




Effectiveness and Safety of Chronic Migraine Preventive Treatments: A Systematic Literature Review

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ABSTRACT

Introduction: Numerous medications are used for the preventive treatment of chronic migraine (CM), including oral treatments, onabotulinumtoxinA (onabotA; BOTOX), and calcitonin gene-related peptide (CGRP) monoclonal antibodies (mAbs). Despite substantial clinical trial evidence, less is published about the real-world experience of these treatments based on data routinely collected from a variety of sources. This systematic review assessed real-world evidence on the effectiveness and safety of preventive treatments for CM in adults.

Methods: A systematic search of MEDLINE, Embase, and the Cochrane library with back-referencing and supplementary searches

retrieved data published between January 2010 and February 2020. Publications were screened, extracted, and quality assessed. Data were narratively synthesized. Search criteria included preventive medications for CM. Evidence was available for topiramate, onabotulinumtoxinA, CGRP mAbs (erenumab, galcanezumab, and fremanezumab). OnabotulinumtoxinA was most commonly assessed (55 studies), followed by erenumab (six studies), multiple CGRP mAbs (one study), and topiramate (one study). Long-term data (> 1 year) were available for onabotulinumtoxinA only, with erenumab reported up to 6 months, topiramate up to 3 months, and multiple CGRP mAbs up to 12 months.

Results: Substantial data demonstrated that onabotulinumtoxinA reduces the number/frequency of headaches, concomitant acute medication use, and impact of headaches on well-being and daily activity. More limited evidence showed benefits for the same parameters with erenumab. Single studies suggested topiramate and multiple CGRP mAbs decrease the number/frequency of headaches and impact of headaches. To date, onabotulinumtoxinA is the only preventive treatment for CM that has long-term safety data in real-world settings reporting treatment-related adverse events of up to 3 years.

Conclusion: While substantial real-world evidence supports the long-term effectiveness and safety of onabotulinumtoxinA, real-world data on other preventive treatments of CM are

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currently limited to short term effectiveness due to their more recent approvals.

Keywords: CGRP monoclonal antibody; Chronic migraine; Erenumab; OnabotulinumtoxinA; Real-world evidence; Topiramate

Key Summary Points

This systematic literature review identified evidence from real-world studies for the preventive treatment of chronic migraine (CM).

Thirty-eight studies met the selection criteria and reported monthly headache or migraine day data: onabotulinumtoxinA ($n = 34$), erenumab ($n = 4$), topiramate versus onabotulinumtoxinA ($n = 1$), and erenumab, galcanezumab, and fremanezumab versus onabotulinumtoxinA ($n = 1$).

The reduction from baseline in monthly headache and migraine days at all time points was statistically significant with all interventions.

OnabotulinumtoxinA had the largest number of studies with the longest follow-up periods, and produced a beneficial effect on the number and frequency of headache or migraine days, concomitant medication use, and impact of headache [i.e., Headache Impact Test-6 (HIT-6)].

No new safety concerns were observed with long-term use of any of these treatments.

INTRODUCTION

Chronic migraine (CM) is defined by the International Headache Society Classification of Headache Disorders (ICHD-3) as a headache occurring on at least 15 days per month for more than 3 months, with migraine on at least

8 days per month [1]. These eight migraine days can be defined by migraine features, aura, or response to migraine-specific treatment. CM can be debilitating for many patients, with negative effects on physical, social, and occupational functioning, and a reduced health-related quality of life [2, 3]. Overall, global CM prevalence is 1–2% [4].

Management of CM is focused on preventive treatment to reduce headache frequency and severity, and to limit reliance on acute treatment. Numerous oral agents are used for the preventive treatment of CM, including antihypertensives (beta-blockers, calcium-channel blockers), antidepressants (tricyclic antidepressants, selective serotonin reuptake inhibitors, noradrenergic and specific serotonergic antidepressants), and anticonvulsants [2]. However, there tends to be limited evidence for their use in CM, and treatments are often discontinued due to lack of efficacy or poor tolerability [2, 5–7].

High-quality clinical trial evidence is available for the use of topiramate, onabotulinumtoxinA (OnabotA; BOTOX), and calcitonin gene-related peptide (CGRP) monoclonal antibodies (mAbs) in CM [2]. OnabotulinumtoxinA was approved in the European Union (EU) for symptom relief in chronic migraine and the USA for prophylaxis of headaches in adult patients with CM in 2010 [8], and has long-term, real-world evidence in a wide patient population [2, 8, 9]. The broad-spectrum antiepileptic drug, topiramate, has been approved for migraine prevention in adults in Europe since 2003 and in the USA since 2004 [10], while CGRP mAbs (erenumab, galcanezumab, fremanezumab, and eptinezumab) have been approved since 2018 [11, 12].

While clinical trial evidence exists for topiramate, onabotulinumtoxinA, and CGRP mAbs, less is known about the comparative real-world effectiveness and safety of these treatments. We conducted a systematic literature review (SLR) to assess and summarize the real-world evidence on the effectiveness and safety of all pharmacological agents used for preventive treatment of CM in adults. As the literature review specifically focuses on real-world studies, the term “effectiveness” (used to describe the degree

of beneficial effect including tolerability under “real-world” clinical settings) rather than “efficacy” (defined as the benefit of treatment under ideal conditions) is used throughout [13].

METHODS

This SLR was conducted in accordance with the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) reporting guidelines [14]. A PRISMA 2009 Checklist is provided as Supplementary file S1.

This article is based on previously conducted studies and does not contain any new studies with human participants or animals performed by any of the authors.

Search Strategy

Searches were performed in Medical Literature Analysis and Retrieval System Online (MEDLINE), the Excerpta Medica database (Embase) via embase.com, and the Cochrane library/Cochrane Central Register of Controlled Trials via Cochrane library to identify relevant real-world data published in any language between 1 January 2010 and 11 February 2020. Each search was conducted using controlled vocabulary and keywords (“migraine” OR “migrainous headache” OR “hemicrania” OR “status hemicranicus” OR “chronic migraine”), and was limited to prospective cohort studies, retrospective cohort studies, cross-sectional studies, and case-control studies involving at least 40 human adult subjects with a reported duration of follow-up. Clinical trials, case series, and case reports were excluded. A summary of the review protocol is provided as Supplementary file S1.

A systematic search approach was used, in which specific disease and study design facets were developed for the embase.com and Cochrane library search strategies. The disease facet was combined with the study design facet using “AND” as the Boolean operator (Supplementary file S3).

In addition to the structured searches, supplementary searches were also conducted to ensure all relevant data were retrieved. Supplementary searches included hand searching of

relevant conferences between January 2017 and March 2020, bibliographic searches of systematic reviews and narrative reviews published in the last 3 years, and manual searches of PubMed, Google, and Google Scholar. Trial registry searches (Clinicaltrials.gov and the EU Clinical Trials Register) were also conducted to retrieve a list of ongoing and planned real-world observational studies for the relevant population.

Selection Criteria

Study selection was undertaken in two steps. Initially, the title and abstract (ti/ab) of each citation was screened to identify a list of potentially relevant studies, then the full-text versions of relevant studies were reviewed to determine the final list of included studies. For both the ti/ab and full-text screening, all citations were included or excluded on the basis of a screening flowchart (Supplementary file S4). The studies that met all predefined criteria for inclusion were included for final extraction, while excluded citations were coded by reason for exclusion.

Data Extraction

Study characteristics, patient characteristics, treatment details (name of intervention, dose, duration, and frequency), as well as effectiveness and safety outcomes [treatment-related adverse events (TRAEs)] were extracted into a Microsoft Excel data extraction sheet.

Quality Assessment

A quality assessment of each full journal publication included in the review was carried out using the Newcastle–Ottawa scale (NOS), in which assessment criteria vary according to study type (cohort studies or case-control studies) [15]. Details are provided as Supplementary file S5.

RESULTS

Study and Patient Characteristics

The PRISMA flow diagram of included studies is shown in Fig. 1. Database searches detected 12,662 potentially relevant citations, with 11 further citations identified through supplementary searches. After removal of duplicates, 382 relevant records were selected through ti/ab screening. Following a detailed examination of the full-text articles, a total of 130 publications comprising 61 primary studies (34 journal publications and 27 conference abstracts) were included for data extraction.

A complete list of included studies along with any linked publications is provided in Supplementary file S6.

Study Characteristics

The disposition of the studies according to key parameters is provided in Table 1. In total, there were 39 prospective cohort studies and 22 retrospective cohort studies. The sample size in the included studies ranged from 42 [16] to 1160 [17]. The 34 journal publications for which quality assessment was conducted were of moderate-to-high quality, and had a score of ≥ 4 on NOS. Studies reported as conference

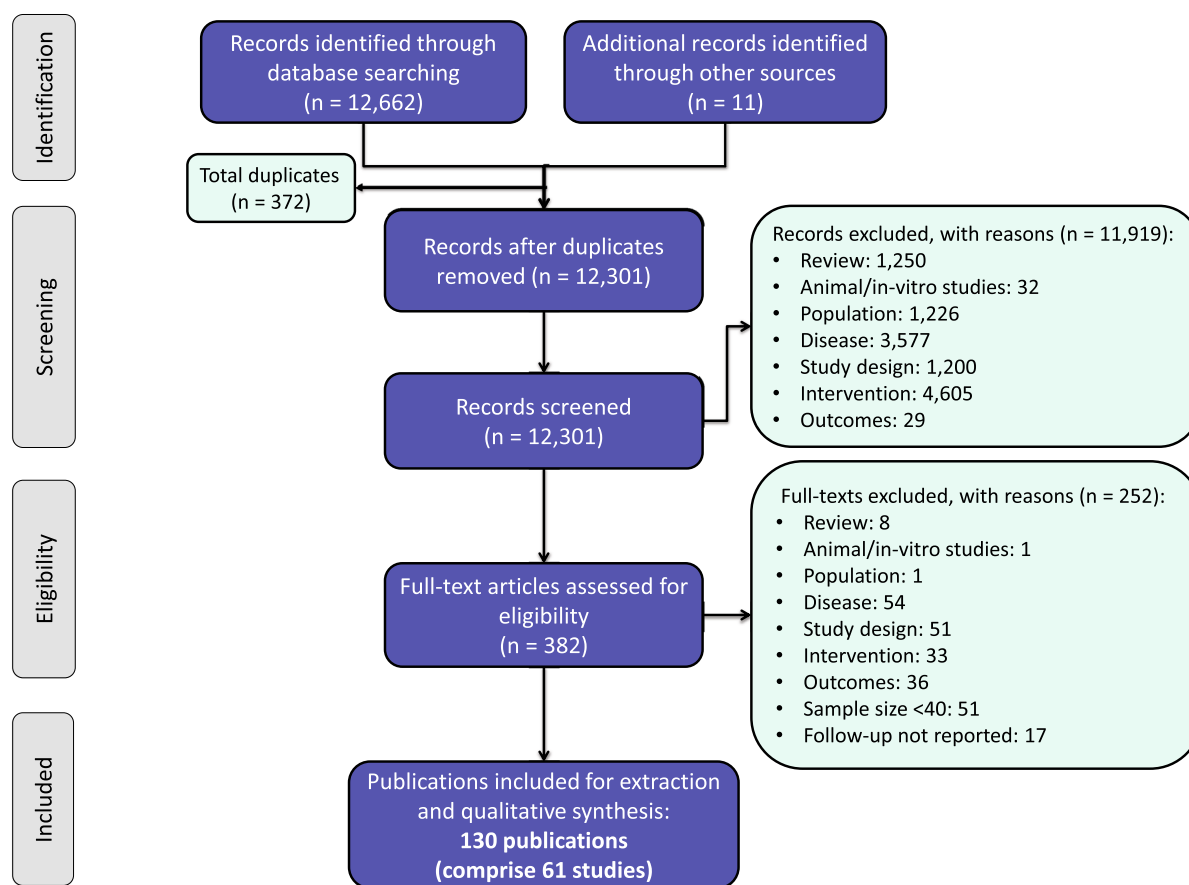


Fig. 1 PRISMA flow diagram for included studies. Because a given study may be reported in more than one publication, we have defined a primary publication as the first full report of the primary outcomes of a study in a

peer-reviewed journal. Additional reports of secondary or exploratory objectives, or subgroup or post-hoc analyses are described as “secondary” or “linked” publications

Table 1 Summary characteristics of included studies according to intervention ($N = 61$)

Parameter	Details	Number of studies				
		OnabotulinumtoxinA	Erenumab	Multiple CGRP mAbs ^a	Topiramate	Total
Type of publication	Journal article	34	–	–	1	34
	Conference abstract	21	6	1	–	27
Study design	Prospective cohort	36	3	–	1	39
	Retrospective cohort	19	3	1	–	22
Sample size	< 100	24	3	1	1	27
	100–500	26	3	–	–	29
	> 500	4	–	–	–	4
	NR	1	–	–	–	1
Data source type	Primary data	36	3	–	1	39
	Medical records or databases	16	2	–	–	18
	Survey	2	–	1	–	2
	Registry	1	–	–	–	1
	NR	–	1	–	–	1
Follow-up duration	1–3 months	7	3	–	1	10
	> 3–6 months	6	3	–	–	9
	> 6–12 months	16	–	1	–	16
	> 12–24 months	14	–	–	–	14
	> 24 months	12	–	–	–	12
Study outcomes	Effectiveness	55	6	1	1	61
	Safety (TRAEs)	6	–	–	–	6
Country	Europe	40	2	–	–	42
	Italy	16	1	–	–	17
	UK	6	–	–	–	6
	Turkey	2	–	–	–	2
	Germany	–	1	–	–	1
	Spain	14	–	–	–	14
	France	1	–	–	–	1

Table 1 continued

Parameter	Details	Number of studies				
		OnabotulinumtoxinA	Erenumab	Multiple CGRP mAbs ^a	Topiramate	Total
	Russia	1	–	–	1	1
	North/South America	9	3	1	–	12
	USA	7	2	1	–	9
	Canada	1	1	–	–	2
	Colombia	1	–	–	–	1
	Asia	2	–	–	–	2
	Korea	1	–	–	–	1
	Taiwan	1	–	–	–	1
	Australia	1	1	–	–	2
	Multiple countries	2	–	–	–	2
	NR	1	–	–	–	1

A study assessing more than one treatment has been counted multiple times

CGRP calcitonin gene-related peptide, *mAbs* monoclonal antibodies, *NR* not reported, *TRAE* treatment-related adverse event

^aIncludes erenumab, galcanezumab, and fremanezumab

abstracts only were not eligible for quality assessment (Table 2).

Among the 61 studies, most ($n = 55$) assessed the effectiveness or safety of onabotulinumtoxinA. Other studies assessed erenumab ($n = 6$), multiple CGRP mAbs ($n = 1$), and topiramate ($n = 1$). No studies assessing the effectiveness or safety of flunarizine, sodium valproate, acetylsalicylic acid, amitriptyline, or any other toxin were identified.

Thirty-nine studies directly assessed patients in hospitals or clinics (primary data), while data were taken from medical records or databases in 18 studies. Other data sources included surveys ($n = 2$) and registries ($n = 1$). Duration of follow-up across included studies ranged from 1 month [18, 19] to 8 years (Hull Migraine study [20]). Forty-two studies were conducted in Europe, 12 in North America, two in Asia, two in Australia, and two were conducted across multiple countries. The country where the study was conducted was not reported in one case. All the included studies reported effectiveness of the

assessed intervention, while TRAEs were reported in only six studies.

Patient Characteristics

Patient characteristics are summarized in Table 3. The mean or median age of participating patients was reported in 43 studies, and ranged from 39.3 years [21] to 54.0 years [22]. Among the 43 studies that reported sex, most patients (71.0% [16] to 97.9% [23]) were female. The mean/median disorder duration ranged from 1.5 years [23] to 33.6 years [24].

The most commonly reported comorbidities among the nine studies with relevant data were anxiety and depression. The proportion of patients receiving prior preventive treatment ranged from 21.0% [25] to 93.0% [26]. Although prior use of preventive medications was reported in 37 studies, no studies were conducted in a purely treatment-naïve population, and no studies conducted subgroup analyses

Table 2 Summary of quality ratings assigned to each study by preventive treatment assessed

Treatment/comparator	Quality rating ^a						Total
	4	5	6	7	8	NA ^b	
CGRP	–	–	–	–	–	1	1
Erenumab	–	–	–	–	–	6	6
OnabotA	6	15	8	4	1	21	55
Topiramate	–	1	–	–	–	–	1
Total	6	15	8	4	1	27	61

CGRP calcitonin gene-related peptide, *OnabotA* onabotulinumtoxinA, NA not applicable

^aStudies were graded from 0 (poorest quality) to 9 (highest quality) using the Newcastle–Ottawa scale for cohort studies or case–control studies, respectively. Please see Supplementary file S5

^bThe 27 included conference abstracts were not eligible for quality assessment

comparing effectiveness or safety outcomes among treatment-naïve patients and those with prior preventive treatment failures. Table 4 provides studies by treatment and prior preventive treatment status.

Effectiveness Outcomes

Effectiveness outcomes assessed in the included studies are summarized in Table 5. The outcomes most commonly assessed were response rate (reduction in headache or migraine days), monthly headache or migraine days, concomitant acute medications used, and Headache Impact Test-6 (HIT-6 score).

Response Rates

Response rates were defined as the reduction in the number of headache or migraine days over a specified time period. The definition of headache day varied across studies, but for the purposes of this study was defined as any day with a headache lasting at least 30 min. A migraine day was defined as any day with headache with migraine features such as photophobia, phonophobia, nausea, vomiting, or worsening with physical activity. Response rates were quantified according to the proportion of patients with ≥ 30% (16 studies), ≥ 50% (30 studies), or ≥ 75% (six studies) reduction in headache or migraine days from baseline at different time points.

Thirty-six studies reported data for response rates. Substantially more data on response rates were available for onabotulinumtoxinA (*n* = 32 studies), compared with erenumab (four studies) and multiple CGRP mAbs (one study). Follow-up data beyond 1 year were available for onabotulinumtoxinA only (up to 4 years), with 1-year data available for multiple CGRP mAbs and 6-month data available for erenumab.

Response rate data across all included studies are summarized in Table 6. All studies reported a reduction in number of headache or migraine days, irrespective of treatment used, at all time points. One comparative study reported as an abstract only [16] reported a higher proportion of patients with ≥ 50% reduction in migraine days at 1 year with multiple CGRP mAbs than

Table 3 Patient characteristics from the included studies

Study name	Treatment	Sample size	Prior treatment status	Age (years), mean SD/ range	Age (years) of CM onset, mean SD	Female, n (%)	CM duration (years), mean SD	Comorbid conditions, n (%)
Hull Migraine study[20]	OnabotA	851	Previously treated	45.0 ^a (14.0–96.0)	–	693 (81.4)	4.0 ^a (0.5–67.0)	–
REPOSE[31]	OnabotA	633	Previously treated	45.4 (11.7)	–	540 (85.3)	5.6 (8.0)	–
Aicua-Rapun (2016) [26]	OnabotA	115	Previously treated	45.3 (12.0)	–	98 (85.2)	–	–
Alessiani (2018) [32]	OnabotA	54	Unknown	–	–	–	–	–
Alpuente (2019) [33]	OnabotA	NR	Unknown	–	–	–	–	–
Andreou (2018) [34]	OnabotA	200	Previously treated	46.0 (11.9)	–	158 (79.0)	5.9 (5.0)	–
Aydinlar (2017) [21]	OnabotA	190	Previously treated	39.3 (10.2)	–	167 (87.9)	–	–
Barad (2019) [35]	OnabotA	402	Previously treated	47.0 ^a (16.0–102.0)	–	332 (82.6)	–	–
Barbanti (2019) [36]	ERE	97	Previously treated	46.8 (10.4)	–	78 (80.4)	29.6 (12.0)	–
Belvis (2018) [37]	OnabotA	90	Unknown	–	–	–	–	–
PREDICT [38]	OnabotA	196	OnabotA –naïve	–	–	–	–	–
Boudreau (2019) [39]	ERE	158	Previously treated	–	–	–	–	–

Table 3 continued

Study name	Treatment	Sample size	Prior treatment status	Age (years), mean SD/ range	Age (years) of CM onset, mean SD	Female, n (%)	CM duration (years), mean SD	Comorbid conditions, n (%)
Burch (2016) [4]	OnabotA	50	Unknown	48.7	-	44 (88.0)	-	-
Burera (2016) [40]	OnabotA	44	Previously treated	50.0 (22.0–76.0)	-	37 (82.2)	14.0 (range: 1.0–32.0)	-
Caronna (2018) [41]	OnabotA	139	Previously treated	47.3 (11.4)	-	115 (82.7)	9.3 (9.0)	Anxiety: 96 (69.1); Depression: 62 (44.9); Fibromyalgia: 24 (17.4)
Cernuda-Morollón (2015) [42]	OnabotA	132	Previously treated	46.3 (12.3)	-	119 (90.2)	10.5 (8.4)	Depression: 61 (46.2); Fibromyalgia: 17 (12.9); Hypertension: 19 (14.4)
Cesaretti (2015) [43]	OnabotA	132	Previously treated	52.0 (23.0–82.0)	-	64 (84.2)	-	-
Ching (2019) [44]	OnabotA	131	Previously treated	42.8 (11.5)	-	111 (84.7)	-	-
Corbelli (2019) [45]	OnabotA	195	Unknown	-	-	160 (82.1)	-	-
de Tommaso (2019) [46]	OnabotA	99	Previously treated	46.1 (13.7)	-	85 (85.9)	-	-
Domínguez (2018a) [47]	OnabotA	725	Previously treated	46.8 (12.0)	-	622 (85.8)	20.4 (18.7)	Depression: 250 (34.5); fibromyalgia: 94 (13.0); any comorbidities ^b : 231 (31.9)
Domínguez (2018b) [23]	OnabotA (Responders)	47	Previously treated	39.4 (12.0)	-	46 (97.9)	1.5 (1.0)	-
	OnabotA (Non-responders)	15		51.6 (9.1)	-	14 (93.9)	1.8 (1.3)	-

Table 3 continued

Study name	Treatment	Sample size	Prior treatment status	Age (years), mean SD/ range	Age (years) of CM onset, mean SD	Female, n (%)	CM duration (years), mean SD	Comorbid conditions, n (%)
Evangelista (2017) [48]	OnabotA	127	Unknown	49.9 (10.8)	–	106 (83.5)	–	–
Favoni (2019) [49]	OnabotA	267	Previously treated	–	–	–	13.0 (11.0)	–
Flood (2017) [22]	OnabotA	463	Unknown	54.0 ^a (IQR: 47.0–59.0)	–	370 (80.0)	–	–
Forbes (2015) [50]	OnabotA	83	Unknown	–	–	–	–	–
García-Azorín (2018) [18]	OnabotA	49	Unknown	43.8	–	45 (91.8)	3.2	–
Gomez-Galvan (2016) [51]	OnabotA	79	Unknown	–	–	–	–	–
Gonzalez-Martinez (2020) [52]	OnabotA	112	Previously treated	43.0 (11.0)	43.3 (11.1)	100 (89.3)	2.4 (3.5)	Anxiety: 66 (58.9)
Grazzi (2015) [53]	OnabotA	66	Unknown	–	–	–	–	–
Grazzi (2016) [54]	OnabotA	53	Unknown	–	–	–	–	–
Guerzoni (2017) [29]	OnabotA	90	Previously treated	45.2 (10.1)	–	76 (84.4)	–	–
Jenkins (2019) [55]	ERE	109	Previously treated	46.4 (18.0–73.0)	–	–	–	–

Table 3 continued

Study name	Treatment	Sample size	Prior treatment status	Age (years), mean SD/ range	Age (years) of CM onset, mean SD	Female, <i>n</i> (%)	CM duration (years), mean SD	Comorbid conditions, <i>n</i> (%)
Jimenez Sanders (2015) [56]	OnabotA	64	Unknown	-	-	-	-	-
Kennedy (2017) [57]	OnabotA	120	Unknown	-	-	-	-	-
Lambru (2016) [58]	OnabotA	178	Unknown	46.0 (12.0)	-	141 (79.2)	-	-
Lee (2016) [19]	OnabotA	70	Previously treated	48.0 (13.6)	-	60 (85.7)	-	Anxiety: 6 (8.5); depression: 10 (14.2); any comorbidities ^b : 4 (5.7)
Lin (2014) [59]	OnabotA	94	Previously treated	47.6 (13.6)	-	79 (84.0)	8.1 (8.3)	-
Maasumi (2015) [60]	OnabotA	359	Unknown	45.1 (13.2)	-	309 (86.1)	-	-
Matharu (2017) [17]	OnabotA (overall)	1160	Both	46.6 (11.8)	-	977 (84.2)	-	-
Naegel (2019) [61]	ERE	79	Previously treated	-	-	-	-	-
Naprienko (2020) [27]	OnabotA	24	Unknown	-	-	-	-	-
Navarrete Perez (2017) [62]	TPM OnabotA	22 117	Unknown	41.0 (11.7)	-	102 (87.2)	-	-
Negro (2016) [28]	OnabotA (195 U)	143	Previously treated	44.9 (12.7)	-	114 (79.7)	9.3 (5.1)	-

Table 3 continued

Study name	Treatment	Sample size	Prior treatment status	Age (years), mean SD/ range	Age (years) of CM onset, mean SD	Female, n (%)	CM duration (years), mean SD	Comorbid conditions, n (%)
	OnabotA (155 U)	132		43.2 (13.5)	–	108 (81.8)	10.2 (4.8)	–
	TPM (IR)	8596		–	–	–	–	–
Pedraza (2015) [63]	OnabotA	52	Previously treated	42.8 (12.7)	–	44 (84.6)	–	–
Ramirez (2013) [64]	OnabotA	190	Unknown	45.2 (9.0–93.0)	26.3 (range: 3.0–72.0)	–	–	–
Ranoux (2017) [65]	OnabotA	63	Previously treated	44.3 (17.0–72.0)	–	43 (75.4)	–	–
Robbins (2019) [66]	ERE	220	Unknown	–	–	–	–	–
Robblee (2019) [67]	ERE	94	Previously treated	49.0	–	82 (87.2)	–	Anxiety: (44.7); depression: (45.7); fibromyalgia: (12.8)
Russo (2016) [24]	OnabotA	52	Previously treated	48.7 (12.9)	38.2 (12.1)	46 (88.5)	9.9 (7.6)	–
Santoro (2015) [68]	OnabotA	113	Unknown	48.0	–	86 (76.0)	–	–
Santoro (2020) [69]	OnabotA	109	Previously treated	48.1 (13.5)	–	82 (75.2)	11.7 (9.8)	–
Sanz (2018) [70]	OnabotA	69	Previously treated	43.2 (15.2)	–	61 (88.4)	–	Anxiety and depression: 14 (20.3)
Sarchielli (2017) [71]	OnabotA	56	Previously treated	45.7 (6.5)	–	47 (83.9)	7.9 (4.3)	–

Table 3 continued

Study name	Treatment	Sample size	Prior treatment status	Age (years), mean SD/ range	Age (years) of CM onset, mean SD	Female, n (%)	CM duration (years), mean SD	Comorbid conditions, n (%)
Schiano di Cola (2019) [25]	OnabotA	84	Previously treated	48.0 (9.7)	–	61 (72.6)	10.1 (6.6)	Anxiety: 44 (60.0); depression: 36 (45.0)
Stark (2019) [72]	OnabotA	211	Previously treated	44.6 (12.5)	–	187 (88.6)	14.5 (12.3)	Anxiety: 17 (8.0); depression: 23 (11.0)
Susie (2018) [73]	OnabotA	100	Previously treated	–	–	–	–	–
Taddei-Allen (2019) [16]	Multiple CGRP mAbs ^d	21	Unknown	47.0	–	15 (71.0)	–	–
Velasco-Juanes (2018) [74]	OnabotA	21	–	47.0	–	19 (90.0)	–	–
Vernieri (2019) [75]	OnabotA	70	Previously treated	48.9 (12.4)	38.8 (14.0)	61 (87.1)	–	–
Yalinay Dikmen (2018) [76]	OnabotA	115	Previously treated	–	–	95 (82.6)	–	–
	OnabotA	180	Previously treated	40.4 (10.5)	–	159 (88.3)	–	–

CGRP calcitonin gene-related peptide, CM chronic migraine, ERE erenumab, IR immediate-release, mAb monoclonal antibody, OnabotA onabotulinumtoxinA, SD standard deviation, TPM topiramate

^aMedian value reported

^bAny comorbidities include hypertension, heart disease, gastrointestinal disease, lung disease, and skin disturbances

^cAny comorbidities include hypo- and hyperthyroidism

^dMultiple CGRP mAbs: erenumab, galcanezumab, fremanezumab

Table 4 Distribution of studies by treatment for prior preventive treatment status

Intervention	Treatment naïve	Previously treated	Failed preventive treatment				Both	Unknown	Total
			≥ 1	≥ 2	≥ 3	NR			
OnabotulinumtoxinA	–	32	4	11	10	7	1	22	55
CGRP antagonist	–	5	–	–	5	–	–	2	7
Erenumab	–	5	–	–	5	–	–	1	6
Multiple ^a	–	–	–	–	–	–	–	1	1
Topiramate	–	–	–	–	–	–	–	1	1
Total	0	37	4	11	15	7	1	23	61

A study assessing more than one treatment has been counted multiple times

CGRP calcitonin gene-related peptide, *NR* studies where number of failed preventive treatments is not reported

Includes erenumab, galcanezumab, and fremanezumab

with onabotulinumtoxinA (62.0% versus 52.0%); although this difference was not statistically significant (quality rating N/A).

Detailed summaries of response rates across included studies are presented in Supplementary file S7.

Monthly Headache or Monthly Migraine Days

Monthly headache days were defined as the number of days in any given month on which a headache lasting at least 30 min was reported. Monthly migraine days were defined as the number of days in any given month on which a headache with migraine features such as photophobia, phonophobia, nausea, vomiting, or worsening with physical activity was reported.

Thirty-eight studies reported data for monthly headache or migraine days. Most studies ($n = 34$) assessed onabotulinumtoxinA and four assessed erenumab, while one study assessed monthly headache days in topiramate compared with onabotulinumtoxinA, and one study assessed monthly migraine days in multiple CGRP mAbs (erenumab, galcanezumab, and fremanezumab) in comparison with onabotulinumtoxinA. At up to 5 years, onabotulinumtoxinA had the longest follow-up data on monthly headache or monthly migraine days, compared with 6 months for erenumab, 12 months for multiple CGRP mAbs, and 3 months for topiramate.

Mean/median monthly headache days and monthly migraine days, and change from baseline, at different time points across included studies are summarized in Table 7. The reduction from baseline in monthly headache days and monthly migraine days at all time points was statistically significant with all interventions. A single study [27] comparing onabotulinumtoxinA with topiramate (NOS quality rating, 5/9) reported that patients treated with onabotulinumtoxinA had significantly fewer monthly headache days compared with topiramate at 3 months (13.8 days versus 14.9 days, $p < 0.05$).

Detailed summaries of monthly headache and migraine days across included studies are presented in Supplementary file S8.

Concomitant Acute Medication Use

Concomitant acute medication use was defined as the usage of opioid and non-opioid analgesics for acute relief of migraine during the study period.

Twenty-six studies reported data for concomitant acute medication use. A large majority ($n = 24$) assessed onabotulinumtoxinA, and only two assessed erenumab. OnabotulinumtoxinA had the longest follow-up data on concomitant medication use (5 years), compared with 3 months for erenumab. No comparative

Table 5 Outcomes among the included studies by intervention in chronic migraine patients

	OnabotulinumtoxinA	Erenumab	Multiple CGRP mAbs ^a	Topiramate	Total
Any effectiveness outcomes	55	6	1	1	61
Response rate (headache or migraine days)	33	4	1	–	37
Monthly headache or migraine days	34	4	1	1	38
Overall frequency of moderate or severe headache days	6	–	–	–	6
Headache severity/intensity	9	1	–	–	10
Migraine severity/intensity	1	1	1	–	2
Headache duration	–	–	–	–	0
Migraine duration	1	–	1	–	1
Concomitant acute medication use	24	2	–	1	26
Concomitant preventive medication use	5	–	–	–	5
Overall HIT-6 score	15	2	1	1	17
Overall MSQ score	2	–	–	–	2
Overall MIDAS score	14	1	–	–	15
Overall EQ-5D score	1	–	–	–	1
SF-36 score	1	–	–	–	1
Overall comorbid anxiety or depression	4	–	–	–	4
Sleep quality	2	–	–	–	2
Adherence	–	–	–	–	0
Persistence	1	–	–	–	1
Patient satisfaction with treatment	4	–	–	1	4
Total ^b	55	6	1	1	61

CGRP calcitonin gene-related peptide, EQ-5D EuroQol 5-Dimension Questionnaire, HIT-6 Headache Impact Test-6, mAb monoclonal antibody, MIDAS Migraine Disability Assessment, MSQ Migraine-Specific Quality of Life, SF-36 Short-form-36

^aMultiple CGRP mAbs: erenumab, galcanezumab, and fremanezumab

^bThe sum of studies exceeds 61 because a few studies that assessed the impact of two different interventions or more than one outcome are counted more than once

studies were identified for concomitant acute medication use.

Mean/median days per month with concomitant acute medication use and change from baseline at different time points among

the included studies are summarized in Table 8. Reduction in concomitant acute medication use from baseline was statistically significant at all time points in most studies.

Table 6 Summary of reductions in headache days or migraine days (proportion of patients) from baseline across included studies

Time point	Reduction in headache or migraine days			
	≥ 30% reduction		≥ 50% reduction	
	OnabotulinumtoxinA (16 studies)	OnabotulinumtoxinA (26 studies)	Erenumab (4 studies)	Multiple CGRP mAbs (1 study)
3 months	12.5–62.0%	42.9–85.6%	35.5–87.5%	–
6 months	11.0–80.2%	17.4–85.7%	31.8–47.6%	–
1 year	8.7–92.9%	14.3–81.8%	–	62.0%
2 years	85.4–94.7%	11.1–96.3%	–	–
3 years	70–100.0%	7.7–100.0%	–	–
4 years	100%	45.5–100.0%	–	–
				OnabotulinumtoxinA (6 studies)
				≥ 75% reduction
				14.2–24.0%
				17.7–36.6%
				27.3–44.0%
				47.4%
				51.9%
				50.0%

CGRP calcitonin gene-related peptide, mAb monoclonal antibody

Detailed summaries of acute medication use across included studies are presented in Supplementary file S9.

Headache Impact Test-6 (HIT-6) Score

HIT-6 score evaluates the effects of headache on general patient well-being and daily activity. The score ranges from 36 to 78, with a higher score indicating a lower level of general well-being and daily activity. The four headache impact severity categories are little or no impact (49 or less), some impact (50–55), substantial impact (56–59), and severe impact (60–78).

Eighteen studies reported data for HIT-6 scores. Of these, 16 assessed onabotulinumtoxinA, two assessed erenumab, and one study each assessed multiple CGRP mAbs and topiramate (in comparison with onabotulinumtoxinA). At up to 3 years, onabotulinumtoxinA had the longest follow-up data on monthly headache or monthly migraine days, compared with 3 months for erenumab, 12 months for multiple CGRP mAbs, and 3 months for topiramate.

Mean/median HIT-6 scores and change from baseline at different time points across the included studies are summarized in Table 9. Reduction in HIT-6 score from baseline was statistically significant at all time points for all interventions. The single study comparing onabotulinumtoxinA with topiramate (NOS quality rating, 5/9) reported that patients treated with onabotulinumtoxinA had a significantly lower score on the HIT-6 scale compared with topiramate at 3 months (39.5 versus 43.2; $p < 0.05$) [27]. The abstract comparing onabotulinumtoxinA and multiple CGRP mAbs (NOS quality rating, N/A) showed that 35.0% of those treated with onabotulinumtoxinA and 44.0% of those treated with multiple CGRP mAbs experienced at least one severity class improvement according to HIT-6 score at 1 year; this difference was not significant [16].

Detailed summaries of HIT-6 score use across included studies are presented in Supplementary file S10.

Table 7 Mean/median monthly headache or migraine days and change from baseline across included studies

	Monthly headache or migraine days (change from baseline)			
	OnabotulinumtoxinA	Erenumab	Topiramate	Multiple CGRP mAbs ^a
Baseline	12.9–27.0	14.2–24.1	23.1	16.0
1 month (change from baseline)	7.0–18.0 (–6.0 to –8.9)	10.6 (–11.6)	16.1 (NR)	–
3 months (change from baseline)	5.0–23.3 (–9.4 to –1.1)	7.1–16.6 (–14.5)	14.9 (NR)	–
6 months (change from baseline)	3.9–19.6 (–2.0 to –14.7)	18.4 (–6.8 to –7.4)	–	–
1 year (change from baseline)	4.3–17.4 (–10.0 to –11.7)	–	–	8.0 (NR)
2 years (change from baseline)	1.1–15.3 (–10.7 to –13.1)	–	–	–
≥ 3 years (change from baseline)	6.1–7.7 (NR)	–	–	–

CGRP calcitonin gene-related peptide, *mAb* monoclonal antibody, NR not reported

^aIncludes erenumab, galcanezumab, and fremanezumab

Table 8 Mean/median days per month with concomitant acute medication use and change from baseline across included studies

	OnabotulinumtoxinA	Erenumab
Baseline	9.0–21.0	11.2–23.6
1 month (change from baseline)	–	9.9 (–15.8)
3 months (change from baseline)	5.3–17.4 (NR)	7.0–7.1 (–15.4)
6 months (change from baseline)	5.0–15.0 (–2.0 to –11.5)	–
1 year (change from baseline)	4.7–16.4 (–4.0 to –12.7)	–
2 years (change from baseline)	3.4–5.3 (NR)	–
≥ 3 years (change from baseline)	2.8 (NR)	–

NR not reported

Safety Outcomes (TRAEs)

Six studies reported data on TRAEs. The duration of these studies ranged from 10 to 36 months, and all evaluated patients were treated with onabotulinumtoxinA.

In four studies with a follow-up of 1 year, the proportion of patients experiencing at least one

TRAE ranged from 0% to 25.1%. One study with a follow-up of 2 years (NOS quality rating, 6/9) reported that 17.5–20.3% of patients experienced at least one TRAE [28], and one study with a follow-up of 3 years (NOS quality rating, 5/9) reported at least one TRAE in 20% of patients [29].

Table 9 Mean/median HIT-6 scores and change from baseline across included studies

	OnabotulinumtoxinA	Erenumab	Topiramate
Baseline	61.2–72.1	66.0–69.2	62.0
3 months (change from baseline)	39.5–72.4 (–15.8)	57.0–58.0 (–12.8)	43.2 (NR)
6 months (change from baseline)	56.4–66.2 (–1.8 to –11.7)	–	–
1 year (change from baseline)	54.6–60.5 (–5.0 to –5.4)	–	–
2 years (change from baseline)	49.0–57.9 (NR)	–	–
3 years (change from baseline)	57.2–62.8 (NR)	–	–

NR not reported

DISCUSSION

This SLR summarizes the real-world evidence available on the effectiveness and safety of preventive treatments for CM in adults. Data were retrieved for onabotulinumtoxinA, CGRP mAbs (erenumab, galcanezumab, and fremanezumab), and topiramate. No studies reporting the effectiveness or safety of flunarizine, sodium valproate, acetylsalicylic acid, amitriptyline, or any other toxin in the preventive treatment of CM were identified within the parameters of this review.

The overwhelming majority of real-world data was reported on onabotulinumtoxinA, with 55 published studies identified. Six studies reported on erenumab, one study reported on multiple CGRP mAbs (erenumab, galcanezumab, and fremanezumab), and one study reported on topiramate. Long-term data (up to 8 years) were available for onabotulinumtoxinA only, with data for multiple CGRP mAbs up to 12 months, erenumab reported up to 6 months, and topiramate up to 3 months. The greater availability of onabotulinumtoxinA data is probably because onabotulinumtoxinA has been approved for CM treatment since 2010, while the data for other interventions are limited due to their more recent approval.

A considerable body of evidence demonstrates that onabotulinumtoxinA is effective in reducing both the number and frequency of headaches among adults with CM, and also

reduces the need for use of concomitant acute medication. In addition, numerous studies reported a reduced impact of headache on patient well-being and daily activity, as assessed by the HIT-6 score. Up to 25% of patients receiving onabotulinumtoxinA in the included studies experienced at least one TRAE, but no new long-term safety concerns were identified.

Similarly, erenumab was also shown to reduce the number and frequency of headaches and concomitant acute medication use, and to decrease the impact of headaches on well-being and daily activity. Single studies suggested topiramate and multiple CGRP mAbs decrease the number/frequency of headaches and impact of headaches. To date, onabotulinumtoxinA is the only preventive treatment for CM that has long-term safety data reporting TRAEs of up to 3 years.

Owing to the lack of high-quality comparative real-world studies, it is not possible to comment on the relative effectiveness of the treatments included in this review. However, the availability of a considerable body of real-world data from a large patient population, encompassing different patient nationalities, ages, comorbidities, and previous prior preventive treatments, provides consistent and predictable evidence for the benefits of onabotulinumtoxinA as a preventive treatment for CM. This body of evidence, as also described in a recently published meta-analysis [30],

supports the effectiveness and safety of this approach in the management of CM.

Although this was a comprehensive SLR conducted according to PRISMA guidelines, a number of limitations should be highlighted. The paucity of data identified for treatments other than onabotulinumtoxinA is a significant limitation, precluding any robust analysis of alternative treatments. Comparisons across treatments are also difficult to establish given the lack of data for treatments other than onabotulinumtoxinA, and because only one publication and one abstract (NOS quality rating 5/9 and N/A, respectively) included a direct comparison of two or more interventions. It is also important to note that the patient populations included across studies are inevitably heterogeneous, and any comparisons of data across multiple studies should therefore be interpreted with caution.

Since the regulatory approval of the CGRP monoclonal antibodies in 2018, numerous additional studies are now being published on these treatments. These publications are not included in this analysis as, for practical considerations, a cut-off date for data collection needed to be established prior to drafting the manuscript. Future analyses will be considered to include more recently approved interventions.

CONCLUSIONS

This SLR identified substantial evidence from real-world studies for onabotulinumtoxinA in the preventive treatment of CM. The review suggests that treatment with onabotulinumtoxinA has a beneficial effect across a broad range of patients in real-world clinical studies on the number and frequency of headache or migraine days, concomitant medication use, and HIT-6. Additionally, no new safety concerns were observed with long-term use. Real-world data were available from conference abstracts only for erenumab and multiple CGRP mAbs (erenumab, galcanezumab, and fremanezumab), and one journal article on topiramate. Although the data in these treatments are more limited, there is some evidence of the

effectiveness of these approaches in the real world.

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Compliance with Ethics Guidelines. This article is based on previously conducted studies and does not contain any new studies with human participants or animals performed by any of the authors.

Data Availability. AbbVie is committed to responsible data sharing regarding the clinical trials we sponsor. This includes access to anonymized, individual and trial-level data (analysis data sets), as well as other information (e.g., protocols, clinical study reports, or analysis plans), as long as the trials are not part of an ongoing or planned regulatory submission. This includes requests for clinical trial data for unlicensed products and indications. These clinical trial data can be requested by any qualified researchers who engage in rigorous, independent scientific research, and will be provided following review and approval of a research proposal and Statistical Analysis Plan (SAP), and execution of a Data Sharing Agreement (DSA). Data requests can be submitted at any time after approval in the US and Europe and after acceptance of this manuscript for publication. The data will be accessible for 12 months, with possible extensions considered. For more information on the process, or to submit a request, visit the following link: <https://www.abbvie.com/our-science/clinical-trials/clinical-trials-data-and-information-sharing/data-and-information-sharing-with-qualified-researchers.html>.

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