Gemeinsamer Bundesausschuss

Kriterien zur Bestimmung der zweckmäßigen Vergleichstherapie

und

Recherche und Synopse der Evidenz zur Bestimmung der zweckmäßigen Vergleichstherapie nach § 35a SGB V

und

Schriftliche Beteiligung der wissenschaftlich-medizinischen Fachgesellschaften und der Arzneimittelkommission der deutschen Ärzteschaft (AkdÄ) zur Bestimmung der zweckmäßigen Vergleichstherapie nach § 35a SGB V

Vorgang: 2024-B-024 Atogepant

Stand: April 2024

I. Zweckmäßige Vergleichstherapie: Kriterien gemäß 5. Kapitel § 6 VerfO G-BA

Atogepant [Migräneprophylaxe] **Kriterien gemäß 5. Kapitel § 6 VerfO**	
Sofern als Vergleichstherapie eine Arzneimittelanwendung in Betracht kommt, muss das Arzneimittel grundsätzlich eine Zulassung für das Anwendungsgebiet haben.	Siehe Übersicht „II. Zugelassene Arzneimittel im Anwendungsgebiet“.
Sofern als Vergleichstherapie eine nicht-medikamentöse Behandlung in Betracht kommt, muss diese im Rahmen der GKV erbringbar sein.	nicht angezeigt
Beschlüsse/Bewertungen/Empfehlungen des Gemeinsamen Bundesausschusses zu im Anwendungsgebiet zugelassenen Arzneimitteln/nicht-medikamentösen Behandlungen	<u>Beschlüsse über die frühe Nutzenbewertung nach § 35a SGB V:</u> - Erenumab (Beschlüsse vom 02. Mai 2019 und 21. Oktober 2021) - Galcanezumab (Beschluss vom 19. September 2019) - Fremanezumab (Beschluss vom 07. November 2019) - Eptinezumab (Beschluss vom 16. Februar 2023)
Die Vergleichstherapie soll nach dem allgemein anerkannten Stand der medizinischen Erkenntnisse zur zweckmäßigen Therapie im Anwendungsgebiet gehören.	Siehe systematische Literaturrecherche

II. Zugelassene Arzneimittel im Anwendungsgebiet

Wirkstoff **ATC-Code** **Handelsname**	**Anwendungsgebiet** (Text aus Fachinformation)
Zu bewertendes Arzneimittel:	
Atogepant Aquipta N02CD07	<u>Anwendungsgebiet laut Zulassung:</u> AQUIPTA wird angewendet zur Prophylaxe von Migräne bei Erwachsenen mit mindestens 4 Migränetagen pro Monat.
Konventionelle Prophylaktika/Therapeutika	
Metoprolol C07AB02 Beloc-ZOK®	Erwachsene: – Migräneprophylaxe
Propranolol C07AA05 Dociton®	– Migräneprophylaxe
Flunarizin N07CA03 Natil®-N	Zur Prophylaxe bei diagnostisch abgeklärter Migräne mit oder ohne Aura bei Patienten mit häufigen und/oder schweren Migräneanfällen.
Topiramat N03AX11 Topamax®	Topiramat ist indiziert bei Erwachsenen zur Prophylaxe von Migräne-Kopfschmerzen nach sorgfältiger Abwägung möglicher alternativer Behandlungsmethoden. Topiramat ist nicht vorgesehen für die Akutbehandlung.
Clostridium botulinum Toxin Typ A M03AX01 BOTOX®	Linderung der Symptome bei erwachsenen Patienten, die die Kriterien einer chronischen Migräne erfüllen (Kopfschmerzen an ≥ 15 Tagen pro Monat, davon mindestens 8 Tage mit Migräne) und die auf prophylaktische Migräne-Medikation nur unzureichend angesprochen oder diese nicht vertragen haben (siehe Abschnitt 4.4 der Fachinformation).
Amitriptylin	– zur prophylaktischen Behandlung von Migräne bei Erwachsenen.

II. Zugelassene Arzneimittel im Anwendungsgebiet	
N06AA09 Saroten®	
Biologika	
Erenumab N02CD01 Aimovig® CGRP-Antagonist	Aimovig ist angezeigt zur Migräne-Prophylaxe bei Erwachsenen mit mindestens 4 Migränetagen pro Monat.
Galcanezumab N02CD02 Emgality® CGRP-Antagonist	Emgality ist angezeigt zur Migräne-Prophylaxe bei Erwachsenen mit mindestens 4 Migränetagen pro Monat.
Fremanezumab N02CD03 Ajovy® CGRP-Antagonist	AJOVY wird angewendet zur Migräneprophylaxe bei Erwachsenen mit mindestens 4 Migränetagen pro Monat.
Eptinezumab N02CD05 Vyepti® CGRP-Antagonist	VYEPTI wird angewendet zur Migräneprophylaxe bei Erwachsenen mit mindestens 4 Migränetagen pro Monat.

Quellen: AMIce-Datenbank, Fachinformationen

Gemeinsamer Bundesausschuss

Abteilung Fachberatung Medizin

Recherche und Synopse der Evidenz zur Bestimmung der zweckmäßigen Vergleichstherapie nach § 35a SGB V

Vorgang: 2024-B-024 (Atogepant)

Auftrag von:	Abt. AM
Bearbeitet von:	Abt. FB Med
Datum:	12. März 2024

Inhaltsverzeichnis

Abkürzungsverzeichnis

AE	Adverse event
ARB	angiotensin II receptor blockers
AWMF	Arbeitsgemeinschaft der wissenschaftlichen medizinischen Fachgesellschaften
BoNTA	botulinum toxin type A
CGRP	Calcitonin gene-related peptide
G-BA	Gemeinsamer Bundesausschuss
GIN	Guidelines International Network
GoR	Grade of Recommendations
HR	Hazard Ratio
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen
KI	Konfidenzintervall
LoE	Level of Evidence
mABs	monoclonal antibodies
MHD	monthly migraine headache days
MMDs	monthly migraine days
NICE	National Institute for Health and Care Excellence
NSAID	Nonsteroidal antiinflammatory drug
OR	Odds Ratio
RR	Relatives Risiko
SIGN	Scottish Intercollegiate Guidelines Network
TCA	tricyclic antidepressants
TPM	topiramate
TRIP	Turn Research into Practice Database
WHO	World Health Organization

1 Indikation

Präventive Behandlung von episodischer Migräne bei Erwachsenen mit mindestens 4 Migräneattacken pro Monat.

Hinweis zur Synopse: Informationen hinsichtlich nicht zugelassener Therapieoptionen sind über die vollumfängliche Darstellung der Leitlinienempfehlungen dargestellt.

2 Systematische Recherche

Es wurde eine systematische Literaturrecherche nach systematischen Reviews, Meta-Analysen und evidenzbasierten systematischen Leitlinien zur Indikation *Migräne* durchgeführt und nach PRISMA-S dokumentiert [A]. Die Recherchestrategie wurde vor der Ausführung anhand der PRESS-Checkliste begutachtet [B]. Es erfolgte eine Datenbankrecherche ohne Sprachrestriktion in: The Cochrane Library (Cochrane Database of Systematic Reviews), PubMed. Die Recherche nach grauer Literatur umfasste eine gezielte, iterative Handsuche auf den Internetseiten von Leitlinienorganisationen. Ergänzend wurde eine freie Internetsuche (*https://www.google.com/*) unter Verwendung des privaten Modus, nach aktuellen deutsch- und englischsprachigen Leitlinien durchgeführt.

Der Suchzeitraum wurde auf die letzten fünf Jahre eingeschränkt und die Recherche am 13.02.2024 abgeschlossen. Die detaillierte Darstellung der Recherchestrategie inkl. verwendeter Suchfilter sowie eine Angabe durchsuchter Leitlinienorganisationen ist am Ende der Synopse aufgeführt. Mit Hilfe von EndNote wurden Dubletten identifiziert und entfernt. Die Recherche ergab 1311 Referenzen.

In einem zweistufigen Screening wurden die Ergebnisse der Literaturrecherche bewertet. Im ersten Screening wurden auf Basis von Titel und Abstract nach Population, Intervention, Komparator und Publikationstyp nicht relevante Publikationen ausgeschlossen. Zudem wurde eine Sprachrestriktion auf deutsche und englische Referenzen vorgenommen. Im zweiten Screening wurden die im ersten Screening eingeschlossenen Publikationen als Volltexte gesichtet und auf ihre Relevanz und methodische Qualität geprüft. Dafür wurden dieselben Kriterien wie im ersten Screening sowie Kriterien zur methodischen Qualität der Evidenzquellen verwendet. Basierend darauf, wurden insgesamt 21 Referenzen eingeschlossen. Es erfolgte eine synoptische Darstellung wesentlicher Inhalte der identifizierten Referenzen.

3 Ergebnisse

3.1 Cochrane Reviews

Herd CP et al., 2019 [9].

Cochrane systematic review and meta-analysis of botulinum toxin for the prevention of migraine

Siehe auch: Shen B et al., 2020 [18]. Impact of the botulinum-A toxin on prevention of adult migraine disorders.

Zielsetzung

To assess the effects of botulinum toxins versus placebo or active treatment for the prevention or reduction in frequency of chronic or episodic migraine in adults.

Methodik

Population:

- 18 years of age and over, suffering from migraine as defined by any edition of the International Headache Society criteria (IHS 1988; IHS 2004; IHS 2013), or meeting reasonable criteria designed to distinguish between migraine and tension-type headache. People with both chronic and episodic migraine were included in this review.

Intervention:

- Injections of botulinum toxin (any sero-type) into head and neck muscles

Komparator:

- placebo injections, active preventative agent or the same drug treatment with a different dose. We also included trials allowing the use of concomitant preventative or rescue treatment.

Endpunkte:

Primärer Endpunkt:

- Number of migraine days per month (frequency with which exclusively migraine-type headaches are experienced).

Sekundäre Endpunkte:

- Number of headache days per month (frequency with which any type of headache inclusive of migraine headache are experienced).
- Number of migraine attacks per month (frequency with which exclusively migraine-type attacks are experienced).
- Headache intensity measures, usually reported as migraine 'severity', measured on verbal or numerical scale.
- Headache index, measured using headache intensity score multiplied by time spent with migraine.
- Duration of migraine (hours).
- Use of rescue medication (number of days on which rescue medication is used per month or number of instances of taking any type/dose of rescue medication per month).
- Patient and clinician global impression scales.

- Generic and disease-specific quality-of-life rating scales (e.g. Headache Impact Test, Migraine Specific Quality of Life).
- Cost effectiveness measured using incremental cost effectiveness ratio or cost per headache day avoided
- Adverse events

Recherche/Suchzeitraum:

- Cochrane Central Register of Controlled Trials (CENTRAL; 2017, Issue 12) via the Cochrane Register of Studies Online (CRSO), 7 December 2017; MEDLINE and MEDLINE in Process (via OVID) 1946 to 7 December 2017; Embase (via OVID) 2017 week 49.

Qualitätsbewertung der Studien:

- Cochrane Risk of Bias Tool

Ergebnisse

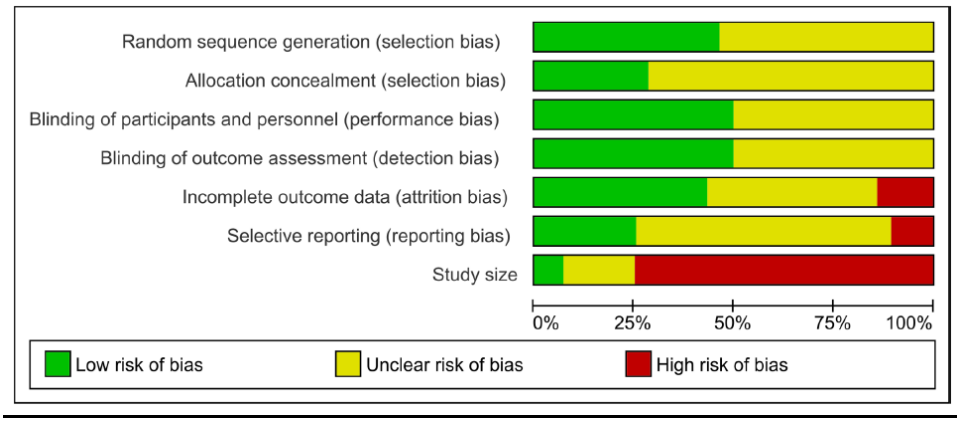
Anzahl eingeschlossener Studien:

- Anzahl eingeschlossene Studien/Patienten (Gesamt): N=28 (n = 4190)

Charakteristika der Population:

- average age of participants was 42 years;
- overall 85% (3491) of the trial participants were women;
- baseline disease characteristics were not well reported and were given in varying formats;
- the ratio of chronic to episodic migraine sufferers was not reported by six trials involving 390 participants; for the remaining trials, the overall ratio was 1872/1928;
- due to the inclusion of chronic and episodic migraine populations in this review, the frequency and severity of migraines in the trial populations, when reported, showed a wide variation between trials;
- three trials did not exclude people with medication overuse headache;
- one trial included only participants who were overusing acute medications; the remaining 11 trials did not consider medication overuse in their eligibility criteria

Qualität der Studien



Studienergebnisse:

Summary of findings for the main comparison. Botulinum toxin type A compared to placebo for the prevention of migraine in adults

Botulinum toxin type A compared to placebo for the prevention of migraine in adults

Patient or population: adults with migraine
Setting: outpatient clinic
Intervention: botulinum toxin type A
Comparison: placebo

Outcomes	Result with placebo	Result with botulinum toxin type A	Relative effect (95% CI)	№ of participants (trials)	Quality of the evidence (GRADE)
Number of migraine days per month: chronic migraine only	The mean number of migraine days (chronic migraine only) ranged from 12 to 20 days	MD 3.1 days lower (4.7 lower to 1.4 lower)	-	1497 (4 RCTs)	⊕⊖⊖⊖ Low[a,b]
Number of migraine days per month	The mean number of migraine days ranged from 4 to 20 days	MD 2.4 days lower (4.0 lower to 0.8 lower)	-	1915 (5 RCTs)	⊕⊖⊖⊖ Very low[a,b,c]
Number of headache days per month: chronic migraine only	The mean number of headache days (chronic migraine only) ranged from 13 to 13.4 days	MD 1.9 days lower (2.7 lower to 1.0 lower)	-	1384 (2 RCTs)	⊕⊕⊕⊕ High
Number of migraine attacks	The mean number of migraine attacks ranged from 1.9 to 7.8 attacks	MD 0.5 attacks lower (1.3 lower to 0.4 higher)	-	2004 (6 RCTs)	⊕⊕⊖⊖ Low[d,e]
Headache intensity measure (Visual Analogue Score 0-10)	The mean severity of migraine (Visual Analogue Score 0-10) ranged from 6.2 to 9.2 cm	MD 3.3 cm lower (4.2 lower to 2.5 lower)	-	209 (4 RCTs)	⊕⊖⊖⊖ Very low[f,g]
Global impression scale assessed with Headache Impact Test-6	The mean global impression scale was 58.6 points	MD 1.6 points higher (2.1 lower to 5.3 higher)	-	45 (1 RCT)	⊕⊖⊖⊖ Very low[f,g]
Total number of participants experiencing an adverse event	Trial population 471 per 1000	603 per 1000 (528 to 693)	RR 1.28 (1.12 to 1.47)	3325 (13 RCTs)	⊕⊕⊕⊖ Moderate[h]

CI: confidence interval; **MD:** mean difference; **RCT:** randomised controlled trial; **RR:** risk ratio

GRADE Working Group grades of evidence

High quality: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate quality: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low quality: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low quality: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

[a]Downgraded once due to inconsistency: statistical heterogeneity observed despite similarities in populations and doses.
[b]Downgraded once due to imprecision: sensitivity analysis testing robustness of result suggested small trials may be overestimating treatment effect. The result of this sensitivity analysis for the chronic migraine group (MD 2 days lower, 95% CI 2.8 days lower to 1.1 days lower, 2 RCTs, N = 1384, results with placebo 12-13 days) is not affected by imprecision and so we judged it to be moderate-quality evidence.
[c]Downgraded once due to indirectness: insufficient evidence to form subgroups representing our distinct populations of interest.
[d]Downgraded once due to indirectness: sensitivity of this outcome measure at risk of being too low to detect clinically meaningful differences.
[e]Downgraded once due to publication bias: evidence found of trials that have never been published that record this outcome.
[f]Downgraded once due to risk of bias: high or unclear risk of selective reporting bias and poor reporting of this outcome measure had a large effect on numbers analysed.
[g]Downgraded twice due to imprecision: trial size small, new trial evidence likely to change result.
[h]Downgraded once due to imprecision: trial size small, new trial evidence likely to change result.

Summary of findings 2. Botulinum toxin type A compared to other established prophylactic agent for the prevention of migraine in adults

Botulinum toxin type A compared to other established prophylactic agent for the prevention of migraine in adults

Patient or population: adults with migraine
Setting: outpatient clinic
Intervention: botulinum toxin type A
Comparison: other established prophylactic agent

Outcomes	Result with other established prophylactic agent	Result with botulinum toxin type A	Relative effect (95% CI)	№ of participants (trials)	Quality of the evidence (GRADE)
Number of migraine days per month: chronic migraine only	One trial using topiramate in its comparison arm reported narratively on this outcome stating that there was no significant difference between groups.		-	43 (1 RCT)	⊕⊖⊖⊖ Very low[a,b,c]
Number of headache days per month	The mean number of headache days was 6.6 days	MD 1 day lower (4.3 lower to 2.3 higher)	-	59 (1 RCT)	⊕⊖⊖⊖ Very low[a,b]
Number of migraine attacks per month	-	-	-	-	-
Headache intensity measure	The mean severity of migraine was 2.3 points	MD 0.4 points lower (0.79 lower to 0.01 lower)	-	46 (1 RCT)	⊕⊖⊖⊖ Very low[a,b]

assessed with 5-point scale, 5 being severe, 1 being mild: chronic migraine only					
Global impression of disease assessed with Migraine impact and disability assessment scores	The mean global impression of disease ranged from 9.8 to 16.5 points	MD 4.3 points higher (28 lower to 37 higher)	-	101 (2 RCTs)	⊕⊖⊖⊖ Very low[a,b]
Total number of participants experiencing an adverse event	Trial population 862 per 1000	724 per 1000 (319 to 1000)	RR 0.76 (0.59 to 0.98)	114 (2 RCTs)	⊕⊖⊖⊖ Very low[a,b]

CI: confidence interval; **MD:** mean difference; **RCT:** randomised controlled trial; **RR:** risk ratio

GRADE Working Group grades of evidence
High quality: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate quality: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low quality: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low quality: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

[a]Downgraded once due to risk of bias: unclear or high risk for selection, performance, detection and attrition bias.
[b]Downgraded twice due to imprecision: trial sizes small, new trial evidence likely to change result.
[c]Downgraded once due to imprecision: narrative description only.

Anmerkung/Fazit der Autoren

Botulinum toxin type A reduces migraine days per month by two days more than placebo in chronic migraine, based on moderate-quality evidence from two large trials. We also saw a reduction of 30% more in the severity of migraines in the treated group than in the placebo group but this was based on very low-quality evidence from four small trials in chronic and episodic migraine, so our confidence in this estimate is low. There is inadequate evidence to support its use in episodic migraine. The results of this review are applicable up to the first nine months of treatment, after which no evidence was available to determine long-term treatment effects or safety.

3.2 Systematische Reviews

Huang T et al., 2022 [11].

Efficacy and safety of calcitonin gene-related peptide antagonists in migraine treatment: A meta-analysis

Siehe auch

- Deng et al., 2020 [5]. Efficacy and safety of calcitonin-gene-related peptide binding monoclonal antibodies for the preventive treatment of episodic migraine - an updated systematic review and meta-analysis
- Abu-Zaid A et al., 2020 [1]. Galcanezumab for the Management of Migraine: A Systematic Review and Meta-Analysis of Randomized Placebo-Controlled Trials.
- Alasad YW et al., 2020 [2]. Monoclonal antibodies as a preventive therapy for migraine: A meta-analysis.
- Gao B et al., 2020 [7]. Safety and Efficacy of Fremanezumab for the Prevention of Migraine: A Meta-Analysis From Randomized Controlled Trials.
- Gklinos P et al., 2020 [8]. Galcanezumab in migraine prevention: a systematic review and meta-analysis of randomized controlled trials.
- Huang I et al., 2019 [10]. Effects of Anti-Calcitonin Gene-Related Peptide for Migraines: A Systematic Review with Meta-Analysis of Randomized Clinical Trials

- Siahaan YMT et al., 2022 [19]. Efficacy and safety of eptinezumab as preventive treatment for episodic/chronic migraine: A systematic review and meta-analysis
- Aleksovska K et al., 2023 [3]. Efficacy and safety of monoclonal antibodies targeting CGRP in migraine prevention. GRADE tables elaborated by the ad hoc working group of the International Headache Society
- Zhong Y et al., 2023 [21]. Efficacy and safety of eptinezumab for migraine: A systematic review and meta-analysis

Fragestellung

In this study, we reviewed the efficacies and safety of CGRP antagonists for migraine treatment.

Methodik

Population:

- Patients with migraines (ICHD-3), with or without aura

Intervention:

- CGRP antagonists with or without conventional drugs for migraine treatment

Komparator:

- conventional drugs or placebo for migraine treatment. Conventional drugs included NSAIDS, triptans, or ergotamines

Endpunkte:

- number of patients with ≥50% reduction from baseline in mean monthly migraine days
- number of pain free patients at 2 h postdose
- number of patients with sustained pain free 2–24 h postdose
- incidences of adverse events

Recherche/Suchzeitraum:

- PubMed, Embase, The Cochrane Library, CNKI, WanFang Data were electronically searched from inception to March 2021

Qualitätsbewertung der Studien:

- Jadad Scale

Ergebnisse

Anzahl eingeschlossener Studien:

- 26 RCTs were included in the final meta-analysis,

Charakteristika der Population/Studien:

- Fifteen RCTs evaluated small molecule CGRP receptor antagonists, eleven RCTs evaluated anti-CGRP monoclonal antibodies

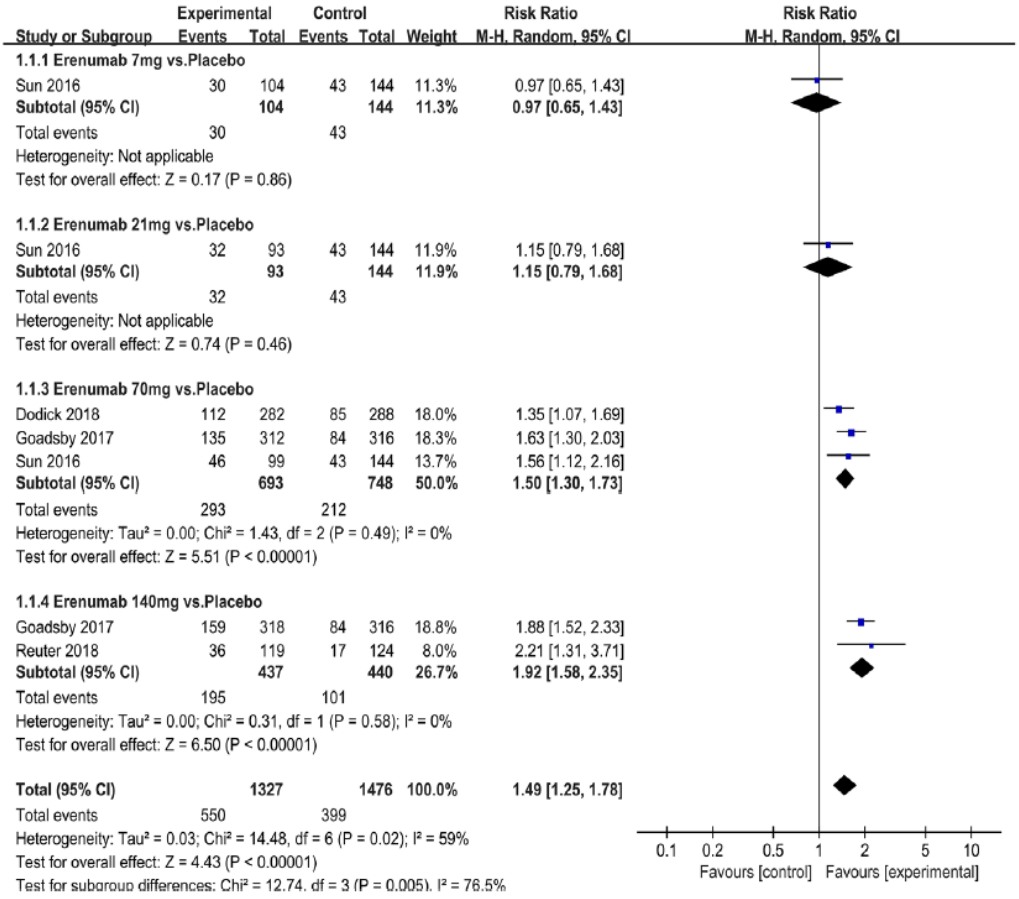
Qualität der Studien:

- Among the included 26 RCTs, only 7 RCTs (Dodick, Lipton, Ailani et al., 2019;Hewitt, Martin et al., 2011; Lipton, Croop et al., 2019; Lipton, Dodick et al., 2019; Olesen et al., 2004; Silberstein et al., 2017; Stauffer et al., 2018) didn't get "5" scores.

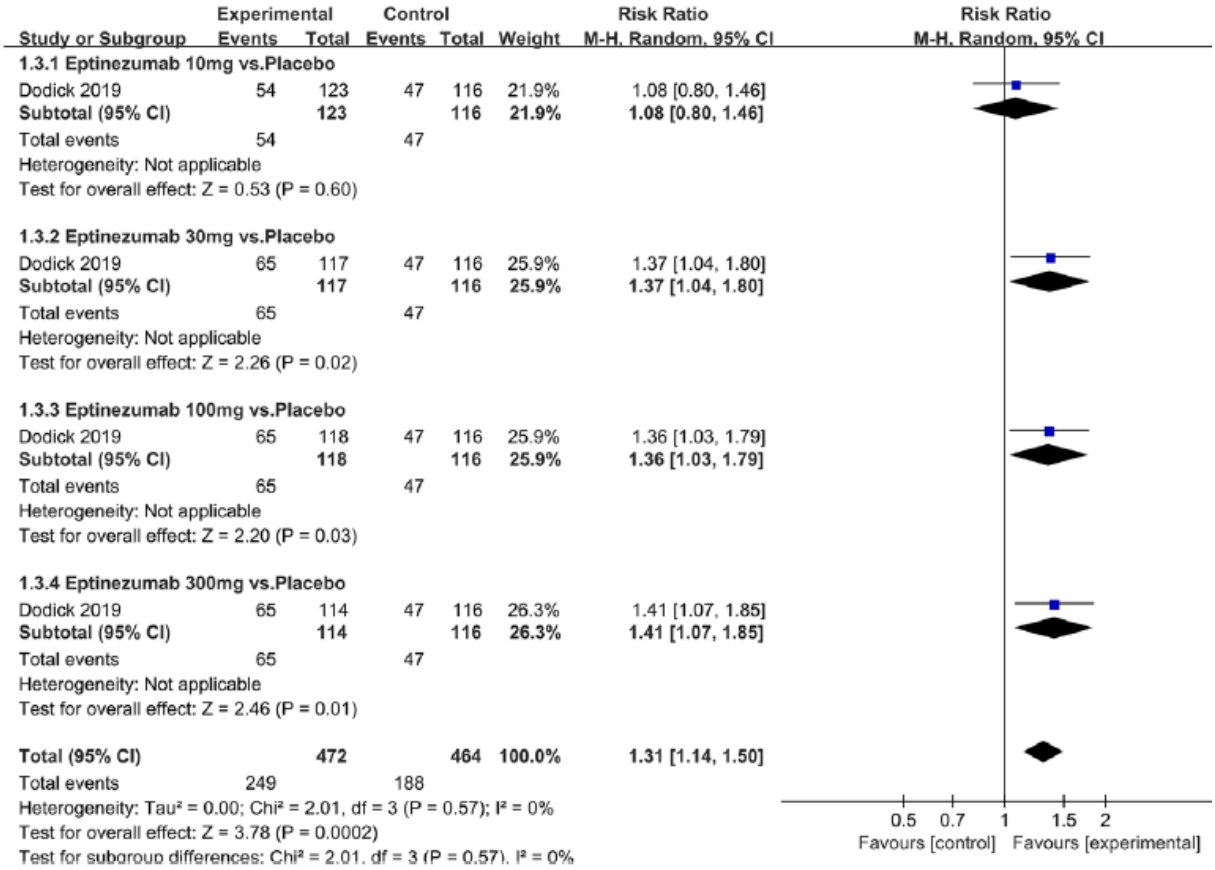
- Besides, most RCTs got scores "≥4" scores except 1 RCT ("2" scores, Lipton, Croop et al., 2019), which illustrated that the quality of the included RCTs was relatively high.

Studienergebnisse:

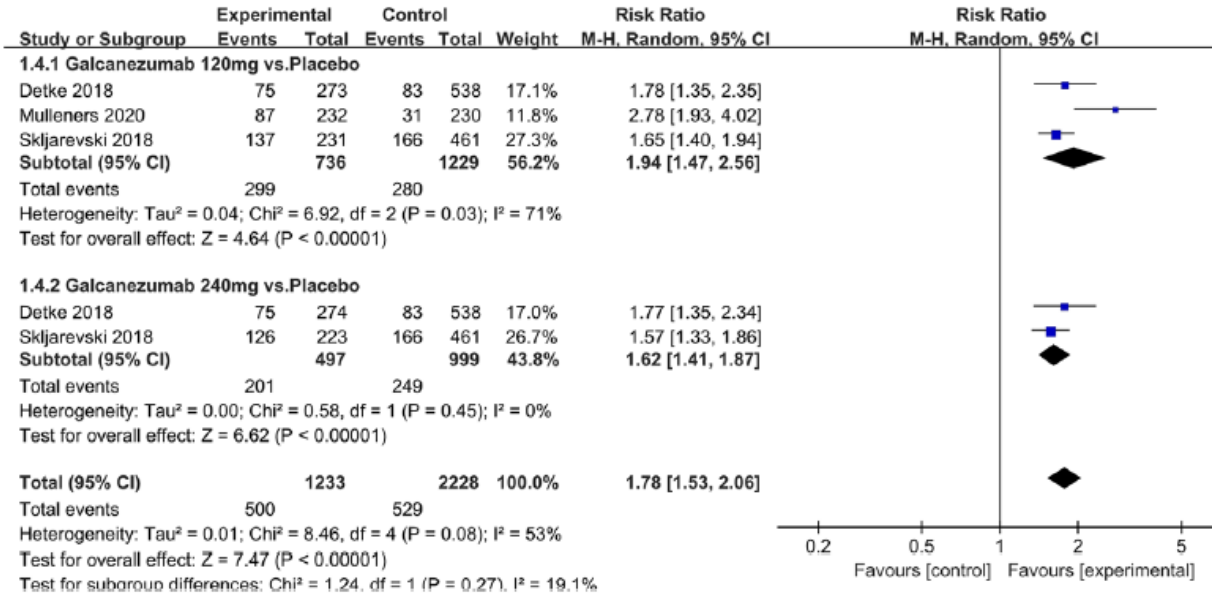
- Number of patients with ≥50% reduction from baseline in mean monthly migraine days was reported in 9 RCTs: random effects model showed that CGRP antagonists exerted better effects, relative to controls (RR=1.50,95%CI [1.39, 1.62], p<.00001); and the meta-analysis of each CGRP antagonist for the outcome indicator of "the number of patients with ≥50% reduction from baseline in mean monthly migraine days" were also performed
- Safety: Twenty-one RCTs reported on treatment-associated adverse outcomes. The random effectsmodel showed that CGRP antagonists were associated with more adverse reactions than controls (RR = 1.08, 95% CI [1.04, 1.12], p < .0001)



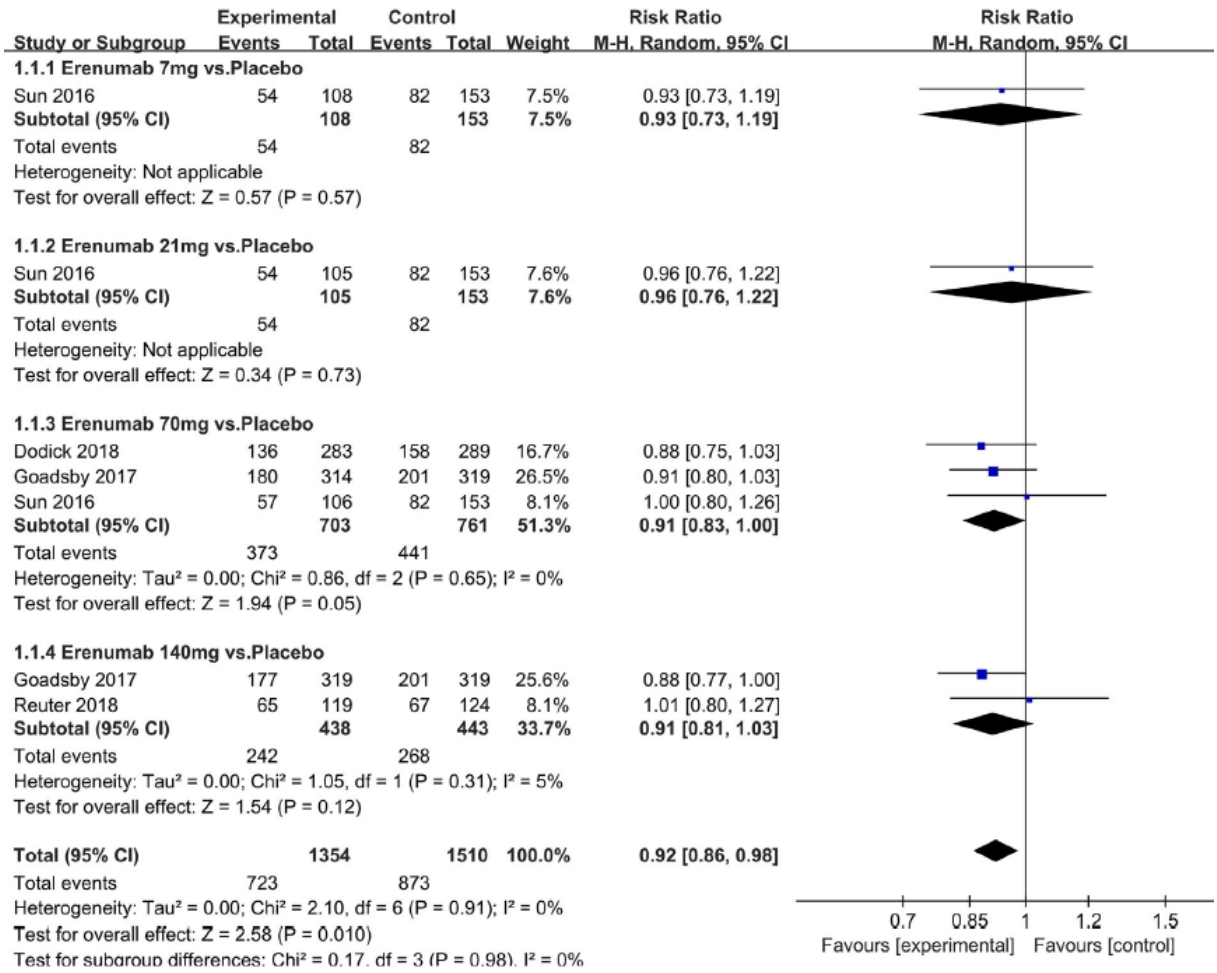
Forest of number of patients with ≥50% reduction from baseline in mean monthly migraine days in Erenumab group



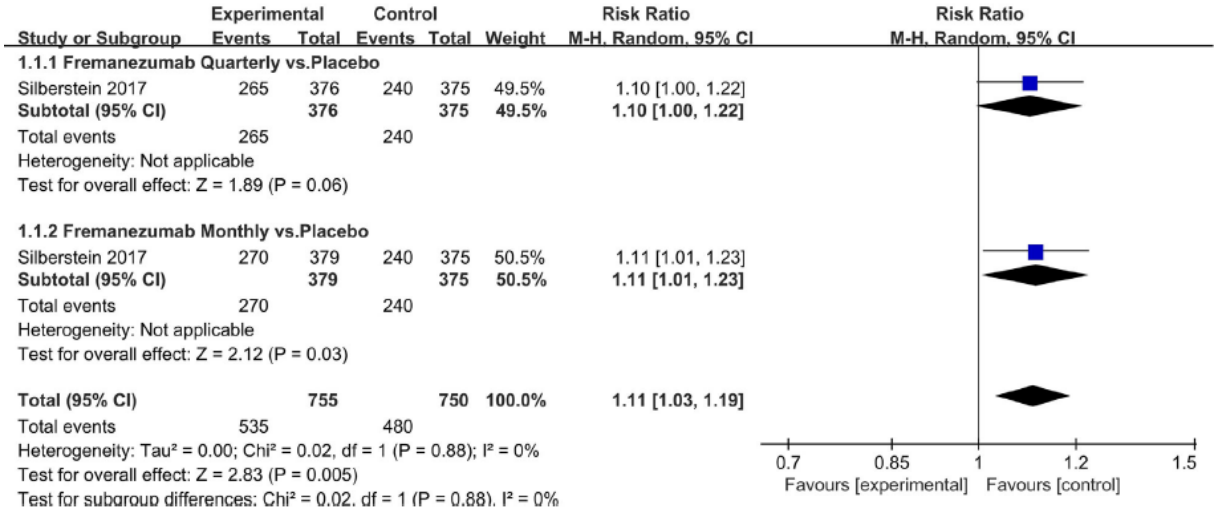
Forrest of number of patients ≥ 50% reduction from baseline in mean monthly migraine days in Eptinezumab group



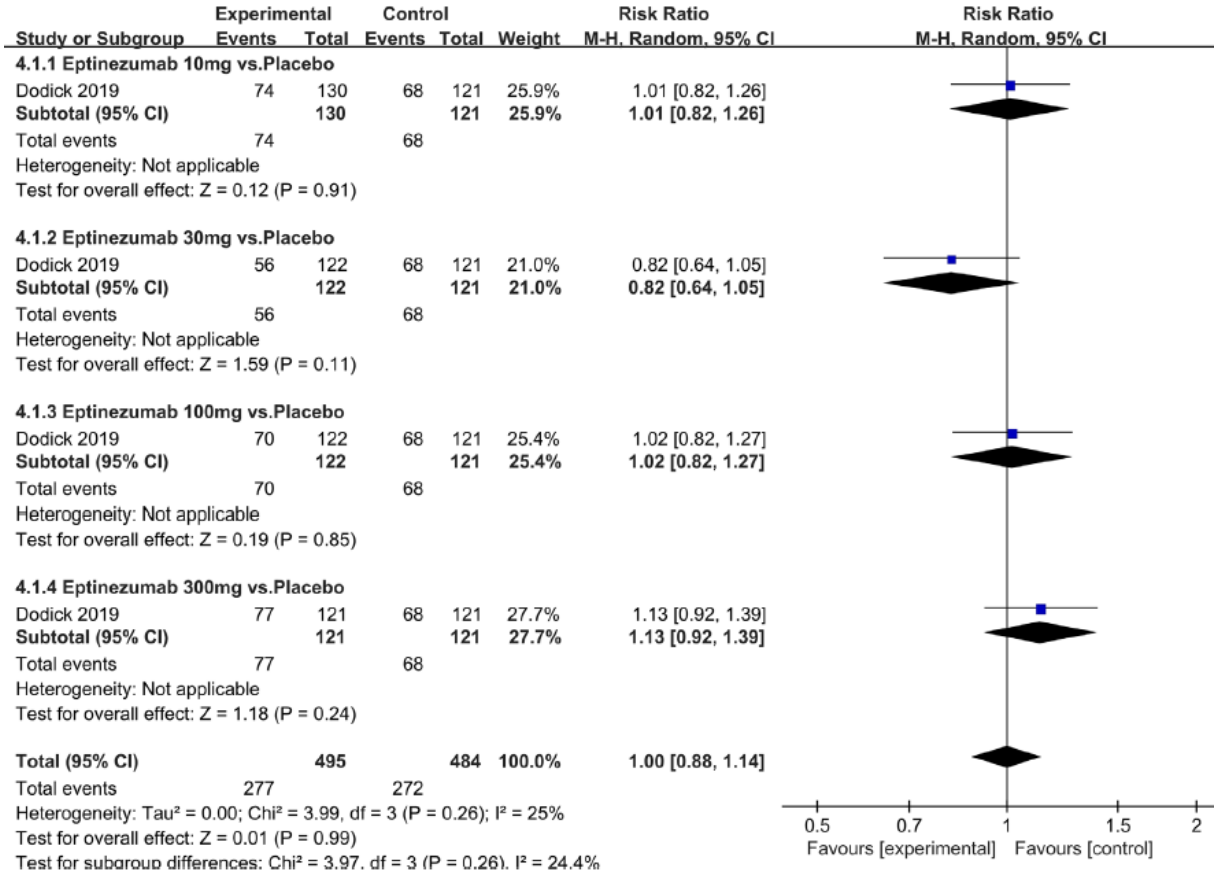
Forrest of number of patients ≥ 50%reduction from baseline in mean monthly migraine days in Galcanezumab group



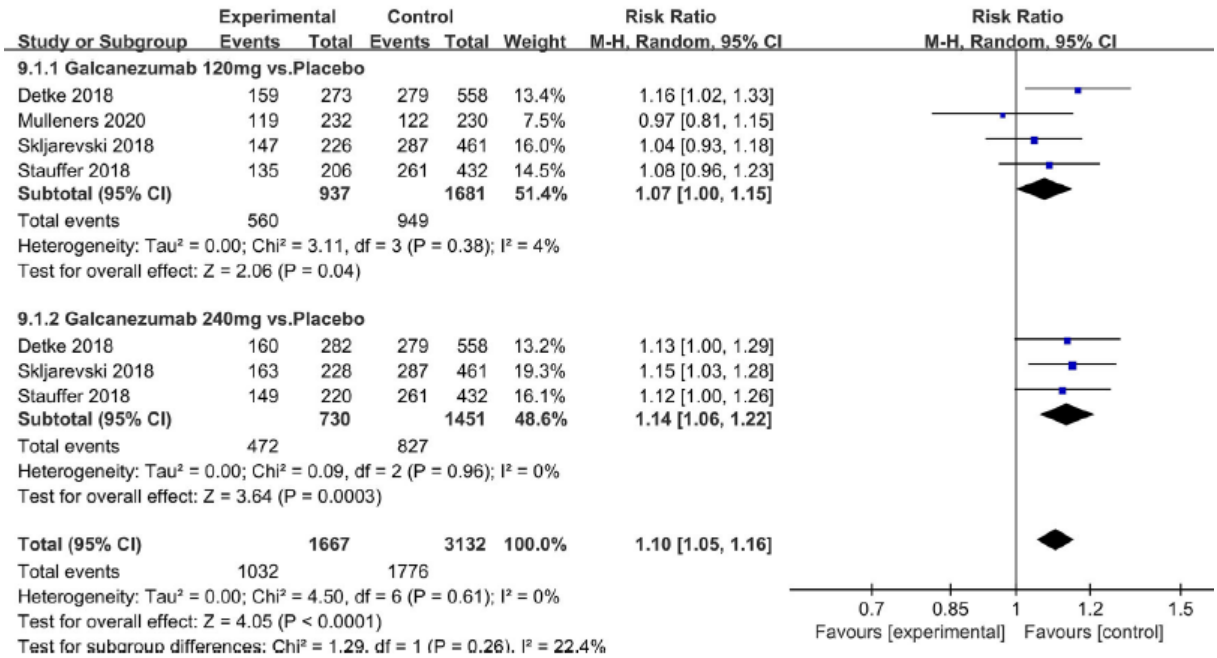
Forest of AEs in Erenumab group



Forest of AEs in Fremanezumab group



Forest of AEs in Eptinezumab group



Forest of AEs in Galcanezumab group

Anmerkung/Fazit der Autoren

CGRP antagonists are significantly effective for migraine treatment; however, they are associated with various adverse events. Due to limitations with regards to quantity and

quality of the included studies, the above conclusions should be verified by more high quality studies.

Kommentare zum Review

- Die Qualitätsbewertung der Primärliteratur wurde anhand der Jadad-Skala vorgenommen. Diese Bewertung ermöglicht keine umfassende Einschätzung des Verzerrungspotenzials
- k. A. zur Patientencharakteristik der eingeschlossenen Studien
- Ergebnisse wurden nur für erstattungsfähige Arzneimittel berichtet
- Limitationen: (1) the included participants in most studies were almost middle-aged and young, with a majority of them being women and (2) the maximum follow-up time was 256 weeks, which is comparatively short to explore the long-term efficacies and safety of the CGRP antagonists on migraine treatment

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Frank F et al., 2021 [6].

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

Siehe auch

- Rafaelli B et al., 2023 [15]. European Headache Federation (EHF) critical reappraisal and meta-analysis of oral drugs in migraine prevention - part 3: topiramate

Fragestellung

In this systematic review and meta-analysis, we evaluated the efficacy as expressed with the 50% response rate for topiramate (TPM), botulinum toxin type A (BoNTA), and CGRP pathway monoclonal antibodies (mABs).

Methodik

Population:

- Episodic and chronic migraine

Intervention:

- Topiramate (TPM), botulinum toxin type A (BoNTA), and CGRP pathway monoclonal antibodies (mABs)

Komparator:

- Placebo

Endpunkte:

- Proportion of subjects reporting a reduction in migraine attack frequency or mean migraine days of 50%, 75% and/or 100%
- Reduction in migraine days or headache days

Recherche/Suchzeitraum:

- We searched the databases CENTRAL, EMBASE, and MEDLINE until 20 March 2020.

Qualitätsbewertung der Studien:

- JADAD score; we excluded studies with a JADAD score below 3

Ergebnisse

Anzahl eingeschlossener Studien:

- Monoclonal antibodies n=19
- Topiramate n=7
- Botulinum toxin type A n=6

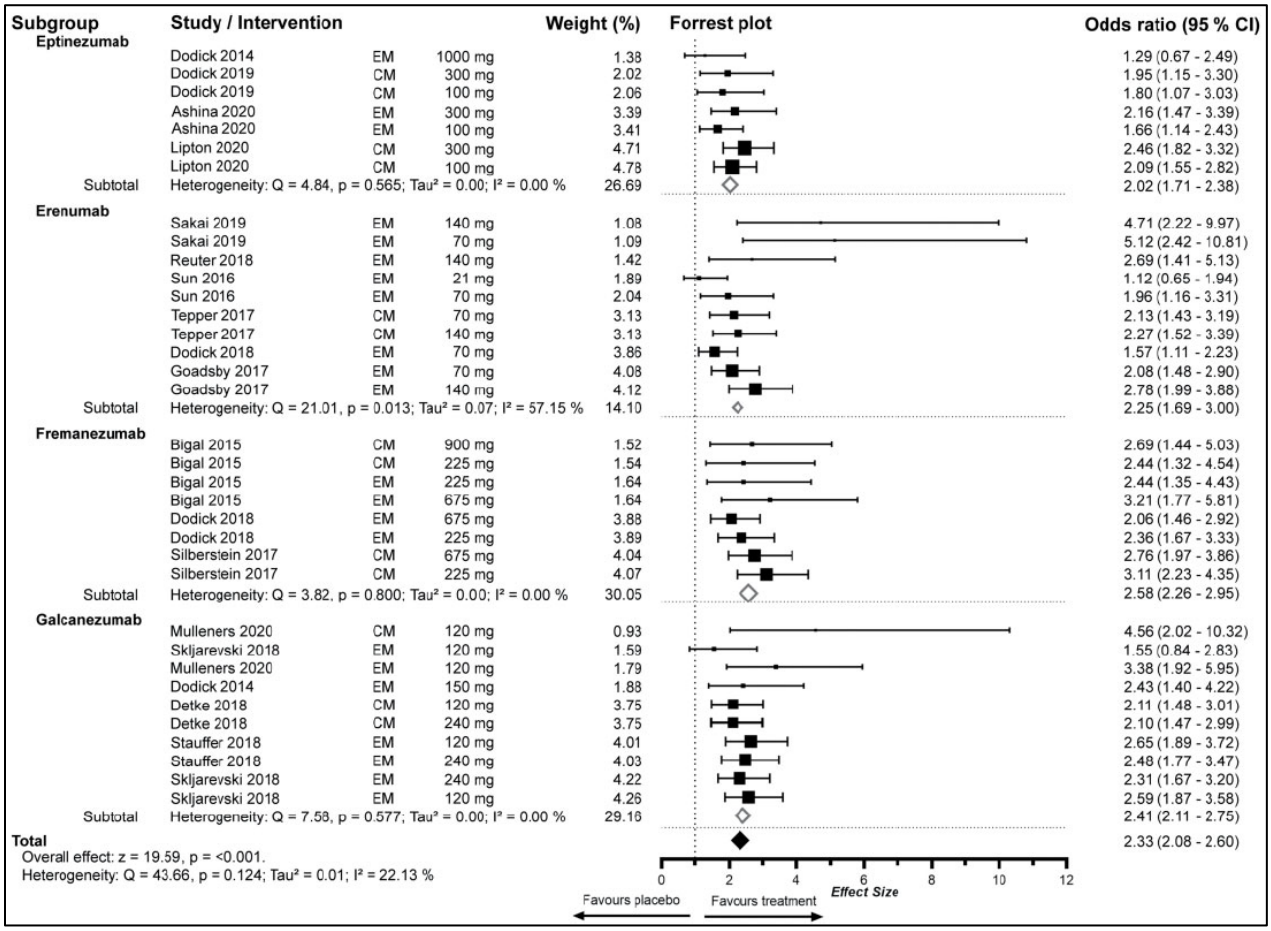
Charakteristika der Population/Studien:

- Total summarized study population was 17,763 participants with 74.9% investigated in trials evaluating mABs, 11.2% in TPM trials and 13.9% in BoNTA studies.
- Mean patient age across all included studies varied between 21.6 to 46.2.
- The mean percentages of participants using concomitant preventative medication during the respective studies varied from 0.0% to 52.5%.
- The mean overall adverse-event rate and drop-out rate ranged from 21.4% to 90% and 0.0% to 62.6% respectively
- Date of publication ranged from 2014 to 2020 for mABs, 2003 to 2006 for TPM and 2000 to 2011 for BoNTA.

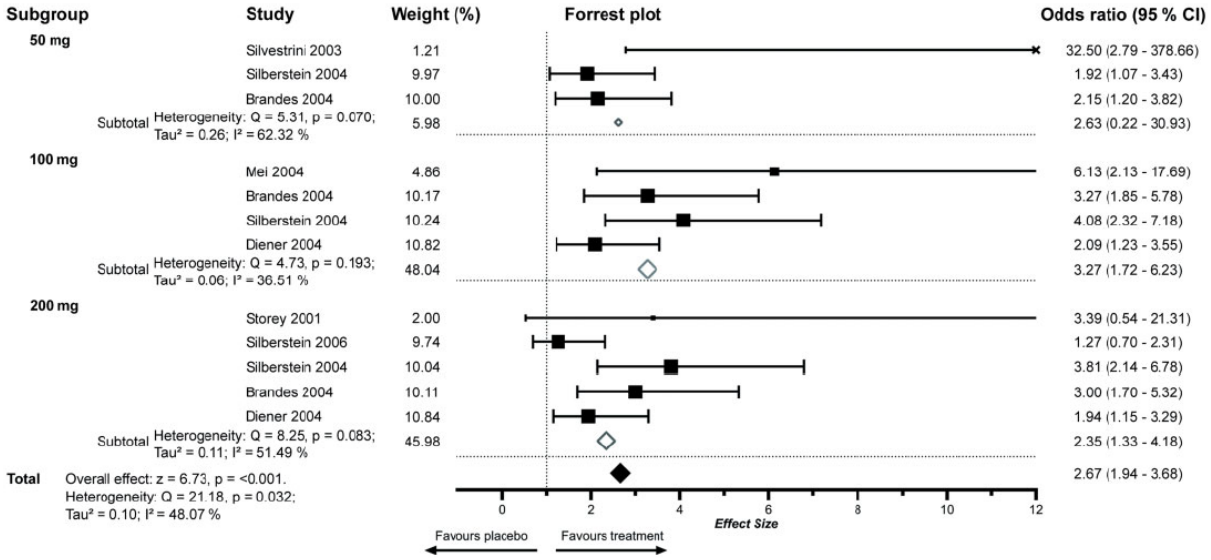
Qualität der Studien:

- studies with a JADAD score below 3 were excluded

Studienergebnisse:



Meta-analysis of 50% response rates of mABs for the prevention of migraine



Meta-Analysis of 50% response rates of TPM separated by dosing regimens

Anmerkung/Fazit der Autoren

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

Kommentare zum Review

- Die Qualitätsbewertung der Primärliteratur wurde anhand der Jadad-Skala vorgenommen. Diese Bewertung ermöglicht keine umfassende Einschätzung des Verzerrungspotenzials, keine detaillierte Darstellung des Jadad-Scores für die eingeschlossenen Studien.
- Ergebnisse wurden nur für erstattungsfähige Arzneimittel berichtet

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Lampl C et al., 2023 [13]

European Headache Federation (EHF) critical re-appraisal and meta-analysis of oral drugs in migraine prevention-part 1: amitriptyline

Fragestellung

The aim of this paper is to critically re-appraise the published trials assessing amitriptyline for migraine prophylaxis.

Methodik

Population:

- migraine patients (adults)

Intervention:

- amitriptyline

Komparator:

- placebo

Endpunkte:

- proportion of patients who experience a 50% or more reduction in migraine days per month,
- migraine days per month
- adverse events leading to discontinuation

Recherche/Suchzeitraum:

- MEDLINE, EMBASE, Cochrane CENTRAL, and ClinicalTrials.gov from inception to August 13, 2022

Qualitätsbewertung der Studien:

- assessed risk of bias by using a modified Cochrane RoB 2.0 tool and the certainty of evidence by using the GRADE approach.

Ergebnisse

Anzahl eingeschlossener Studien:

- n=3 RCTs (622 patients)
  - 31. Couch JR, Hassanein RS (1979) Amitriptyline in migraine prophylaxis. Arch Neurol 36:695–699
  - 33. Couch JR (2011) Amitriptyline in the prophylactic treatment of migraine and chronic daily headache. Headache 51(1):33–51
  - 34. Gonçalves AL, Martini Ferreira A, Ribeiro RT, Zukerman E, Cipolla-Neto J, Peres MF (2016) Randomised clinical trial comparing melatonin 3 mg, amitriptyline 25 mg and placebo for migraine prevention. J Neurol Neurosurg Psychiatry 87(10):1127–1132

Charakteristika der Population und Qualität der Studien:

- More than three quarters of patients were middle-aged women.
- Two trials recruited patients with a minimum of two migraine days per month [31, 33] and one trial recruited patients with a minimum of 4 migraine days per month and a maximum of 15 headache days per month [34].
- Two out of three trials and one out of two trials were at high risk of bias due to missing outcome data for 50% or more reduction in monthly migraine days and adverse events leading to discontinuation, respectively.
- One trial, reporting on monthly migraine days, was at low risk of bias

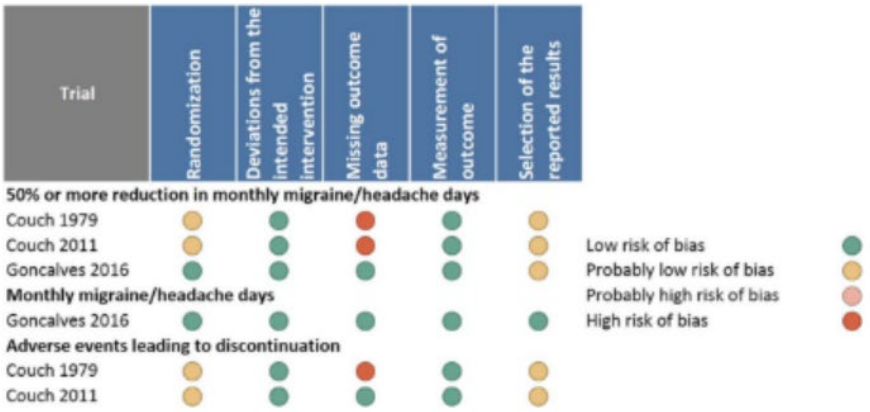


Fig. 3 Risk of bias ratings. Two out of three trials and one out of two trials were at high risk of bias due to missing outcome data for 50% or more reduction in monthly migraine days and adverse events leading to discontinuation, respectively. One trial, reporting on monthly migraine days, was at low risk of bias

Studienergebnisse:

- 50% responder rate: moderate certainty evidence that amitriptyline increases the proportion of patients who experience a 50% or more reduction in monthly migraine days, compared to placebo (relative risk: 1.60 (95% CI 1.17 to 2.19); absolute risk difference: 165 more per 1,000 (95% CI 47 more to 327 more).
- Monthly migraine days: Only one trial, including 118 patients, reported on the reduction in monthly migraine days [34]. The trial was rated at low risk of bias. We found high certainty evidence that amitriptyline reduces monthly migraine days.
- Adverse events leading to discontinuation: Two trials, including 507 patients, reported on adverse events leading to discontinuation [31, 33]. One of the two trials was rated at high risk of bias due to missing outcome data [30]. We found moderate certainty evidence that amitriptyline probably increases the proportion of patients who discontinue due to adverse events compared to placebo. The certainty of evidence was downgraded by one level due to risk of bias

Table 2 Amitriptyline compared to placebo for migraine prophylaxis

Patient or population: migraine
Intervention: prophylaxis with amitriptyline
Comparison: placebo

Outcomes	№ of participants (studies)	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects[a]	
				Risk with placebo	Risk difference with Amitriptyline
50% or more reduction in monthly migraine days	389 (3 RCTs)	Moderate (downgraded due to risk of bias)	RR 1.60 (1.17 to 2.19)	275 per 1,000	165 more per 1,000 (47 more to 327 more)
Monthly migraine days	118 (1 RCT)	High	-	NA	MD 1.2 migraine days fewer (2.1 fewer to 0.3 fewer)
Adverse events leading to discontinuation	507 (2 RCTs)	Moderate (downgraded due to risk of bias)	RD 0.05 (0.01 to 0.10)	0 per 1,000	50 more per 1,000 (10 more to 100 more)

CI confidence interval, *MD* mean difference, *RR* risk ratio, *RD* Risk difference

GRADE Working Group grades of evidence

High certainty: we are very confident that the true effect lies close to that of the estimate of the effect

Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different

Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect

Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect

[a] The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI)

Anmerkung/Fazit der Autoren

Our meta-analysis showed that amitriptyline may have a prophylactic role in migraine patients, however these results are far from robust. This warrants further large-scale research to evaluate the role of amitriptyline in migraine prevention.

Kommentare zum Review

- Two of the three trials were industry-funded and performed in the USA [31, 33] and the third trial was funded by a public grant from Brazil [34].

Deligianni CI et al., 2023 [4]

European Headache Federation (EHF) critical re-appraisal and meta-analysis of oral drugs in migraine prevention-part 2: flunarizine

Fragestellung

In this systematic review and meta-analysis, we aimed to identify and rate the evidence for efficacy of flunarizine, a repurposed, first- or second-line treatment for migraine prophylaxis.

Methodik

Population:

- Adult patients with common migraine, classical migraine, migraine with aura, migraine without aura

Intervention:

- flunarizine

Komparator:

- placebo

Endpunkte:

- proportion of patients with a 50% or more reduction in migraine days per month
- change in migraine days per month
- adverse events leading to discontinuation.

Recherche/Suchzeitraum:

- MEDLINE, EMBASE, Cochrane CENTRAL, and ClinicalTrials.gov from inception to August 13, 2022

Qualitätsbewertung der Studien:

- We assessed the risk of bias using a modified Cochrane RoB 2.0 tool.

Ergebnisse

Anzahl eingeschlossener Studien:

- n=3 RCTs (188 participants)
  - 21. Louis PA (1981) Double-blind Placebo-controlled Prophylactic Study of Flunarizine (Sibelium) in Migraine. Headache 21:235–239

- 24. Sørensen PS, Hansen K, Olesen J (1986) A placebo-controlled, doubleblind, cross-over trial of flunarizine in common migraine. Cephalalgia 6:7–14
- 25. Freitag FG, Diamond S, Diamond M. A placebo controlled trial of flunarizine in migraine prophylaxis. Cephalalgia 11(suppl 11): 157–158.

Charakteristika der Population und Qualität der Studien

- Most of the patients were females.

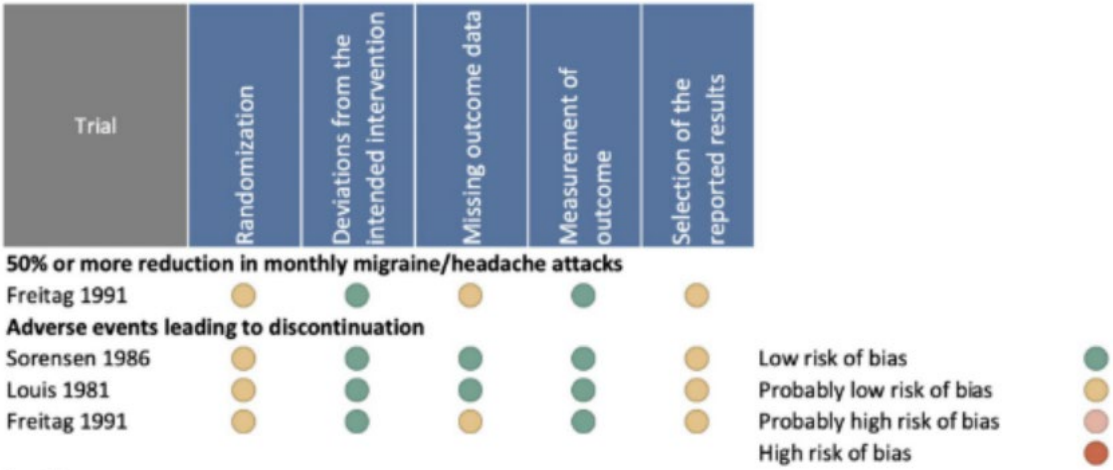


Fig. 3 Risk of bias assessment

Studienergebnisse:

- 50% responder rate: The outcome of 50% or more reduction in migraine days per month was not reported. One study reported on the 50% reduction in migraine attacks in favor of flunarizine with a low or probably low risk of bias [25]
- Monthly migraine days: No available data.
- Adverse events leading to discontinuation: We could only perform a quantitative analysis on AEs leading to discontinuation showing that significantly more participants treated with flunarizine discontinued treatment than those treated with placebo. In the pooled analysis, ten participants treated with flunarizine reported AEs but six withdrew from the treatment [21, 24, 25]. In the placebo arm, five participants reported AEs and three withdrew. This outcome was rated as low or probably low risk of bias for all three RCTs and of high certainty according to the GRADE approach. Mild daytime sedation and weight gain were the most common AEs leading to discontinuation [21, 24, 25]. However, several AEs such as dry mouth and stomach complaints as well as daytime sedation were also reported by patients treated with placebo [21].

Table 2 Flunarizine compared to placebo for migraine prophylaxis

Patient or population: migraine
Intervention: prophylaxis with flunarizine
Comparison: placebo

Outcomes	№ of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with placebo	Risk difference with flunarizine
50% or more reduction in monthly migraine days	No data				
Monthly migraine days	No data				
Adverse events leading to discontinuation	188 (3 RCTs)	High	RD 0.02 (-0.03 to 0.06)	0 per 1,000	20 more per 1,000 (30 fewer to 60 more)

CI Confidence interval, *RD* Risk difference

GRADE Working Group grades of evidence: High certainty; we are very confident that the true effect lies close to that of the estimate of the effect

The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI)

Anmerkung/Fazit der Autoren

Published flunarizine trials predate the recommended endpoints for evaluating migraine prophylaxis drugs, hence the lack of an adequate assessment for these endpoints. Further, modern-day, large-scale studies would be valuable in re-evaluating the efficacy of flunarizine for the treatment of migraines, offering additional insights into its potential benefits.

Lampl C et al., 2023 [12]

The comparative effectiveness of migraine preventive drugs: a systematic review and network meta-analysis

Siehe auch

- Yang CP et al., 2021 [20]. 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

Fragestellung

While there are several trials that support the efficacy of various drugs for migraine prophylaxis against placebo, there is limited evidence addressing the comparative safety and efficacy of these drugs. We conducted a systematic review and network meta-analysis to facilitate comparison between drugs for migraine prophylaxis.

Methodik

Population:

- episodic or chronic migraine in adults

Intervention:

- pharmacologic interventions for migraine prophylaxis (antidepressants, antiepileptics, antihypertensives, CGRP(r)mAbs, calcium channel blockers and gepants)

Komparator:

- placebo

Endpunkte:

- Proportion of patients who experience a 50% or more reduction in migraine days per month, number of migraine days per month, and adverse events leading to discontinuation

Recherche/Suchzeitraum:

- we searched MEDLINE, EMBASE, Cochrane CENTRAL, and ClinicalTrials.gov from inception to August 13, 2022

Qualitätsbewertung der Studien:

- RoB 2.0

Ergebnisse

Anzahl eingeschlossener Studien:

73 RCTs

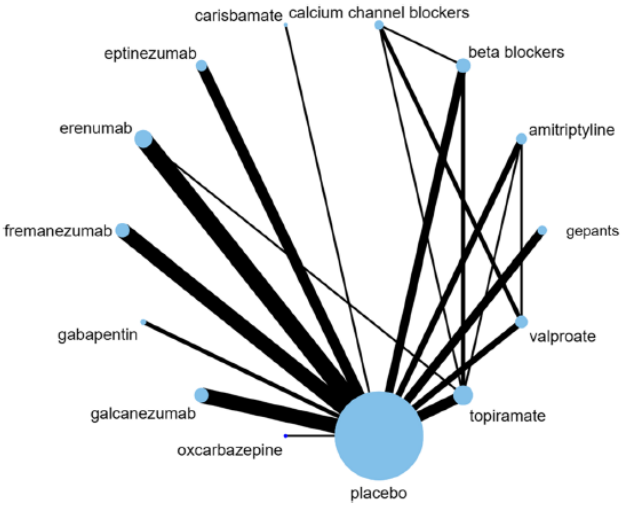
Charakteristika der Population und Qualität der Studien

Table 1 Trial characteristics

Registered	**44 (59%)**
Funding	
Industry	**54 (73%)**
Government	4 (5%)
Institution	2 (3%)
Not-for-profit	0 (0%)
None	1 (1%)
Not reported	13 (17%)
Mean age	41
Male (%)	16%
Migraine with aura (%)	18 (45%)
Prior prophylaxis (%)	28 (49%)
Mean migraine days/month	11
Interventions	
Amitriptyline	7 (10%)
Beta-blockers	13 (18%)
Calcium Channel Blockers	8 (11%)
Carismabate	2 (3%)
Eptinezumab	5 (7%)
Erenumab	9 (13%)
Fremanezumab	7 (10%)
Gabapentin	2 (3%)
Galcanezumab	7 (10%)
Gepants	4 (6%)
Oxcarbazepine	1 (1%)
Pregabalin	1 (1%)
Topiramate	13 (18%)
Valproate	8 (11%)

Studienergebnisse:

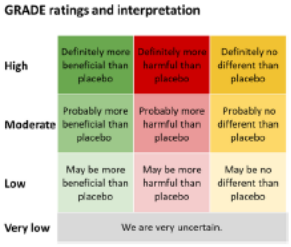
- 50% or more reduction in monthly migraine days



  - Fifty-seven trials with 26,378 patients reported on 50% or more reduction in monthly migraine days and could be incorporated into the network meta-analysis
  - We found high certainty evidence that fremanezumab, eptinezumab, erenumab, galcanezumab, gepants, and topiramate increase the proportion of patients who experience a 50% or more reduction in monthly migraine days compared to placebo.
  - We found moderate certainty evidence that beta-blockers, valproate, and amitriptyline probably increase the proportion of patients who experience a 50% or more reduction in monthly migraine days and that carisbamate and oxcarbazepine are probably not different than placebo.
  - we found low certainty evidence that gabapentin may increase the proportion of patients who experience a 50% or more reduction in monthly migraine days and very low certainty evidence for calcium channel blockers.
  - Fremanezumab appeared the most beneficial, with high certainty evidence that it increases the proportion of patients who experience a 50% or more reduction in monthly migraine days compared to gepants, topiramate, and carisbamate. Fremanezumab shows moderate certainty of superiority compared to amitriptyline, betablockers, calcium channel blockers, oxcarbezapine, galcanezumab, eptinezumab, erenumab, and valproate and low certainty evidence compared to gabapentin
- Monthly migraine/headache days
  - Sixty-two trials, including 29,156 patients, reported on monthly migraine or monthly headache days
  - We found high certainty evidence that, compared to placebo, fremanezumab, erenumab, galcanezumab, eptinezumab, gepants, topiramate, and beta-blockers reduce monthly migraine days, and that oxcarbazepine and gabapentin are not different from placebo
  - We also found moderate certainty evidence that valproate, amitriptyline, and calcium channel blockers are probably not different from placebo
- Adverse events leading to discontinuation
  - Sixty-six trials, including 29,327 patients, reported adverse events leading to discontinuation

- We found high certainty evidence that valproate and amitriptyline result in more adverse events leading to discontinuation, compared to placebo, and that erenumab is not different than placebo.
- We found moderate certainty evidence that topiramate, beta-blockers, oxcarbazepine, and gabapentin probably result in more adverse events and that frenanezumab, galcanezumab, eptinezumab, gepants, and carisbamate are probably not different from the trials on these drugs placebo
- We found low certainty evidence that calcium channel blockers may increase adverse events compared with placebo

Drug	50% reduction in monthly migraine days	Monthly migraine days	Adverse events leading to discontinuation
Baseline risk	275 per 1000	*NA*	*NA*
Results	*Risk difference in 1000 people (95% CI)*	*Difference in mean monthly migraine days (95% CI)*	*Risk difference in 1000 people (95% CI)*
fremanezumab	341.1 more (219 to 493.23)	2.22 fewer (-2.8 to -1.65)	3.9 more (-17.5 to 25.3)†
erenumab	206 more (122.7 to 306.74)	1.6 fewer (-2.05 to -1.6)	0.3 more (-19.2 to 19.8)
galcanezumab	223.9 more (132 to 336.7)	1.97 fewer (-2.48 to -1.47)	9.5 more (-11.5 to 30.4)†
eptinezumab	173 more (79,1 to 291,75)	1,85 fewer (-2,5 to -1,21)	9.4 more (-15,3 to 34,2)†
gepants	146·8 more (49.4 to 273.54)	1.12 fewer (-1.74 to -0.5)	2.6 more (-27.2 to 32.4)†
topiramate	123·5 more (49.6 to 214.16)	0.73 fewer (-1.16 to -0.3)	88.8 more (64.3 to 113.4) ‡
beta-blocker	136·6 more (43,2 to 257,47)*	0,69 fewer (-1,21 to -0,17)	23.9 more (-6,4 to 54,2)†
valproate	215 more (89.4 to 383.71)*	0.37 more (-0.44 to 1.19) *	67.1 more (27.2 to 107)
amitriptyline	143·6 (36.7 to 287.08)*	0.9 fewer (-1.91 to 0.1) *	64 more (24.1 to 103.9)
carisbamate	67·7 fewer (-159.7 to 97.61)†		2.6 more (-96.1 to 101.3)†
oxcarbazepine	41·3 more (-118.1 to 362.44)†	0.37 more (-1.06 to 1.8)	47.1 more (-54. to 149)†
gabapentin/pregabalin	80·2 more (-48.6 to 282.18)* †	0.03 more (-1.17 to 1.22)	50.4 more (-15.5 to 116.4)†
calcium channel blocker	101 more (-5.4 to 249.4)* † ‡	0.65 fewer (-1.29 to -0·.1) *	33.5 more (-5.7 to 72.7) * †
MCID/MID	*15%*	*2 MMD*	*2%*



Anmerkung/Fazit der Autoren

We show that CGRP(r)mAbs have the highest efficacy and the lowest incidence of adverse events compared to placebo, closely followed by gepants. We also show that commonly used drugs, like amitriptyline, beta-blockers, and topiramate, appear not only be less effective than CGRP(r)mAbs) and gepants, but they are associated with substantially higher risk of adverse events—an important issue since more than half of patients discontinue prophylactic migraine drugs within 6 months, attributed to poor efficacy and tolerability

3.3 Leitlinien

Sacco S et al., 2022 [16].

European Headache Federation guideline on the use of monoclonal antibodies targeting the calcitonin gene related peptide pathway for migraine prevention - 2022 update

Zielsetzung/Fragestellung

A previous European Headache Federation (EHF) guideline addressed the use of monoclonal antibodies targeting the calcitonin gene-related peptide (CGRP) pathway to prevent migraine. Since then, randomized controlled trials (RCTs) and real-world evidence have expanded the evidence and knowledge for those treatments. Therefore, the EHF panel decided to provide an updated guideline on the use of those treatments.

Methodik

Grundlage der Leitlinie

- Repräsentatives Gremium: keine Patientenbeteiligung.
- Interessenkonflikte und finanzielle Unabhängigkeit dargelegt.
- Systematische Suche, Auswahl und Bewertung der Evidenz.
- Formale Konsensusprozesse und externes Begutachtungsverfahren unklar.
- Empfehlungen der Leitlinie sind eindeutig und die Verbindung zu der zugrundeliegenden Evidenz ist im Hintergrund dargestellt.
- Regelmäßige Überprüfung der Aktualität unklar.

Recherche/Suchzeitraum:

- Up to February 2022

LoE / GoR

- Grade approach

Grading of the quality of evidence	
High ⊕⊕⊕⊕	We are very confident that the true effect lies close to that of the estimate of the effect
Moderate ⊕⊕⊕◯	We are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low ⊕⊕◯◯	Our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect
Very low ⊕◯◯◯	We have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect
Strength of the recommendation	
Strong (↑↑)	the panel is confident that the desirable effects of adherence to a recommendation outweigh the undesirable effects
Weak (↑)	the panel concludes that the desirable effects of adherence to a recommendation probably outweigh the undesirable effects, but is not confident

Recommendations

Recommendation	Quality of evidence[a]	Strength of the recommendation
In individuals with episodic migraine we recommend eptinezumab, erenumab, fremanezumab and galcanezumab as preventive treatment	Eptinezumab 100 mg and 300 mg (q): moderate ⊕⊕⊕◯ Erenumab 70 mg (m) and 140 mg (m): high ⊕⊕⊕⊕ Fremanezumab 225 (m) and 675 (q): high ⊕⊕⊕⊕ Galcanezumab 120 mg (m) + 240 mg (ld): high ⊕⊕⊕⊕	Strong ↑↑
In individuals with chronic migraine we recommend eptinezumab, erenumab, fremanezumab and galcanezumab as preventive treatment	Eptinezumab 100 mg and 300 mg (q): high ⊕⊕⊕⊕ Erenumab 70 mg (m): high ⊕⊕⊕⊕ Erenumab 140 mg (m): moderate ⊕⊕⊕◯ Fremanezumab 225 mg (m): moderate ⊕⊕⊕◯ Fremanezumab 675 mg (q): high ⊕⊕⊕⊕ Galcanezumab 120 mg (m) + 240 mg (ld): high ⊕⊕⊕⊕	Strong ↑↑
In individuals with episodic or chronic migraine we recommend erenumab over topiramate as preventive treatment because of better tolerability	Low ⊕⊕◯◯	Strong ↑↑

(m) indicates monthly, *(q)* indicates quarterly, *ld* indicates loading dose

[a] For drugs with differences in the quality of evidence across the different outcomes we provided the overall rating according to the highest quality of evidence since the risk of bias was considered minor

Evidence-based recommendation – question 1

In individuals with episodic migraine, is preventive treatment with monoclonal antibodies targeting the CGRP pathway as compared to placebo, effective and safe?

In individuals with episodic migraine, we recommend eptinezumab, erenumab, fremanezumab and galcanezumab as preventive treatment

Quality of evidence: moderate to high

Strength of the recommendation: strong

References: 7–10, 15, 16, 18, 21, 24–26, 28, 29

Evidence-based recommendation – question 2

In individuals with chronic migraine, is preventive treatment with monoclonal antibodies targeting the CGRP pathway as compared to placebo, effective and safe?

In individuals with chronic migraine, we recommend eptinezumab, erenumab, fremanezumab and galcanezumab as preventive treatment

Quality of evidence: moderate to high

Strength of the recommendation: strong

References: 8, 11, 13, 17, 19, 20, 22, 23, 27, 29

Evidence-based recommendation – question 3

In individuals with migraine, is preventive treatment with monoclonal antibodies targeting the CGRP pathway, as compared to another migraine preventive treatment, more effective and/or tolerable?

In individuals with episodic or chronic migraine we recommend erenumab over topiramate as preventive treatment

Quality of evidence: low

Strength of the recommendation: strong

References: 14

Expert Consensus Statements

Question	Statement
1. When should treatment with monoclonal antibodies targeting the CGRP pathway be offered to individuals with migraine?	In individuals with migraine who require preventive treatment, we suggest monoclonal antibodies targeting the CGRP pathway to be included as a first line treatment option.
2. How should other preventive treatments be managed when using monoclonal antibodies targeting the CGRP pathway in individuals with migraine?	In individuals with episodic or chronic migraine there is insufficient evidence to make suggestions regarding the combination of monoclonal antibodies targeting the CGRP with other preventatives to improve migraine clinical outcomes
3. When should treatment efficacy in individuals with migraine on treatment with anti-CGRP monoclonal antibodies be firstly evaluated?	In individuals with episodic or chronic migraine who start a new treatment with one monoclonal antibody targeting the CGRP pathway we suggest evaluating efficacy after a minimum of 3 consecutive months on treatment
4. When should treatment with anti-CGRP monoclonal antibodies be paused in individuals with migraine?	In individuals with episodic or chronic migraine we suggest considering a pause in the treatment with monoclonal antibodies targeting the CGRP pathway after 12-18 months of continuous treatment. If deemed necessary, treatment should be continued as long as needed. In individuals with migraine who pause treatment, we suggest restarting the treatment if migraine worsens after treatment withdrawal.
5. Should individuals with migraine and medication overuse offered treatment with monoclonal antibodies targeting the CGRP pathway?	In individuals with migraine and medication overuse, we suggest offering monoclonal antibodies targeting the CGRP pathway.
6. In individuals with migraine who are non-responders to one monoclonal antibody targeting the CGRP pathway, is switching to a different antibody an option?	In individuals with migraine with inadequate response to one monoclonal antibody targeting the CGRP pathway, there is insufficient evidence on the potential benefits of antibody switch but switching may be an option.
7. In which individuals with migraine is caution suggested when considering treatment with monoclonal antibodies targeting the CGRP pathway?	We suggest avoiding monoclonal antibodies targeting the CGRP pathway in pregnant or nursing women. We suggest caution and decision on a case-by-case basis in the presence of vascular disease or risk factors and Raynaud phenomenon. We suggest caution in erenumab use in individuals with migraine with history of severe constipation.

Referenzen aus Leitlinien

Question 1:

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9. Skljarevski V, Matharu M, Millen BA, Ossipov MH, Kim BK, Yang JY (2018) Efficacy and safety of galcanezumab for the prevention of episodic migraine: results of the EVOLVE-2 phase 3 randomized controlled clinical trial. Cephalalgia 38(8):1442–1454

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Scottish Intercollegiate Guidelines Network (SIGN), 2018; Revised September 2022 [17].

Pharmacological management of migraine - A national clinical guideline
Healthcare Improvement Scotland (HIS)

Zielsetzung

This guideline provides recommendations based on current evidence for best practice in the acute and prophylactic management of adults with migraine using pharmacological therapies or devices. The focus is on adults with acute migraine and preventative treatment in patients with episodic or chronic migraine and medication-overuse headache. Studies of children with migraine were not included, however the recommendations could be considered for treating adolescents with migraine.

The guideline excludes complementary, physical and psychological therapies, and specialist surgical interventions.

Methodik

Grundlage der Leitlinie

- Update: This guideline updates and replaces section 6 of SIGN 107: Diagnosis and management of headache in adults.
- Repräsentatives Gremium.
- Interessenkonflikte und finanzielle Unabhängigkeit dargelegt.
- Systematische Suche, Auswahl und Bewertung der Evidenz.
- Konsensusprozesse und externes Begutachtungsverfahren dargelegt.

- Empfehlungen der Leitlinie sind eindeutig und die Verbindung zu der zugrundeliegenden Evidenz ist explizit dargestellt.
- Regelmäßige Überprüfung der Aktualität gesichert.

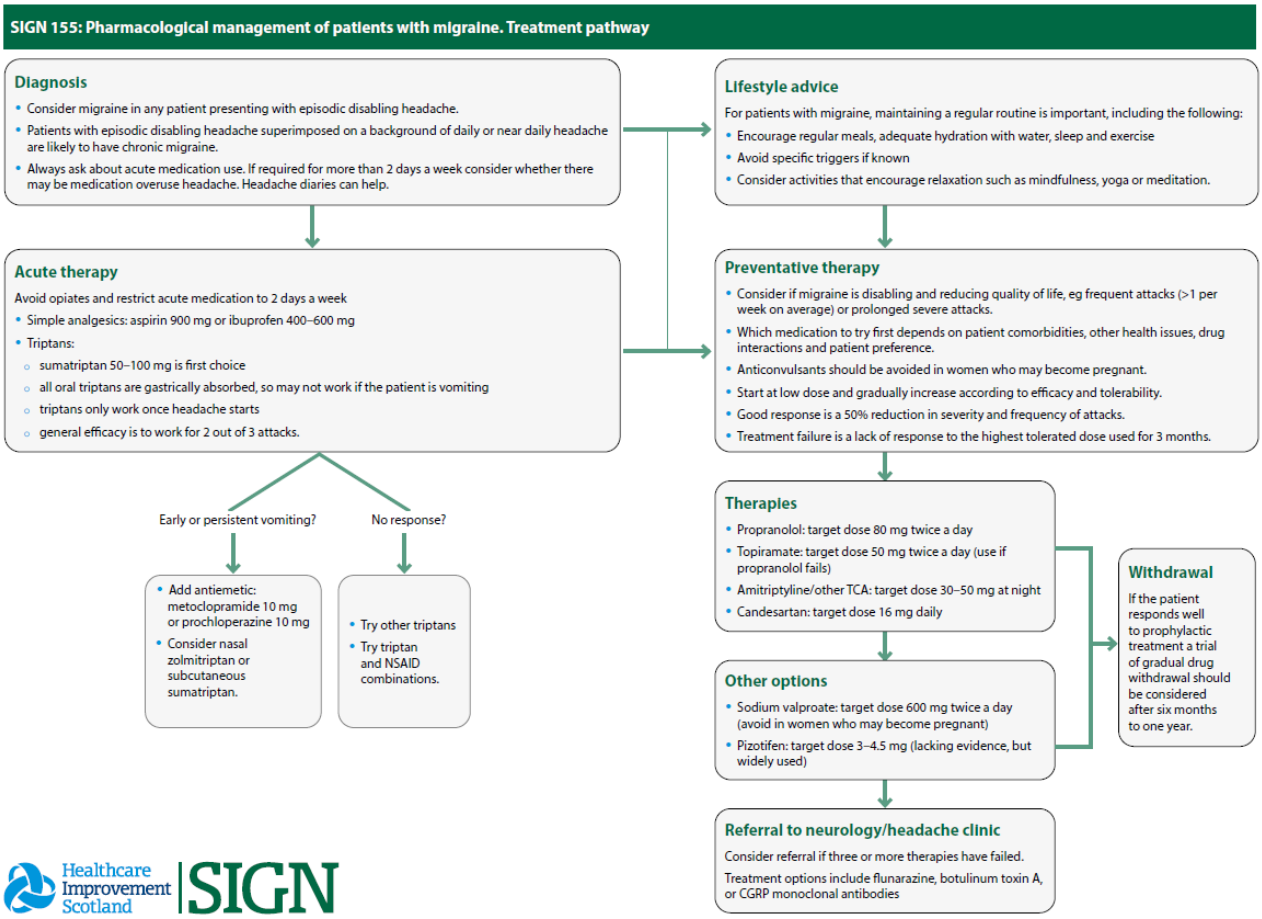
Recherche/Suchzeitraum:

- Systematic literature review: Databases searched include Medline, Embase, Cinahl, PsycINFO and the Cochrane Library. The year range covered was 2011–2016. Internet searches were carried out on various websites including the US National Guidelines Clearinghouse.
- Literature search for patient issues: Databases searched include Medline, Embase, Cinahl and PsycINFO, and the results were summarised by the SIGN Patient Involvement Officer and presented to the guideline development group.
- For the update a search was conducted using Medline, Embase and the Cochrane Library, year range 2016–2022.

LoE & GoR

KEY TO EVIDENCE STATEMENTS AND RECOMMENDATIONS	
LEVELS OF EVIDENCE	
1^{++}	High-quality meta-analyses, systematic reviews of RCTs, or RCTs with a very low risk of bias
1^{+}	Well-conducted meta-analyses, systematic reviews, or RCTs with a low risk of bias
1^{-}	Meta-analyses, systematic reviews, or RCTs with a high risk of bias
2^{++}	High-quality systematic reviews of case-control or cohort studies High-quality case-control or cohort studies with a very low risk of confounding or bias and a high probability that the relationship is causal
2^{+}	Well-conducted case-control or cohort studies with a low risk of confounding or bias and a moderate probability that the relationship is causal
2^{-}	Case-control or cohort studies with a high risk of confounding or bias and a significant risk that the relationship is not causal
3	Non-analytic studies, eg case reports, case series
4	Expert opinion
RECOMMENDATIONS	
Some recommendations can be made with more certainty than others. The wording used in the recommendations in this guideline denotes the certainty with which the recommendation is made (the 'strength' of the recommendation). The 'strength' of a recommendation takes into account the quality (level) of the evidence. Although higher-quality evidence is more likely to be associated with strong recommendations than lower-quality evidence, a particular level of quality does not automatically lead to a particular strength of recommendation. Other factors that are taken into account when forming recommendations include: relevance to the NHS in Scotland; applicability of published evidence to the target population; consistency of the body of evidence, and the balance of benefits and harms of the options.	
R	For '**strong**' recommendations on interventions that '**should**' be used, the guideline development group is confident that, for the vast **majority** of people, the intervention (or interventions) will do more good than harm. For '**strong**' recommendations on interventions that '**should not**' be used, the guideline development group is confident that, for the vast **majority** of people, the intervention (or interventions) will do more harm than good.
R	For '**conditional**' recommendations on interventions that should be '**considered**', the guideline development group is confident that the intervention will do more good than harm for **most** patients. The choice of intervention is therefore more likely to vary depending on a person's values and preferences, and so the healthcare professional should spend more time discussing the options with the patient.
GOOD-PRACTICE POINTS	
✓	Recommended best practice based on the clinical experience of the guideline development group.

Pharmacological prevention of migraine



4.2 BETA BLOCKERS

Empfehlung: Propranolol (80–160 mg daily) is recommended as a first-line prophylactic treatment for patients with episodic or chronic migraine.

A well-conducted systematic review identified a large number of trials on the use of beta blockers for prophylaxis of migraine, mostly from the 1980s. The individual trials were rated as low quality and of short duration (<3 months). [46] Propranolol (80–160 mg) reduced the frequency of episodic migraine by ≥50% compared to placebo (NNT=4, 95% CI 3 to 7). [46] Metoprolol (200 mg daily, slow release) reduced migraine severity, but no consistent benefits in reduction of migraine frequency or use of acute analgesics was shown. [46] Atenolol 50–200 mg daily was reported to reduce frequency of episodic migraine and use of acute therapies. [46] Direct comparative trials of the effectiveness of propranolol with other medications used for migraine prevention in patients with episodic and chronic migraine were of low quality due to risk of bias and failure to analyse data according to intention-to-treat principles. Within these constraints the likelihood of a 50% reduction in headache frequency did not differ between propranolol and topiramate. Propranolol was better than nifedipine but there was no clear evidence to suggest it was better than other beta blockers such as metoprolol and timolol. Similarly there was no difference when compared to amitriptyline or nortriptyline. The use of combined tricyclic antidepressant and propranolol was no better than propranolol monotherapy. [46] Propranolol use led to treatment side effects more commonly than placebo and specific adverse events leading to discontinuation included nausea (43 per 1,000 treated) and diarrhoea (89 per 1,000 treated). [46] However, it is a well-established therapy and is widely used in NHS Scotland. Beta blockers should be used with caution if the patient has a history of asthma. [17] Patients using rizatriptan and propranolol should be given a maximum dose of 5 mg rizatriptan as propranolol increases the plasma concentration of rizatriptan. Rizatriptan should not be taken within two hours of taking propranolol. [17] (LoE: 1++)

4.3 TOPIRAMATE

Empfehlung: Topiramate (50–100 mg daily) is recommended as a prophylactic treatment for patients with episodic or chronic migraine.

Empfehlung: Before commencing treatment women who may become pregnant should be advised of the associated risks of topiramate during pregnancy, the need to use effective contraception and the need to seek further advice on migraine prophylaxis if pregnant or planning a pregnancy.

Three systematic reviews reported on the efficacy of topiramate compared to placebo in patients with episodic and chronic migraine. [46-48] Pooled analysis from nine RCTs (1,700 patients; treatment duration 4–52 weeks) comparing topiramate to placebo reported use of topiramate resulted in twice as many patients reporting a ≥50% reduction in headache frequency (RR 2.02, 95% CI 1.57 to 2.60; NNT=4, 95% CI 3 to 6), one less headache per 28 days and an improvement in quality of life outcomes. [48] In patients with chronic migraine, low-quality evidence suggests that topiramate reduces monthly migraine days, frequency of associated symptoms and is more effective in reducing monthly migraine attacks by 25% when compared to placebo. [46] Topiramate also improved quality of life and migraine-related disability scores. [46] Topiramate at doses of 50–200 mg daily is effective in reducing monthly migraine frequency and monthly migraine days by 50% or more (absolute reduction of five migraine days/month for topiramate at a dose of 100 mg/day). [46] Meta-analysis of three trials that used multiple doses of topiramate demonstrated that 200 mg daily is no more effective than 100 mg daily. [48] Improvement in quality of life measures, general health status, self-reported vitality and use of acute drugs was also reported. [46] In seven trials of topiramate versus active comparators (amitriptyline, flunarizine, propranolol, sodium valproate and relaxation) topiramate was found to be no better than any comparator except for a small, but significant, benefit over sodium valproate. However, these trials were underpowered and further evidence is needed to confirm these findings. [48] (LoE: 1++)

Topiramate 100 mg daily was associated with a higher rate of adverse events than placebo, although these were mild to moderate. [47, 48] Adverse effects include nausea, paraesthesia, anorexia and weight loss. [47-49] Cognitive adverse effects are common, vary in severity, tend to be dose-related and often define drug tolerability. [50] As depression is also a common side effect, topiramate should be used with caution in patients with depression. [17] Exposure to topiramate during the first trimester of pregnancy has an increased risk of abnormal oral cleft development in infants (OR 6.2, 95% CI 3.13 to 12.51). [51] It should not be used by women who are breastfeeding as it can be present in breast milk. [17] (LoE: 1++, 1+, 4)

4.4 TRICYCLIC ANTIDEPRESSANTS

Empfehlung: Amitriptyline (25–150 mg at night) should be considered as a prophylactic treatment for patients with episodic or chronic migraine.

Empfehlung: In patients who cannot tolerate amitriptyline a less sedating tricyclic antidepressant should be considered.

TA systematic review reported patients with episodic migraine (on average 4.7 migraines per month) treated with tricyclic antidepressants (TCAs) experienced a reduction of 1.4 headaches per month. [52] Study duration varied from four to 24 weeks and the studies were rated as having a high risk of bias. [52] The average dose of TCA used was 50% of the maximum dose (eg the dose range for amitriptyline was 10 mg to 150 mg with a pooled mean dose of 80 mg). In most studies doses were titrated. There was some evidence that higher doses resulted in greater benefit but the difference between higher and lower doses was not significant. Patients with episodic migraine taking TCAs had an 80% chance of a 50% improvement in headaches (RR 1.80, 95% CI 1.24 to 2.62) compared to placebo. There was a small ongoing reduction in headache frequency with continued treatment with TCAs. [52] (LoE: 1++, 1+)

A further meta-analysis found that amitriptyline (100 mg) was more effective than placebo in achieving a ≥50% reduction in headache frequency but more so in those with higher headache frequencies. This was based on low-quality evidence. [46] In comparative trials, low-dose (eg an average amitriptyline dose of 50 mg) TCAs were more likely to produce at least a 50% improvement in episodic migraine headache frequency than SSRIs. Studies comparing beta blockers and TCAs, amitriptyline and topiramate, and amitriptyline and flunarizine found no difference in the likelihood of gaining a 50% reduction in headache attacks. However there are relatively few trials and most were underpowered to assess clinical equivalence. [46] (LoE: 1++)

Across 37 studies of various TCAs, only dry mouth and drowsiness were reported as more frequent in the TCA group than the placebo group. Some TCAs are less sedating than others. [17] Withdrawal from treatment due to an adverse event was similar between patients taking placebo or TCA. [52] (LoE: 1+)

4.5 CANDESARTAN

Emfpehlung: Candesartan (16 mg daily) can be considered as a prophylactic treatment for patients with episodic or chronic migraine.

A systematic review identified two small RCTs of moderate quality that demonstrated the efficacy ofcandesartan (16 mg).[53] One of the studies reported a relative reduction of 26% in headache days.[54] In theother study, candesartan had similar efficacy to propranolol 160 mg for the secondary outcome of ≥50%reduction in migraine days (proportion of responders: 43% for candesartan, 40% for propranolol and 23%for placebo).[55] Candesartan is usually well tolerated and early trial data suggested no increase in the rate of adverse events compared to the placebo rate.[54] (LoE: 1+)

The evidence base for candesartan is small and further trials are unlikely to be conducted. However, candesartan is a widely used and inexpensive drug with a good side-effect profile, and no potential cognitive effects.

4.6 SODIUM VALPROATE

Empfehlung: Sodium valproate (400–1,500 mg daily) can be considered as a prophylactic treatment for patients with episodic or chronic migraine.

Empfehlung: Prescribers should be aware that sodium valproate is associated with an increased risk of foetal malformations and poorer cognitive outcomes in children exposed to valproate in utero. For women who may become pregnant sodium valproate should only be considered as a prophylactic treatment when:

- other treatment options have been exhausted
- patients are using adequate contraception.

For patients with episodic migraine, sodium valproate is more effective than placebo providing a ≥50% reduction in headache frequency over eight to twelve weeks (RR 2.83, 95% CI 1.27 to 6.31; NNT=3, 95% CI 2 to 9) in pooled data from two small trials (n=63), using doses ranging from 400–1500 mg daily. [56] There was no difference in efficacy when compared to flunarizine, and sodium valproate 500 mg was not as effective as high-dose topiramate (400 mg) in pooled analysis of two small trials. [56] There was variable reporting on adverse effects in the trials included in the Cochrane review. Those reported were mild but common and included fatigue, dizziness, tremor and weight gain. [56] Children exposed to sodium valproate in utero are at high risk of serious developmental disorders and congenital malformations, so it should not be used by pregnant women. [57] Sources of further advice for prescribing sodium valproate for women who may become pregnant are available in section 7.2 and the MHRA patient information card and checklist can be found in Annex 4. Sodium valproate is unlicensed for the treatment of patients with migraine (see section 1.3.2). (LoE: 1++)

4.7 CALCIUM CHANNEL BLOCKERS

Empfehlung: Flunarizine (10 mg daily) should be considered as a prophylactic treatment for patients with episodic or chronic migraine.

Low-quality studies, mostly from the 1980s and of variable design and size, reported some, but not consistent, benefit from verapamil, nimodipine, nifedipine or nicardipine over placebo in patients with episodic or chronic migraine. [46, 53] (LoE: 1++, 1+)

Meta-analysis of seven trials of flunarazine at a dose of 10 mg daily reported a moderate benefit in patients with episodic migraine compared to placebo. The standardised mean difference (SMD) for reduction in headache frequency was -0.60 (95% CI -1.2 to 0.005) at eight weeks and -0.84 (95% CI -1.3 to 0.34) at 12 weeks. No significant benefit was found at four weeks.53 The trials included in the meta-analysis were small. (LoE: 1+)

Comparative trial data was limited, but there is some evidence that flunarazine has similar efficacy to propranolol, topiramate and sodium valproate. [53, 58] (LoE: 1++)

Flunarazine is often well tolerated.58 Depression is a possible side effect, so it should be used with caution in patients with depression. [58, 59] […] Clinicians should be familiar with the side-effect profile. [59]

4.9 GABAPENTIN AND PREGABALIN

Empfehlung: Gabapentin should not be considered as a prophylactic treatment for patients with episodic or chronic migraine.

There is limited evidence from two small trials of gabapentin that high doses (1,800–2,400 mg) are significantly superior to placebo for patients with episodic migraine, but the pooled data from six trials of gabapentin (1,000

patients) suggest no consistent benefit over placebo in the prophylaxis of adults with episodic migraine at any dose.[61] (LoE: 1++)

Adverse effects were common, particularly with high doses of gabapentin, including fatigue, dizziness, flulike symptoms, somnolence and cognitive disturbance.[61] (LoE: 1++)

There is a lack of evidence on the use of pregabalin in patients with episodic migraine.[61] (LoE: 1++)

If migraine is part of a chronic pain syndrome, further advice on the use of pregabalin is available in SIGN 136: Management of chronic pain.[62]

Use of gabapentin or pregabalin is associated with increased risk of addiction.[63] (LoE: 4)

4.10 ANGIOTENSIN-CONVERTING ENZYME INHIBITORS

A systematic review identified one trial of 60 patients with episodic migraine (with or without hypertension), where 12 weeks of treatment with lisinopril was better than placebo in reducing migraine days/severity and body pain, but did not reduce use of acute therapies.46 Another small RCT (n=24) found captopril reduced headache and improved depression over 32 weeks.[46] (LoE: 1++)

4.11 SELECTIVE SEROTONIN REUPTAKE INHIBITORS AND SEROTONIN NOREPINEPHRINE REUPTAKE INHIBITORS

A Cochrane review identified 11 RCTs of the use of SSRIs and one RCT of venlafaxine, a serotonin norepinephrine reuptake inhibitor (SNRI) for the management of patients with migraine.[64] Most of the studies were considered poor in quality, due to incomplete reporting of adverse events, lack of adequate follow up, lack of power and inconsistent use of outcome events. Overall, there was a lack of evidence to support the use of SSRIs or venlafaxine for migraine prophylaxis. One trial suggested that venlafaxine had similar efficacy to amitriptyline but was better tolerated.[64] (LoE: 1++)

4.12 OTHER ANTIEPILEPTICS

A Cochrane review found no consistent evidence of efficacy in patients with episodic migraine for acetazolamide, lamotrigine, clonazepam, oxcarbazepine, viagabatrin or zonisamide when compared to placebo.65 Levetiracetam 1,000 mg daily was superior to placebo in reducing headache frequency and in the proportion of headache responders, but was not superior to topiramate 100 mg daily in reducing headache frequency. Further trials are needed to determine its efficacy. Carbamazepine was superior to placebo in the proportion of responders, which was deemed clinically significant, but high rates of adverse events were noted.[65] (LoE: 1++)

4.13 BOTULINUM TOXIN A

Empfehlung: Botulinum toxin A is not recommended for the prophylactic treatment of patients with episodic migraine.

Empfehlung: Botulinum toxin A is recommended for the prophylactic treatment of patients with chronic migraine where medication overuse has been addressed and patients have been appropriately treated with three or more oral migraine prophylactic treatments.

GOOD-PRACTICE POINT: Botulinum toxin A should only be administered by appropriately trained individuals under the supervision of a headache clinic or the local neurology service.

Systematic reviews on the efficacy of botulinum toxin A are based mainly on two large multicentre RCTs, the Phase III REsearch Evaluating Migraine Prophylaxis Therapy (PREEMPT) 1 and PREEMPT 2. Both trials were conducted in patients with chronic migraine over 24 weeks. Patients received two sets of injections at 12 week intervals, followed by an open label phase. [46, 66, 67] In PREEMPT 1 the primary endpoint of reduction in headache episodes from baseline compared to placebo was negative. However, there was significant reduction in secondary endpoints of headache days with botulinum toxin A versus placebo (-7.8 v -6.4; p=0.006) and migraine days (-7.6 v -6.1; p=0.002). [68] In PREEMPT 2 the primary endpoint was changed (prior to completion of the trial and before analysis) to reduction in headache days. It was stated that this was a better measure than headache episodes in patients with chronic migraine due to the prolonged, continuous nature of their headaches. There was a significant reduction in both headache days for botulinum toxin A versus placebo (-9.0 v -6.7; p<0.001) and migraine days (-8.7 v -6.3; p<0.001) compared with baseline. There was also a significant reduction in headache episodes in PREEMPT 2 for botulinum toxin A versus placebo (-5.3 v -4.6; p=0.003). [69] Post hoc analysis of pooled data from both trials of those patients who had previously used three or more migraine preventatives reported a bigger difference, compared to placebo, in headache days and migraine days for botulinum toxin A (-7.4 v -4.7; p<0.001) and migraine days (-7.1 v -4.3; p<0.001) compared with baseline. [70] (LoE: 1++, 1+)

In both PREEMPT trials about two thirds of the patients overused abortive treatments. In such patients MOH should be addressed first (see section 5). However, in patients where treatment of MOH has been unsuccessful, botulinum

toxin A should still be considered. A meta-analysis of trials of patients with episodic migraine or tension-type headache found no differencein efficacy compared to placebo. [66] (LoE: 1+)

Five individual RCTs provided low-strength evidence about the comparative effectiveness of botulinum toxin A versus other drugs for chronic migraine prevention in 350 adults ages 18–65 with 12–24 migraine days per month. No significant differences in likelihood of migraine prevention or improvement in migraine disability assessment were found for botulinum toxin A compared to topiramate. Absolute scores of the Headache Impact Test were significantly better with topiramate than botulinum toxin A, however, the need for acute drugs did not differ between the two. A single RCT examined the comparative effectiveness of botulinum toxin A versus divalproex sodium and found no differences between the two drugs for migraine prevention, migraine-related disability, or quality of life. [46] (LoE: 1++)

Adverse events were slightly more common in patients injected with botulinum toxin A compared to placebo (RR 1.25, 95% CI, 1.14 to 1.36), although they were not more likely to withdraw from the study as a result. Adverse events included ptosis, muscle weakness, neck pain and stiffness, paraesthesia and skin tightness. [46, 66] (LoE: 1++, 1+)

Botulinum toxin A (Botox®) has been accepted with restricted use in NHSScotland for adults with chronic migraine (headaches on at least 15 days per month of which at least eight days are with migraine) whose condition has failed to respond to ≥3 prior oral prophylactic treatments, where medication overuse has been appropriately managed. [70] This was based on clinical effectiveness and a cost-utility analysis (Markov model) which compared botulinum toxin A to best supportive care, over a three-year time horizon. […] Botulinum toxin A is required to be administered by appropriately trained personnel in hospital specialist centres, which may have implications for service delivery.

4.14 CALCITONIN GENE-RELATED PEPTIDE MONOCLONAL ANTIBODIES

Empfehlung: Erenumab, fremanezumab and galcanezumab are recommended for the prophylactic treatment of patients with chronic migraine where medication overuse has been addressed and patients have not benefitted from appropriate trials of three or more oral migraine prophylactic treatments.

Empfehlung: Fremanezumab and galcenezumab can be considered for the prophylactic treatment of patients with episodic migraine where medication overuse has been addressed and patients have not benefitted from appropriate trials of three or more oral migraine prophylactic treatments.

Three calcitonin-gene-related peptide (CGRP) monoclonal antibodies are available for use in NHSScotland. Erenumab targets the CGRP receptor. Fremanezumab and galcanezumab target the CGRP ligand. All are provided by monthly subcutaneous injections. Fremanezumab can also be given quarterly. A further CGRP monoclonal antibody, eptinezimab, also targets the CGRP ligand. It is only available as a quarterly intravenous infusion and is not currently available for use in NHSScotland.

Meta-analyses have demonstrated the effectiveness of CGRP monoclonal antibodies, with significant reductions in monthly migraine days (MMDs) compared to placebo in patients with episodic and chronic migraine.114-118 The meta-analyses included RCTs of each therapy as described below. Studies of the three CGRP monoclonal antibodies available in NHSScotland varied in the number of preventives participants were allowed to have tried prior to inclusion in the trial (LoE1++)

Two RCTs assessed the efficacy of erenumab in patients with episodic migraine: STRIVE and ARISE.119,120 A further RCT, LIBERTY, assessed its efficacy in patients with harder-to-treat episodic migraine (defined as prior failure of 2–4 migraine preventive agents).121 The majority of participants in these RCTs had a higher frequency of episodic migraine (8–14 days per month). There was a significant reduction in MMDs compared to placebo at 12 weeks in both STRIVE (-3.2 with 70 mg vs -3.7 with 140 mg vs -1.8 with placebo p<0.001) and ARISE (-2.9 with 70 mg vs -1.8 with placebo p<0.001).119,120 There was a ≥50% reduction in MMDs in 43.3% of participants with 70 mg and in 50% with 140 mg in STRIVE, and in 39.7% in ARISE.119,120 In the harder-to-treat population (LIBERTY) the reduction in MMDs with 140 mg at 12 weeks was lower (-1.8), but there was a much smaller placebo rate (-0.2), p=0.004. A ≥50% reduction in MMDs was reported in 30% of participants with 140 mg compared to 14% with placebo.121 (LoE1++)

In patients with chronic migraine, a high-quality phase 2 RCT of erenumab reported a significant reduction in MMDs compared to placebo at 12 weeks (-6.6 with 70 mg vs -6.6 with 140 mg vs -4.2 with placebo, p<0.001) from a baseline of 18 MMDs.122 There was a ≥50% reduction in MMDs in 40% of participants with 70 mg and in 41% with 140 mg. Forty-one percent of patients enrolled in the study overused abortive treatments, reflecting clinical experience where medication overuse headache remains common in patients presenting with chronic migraine (see section 5). (LoE1++)

A follow-up study of a phase 2 RCT in patients with episodic migraine showed that reductions in MMDs were sustained.130,131 Those in the placebo group were transferred onto 70 mg erenumab monthly and achieved a similar reduction in MMDs by week 16 compared to the group originally randomised to 70 mg. The 70 mg dose was

continued to week 64 and then increased to 140 mg. The mean change in MMDs from a baseline of 8.7 MMDs was -5.3 at 5 years and a ≥50% reduction was achieved in 71% of paticipants. 130 (LoE2++)

The HALO episodic migraine trial compared monthly doses of fremanezumab (225 mg) to quarterly doses (675 mg) or placebo. The baseline number of migraine days was 8.9±2.6 for the cohort receiving a monthly dose and 9.3±2.7 for the quarterly cohort, indicating that the majority of participants had a higher frequency of episodic migraine. There was a significant reduction in MMDs (-3.7 in the group who received monthly fremanezumab (225 mg) vs -3.4 with quarterly fremanezumab (675 mg), vs -2.2 with placebo (p<0.001)).123 In the open-label extension study, which included episodic migraine, chronic migraine and new enrollees, this increased to -5.1 MMDs with the monthly dose and -5.2 with the quarterly dose at 12 months in the episodic migraine cohort.132 There was a ≥50% reduction in MMDs in 41% of participants with the monthly dose and in 44.4% with the quarterly dose, which increased to 68% and 66% respectively at 12 months.123,132 (LoE1++, LoE 2++)

In the chronic migraine cohort of the HALO trial there was a significant reduction in MMDs compared to placebo at 12 weeks (-5.0 in the group who received monthly fremanezumab (675 mg loading and 225 mg monthly thereafter) vs -4.9 with quarterly fremanezumab (675 mg) vs -3.2 with placebo p<0.001).124 This increased to -8.0 for the monthly dose and -7.2 with the quarterly dose in the open-label extension study.132 There was a ≥50% reduction in MMDs in 47.7% with the monthly dose and 38% with the quarterly dose, which increased to 57% and 53% respectively at 12 months.124,132 The dose of 675 mg then a monthly dose of 225 mg used in the trial differs from the licensed monthly dose of 225 mg monthly or 675 mg quarterly. (LoE1++, LoE 2++)

In a study, FOCUS, of patients who had had treatment failure with up to four previous therapies, in which 60% of the patients had chronic migraine and 40% had episodic, the reduction in MMDs at 12 weeks was -4.1 with monthly fremanezumab (225 mg), and -3.7 with quarterly fremanezumab (675 mg). The 50% responder rate was 34% for both regimens.125 (LoE1++)

In the EVOLVE 1 and EVOLVE 2 RCTs of galcanezumab in patients with episodic migraine, there was a significant reduction in monthly migraine headache days (MHD) compared to placebo at 12 weeks (EVOLVE 1: -4.7 with 120 mg vs -4.6 with 240 mg vs -2.8 with placebo p<0.001, and EVOLVE 2: -4.3 with 120 mg vs -4.2 with 240 mg vs -2.3 with placebo p<0.001).126,127 There was a ≥50% reduction in monthly MHDs in 62.3% of participants with 120 mg and in 60.9% with 240 mg in EVOLVE 1, and in 59.3% with 120 mg and in 56.5% with 240 mg in EVOLVE 2. The baseline number of migraine days in EVOLVE 1 was 9.2±3.1 with 120 mg and 9.1±2.9 with 240 mg, and in EVOLVE 2 it was 9.07±2.9 with 120 mg and 9.06±2.9 with 240 mg, indicating that the trial cohort had higher frequency episodic migraine. (LoE1++)

An RCT, REGAIN, of galcanezumab in patients with chronic migraine (64% of whom overused abortive treatments) reported a significant reduction in monthly MHDs compared to placebo at 12 weeks (-4.8 with 120 mg vs -4.6 with 240 mg vs -2.7 with placebo, p<0.001, from a baseline of 19.4 monthly MHDs).128 There was a ≥50% reduction in monthly MHDs in 27.6% of participants with 120 mg and in 27.5% with 240 mg. Ninety-nine percent of patients entered the open-label extension with 81% completing 12 months of treatment. Patients remained blinded as per their original allocation. At month three all patients were given a 240 mg loading dose and then maintained on 120 mg monthly (with the option of a 120 mg top up at the discretion of the treating clinician). At 12 months the reduction in monthly MHDs improved to -9.0 in the previous 120 mg group, -8.0 in the previous 240 mg group and -8.5 in the previous placebo group.133 In the CONQUER RCT in patients with harder-to-treat migraine, participants received galcanezumab 120 mg or placebo.129 This included a loading dose of either 2 x 120 mg galcanezumab or 2 x placebo injections. (LoE1++)

At 12 weeks the reduction in monthly MHDs was -2.9 with 120 mg vs -0.3 with placebo in patients with episodic migraine (p<0.0001), 48.1% had a ≥50% reduction in monthly MHDs. For patients with chronic migraine the reduction was -6.0 with 120 mg galcanezumab vs -2.2 with placebo (p<0.0001), and 32% had a ≥50% reduction in monthly MHDs.129 All except two patients who completed the double-blind phase entered the open-label phase and 96% of these completed the study.134 All patients previously in the placebo group had a 240 mg loading dose at month three (2 x 120mg in the placebo group and 1 x 120mg and 1 x placebo in the 120 mg group). At 6 months the reduction in monthly MHDs was -3.8 for the previous 120 mg group versus -4.5 for the previous placebo group in patients with episodic migraine and -8.2 for the previous 120 mg group vs -6.5 for the previous placebo group in patients with chronic migraine.134 (LoE1++, LoE 2++)

When compared to topiramate in an RCT, erenumab was more effective in reducing MMDs (-5.86 erenumab vs -4.02 topiramate). There was a ≥50% reduction in MMDs in 55.4% of participants in the erenumab group compared with 31.2% in the topiramate group. Erenumab was significantly better tolerated than topiramate (used at standard doses); 10.6% of the erenumab cohort discontinued treatment compared to 38.9% on topiramate.135 Results from a network meta-analysis comparing CGRP monoclonal antibodies to topiramate or botulinum toxin A are limited.136 More head-to-head trials are needed before a recommendation can be made. The primary endpoint for CGRP trials is MMDs, whereas trials of botulinum toxin A used MHD therefore they are not directly comparable. (LoE1+)

Subgroup analyses of patients with migraine and concomitant medication overuse in trials of erenumab, fremanezumab and galcanezumab demonstrated similar efficacy to those without medication overuse.137-139 These subgroup analyses also demonstrated that the CGRP monoclonal antibodies reduced the use of acute medications. In the parent studies, medication overuse was defined as simple analgesia (eg paracetamol or NSAIDs) taken on 15 days per month, triptans on 10 days per month, and combination analgesics (including those with

simple analgesia and opioids) taken on 10 days per month. Although inclusion criteria varied between studies, all of the parent studies had some restriction on the intake of opioid and/or barbiturate containing medications. (LoE2++)

There are very limited data, in two small case series, describing outcomes of switching to a second CGRP monoclonal antibody if the first is ineffective.140,141 Further evidence is needed before a recommendation can be made. (LoE3)

All three CGRP monoclonal antibodies are well tolerated. Limited side effects were seen in the RCTs, and these were similar between the treatment and placebo groups.114-118 Injection site reactions were the most common adverse event reported.114-118 No increased rate of adverse event was reported in the extension studies.130,132,133 (LoE1++)

4.15 OCCIPITAL NERVE BLOCK

Four small RCTs measured short-term benefit (one week up to 28 days) of greater occipital nerve (GON) blocks. Each trial used different regimens. Three of the trials reported a reduction in headache frequency compared to placebo.71-73 The other trial reported no difference, however this could have been due to the placebo group receiving a small dose of lidocaine.74 Although they are used in headache clinics in Scotland further evidence is required before recommendations for use can be made. (LoE: 1+, 1-)

Department of Veterans Affairs Department of Defense (VA/DoD), 2023 [14].

Clinical practice guideline for management of headache

Zielsetzung/Fragestellung

The guidelines are designed to provide information and assist decision making. They are not intended to define a standard of care and should not be construed as one. Neither should they be interpreted as prescribing an exclusive course of management. Further, inclusion of recommendations for specific testing, therapeutic interventions, or both within these guidelines does not guarantee coverage of civilian sector care.

Methodik

Grundlage der Leitlinie

- Repräsentatives Gremium.
- Interessenkonflikte und finanzielle Unabhängigkeit dargelegt.
- Systematische Suche, Auswahl und Bewertung der Evidenz.
- Formale Konsensusprozesse unklar. Externes Begutachtungsverfahren dargelegt.
- Empfehlungen der Leitlinie sind eindeutig und die Verbindung zu der zugrundeliegenden Evidenz ist explizit dargestellt.
- Regelmäßige Überprüfung der Aktualität unklar.

Recherche/Suchzeitraum:

- Embase, Medline, PsychInfo, Agency for Healthcare Research and Quality to August 16, 2022.

LoE / GoR

- The Work Group used the GRADE approach to craft each recommendation and determine its strength. Per the GRADE approach, recommendations must be evidence based and cannot be made based on expert opinion alone. The GRADE approach uses the following four domains to inform the strength of each recommendation
  - Balance of desirable and undesirable outcomes
  - Confidence in the quality of the evidence
  - Values and preferences

- Other implications, as appropriate (Resource use, Equity, Acceptability, Feasibility, Subgroup considerations)

- Using these four domains, the Work Group determined the relative strength of each recommendation (Strong or Weak). Strong recommendation generally indicates High or Moderate confidence in the quality of the available evidence, a clear difference in magnitude between the benefits and harms of an intervention, similar patient values and preferences, and understood influence of other implications

Recommendation Strength and Direction	General Corresponding Text
Strong for	We recommend . . .
Weak for	We suggest . . .
Neither for nor against	There is insufficient evidence to recommend for or against . . .
Weak against	We suggest against . . .
Strong against	We recommend against . . .

Empfehlungen

B. Pharmacotherapy

b. Migraine – Preventive

Recommendation

4. We recommend candesartan or telmisartan for the prevention of episodic migraine.
(Strong for | Reviewed, New-replaced)

Discussion

An SR by Jackson et al. (2015) reported results of three RCTs examining angiotensin II receptor blockers (ARB) in the prevention of episodic migraine, with two studies focusing on candesartan and the third on telmisartan.(116, 118-120)

The SR by Jackson et al. (2015) found a significant reduction in headache frequency per month in the prevention of episodic migraine, favoring the aforementioned ARBs over placebo (standardized mean difference [SMD]: -1.12; 95% confidence interval [CI]: -1.97 to -0.27; I2: 29.1%).(116) However, rates of AEs were either on par with placebo or higher in those receiving ARBs.(118, 120) A parallel design RCT randomized patients (n=60) with migraine with or without aura who experienced 2–6 migraine days per month to two separate treatment periods.(120) After a 12-week period, the mean number of headache days was statistically lower among patients receiving candesartan than those randomized to placebo (13.6 versus 18.5 days; p=0.001). Additionally, the mean reduction in monthly migraine days was lower among those receiving candesartan compared with placebo (12.6 versus 9.0 days; p<0.001). Outcomes, including hours with migraine, hours with headache, level of disability, and days of sick leave, statistically favored candesartan over placebo. Adverse events were similar in the two treatment periods, such that acceptability and tolerability of candesartan approximated what was seen in the placebo arm.

A crossover RCT randomized adults (n=72) with episodic (n=71) or chronic migraine (n=1) into three 12-week treatment periods: candesartan (16 mg), slow-release propranolol (160 mg), or placebo.(119) The primary outcome for this study was migraine days per 4 weeks with a secondary outcome of headache days per 4 weeks. A statistically significant reduction of migraine days was found in both the candesartan (0.58) and propranolol (0.62) groups, compared with placebo. Reduction in headache days for each active pharmacotherapy was not reported.

Diener et al. (2009) reported a significant improvement in migraine days in patients receiving telmisartan compared with placebo (1.65 versus 1.15; p=0.03) from the 4-week baseline period compared with the last 4 weeks of a 12-week treatment period. The rate of AEs was similar between groups.(118)

Because ARBs are associated with hyperkalemia, renal failure, and hypotension, providers should monitor electrolytes, renal function, and blood pressure. Providers considering prescribing these ARBs should be aware that this class is contraindicated in pregnancy and that appropriate counseling among individuals of childbearing age regarding ARB-associated fetal toxicity should be provided.(116) Patient and provider values

and preferences would be similar because ARBs are accessible and well tolerated and could be prescribed by primary and specialty care providers alike.

The Work Group considered the assessment of the evidence put forth in the 2020 VA/DoD Headache CPG.(116, 118-120) No new studies on the effect of candesartan or telmisartan met the inclusion criteria for the 2023 VA/DoD Headache CPG systematic evidence review. Therefore, this recommendation is categorized as Reviewed, New-replaced. Although the available evidence base has not changed since the 2020 VA/DoD Headache CPG, the Work Group noted that across the three studies reviewed in the SR by Jackson et al. (2015), only one study either had a diagnosis of or met criteria for chronic migraine. Hence, this recommendation is now restricted to episodic migraine, whereas the 2020 VA/DoD Headache CPG included both episodic and chronic migraine. The Work Group's confidence in the quality of the evidence was moderate. A statistically significant reduction in the number of headache or migraine days or both was found. The benefits of improved headache control outweighed the burden of taking a daily medication with a favorable side-effect profile. Thus, the Work Group made the following recommendation: We recommend candesartan or telmisartan for the prevention of episodic migraine.

Recommendation

5. We recommend erenumab, fremanezumab, or galcanezumab for the prevention of episodic or chronic migraine.
   (Strong for | Reviewed, New-replaced)

Summary of the Evidence for CGRP Inhibitors

Since the 2020 VA/DoD Headache CPG, literature (not included in the evidence base nor impacting the strength of this recommendation) suggests that the use of erenumab, fremanezumab, and galcanezumab has grown and providers have become increasingly more familiar and comfortable with the use of mAbs for the prevention of episodic and chronic migraine.(141) Overall, these therapies are efficacious, well tolerated, and safe. They have been found to work in a broader array of patient populations, including patients living in the Middle East, Latin America, Japan, Korea, and other parts of Asia. Monoclonal antibodies have also been shown to be efficacious when patients have experienced treatment failures with other migraine preventive pharmacotherapies. Although erenumab, fremanezumab, and galcanezumab all resulted in statistically significant reductions in monthly migraine days, NMA data shows that erenumab is associated with the greatest reduction in monthly migraine days, followed by galcanezumab and then fremanezumab. These therapies are largely well tolerated, with some dosing regimens of fremanezumab and galcanezumab having statistically higher rates of AEs when compared with placebo or control groups. There have been no comparative effectiveness clinical trials of mAbs. When selecting an mAb, providers should be aware that some studies have shown, compared with placebo, an increased risk of developing hypertension while on erenumab, whereas other studies (not included in the evidence base nor impacting the strength of this recommendation) have not demonstrated this finding to be the case.(142, 143) Although not included in the evidence base nor impacting the strength of this recommendation, severe constipation has also been reported with erenumab in some studies, whereas other studies have reported a constipation risk to be similar between erenumab and other mAbs.(144, 145)

Continued collection and analyses of real-world data for mAb use, alone or in combination with other therapies, among patients living with migraine should continue. In one real-world data study of patients with episodic or chronic migraine (not included in the evidence base nor impacting the strength of this recommendation), they received erenumab for an average of 6.9 ± 2.7 months. Compared with baseline, a change occurred in both mean monthly headache days (-7.5 days; CI: 14.9 ± 6.6–7.4 ± 6.2; p<0.0001) and mean monthly migraine days (-6.2 days; CI: 12.1 ± 5.9–5.9 ± 5.5; p<0.0001) after 3 months of erenumab therapy.(146) In a combination therapy study (not included in the evidence base nor impacting the strength of this recommendation), Scuteri et al. (2022) conducted an SR and NMA examining the efficacy and safety of combination mAbs and onabotulinumtoxinA for chronic migraine.(147) The combination of each therapy resulted in a change of monthly headache days of -2.67 (95% CI: -4.42–0.93; n=393) after 3 months of combined treatment, higher than both mAb (1.94 days; p<0.0001) and onabotulinumtoxinA (1.86 days; p<0.0001) alone when compared with baseline. The authors for this SR and NMA reported that the quality of evidence was moderate.

The Work Group systematically reviewed evidence related to this recommendation (131-140) and considered the assessment of the evidence put forth in the 2020 VA/DoD Headache CPG.(121-130) Therefore, it is categorized as Reviewed, New-replaced. The Work Group's confidence in the quality of the evidence was moderate. The Work Group determined that the benefits of erenumab, fremanezumab, and galcanezumab outweighed the harms and burdens because the AEs were generally not statistically significant or significantly harmful. Patients would likely have some variation related to values and preferences for injectable mAbs. For

example, patients might prefer a once monthly option compared with treatments that might be once, twice, or thrice daily and have higher AE rates than placebo. Even though some might not want to experience a needle, patients are generally tolerant of injections given via an auto-injector. Moreover, providers are generally comfortable with prescribing auto-injectable therapies. Providers likely have become more comfortable with CGRP mAbs because this class of medications now has longer-term efficacy, effectiveness, safety, and tolerability data. In considering the safety profile of CGRP inhibitors in pregnancy and lactation, no human data is currently available. In an analysis from the WHO pharmacovigilance database, "no specific maternal toxicities, patterns of major birth defects, or increased reporting of spontaneous abortion were found" for galcanezumab, fremanezumab, and erenumab.(148) As such, the role of mAbs in pregnancy and lactation has not been established. Thus, the Work Group made the following recommendation: We recommend erenumab, fremanezumab, or galcanezumab for the prevention of episodic or chronic migraine.

Recommendation

6. We suggest intravenous eptinezumab for the prevention of episodic or chronic migraine.
   (Weak for | Reviewed, New-added)

Discussion

Ashina et al. (2020) examined the efficacy and safety of eptinezumab as a preventive treatment in a phase 3, randomized, double-blind, placebo-controlled study within an episodic migraine population.(149) Patients were randomized to either 30 mg of eptinezumab (n=224), 100 mg of eptinezumab (n=225), 300 mg of eptinezumab (n=224), or a placebo (n=225) via IV infusion. The primary efficacy endpoint was observed through a change in mean monthly migraine days for weeks 1–12 from the baseline. At 30 mg, 100 mg, and 300 mg doses of eptinezumab, there was a -4.0, -3.9, and -4.3 day reduction in monthly migraine days, respectively, compared with placebo (-3.2; p=0.0001). Treatment-emergent AEs, including upper respiratory tract infections and fatigue, occurred at low rates, though at higher rates than seen in the placebo arm.

Lipton et al. (2020) examined the efficacy and safety of eptinezumab as a preventive treatment within a phase 3, randomized, double-blind, placebo-controlled study within the chronic migraine population.(150) Patients were randomized to be administered 100 mg of eptinezumab (n=356), 300 mg of eptinezumab (n=350), or a placebo (n=366) via IV infusion. On average, patients reported 16.1±4.6 monthly migraine days and 20.5±3.1 monthly headache days at baseline across groups. The primary efficacy endpoint was observed through a change in mean monthly migraine days for weeks 1-12 from the baseline. Eptinezumab significantly improved monthly migraine days during weeks 1–12 (i.e., first dosing interval) at both the 100 mg dose (-7.7) and the 300 mg dose (-8.2) compared with placebo (-5.6; p<0.0001). Treatment-emergent AEs were fairly distributed across the three groups and included nasopharyngitis, upper respiratory tract infections, and fatigue. Silberstein et al. (2020) reported an incremental reduction in mean monthly migraine days and lower rates of treatment-emergent AEs from weeks 13–23 (i.e., second dosing interval) through 24 weeks.(151)

Ashina et al. (2022) examined the efficacy and safety of eptinezumab as a preventive treatment for episodic or chronic migraine among patients who had experienced two to four previous preventive treatment failures within a phase 3b, multi-arm, randomized, double-blind, placebo-controlled trial.(152) Patients who had at least 4 monthly migraine days (n=891) were randomized to receive at least one dose of 100 mg eptinezumab (n=299), 300 mg eptinezumab (n=294), or a placebo (n=298). The primary efficacy outcome was observed through a change in mean monthly migraine days from baseline to weeks 1–12. Both the eptinezumab 100 mg dose (-4.8) and eptinezumab 300 mg dose (-5.3) resulted in a statistically significant reduction in mean monthly migraine days from baseline throughout the study period compared with both doses of the placebo (p<0.0001). As both the 100mg and 300 mg doses of eptinezumab saw a reduction in HIT-6 score by more than six points, both doses also resulted in a clinically significant reduction in HIT-6 scores. Further, a statistically significant improvement was observed in key secondary endpoints, such as HIT-6 scores at week 12, both ≥50% and ≥75% responder rates and mean monthly migraine days in weeks 13–24 for eptinezumab 100 mg and 300 mg doses compared with placebo. COVID-19 was the most reported treatment-emergent AE, followed by nasopharyngitis and fatigue.

In an SR and meta-analysis examining the efficacy and safety of eptinezumab for the prevention of episodic or chronic migraine, Siahaan et al. (2022) analyzed data from patients with migraine (n=2,730) who participated in any of four RCTs of eptinezumab.(153). This analysis demonstrated that eptinezumab use was associated with a greater reduction in both monthly migraine days from baseline through week 12 and migraine reduction the day after infusion. Eptinezumab use was also associated with lower HIT-6 scores at weeks 4 and 12 and ≥50 and ≥75% responder rates compared with placebo. Additionally, rates of AEs between eptinezumab and placebo were comparable (RR: 1.01; 95% CI: 0.96–1.07; p=0.63; I2 = 0%). Interestingly, outcomes were unaffected by the duration of migraine, age, gender, or body mass index BMI). A separate meta-analysis of eptinezumab by

Yan et al. (2021), which examined different dosing regimens and their efficacy and safety, reported that all doses used in the RCTs significantly reduced mean monthly migraine days; this finding was especially true of the 300 mg dose.(154) Similarly to the analysis by Siahaan et al. (2022), no statistically significant difference occurred between eptinezumab and placebo in regard to treatment-emergent AEs.(153, 154)

In a subgroup analysis (not included in the evidence base nor impacting the strength of this recommendation) focusing on patients diagnosed with both chronic migraine and MOH, patients meeting the criteria for both headache types experienced 16.7±4.6 monthly migraine days across treatment groups.(155) Both the eptinezumab 100 mg dose (-8.4) and eptinezumab 300 mg dose (-8.6) resulted in a statistically significant reduction in mean monthly migraine days from baseline throughout the study period compared with the placebo dose ($p<0.0001$).

Patient preferences vary regarding this treatment. As per administration protocol, an infusion of eptinezumab is administered over a 30-minute period (±15 minutes) with additional time attributed to being monitored for at least 2 hours after the infusion is completed. Patients would also have to travel to and from the infusion center and arrange for time off from personal and professional responsibilities. However, these visits could potentially be coupled with another needed visit to health care providers co-located within the same medical center. Additionally, patient response to eptinezumab is observed quickly after the first dose. According to Diener et al. (2021), a statistically significant reduction in migraine occurred 1 day after infusion; 28.6% of patients receiving the 100 mg dose had a migraine and 27.8% of patients receiving the 300 mg dose had a migraine, whereas 42.3% of patients receiving the placebo had a migraine ($p<0.0001$).(155) Across studies, eptinezumab is proven to be an efficacious, safe, and tolerable treatment option for the prevention of episodic and chronic migraine, regardless of the duration of migraine, age, gender, or BMI. Eptinezumab also has value among patients who have been treating refractory migraine and those who experience MOH. In considering the safety profile of eptinezumab in pregnancy and lactation, the risk of adverse outcomes in pregnancy has not been characterized.

The Work Group systematically reviewed evidence related to this recommendation. (149, 150, 152-154) Therefore, it is categorized as Reviewed, New-added. The Work Group's confidence in the quality of the evidence was high. The Work Group determined that the benefits of eptinezumab slightly outweighed the harms and burdens because the treatment was found to be efficacious for the prevention of both episodic and chronic migraine as well as safe and tolerable for patients. Patient values and preferences varied, with an important differentiating factor for patients being the commitment to receiving infusions. Despite the high confidence in the quality of the evidence, efficacy of eptinezumab, and favorable safety and tolerability profile, the Work Group acknowledged that there is a lack of long-term safety data for eptinezumab.

Additionally, given that eptinezumab received its FDA approval for migraine prevention in 2020, the Work Group recognized that drug withdrawals in the U.S. occur in a bimodal distribution (within 1–5 years of release to the market, later at 15–20 years, or near the time of patent expiration). Furthermore, in the U.S., it is estimated that fewer than 1% of AEs are reported; hence, by the time safety signal becomes apparent, more than just those for whom AEs were reported might have been affected.(156-160) Thus, the Work Group made the following recommendation: We suggest intravenous eptinezumab for the prevention of episodic or chronic migraine.

Recommendation

7. We suggest lisinopril for the prevention of episodic migraine.
   (Weak for | Reviewed, Not changed)

Discussion

As an angiotensin-converting enzyme inhibitor, lisinopril is commonly used within primary and specialty care settings.

An SR by Jackson et al. (2015) reported the results of one RCT examining the efficacy of lisinopril as a preventive therapy for migraine.(116) Patients (n=60) ages 18–60 years with an episodic migraine received either lisinopril (10 mg once daily for 1 week followed by 20 mg once daily for 11 weeks) or placebo. After a 12-week intervention period, among the patients who completed the study (n=47), several endpoints were significantly improved among those taking lisinopril, including the number of headache days (-1.4 [-2.6 to -0.2]; mean reduction of 17%; standard deviation [SD]: 5–30%), migraine days (reduction of 21%; SD: 9–34%), and hours with headache (reduction of 20%; SD: 5–36%) compared with placebo. The headache severity index was significantly reduced by 20% (SD: 3–37%) among patients taking lisinopril compared with placebo. In considering this trial, the SR by Jackson et al. (2015) favored the treatment of episodic migraine with lisinopril over placebo (SMD: -0.47; 95% CI: -0.88–0.06).(116)

Lisinopril is contraindicated in pregnant patients and individuals of childbearing age who are not actively using contraception.(161) Human studies have not been conducted regarding the risks or benefits of use while breastfeeding.

The Work Group considered the assessment of the evidence put forth in the 2020 VA/DoD Headache CPG because no new studies on the effect of lisinopril met inclusion criteria for the 2023 VA/DoD Headache CPG systematic evidence review.(116) Therefore, this recommendation is categorized as Reviewed, Not changed. The Work Group's confidence in the quality of the evidence was low. The benefits slightly outweighed the harms, especially because most patients who develop migraine headaches are between ages 18 and 55 years and, therefore, are generally in a separate demographic from those who develop vascular disease. Because the medication is well tolerated and does not have a similar stigma reported in patients taking antidepressants for headache control, patients likely have similar preferences regarding this treatment. Provider preferences would also be similar because lisinopril is widely prescribed within primary and specialty care settings. Thus, the Work Group made the following recommendation: We suggest lisinopril for the prevention of episodic migraine.

Recommendation

8. We suggest oral magnesium for the prevention of migraine.
   (Weak for | Not reviewed, Not changed)

Recommendation

9. We suggest topiramate for the prevention of episodic and chronic migraine.
   (Weak for | Reviewed, New-replaced)

Discussion

Evidence suggests topiramate improves monthly migraine days for episodic and chronic migraines as demonstrated in two SRs.(140, 165) An SR by Overeem et al. (2021) demonstrated a statistically significant improvement in monthly migraine days by -1.11 in patients with episodic migraine (n=1,903), with a number needed to treat (NNT) of seven (50% responder rate) and number needed to harm (NNH) of 12, which includes cognitive, sensory, pain, and GI side effects.(165) An SR by Yang et al. (2021) demonstrated a statistically significant improvement in monthly migraine days by -2.30 compared with placebo in patients with chronic migraine.(140) These findings were consistent with the 2020 VA/DoD Headache CPG findings based largely on an SR by Mulleners et al. (2015), which examined the efficacy of topiramate as a treatment option for adults with episodic migraine.(166) This SR included 17 unique studies comparing various doses of topiramate (50–200 mg per day across studies) and examined the effect of topiramate on the Migraine-Specific Quality of Life Questionnaire (MSQL) and ≥50% responder rate. The mean duration of therapy was 19 weeks. When compared with placebo, topiramate significantly reduced the frequency of headaches and improved the ≥50% responder rate.

Adverse events increased with escalating topiramate doses, including cognitive, sensory, and GI side effects. Compared with placebo, topiramate has greater odds of AEs, including nausea, dizziness, and somnolence (OR: 1.35; 95% CI: 1.06–1.73) and withdrawal because of AEs (OR: 2.08; 95% CI: 1.56, 2.78).(167) The most common AEs included dizziness or vertigo, paresthesia, cognitive complaints, somnolence, and taste perversion.(140, 165, 166) Providers are encouraged to titrate slowly when starting a patient on topiramate to reduce the risk of side effects, including cognitive side effects.

Consideration of comorbidity profiles is important when discussing potential benefits and harms. For instance, topiramate might be effective for patients with concurrent obesity, epilepsy, or alcohol use disorder. On the other hand, it might be less appropriate for patients with renal calculi, low weight, eating disorders, and baseline cognitive difficulties. Topiramate also has a risk of causing metabolic acidosis. Providers should engage in discussions with patients regarding effective contraception because of the reduced efficacy of contraception at topiramate doses >200 mg. Additionally, topiramate use during pregnancy (particularly during the first trimester) has an increased risk of teratogenicity.(168)

Patient preferences vary regarding this treatment. The patient focus group noted that topiramate can be burdensome because of side effects and that it can be difficult to remember to take medication daily. On the other hand, this medication is easily obtained and prescribed in primary care settings, although topiramate must be titrated slowly to minimize side effects, which can be burdensome for prescribers and patients. The cognitive side effects can also be extremely bothersome for patients, especially in patients with TBI or PTH, and should be used cautiously or avoided; however, patients with concomitant alcohol use disorders, seizures, or obesity might prefer this treatment.

The Work Group systematically reviewed evidence related to this recommendation (140, 165) and considered the assessment of the evidence put forth in the 2020 VA/DoD Headache CPG.(166, 167) Therefore, it is categorized as Reviewed, New-replaced. The Work Group's confidence in the quality of the evidence was moderate. The body of evidence had some limitations including ROB.(140, 165) The benefits of topiramate in improving monthly migraine days in patients with chronic and episodic migraines slightly outweighed the potential harm of AEs, such as cognitive effects and paresthesia. Patient values and preferences vary because some patients might prefer not to take medication, and they might have concerns about potential cognitive effects or other side effects of topiramate. Other patients might prefer to take a medication that might help with weight loss, such as topiramate. Thus, the Work Group made the following recommendation: We suggest topiramate for the prevention of episodic and chronic migraine.

Recommendation

10. We suggest propranolol for the prevention of migraine.
    (Weak for | Reviewed, Not changed)

Discussion

No new evidence on propranolol for the prevention of migraine headache was retrieved during the systemic evidence review carried out as part of this CPG update. An SR of three RCTs (n=238) by He et al. (2017) from the 2020 VA/DoD Headache CPG suggested propranolol decreases migraine headache days: −0.29 (CI: -0.49 to -0.09) when compared with placebo.(167) The SR found the ≥50% responder rate was not statistically significant when compared with placebo. He et al. (2017) also demonstrated no statistically significant differences in all-cause study withdrawal or withdrawal because of AEs when compared with placebo.(167) AEs of propranolol can include fatigue, dizziness, lightheadedness, exercise intolerance, and sexual dysfunction. The systematic evidence review did not provide specific dosing recommendations or dosing strategies (e.g., long-acting versus short-acting preparations). In patients requiring high doses or with a history of cardiac disease, electrocardiograms (ECG) might be needed for monitoring. Propranolol is used to treat hypertension and certain types of tremors and might be effective for patients with these comorbid conditions.

Patient preferences vary regarding this treatment. Some patients might find propranolol less favorable than other evidence-based treatments, such as topiramate or the CGRP receptor antagonists, because of propranolol's effect on heart rate, particularly in patients who exercise frequently and are unable to maximize their heart rate during cardiovascular (CV) activity. Further, dosing multiple times a day and the risk of orthostasis and bradycardia might be burdensome and could potentially cause discontinuation. Patients with concomitant anxiety might find propranolol helpful for their headaches and anxiety.

The Work Group considered the assessment of the evidence put forth in the 2020 VA/DoD Headache CPG.(167) Therefore, this recommendation is categorized as Reviewed, Not changed. The Work Group's confidence in the quality of the evidence was moderate. The body of evidence had some limitations including small sample size, limited duration of follow-up (12–16 weeks), and imprecision.(167) The benefits of propranolol slightly outweighed the potential harms and AEs. Patient values and preferences were similar because of the low side-effect profile. The Work Group also considered this recommendation's impact on patients with anxiety, tremors, or hypertension. Thus, the Work Group made the following recommendation: We suggest propranolol for the prevention of migraine.

Recommendation

11. We suggest valproate for the prevention of episodic migraine.
    (Weak for | Reviewed, New-replaced)

Discussion

Mulleners et al. (2015) performed a meta-analysis of antiepileptics in migraine prophylaxis that included 10 eligible valproate studies.(166) Active interventions included topiramate, propranolol, and flunarizine in a range of doses (400–1,500 mg per day) and study duration (8–12 weeks, average 11 weeks).(166)

In six placebo-controlled trials, valproate was found to be more effective in treating episodic migraine at all assessed time points, including 4, 8, and 12 weeks.(169-174) Four placebo-controlled divalproex sodium trials showed patients receiving active treatment were twice as likely to experience a 50% reduction in headache frequency.(172, 175-177) One trial found that sodium valproate was significantly superior to placebo for the same metric but different between treatments.(171)

Mulleners et al. (2015), which included two crossover trials of sodium valproate, showed significant headache frequency reduction in the active group compared with the placebo group of approximately four headaches per 28 days.(170, 171) Comparisons with flunarizine (176) and propranolol (172) were not significantly

different between treatments. No placebo-controlled studies reported QoL measures. No evidence of a difference in response to increased dose was found.

Side effects of valproate include boxed warnings for hepatotoxicity and pancreatitis, including fatal hemorrhagic cases. Hepatotoxicity can be fatal and might occur within the first 6 months of treatment. Monitoring liver function for the occurrence of thrombocytopenia, leukopenia, eosinophilia, and anemia might be warranted, especially in patients with a risk of mitochondrial disease. Valproate can cause serious congenital malformations, especially affecting the brain and spinal cord, and can also cause disabilities in coordination, learning, communication, and behavior in babies exposed to the medication before birth.(178) Potential weight gain might be of particular concern in active duty Service members.(166, 179-181). Additional noteworthy AEs associated with valproate include alopecia, somnolence, GI upset, tremors, and hyperammonemia.(182)

Evidence from an SR by Jackson et al. (2015) included four RCTs on valproate for episodic or mixed chronic daily headache or both with a primary outcome of headache days per month.(116) In all four RCTs, valproate showed a clear benefit in terms of reduction of headache days per month compared with placebo for episodic migraine (-1.5 headache per month; 95% CI: -2.1 to -0.8). The quality of evidence for this review was moderate.

The Work Group considered the evidence put forth in the 2020 VA/DoD Headache CPG because no additional studies met inclusion criteria for the 2023 VA/DoD Headache CPG systematic evidence review.(116, 166) Therefore, this recommendation is categorized as Reviewed, New-replaced. The Work Group's confidence in the quality of the evidence was moderate. The body of evidence had some limitations, including a lack of relevant newly published studies on the topic. The benefits slightly outweighed the harms and burdens of this medication because valproate has demonstrated a beneficial reduction of headache days per month for individuals with episodic migraine. Patient values and preferences varied because certain patients might be willing to take valproate formulations for prophylaxis given its long-standing evidence for benefit. However, other patients might find hair loss and weight gain especially burdensome, and women migraineurs of child-bearing age would have to consider the implication of contraceptive compliance. Despite its long history in medical use, serious but rare side effects limit the use of this medication by providers when prescribing. Thus, the Work Group made the following recommendation: We suggest valproate for the prevention of episodic migraine.

Recommendation

12. We suggest memantine for the prevention of episodic migraine.
    (Weak for | Reviewed, New-added)

Discussion

Evidence suggests memantine improves monthly migraine headaches and monthly migraine days as well as migraine-related disability in patients with episodic migraine. This recommendation is based on two RCTs by Noruzzadeh et al. (2016) (n=52) and Shanmugam et al. (2019) (n=59) within an SR by Mistry et al. (2021).(183-185) In both RCTs, the authors found improvement in the primary endpoint of monthly frequency of migraine headaches; two fewer migraines per month at 12 weeks and three fewer per month at 24 weeks versus placebo in the Noruzzadeh et al. (2016) (184) and Shanmugan et al. (2019) trials,(185) respectively. The two RCTs also evaluated different secondary endpoints. Norrazudeh et al. (2016) examined reduction in monthly migraine days (baseline of 10 days to 2 days for memantine versus 10 days to 8 days for placebo) and improvement in Migraine Disability Assessment (MIDAS) rank (baseline of moderate disability improved to mild with memantine versus no change with placebo), although Shanmugam et al. (2019) included an assessment of ≥50% improvement from baseline (85% for memantine versus 51% for placebo) and number of rescue treatments needed (approximate baseline of 9 treatments reduced to 0.75 treatments for memantine and 3.72 treatments for placebo).(184, 185) Effect sizes were large (Cohen d>0.8), though both RCTs were small.(184, 185) Based on the trial by Shanmugam et al. (2019), the NNT with memantine for a 50% reduction in migraine frequency is three.(185)

Patient preferences vary regarding this treatment. Memantine is easily accessible to patients and can be offered by any prescriber (i.e., no specialist appointment required). Memantine has some adverse effect burden for the patient (e.g., dizziness, somnolence, nausea reported both in the reviewed RCTs and product labelling). Memantine has minimal resource implications for the health system.

The Work Group systematically reviewed evidence related to this recommendation.(183) Therefore, it is categorized as Reviewed, New Added. Using USPSTF criteria, both RCTs were rated as good quality, but concerns arose about small sample sizes and external validity (e.g., generalizability) with a VA or DoD population. Therefore, the Work Group's confidence in the quality of the evidence was moderate.(183) The benefits of memantine for reduction in migraine frequency and monthly migraine days outweighed the potential harms of AEs, which were determined to be mild and not clearly different from placebo. Patient

values and preferences were deemed similar because most patients would prefer an effective treatment with minimal side effects and low cost as well as no referral to advanced specialty care required. Thus, the Work Group made the following recommendation: We suggest memantine for the prevention of episodic migraine.

Recommendation

13. We suggest atogepant for the prevention of episodic migraine.
(Weak for | Reviewed, New-added)

Recommendation

14. We suggest onabotulinumtoxinA injection for the prevention of chronic migraine.
(Weak for | Reviewed, Not changed)

Discussion

The Work Group reviewed two SRs by Barad et al. (2022) and Yang et al. (2021).(140, 187) Barad et al. (2022) completed an SR of the literature on local interventional procedures, including nerve blocks, trigger point injections, implantable stimulation, and chemodenervation.(187) An additional SR was included in the 2020 VA/DoD Headache CPG evidence base supporting this recommendation.(188) The review that focused on chemodenervation with onabotulinumtoxinA included two RCTs of moderate size (n=1384); these trials demonstrated a decrease in 1.8 headache days per month for chemodenervation compared with placebo. The SMD for this intervention was -0.28, which is considered small, a statistically significant effect size favored onabotulinumtoxinA.(187) The Work Group's confidence in the quality of this evidence was moderate. Yang et al. (2021) completed an SR that focused on the comparative effectiveness of interventions for chronic migraine, including erenumab, onabotulinumtoxinA, and topiramate.(140) The Work Group focused on the five RCTs in this SR evaluating onabotulinumtoxinA (n=1,574), a few of which were also included in the SR by Barad et al. (2022).(140, 187) For the critical outcome of change in headache days, the SR by Yang et al. (2021) found a reduction of 1.9 headache days in patients treated with onabotulinumtoxinA compared with placebo.(140) The Work Group's confidence in the quality of this evidence was also moderate.

Adverse events were greater for the onabotulinumA treatment arms in both SRs. Barad et al. (2022) reported an AE rate of 29% in the treatment arm compared with 12% in the placebo arm, and Yang et al. (2021) noted an OR of 0.64 for AEs in the placebo group compared with the treatment arm.(140, 187) Despite the higher rate of AEs, these AEs were mild (e.g., neck pain, injection-site pain, drooping eyelid) and the treatment was well tolerated with decreasing AE rates with repeated treatments. Burdens for the individual include quarterly travel to receive the injections. Overall, the systematic evidence review shows a small, but statistically significant treatment effect with limited burdens to the patient, which supports this intervention as a treatment option for the management of chronic migraine.

Large variation occurs in patient preferences regarding this treatment. The patient focus group noted a desire for treatments beyond oral medications but also expressed a need for more virtual care options, through which onabotulinumtoxinA cannot be administered. The relative infrequency of the treatment for many would be viewed as a benefit; however, some patients have "needle phobia" and would not tolerate the necessary multiple injections. System considerations include the resource use related to the cost of training personnel and equity concerns because the treatment requires specialized providers and the medication must be stored in controlled temperatures and reconstituted by the treatment team at, or near, the time of the injection.

The Work Group systematically reviewed evidence related to this recommendation (140, 187) and considered the assessment of the evidence put forth in the 2020 VA/DoD Headache CPG.(188) Therefore, it is categorized as Reviewed, Not changed. The Work Group's confidence in the quality of the evidence was moderate. The body of evidence had some limitations, including industry sponsoring of the large RCTs and small statistical effect sizes.(140, 187) The benefits of onabotulinumtoxinA injections slightly outweighed the potential harm given the mild AE profile and limited patient burden. Patient values and preferences varied largely because some patients might prefer the relatively infrequent need for treatment and lack of oral medications and potential side effects, although others would opt against injections. Thus, the Work Group made the following recommendation: We suggest onabotulinumtoxinA injection for the prevention of chronic migraine.

Recommendation

15. We suggest against abobotulinumtoxinA or onabotulinumtoxinA injection for the prevention of episodic migraine.
(Weak against | Reviewed, Not changed)

Recommendation

16. There is insufficient evidence to recommend for or against rimegepant for the prevention of episodic migraine.
(Neither for nor against | Reviewed, New-added)

Recommendation

17. We suggest against the use of gabapentin for the prevention of episodic migraine.
(Weak against | Reviewed, New-replaced)

Recommendation

18. There is insufficient evidence to recommend for or against levetiracetam for the prevention of episodic migraine.
(Neither for nor against | Reviewed, New-added)

Discussion

Yen et al. (2021) performed an SR and meta-analysis regarding the efficacy of levetiracetam in migraine prophylaxis.(191) The group analyzed eligible data from four RCTs (n=192) and four prospective studies (n=85) published between 2005 and 2019. Two trials focused on the efficacy of levetiracetam on pediatric migraine,(192, 193) while the others discussed use of levetiracetam in adult migraines.(194-197) The studies employed a variety of levetiracetam dosing strategies within the therapeutic range of 500–3,000 mg per day, and follow-up periods ranged from 1–12 months.

The main outcome was the number of patients with >50% headache frequency reduction. Meta-analysis of the four RCTs demonstrated a significantly larger number of participants with >50% headache frequency reduction in the levetiracetam group than the placebo group (overall RR: 0.46; 95% CI: 0.35–0.61).(194-197)

Other outcomes included degree of disability, drug intake value, and number of patients achieving migraine free status. The mean degree of disability was assessed in only one RCT, which reported a significant reduction in migraine disability in the levetiracetam group (from baseline 3.33 ± 0.81 to 1.66 ± 0.76) compared with the placebo group (baseline 3.19 ± 0.94 to 2.38 ± 0.94).(194) Rapoport et al. (2005) assessed the degree of disability using MIDAS score, which was significantly reduced after using levetiracetam for 3 months (62.8 days per month at baseline to 40.8 days per month).(198) Pizza et al. (2011) reported a significant reduction in abortive drug intake for acute headache symptoms compared with baseline values.(199) Some studies reported the number of patients being migraine free after intervention. In Brighina et al. (2006), 7 of 16 patients, and 4 of 20 patients in Pakalnis et al. (2007) were completely migraine-free after the entire medication process.(200, 201)

Mild to moderate adverse effects of levetiracetam were observed in the studies, including irritability;(194, 201) somnolence;(194, 197, 199-201) dizziness or lethargy;(196, 197, 199, 200) asthenias;(194, 201) daytime sedation;(196) weight gain; memory problems;(201) lack of concentration;(198, 199) epigastric pain;(199, 200) and moodiness and hyperactive behavior.(197) The studies reported no significant difference between levetiracetam and placebo groups, and no severe adverse effects were attributed to levetiracetam

The Work Group systematically reviewed evidence related to this recommendation. (191) Therefore, it is categorized as Reviewed, New-added. The Work Group's confidence in the quality of the evidence was very low. All studies reported acceptable randomization processes and blinding of patients and providers. There was heterogeneity in the included patients, although some studies did not distinguish between migraine types (episodic or chronic; with or without aura), which might have influenced the results of pooled data, and the participant age groups varied among the studies (4–72 years). The benefits of levetiracetam, including reduced headache frequency and severity in adult and pediatric migraineurs, were balanced with the potential harms of adverse effects. Levetiracetam might present an attractive prophylactic option for migraine because of lack of hepatic metabolism and minimal drug interactions.(202) Levetiracetam was generally well tolerated in this SR and meta-analysis, with mild-to-moderate AEs. Patient values and preferences varied. Patients with epilepsy might prefer to treat both conditions with one medication, noting that teratogenic potential appears to be less relative to other antiepileptic medications.(203) However, patients with comorbid PTSD or depression might prefer to avoid adverse effects that could worsen mood. Thus, the Work Group made the following recommendation: There is insufficient evidence to recommend for or against levetiracetam for the prevention of episodic migraine.

4 Detaillierte Darstellung der Recherchestrategie

Cochrane Library - Cochrane Database of Systematic Reviews (Issue 02 of 12, February 2024) am 12.02.2024

#	Suchfrage
1	MeSH descriptor: [Migraine Disorders] explode all trees
2	(migrain*):ti,ab,kw
3	(hemicrania*):ti,ab,kw
4	#1 OR #2 OR #3
5	#4 with Cochrane Library publication date from Feb 2019 to present, in Cochrane Reviews

Systematic Reviews in PubMed am 12.02.2024

verwendete Suchfilter:
Konsentierter Standardfilter für Systematische Reviews (SR), Team Informationsmanagement der Abteilung Fachberatung Medizin, Gemeinsamer Bundesausschuss, letzte Aktualisierung am 14.02.2023.

#	Suchfrage
1	"migraine disorders"[mh]
2	migrain*[tiab]
3	hemicrania*[tiab]
4	#1 OR #2 OR #3
5	(#4) AND (systematic review[ptyp] OR meta-analysis[ptyp] OR network meta-analysis[mh] OR (systematic*[tiab] AND (review*[tiab] OR overview*[tiab])) OR metareview*[tiab] OR umbrella review*[tiab] OR "overview of reviews"[tiab] OR meta-analy*[tiab] OR metaanaly*[tiab] OR metanaly*[tiab] OR meta-synthes*[tiab] OR metasynthes*[tiab] OR meta-study[tiab] OR metastudy[tiab] OR integrative review[tiab] OR integrative literature review[tiab] OR evidence review[tiab] OR ((evidence-based medicine[mh] OR evidence synthes*[tiab]) AND review[pt]) OR ((("evidence based" [tiab:~3]) OR evidence base[tiab]) AND (review*[tiab] OR overview*[tiab])) OR (review[ti] AND (comprehensive[ti] OR studies[ti] OR trials[ti])) OR ((critical appraisal*[tiab] OR critically appraise*[tiab] OR study selection[tiab] OR ((predetermined[tiab] OR inclusion[tiab] OR selection[tiab] OR eligibility[tiab]) AND criteri*[tiab]) OR exclusion criteri*[tiab] OR screening criteri*[tiab] OR systematic*[tiab] OR data extraction*[tiab] OR data synthes*[tiab] OR prisma*[tiab] OR moose[tiab] OR entreq[tiab] OR mecir[tiab] OR stard[tiab] OR strobe[tiab] OR "risk of bias"[tiab]) AND (survey*[tiab] OR overview*[tiab] OR review*[tiab] OR search*[tiab] OR analysis[ti] OR apprais*[tiab] OR research*[tiab] OR synthes*[tiab]) AND (literature[tiab] OR articles[tiab] OR publications[tiab] OR bibliographies[tiab] OR published[tiab] OR citations[tiab] OR database*[tiab] OR references[tiab] OR reference-list*[tiab] OR papers[tiab] OR trials[tiab] OR studies[tiab] OR medline[tiab] OR embase[tiab] OR cochrane[tiab] OR pubmed[tiab] OR "web of science" [tiab] OR cinahl[tiab] OR cinhal[tiab] OR scisearch[tiab] OR ovid[tiab] OR ebsco[tiab] OR scopus[tiab] OR epistemonikos[tiab] OR prospero[tiab] OR

#	Suchfrage
	proquest[tiab] OR lilacs[tiab] OR biosis[tiab])) OR technical report[ptyp] OR HTA[tiab] OR technology assessment*[tiab] OR technology report*[tiab])
6	(#5) AND ("2019/02/01"[PDAT] : "3000"[PDAT])
7	(#6) NOT "The Cochrane database of systematic reviews"[Journal]
8	(#7) NOT (retracted publication [pt] OR retraction of publication [pt] OR preprint[pt])

Leitlinien in PubMed am 12.02.2024

verwendete Suchfilter:
Konsentierter Standardfilter für Leitlinien (LL), Team Informationsmanagement der Abteilung Fachberatung Medizin, Gemeinsamer Bundesausschuss, letzte Aktualisierung am 21.06.2017.

#	Suchfrage
1	"migraine disorders"[mh]
2	"migrain*"[ti]
3	"hemicrania*"[ti]
4	"headache disorders, primary"[mh:noexp]
5	"Headache Disorders"[mh:noexp]
6	"headache"[majr]
7	"headache*"[ti]
8	#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7
9	(#8) AND (Guideline[ptyp] OR Practice Guideline[ptyp] OR guideline*[Title] OR Consensus Development Conference[ptyp] OR Consensus Development Conference, NIH[ptyp] *OR recommendation*[ti])*
10	(#9) AND ("2019/02/01"[PDAT] : "3000"[PDAT])
11	(#10) NOT (retracted publication [pt] OR retraction of publication [pt] OR preprint[pt])

Iterative Handsuche nach grauer Literatur, abgeschlossen am 13.02.2024

- Arbeitsgemeinschaft der Wissenschaftlichen Medizinischen Fachgesellschaften (AWMF)
- Nationale VersorgungsLeitlinien (NVL)
- National Institute for Health and Care Excellence (NICE)
- Scottish Intercollegiate Guideline Network (SIGN)
- World Health Organization (WHO)
- ECRI Guidelines Trust (ECRI)
- Dynamed / EBSCO
- Guidelines International Network (GIN)
- Trip Medical Database

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Beteiligung von Fachgesellschaften und der AkdÄ zu Fragen der Vergleichstherapie nach §35a Abs. 7 SGB V i.V.m. VerfO 5. Kapitel § 7 Abs. 6

Verfahrens-Nr.: 2024-B-024

Verfasser	
Name der Institution	Deutsche Migräne- und Kopfschmerzgesellschaft (DMKG) Deutsche Gesellschaft für Neurologie (DGN)
Namen aller beteiligten Sachverständigen	
Datum der Erstellung	12. März 2024

Indikation
…wird angewendet zur Prophylaxe von Migräne bei Erwachsenen mit mindestens 4 Migränetagen pro Monat.
Fragen zur Vergleichstherapie
Was ist der Behandlungsstandard in o.g. Indikation unter Berücksichtigung der vorliegenden Evidenz? Wie sieht die Versorgungspraxis in Deutschland aus? *(Bitte begründen Sie Ihre Ausführungen; geben Sie ggf. zitierte Quellen in einer Referenzliste an.)*
Betroffene Erwachsene mit Migräne, die an 3 und mehr Migräneattacken im Monat leiden, die die Lebensqualität beeinträchtigen, kann nach der gemeinsamen Leitlinie der DGN und der DMKG eine Migräneprophylaxe angeboten werden. Basismaßnahmen stellen die Edukation der Betroffenen, das regelmäßige Ausüben von Entspannungsverfahren und Ausdauersport dar. Ab 4 Migränetagen im Monat können auch medikamentöse prophylaktische Maßnahmen zum Einsatz kommen. An Substanzen zur Migräneprophylaxe stehen mit Zulassung in dieser Indikation zur Verfügung: Amitriptylin, Metoprolol, Propranolol, Flunarizin, Topiramat, Erenumab, Galcanezumab, Fremanezumab, und Eptinezumab sowie für betroffene mit chronischer Migräne (≥ 15 Kopfschmerztage) OnabotulinumtoxinA. Der Behandlungstandard berücksichtigt jedoch nicht nur die formale Zulassung (≥4 Migränetage / Monat) der genannten Substanzen sondern auch die Erstattungssituation. Aktuell sind die herkömmlichen Substanzen (Betarezeptorenblocker, Topiramat, Amitriptylin, Flunarizin) die Therapie der ersten Wahl. In der täglichen ärztlichen Praxis werden dabei die Beta-Blocker (Metoprolol oder Propanolol) oder Amitriptylin zuerst eingesetzt. Aufgrund der Notwendigkeit zur mehrfach täglichen Verabreichung von Propranolol wird Metoprolol der Vorzug gegeben. Bei Flunarizin ist zu berücksichtigen, dass nach der Fachinformation eine Behandlung nicht länger als 6 Monate erfolgen sollte, im klinischen Alltag jedoch oft längere Therapiephasen erforderlich sind. Aufgrund der aktuellen Empfehlungen der EMA und des BfArm (Rote Hand-Brief) kann Topiramat nur noch eingeschränkt eingesetzt werden. Frauen im gebärfähigen Alter müssen vor Verordnung von Topiramat einen Schwangerschaftstest durchführen und darüber aufgeklärt werden, dass eine sichere Verhütung (orale Kontrazeption und Barrieremethode) eingesetzt werden muss. Aufgrund der Vielzahl der zur Verfügung stehenden Alternativen zur medikamentösen Prophylaxe der Migräne wird im klinischen Kontext Topiramat mittlerweile nur noch in Einzelfällen bei Frauen im gebärfähigen Alter unter Berücksichtigung der Anforderungen zur Aufklärung eingesetzt. Da die Migräne mit einer 12-Monats-Prävalenz von 14,8 % bei Frauen und 6 % der Männer in Deutschland

auftritt, kann Topiramat nicht als geeignete Vergleichssubstanz herangezogen werden, da ein Großteil der von Migräne betroffenen nicht mit Topiramat behandelt werden sollen.
Die 4 monoklonalen Antikörper gegen CGRP bzw. CGRP-Rezeptor sind bezüglich ihrer wissenschaftlichen Evidenz als gleichwertig anzusehen. Die Erstattungssituation ist jedoch unterschiedlich:
Für Erenumab wird nur eine Vortherapie mit einer anderen Migräneprophylaxe gefordert (G-BA-Beschluss vom 02.05.2019 sowie vom 21.10.2021). Für Galcanezumab und Fremanezumab sind Vorbehandlungen mit Beta-Blocker, Amitryiptylin, Topiramat sowie Flunarizin und im Fall der chronischen Migräne Botulinumtoxin zu fordern. Da für Eptinezumab im Rahmen des GBA-Verfahrens kein Zusatznutzen zuerkannt wurde, sind Vortherapien nicht erforderlich, es entfällt dadurch jedoch auch der Status einer „bundesweiten Praxisbesonderheit“, sodass die Substanz im klinischen Alltag nachrangig, insbesondere beim Wechsel von monoklonalen Antikörpern, eingesetzt wird.

Gibt es Kriterien für unterschiedliche Behandlungsentscheidungen in der o.g. Indikation, die regelhaft berücksichtigt werden? Wenn ja, welche sind dies und was sind in dem Fall die Therapieoptionen?
(Bitte begründen Sie Ihre Ausführungen; geben Sie ggf. zitierte Quellen in einer Referenzliste an.)

Neben den oben genannten grundsätzlichen Ausführungen zur Zulassung, zu Einschränkungen der Verordnung bei Frauen im gebärfähigen Alter und zur Erstattungsfähigkeit werden klinische Parameter herangezogen, um eine Auswahl von Migräneprophylaktika zu treffen. Im Wesentlichen wird hierbei auf Begleiterkrankungen und die Lebensumstände der betroffenen Person Bezug genommen. Dies wird im Folgenden beispielhaft ausgeführt, die individuellen Therapieentscheidungen werden darüber hinaus persönliche Erfahrung der Verordner und auch Patientenpräferenzen mitberücksichtigen:
Betablocker können dann nicht zum Einsatz kommen, wenn es vor oder unter ihrem Einsatz zur Bradykardie oder relevanten Hypotonie sowie Reizleitungsstörung im EKG kommt. Weitere Kontraindikationen sind Asthma bronchiale oder eine schwere Schuppenflechte.
Amitriptylin ist aufgrund der Tendenz zur Gewichtszunahme ungünstig, wenn ohnehin bereits eine klinisch relevante Adipositas vorliegt. Amitriptylin ist hingegen günstig, wenn psychische Komorbidität (Insomnie, Depressivität, Angststörung) vorliegen. Auch bei Amitriptylin müssen unter Therapie EKG-Ableitungen und Laborkontrollen erfolgen und können sich im Verlauf als Kontraindikation für den Einsatz erweisen.
Flunarizin führt tendenziell zur Gewichtszunahme, außerdem kann eine Depression ausgelöst oder verstärkt werden, woraus sich klinische Kontraindikationen ergeben.
Neben den bereits genannten Einschränkungen zur Verordnung bei Frauen im gebärfähigen Alter kann Topiramat bei Nierensteinen nicht eingesetzt werden und wird bei psychischer Komorbidität zurückhaltend eingesetzt, da Depression und Angststörung unter der Einnahme von Topiramat zunehmen können. Außerdem kann Topiramat zu reversiblen kognitiven Nebenwirkungen führen, was gelegentlich ebenfalls zum Absetzen der Substanz zwingt.
OnabotulinumtoxinA zeichnet sich durch gute Verträglichkeit aus, ist jedoch nur für den Einsatz bei chronischer Migräne zugelassen.
Die monoklonalen Antikörper Erenumab, Galcanezumab, Fremanezumab und Eptinezumab zeichnen sich durch eine gute Wirksamkeit, einen im Vergleich zu den oralen Substanzen raschen Wirkungseintritt und eine ausgesprochen niedrige Nebenwirkungsrate aus. Ihr Einsatz kann nur erfolgen, wenn die oben genannten Erstattungsvoraussetzungen erfüllt sind.

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Beteiligung von Fachgesellschaften und der AkdÄ zu Fragen der Vergleichstherapie nach §35a Abs. 7 SGB V i.V.m. VerfO 5. Kapitel § 7 Abs. 6

Verfahrens-Nr.: 2024-B-024

Verfasser	
Name der Institution	Arzneimittelkommission der deutschen Ärzteschaft (AkdÄ), Bundesärztekammer, Dezernat 6 – Wissenschaft, Forschung und Ethik, Herbert-Lewin-Platz 1, 10623 Berlin (www.akdae.de)
Namen aller beteiligten Sachverständigen	
Datum der Erstellung	26. Februar 2024

(Bei mehreren beteiligten Fachgesellschaften bitte mit entsprechenden Angaben.)

Indikation
…wird angewendet zur Prophylaxe von Migräne bei Erwachsenen mit mindestens 4 Migränetagen pro Monat.
Fragen zur Vergleichstherapie
Was ist der Behandlungsstandard in o. g. Indikation unter Berücksichtigung der vorliegenden Evidenz? Wie sieht die Versorgungspraxis in Deutschland aus? *(Bitte begründen Sie Ihre Ausführungen; geben Sie ggf. zitierte Quellen in einer Referenzliste an.)*
Die Indikation für eine medikamentöse Prophylaxe ist individuell zu stellen: Dabei sollten realistische Therapieziele und potenzielle Nebenwirkungen der Medikation gegeneinander abgewogen werden. Anhaltspunkte, die für eine medikamentöse Prophylaxe sprechen, sind ein hoher Leidensdruck, mindestens drei Attacken mit deutlicher Beeinträchtigung der Lebensqualität pro Monat oder eine Einnahme von Analgetika an zehn oder mehr Tagen pro Monat. Es wurde geschätzt, dass bei mindestens jedem vierten Patienten mit Migräne in den USA eine Indikation für eine medikamentöse Migräneprophylaxe vorliegt (1). Die medikamentöse Prophylaxe der Migräne ist jedoch häufig unbefriedigend: Bis zur Einführung monoklonaler Antikörper standen lediglich Wirkstoffe zur Verfügung, die ursprünglich für andere Indikationen entwickelt wurden und deren Nebenwirkungen und begrenzte Wirksamkeit durch eine Adhärenzrate von unter 30 % nach sechs Monaten illustriert wird (2). Es sollte zunächst ein für diese Indikation zugelassener oral einzunehmender Wirkstoff verordnet werden: Metoprolol, Propranolol, Flunarizin, Amitriptylin und Topiramat (3). Auch die Wirksamkeit von Valproinsäure ist in mehreren kontrollierten Studien nachgewiesen. Valproinsäure ist off-label jedoch nur verordnungsfähig, wenn eine Behandlung mit allen anderen zugelassenen Arzneimitteln nicht wirksam war oder kontraindiziert ist und darf bei Frauen im gebärfähigen Alter wegen Teratogenität nicht eingesetzt werden. Valproinsäure spielt in der Prophylaxe der Migräne daher nur noch eine marginale Rolle. Nach neuer Erkenntnis darf Topiramat bei Frauen im gebärfähigen Alter, die keine hochwirksame Verhütungsmethode anwenden, wegen des Risikos von Fehlbildungen, fetalen Wachstumsbeeinträchtigungen und neurologischen Entwicklungsstörungen ebenfalls nicht angewendet werden (4). Da eine Prophylaxe überwiegend bei Frauen im gebährfähigen Alter indiziert ist, kommen in der Versorgungspraxis oft lediglich Betablocker,

Amitriptylin und Flunarizin als orale Migräneprophylaxe infrage. Kein Medikament hat einen nachgewiesenen Vorteil hinsichtlich seiner Wirksamkeit (5, 6). Die Auswahl des Wirkstoffs richtet sich vielmehr nach den potenziellen Nebenwirkungen: Die Wahl sollte auf ein Präparat fallen, dessen typisches Nebenwirkungsprofil für den individuellen Patienten akzeptabel ist bzw. dessen ursprüngliche Indikation therapeutisch genutzt werden kann. Die Wirkung sollte mittels eines Kopfschmerzkalenders zwei bis drei Monate nach Erreichen der tolerablen Zieldosis evaluiert werden. Bei ungenügender Wirksamkeit – das heißt in der Regel, wenn die Häufigkeit der Migränetage nicht um mindestens 50 % sinkt (bei chronischer Migräne um mindestens 30 %) – oder bei Unverträglichkeit sollte auf einen anderen Wirkstoff gewechselt werden.

Bisher liegt in der EU für vier monoklonale Antikörper gegen das Calcitonin Gene-Related Petide (CGRP) bzw. den CGRP-Rezeptor eine Zulassung zur Prophylaxe von Migräne bei Erwachsenen mit mindestens vier Migränetagen pro Monat vor: Erenumab (Aimovig®), Galcanezumab (Emgality®), Fremanezumab (Ajovy®) und Eptinezumab (Vyepti®). Die Applikation erfolgt subkutan vierwöchentlich bei Erenumab und Galcanezumab. Bei Fremanezumab ist alternativ zu einer monatlichen Applikation auch eine vierteljährliche Gabe möglich. Eptinezumab wird alle zwölf Wochen intravenös verabreicht. Eine Verordnung der monoklonalen Antikörper Galcanezumab, Fremanezumab und Eptinezumab zur Migräneprophylaxe ist gemäß den Beschlüssen des G-BA bei Erwachsenen mit mindestens vier Migränetagen pro Monat möglich, die auf keine der konventionellen medikamentösen Therapien (Metoprolol bzw. Propranolol, Flunarizin, Topiramat, Amitriptylin) ansprechen, für diese nicht geeignet sind oder die diese nicht vertragen (3). Bei Patienten mit chronischer Migräne wird empfohlen, dass diese zusätzlich auf eine Therapie mit Onabotulinumtoxin A nicht angesprochen haben. Für Erenumab stellte der G-BA in einer Neubewertung auf Grundlage der HERMES-Studie einen Anhaltspunkt für einen beträchtlichen Zusatznutzen fest (7). Erenumab ist daher als einziger monoklonaler Antikörper ohne Vortherapie mit konventionellen Wirkstoffen zur Migräneprophylaxe zulasten der GKV verordnungsfähig (3). Eine budgetneutrale Verordnung von Erenumab im Rahmen einer bundesweiten Praxisbesonderheit ist anerkannt, wenn mindestens eine Vortherapie (Metoprolol, Propranolol, Topiramat, Amitriptylin, Flunarizin oder Onabotulinumtoxin A) nicht wirksam war bzw. nicht vertragen wurde oder Kontraindikationen gegen alle diese Wirkstoffe bestehen (3). In der Versorgungspraxis wird daher in der Regel zumindest eine konventionelle Vortherapie verordnet, bevor Erenumab eingesetzt wird. Wenn nach drei Monaten (bzw. nach sechs Monaten bei Eptinezumab) kein befriedigender Therapieeffekt vorliegt, sollte die Behandlung mit dem verwendeten monoklonalen Antikörper beendet werden. Die Wirksamkeit der monoklonalen Antikörper ist im indirekten Vergleich nicht höher als jene der bisher verfügbaren Wirkstoffe zur Migräneprophylaxe (8-10). Hinsichtlich der Verträglichkeit und Adhärenz sind die monoklonalen Antikörper gegenüber bisher verfügbaren Wirkstoffen jedoch deutlich vorteilhaft (11). Daten, die einen direkten Vergleich der monoklonalen Antikörper untereinander ermöglichen, liegen nicht vor. Ein indirekter Vergleich der Wirksamkeit der monoklonalen Antikörper ist erschwert, da die Reduktion der Migränetage um mindestens 50 % als Endpunkt in den verschiedenen Zulassungsstudien auf verschiedene Arten berechnet wurde (12), Metaanalysen sprechen aber gegen relevante Unterschiede hinsichtlich der Effektstärke (13). Bisher liegt lediglich eine Studie vor, die einen monoklonalen Antikörper mit einem oralen zur Migräneprophylaxe zugelassenen Wirkstoff vergleicht: In der doppelblinden HERMES-Studie bei Patienten mit episodischer bzw. chronischer Migräne führte Erenumab zu einer stärkeren Reduktion von Migränetagen und eine geringeren Abbruchrate wegen Nebenwirkungen als Topiramat (14). Allerdings wurde das Design der Studie kritisiert, da die Studienmedikation bei Auftreten von Nebenwirkungen nicht reduziert werden konnte, die Zieldosis im Topiramat-Arm vorgegeben war, im Erenumab-Arm dagegen individuell gewählt werden konnte und bei Abbruch der Studientherapie im Topiramat-Arm kein alternativer, zur Migräneprophylaxe zugelassener Wirkstoff eingenommen werden konnte (7). Die hohe Abbruchrate im Topiramat-Arm führte dazu, dass ein großer Anteil der Patienten, die eine Vergleichstherapie erhielten, über den längsten Zeitraum der Erhaltungsphase unbehandelt war (14). Diese Faktoren führen zu einem Bias, der den

Topiramat-Arm der Studie benachteiligt. In der klinischen Praxis wird bei Unverträglichkeit eines Wirkstoffs in der Migräneprophylaxe üblicherweise auf einen anderen Wirkstoff gewechselt. Zudem ist die Dosis der Migräneprophylaxe individuell anzupassen, um die Rate an Nebenwirkungen zu minimieren. Eine Studie mit Migränepatienten sollte eine Vergleichstherapie unter Berücksichtigung dieser Gesichtspunkte im Sinne einer „Best clinical practice" durchführen.

Die Versorgungspraxis in Deutschland wird durch eine große Beobachtungsstudie dargestellt, die 243.471 Patienten mit Migräne einschloss, die zwischen 2008 und 2016 behandelt wurden (15). 22,3 % der Patienten erhielten mindestens ein Rezept für einen für die Migräneprophylaxe zugelassenen Wirkstoff oder Valproinsäure; bei Patienten mit komplizierter Migräne (einschließlich chronische Migräne) war dies bei 38,0 % der Fall. Mit Abstand am häufigsten wurden Betablocker verordnet (53,8 %), vermutlich jedoch bei vielen Patienten mit internistischer Indikation und nicht primär als Migräneprophylaxe. Nur wenigen Patienten (4,0 %) wurde mehr als ein zur Migräneprophylaxe zugelassener Wirkstoff oder Valproinsäure verordnet. In einer weiteren epidemiologischen Studie nahmen nur 2,4 % der Teilnehmer in Deutschland mit mindestens fünf Migränetagen pro Monat eine medikamentöse Prophylaxe ein (16). Die OVERCOME-Studie basiert auf den Daten von über 20.000 Erwachsenen in Deutschland und Spanien, bei denen die Diagnose einer Migräne über einen internetbasierten Survey ermittelt wurde (17). Der Anteil derer, die aufgrund Häufigkeit und Schwere der Migräne für eine Prophylaxe geeignet waren, betrug 13,2 %, davon erhielten 73,9 % zum Zeitpunkt der Studie keine medikamentöse Prophylaxe. Antiepileptika wurden von 12,4 %, Antidepressiva von 15,1 % und Antihypertensiva von 14,7 % der Teilnehmer eingenommen, die für eine medikamentöse Prophylaxe geeignet waren. Allerdings wurde nicht ermittelt, ob diese Wirkstoffe explizit zur Migräneprophylaxe oder für eine andere Indikation verschrieben wurden. Eine Behandlung mit Onabotulinumtoxin A erhielten 2,4 % der Teilnehmer, bei denen eine Indikation für eine Migräneprophylaxe vorlag.

Gibt es Kriterien für unterschiedliche Behandlungsentscheidungen in der o. g. Indikation, die regelhaft berücksichtigt werden? Wenn ja, welche sind dies und was sind in dem Fall die Therapieoptionen?
(Bitte begründen Sie Ihre Ausführungen; geben Sie ggf. zitierte Quellen in einer Referenzliste an.)

Eine Sonderstellung nimmt die medikamentöse Prophylaxe der chronischen Migräne ein, für die neben den vier in der EU zugelassenen monoklonalen Antikörper lediglich Topiramat und Botulinumtoxin zugelassen sind. Für andere, bei der episodischen Migräne nachweisbar wirksame Migräneprophylaktika ist die Studienlage hinsichtlich der chronischen Migräne unzureichend (3).

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