 (−2.31, 0.78)	−0.76 (−2.78, 1.25)	−0.56 (−2.11, 0.98)	−0.58 (−1.76, 0.60)	0.13 (−1.32, 1.06)	−0.12 (−1.23, 0.99)	F675STAT675QM	*** −1.33 (− 2.17, − 0.50)**
−1.50 (−3.33, 0.33)	−1.30 (−3.49, 0.89)	−1.30 (−3.49, 0.89)	−1.20 (−2.95, 0.55)	−1.07 (−3.25, 1.11)	−1.00 (−3.19, 1.19)	−1.00 (−2.81, 0.81)	−0.80 (−2.99, 1.39)	−0.81 (−2.77, 1.14)	−0.37 (−2.51, 1.77)	−0.36 (−2.45, 1.74)	−0.24 (−2.21, 1.74)	Ep10STAT	−1.10 (−2.76, 0.56)
*** −2.60 (− 4.43, − 0.77)**	*** −2.40 (− 3.68, − 1.12)**	*** −2.40 (− 3.68, − 1.12)**	*** −2.30 (− 4.06, − 0.54)**	*** −2.17 (− 3.43, − 0.91)**	*** −2.10 (− 3.38, − 0.82)**	*** −2.10 (− 3.91, − 0.29)**	*** −1.90 (− 3.18, − 0.62)**	*** −1.91 (− 2.72, − 1.11)**	*** −1.47 (− 2.66, − 0.28)**	*** −1.46 (− 2.56, − 0.35)**	*** −1.34 (− 2.20, − 0.47)**	−1.10 (−2.88, 0.68)	Pla

Pairwise (upper-right portion) and network (lower-left portion) meta-analysis results are presented as estimate effect sizes for the outcome of change in monthly migraine days in patients with chronic migraine. Interventions are reported in order of mean ranking of change in monthly migraine days, and outcomes are expressed as the mean difference (MD) (95% confidence intervals). For the pairwise meta-analyses, MD of less than 0 indicated that the treatment specified in the row yielded greater improvement than that specified in the column. For the network meta-analysis (NMA), MD of less than 0 indicates that the treatment specified in the column yielded greater improvement than that specified in the row. Bold results marked with * indicate statistical significance

Primary Outcome: Response Rate (Defined as at Least a 50% Reduction in Monthly Migraine Days)

Eleven articles with fourteen individual treatment arms were investigated in the current NMA. In the NMA, all the interventions were associated with a significantly better response rate than the placebo/control, except for Ep10STAT (OR = 1.15, 95% CIs = 0.69 to 1.89) (Table 3 and Fig. 2D). According to the SUCRA, 675 mg fremanezumab administered in the first month followed by 225 mg administered in the second and third months (F675STAT675QM) (OR = 2.96, 95% CIs = 2.20 to 3.97 compared with placebo) demonstrated the best response rate among all interventions, followed by monthly doses of 900 mg fremanezumab (F900QM) (OR = 2.98, 95% CIs = 1.72 to 5.16 compared with placebo) and a single dose of 675 mg fremanezumab (F675STAT) (OR = 2.64, 95% CIs = 1.91 to 3.64 compared with placebo) (eTable 4B).

Secondary Outcome: Monthly Days with Acute Migraine-Specific Medication Use

A total of six articles with nine individual treatment arms were investigated in the current NMA. In the NMA, almost all interventions were associated with significantly fewer monthly days with acute migraine-specific medication use than the placebo/control, except for topiramate (MD = − 1.31 day, 95% CIs = − 3.98 to 1.36) and onabotulinumtoxinA (MD = − 0.73 day, 95% CIs = − 3.29 to 1.84) (eTable 5A and eFigure 1A and 2A). According to the SUCRA, the association with the individual interventions and the reduced monthly days of acute migraine-specific medication use were ranked. In brief, the Er140QM group (MD = − 2.50 days, 95% CIs = − 3.83 to − 1.17 compared with placebo) was associated with the fewest monthly days of acute migraine-specific medication use among all the interventions, followed by the group that received 120 mg galcanezumab monthly with a loading dose of 240 mg at baseline (G240STAT120QM) (MD = − 2.50 days, 95% CIs = − 3.99 to − 1.01 compared with placebo) and the F675STAT675QM group (MD = − 2.30 days, 95% CIs = − 3.70 to − 0.90 compared with placebo) (eTable 4C).

Acceptability with Respect to Drop-out Rate

Twelve articles with fourteen individual treatment arms were investigated in the current NMA. Only 240 mg galcanezumab monthly with a loading dose of 240 mg at baseline (G240STAT240QM) (OR = 0.43, 95% CIs = 0.22 to 0.84) was associated with a significantly lower drop-out rate than the placebo/control groups (eTable 5B and eFigure 2A and 2B). According to the SUCRA, the association with the individual interventions and the drop-out rate were ranked. In brief, the G240STAT240QM group was associated with the lowest drop-out rate among all interventions, followed by the G240STAT120QM group (OR = 0.59, 95% CIs = 0.32 to 1.08 compared with the placebo/control group) and the Er140QM group (OR = 0.52, 95% CIs = 0.18 to 1.48 compared with the placebo/control group) (eTable 4D).

Acceptability Considering the Rate of Any Reported AEs

Twelve articles with fourteen individual treatment arms were investigated in the current NMA. Only topiramate (OR = 1.79, 95% CIs = 1.18 to 2.71), onabotulinumtoxinA (OR = 1.65, 95% CIs = 1.34 to 2.03), F675STAT675QM (OR = 1.44, 95% CIs = 1.10 to 1.89), G240STAT120QM (OR = 1.37, 95% CIs = 1.02 to 1.84), and F675STAT (OR = 1.35, 95% CIs = 1.00 to 1.83) were associated with significantly higher rates of AEs than the placebo/control groups (eTable 5C and eFigure 1C and 2C). According to the SUCRA, a single dose of 30 mg eptinezumab (OR = 0.66, 95% CIs = 0.40 to 1.10 compared with placebo/control) was associated with the lowest rate of any AEs among all the interventions, followed by the placebo group and Ep10STAT (OR = 1.03, 95% CIs = 0.63 to 1.70 compared with placebo/control) (eTable 4E).

Risk of Bias, Inconsistency, Publication Bias, and GRADE Ratings

We found that 82.4% (75/91 items), 14.3% (13/91 items), and 3.3% (3/91 items) of the included studies had an overall low, unclear, and high risk of bias, respectively. The vague reporting of allocation concealment of the studies further contributed to the risk of bias (eFigure 3A–3B).

Funnel plots of publication bias across the included studies (eFigure 4A–4J) revealed general symmetry, and the results of Egger's test indicated no significant publication bias among the articles included in the NMA. In general, NMAs did not demonstrate inconsistency, concerning either local inconsistency, as assessed using the loop-specific approach and the node-splitting method, or global inconsistency, as determined using the design-by-treatment method. The results of GRADE evaluation have been listed in the eTable 8A–8B. In brief, the overall quality of evidence of the overall NMA, direct evidence, and indirect evidence were low to medium.

Discussion

To our knowledge, this is the first NMA addressing the effectiveness and acceptability of mAbs reacting with CGRP compared to traditional prophylaxis for CM management.

Table 3 League table of the primary outcome: 50% response rate

F675STAT675QM	0.91 (0.50, 1.65)	1.14 (0.85, 1.53)										***2.96 (2.20, 3.97)**
0.99 (0.58, 1.71)	F900QM											***2.70 (1.45, 5.00)**
1.12 (0.84, 1.49)	1.13 (0.63, 2.04)	F675STAT										***2.73 (1.95,3.83)**
1.30 (0.79, 2.13)	1.31 (0.66, 2.58)	1.16 (0.69, 1.94)	Er140QM	1.06 (0.70, 1.59)								***2.28 (1.53,3.41)**
1.37 (0.83, 2.25)	1.38 (0.70, 2.72)	1.22 (0.73, 2.04)	1.05 (0.70, 1.59)	Er70QM								***2.16 (1.45, 3.23)**
1.42 (0.90, 2.26)	1.44 (0.75, 2.76)	1.27 (0.79, 2.05)	1.10 (0.64, 1.88)	1.04 (0.61, 1.78)	G240STAT120QM	1.01 (0.69, 1.46)						***2.08 (1.46, 2.96)**
1.43 (0.90, 2.27)	1.44 (0.75, 2.77)	1.28 (0.79, 2.06)	1.10 (0.65, 1.88)	1.05 (0.61, 1.79)	1.01 (0.69, 1.46)	G240STAT240QM						***2.07 (1.45, 2.94)**
1.52 (0.84, 2.73)	1.53 (0.72, 3.24)	1.35 (0.74, 2.48)	1.17 (0.61, 2.24)	1.11 (0.58, 2.12)	1.06 (0.57, 1.98)	1.06 (0.57, 1.97)	Ep300STAT	1.05 (0.63, 1.75)	1.09 (0.66, 1.81)			***1.70 (1.03, 2.80)**	***1.95 (1.17, 3.25)**
1.60 (0.89, 2.88)	1.61 (0.76, 3.41)	1.43 (0.78, 2.61)	1.23 (0.64, 2.36)	1.17 (0.61, 2.24)	1.12 (0.60, 2.09)	1.12 (0.60, 2.08)	1.05 (0.63, 1.75)	Ep30STAT	1.03 (0.62, 1.71)			1.61 (0.98, 2.65)	***1.85 (1.11, 3.08)**
1.65 (0.92, 2.97)	1.66 (0.79, 3.52)	1.47 (0.81, 2.69)	1.27 (0.67, 2.44)	1.21 (0.63, 2.31)	1.16 (0.62, 2.16)	1.15 (0.62, 2.15)	1.09 (0.66, 1.81)	1.03 (0.62, 1.71)	Ep100STAT			1.56 (0.95, 2.56)	***1.79 (1.08, 2.98)**
***1.80 (1.18, 2.76)**	1.82 (0.97, 3.41)	***1.61 (1.03, 2.51)**	1.39 (0.84, 2.30)	1.32 (0.80, 2.18)	1.27 (0.79, 2.02)	1.26 (0.79, 2.01)	1.19 (0.66, 2.16)	1.13 (0.62, 2.04)	1.09 (0.60, 1.98)	Onabot	0.86 (0.39, 1.88)		***1.69 (1.22, 2.33)**
***1.84 (1.11, 3.05)**	1.86 (0.94, 3.68)	1.65 (0.98, 2.77)	1.42 (0.80, 2.52)	1.35 (0.76, 2.39)	1.30 (0.75, 2.22)	1.29 (0.75, 2.21)	1.22 (0.63, 2.34)	1.15 (0.60, 2.22)	1.12 (0.58, 2.14)	1.02 (0.65, 1.62)	Topiramate		3.08 (0.33, 28.48)
***2.58 (1.44, 4.61)**	***2.60 (1.23, 5.46)**	***2.30 (1.27, 4.18)**	***1.99 (1.05, 3.78)**	1.88 (0.99, 3.58)	1.81 (0.98, 3.34)	1.80 (0.97, 3.33)	***1.70 (1.03, 2.80)**	1.61 (0.98, 2.65)	1.56 (0.95, 2.56)	1.43 (0.79, 2.57)	1.40 (0.73, 2.67)	Ep10STAT	1.15 (0.70, 1.90)
***2.96 (2.20, 3.97)**	***2.98 (1.72, 5.16)**	***2.64 (1.91, 3.64)**	***2.28 (1.53, 3.41)**	***2.16 (1.45, 3.23)**	***2.08 (1.46, 2.96)**	***2.07 (1.45, 2.94)**	***1.95 (1.17, 3.25)**	***1.85 (1.11, 3.08)**	***1.79 (1.08, 2.98)**	***1.64 (1.21, 2.22)**	***1.60 (1.07, 2.41)**	1.15 (0.69, 1.89)	Pla

Pairwise (upper-right portion) and network (lower-left portion) meta-analysis results are presented as estimate effect sizes for the outcome of a 50% response rate in patients with chronic migraine. Interventions are reported in order of mean ranking of 50% response rate, and outcomes are expressed as odds ratio (OR) (95% confidence intervals). For the pairwise meta-analyses, an OR higher than 1 indicated that the treatment specified in the row had a better response rate than that specified in the column. For the network meta-analysis (NMA), ORs higher than 1 indicate that the treatment specified in the column had a better response rate than that specified in the row. Bold results marked with * indicate statistical significance

Onabot onabotulinumtoxinA, *CGRP* calcitonin gene-related peptide, *CI* confidence interval, *Ep300STAT* eptinezumab 300 mg STAT, *Ep100STAT* eptinezumab 100 mg STAT, *Ep10STAT* eptinezumab 10 mg STAT, *Ep30STAT* eptinezumab 30 mg STAT, *Er140QM* erenumab 140 mg monthly, *Er70QM* erenumab 70 mg monthly, ES effect size, *F675STAT675QM* fremanezumab 675 mg monthly with loading dose with 675 mg at baseline, *F675STAT* single dose of fremanezumab 675 mg group, *F900QM* monthly fremanezumab 900 mg group, *G240STAT120QM* galcanezumab 120 mg monthly with loading dose with 240 mg at baseline, *G240STAT240QM* galcanezumab 240 mg monthly with loading dose with 240 mg at baseline, *mAB* monoclonal antibody, MD mean difference, *NMA* network meta-analysis, *OR* odds ratio, *Pla* placebo/control, *RCT* randomized controlled trial, *SUCRA* surface under the cumulative ranking curve, *Topiramate* oral topiramate treatment

Clinicians can make relevant comparisons of CGRP mAbs with traditional pharmacologic treatments based on our findings. In addition, this NMA is a collective affirmation that the application of CGRP mAbs provides significant value to patients with CM and is likely to serve as the new guideline for CM prevention. Our study findings suggest that all four CGRP mAbs demonstrated efficacy, safety, and acceptability compared to the traditional prophylaxis for CM.

A major strength of our study is the use of NMA, which is advantageous for estimating the multiple comparisons of the efficacy, safety, and superiority of numerous experimental pharmacologic interventions that have not been directly compared, providing more information and a higher level of evidence than RCTs and traditional meta-analyses [42]. Our findings are crucial to the clinical management of CM. First, inhibition of the CGRP pathway is superior to treatments with unclear mechanisms of action, and these results reinforce the prophylactic effects of CGRP mAbs against CM. Second, CGRP mAbs provide important insights into the relevance of CGRP in the pathophysiology of CM, which can apply to a broad population of migraine patients, and using CGRP mAbs is a disease-targeted and biologically specific approach for this disease state. Third, future well-designed RCTs investigating the long-term effects and safety profiles of CGRP mAbs are warranted to corroborate these findings of our NMA.

Based on the high frequency, severity, and impact on quality of life, patients with CM are identified as candidates for preventive treatment [7]. In patients who receive oral migraine prevention medication, side effects are often problematic, efficacy rates are modest, and nonadherence is significant, which are key limitations of available preventive treatments [5, 9]. Furthermore, none of the currently available oral preventive treatments, including calcium-channel antagonists, tricyclic antidepressants, antidepressants, antiepileptics, and antihypertensives, was developed specifically for migraine or CM [7, 8]. In fact, onabotulinumtoxinA and topiramate are class I drugs with level A evidence for CM with and without analgesic overuse, while other oral preventive agents, such as sodium valproate, gabapentin, pregabalin, amitriptyline, and tizanidine, are considered alternative preventive treatments with lower evidence levels [7]. Despite the efficacy of topiramate for CM prophylaxis, it is associated with a high rate (66–82.5%) of AEs at the recommended dose (100 mg/day) [7]. AEs commonly associated with topiramate include paresthesia, fatigue, difficulties with memory, concentration or attention, and taste perversion. In the current NMA study, topiramate showed the highest rate of AEs among all interventions. OnabotulinumtoxinA was reported to be effective with very good acceptability for the treatment of CM and is approved both by the European Medicines Agency and by the US Food and Drug Administration (FDA) for CM prophylaxis [13]. Effective use of onabotulinumtoxinA treatment for the prevention of CM may prove beneficial for avoiding poor adherence and compliance with drug regimens such as daily dosing and dosage titration schedules and tends to be better tolerated than various oral prophylactic treatments, including topiramate [13]. However, the higher cost, invasiveness, multiple injection sites, and inconvenience of onabotulinumtoxinA preclude its widespread use. In addition, approximately one-third of CM patients do not respond well to onabotulinumtoxinA [43]. Currently, onabotulinumtoxinA is recommended as a second-line option for CM patients who have not responded adequately or are intolerant to commonly prescribed oral pharmacies [43].

According to the Guidelines of the International Headache Society for controlled trials of preventive treatment of CM in adults, the primary endpoint in controlled trials of preventive treatment of CM should be either change in migraine days, change in moderate to severe headache days, or response rate [12]. In the present study, we selected change in monthly migraine days and a 50% reduction in monthly migraine days as primary end points and monthly days with acute migraine-specific medication rescue and acceptability as secondary outcomes. In the current NMA study, fremanezumab (TEV-48125) was used in two trials at 3 different dosages (675 mg quarterly or 675 mg in the first month followed by 225 mg in the second and third month) versus placebo in a phase III trial (675/225 mg); 675/225 mg or 900 mg monthly for 3 months versus placebo in a phase II trial. As suggested by the rank probability of SUCRA, fremanezumab 675/225 mg exhibited the best improvement in terms of a 50% reduction in monthly migraine days. The improvement in the 50% response rate means that the monthly burden of migraine decreases substantially. Additionally, fremanezumab led to a significant decrease in the number of headache hours starting as soon as 3 days after the highest dose (900 mg) was administered and 7 days after lower doses (675/225 mg) were administered [37]. Of the four CGRP mAbs, three are administered subcutaneously, and eptinezumab (ADL403) is the only one that is administered intravenously (IV). IV administration provides 100% bioavailability with C_{max} (maximal plasma concentration), occurring at nearly the end of infusion, which facilitates the potential for a rapid onset [41]. A post hoc analysis suggested that patients could achieve a clinically meaningful reduction in migraine activity as early as day 1 postinfusion of eptinezumab [41]. Meanwhile, the SUCRA results showed that a single high-dose of eptinezumab (300 mg) was associated with the best improvement in terms of change in monthly migraine days. Among four CGRP mAbs, erenumab (AMG334) is the only fully human monoclonal antibody that reacts with the receptor of CGRP and demonstrated the best improvement in terms of change in acute migraine-specific medication by a monthly dosage of 140 mg erenumab for 3 months in our NMA study. The

importance of reducing acute migraine-specific medicine use days is relevant for patients with CM who concomitantly have medication overuse headaches. Previous studies have examined the effect of topiramate and onabotulinumtoxinA in patients with CM, which showed that the efficacy in the medication overuse subgroup was similar to that of the overall population, with a significant reduction in the frequency of headache days and other headache symptom measures [44]. These results, along with current studies of CGRP mAbs, suggest that migraine preventive medications are not necessarily limited by acute headache medication overuse [45]. Future studies need to implement head-to-head comparative effectiveness trials between different classes of medications or among medications in the same class to evaluate the specific clinical outcomes of CM.

The outcome of mean changes of monthly migraine days indicates the efficacy of a treatment in improving the frequency of migraine days. The outcome of 50% response rate indicates the odds of a treatment in relieving at least 50% of the frequency of migraine days. Both outcomes are important to migraine care but with different measurement unit. Topiramate is efficacious for both outcomes when compared with a placebo. For the outcome of monthly migraine days, topiramate is not superior or inferior to any other active treatment (Table 2). However, for the outcome of a 50% response rate, topiramate is only inferior to F675STAT675QM. Therefore, future RCTs addressing both outcomes should be warranted to provide a more comprehensive information about target outcomes for clinical practice.

In this study, all four CGRP mAbs demonstrated excellent safety, acceptability, and efficacy profiles in CM patients. Neither cardiovascular nor immunological safety concerns have emerged in clinical trials [13]. Monthly doses of 240 mg galcanezumab were associated with the lowest drop-out rate among all interventions. The high molecular weight of the CGRP-mAbs compounds cannot pass through the blood–brain barrier like what compounds from oral preventive medications for CM can do. This possibly reduces the likelihood of central nervous system-related AEs. Nonetheless, patients in the CGRP mAb group experienced more injection site discomfort than those in the placebo group, but the incidence of discontinuation due to AEs was similar between the two groups. These results demonstrate that CGRP mAb is a well-tolerated and promising drug.

Limitation

Several limitations to the current NMA should be considered. First, due to the limited data, we only focused on the short-term AEs of mAbs during the double-blind period, whereas we neglected long-term effects. These short-term trials provide limited certainty about safety and acceptability. The long-term safety of CGRP binding mAbs remains unknown and needs to be investigated in large RCTs. Second, the inclusion criteria also varied among the included studies. Some studies only enrolled patients who were not receiving migraine preventive medications, while other studies allowed the enrollment of patients with concomitant use of preventive medications. The different baseline characteristics might impose unwanted bias on the final statistical results. Therefore, clinicians should consider specific preventive strategies in specific clinical conditions to avoid the potential bias, such as concomitant medications. Third, the double-blind period was not the same in our included studies, ranging from 3 to 6 months, which might contribute to heterogeneity. Fourth, the current study did not take the cost-effectiveness into account in the analysis. Therefore, the result of current study should not be directly considered the guideline of clinical treatment. Fifth, the unclear risk of bias in allocation concealment might impose potential risk of bias to the strength of evidence in the current NMA. Six, although the three outcomes are inter-correlated (i.e., changes in monthly migraine days, response rate, and monthly days of acute migraine-specific medication use), we could not determine the best treatment over the three outcomes. This is because some of the included treatments did not provide all the three outcomes. Besides, the SUCRA value indicates the probability of a treatment being the best without considering the magnitude of differences in effects between treatments [46]. Seventh, there were several substantial discrepancies among the included RCTs, such as different diagnostic criteria of CM, treatment duration (ranged from 4 to 49 weeks, mean duration = 19.3 weeks), and different primary endpoint (mean monthly migraine days vs. mean monthly headache days). These might limit the power of comparisons. Eighth, our main findings of NMA used placebo as a reference treatment, while we included several head-to-head studies. This implied that the comparisons with placebo in head-to-head studies were derived from indirect effects. However, these head-to-head studies may provide direct effects on head-to-head comparisons between different active drugs in our NMA. Finally, although our study is strengthened by comparing different treatments with NMA, the analysis is based on an overall limited number of studies and the results depend on the studies included and the possible comparisons within them, which limit the generalizability of the study results to broader populations. Because there are several limitations, the findings of the current NMA should be taken into consideration with caution.

Conclusion

The results of this NMA suggest that most CGRP mAbs showed superior efficacy to currently available treatments with good acceptability. However, the significant

heterogeneity among the trials may hinder firm conclusions. These results suggest that CGRP mAbs may be viable therapeutic alternatives for patients with CM in whom currently available preventive treatments have failed. However, because of lack of consideration of cost-effectiveness in the current analysis, clinicians should not directly consider the results as the guideline of clinical treatment.

Required Author Forms Disclosure forms provided by the authors are available with the online version of this article.

Disclosures This research was supported in part by grants from the Ministry of Science and Technology, Taiwan (MOST 108–2321-B-010–014-MY2, MOST 108–2314-B-010–023-MY3), and Brain Research Center, National Yang-Ming University from The Featured Areas Research Center Program within the framework of the Higher Education Sprout Project by the Ministry of Education (MOE) in Taiwan. The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript. All the authors did not have any financial conflict in the current work, except for the author mentioned below. Shuu-Jiun Wang has served on the advisory boards of Eli Lilly, Daiichi-Sankyo, Taiwan Pfizer, and Taiwan Novartis. Shuu-Jiun Wang has received honoraria as a speaker or moderator for Allergan, Pfizer, Eli Lilly, Bayer, and Eisai. Shuu-Jiun Wang has received research grants from the Taiwan Minister of Technology and Science, National Yang-Ming University, Taipei Veterans General Hospital, Taiwan Headache Society, Taiwan Norvatis, and Taiwan Eli Lilly.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s13311-021-01128-0.

References

1. Bigal ME, Serrano D, Reed M, Lipton RB. Chronic migraine in the population: burden, diagnosis, and satisfaction with treatment. Neurology 2008;71: 559-566.
2. Stark RJ, Ravishankar K, Siow HC, Lee KS, Pepperle R, Wang SJ. Chronic migraine and chronic daily headache in the Asia-Pacific region: a systematic review. Cephalalgia 2013;33: 266-283.
3. Bigal ME, Sheftell FD, Rapoport AM, Lipton RB, Tepper SJ. Chronic daily headache in a tertiary care population: correlation between the International Headache Society diagnostic criteria and proposed revisions of criteria for chronic daily headache. Cephalalgia 2002;22: 432-438.
4. Headache Classification Committee of the International Headache Society (IHS) The International Classification of Headache Disorders, 3rd edition. Cephalalgia 2018;38: 1–211.
5. Buse DC, Manack AN, Fanning KM, et al. Chronic migraine prevalence, disability, and sociodemographic factors: results from the American Migraine Prevalence and Prevention Study. Headache 2012;52: 1456-1470.
6. Blumenfeld AM, Bloudek LM, Becker WJ, et al. Patterns of use and reasons for discontinuation of prophylactic medications for episodic migraine and chronic migraine: results from the second international burden of migraine study (IBMS-II). Headache 2013;53: 644-655.
7. Giacomozzi AR, Vindas AP, Silva AA, Jr., et al. Latin American consensus on guidelines for chronic migraine treatment. Arq Neuropsiquiatr 2013;71: 478-486.
8. Hepp Z, Dodick DW, Varon SF, Gillard P, Hansen RN, Devine EB. Adherence to oral migraine-preventive medications among patients with chronic migraine. Cephalalgia 2015;35: 478-488.
9. American Headache S. The American Headache Society Position Statement On Integrating New Migraine Treatments Into Clinical Practice. Headache 2019;59: 1-18.
10. 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.
11. 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.
12. 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.
13. Agostoni EC, Barbanti P, Calabresi P, et al. Current and emerging evidence-based treatment options in chronic migraine: a narrative review. J Headache Pain 2019;20: 92.
14. Hutton B, Salanti G, Caldwell DM, et al. The PRISMA extension statement for reporting of systematic reviews incorporating network meta-analyses of health care interventions: checklist and explanations. Ann Intern Med 2015;162: 777-784.
15. 15. Chang HY, Tseng PT, Stubbs B, et al. The efficacy and tolerability of paliperidone in mania of bipolar disorder: A preliminary meta-analysis. Exp Clin Psychopharmacol 2017;25: 422-433.
16. Chen JJ, Zeng BS, Wu CN, et al. Association of Central Noninvasive Brain Stimulation Interventions With Efficacy and Safety in Tinnitus Management: A Meta-analysis. JAMA Otolaryngol Head Neck Surg 2020.
17. Hsieh MT, Tseng PT, Wu YC, et al. Effects of different pharmacologic smoking cessation treatments on body weight changes and success rates in patients with nicotine dependence: A network meta-analysis. Obes Rev 2019.
18. Su KP, Tseng PT, Lin PY, et al. Association of Use of Omega-3 Polyunsaturated Fatty Acids With Changes in Severity of Anxiety Symptoms: A Systematic Review and Meta-analysis. JAMA Netw Open 2018;1: e182327.
19. Sun CK, Tseng PT, Wu CK, et al. Therapeutic effects of methylphenidate for attention-deficit/hyperactivity disorder in children with borderline intellectual functioning or intellectual disability: A systematic review and meta-analysis. Sci Rep 2019;9: 15908.
20. Tseng PT, Chen YW, Chung W, et al. Significant Effect of Valproate Augmentation Therapy in Patients With Schizophrenia: A Meta-analysis Study. Medicine (Baltimore) 2016;95: e2475.
21. Tseng PT, Chen YW, Lin PY, et al. Significant treatment effect of adjunct music therapy to standard treatment on the positive, negative, and mood symptoms of schizophrenic patients: a meta-analysis. BMC Psychiatry 2016;16: 16.
22. Tseng PT, Chen YW, Tu KY, et al. Light therapy in the treatment of patients with bipolar depression: A meta-analytic study. Eur Neuropsychopharmacol 2016;26: 1037-1047.
23. Tseng PT, Yang CP, Su KP, et al. The association between melatonin and episodic migraine: a pilot network meta-analysis of randomized controlled trials to compare the prophylactic effects with exogenous melatonin supplementation and pharmacotherapy. J Pineal Res 2020; e12663.
24. Wu CK, Tseng PT, Wu MK, et al. Antidepressants during and after Menopausal Transition: A Systematic Review and Meta-Analysis. Sci Rep 2020;10: 8026.

25. Wu YC, Tseng PT, Tu YK, et al. Association of Delirium Response and Safety of Pharmacological Interventions for the Management and Prevention of Delirium: A Network Meta-analysis. JAMA Psychiatry 2019.
26. Yang CP, Tseng PT, Pei-Chen Chang J, Su H, Satyanarayanan SK, Su KP. Melatonergic agents in the prevention of delirium: A network meta-analysis of randomized controlled trials. Sleep Med Rev 2020;50: 101235.
27. Zeng BS, Lin SY, Tu YK, et al. Prevention of Postdental Procedure Bacteremia: A Network Meta-analysis. J Dent Res 2019;98: 1204-1210.
28. Zhou X, Teng T, Zhang Y, et al. Comparative efficacy and acceptability of antidepressants, psychotherapies, and their combination for acute treatment of children and adolescents with depressive disorder: a systematic review and network meta-analysis. Lancet Psychiatry 2020;7: 581-601.
29. White IR. Network meta-analysis. The Stata Journal 2015;15: 951-985.
30. Salanti G, Ades AE, Ioannidis JP. Graphical methods and numerical summaries for presenting results from multiple-treatment meta-analysis: an overview and tutorial. J Clin Epidemiol 2011;64: 163-171.
31. Freitag FG, Diamond S, Diamond M, Urban G. Botulinum Toxin Type A in the treatment of chronic migraine without medication overuse. Headache 2008;48: 201-209.
32. Mathew NT, 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: 1466-1478.
33. 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.
34. 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.
35. Cady RK, Schreiber CP, Porter JA, Blumenfeld AM, Farmer KU. A multi-center double-blind pilot comparison of onabotulinumtoxinA and topiramate for the prophylactic treatment of chronic migraine. Headache 2011;51: 21-32.
36. Cady R, Turner I, Dexter K, Beach ME, Cady R, Durham P. 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.
37. Bigal ME, Dodick DW, Krymchantowski AV, et al. TEV-48125 for the preventive treatment of chronic migraine: Efficacy at early time points. Neurology 2016;87: 41-48.
38. Silberstein SD, Dodick DW, Bigal ME, et al. Fremanezumab for the Preventive Treatment of Chronic Migraine. N Engl J Med 2017;377: 2113-2122.
39. 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.
40. Detke HC, Goadsby PJ, Wang S, Friedman DI, Selzler KJ, Aurora SK. Galcanezumab in chronic migraine: The randomized, double-blind, placebo-controlled REGAIN study. Neurology 2018;91: e2211-e2221.
41. 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.
42. Kontopantelis E, Springate DA, Reeves D. A re-analysis of the Cochrane Library data: the dangers of unobserved heterogeneity in meta-analyses. PLoS One 2013;8: e69930.
43. Tassorelli C, Tedeschi G, Sarchielli P, et al. Optimizing the long-term management of chronic migraine with onabotulinumtoxinA in real life. Expert Rev Neurother 2018;18: 167-176.
44. Silberstein SD, Blumenfeld AM, Cady RK, et al. OnabotulinumtoxinA for treatment of chronic migraine: PREEMPT 24-week pooled subgroup analysis of patients who had acute headache medication overuse at baseline. J Neurol Sci 2013;331: 48-56.
45. Tepper SJ, Diener HC, Ashina M, et al. Erenumab in chronic migraine with medication overuse: Subgroup analysis of a randomized trial. Neurology 2019;92: e2309-e2320.
46. Mbuagbaw L, Rochwerg B, Jaeschke R, et al. Approaches to interpreting and choosing the best treatments in network meta-analyses. Syst Rev 2017;6: 79.

Authors and Affiliations

Chun-Pai Yang[1,2] · Bing-Yan Zeng[3,14] · Ching-Mao Chang[4,5,6] · Po-Hsuan Shih[6,7] · Cheng-Chia Yang[8] · Ping-Tao Tseng[9,10,11] · Shuu-Jiun Wang[5,12,13]

1 Department of Neurology, Kuang Tien General Hospital, Taichung, Taiwan

2 Department of Nutrition, Hungkuang University, Taichung, Taiwan

3 Division of Endocrinology and Metabolism, Department of Internal Medicine, E-Da Hospital, Kaohsiung, Taiwan

4 Center for Traditional Medicine, Taipei Veterans General Hospital, Taipei, Taiwan

5 Faculty of Medicine, College of Medicine, National Yang Ming Chiao Tung University, Taipei, Taiwan

6 Institute of Traditional Medicine, National Yang Ming Chiao Tung University, Taipei, Taiwan

7 Department of Chinese Medicine, Cheng Hsin General Hospital, Taipei, Taiwan

8 Department of Healthcare Administration, Asia University, Taichung, Taiwan

9 Prospect Clinic for Otorhinolaryngology & Neurology, Kaohsiung City, Taiwan

10 Department of Psychology, College of Medical and Health Science, Asia University, Taichung, Taiwan

11 Institute of Biomedical Sciences, National Sun Yat-Sen University, Kaohsiung, Taiwan

12 Department of Neurology, Neurological Institute, Taipei Veterans General Hospital, Taipei, Taiwan

13 Brain Research Center, National Yang Ming Chiao Tung University, Taipei, Taiwan

14 Division of Endocrinology & Metabolism, Department of Internal Medicine, E-DA Dachang Hospital, Kaohsiung, Taiwan