Gemeinsamer Bundesausschuss

Kriterien zur Bestimmung der zweckmäßigen Vergleichstherapie

und

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

Vorgang: Migräneprophylaxe

Stand: Juni 2020

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

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 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 zur frühen Nutzenbewertung nach §35a SGB V:</u> - D-407 Erenumab (Beschluss vom 2019-05-02) - D-445 Galcanezumab (Beschluss vom 2019-09-19) - D-460 Fremanezumab (Beschluss vom 2019-11-07)
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:	
	Migräneprophylaxe bei erwachsenen Patienten mit mindestens 4 Migränetagen pro Monat.
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 N06AA09 Saroten®	– zur prophylaktischen Behandlung von Migräne bei Erwachsenen.
Biologika	
Erenumab	Aimovig ist angezeigt zur Migräne-Prophylaxe bei Erwachsenen mit mindestens 4 Migränetagen pro Monat.

II. Zugelassene Arzneimittel im Anwendungsgebiet	
N02CD01 Aimovig	
Fremanezumab N02CD02 Emgality	Emgality ist angezeigt zur Migräne-Prophylaxe bei Erwachsenen mit mindestens 4 Migränetagen pro Monat.
Galcanezumab N02CD03 AJOVY	AJOVY wird angewendet zur Migräneprophylaxe bei Erwachsenen mit mindestens 4 Migränetagen pro Monat.

Quellen: AMIS-Datenbank, Fachinformationen.

Gemeinsamer Bundesausschuss

Abteilung Fachberatung Medizin

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

Vorgang: Migräneprophylaxe

Auftrag von:	Abt. AM
Bearbeitet von:	Abt. FB Med
Datum:	25. März 2020

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Abkürzungsverzeichnis

AE/s	Adverse Event/s
AM-RL	Arzneimittel-Richtlinie
AWMF	Arbeitsgemeinschaft der wissenschaftlichen medizinischen Fachgesellschaften
CM	Chronic Migraine
(anti-) CGRP/ CGRP mAb	Anti-Calcitonin Gene-Related Peptide
CRSO	Cochrane Register of Studies Online
ECRI	ECRI Guidelines Trust
EHF	European Headache Federation
EM	Episodic Migraine
G-BA	Gemeinsamer Bundesausschuss
GIN	Guidelines International Network
GoR	Grade of Recommendations
HR	Hazard Ratio
ICHD-III	International Classification of Headache Disorders III
IHS	International Headache Society
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen
KI	Konfidenzintervall
LoE	Level of Evidence
NICE	National Institute for Health and Care Excellence
NNTH	Number Needed To Harm
OR	Odds Ratio
RR	Relatives Risiko
SAE/s	Serious Adverse Events
SIGN	Scottish Intercollegiate Guidelines Network
TRIP	Turn Research into Practice Database
WHO	World Health Organization

1 Indikation

Migräneprophylaxe bei erwachsenen Patienten mit mindestens 4 Migränetagen pro Monat.

2 Systematische Recherche

Es wurde eine systematische Literaturrecherche nach systematischen Reviews, Meta-Analysen und evidenzbasierten systematischen Leitlinien zur Indikation *Migräne* durchgeführt. Der Suchzeitraum wurde auf die letzten 5 Jahre eingeschränkt und die Recherche am 25.02.2020 abgeschlossen. Die Suche erfolgte in den aufgeführten Datenbanken bzw. Internetseiten folgender Organisationen: The Cochrane Library (Cochrane Database of Systematic Reviews), MEDLINE (PubMed), AWMF, ECRI, G-BA, GIN, NICE, TRIP, SIGN, WHO. Ergänzend erfolgte eine freie Internetsuche nach aktuellen deutschen und europäischen Leitlinien. Die detaillierte Darstellung der Suchstrategie ist am Ende der Synopse aufgeführt.

In einem zweistufigen Screening wurden die Ergebnisse der Literaturrecherche bewertet. Die Recherche ergab 864 Quellen. 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 Quellen 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 20 Quellen eingeschlossen. Es erfolgte eine synoptische Darstellung wesentlicher Inhalte der identifizierten Referenzen.

3 Ergebnisse

3.1 G-BA-Beschlüsse/IQWiG-Berichte

G-BA, 2020 [3].

Richtlinie über die Verordnung von Arzneimitteln in der vertragsärztlichen Versorgung (AM-RL); Anlage VI zum Abschnitt K der Arzneimittel-Richtlinie: Verordnungsfähigkeit von zugelassenen Arzneimitteln in nicht zugelassenen Anwendungsgebieten (sog. Off-Label-Use), letzte Änderung in Kraft getreten am: 29.02.2020 - V. Valproinsäure bei der Migräneprophylaxe im Erwachsenenalter

1. Hinweise zur Anwendung von Valproinsäure gemäß § 30 Abs. 2 AM-RL

   a) Nicht zugelassenes Anwendungsgebiet (Off-Label-Indikation): Migräneprophylaxe von Erwachsenen ab 18 Jahren, wenn eine Behandlung mit anderen dafür zugelassenen Arzneimitteln nicht erfolgreich war oder kontraindiziert ist. Die Verordnung darf nur durch Fachärzte für Nervenheilkunde, für Neurologie und/oder Psychiatrie oder für Psychiatrie und Psychotherapie erfolgen. Weiterhin liegen keine Hinweise für die Wirksamkeit von Valproinsäure zur Migräne-Prophylaxe bei Kindern und Jugendlichen vor (siehe auch Anlage VI Teil B Nr. VII).

   b) Behandlungsziel: klinisch relevante Reduzierung der Frequenz von Migräneattacken (≥ 50%)

   c) Folgende Wirkstoffe sind zugelassen:
   Metoprololtartrat (Ph.Eur.)
   Propanololhydrochlorid
   Flunarizin
   Topiramat
   Dihydroergotamin (mesilat)

   d) Spezielle Patientengruppe: Erwachsene mit Migräne, mit oder ohne Aura, bei denen eine Migräneprophylaxe indiziert ist, wenn eine Therapie mit allen anderen dafür zugelassenen Arzneimitteln nicht erfolgreich war, wegen Nebenwirkungen abgebrochen werden musste oder wegen Kontraindikationen nicht initiiert werden konnte.

   Auch bei Patienten mit einer Epilepsie oder bipolaren Störung, für deren Behandlung Valproinsäure zugelassen ist, kann eine Migräneprophylaxe erforderlich sein. Da aussagefähige Studien zu einer kombinierten Indikation („Doppelindikation“) nicht vorliegen, bedarf der Einsatz von Valproinsäure bei dieser Patientengruppe einer besonderen fallindividuellen Abwägung, insbesondere ist das Nutzen-Risiko-Verhältnis von Valproinsäure im Vergleich zu vorbestehenden oder alternativen Therapieregimen auch fachärztlich zu bewerten.

   Für diese spezielle Patientengruppe sind die erheblichen teratogenen Wirkungen und das Auftreten von Suizidgedanken und suizidalem Verhalten von besonderer Bedeutung und daher gemäß § 30 Absatz 2 Satz 2 und 3 die jeweiligen Angaben hierzu wie z. B. zum Ausschluss von Schwangerschaft, zu notwendigen Methoden der Kontrazeption sowie zu Aufklärungs- und Dokumentationspflichten besonders zu berücksichtigen.

e) Patienten, die nicht behandelt werden sollten:
   - Schwangere und stillende Frauen sind in jedem Fall von der Behandlung auszunehmen.
   - Frauen im gebärfähigen Alter, wenn keine effektive Methode der Kontrazeption vorgenommen wird.
   - Patienten mit episodischen Kopfschmerzen vom Spannungstyp oder medikamenten-induzierten Kopfschmerzen.

f) Dosierung: Es wird eine Monotherapie mit einer anfänglichen Tagesdosis von 500 mg/Tag empfohlen, die ggf. wirkungsabhängig bis 1500 mg/Tag gesteigert werden kann. Tagesdosen über 1500 mg sind nicht ausreichend untersucht.

g) Behandlungsdauer: Die therapeutische Wirksamkeit kann erst nach einer Behandlungsdauer von 3 Monaten, unter Berücksichtigung der individuellen Attackenfrequenz beurteilt werden. Hierzu ist ein Schmerztagebuch durch den Patienten zu führen. In der Regel wird eine Langzeittherapie erforderlich sein.

h) Wann sollte die Behandlung abgebrochen werden? Neben den in der Fachinformation aufgeführten Gründen sollte die Behandlung abgebrochen werden, wenn das Therapieziel einer 50%igen Reduktion der Attackenfrequenz nicht erreicht wird. Im Falle einer geplanten oder festgestellten Schwangerschaft ist die Behandlung abzubrechen.

i) Nebenwirkungen/Wechselwirkungen, wenn diese über die zugelassene Fachinformation hinausgehen oder dort nicht erwähnt sind: In den geprüften Studien wurde unter Ko-Therapie mit Triptanen über keine Wechselwirkungen berichtet.

j) Zustimmung des pharmazeutischen Unternehmers: Die folgenden pharmazeutischen Unternehmer haben für ihre Valproinsäure-haltigen Arzneimittel eine Anerkennung des bestimmungsgemäßen Gebrauchs abgegeben (Haftung des pharmazeutischen Unternehmers), sodass ihre Arzneimittel für die vorgenannte Off-Label-Indikation verordnungsfähig sind:

   ACA Müller ADAG Pharma AG

   betapharm Arzneimittel GmbH

   Dolorgiet GmbH & Co. KG

   IIP – Institut für industrielle Pharmazie Forschungs- und Entwicklungsgesellschaft mbH

   TAD Pharma GmbH

   Nicht verordnungsfähig sind in diesem Zusammenhang die Valproinsäurehaltigen Arzneimittel der Firmen 1 A Pharma GmbH, AbZ-Pharma GmbH, ALIUD PHARMA GmbH, Aristo Pharma GmbH, CC Pharma GmbH, Declimed GmbH, DESITIN ARZNEIMITTEL GMBH, EMRAmed Arzneimittel GmbH, EurimPharm Arzneimittel GmbH, HEUMANN PHARMA GmbH & Co. GENERICA KG, Hexal AG, kohlpharma GmbH, Mylan dura GmbH, neuraxpharm Arzneimittel GmbH, Orifarm GmbH, ratiopharm GmbH, Sandoz Pharmaceuticals GmbH, Sanofi-Aventis Deutschland GmbH, STADApharm GmbH, TEVA GmbH, Winthrop Arzneimittel GmbH und Zentiva Pharma GmbH, da keine entsprechende Erklärung vorliegt.

2. Anforderungen an eine Verlaufsdokumentation gemäß § 30 Abs. 4 AM-RL: entfällt

G-BA, 2019 [4].

Richtlinie über die Verordnung von Arzneimitteln in der vertragsärztlichen Versorgung (AM-RL); Anlage XII: (Frühe) Nutzenbewertung nach § 35a SGB V; Geltende Fassung zum Beschluss vom 2. Mai 2019 / 19. September 2019 - Erenumab

Anwendungsgebiet

Aimovig ist angezeigt zur Migräne-Prophylaxe bei Erwachsenen mit mindestens 4 Migränetagen pro Monat.

Zweckmäßige Vergleichstherapien

a) Unbehandelte erwachsene Patienten und Patienten, die auf mindestens eine prophylaktische Medikation nur unzureichend angesprochen oder diese nicht vertragen haben oder für diese nicht geeignet sind

Metoprolol oder Propranolol oder Flunarizin oder Topiramat oder Amitriptylin unter Berücksichtigung der Zulassung und der Vortherapie

b) Erwachsene Patienten, die auf die medikamentösen Therapien/Wirkstoffklassen Metoprolol, Propranolol, Flunarizin, Topiramat, Amitriptylin nicht ansprechen, für diese nicht geeignet sind oder diese nicht vertragen

Valproinsäure[1] oder Clostridium botulinum Toxin Typ A[2]

[1] Entsprechend Anlage VI zum Abschnitt K der Arzneimittel-Richtlinie: wenn eine Behandlung mit allen anderen dafür zugelassenen Arzneimitteln nicht erfolgreich war oder kontraindiziert ist.

[2] Entsprechend der Zulassung nur für die chronische Migräne.

c) Erwachsene Patienten, die auf keine der genannten medikamentösen Therapien/ Wirkstoffklassen (Metoprolol, Propranolol, Flunarizin, Topiramat, Amitriptylin, Valproinsäure, Clostridium botulinum Toxin Typ A) ansprechen, für diese nicht geeignet sind oder diese nicht vertragen

Best Supportive Care

Ausmaß des Zusatznutzens

a) Zusatznutzen nicht belegt

b) Zusatznutzen nicht belegt

c) Anhaltspunkt für einen beträchtlichen Zusatznutzen

G-BA, 2019 [6].

Richtlinie über die Verordnung von Arzneimitteln in der vertragsärztlichen Versorgung (AM-RL); Anlage XII: (Frühe) Nutzenbewertung nach § 35a SGB V; Geltende Fassung zum Beschluss vom 19. September 2019 - Galcanezumab

Anwendungsgebiet

Emgality ist angezeigt zur Migräne-Prophylaxe bei Erwachsenen mit mindestens 4 Migränetagen pro Monat.

Zweckmäßige Vergleichstherapien

a) Unbehandelte erwachsene Patienten und Patienten, die auf mindestens eine prophylaktische Medikation nur unzureichend angesprochen oder diese nicht vertragen haben oder für diese nicht geeignet sind.

Metoprolol oder Propranolol oder Flunarizin oder Topiramat oder Amitriptylin unter Berücksichtigung der Zulassung und der Vortherapie

b) Erwachsene Patienten, die auf die medikamentösen Therapien / Wirkstoffklassen Metoprolol, Propranolol, Flunarizin, Topiramat, Amitriptylin nicht ansprechen, für diese nicht geeignet sind oder diese nicht vertragen.

Valproinsäure[1] oder Clostridium botulinum Toxin Typ A[2]

[1] Entsprechend Anlage VI zum Abschnitt K der Arzneimittel-Richtlinie: wenn eine Behandlung mit allen anderen dafür zugelassenen Arzneimitteln nicht erfolgreich war oder kontraindiziert ist.

[2] Entsprechend der Zulassung nur für die chronische Migräne.

c) Erwachsene Patienten, die auf keine der genannten medikamentösen Therapien / Wirkstoffklassen (Metoprolol, Propranolol, Flunarizin, Topiramat, Amitriptylin, Valproinsäure, Clostridium botulinum Toxin Typ A) ansprechen, für diese nicht geeignet sind oder diese nicht vertragen.

Best Supportive Care

Ausmaß des Zusatznutzens

a) Zusatznutzen nicht belegt
b) Zusatznutzen nicht belegt
c) Anhaltspunkt für einen beträchtlichen Zusatznutzen

G-BA, 2019 [5].

Richtlinie über die Verordnung von Arzneimitteln in der vertragsärztlichen Versorgung (AM-RL); Anlage XII: (Frühe) Nutzenbewertung nach § 35a SGB V; Geltende Fassung zum Beschluss vom 07. November 2019 - Fremanezumab

Anwendungsgebiet

AJOVY® ist angezeigt zur Migräneprophylaxe bei Erwachsenen mit mindestens 4 Migränetagen pro Monat.

Zweckmäßige Vergleichstherapien

a) Unbehandelte erwachsene Patienten und Patienten, die auf mindestens eine prophylaktische Medikation nur unzureichend angesprochen oder diese nicht vertragen haben oder für diese nicht geeignet sind.

Metoprolol oder Propranolol oder Flunarizin oder Topiramat oder Amitriptylin unter Berücksichtigung der Zulassung und der Vortherapie

b) Erwachsene Patienten, die auf die medikamentösen Therapien / Wirkstoffklassen Metoprolol, Propranolol, Flunarizin, Topiramat, Amitriptylin nicht ansprechen, für diese nicht geeignet sind oder diese nicht vertragen.

Valproinsäure[1] oder Clostridium botulinum Toxin Typ A[2]

[1] Entsprechend Anlage VI zum Abschnitt K der Arzneimittel-Richtlinie: wenn eine Behandlung mit allen anderen dafür zugelassenen Arzneimitteln nicht erfolgreich war oder kontraindiziert ist.

[2] Entsprechend der Zulassung nur für die chronische Migräne.

c) Erwachsene Patienten, die auf keine der genannten medikamentösen Therapien / Wirkstoffklassen (Metoprolol, Propranolol, Flunarizin, Topiramat, Amitriptylin, Valproinsäure, Clostridium botulinum Toxin Typ A) ansprechen, für diese nicht geeignet sind oder diese nicht vertragen.

Best Supportive Care

Ausmaß des Zusatznutzens

a) Zusatznutzen nicht belegt

b) Zusatznutzen nicht belegt

c) Anhaltspunkt für einen beträchtlichen Zusatznutzen

3.2 Cochrane Reviews

Herd CP et al., 2018 [7].

Botulinum toxins for the prevention of migraine in adults (Review)

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: we considered the following ways of recording adverse events, listed in preferred order:
  - total number of participants experiencing any type of adverse event;
  - total number of participants experiencing the specific adverse event types; blepharoptosis, muscle weakness, neck pain and injection site pain;
  - total number of participants experiencing a treatment-related adverse event, as determined by trial investigators;
  - withdrawals due to 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.
- The World Health Organization's International Clinical Trials Registry Platform (ICTRP)(www.who.int/ictrp/en/);
- ClinicalTrials.gov (clinicaltrials.gov/).
- reference lists of relevant review articles and included trial reports for additional trials
- citation searches on key articles.

Qualitätsbewertung der Studien:

- criteria outlined in the Cochrane Handbook for Systematic Reviews of Interventions (Higgins 2011b) and guidelines from Cochrane Pain, Palliative and Supportive Care:
  - Random sequence generation (checking for possible selection bias)
  - Allocation concealment (checking for possible selection bias)
  - Blinding of participants and personnel (checking for possible performance bias)
  - Blinding of outcome assessment (checking for possible detection bias)
  - Incomplete outcome data (checking for possible attrition bias due to the amount, nature and handling of incomplete outcome data)
  - Selective reporting (checking for possible reporting bias)
  - Size of trial (checking for possible biases confounded by small size)
- Assessment of heterogeneity by using Chi^2 test and I^2 statistic:

  A number of differences in trial designs were likely to cause heterogeneity in our meta-analyses and we planned the following subgroup analyses to test for variation in effect:
  - trials including medication overuse headache versus trials excluding people with this diagnosis;
  - different sero-types of botulinum toxin (e.g. A versus B) and within sero-types (Dysport versus Botox);

- o different types of agents for the prevention of migraine versus botulinum toxin;
- o accepted and licensed 31 injection pattern versus other injection patterns used.

At least two trials and 200 participants per group were required for any particular subgroup analysis to be carried out.

- Assessment of quality of evidence by GRADE approach ('Summary of findings' tables)
- Sensitivity analysis for the primary outcome only

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

Figure 2. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included trials

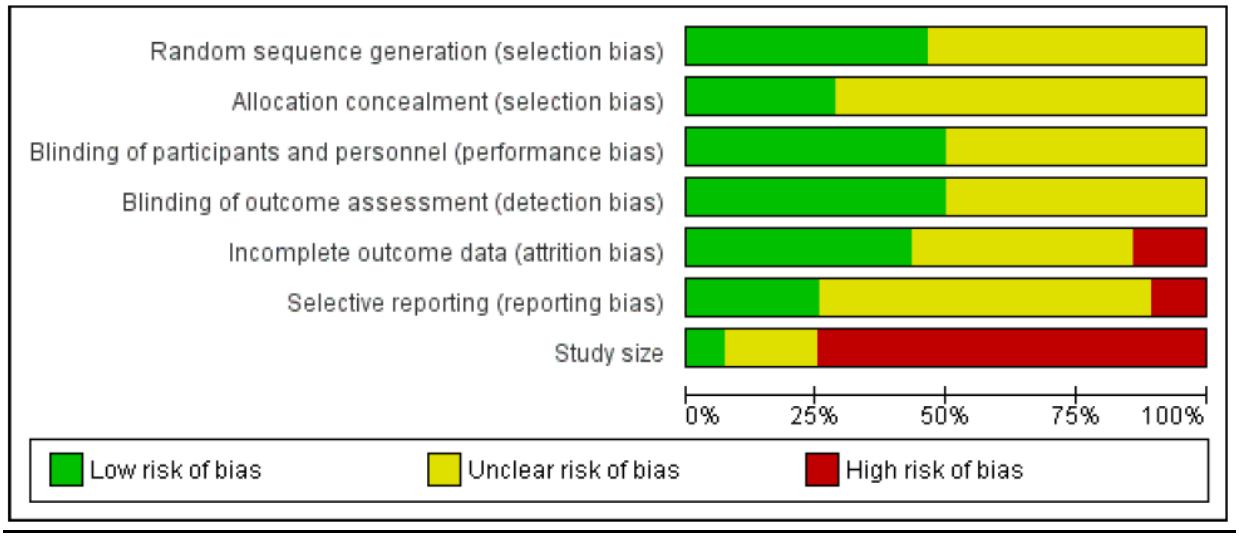
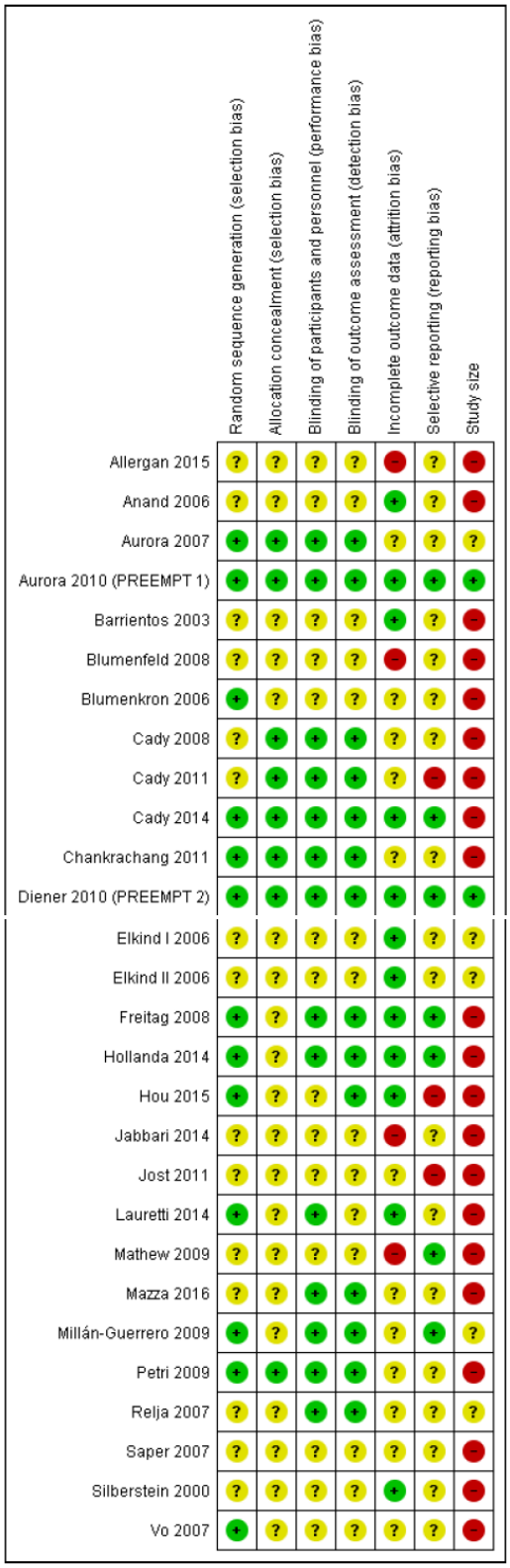


Figure 3. Risk of bias summary: review authors' judgements about each risk of bias item for each included trial.



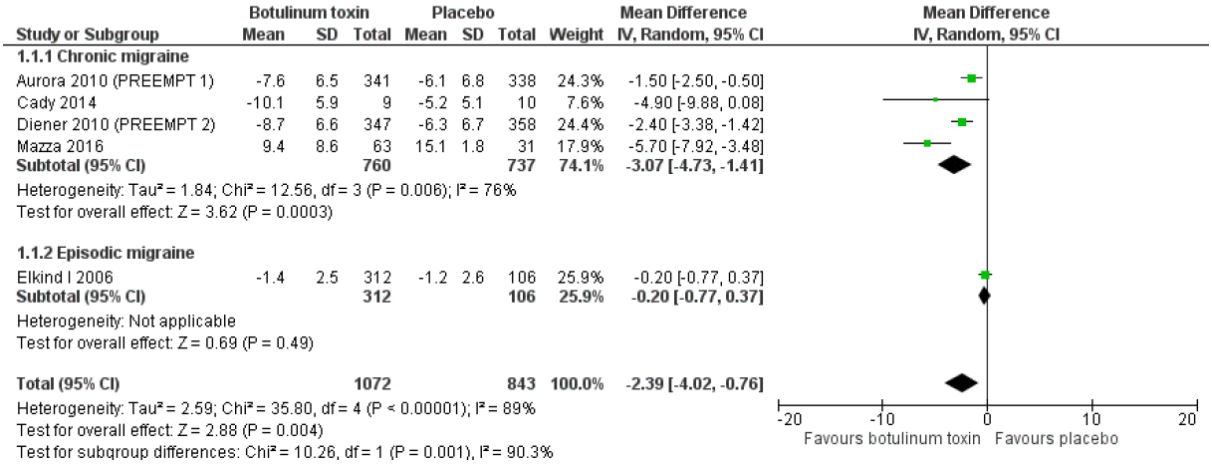
- The episodic-migraine subgroup in this analysis contained only a single trial (Elkind I 2006; N = 418), the results of which showed no between-group difference in number of migraine days per month between those treated with botulinum toxin and those treated with placebo (P = 0.49). The test for subgroup difference showed a statistically significant heterogeneity

between the results of this population and the chronic migraine subgroup for both the original and the sensitivity analyses (P = 0.001 for both, I^2 = 90 and 91% respectively). We judged the quality of the evidence for the change in number of migraine days for the chronic migraine population to be low. We downgraded by one level for inconsistency due to unexplained statistical heterogeneity and one further level for imprecision due to the lack of robustness to sensitivity analysis. We judged the quality of the results of the sensitivity analysis to be moderate, as the heterogeneity was removed and so this could be upgraded by one level. For the whole migraine population, we downgraded the evidence one further level, to give a rating of very low quality, for indirectness due to insufficient evidence to form subgroups representing our distinct populations of interest.

Studienergebnisse:

- Primary outcome: number of migraine days per month

Figure 4. Forest plot of comparison 1. Botulinum toxin type A versus placebo, outcome: 1.1 Number of migraine days. Mazza 2016 and Cady 2014 removed for sensitivity analysis of small trial effect. Data for Mazza 2016 is endpoint data.



- Secondary outcomes
  - Number of headache days per month

    Only the two PREEMPT trials contributed data for analysis of number of headache days per month with a pooled estimate of -1.9 days (95% CI -2.7 to -1.0; I2 = 37%) in favour of treatment (Aurora 2010 (PREEMPT 1); Diener 2010 (PREEMPT 2)). […] We judged the quality of the evidence for the change in number of headache days to be high.
  - Number of migraine attacks per month

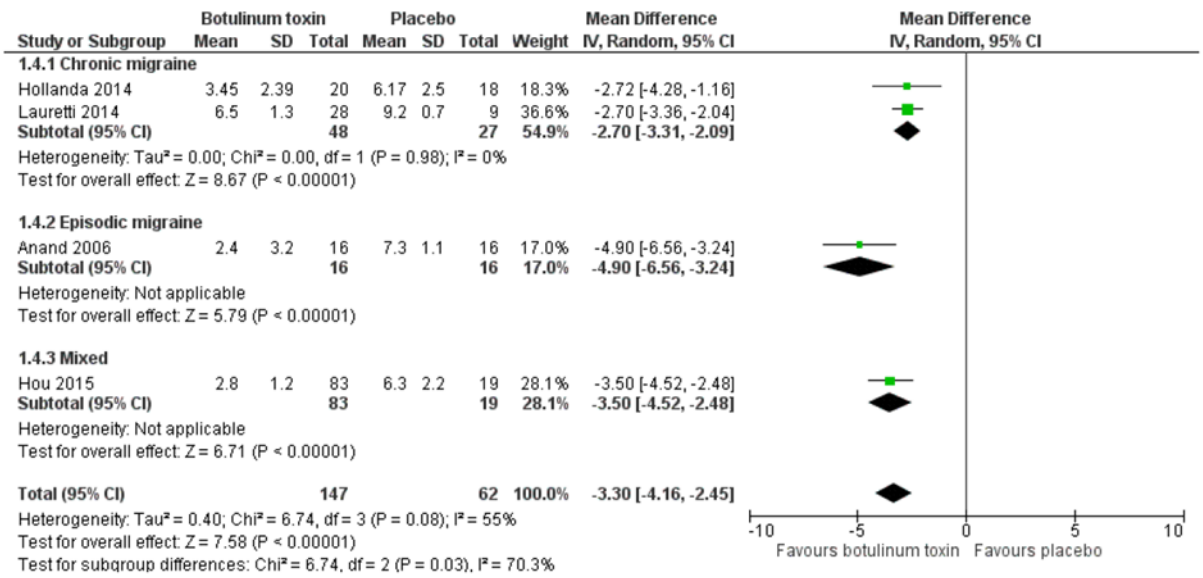
    Data from six trials were available for the analysis of number of migraine attacks per month (Aurora 2007; Aurora 2010 (PREEMPT 1); Chankrachang 2011; Hou 2015; Relja 2007; Saper 2007). There was no statistically significant difference for the number of migraine attacks between botulinum toxin and placebo injections with a pooled estimate of -0.5 attacks (95% CI -1.3 to 0.4, I2 = 89%, P = 0.30; Analysis 1.3). This analysis included both chronic and episodic migraineurs, with a total of 2004 participants included. […]

    We judged the quality of the evidence for the change in number of migraine attacks to be low. We downgraded by one level for indirectness, due to our concern that the sensitivity of this outcome measure was too low to detect clinically meaningful difference, and one

additional level for publication bias, due to evidence of trials that recorded this outcome but have never been published.

o Headache intensity measures

Figure 5. Forest plot of comparison 1. Botulinum toxin type A versus placebo, outcome: 1.4 Severity of migraine (Visual Analogue Score 0-10)



We judged the quality of the evidence for the change in VAS score to be very low. We downgraded by one level for risk of bias, due to poor reporting of the outcome, which had a large effect on number of participants included in the analysis, and two additional levels for imprecision, as all included trials were all small and new trial evidence would be very likely to change the result.

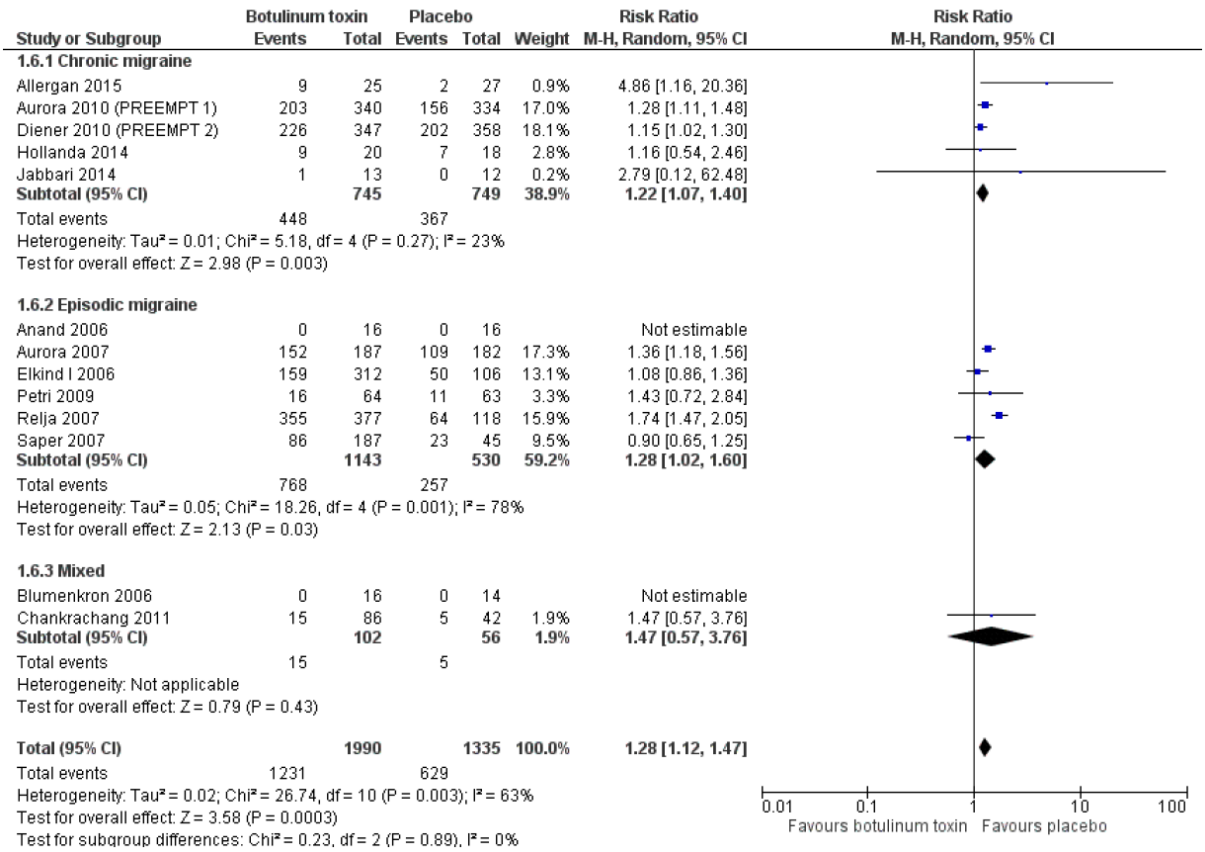
o Duration of migraine

Only one trial reported duration of migraine in a format we could use in our analysis (Hou 2015). Their results showed an improvement in duration of migraine of -5.1 hours (95% CI -6.2 to -4.0) in favour of botulinum toxin for a mixed population of 66 episodic migraine participants and 36 chronic migraine participants. […]

We judged the quality of the evidence for this outcome to be very low. We downgraded by two levels due to imprecision as the single included trial was small and new trial evidence would be very likely to change the result; we downgraded by one additional level for riskof bias, due to selective reporting bias which had a large effect on number of participants included in the analysis.

o Adverse events

Figure 6. Forest plot of comparison 1. Botulinum toxin type A versus placebo, outcome: 1.6 Total adverse events



We judged the quality of the evidence for the total adverse events outcome to be moderate. We downgraded by one level for imprecision, as many of the included trials were small and new trial evidence would be likely to change the result.

Anmerkung/Fazit der Autoren

- Efficacy
  Uncertainty remains around the estimate of effect of botulinum toxin on our primary outcome, the number of migraine days experienced per month for people with chronic migraine. The data showed a reduction of 3 days (-3.1, 95% CI -4.7 to -1.4, low-quality evidence) for this outcome measure over and above the placebo effect. This result did not prove to be reliable when tested using sensitivity analysis for effects of small trial bias. We had greater confidence in the more conservative estimate of a 2-day improvement (-2.0, 95% CI -2.8 to -1.1, moderate-quality evidence). This came only from trials at low risk of bias from trial size (Aurora 2010 (PREEMPT 1); Diener 2010 (PREEMPT 2)). All participants included in this analysis had chronic migraine with a high baseline frequency of around 20 days per month. The data showed a large placebo effect on their symptoms of improvement of over 6 days. Just how clinically meaningful this result is remains difficult to determine. It does approach reductions observed in topiramate versus placebo trials of 3.7 (Diener 2007) and 1.5 migraine days per month (Silberstein 2007). Recent trials of the novel anti-calcitonin gene-related peptide (CGRP) monoclonal antibody treatment option found a reduction of around 2 headache days per month (Giamberardino 2016; Silberstein 2017) and up to 2 migraine

days, depending on dose, when compared with placebo (Goadsby 2017). This is in keeping with previous trials with prophylactic agents. Insufficient data were available to draw conclusions for the episodic migraine population from this outcome measure as we identified only a single trial experimenting with doses well below those recommended by the UK national guidelines (Elkind I 2006). We had hoped to use subgroup analysis to investigate the effect of including people with the additional medication overuse headache diagnosis but we could not carry out this analysis as we did not identify sufficient data to create the subgroups.

Secondary outcome measures were inconsistent in showing a treatment effect. Botulinum toxin was better than placebo in reducing the number of days with any type of headache by two days per month, based on evidence judged to be high-quality. We did not observe any significant difference from placebo for number of migraine attacks per month in those with episodic migraine (lowquality evidence); this may be as a result of variable parameters in this outcome measure, which was generally poorly defined in trial reports. There was a reduction in favour of botulinum treatment of migraine severity on a visual analogue scale of 3 cm on a 10 cm scale (very low-quality evidence), compared with placebo. This difference is in excess of the minimal clinically important difference of between 1.0 cm and 1.4 cm reported for other chronic pain conditions (Hawker 2011). The migraine severity analysis included trials with episodic migraine populations and the effect size was shown to be similar to that seen for chronic migraineurs. There was no significant heterogeneity between the two population subgroups. All trials contributing to the analysis of migraine severity were small and so the quality of this evidence is very low and likely to change with the emergence of new evidence from larger, higher-quality trials. If all trials had used a uniform outcome measure for severity of migraine, we could have included an additional 2298 participants in our analyses for this outcome, giving much greater confidence in the results.

- Safety and tolerability

  Data from 23 trials included in this review reported few adverse events as a result of treatment with botulinum toxin. There was an increased risk of adverse events in the botulinum toxin group compared with placebo (moderate-quality evidence), but these events were not serious and were transient.

- Assessment of reporting biases

  We considered the use of funnel plots to assess the risk of publication bias but did not carry them out. We made this decision because of the small number of trials included in the individual meta-analyses and the true heterogeneity in the trial design (dose, injection paradigm) and populations studied (migraine subclassifications), which would make it impossible to draw useful conclusions from the plots.

Kommentare zum Review

- Der Vergleich zwischen botulinum toxin und einem aktiven Komparator ist auf Grund geringer quantitativer (n = 1 Studie für den primären Endpunkt) sowie qualitativer Evidenz nicht dargestellt.

3.3 Systematische Reviews

Deng H et al., 2020 [2].

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

Siehe auch: Zhao X et al., 2020 [19]. Efficacy and safety of galcanezumab for preventive treatment of migraine: a systematic review and meta-analysis

Xu D et al., 2019 [18]. Safety and tolerability of calcitonin-gene-related peptide binding monoclonal antibodies for the prevention of episodic migraine - a meta-analysis of randomized controlled trials

Ren Z et al., 2019 [13]. The treatment efficacy of galcanezumab for migraine: A meta-analysis of randomized controlled trials

Lattanzi S et al., 2019 [10]. Erenumab for Preventive Treatment of Migraine: A Systematic Review and Meta-Analysis of Efficacy and Safety

Zhu Y et al., 2018 [20]. The efficacy and safety of calcitonin gene-related peptide monoclonal antibody for episodic migraine: a meta-analysis

Hou M et al., 2017 [8]. The effect and safety of monoclonal antibodies to calcitonin gene-related peptide and its receptor on migraine: a systematic review and meta-analysis

Zielsetzung

Although a previous meta-analysis has assessed the efficacy and safety of CGRP mAbs for episodic migraine [13], several new high-quality randomized control trials (RCTs) are not included in the published meta-analysis [14–18]. Therefore, we conducted an updated metaanalysis to comprehensively investigate[d] the efficacy and safety of CGRP mAbs for the preventive treatment of episodic migraine.

Methodik

Population:

- Adults aged ≥18 years, regardless of gender or ethnicity
- Subjects diagnosed with episodic migraine according to the International Classification of Headache Disorders III (ICHD-III) for at least 1 year prior to enrollment

Intervention:

- CGRP mAb therapy:
  - Erenumab 70 mg
  - Erenumab 140 mg
  - Eptinezumab 1000 mg
  - Fremanezumab 225 mg
  - Galcanezumab 120 mg
  - Galcanezumab 150 mg

Komparator:

- Placebo

Endpunkte:

- Primäre Endpunkte
  - Changes in the number of monthly migraine days from baseline to endpoint
  - monthly acute migraine-specific medication days.
- Sekundärer Endpunkt
  - 50% reduction from baseline in the mean number of migraine days per month
- Sicherheitsendpunkte
  - proportion of participants who suffered adverse events (AEs).
  - proportions of patients who withdrew from treatment due to AEs and experienced any serious AEs (SAEs)

Recherche/Suchzeitraum:

- MEDLINE, EMBASE, the Cochrane Controlled Trials Register (CENTRAL), and Web of Science (from inception to 9th, March,2019)

Qualitätsbewertung der Studien:

- The Cochrane Collaboration's tool was used to assess the risk of bias.
- The heterogeneity between trials was examined using the I^2 statistic.

Ergebnisse

Anzahl eingeschlossener Studien:

- Eleven studies with data from 4402 unique participants were included.

Charakteristika der Population:

Table 1 Characteristics of the included studies

Study (reference no.)	Year	Study design (NCT No.)	Interventions	Sex (male/female),Age (mean ± SD)	Baseline Migraine-days per month (mean ± SD)	Follow-up
Uwe Reuter [14]	2018	RCT phase3b, NCT03096834	erenumab 140 mg Placebo	24/97,44.6 ± 10.5 22/103,44.2 ± 10.6	9.2 ± 2.6 9.3 ± 2.7	12w
David W Dodick [15]	2017	RCT phase 3, NCT02483585	erenumab 70 mg Placebo	41/245,42 ± 11 44/247,42 ± 12	8.1 ± 2.7 8.4 ± 2.6	12w
Peter J. Goadsby [24]	2017	RCT phase 3, NCT02456740	erenumab 70 mg Placebo	49/268,41.1 ± 11.3 45/274,41.3 ± 11.2	8.3 ± 2.5 8.2 ± 2.5	24w
Hong Sun [25]	2016	RCT phase 2, NCT01952574	erenumab 70 mg Placebo	25/82, 42.6 ± 9.9 28/132,41.4 ± 10.0	8.6 ± 2.5 8.8 ± 2.7	12w
David W Dodick [26]	2014	RCT phase 2, NCT01772524	Eptinezumab 1000 mg Placebo	14/67,38.6 ± 10.8 16/66,39.0 ± 9.6	8.4 ± 2.1 8.8 ± 2.7	12w
David W. Dodick [16]	2018	RCT phase 3, NCT02629861	Fremanezumab 225 mg Placebo	46/244,42.9 ± 12.7 47/247, 41.3 ± 12.0	8.9 ± 2.6 9.1 ± 2.7	12w
Marcelo E Bigal [27]	2015	RCT phase 2b, NCT02025556	Fremanezumab 225 mg Placebo	9/87,40.8 ± 12.4 12/92,42.0 ± 11.6	11.5 ± 1.9 11.5 ± 2.24	12w
Vladimir Skljarevski# [28]	2018	RCT phase 2b, NCT02163993	Galcanezumab 120 mg Placebo	42/231,40.6 ± 11.9 28/109,39.5 ± 12.1	6.7 ± 2.6 6.6 ± 2.7	12w
Vladimir Skljarevski [18]	2017	RCT Phase 3, NCT02614196	galcanezumab 120 mg Placebo	34/197,40.9 ± 11.2 68/393,42.3 ± 11.3	9.07 ± 2.9 9.2 ± 3.0	24w
Virginia L. Stauffer [17]	2018	RCT phase 3, NCT02614183	galcanezumab 120 mg Placebo	32/181,40.9 ± 11.9 71/362,41.3 ± 11.4	9.2 ± 3.1 9.1 ± 3.0	24w
David W Dodick [29]	2014	RCT phase 2, NCT01625988	galcanezumab 150 mg Placebo	19/88,40.9 ± 11.4 14/96,41.9 ± 11.7	6.7 ± 2.4 7.0 ± 2.5	12w

RCT Randomized controlled trial, *SD* Standard deviation. #The specific information can only be achieved in the total CGRP monoclonal antibodies treatment group

Qualität der Studien:

Table 2 Assessment on the methodological strategies of the included studies

Trial ID	Random sequence generation	Allocation concealment	Blinding	Incomplete outcome data	Selective outcome reporting	Other sources of bias
Uwe Reuter 2018	Low risk	Low risk	Low risk	Low risk	Low risk	Unclear risk
David W Dodick 2017	Low risk	Low risk	Low risk	Low risk	Low risk	Unclear risk
Peter J. Goadsby 2017	Low risk	Low risk	Low risk	Low risk	Low risk	Unclear risk
Hong Sun 2016	Low risk	Low risk	Low risk	Low risk	Low risk	Unclear risk
David W Dodick 2014	Low risk	Low risk	Low risk	Low risk	Low risk	Unclear risk
David W. Dodick 2018	Low risk	Low risk	Low risk	Low risk	Low risk	Unclear risk
Marcelo E Bigal 2015	Low risk	Low risk	Low risk	Low risk	Low risk	Unclear risk
Vladimir Skljarevski 2018	Low risk	Low risk	Low risk	Low risk	Low risk	Unclear risk
Vladimir Skljarevski 2017	Low risk	Low risk	Low risk	Low risk	Low risk	Unclear risk
Virginia L. Stauffer 2018	Low risk	Low risk	Low risk	Low risk	Low risk	Unclear risk
David W Dodick 2014	Low risk	Low risk	Low risk	Low risk	Low risk	Unclear risk

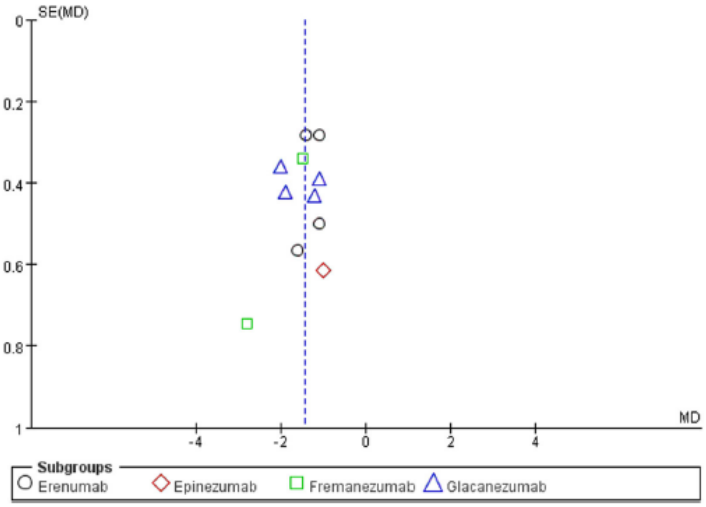


Fig. 7 Funnel plot of effect size by standard error (surrogate for study size) across all studies. No obvious asymmetry was identified in the funnel plot, indicating that there was no publication bias. *SE* standard error, *MD* mean difference

Studienergebnisse:

- Monthly migraine days

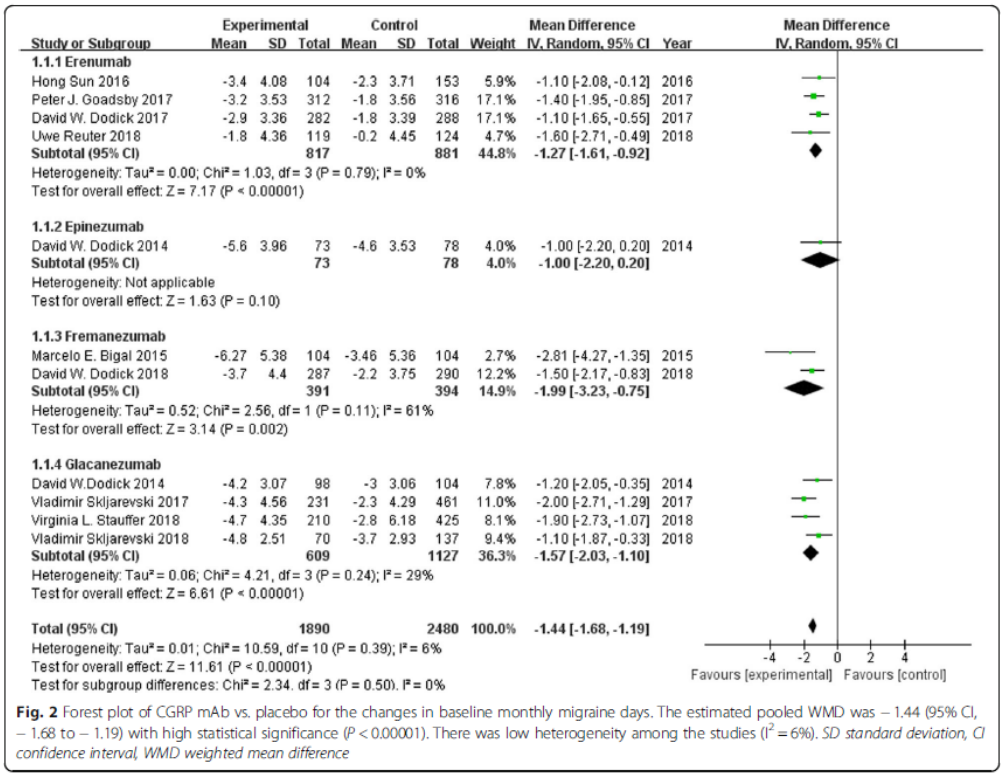


Fig. 2 Forest plot of CGRP mAb vs. placebo for the changes in baseline monthly migraine days. The estimated pooled WMD was − 1.44 (95% CI, − 1.68 to − 1.19) with high statistical significance ($P < 0.00001$). There was low heterogeneity among the studies ($I^2 = 6\%$). *SD standard deviation, CI confidence interval, WMD weighted mean difference*

- Monthly acute migraine-specific medication days

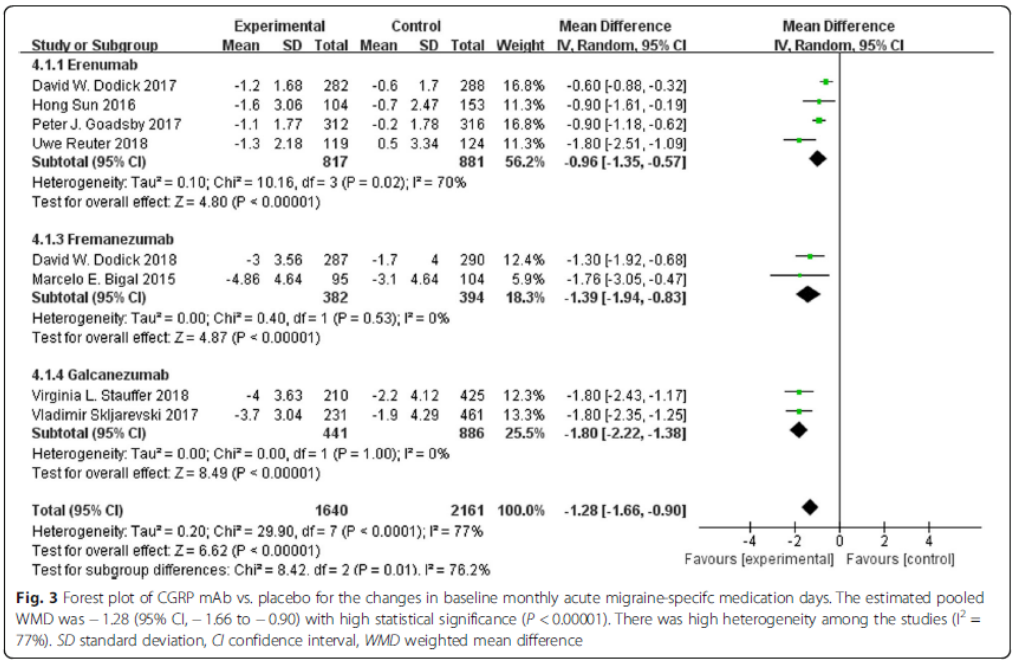


Fig. 3 Forest plot of CGRP mAb vs. placebo for the changes in baseline monthly acute migraine-specifc medication days. The estimated pooled WMD was − 1.28 (95% CI, − 1.66 to − 0.90) with high statistical significance ($P < 0.00001$). There was high heterogeneity among the studies ($I^2 = 77\%$). *SD* standard deviation, *CI* confidence interval, *WMD* weighted mean difference

- ≥ 50% reduction from baseline in monthly migraine days

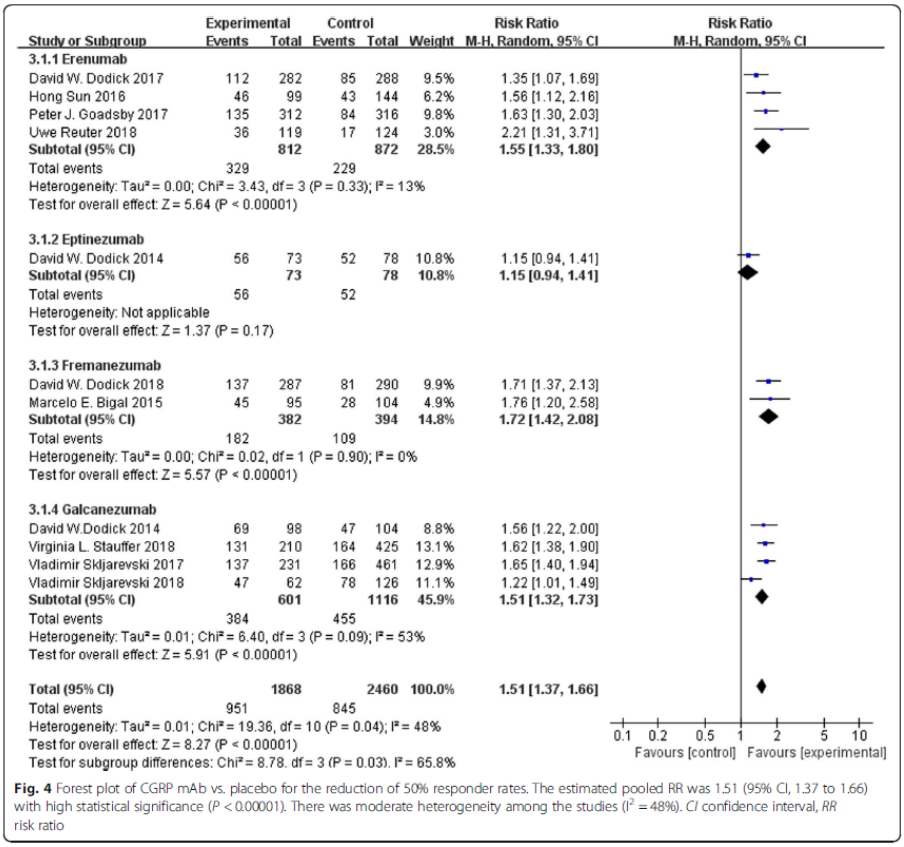


Fig. 4 Forest plot of CGRP mAb vs. placebo for the reduction of 50% responder rates. The estimated pooled RR was 1.51 (95% CI, 1.37 to 1.66) with high statistical significance (*P* < 0.00001). There was moderate heterogeneity among the studies (I^2 = 48%). *CI* confidence interval, *RR* risk ratio

- AEs

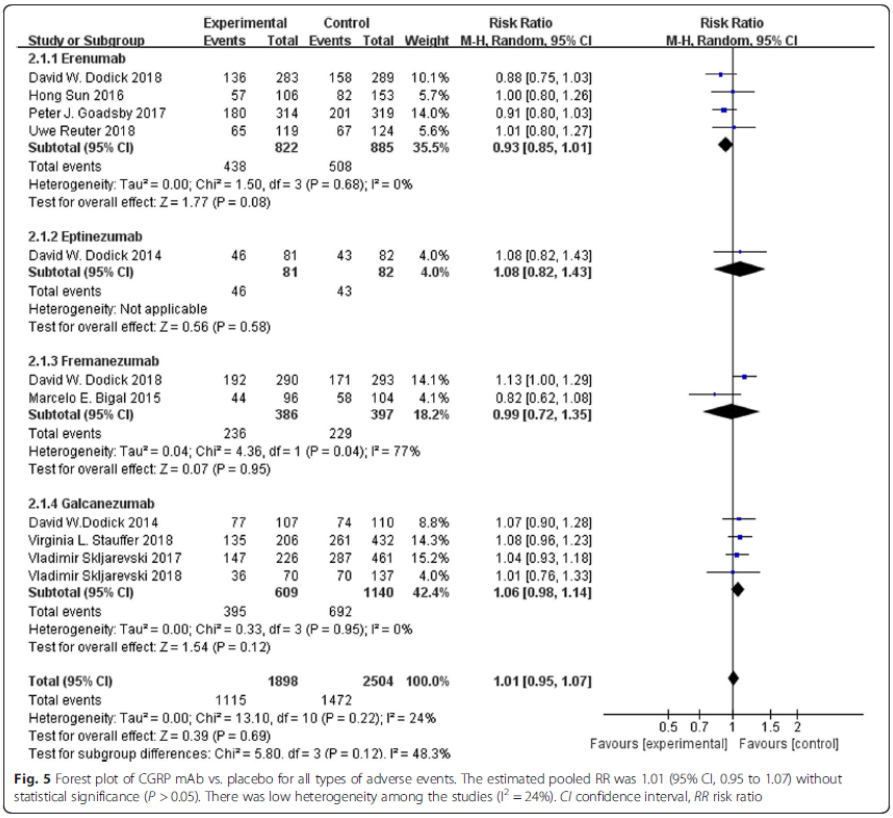


Fig. 5 Forest plot of CGRP mAb vs. placebo for all types of adverse events. The estimated pooled RR was 1.01 (95% CI, 0.95 to 1.07) without statistical significance (*P* > 0.05). There was low heterogeneity among the studies (I^2 = 24%). *CI* confidence interval, *RR* risk ratio

Table 3 Summary of adverse events among the included RCTs

	CGRP mAb(n/N)	Placebo(n/N)	I^2	odds ratio [95% CI]	*p* value
Withdrawal due to AEs	38/1898	35/2504	0%	1.46[0.90,2.37]	0.12
Specific AEs					
any serious events	1115/1898	1472/2504	25%	1.02[0.90,1.15]	0.79
dizziness	29/835	31/1313	0%	1.47[0.87,2.49]	0.15
fatigue	36/1515	39/1825	0%	1.15[0.72,1.83]	0.55
influenza	26/1231	41/1758	5%	0.87[0.53,1.45]	0.6
injection site pain	167/1501	148/1837	35%	1.44[1.13,1.84]	**0.004**
migraine	12/1086	17/1379	11%	0.83[0.41,1.71]	0.62
nasopharyngitis	115/1817	163/2422	1%	0.96[0.75,1.24]	0.78
nausea	34/1553	61/1919	0%	0.68[0.45,1.05]	0.08
upper respiratory tract infection	117/1692	123/2072	0%	1.25[0.96,1.63]	0.1
urinary tract infection	22/1270	33/1519	0%	0.91[0.53,1.56]	0.73

Anmerkung/Fazit der Autoren

[…] we found that CGRP mAbs could reduce the numbers of monthly migraine days and acute migraine-specific medication days, as well as improve the 50% responder rate, as compared to placebo group. TSA was used to adjust random errors and calculate the sample size needed, and it was found that the evidence in our meta-analysis was reliable and conclusive. In addition, CGRP-binding mAbs were well tolerated among episodic migraineurs, as the incidence of AEs and treatment withdrawal rates were relatively similar between CGRP mAbs and placebo groups. Moreover, only injection-site pain was significantly different between CGRP mAbs and placebo groups. We speculated that it could be related to the subcutaneous delivery route of CGRP mAb administration. The outcomes of subgroup analysis revealed that erenumab, fremanezumab and galcanezumab exhibited similar efficacy and safety in patients with episodic migraine.

Nevertheless, there are several limitations that need to be addressed. Firstly, different dosages of the same mAb were encompassed in the subgroup analysis, which might increase the between-study heterogeneity. For example, all the included studies for applied 70 mg of erenumab per month, with an exception of 140 mg per month in one RCT. Secondly, not all the outcome measures were from the same time point among the different trials. Most of the double-blind, placebo controlled trials lasted for 12 weeks, except for three studies with 24 weeks [17, 18, 24]. For the STRIVE trial, despite that the primary end point was the change in the mean number of monthly migraine days from baseline to months 4–6 [24], we extracted the supplemental data starting from the third month (i.e. 9–12 weeks) in order to enhance comparability. Moreover, since the original data were unretrievable, we could only extracted the outcome values at month 6 for two studies [17, 18]. Thirdly, different inclusion criteria could bias the results. For instance, the LIBERTY study included eligible participants who had previously been treated unsuccessfully (in terms of efficacy or tolerability, or both) with 2–4 conventional preventive therapies [14]. However, in the STRIVE trial, patients were excluded if they had no therapeutic response to more than two classes migraine preventive therapy [24].

Kommentare zum Review

- Alle im vorliegenden SR diskutierten Studien (n = 11) wurden auch in das SR von Huang et al, 2019 [9] eingeschlossen. Das vorliegende SR ist dennoch dargestellt, da Unterschiede bezüglich der diskutieren Endpunkte in den beiden SRs vorliegen.

- Die Risk of Bias-Assessments von Huang I et al., 2019 [9] und Deng H et al., 2020 [2] unterscheiden sich. Huang I et al., 2019 [9] beurteilen ein hohes (1) bzw. unklares (2) Risiko für Bias bezüglich der Domäne „blinding of outcome assessment“ in der Studie (1) NCT01952574 (Hong Sun et al., 2016) bzw. (2) NCT02614183 (Stauffer et al, 2018) während Deng H et al., 2020 [2] zu beiden Studien die Domäne „Blinding“ mit einem niedrigen Risiko für Bias bewerten. Zudem bewerten Huang I et al., 2019 [9] alle Studien mit einem hohen Biasrisiko bezüglich der Domäne „Other bias“, während Deng H et al., 2020 [2] ein unklares Risiko bezüglich „Other sources of bias“ einschätzen. Diese Unterschiede könnten auf die Nutzung verschiedener Biasbewertungsweisen und damit einhergehenden Domänendefinitionen zurückgehen.

Huang I et al., 2019 [9].

Effects of Anti-Calcitonin Gene-Related Peptide for Migraines: A Systematic Review with Meta-Analysis of Randomized Clinical Trials

Siehe auch: „Siehe auch“-Verweise bei Deng H et al, 2020 [2] innerhalb der ES.

Zielsetzung

We aimed to evaluate the response rate of migraines by using anti-calcitonin gene-related peptide (anti-CGRP) for patients with migraines.

Methodik

Population:

- patients with migraine from Argentina, Canada, Europe, Israel, Korea, Mexico, Russia, Taiwan, Turkey, and the USA between July 2012 and October 2017.

Intervention:

- anti-CGRP:
  - Eptinezumab
  - Erenumab
  - Frenamezumab
  - Galcanezumab

Komparator:

- Placebo

Endpunkte:

- Response rate 50%
  - First month
  - Second month
  - Third month
  - From baseline to week 12

Recherche/Suchzeitraum:

- PubMed, and […] Cochrane Library (including Cochrane CENTERL), Embase, and Web of Science.
- The final search was completed on 29 March 2019.

Qualitätsbewertung der Studien:

- Cochrane Risk of Bias Tool

Ergebnisse

Anzahl eingeschlossener Studien:

- Qualitative synthesis: 16 RCTs (n = 9439)
- Quantitative synthesis: 13 RCTs

Charakteristika der Population:

Study	Episodic / Chronic	Aura	Intervention period	Follow-up
NCT01772524	Episodic	Without + with aura	12 weeks	12 weeks
NCT02456740	Episodic	Non-specific	28 weeks	12 weeks
NCT01952574	Episodic	Non-specific	12 weeks	12 weeks
NCT02066415	Chronic	Non-specific	12 weeks	12 weeks
NCT02483585	Episodic	Without + with aura	40 weeks	12 weeks
NCT03096834	Episodic	Without + with aura	12 weeks	12 weeks
NCT02629861	Episodic	Non-specific	12 weeks	12 weeks
NCT02621931	Chronic	Non-specific	12 weeks	12 weeks
NCT02021773	Chronic	Without + with aura	12 weeks	4 weeks
NCT02025556	Episodic	Without + with aura	12 weeks	4 weeks
NCT02614183	Episodic	Non-specific	26 weeks	18 weeks
NCT02163993	Episodic	Non-specific	12 weeks	12 weeks
NCT01625988	Episodic	Without + with aura	12 weeks	12 weeks
NCT02614196	Episodic	Non-specific	26 weeks	18 weeks
NCT02614261	Chronic	Without + with aura	52 weeks	18 weeks
NCT02614287	Episodic and chronic	Without + with aura	52 weeks	18 weeks

These trials gave anti-CGRP for at least 12 weeks, and the longest treatment duration was 52 weeks. The trials completed a follow-up of at least four weeks, and the longest follow-up duration was four months. Eleven trials focused on episodic migraine, and four trials investigated chronic migraine. The other one recruited both populations of episodic migraine and chronic migraine. These trials did not set criteria for aura (Table S1). The age of patients ranged from 18 to 70 years old. Most of the patients were females (n = 7992; 84.67%), and there were only 1447 males (15.33%). Most trials in this systematic review and meta-analysis presented a low selection bias, performance bias, attrition bias, and reporting bias (Table S2).

Table 1. Characteristics of the included randomized controlled trials.

Trial	Area	Recruitment Duration	Medication	Patients (*n*)	Age	Male/Female
NCT01772524 [39]	USA	Jan. 28, 2013 ~ Dec. 23, 2013	Eptinezumab 1000 mg/placebo	163	18–55	30/133
NCT02456740 [40,57]	Canada, Europe, Turkey, USA	Jul. 2015 ~ Sep. 5, 2016	Erenumab 70 mg/140 mg/placebo	955	18–65	141/814
NCT01952574 [41,44]	Canada, Europe, USA	Aug. 6, 2013 ~ June 30, 2014	Erenumab 7 mg/21 mg/70 mg/placebo	483	18–60	94/389
NCT02066415 [42,43,57]	Canada, Europe, USA	Apr. 3, 2014 ~ Dec. 4, 2015	Erenumab 70 mg/140 mg/placebo	667	18–65	115/552
NCT02483585 [45]	Canada, Europe, USA	Jul. 2015 ~ Jul. 2016	Erenumab 70 mg/placebo	577	18–65	85/492
NCT03096834 [58]	Australia, Europe	Mar. 20, 2017 ~ Oct. 27, 2017	Erenumab 140 mg/placebo	246	18–65	46/200
NCT02629861 [46]	Canada, Europe, Russia, USA	Mar. 23, 2016 ~ Apr. 10, 2017	Fremanezumab 225 mg monthly/ 3-225 mg single higher dose/placebo	875	18–70	133/742
NCT02621931 [47]	USA	Mar. 2016 ~ Jan. 2017	Fremanezumab 675 mg + 2-225 mg/ 675 mg + 2-placebo/placebo	1130	18–70	139/991
NCT02021773 [48–51]	USA	Jan. 2014 ~ Dec. 2014	Fremanezumab 900 mg/675-225 mg/placebo	263	18–65	37/226
NCT02025556 [59]	USA	Jan. 2014 ~ Jan. 2015	Fremanezumab 675 mg/225 mg/placebo	297	18–65	36/261
NCT02614183 [52,60,61]	Canada, USA	Jan. 11, 2016 ~ Mar. 22, 2017	Galcanezumab 120 mg/240 mg/placebo	858	18–65	140/818
NCT02163993 [53,56,64]	USA	July 7, 2014 ~ Aug. 19, 2015	Galcanezumab 5 mg/50 mg/120 mg/ 300 mg/placebo	410	18–65	70/340
NCT01625988 [55]	USA	July 31, 2012 ~ Sep. 18, 2013	Galcanezumab 150 mg/placebo	217	18–65	33/184
NCT02614196 [54,60,61]	Argentina, Europe, Israel, Korea, Mexico, Taiwan, USA	Jan. 2016 ~ Mar. 2017	Galcanezumab 120 mg/240 mg/placebo	915	18–65	134/781
NCT02614261 [61,62]	Argentina, Canada, Europe, Israel, Mexico, Taiwan, USA	Jan. 2016 ~ Mar. 2017	Galcanezumab 120 mg/240 mg/placebo	1113	18–65	167/946
NCT02614287 [63]	Canada, Europe, USA	Dec. 2015 ~ Sep. 2017	Galcanezumab 120 mg/240 mg/placebo	270	18–65	47/223

Qualität der Studien:

Study	1	2	3	4	5	6	7
NCT01772524	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	High risk
NCT02456740	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	High risk
NCT01952574	Low risk	Low risk	Low risk	High risk	Low risk	Low risk	High risk
NCT02066415	Low risk	Low risk	Low risk	High risk	Low risk	Low risk	High risk
NCT02483585	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	High risk
NCT03096834	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	High risk
NCT02629861	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	High risk
NCT02621931	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	High risk
NCT02021773	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	High risk
NCT02025556	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	High risk
NCT02614183	Low risk	Low risk	Low risk	Unclear	Low risk	Low risk	High risk
NCT02163993	Low risk	Unclear	Low risk	Low risk	Low risk	Low risk	High risk
NCT01625988	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	High risk
NCT02614196	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	High risk
NCT02614261	Low risk	Low risk	Unclear	Unclear	Low risk	Low risk	High risk
NCT02614287	Unclear	High risk	Unclear	Unclear	High risk	Low risk	High risk

1 sequence generation; 2 allocation concealment; 3 blinding of participants and personnel; 4 blinding of outcome assessment; 5 incomplete outcome data; 6 selective reporting; 7 other bias.

Studienergebnisse:

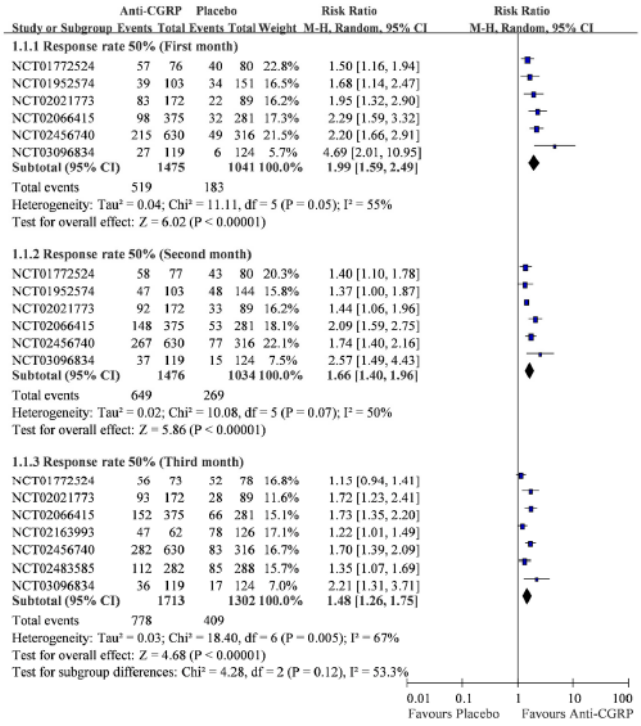


Figure 2. The 50% reduction rate of anti-CGRP and placebo.

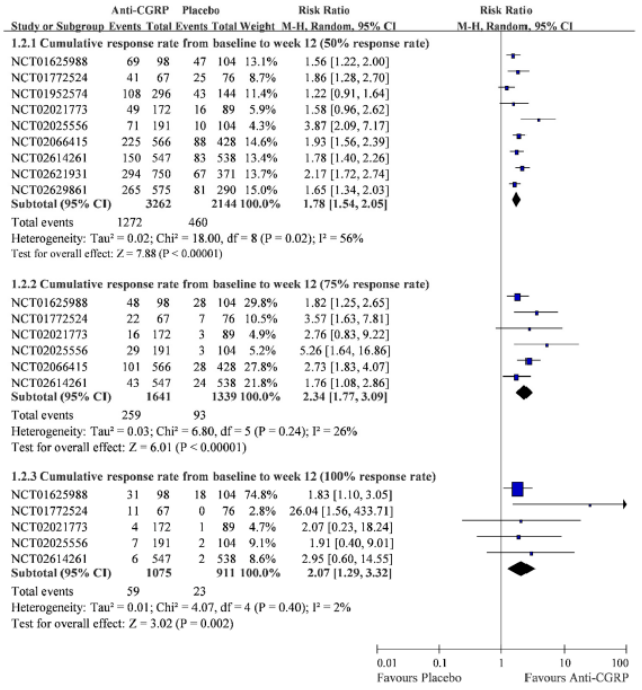


Figure 3. Cumulative response rate from the initial to the 12th month between anti-CGRP and placebo.

Anmerkung/Fazit der Autoren

In this study, we synthesized 16 trials. Our data showed that, as compared with placebo, treatment with anti-CGRP medications was associated with a significant progressive decrease of the response rate of migraine days during the three-month period. Though the heterogeneity is low in the overall three-month analysis data, the I-square is quite high (51.4%), reflecting the

differences between months and types of anti-CGRP medications. According to the Figure 2, the efficacy of medications decreased through time, showing a slightly descending trend. Moreover, there was an individual difference in each four types of the anti-CGRP medications. Among them, Frenamezumab had the least efficacy. In other words, anti-CGRP medications showed effective results in treating migraine, but the efficacy may be dependent on the time and types of medications used.

First, this meta-analysis cannot distinguish the effects from different dosages because the dosages among different types of anti-CGRP treatments cannot be converted easily. Dosage effects was also a limitation in the previous syntheses. Therefore, further studies should investigate dosage effects among different type of anti-CGRP treatments. Secondly, this meta-analysis did not synthesize the monthly migraine days, reduction of migraine days, monthly headache days, or reduction of headache days. This limitation may result in a lack of intuitive information (mean difference), but using the response rate can keep results unaffected by an extreme value. Moreover, response rates presenting the percentage of reduction in migraine days could be an index of the improvement. Thirdly, few evidences reported a 75% or 100% response rate each month. Thus, this meta-analysis cannot give a clear picture about how the anti-CGRP reaches a 75% or 100% response rate of migraine monthly. However, this study still proved an overview showing that the anti-CGRP is a highly effective treatment for migraine according to the cumulative 75% and 100% response rate.

Kommentare zum Review

- Folgende Studien (n = 11) wurden auch in das SR von Deng H et al, 2020 [2] eingeschlossen:
  - NCT01625988 (Dodick et al., 2014a)
  - NCT01772524 (Dodick et al., 2014b)
  - NCT01952574 (Sun et al., 2016)
  - NCT02025556 (Bigal et al., 2015)
  - NCT02163993 (Skljarevski et al., 2017)
  - NCT02456740 (Goadsby et al., 2017)
  - NCT02483585 (Dodick et al., 2017)
  - NCT02614183 (Stauffer et al., 2018)
  - NCT02614196 (Skljarevski et al., 2018)
  - NCT02629861 (Dodick et al., 2018)
  - NCT03096834 (Reuter et al., 2018)
- Siehe das Kommentar (zum Review) bezüglich unterschiedlicher Risk of Bias-Assessments zur Darstellung von Deng H et al, 2020 [2] innerhalb der Evidenzsynopse.

Stubberud A et al., 2019 [17].

Flunarizine as prophylaxis for episodic migraine: a systematic review with meta-analysis

Zielsetzung

The primary aims of this meta-analysis are: (1) to retrieve and describe the scientific quality of randomized controlled trials (RCTs) investigating flunarizine as migraine prophylaxis; and (2) to assess the pooled evidence of effectiveness, tolerability, and safety in these trials.

Methodik

Population:

- Included studies were not required to have strictly applied the International Headache Society diagnostic criteria [24, 25] as long as the migraine diagnoses were based on their list of distinctive features, such as nausea/vomiting, severe pain, pulsating pain, unilaterality, photophobia/phonophobia, or aura. Trials combining migraine and other headache types were excluded.

Intervention:

- flunarizine

Komparator:

- placebo or other pharmacological and nonpharmacological treatments with proven efficacy

Endpunkte:

- Primärer Endpunkt
  - mean reduction in migraine frequency
- Sekundäre Endpunkte
  - proportion of responders
  - (≥ 50% reduction in migraine frequency)
  - intensity and duration of migraine headache
  - doses of acute medication
  - disability
  - quality of life
  - AEs.

Recherche/Suchzeitraum:

- MEDLINE, Embase, and CENTRAL
- database search updated to November 13, 2017

Qualitätsbewertung der Studien:

- Cochrane Collaboration risk assessment tool

Ergebnisse

Anzahl eingeschlossener Studien:

- n = 25

Charakteristika der Population:

Table 1

Characteristics of included studies in summary.

Allais et al.[2]	Methods	Prospective, open RCT.
	Participants	Migraine without aura diagnosis according to IHS criteria. 160 participants; 150 completers; mean age 37.8 years; 160 females.
	Interventions	Flunarizine 10 mg/day vs acupuncture.
	Outcomes	1, 3, 5, and 8.
Bordini et al.[8]	Methods	Prospective, double-blind RCT.
	Participants	Migraine diagnosis according to IHS criteria. 45 participants; 38 completers; mean age 31.2 years; 41 females and 4 males.
	Interventions	Flunarizine 10 mg/day vs propranolol 60 mg/day vs flunarizine + propranolol 10 mg/day + 60 mg/day.
	Outcomes	1 and 8.
Cerbo et al.[10]	Methods	Prospective, double-blind RCT.
	Participants	Characteristic migraine symptoms. 30 participants; 27 completers; age range 23 to 54 years; 14 females and 16 males.
	Interventions	Flunarizine 15 mg/day vs pizotifen 1.5 mg/day.
	Outcomes	8.
Diamond and Freitag[13]	Methods	Prospective, double-blind RCT.
	Participants	Two-year migraine history. 143 participants; 101 completers; mean age 35 years; 75 females and 26 males.
	Interventions	Flunarizine 10 mg/day vs placebo.
	Outcomes	1.
Diener et al.[15]	Methods	Prospective, double-blind RCT.
	Participants	Inclusion criteria: migraine as defined by IHS. 810 participants; 783 included in intention to treat analysis; median age 37 years; 658 females and 150 males.
	Interventions	Flunarizine 5 mg/day vs flunarizine 10 mg/day vs propranolol 160 mg/day.
	Outcomes	1, 2, 4, 5, and 8.
Frenken and Nuijten[20]	Methods	Prospective, double-blind RCT.
	Participants	Common or classic migraine as defined by IHS. 35 participants; 35 completers; age range 20 to 51 years; 29 females and 6 males.
	Interventions	Flunarizine 10 mg/day vs placebo.
	Outcomes	1, 2, and 8.
Gawel et al.[22]	Methods	Prospective, double-blind RCT.
	Participants	Migraine headache as defined by the World Federation of Neurology Research Group. 94 participants; 89 completers; mean age 35.7 years; 85 females and 9 males.
	Interventions	Flunarizine 10 mg/day vs propranolol 160 mg/day.
	Outcomes	1, 3, 4, and 8.
Louis[35]	Methods	Prospective, double-blind RCT.
	Participants	Classic or common migraine with throbbing or pulsating attacks. 58 participants; 58 completers; mean age 29 years; 29 females and 29 males.
	Interventions	Flunarizine 10 mg/day vs placebo.
	Outcomes	1, 2, and 8.
Louis and Spierings[36]	Methods	Prospective, double-blind RCT.
	Participants	Classic or common migraine diagnosed according to IHS criteria. 75 participants; 72 completers; mean age 37 years; 40 females and 32 males.
	Interventions	Flunarizine 10 mg/day vs pizotifen 2 to 3 mg/day.
	Outcomes	1 and 8.
Ludin[37]	Methods	Prospective, double-blind RCT.
	Participants	Headache attacks with characteristic features of migraine. 71 participants; 48 completers; mean age 34.3 years; 51 females and 20 males.
	Interventions	Flunarizine 10 mg/day vs propranolol 120 mg/day.
	Outcomes	1, 2, 3, 4, 5, and 8.
Luo et al.[38]	Methods	Prospective, open RCT.
	Participants	Migraine diagnosis according to IHS criteria. 150 participants; 126 completers; mean age 43 years; 90 females and 36 males.
	Interventions	Flunarizine 5 mg/day vs topiramate 25 to 100 mg/day vs flunarizine + topiramate 5 mg/day + 25 to 100 mg/day.
	Outcomes	1 and 8.
Lutschg and Vassella[39]	Methods	Prospective, double-blind RCT.
	Participants	Children with classic or common migraine with characteristic migraine symptoms. 33 participants; 32 completers; mean age 10.5 years; 17 females and 16 males.
	Interventions	Flunarizine 5 to 10 mg/day vs propranolol 30 to 120 mg/day.
	Outcomes	1 and 8.

Table 1 (*continued*)

Mentenopoulos et al.[42]	Methods	Prospective, double-blind RCT.
	Participants	Migraine diagnosis according to IHS criteria. 30 participants; 15 completers; median age 44 years; 16 females and 4 males.
	Interventions	Flunarizine 10 mg/day vs placebo
	Outcomes	2 and 8.
Mitsikostas and Polychronidis[43]	Methods	Prospective, double-blind RCT.
	Participants	Migraine diagnosis according to IHS criteria. 44 participants; 41 completers; mean age 36.1 years; 31 females and 13 males.
	Interventions	Flunarizine 10 mg/day vs sodium valproate 1000 mg/day.
	Outcomes	2 and 8.
Pini et al.[45]	Methods	Prospective, double-blind RCT.
	Participants	Diagnosis of classic or common migraine. 20 participants; 29 completers; mean age 39.5 years; 24 females and 5 males.
	Interventions	Flunarizine 10 mg/day vs placebo.
	Outcomes	1.
Rascol et al.[47]	Methods	Prospective, double-blind RCT.
	Participants	Migraine diagnosis according to IHS criteria. 35 participants; 32 completers; median age 38 years; 25 females and 10 males.
	Interventions	Flunarizine 10 mg/day vs pizotifen 2.19 mg/day.
	Outcomes	1 and 8.
Shimell et al.[51]	Methods	Prospective, double-blind RCT.
	Participants	Migraine diagnosis according to IHS criteria. 58 participants; 49 completers; mean 34.5 years; 40 females and 17 males.
	Interventions	Flunarizine 10 mg/day vs propranolol 180 mg/day.
	Outcomes	1 and 8.
Sorge and Marano[53]	Methods	Prospective, double-blind RCT.
	Participants	Children with migraine diagnosed according to the Valquist criteria. 48 participants; 42 completers; mean age 10.6 years; 27 females and 21 males.
	Interventions	Flunarizine 5 mg/day vs placebo.
	Outcomes	1, 4, and 8.
Sorge et al.[54]	Methods	Prospective, double-blind cross-over trial.
	Participants	Children with migraine diagnosed according to the Valquist criteria. 70 participants; 63 completers; mean age 10.6 years; 36 females and 34 males.
	Interventions	Flunarizine 5 mg/day vs placebo.
	Outcomes	1, 4, and 8.
Soyka and Oestreich[55]	Methods	Prospective, double-blind RCT.
	Participants	Classic or common migraine with characteristic features. 87 participants; 69 completers; mean age 42.5 years; 51 females and 18 males.
	Interventions	Flunarizine 10 mg/day vs propranolol 120 mg/day.
	Outcomes	1, 4, and 8.
Soyka and Oestreich[56]	Methods	Prospective, double-blind RCT.
	Participants	Classic or common migraine with characteristic features. 434 participants; 336 completers; mean age 42 years; 265 females and 61 males.
	Interventions	Flunarizine 10 mg/day vs propranolol 120 mg/day.
	Outcomes	1, 4, and 8.
Sørensen et al.[58]	Methods	Prospective, double-blind cross-over trial.
	Participants	Migraine diagnosis according to IHS criteria, modified by Olesen et al. 29 participants; 27 completers; median age 40 years; 23 females and 6 males.
	Interventions	Flunarizine 10 mg/day vs placebo.
	Outcomes	1.
Sørensen[52]	Methods	Prospective, double-blind RCT.
	Participants	Migraine diagnosis according to IHS criteria. 149 participants; 127 completers; median age 42 years; 118 females and 31 males.
	Interventions	Flunarizine 10 mg/day vs propranolol 120 mg/day.
	Outcomes	1 and 8.
Vijayalakshmi et al.[65]	Methods	Prospective, open RCT.
	Participants	Migraine diagnosis according to IHS criteria. 60 participants.
	Interventions	Flunarizine 20 mg/day vs acupuncture.
	Outcomes	6.
Wang et al.[66]	Methods	Prospective single-blind RCT.
	Participants	Migraine diagnosis according to IHS criteria. 140 participants; 120 completers; mean age 39.5 years; 119 females and 21 males.
	Interventions	Flunarizine 10 mg/day vs acupuncture.
	Outcomes	1, 3, 5, 6, and 8.

1 — migraine frequency; 2 — responders to treatment; 3 — migraine intensity; 4 — headache duration; 5 — drug consumption; 6 — quality of life; 7 — disability; 8 — adverse events.
IHS, International Headache Society; RCT, randomized controlled trial.

Qualität der Studien:

- Risk of bias

Of 175 risk of bias items scored, 34.3% were deemed as low, 48.0% as unclear, and 17.7% as high (Fig. 2). At least one “high risk” score was assigned to 19 of the 25 studies (Fig. 3). A “low risk” of selection bias score was assigned to 6 studies [2, 15, 42, 47, 65, 66] providing a description of a computer-generated randomization and 2 studies [15, 66] providing a

description of appropriate allocation concealment—the remaining selection bias judgments were of “unclear risk.” “Low risk” of performance bias was assigned to 3 studies [52, 54, 66] providing an accurate description of blinding procedures, whereas 6 studies [2, 37, 38, 43, 53, 65] were deemed to have insufficient blinding of participants and personnel, and thus a “high risk” of bias. Three studies provided sufficient description of blinding of outcome assessors. [2, 37, 66] Ten studies [8, 13, 22, 38, 42, 47, 53–56] assigned a “high risk” of attrition bias because they made completers-only analyses without reporting reasons for withdrawals, or because reasons for withdrawal were associated with the outcome. Five additional studies [2, 10, 36, 43, 58] provided completers-only analyses with limited attrition, or the reported reasons for attrition were not associated with the outcome - these bias categories were rated as “unclear risk.” Furthermore, 12 of the studies were assigned a “high risk” of selective reporting. Finally, 2 studies were assigned a “high risk” of other bias - one for only including women and [2] the other for only including previous responders to migraine prophylactics. [13]

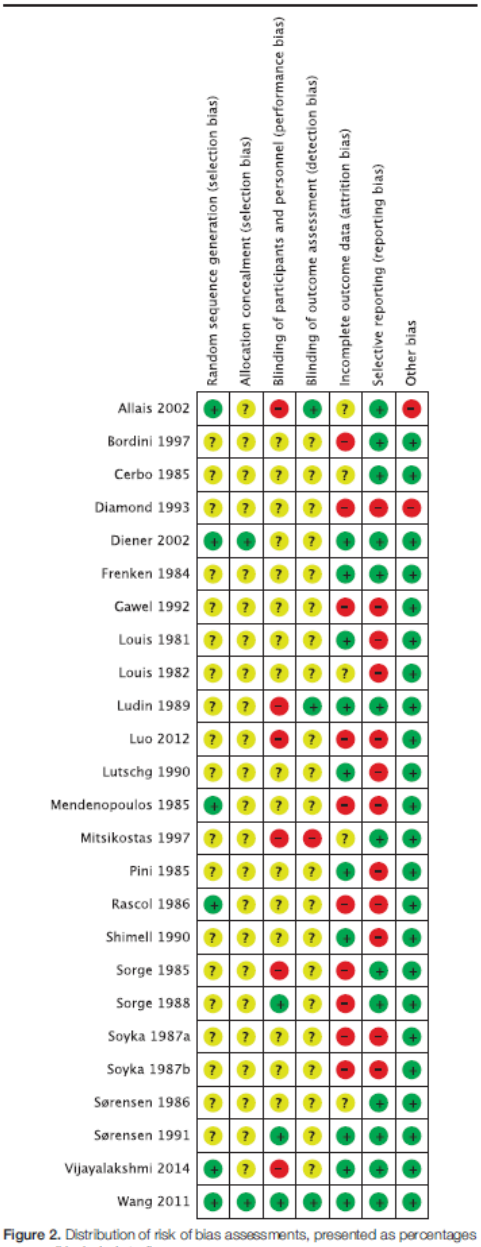


Figure 2. Distribution of risk of bias assessments, presented as percentages across all included studies.

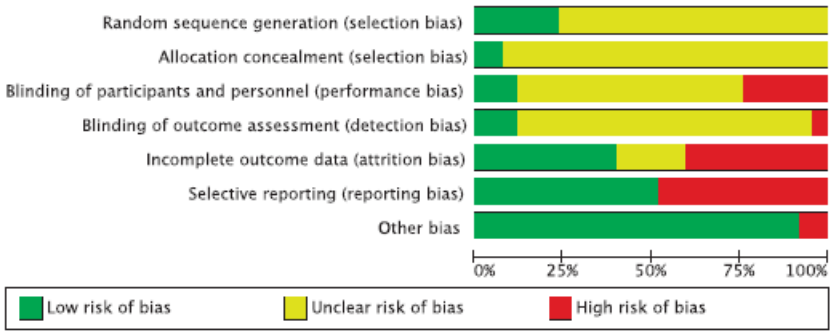


Figure 3. Judgment for each risk of bias item for each included study.

Studienergebnisse:

- 3.4.1. Flunarizine vs placebo

Flunarizine was superior to placebo in reducing migraine frequency after 3 months of active treatment (MD -0.44; 95% CI -0.61 to -0.26; Fig. 4) in the pooled analysis of 5 studies (249 participants [13, 20, 35, 45, 58]). A sensitivity analysis ignoring trials with imputed data [20, 58] produced a similar estimate (MD -0.43; 95% CI -0.60 to -0.25). Flunarizine also showed higher responder proportion than placebo (OR 8.86; 95% CI 3.57-22.0; Fig. 5) in the pooled analysis of 3 studies (113 participants [20, 35, 42]). The number needed to treat to benefit was 3 (95% CI 2-4), based on an assumed control risk of 0.28 calculated from the baseline migraine frequency of the control groups.

- 3.4.2. Flunarizine direct dose comparisons

A single study (524 participants [15]) comparing 5-mg vs 10-mg doses of flunarizine revealed no difference in effect on headache frequency after 4 months of active treatment (MD 0.20; 95% CI 0.08 to 0.48).

- 3.4.3. Flunarizine vs propranolol

No difference between 10-mg flunarizine and all doses of propranolol (60-160 mg) was observed after 4 months of active treatment (MD -0.08; 95% CI -0.34 to 0.18; Fig. 6) in the pooled analysis of 7 studies (1151 participants [8, 15, 22, 37, 51, 55, 56]). A sensitivity analysis ignoring trials with imputed data [8, 22, 51] showed a similar result (MD -0.07; 95% CI -0.33 to 0.20). Figure 6 shows the effect estimates for different doses of propranolol. A pooled analysis of 2 trials comparing responders to treatment (581 participants [15, 37]) revealed no difference between the 2 drugs (OR 1.19; 95% CI 0.86-1.64). Using an assumed control risk from the control groups in the included studies, at 0.19, the number needed to treat to benefit in favor of flunarizine was 36 (CI not defined). For secondary outcomes in flunarizine vs propranolol trials, 2 studies (135 participants [22, 37]) showed no difference in intensity of migraine attacks after 4 months of treatment (MD 0.22; 95% CI -0.12 to 0.57); 5 studies (1063 participants [15, 22, 37, 55, 56]) showed no difference in headache duration after 4 months of treatment (MD 0.60; 95% CI -1.48 to 2.69); and 2 studies (583 participants [15, 37]) demonstrated no difference in use of abortive drugs between the groups (SMD 0.07; 95% CI -0.09 to 0.23).

- 3.4.5. Flunarizine vs drugs other than propranolol or pizotifen

A single trial (127 participants [52]) comparing flunarizine with metoprolol found no difference in migraine frequency after 3 months of treatment (MD -0.10; 95% CI 21.08 to 0.88). One study (41 participants [43]) comparing flunarizine with sodium valproate found no difference between the drugs (OR 1.07; 95% CI 0.28-4.12). A third parallel design and open trial (83 participants

[38]) compared flunarizine with topiramate. At 3 months, no significant difference was found between the 2 treatments with respect to migraine frequency (MD -0.30; 95% CI -0.97 to 0.37).

- 3.4.8. Safety and tolerability

Adverse events were reported in 3 of 6 placebo-controlled trials. Flunarizine users did not have higher risk of experiencing any one or more AEs, compared with placebo (RD 0.04; 95% CI -0.08 to 0.17; Fig. 7) in the pooled analyses of these trials. [20, 35, 42] The following mild-to-moderate AEs were reported in the placebocontrolled trials: Weight gain (NNTH 6; CI not defined); daytime sedation (NNTH 8; 95% CI 4-50); stomach complaints (NNTH not defined); and dry mouth (NNTH not defined). No serious AEs were reported in any of the placebo-controlled trials and only one flunarizine-treated participant withdrew due to AEs. [58] The single study [15] comparing doses of flunarizine found that 88 of 263 (33.5%) participants in the 5-mg group experienced one or more AEs, whereas 88 of 275 (32%) participants in the 10-mg group experienced one or more AEs. None of the trials comparing flunarizine with active treatment reported any serious AEs. Six studies (1133 participants [8, 15, 22, 51, 55, 56]) of flunarizine vs propranolol found no difference in the occurrence of any AEs (RD -0.04; 95% CI 2 0.09 to 0.02). Figure 8 gives a summary of the frequency of AEs reported in more than one of the flunarizine vs propranolol trials. Two combined AE categories were created, the first including synonyms for sedation and somnolence, and the second including synonyms for fatigue and asthenia. The flunarizine vs pizotifen trials had insufficient reporting of AEs to allow for metaanalysis. Finally, 2 trials of flunarizine vs acupuncture (270 participants [2, 66]) found a higher proportion of AEs among flunarizine users (RD 0.15; 95% CI 0.07-0.23). Depression was only reported in 3 of 25 studies [2, 15, 52] - in total 2.9% (20/683) of the flunarizine users. In one of these studies, a flunarizine vs propranolol trial, [15] 7/263 of 5-mg dose flunarizine users and 2/275 of 10-mg flunarizine users experienced depression. Extrapyramidal symptoms were reported in 1 of 25 studies [52] - among 2.7% (2/74) of the flunarizine users during the run-in phase. No extrapyramidal symptoms were observed during or after flunarizine treatment in any of the included studies. The reported data on AEs in the 2 placebo-controlled trials of flunarizine in children were insufficient for meta-analysis. One of these (48 participants [53]) reported that 3 of 24 participants discontinued due to AEs, whereas the other study (70 participants [54]) reported weight gain in 14 and drowsiness in 6 of all analyzed participants.

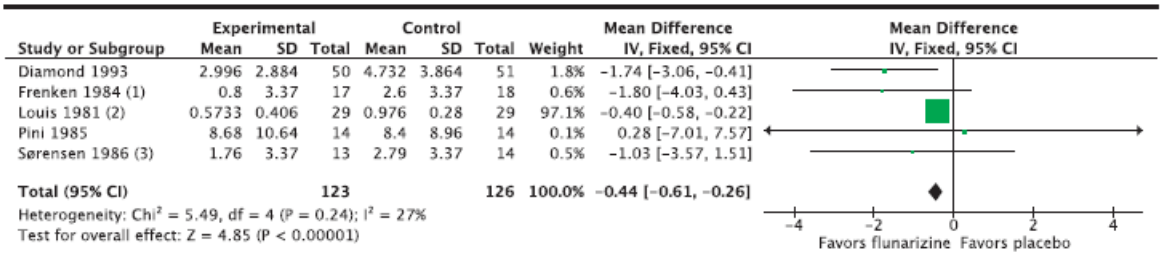


Figure 4. Forest plot of flunarizine vs placebo for migraine frequency. 95% CI, 95% confidence interval; (1), SDs imputed; (2), SD calculated from individual patient data; (3), point estimates extracted from figures; IV, inverse variance; SD, standard deviation.

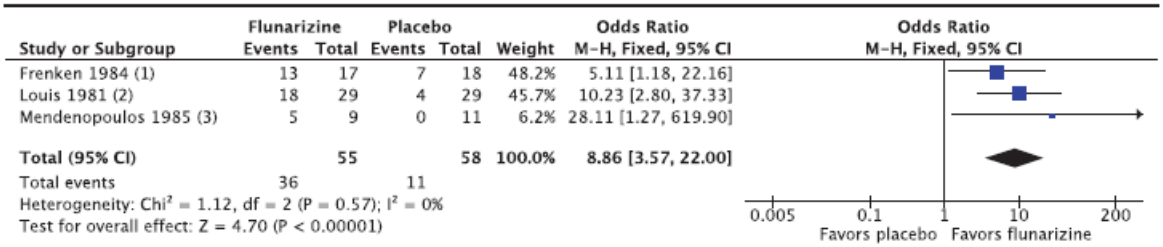


Figure 5. Forest plot of flunarizine vs placebo for responders to treatment (≥50% reduction in migraine frequency). 95% CI, 95% confidence interval; (1), data extracted from figures; (2), data extracted from figures; (3), data extracted from figures; M-H, Mantel-Haenszel.

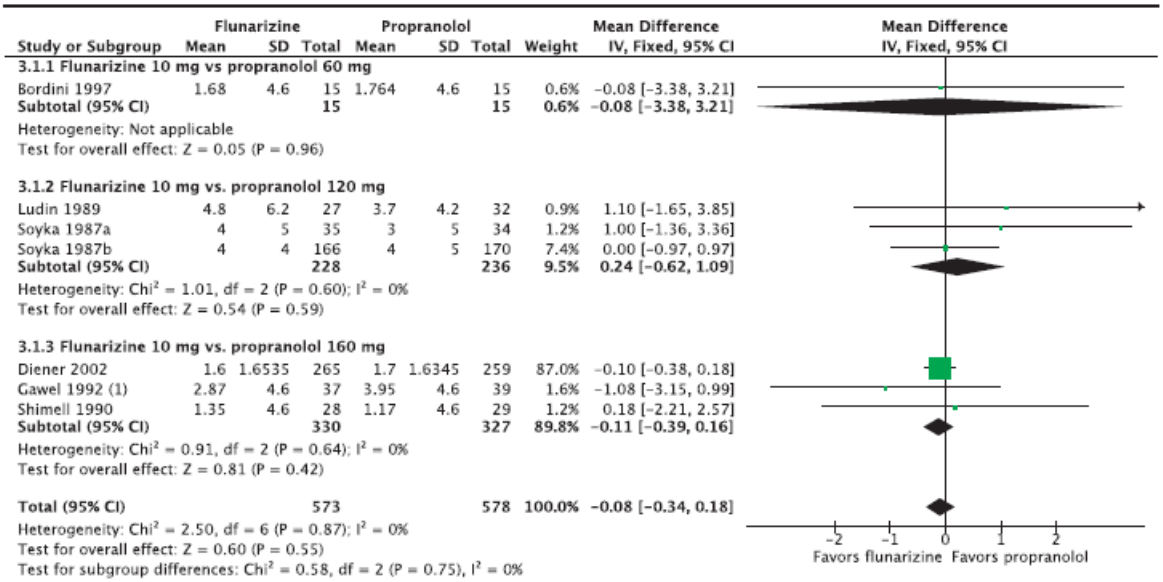


Figure 6. Forest plot of flunarizine vs propranolol for migraine frequency. 95% CI, 95% confidence interval; (1), data extracted from figures; IV, inverse variance; SD, standard deviation.

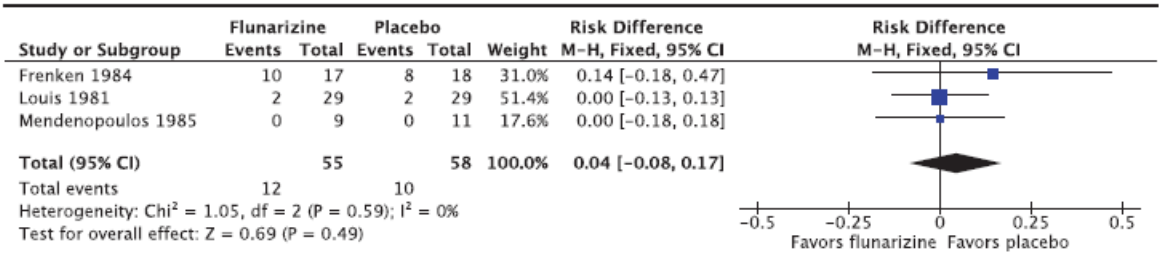


Figure 7. Forest plot of flunarizine vs placebo for adverse events. 95% CI, 95% confidence interval; M-H, Mantel-Haenszel.

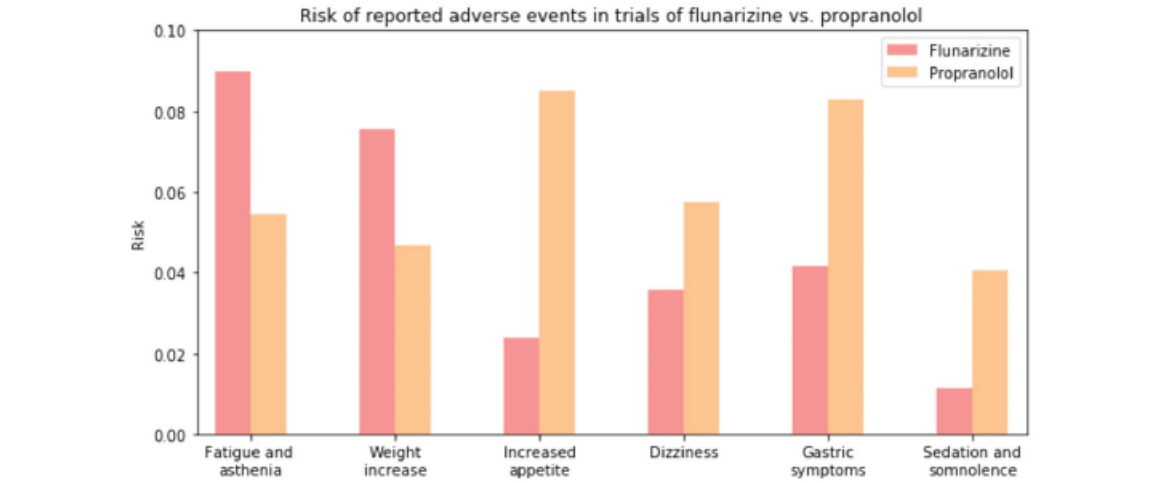


Figure 8. Distribution of adverse events reported in more than one study for trials of flunarizine vs propranolol. AEs, adverse events.

Anmerkung/Fazit der Autoren

Despite positive findings, most of the placebo-controlled trials currently available lack sufficient power to properly assess the effect size of the intervention. In fact, several of the studies are underpowered in their sample size, and none provides sample size calculations. A power analysis reveals that a sample size of 64 participants is required in each treatment arm to identify

a significant difference given an effect size of 0.5 and a power of 0.8 at the 0.05 significance level. [27] Only one of the placebocontrolled parallel trials recruited more participants.13 Similarly, the sample sizes for most individual trials investigating flunarizine vs active comparators were far too low, for noninferiority analysis. [30] Only one study [15] provided sample size calculations, concluding with a necessary sample size of over 260 participants per arm to prove that flunarizine was at least as effective as propranolol. Consequently, this study was weighed at 87.0% in the meta-analysis for headache frequency and highlights the importance of conducting sufficiently powered studies.

A limitation of this review is the variability and incompleteness of data in the included studies. This required us to complete a series of conversions and calculations from scarce primary data to allow for pooled analysis of the eligible studies. In some studies, we also had to impute missing variance data. This is hypothesized not to introduce bias [21] but still makes the pooled estimate less certain. Nonetheless, omitting all studies with missing variance data could have yielded a biased point estimate because these studies may not be a random subset of all studies. [21] However, the sensitivity analyses indicate that the assumptions made on imputing data are valid. One should also keep in mind the limitations of the AE analyses due to heterogeneous and often incomplete reporting in many studies. For example, 2 studies [55, 56] analyzed effectiveness of data only from participants with “accepted rating sheets” but still reported AEs from all participants. If we assume all dropouts were due to ineffectiveness, there could potentially be a large mismatch between the reported effect and the number of AEs. Similar attrition bias might also have been present in several of the included studies. Current evidence indicates that 10-mg flunarizine is as effective as other well-established alternatives, such as propranolol, but with an AE profile focused on fatigue, somnolence, and weight increase. Guidelines give grade A recommendation to flunarizine as migraine prophylaxis, derived from results presented in individual and, to a large extent, old studies. This review supports this recommendation, but our conclusion is mainly based on the same sources. Methodological quality issues in the included studies—several of them involves substantial risks of bias— hamper us from concluding whether today’s limited use of flunarizine represents healthy skepticism or a neglect of a subgroup of patients in need of additional prophylactic drug options. To avoid simply putting a new timestamp on something that is outdated, new placebo-controlled RCTs meeting the latest methodological standards are required.

Kommentare zum Review

- Folgende Darstellungen innerhalb der LL wurden in der Evidenzsynopse auf Grund einer zurzeit fehlenden Zulassung der jeweiligen Intervention im AWG bzw. einer Nonkonformität mit dem AWG (3.4.7.) nicht aufgeführt:
  - 3.4.4. Flunarizine vs pizotifen
  - 3.4.6. Flunarizine vs acupuncture
  - 3.4.7. Flunarizine in children

Bruloy E et al., 2019 [1].

Botulinum Toxin versus Placebo: A Meta-Analysis of Prophylactic Treatment for Migraine

Zielsetzung

[…] the objective of this metaanalysis […] was to assess the effectiveness of botulinum toxin type A injections on changes in the frequency of migraines, its impact on the quality of life, but also its safety versus placebo when injected into pericranial muscles as a preventive treatment for migraines in adults.

Methodik

Population:

- patients receiving botulinum toxin versus placebo injections into head and neck muscles as preventive treatment for migraine

Intervention:

- botulinum toxin

Komparator:

- Placebo

Endpunkte:

- Primärer Endpunkt
  - change in the number of headache episodes per month from baseline to month 3
- Sekundäre Endpunkte
  - Change [in the number of headache episodes per month] was also analysed from baseline to month 2 […] together with quality of life and adverse events at month 3

Recherche/Suchzeitraum:

- MEDLINE, Embase, and the Cochrane Library from inception to August of 2016

Qualitätsbewertung der Studien:

- Review Manager program to assess level of evidence and risk of bias

Ergebnisse

Anzahl eingeschlossener Studien:

- n = 17 randomized, double-blinded, and placebo-controlled trials

Charakteristika der Population:

The 17 studies included 3646 patients, of which 3143 were female (86.21 percent), 2095 had episodic migraines (57 percent), and 1551 had chronic migraines (43 percent). Most patients used a fixed-site protocol (16 of 17). The median frequency of migraine crises per month was 6.5 (range, 4.37 to 25.1). The average age of included patients was 42.8 years (range, 18 to 65 years) in studies where they were clearly defined in the inclusion criteria (14 of 17). Prophylactic treatments were allowed in 10 studies but had to have stable doses and regimens given for 1 to 3 months before the first injections and throughout the study. All of the selected studies described symptomatic treatments and the use of analgesic medications (Table 1).

Table 1. Randomized Controlled Trials on Botulinum Toxin Type A and Migraine That Were Selected for the Meta-Analysis

Source	Location	Inclusion Criteria	FS and FTP Maximum Dose	Double-Blind Whole Study	Sample (P/B)	Dropouts (%)
Silberstein, 2000	12 headache centers across the United States	EM: Subjects were eligible for this study if they had experienced an average of 2–8 moderate to severe migraines per month over the previous 3 mo	FS: 25/75	90/120	123 (P = 41, B25 = 42, B75 = 40)	1 (1)
Barrientos, 2002	1 Chilean center	EM	FS: 50	90/90	30 (P = 15, B = 15)	0 (0)
Evers, 2004	1 German center	EM: average frequency of 2–8 attacks per month in the preceding 3 mo	FS: 16/100	90/90	60 (P = 20, B16 = 20, B100 = 20)	0 (0)
Elkind, 2006	16 North American study centers	EM: Eligible patients were to have an average of 4–8 moderate to severe migraines per month that occurred with a stable frequency and severity	FS: 7.5/25/50	120/480	401 (P = 106, B7,5 = 105, B25 = 101, B50 = 106)	38 (9)
Aurora, 2007	20 North American study centers	EM: 4 moderate to severe migraine episodes but ≤15 headache days per month (confirmed by a headache diary)	FTP: 110/260	270/330	369 PNR: 203 (P = 100, B = 103) PR: 166 (P = 82, B = 84)	84 (23)
Cady 2007	1 American center	EM: Headache Impact Test (HIT)-6 score greater than 56 were eligible to participate	FS: 139	90/180	59 (P = 19, B = 40)	5 (8%)
Rejla 2007	37 study centers in nine countries	EM: 3 moderate to severe untreated or treated migraine episodes per month	FS: 75/150/225	270/330	495 PNR = 322 (P = 72, B75 = 83, B150 = 82, B225 = 85) PR = 173 (P = 46, B75 = 40, B150 = 43, B225 = 44)	80 (19)
Saper, 2007	7 North American study centers	EM: average of 4–8 moderate to severe migraine headaches per month	FS: Frontal, 10; temporal, 6; glabellar: 9, FTG, 25	90/120	232 (P = 45, $B_{frontal}$ = 44, $B_{temporal}$ = 45, $B_{glabellar}$ = 49, B_{FTG} = 49)	7 (3)
Vo, 2007	1 American center	CM: >5 times/mo	FS: 205	90/120	32 (P = 17, B = 15)	11 (35)
Freitag, 2008	1 American center	CM: 15 headache days during the prospective baseline phase	FS: 100	120/160	36 (P = 18, B = 18)	5 (12)
Petri, 2009	16 German centers	EM: 3–6 attacks per month	FS: 80/210	90/120	122 (P = 62, B80 = 29, B210 = 31)	5 (4)
Aurora, 2010	56 North American sites	CM: >15 headache days	FS: 155 ± FTP: 40	180/450	679 (P = 338, B = 341)	88 (13)
Diener, 2010	66 global sites	CM: 15 days/4 wk	FS: 155 ± FTP: 40	180/450	705 (P = 358, B = 347)	60 (9)
Chankrachang, 2011	6 centers in Thailand	EM: an average of 2–8 migraine attacks per month over the 3 mo before a screening period	FS: 120/240	90/120	128 (P = 42, B120 = 43, B240 = 43)	9 (7)
Sandrini, 2011	Italian centers	CM: >15 headache days every 4 wk in the past 3 mo	FS: 100	90/210	68 (P = 35, B = 33)	12 (17.7)
Hollanda, 2014	1 Brazilian center	CM	FS: 96	90/90	38 (P = 18, B = 20)	0 (0)
Hou, 2015	1 Chinese center	EM and CM: (35.3% chronic migraine)	FS: 25	120/120	60 (P = 19, B = 41)	0 (0)

EM, episodic migraines; CM, chronic migraines; P, placebo group; B, botulinum toxin type A group; FS, fixed site; FTP, follow the pain; FTG, all three areas (frontal, temporal, and glabellar).

Qualität der Studien:

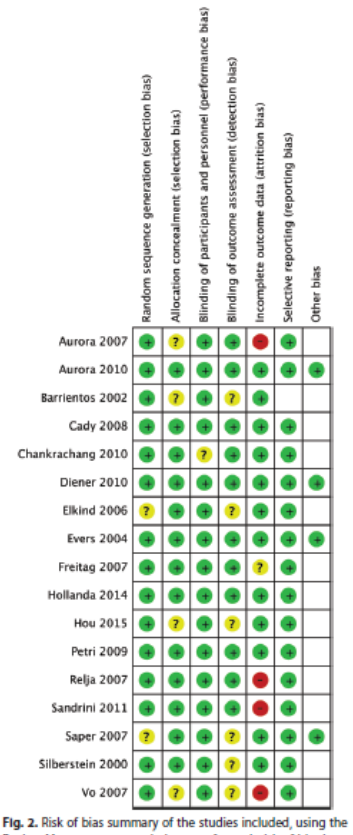


Fig. 2. Risk of bias summary of the studies included, using the Review Manager program: judgments for each risk-of-bias item for each included study.

Studienergebnisse:

- Changes in headache episodes per month between baseline and month 3

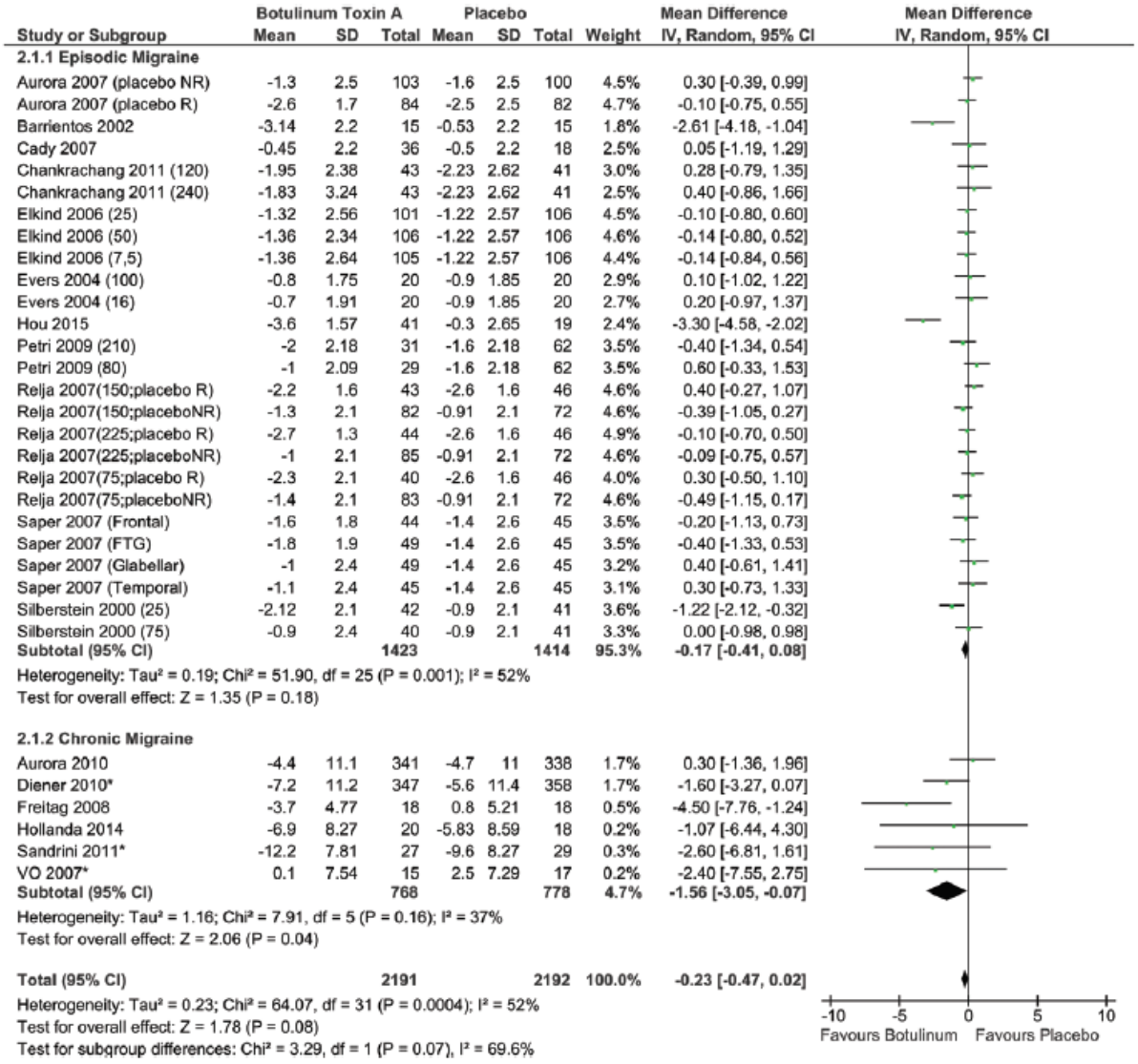


Fig. 3. Forest plot of changes in headache episodes per month between baseline and month 3. *Studies using changes in numbers of headache days per month were also included in the meta-analysis to decrease heterogeneity. *IV*, inverse variance; *NR*, nonresponders; *R*, responders.

- Changes in headache episodes per month between baseline and month 2

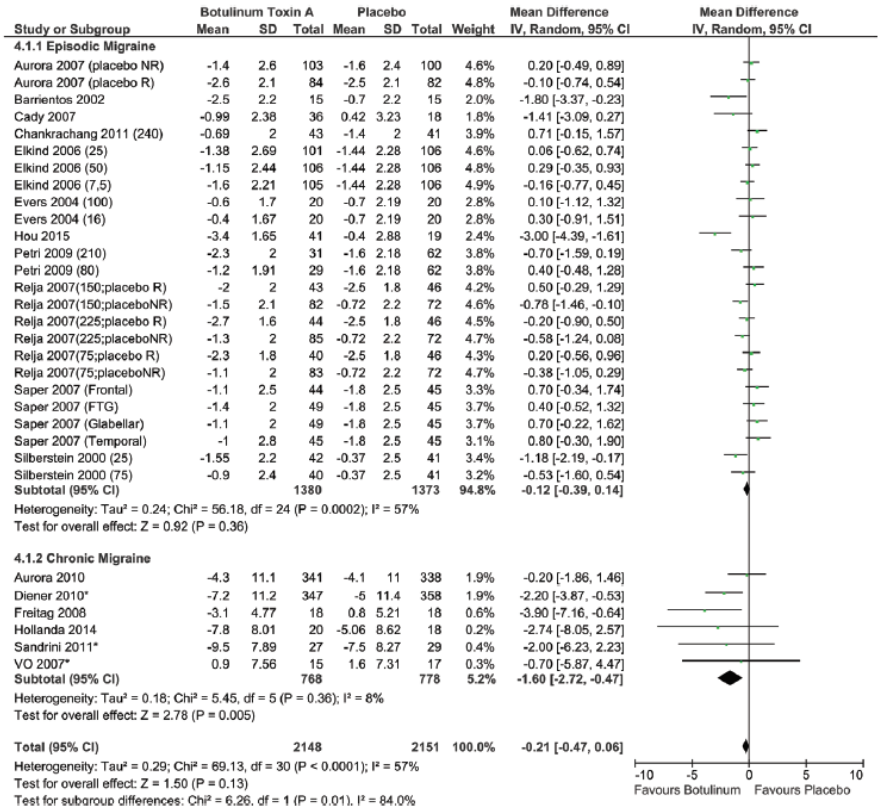


Fig. 4. Forest plot of changes in numbers of headache episodes per month between baseline and month 2. *Studies that used changes in numbers of headache days per month were included in the meta-analysis to decrease heterogeneity. *IV*, inverse variance; *NR*, nonresponders; *R*, responders

- Qualitiy of life at 3 months

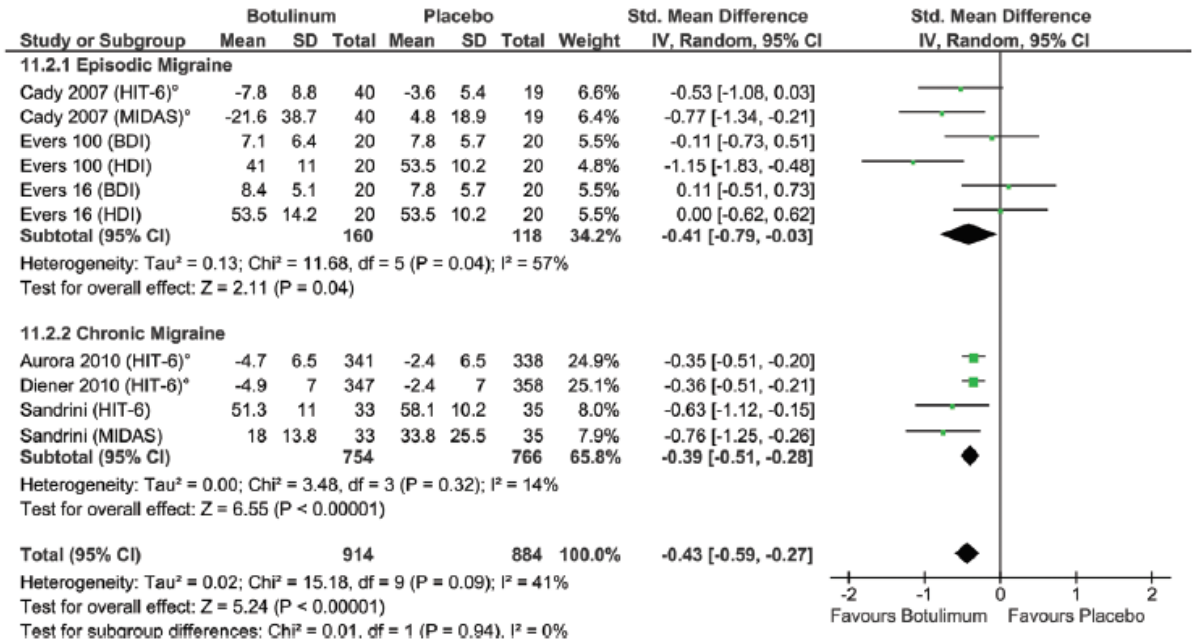


Fig. 5. Forest plot of quality of life at 3 months. Higher scores indicate a lower quality of life. *Std*, standardized; *IV*, inverse variance; *HIT-6*, Headache Impact Test; *MIDAS*, Migraine Disability Assessment; *BDI*, Beck Depression Inventory–II; *HDI*, Headache Disability Inventory. °Studies that used changes in quality of life from baseline to 3 months were included in the meta-analysis to decrease heterogeneity.

- Adverse Events at 3 months

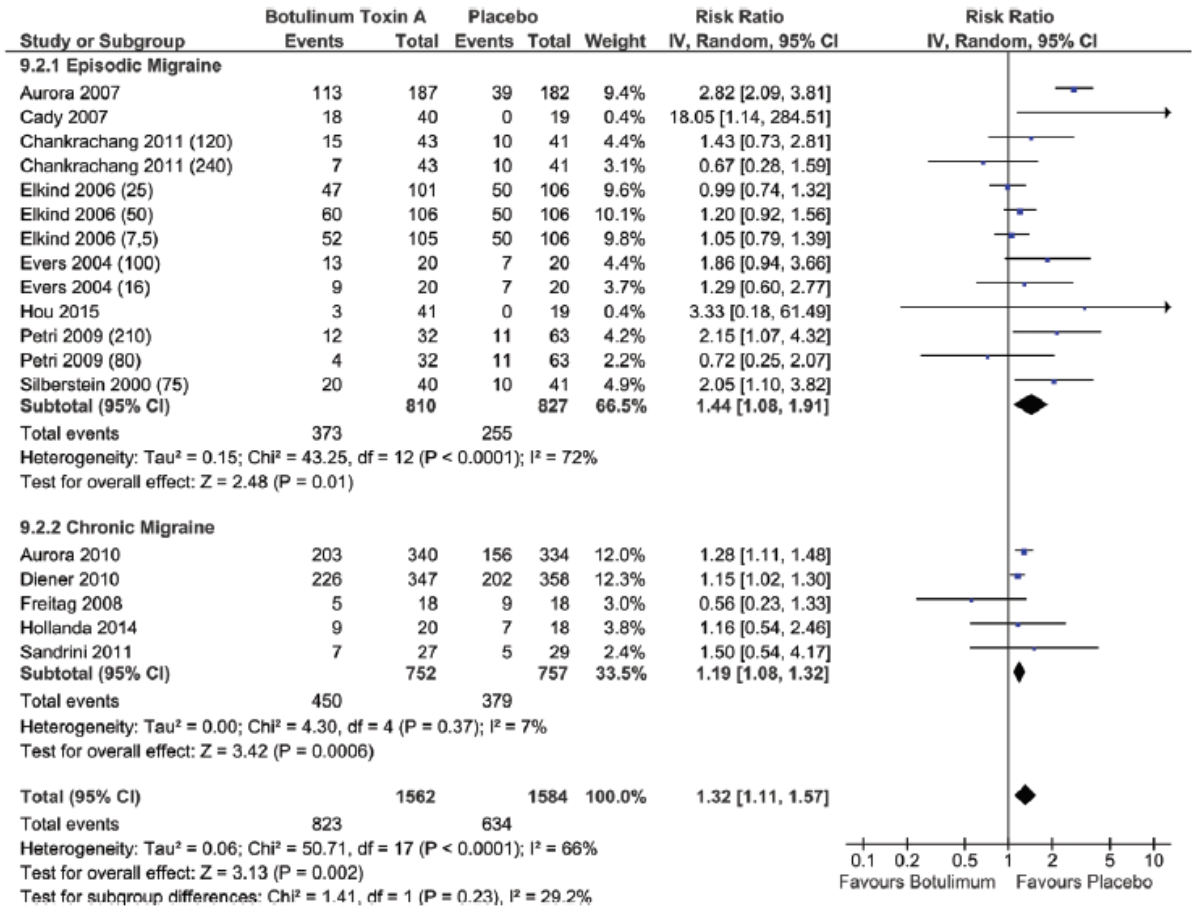


Fig. 6. Forest plot of adverse events at 3 months. *IV*, inverse variance.

Anmerkung/Fazit der Autoren

This lack of significance, particularly for episodic migraines, could be explained by a high response rate to placebo, which is often encountered in trials that explore pain disorders such as migraine. [41, 42] A recent study by et al. reported that placebo response ranged from 14 to 50 percent in clinical trials that analyzed preventive migraine treatments. [43] The placebo effect is also closely dependent on the desire to take part in a botulinum toxin type A trial versus placebo. In this setting, the cosmetic benefits of injecting botulinum toxin and its associated low-risk side effects compare favorably with other prophylactic migraine medications, thus increasing patients' willingness to enter such studies and inflating the placebo effect. Indeed, open-label studies emphasize a greater favorable association between botulinum toxin type A and migraines. The statistical tendency of botulinum toxin to reduce the frequency of episodic migraines needs to be assessed further in double-blind, placebo controlled, randomized trials. Nonetheless, the cosmetic use of botulinum toxin type A may have reduced efficacy in botulinum groups. The occurrence of muscular paralysis, mainly in the frontalis, procerus, and corrugators, can reveal - both to the blinded patient and to the investigator - which treatment they are receiving. This can thus increase the placebo effect and reduce the response to botulinum toxin type A. According to Solomon, [44] the loss of treatment blinding was highlighted in two randomized, double- blind, placebo-controlled trials that evaluated how many patients guessed which treatment they had received. Mathew et al. [45] reported that 85.1 percent of patients had

correctly identified they were receiving botulinum toxin. This clearly shows the importance of blindness in randomized, double- blinded, placebo-controlled trials that evaluate the prophylactic effects of botulinum toxin. However, our study has some limitations. First, despite our attempts to contact the authors, we were unable to obtain all patient-level data and had to work using aggregate data; nevertheless, this may have avoided discrepancies between the studies included (particularly for episodic migraines, where statistical heterogeneity was significant). Second, outcomes were various, such as the clustering of migraine frequency when presented as migraine-days per month and number of crises per month. However, the data between groups were clinically similar, and our inclusion of data from all of the trials in the analyses reduced statistical heterogeneity. Finally, we did not include controlled trials examining other prophylactic oral medications in our meta-analysis. Other studies have compared botulinum toxin injections to various prophylactic oral medications, such as topiramate, [14] amitriptyline, [13] valproate, [50] and methylprednisolone. [51] These studies do not demonstrate any superiority of other oral treatments over botulinum toxin.

3.4 Leitlinien

Sacco S et al., 2019 [15].

European headache federation guideline on the use of monoclonal antibodies acting on the calcitonin gene related peptide or its receptor for migraine prevention

Siehe auch: Sacco S et al., 2019 [14] Correction to: European headache federation guideline on the use of monoclonal antibodies acting on the calcitonin gene related peptide or its receptor for migraine prevention

Zielsetzung

The European Headache Federation (EHF) initiated this project to provide clinical guidance on the use of the CGRP mAbs. The aim of this guideline is to provide evidence-based and expert-based guidance to clinicians for the management of episodic migraine (EM) and chronic migraine (CM) with CGRP mAbs.

Methodik

„Die Leitlinie erfüllt nicht ausreichend die methodischen Anforderungen. Aufgrund fehlender höherwertiger LL-Evidenz, die Erenumab, Fremanezumab und Galcanezumab diskutiert, wird die LL jedoch ergänzend dargestellt.“

Grundlage der Leitlinie

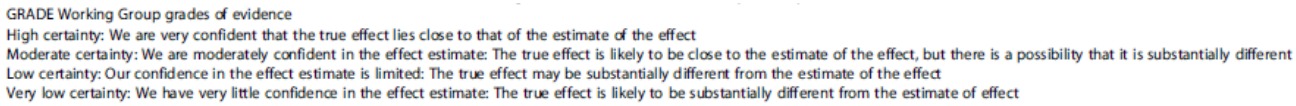
- Repräsentatives Gremium - trifft nicht zu;
- Interessenkonflikte und finanzielle Unabhängigkeit dargelegt - trifft zu;
- Systematische Suche, Auswahl und Bewertung der Evidenz - trifft zu;
- Formale Konsensusprozesse und externes Begutachtungsverfahren dargelegt - trifft teilweise zu;
- Empfehlungen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

Recherche/Suchzeitraum:

- An initial literature search included all papers indexed on PubMed and Scopus, from inception to April 2, 2018. The systematic literature search was repeated at the end of the consensus procedure to include all relevant papers published until November 2018.

LoE

- GRADE system and Summary of findings tables


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

GoR

- Strength (strong or weak) and direction (for or against) of recommendation were determined on basis of balance between desirable and undesirable effects, quality of evidence, values and preferences and costs [18]. If GRADE was not applicable, an ungraded good practice statement based on experts' opinions was given, according to the available level of evidence.

Sonstige methodische Hinweise (Bei Einschränkung der o. g. Kriterien)

- Eine Verbindung zu der zugrundeliegenden Evidenz ist nicht explizit dargestellt bzw. entsprechen Empfehlungen die Expertenmeinungen, da es sich um einen „Consensus Article from experts in the topic" handelt.
- Es fehlen relevante deskriptive Autorenangaben. Verfügbare Angaben lassen auf einen homogenen wissenschaftlichen Hintergrund der Autoren und Autorinnen schließen. Patientenvertreter scheinen nicht an der LL-Entstehung beteiligt gewesen zu sein.
- Es fehlen Details zum Konsentieren von unterschiedlichen Expertenmeinungen. Ein externes Begutachtungsverfahren wird nicht deutlich.
- In die LL aufgenommene Studien werden überwiegend auch von Deng H et al., 2020 [2] und Huang I et al., 2019 [9] referenziert (s. o.).

Ergebnisse

Risk of Bias

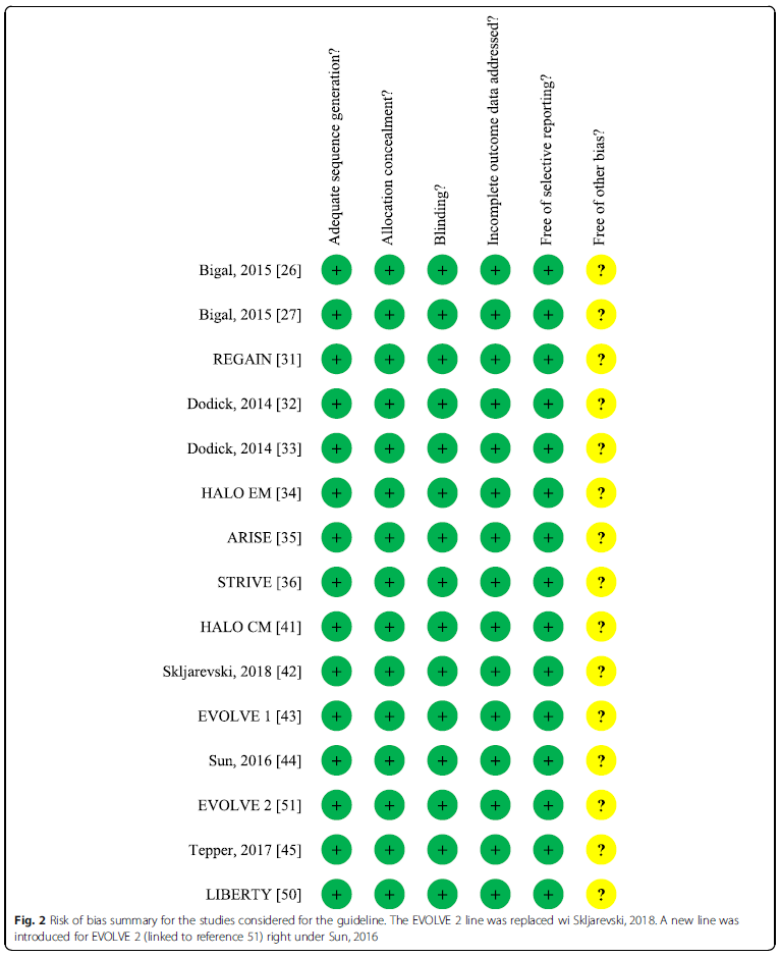


Fig. 2 Risk of bias summary for the studies considered for the guideline. The EVOLVE 2 line was replaced wi Skljarevski, 2018. A new line was introduced for EVOLVE 2 (linked to reference 51) right under Sun, 2016

Table 3 Certainty in the assessment of efficacy outcomes for anti-calcitonin gene-related peptide monoclonal antibodies for prevention in episodic migraine

	Certainty assessment							Certainty
	Number of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	
Eptinezumab								
1000 mg quarterly ev	1	RCT	not serious	serious[a]	not serious	serious[b]	none	⊕⊕○○ LOW
Erenumab								
70 monthly sc (except functional improvement)	3	RCT	not serious	not serious	not serious	not serious	none	⊕⊕⊕⊕ HIGH
70 monthly sc (functional improvement)	1	RCT	not serious	serious[a]	not serious	not serious	none	⊕⊕⊕○ MEDIUM
140 monthly sc	1	RCT	not serious	serious[a]	not serious	not serious	none	⊕⊕⊕○ MEDIUM
Fremanezumab								
225 monthly sc	2	RCT	not serious	not serious	not serious	not serious	none	⊕⊕⊕⊕ HIGH
675 quarterly sc	1	RCT	not serious	serious[a]	not serious	not serious	none	⊕⊕⊕○ MEDIUM
Galcanezumab								
240 mg ld + 120 mg monthly sc	2	RCT	not serious	not serious	not serious	not serious	none	⊕⊕⊕⊕ HIGH
240 mg monthly sc	2	RCT	not serious	not serious	not serious	not serious	none	⊕⊕⊕⊕ HIGH

sc: subcutaneous; ev: endovenous; RCT: randomized controlled trial. [a]Inconsistency because of lack of replication; [b]Imprecision because of exploratory study. The inconsistency for the Galcanezumab study was changed from serios to not serios, and the certainty from medium to high

Table 4 Certainty in the assessment of efficacy outcomes for anti-calcitonin gene-related peptide monoclonal antibodies for prevention in chronic migraine

	Certainty assessment							Certainty
	Number of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	
Erenumab								
70 monthly sc	1	RCT	not serious	serious[a]	not serious	not serious	none	⊖⊖⊖○ MEDIUM
140 monthly sc	1	RCT	not serious	serious[a]	not serious	not serious	none	⊖⊖⊖○ MEDIUM
Fremanezumab								
675 quarterly sc	1	RCT	not serious	serious[a]	not serious	not serious	none	⊖⊖⊖○ MEDIUM
675 ld + 225 quarterly sc (except functional improvement)	2	RCT	not serious	not serious	not serious	not serious	none	⊖⊖⊖⊖ HIGH
675 ld + 225 quarterly sc (functional improvement)	1	RCT	not serious	serious[a]	not serious	not serious	none	⊖⊖⊖○ MEDIUM
Galcanezumab								
240 mg ld + 120 mg monthly sc	1	RCT	not serious	serious[a]	not serious	not serious	none	⊖⊖⊖○ MEDIUM
240 mg monthly sc	1	RCT	not serious	serious[a]	not serious	not serious	none	⊖⊖⊖○ MEDIUM

[a]Inconsistency because of lack of replication
sc subcutaneous, *ld* loading dose, *RCT* randomized controlled trial

Empfehlungen

Table 5 Recommendations on the use of calcitonin gene-related peptide monoclonal antibodies for the prevention of episodic and chronic migraine

Setting	Drug	Recommendation	Quality of evidence	Strength of the recommendation
Migraine prevention in patients with episodic migraine	Eptinezumab 1000 mg quarterly	Suggested	⊖⊖○○ LOW	↑? Weak
	Erenumab 70 mg monthly	Recommended	⊖⊖⊖⊖ HIGH	↑↑ Strong
	Erenumab 140 mg monthly	Recommended	⊖⊖⊖○ MEDIUM	↑↑Strong
	Fremanezumab 225 mg monthly	Recommended	⊖⊖⊖⊖ HIGH	↑↑ Strong
	Fremanezumab 675 mg quarterly	Recommended	⊖⊖⊖○ MEDIUM	↑↑Strong
	Galcanezumab 240 mg loading dose + 120 mg monthly	Recommended	⊖⊖⊖⊖ HIGH	↑↑ Strong
	Galcanezumab 240 mg monthly	Recommended	⊖⊖⊖⊖ HIGH	↑↑ Strong
Migraine prevention in patients with chronic migraine	Erenumab 70 mg monthly	Recommended	⊖⊖⊖○ MEDIUM	↑↑Strong
	Erenumab 140 mg monthly	Recommended	⊖⊖⊖○ MEDIUM	↑↑Strong
	Fremanezumab 675 mg quarterly	Recommended	⊖⊖⊖○ MEDIUM	↑↑Strong
	Fremanezumab 675 mg loading dose + 225 mg monthly	Recommended	⊖⊖⊖⊖ HIGH	↑↑ Strong
	Galcanezumab 240 mg loading dose + 120 mg monthly	Recommended	⊖⊖⊖○ MEDIUM	↑↑Strong
	Galcanezumab 240 mg monthly	Recommended	⊖⊖⊖○ MEDIUM	↑↑Strong

Symbols depict the strength of the recommendation according to the GRADE system. The quality of evidence for the Galcanezumab study was changed from medium to high

Table 19 Recommendations about the use of anti-calcitonin gene-related peptide monoclonal antibodies in subjects with migraine

Clinical question	Recommendation	Strength of the recommendation
1. When should treatment with anti-CGRP monoclonal antibodies be offered to patients with migraine?	In patients with episodic migraine who have failed at least two of the available medical treatments or who cannot use other preventive treatments because of comorbidities, side effects or poor compliance, we suggest the use of erenumab, fremanezumab, or galcanezumab In patients with chronic migraine who have failed at least two of the available medical treatments or who cannot use other preventive treatments because of comorbidities, side effects or poor compliance, we suggest the use of erenumab, fremanezumab, or galcanezumab	Experts' opinion
2. How should other preventive treatments be managed when using anti-CGRP monoclonal antibodies in patients with migraine?	In patients with episodic migraine, before starting erenumab, galcanezumab or fremanezumab we suggest to stop oral preventive drugs unless the patient had a previous history of chronic migraine before prevention; in this case, we suggest to add the anti-CGRP monoclonal antibody to the ongoing treatment and to re-assess the need of treatment withdrawal In patients with chronic migraine who are on treatment with any oral drug with inadequate treatment response we suggest to add erenumab, fremanezumab, or galcanezumab and to consider later withdrawal of the oral drug In patients with chronic migraine who are on treatment with onabotulinumtoxinA with inadequate treatment response we suggest to stop onabotulinumtoxinA before initiation of erenumab, fremanezumab, or galcanezumab In patients with chronic migraine who are on treatment with erenumab, fremanezumab, or galcanezumab and who may benefit from additional prevention we suggest to add oral preventive drugs	Experts' opinion
3. When should treatment with anti-CGRP monoclonal antibodies be stopped in patients with migraine?	In patients with episodic migraine, we suggest to consider to stop treatment with erenumab, fremanezumab, and galcanezumab after 6–12 months of treatments In patients with chronic migraine, we suggest to consider to stop treatment with erenumab, fremanezumab, and galcanezumab after 6–12 months of treatments	Experts' opinion
4. Should medication overuse be treated before offering treatment anti-CGRP monoclonal antibodies to patients with chronic migraine?	In patients with chronic migraine and medication overuse, we suggest to use erenumab, fremanezumab, and galcanezumab before or after withdrawal of acute medications	Experts' opinion
5. In which patients anti-CGRP monoclonal antibodies are not to be used?	In patients with migraine, we suggest to avoid anti-CGRP monoclonal antibodies in pregnant or nursing women, in individuals with alcohol or drug abuse, cardio and c erebrovascular diseases, and with severe mental disorders	Experts' opinion
6. Should binding and/or neutralizing antibodies be monitored?	In patients with migraine on treatment with anti-CGRP monoclonal antibodies, we suggest not to test binding and/or neutralizing antibodies in daily clinical practice; we suggest to further study the possible implications of binding and/or neutralizing antibodies	Experts' opinion

PICO question 1:	In patients with EM, is preventive treatment with CGRP mAbs as compared to placebo, effective and safe?
Population:	patients with EM
Intervention:	any preventive CGRP mAb
Comparison:	placebo
Outcome:	reduction in days of migraine or headache, reduction in the use of acute attack medication, improvement in function, responder ratio (patients with > 50% reduction in migraine or headache days), serious adverse events (SAEs), mortality (grade of importance: critical)

Clinical Guidance

Available studies indicated that erenumab, fremanezumab, and galcanezumab are effective for prevention in patients with EM. They reduce the number of headache or migraine days, reduce the number of days using acute medications, improve disability. Evidence for erenumab, fremanezumab, and galcanezumab is based on phase II and III RCTs. For eptinezumab benefits are not entirely clear and improvement was significant only in the reduction of medications used for acute attacks; additionally, evidence is based on an exploratory phase II RCT. Eptinezumab is administered via intravenous injection while

erenumab, fremanezumab, and galcanezumab are administered via subcutaneous injections. Ease of use represents a potential advantage as CGRP mAbs offer the convenience and adherence benefits of monthly or quarterly dosing allowing avoidance of the daily pill burden. Treatment effect was evident after the first injection and patients continued to improve within the fifth month of treatment [42, 43, 51]. The quick onset of action is a potential advantage of CGRP mAbs as compared to conventional treatments. Reduction in migraine days with CGRP mAbs were only modest and ranged from 1 to 2 when compared to placebo. However, the absolute effect of treatment was larger considering also the placebo effect. Perhaps, more clinically significant is the at least 50% responder rate, which was consistently increased with treatment in a clinically meaningful way. A proportion of patients may have a 100% response rate to CGRP mAbs [37, 39]. The open-label extension of the phase II RCT of erenumab reported low discontinuation rates [24] which is in contrast to current migraine prophylactics that are associated with high discontinuation rates [8, 52, 53]. Post-hoc analyses of the RCTs indicated that treatment with fremanezumab is associated with improved normal function performance on headache free days [46] and that treatment with galcanezumab is associated with overall functional improvement [23]. At the moment, it cannot be determined whether unique patient populations will have a response to a specific drug. Data from RCTs indicated that the CGRP mAbs are safe. No relevant SAEs were registered. One death occurred in the phase III RCT on fremanezumab [34] and one death occurred in the open label extension trial on erenumab [24]. Both deaths were considered unrelated to the study drugs. However, it should be noted that further data from the real-life setting are needed to support safety and to provide information on the long-term use.

PICO question 2:	In patients with CM, is preventive treatment with CGRP mAbs as compared to placebo, effective and safe?
Population:	patients with CM
Intervention:	any CGRP mAb
Comparison:	placebo
Outcome:	reduction in days of migraine or headache, reduction in the use of acute attack medication, Improvement in function, responder ratio (patients with > 50% reduction in migraine or headache days), serious adverse events, mortality (grade of importance: critical)

Clinical guidance

Available studies indicate that erenumab, fremanezumab, and galcanezumab are effective for prevention in patients with CM. They reduce the number of headache days, reduce the number of days using acute medications, improve disability, and are safe. For erenumab evidence is based on a phase II RCT which however was not a dose finding exploratory study but a RCT to assess safety and efficacy. For fremanezumab evidence is based also on phase II and on a phase III RCT while for galcanezumab it is based on a phase III RCT. Studies included patients with a long history of disease and those who had previously failed two or more preventive medications. The trials did not include patients with more refractory disease such as those who had not had a response to two clusters of preventive medications.

Clinical question 1: When should treatment with CGRP mAbs be offered to patients with migraine?

In EM, CGRP mAbs were evaluated both in patients with and without previous drug failure. So far, in most of the available phase II and phase III RCTs, participants with previous failure of as few as 2 preventive medication classes for migraine were excluded. This implies that efficacy can be different for patients with severe, treatment-resistant migraine. Only in the LIBERTY study on erenumab 140 mg monthly patients treated unsuccessfully with between two and four preventive treatments were included. The study confirmed effectiveness of erenumab in this subgroup of patients. However, no results were provided for patients stratified according to previous preventive failure versus non tolerability. In CM, erenumab, fremanezumab, and galcanezumab were evaluated both in patients with and without previous drug failure. Data on erenumab indicated that the drug is effective even in patients with failure to previous drugs. Patients who had previous use of onabotulinumtoxinA were included in RCTs but no information referring to previous efficacy of onabotulinumtoxinA and response to study treatment is available. Erenumab, fremanezumab, and galcanezumab were not evaluated in patients with CM refractory to current available medical treatments. However, due to the poor quality of life of patients with refractory CM it is reasonable to treat them in daily clinical practice with erenumab, fremanezumab, or galcanezumab. Post-marketing studies are needed to provide information about efficacy of CGRP mAbs in refractory CM. […] Efficacy, safety, good tolerability profile and ease of use may represent advantages of CGRP mAbs drugs which may lead patients to prefer those drugs as first-line options. Rather than only efficacy, CGRP mAbs have advantages referring to side effects and treatment administration. Poor response in patients with migraine may also be attributed to lack of compliance to available medical treatments because of the need of taking multiple doses of the drugs or side effects. CGRP mAbs may represent suitable options for patients who have contraindications to other preventive treatments because of comorbidities or side effects and in patients who have poor compliance to other treatments where strategies to improve compliance have failed. At the moment, limiting prescription to patients with prior drug failure may represent a reasonable option until pharmaeconomics studies will provide more data. It is important to point out that patients with multiple drug failures were mostly excluded by RCTs. It is important to note that early treatment of patients with high frequency EM may prevent CM with important impact on individuals and society. Final recommendations based on experts' opinions are reported in Table 19.

Clinical question 2: How should other preventive treatments be managed when using CGRP mAbs in patients with migraine?

We have scarce information on how to manage other oral preventive treatments in association with anti-CGRP mAb in patients with migraine. No interaction is supposed by CGRP mAbs and available preventive treatments. Data on erenumab and fremanezumab suggest that the two drugs are beneficial also when added to ongoing oral preventive treatment. Combined use of other prophylactics and CGRP mAbs may be considered in patients with insufficient response to a single type prophylactics. If patients are on preventive drugs that do have some but not sufficient effect, anti-CGRP antibodies can be added because no interaction is expected. When a possible efficacy of anti-CGRP mAb is established in a given patient it should be discussed with the patient whether withdrawal from the oral prophylactic drug should be tried. In patients with CM, it is reasonable not to stop current ongoing migraine preventive drugs in patients before initiating the use of erenumab, fremanezumab, or galcanezumab in order to avoid possible rebound effects. Withdrawal of other preventive drugs may be done later in patients showing favorable clinical response after starting anti-CGRP mAb. A further point is to clarify, in patients with CM who had favorable response to anti-CGRP mAb but who may continue to experience a significant burden of migraine attacks if adding-on any preventive strategy may further improve attacks frequency, attacks severity, use of preventive drugs and quality of life. At the moment, no such information is available but it is reasonable to allow the use of additional preventive drugs where prevention with anti-CGRP mAb is still considered not optimal. No information on current use of erenumab, fremanezumab, and galcanezumab with onabotulinumtoxinA is available and this association is not supported at the moment. For those patients who are on botulinum toxin and who show an inadequate response, withdrawal of onabotulinumtoxinA with start of the anti-CGRP mAb may be considered. While in the trials there were time restriction referring to onabotulinumtoxinA withdrawal and start of the anti-CGRP mAb, they represented procedures to avoid confounders and are not reasonable in daily clinical practice. At the moment, we do not know whether it is reasonable to consider combining onabotulinumtoxinA with anti-CGRP mAb in patients who have a suboptimal response to each of those drugs. Final recommendations based on experts' opinions are reported in Table 19.

Clinical question 3: When should treatment with CGRP mAbs be stopped in patient with migraine?

Clinical guidance

As a general rule, treatment can be stopped if migraine is considered too infrequent to justify preventive treatment or if treatment is considered not effective. Data from the available trials suggest that the effective reduction of monthly headache or migraine days due to treatment with CGRP mAbs may be observed very early, after less than one month from the first dose. Data from RCTs suggest that patients may have additional benefits with continuation of treatment and that some patients who have worsening with treatment or who are considered non-responders may have improvement with continuation of treatment. For those reason it is reasonable not to stop treatment before 3 months even in the absence of a clinical response. Further studies are needed to better assess whether some patients might have even a more delayed response to CGRP mAbs, and to provide information about the durability of the response to treatment with CGRP mAbs. Further data are also needed to clarify whether the response may be sustained even after withdrawal of the CGRP mAbs. For the moment it is reasonable to manage the duration of treatment with CGRP mAbs not differently to other available preventive strategies and to continue it for at least 6–12 in patients who have beneficial effects with those drugs. Factors contributing to response/nonresponse have yet to be elucidated and clinical judgment should be exercised when deciding whether to discontinue treatment. Tachyphylaxis of preventive treatments for migraine is a frequent problem in the clinical setting. A post-hoc analysis of patients treated with fremanezumab in the phase II study supported a sustained efficacy, over the 3-month trial period, in a substantial percentage of those who show an initial response [37]. One-year interim analysis of a phase II study of erenumab 70 mg suggest that benefits persist over time [24]. Final recommendations based on experts' opinions are reported in Table 19.

Clinical question 4: Should medication overuse be treated before offering treatment CGRP mAbs to patients with CM?

Clinical guidance

We have no direct data about the impact of MOH on the treatment of CM with CGRP mAbs. However, the available RCTs of erenumab, fremanezumab, and galcanezumab all enrolled consistent proportions of patients with untreated MOH. Therefore, it might be reasonable to offer treatment with CGRP mAbs to patients with MOH. We have, at this moment, no evidence to indicate that the effect of CGRP mAbs is increased if preceded by detoxification and further research is needed on this issue. Some adopt withdrawal strategies before offering preventive medications to patients with CM and MOH and some of the available evidence indicate that detoxification is feasible and effective [54]. However, detoxification is not easy and feasible with all patients and dedicated resources, which are not always available, are needed. We have no data which indicate if the use of CGRP mAbs may favor detoxification in patients with CM and MOH. Of note, the frequent use of butalbital-containing medications was an exclusion criterion from the trials; therefore, current evidence suggests avoiding the overuse of butalbital before starting treatment with CGRP mAbs. Final recommendations based on experts' opinions are reported in Table 19.

Clinical question 5: In which patients CGRP mAbs are not to be used?

Clinical guidance

CGRP mAbs are unlikely to produce drug interactions or affect the course of ongoing disease which may be particularly relevant in patients with comorbidities. CGRP is the most potent vasodilator peptide known [55] and has been theoretically considered as dangerous in patients with diseases of the vascular system. In the cardiovascular system, CGRP is present in nerve fibers that innervate blood vessels and the heart and participates in the regulation of blood pressure [56]. For this reason, patients with cardio and cerebrovascular disease were excluded from available clinical trials. In available studies, there is no evidence of increased cardiovascular events or any other serious concerns. However, the duration of available

studies is much shorter than the duration in the clinical settings and registries should record any SAEs to see the long-term effects of continuous blockade of the CGRP pathway. Additionally, there was no effect on treadmill exercise time in patients with angina who received telcagepant, a small-molecule CGRP antagonist [57]. These results supplement those from a placebo-controlled study of erenumab in a high-risk population of patients with stable angina with a median age of 65 years, in which inhibition of the canonical CGRP receptor with erenumab did not adversely affect total exercise time in a treadmill test, among other safety endpoints [57]. Long-term safety studies with CGRP mAbs are needed to further characterize potential cardiovascular effects. More data from migraine patients with comorbid cardiovascular conditions in a real-world setting may help further assess the theoretical cardiovascular risk of blocking the CGRP pathway. Final recommendations based on experts' opinions are reported in Table 19.

Clinical question 6: Should binding and/or neutralizing antibodies be monitored?

Clinical guide

Data from individual studies indicate that binding and/or neutralizing antibodies occur infrequently and may have a variable course over time. At the moment, the presence of binding and/or neutralizing antibodies has not been associated with poor response to treatment or adverse events. Consequently, there is no evidence which may support the need of antibodies testing in routine clinical practice. However, this issue should be further studied. In fact, duration of treatment in available studies is limited in time and it cannot be excluded that the rate of occurrence of binding and/or neutralizing antibodies in available clinical studies was too low to establish firm conclusions about their possible implications. Pooled data from available RCTs or data from real life studies may add better evidence and further research should clarify the role of binding and/or neutralizing antibodies in patients with poor clinical response and side effects. Final recommendations based on experts' opinions are reported in Table 19.

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Scottish Intercollegiate Guidelines Network (SIGN), 2018 [16].

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 - trifft zu;
- Interessenkonflikte und finanzielle Unabhängigkeit dargelegt - trifft zu;
- Systematische Suche, Auswahl und Bewertung der Evidenz - trifft zu;
- Formale Konsensusprozesse und externes Begutachtungsverfahren dargelegt - trifft teilweise zu;

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

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.

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.

Sonstige methodische Hinweise (Bei Einschränkung der o. g. Kriterien)

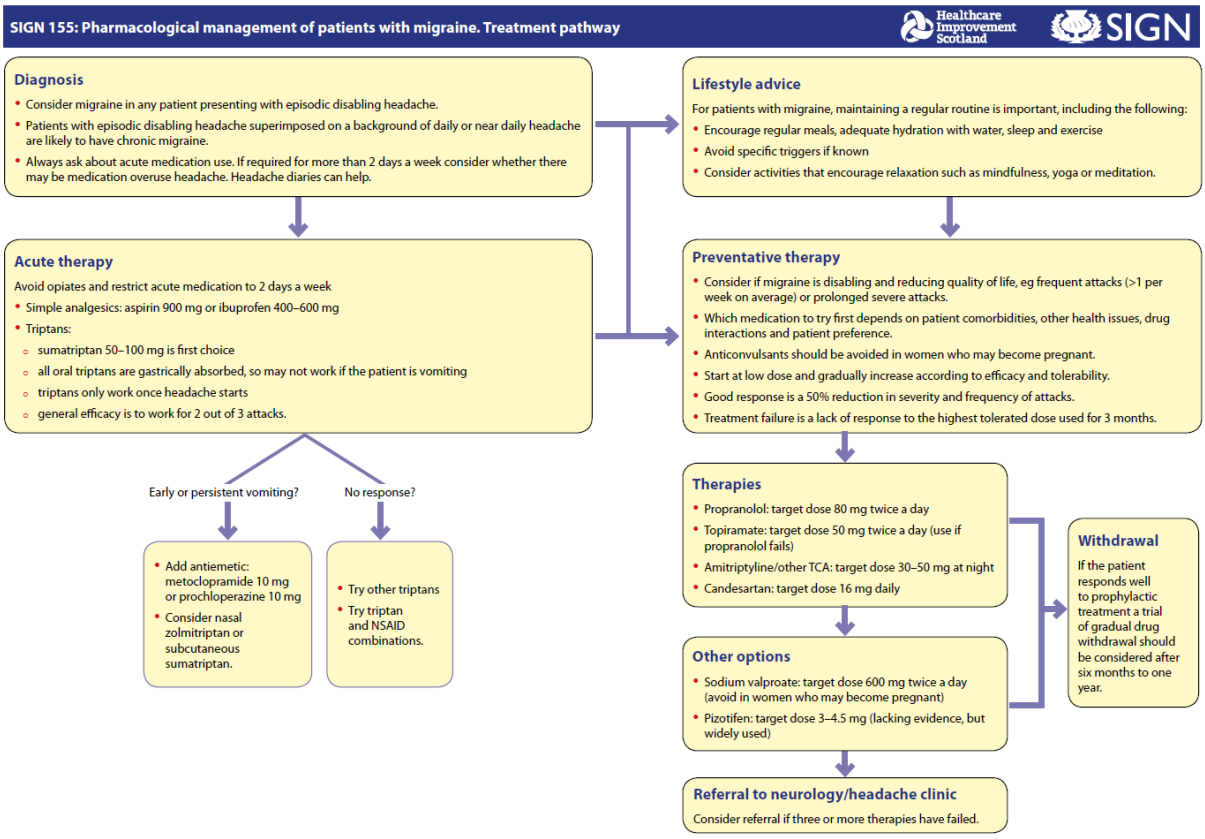
- Formale Konsensusprozesse sind nicht eindeutig dargelegt;
- Überprüfung der Aktualität: This guideline was issued in 2018 and will be considered for review in three years. The review history, and any updates to the guideline in the interim period, will be noted in the review report, which is available in the supporting material section for this guideline on the SIGN website: www.sign.ac.uk
- Folgende Kapitel sind auf Grund einer zurzeit fehlenden Zulassung der diskutierten Arzneimittel im AWG nicht aufgeführt:
  - 4.5 CANDESARTAN;
  - 4.8 PIZOTIFEN;
  - 4.9 GABAPENTIN AND PREGABALIN;
  - 4.10 ANGIOTENSIN-CONVERTING ENZYME INHIBITORS;
  - 4.11 SELECTIVE SEROTONIN REUPTAKE INHIBITORS AND SEROTONIN NOREPINEPHRINE REUPTAKE INHIBITORS;
  - 4.12 OTHER ANTIEPILEPTICS;
  - 4.16.1 TRIPTANS;
  - 4.16.2 PROSTAGLANDIN INHIBITORS;
  - 4.16.3 NON-STEROIDAL ANTI-INFLAMMATORY DRUGS;
  - 4.16.4 OESTROGENS;
  - 4.16.5 HORMONAL PROPHYLAXIS.

Empfehlungen

An algorithm of a suggested treatment pathway can be found in Annex 3. The decision regarding which medication to try first is dependent on evidence of effectiveness, patient comorbidities, other risk factors, drug interactions and patient preference. It is important to ensure adequate contraception whilst on preventative therapies as some have risks of teratogenicity and others can potentially cause harm to unborn babies. Given that migraine without aura often improves during pregnancy women should aim to stop migraine prophylactic treatments before pregnancy. [12] Migraine with aura often continues unchanged. [12] Before commencing treatment, potential harmful effects of therapies need to be discussed with women who are, or may become, pregnant. No evidence was identified on which to base recommendations on preventative treatments for women during pregnancy.

Treatment pathway

This pathway is drawn from evidence identified in the guideline, the British National Formulary [17] and the clinical experience of the guideline development group.



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 NHSScotland. 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+)

4.6 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.

Before commencing treatment women should be informed of:

- the risks associated with taking valproate during pregnancy
- the risk that potentially harmful exposure to valproate may occur before a women is aware she is pregnant
- the need to use effective contraception
- the need to seek further advice on migraine prophylaxis if pregnant or planning a pregnancy.

GOOD-PRACTICE POINT: When prescribing sodium valproate for women who may become pregnant check the MHRA website for current advice. The MHRA checklist must be used (see Annex 4).

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]

4.13 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.

4.15 CALCITONIN GENE-RELATED PEPTIDE

Calcitonin gene-related peptide (CGRP) monoclonal antibodies are in development for the treatment of patients with migraine. Four well-conducted phase 2 RCTs on CGRP monoclonal antibodies for patients with frequent episodic migraine were identified. [75-78] All four showed that the treatment was more effective than placebo and safe. Few adverse effects were reported. Two phase 3 RCTs on CGRP monoclonal antibodies were identified, one in patients with episodic migraine and one in patients with chronic migraine. [79, 80] Both showed that treatment was more effective than placebo and safe. Assessment by regulatory bodies and results from further phase 3 trials are awaited. (LoE: 1+, 1++)

One phase 2 study on the CGRP receptor antagonist telcagepant was identified. [81] The trial was terminated early due to hepatotoxicity concerns in two patients. (LoE: 1+)

4.15 MENSTRUAL MIGRAINE PROPHYLAXIS

The drop in oestrogen just prior to menstruation is a known trigger for migraine and in women migraine is more frequent, more severe and harder to treat just before and during menstruation. [11, 12] In some women migraine only occurs (pure menstrual migraine) or predominantly occurs (menstrually-related migraine) from two days before the start of bleeding until three days after. In these women perimenstrual strategies may be used instead of, or in addition to, standard, continuous prophylaxis. The menstrual cycle has to be regular for treatment to be effective.

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Headaches: Diagnosis and management of headaches in young people and adults
National Institute for Health and Care Excellence

Siehe auch: NICE, 2015 [11] Addendum to Clinical Guideline 150, Headaches in over 12s: diagnosis and management

Zielsetzung

To develop a clinical guideline for the diagnosis and management of headaches in adolescents and adults.

Methodik

Grundlage der Leitlinie

- Update November 2015 & February 2020;
- Repräsentatives Gremium – trifft teilweise zu;
- Interessenkonflikte und finanzielle Unabhängigkeit dargelegt- trifft zu;
- Systematische Suche, Auswahl und Bewertung der Evidenz - trifft zu;
- Formale Konsensusprozesse und externes Begutachtungsverfahren dargelegt – trifft teilweise zu;
- Empfehlungen der Leitlinie sind eindeutig und die Verbindung zu der zugrundeliegenden Evidenz ist explizit dargestellt - trifft teilweise zu/unklar;
- Regelmäßige Überprüfung der Aktualität gesichert - trifft zu.

Recherche/Suchzeitraum:

- MEDLINE;
- Embase;
- The Cochrane Library was searched for all intervention questions;
- Cinahl for diaries, treatment questions and patient information;
- PsycINFO for education and self-management programmes, psychological therapies, medication over use headaches and patient information;
- AMED for non-pharmacological treatment of headaches.
- All searches were updated on 13 March 2012.
- Update on 16 January 2015:
  - CDSR (Wiley);

- Database of Abstracts of Reviews of Effects – DARE (Wiley);
- HTA database (Wiley);
- CENTRAL (Wiley);
- EBM Reviews (Ovid);
- MEDLINE (Ovid);
- MEDLINE In-Process (Ovid);
- EMBASE (Ovid).

LoE/GoR

Table 2: Description of quality elements in GRADE for intervention studies

Quality element	Description
Limitations	Limitations in the study design and implementation may bias the estimates of the treatment effect. Major limitations in studies decrease the confidence in the estimate of the effect.
Inconsistency	Inconsistency refers to an unexplained heterogeneity of results.
Indirectness	Indirectness refers to differences in study population, intervention, comparator and outcomes between the available evidence and the review question, or recommendation made.
Imprecision	Results are imprecise when studies include relatively few participants and few events and thus have wide confidence intervals around the estimate of the effect relative to the clinically important threshold.
Publication bias	Publication bias is a systematic underestimate or an overestimate of the underlying beneficial or harmful effect due to the selective publication of studies.

Table 3: Levels of quality elements in GRADE

Level	Description
None	There are no serious issues with the evidence
Serious	The issues are serious enough to downgrade the outcome evidence by one level
Very serious	The issues are serious enough to downgrade the outcome evidence by two levels

Grading the quality of clinical evidence

After results were pooled, the overall quality of evidence for each outcome was considered. The following procedure was adopted when using GRADE:

1. A quality rating was assigned, based on the study design. RCTs start HIGH and observational studies as LOW, uncontrolled case series as LOW or VERY LOW.
2. The rating was then downgraded for the specified criteria: Study limitations, inconsistency, indirectness, imprecision and reporting bias. These criteria are detailed below. Observational studies were upgraded if there was: a large magnitude of effect, dose-response gradient, and if all plausible confounding would reduce a demonstrated effect or suggest a spurious effect when results showed no effect. Each quality element considered to have 'serious' or 'very serious' risk of bias were rated down -1 or -2 points respectively.
3. The downgraded/upgraded marks were then summed and the overall quality rating was revised. For example, all RCTs started as HIGH and the overall quality became MODERATE, LOW or VERY LOW if 1, 2 or 3 points were deducted respectively.
4. The reasons or criteria used for downgrading were specified in the footnotes.

Sonstige methodische Hinweise

- Involvierung eines Patientenvertreters unklar.
- Die Empfehlungen der LL basieren unteranderem auf ökonomische Überlegungen, die nicht dem deutschen Versorgungskontext entsprechen.
- Die Verbindung zu der zugrundeliegenden Evidenz ist teilweise nicht explizit dargestellt.

Empfehlungen

Migraine with aura

1.2.2 Suspect aura in people who present with or without headache and with neurological symptoms that:
- are fully reversible and
- develop gradually, either alone or in succession, over at least 5 minutes and
- last for 5–60 minutes. [2012]

- Relative values of different outcomes & Quality of evidence

An accurate diagnosis of primary headache disorder will help direct appropriate treatment. The recommendations for diagnosis are based on existing criteria from the International Headache Society Classification: ICHD-II. The GDG used informal consensus to agree the wording of the recommendations, adapting the ICHD-II criteria for use by non-headache specialists. No economic evidence was found on the use of key diagnostic features to diagnose different types of headaches.

1.2.3 Diagnose migraine with aura in people who present with or without headache and with one or more of the following typical aura symptoms that meet the criteria in recommendation 1.2.2:
- visual symptoms that may be positive (for example, flickering lights, spots or lines) and/or negative (for example, partial loss of vision)
- sensory symptoms that may be positive (for example, pins and needles) and/or negative (for example, numbness)
- speech disturbance. [2012]

- Relative values of different outcomes & Quality of evidence

An accurate diagnosis of primary headache disorder will help direct appropriate treatment. The recommendations for diagnosis are based on existing criteria from the International Headache Society Classification: ICHD-II. The GDG used informal consensus to agree the wording of the recommendations, adapting the ICHD-II criteria for use by non-headache specialists. No economic evidence was found on the use of key diagnostic features to diagnose different types of headaches.

- Other considerations

The GDG considered it important to emphasise that migraine with aura is diagnosed even in people who do not get headache associated with their aura.

1.2.4 Consider further investigations and/or referral for people who present with or without migraine headache and with any of the following atypical aura symptoms that meet the criteria in recommendation 1.2.2:
- motor weakness or
- double vision or
- visual symptoms affecting only one eye or
- poor balance or
- decreased level of consciousness. [2012]

- Relative values of different outcomes & Quality of evidence

An accurate diagnosis of primary headache disorder will help direct appropriate treatment. The recommendations for diagnosis are based on existing criteria from the International Headache Society Classification: ICHD-II. The GDG used informal consensus to agree the wording of the recommendations, adapting the ICHD-II criteria for use by non-headache specialists. No economic evidence was found on further investigation for people with possible rare aura symptoms.

- Other considerations

The GDG considered that the non-specialist needed to be aware of atypical aura but that people with these symptoms needed specialist assessment to make the diagnosis. Clinical terms have been reworded in lay language in the recommendation, however symptoms may also be referred to as: dysarthria (slurred speech), diplopia (double vision), monocular visual symptoms (visual symptoms in one eye only), ataxia (poor balance). Possible subtypes of atypical migraine specified in the ICHD-II include: basilar type migraine, familial hemiplegic migraine and sporadic hemiplegic migraine.

Menstrual-related migraine

1.2.5 Suspect menstrual-related migraine in women and girls whose migraine occurs predominantly between 2 days before and 3 days after the start of menstruation in at least 2 out of 3 consecutive menstrual cycles. [2012]

- Relative values of different outcomes & Quality of evidence

An accurate diagnosis of primary headache disorder will help direct appropriate treatment. The recommendations for diagnosis are based on existing criteria from the International Headache Society Classification: ICHD-II, as well as additional evidence from an expert advisor for menstrual migraine. The GDG used informal consensus to agree the wording of the recommendations, adapting the ICHD-II criteria for use by non-headache specialists. No economic evidence was found on the use of key diagnostic features to diagnose different types of headaches.

- Other considerations

The GDG considered that there was no need to differentiate between menstrual related migraine and pure menstrual migraine as treatment options would be the same and would be tailored according to the individual. If migraine occurs at the time of menstruation in two consecutive menstrual cycles, the GDG agreed that a diagnosis of menstrual related migraine can be made.

1.2.6 Diagnose menstrual-related migraine using a headache diary (see recommendation 1.1.4) for at least 2 menstrual cycles. [2012]

- Relative values of different outcomes & Quality of evidence

An accurate diagnosis of primary headache disorder will help direct appropriate treatment. This recommendation was based on evidence from an expert advisor for menstrual migraine (Anne MacGregor, Associate Specialist Barts Sexual Health Centre, St Bartholomew's Hospital). The GDG used informal consensus to agree the wording. No economic evidence was found on the use of key diagnostic features to diagnose different types of headaches.

- Other considerations

The GDG considered that there was no need to differentiate between menstrual related migraine and pure menstrual migraine as treatment options would be the same, but would be tailored according to the individual. If migraine occurs at the time of menstruation in two consecutive menstrual cycles, the GDG agreed that a diagnosis of menstrual related migraine can be made. It was considered that a diary would increase the accuracy of the history taken and would be superior to relying on recall for diagnosis.

Migraine with or without aura

Prophylactic treatment

1.3.16 Discuss the benefits and risks of prophylactic treatment for migraine with the person, taking into account the person's preference, comorbidities, risk of adverse events and the impact of the headache on their quality of life. [2012]

- Relative values of different outcomes & Quality of evidence

This recommendation was based on GDG informal consensus opinion.

- Trade off between clinical benefits and harms

The risks and benefits of each of the medicines available should be discussed with the person. By the end of the discussion, the person should understand their risk of migraine recurrence and severity with and without prophylaxis and their risk of adverse effects. If the person is a woman of child-bearing potential, she should be made aware of the teratogenic risks of topiramate, and, if relevant, its potential to reduce the reliability of combined hormonal contraception at doses greater than 200mg/day.

- Other considerations

The recommended treatments were supported by the evidence reviewed, however when to start prophylactic treatment was not part of the review question. The GDG agreed this should mainly be determined by patient choice. Informal consensus methods were used to form the recommendation. The GDG noted that there is anecdotal evidence that if someone has medication overuse headache prophylaxis doesn't work. Different people may value the risks and benefits of different choices for prophylaxis. Choices may also be informed by the effectiveness of acute medication for that individual.

1.3.17 Offer topiramate or propranolol [12] for the prophylactic treatment of migraine according to the person's preference, comorbidities and risk of adverse events.

Advise women and girls of childbearing potential that topiramate is associated with a risk of fetal malformations and can impair the effectiveness of hormonal contraceptives. Ensure they are offered suitable contraception if needed. [2015]

- Relative values of different outcomes & Quality of evidence

The GDG agreed that change in patient reported migraine days is the most important outcome for decision making. Responder rate was also considered to be important. The evidence was based on low to high quality evidence. The trials of topiramate and propranolol included people from age 12 and above. One of the topiramate studies investigated people with chronic migraine defined as having >15 headaches per month, the rest of the studies included people who had <15 headaches per month, the average being around 6. There was also some evidence for telmisartan from one small study (low quality evidence). The GDG agreed that this evidence wasn't strong enough to form a recommendation for an off-license treatment. The evidence for gabapentin was for change in migraine frequency and intensity and therefore could not be included in the network meta-analysis. However, there was moderate quality evidence for reduction in migraine frequency and intensity compared to placebo. The recommendations are based on studies investigating treatment for between 3 and 6 months. The evidence for longer term use showed no maintained benefit (moderate to high quality). The economic evidence has direct applicability and minor limitations.

- Trade off between clinical benefits and harms

The risks and benefits of topiramate, propranolol and their other options should be discussed with the person. By the end of the discussion, they should understand their risk of migraine recurrence and severity with each option and their risk of adverse effects. Prescribers should consult the summary of product characteristics (SPC) and the latest BNF to familiarise themselves with side effects, contraindications and the availability of once-daily dosage forms. For women of child-bearing age not on appropriate contraceptives beta-blockers should be used in preference to topiramate.

Siehe auch 2.6 Evidence to recommendations.

1.3.18 Consider amitriptyline [13] for the prophylactic treatment of migraine according to the person's preference, comorbidities and risk of adverse events. [new 2015]

Die direkte Evidenzverknüpfung ist nicht ersichtlich. Siehe 2.6 Evidence to recommendations.

1.3.19 Do not offer gabapentin for the prophylactic treatment of migraine. [new 2015]

Die direkte Evidenzverknüpfung ist nicht ersichtlich. Siehe 2.6 Evidence to recommendations.

2.6 Evidence to recommendations [new 2015]

- Relative value of different outcomes & Quality of evidence

The Committee valued the outcome 'change in migraine/headache days' highly because it incorporates both migraine frequency and duration, and so was considered a good estimate of the effectiveness of prophylactic medication because either a reduction in the frequency or duration of migraine is a valuable outcome for patients. The outcome 'change in migraine/headache days' was therefore prioritised for network metaanalysis and formed the basis of the economic model. 50% responder was considered important as a 50% reduction in migraine frequency is considered an adequate response to prophylactic medication clinically. Migraine severity was valued highly because the severity of migraine was considered to be an important outcome for patients, which is not captured by measures of frequency or duration; a prophylactic medication could be considered useful even if it had no effect on migraine frequency, but reduced the severity of attacks. Quality of life was valued less highly as the Committee considered that this outcome was difficult to accurately measure and would be reflected in the 3 critical outcomes. Likewise, change in migraine/headache frequency and change in acute medication use were valued less highly because they were considered likely to be reflected in the critical outcomes. The network meta-analysis for the outcome 'change in migraine days' was overall low in quality; many of the trials had large dropout rates and the effect estimates for many of the interventions were associated with high degrees of uncertainty. In particular, the 95% credible intervals (which, like confidence intervals for traditional analysis give an estimate of the precision of an effect) for the mean difference in change in migraine days between amitriptyline and placebo were wide and encompassed 0. The consistency between direct and indirect evidence could not be assessed because there were no loops in the network (other than one formed by a single 3-arm trial). However, the effect estimates for the network meta-analysis and pair-wise analyses were broadly consistent. All trials that formed the network metaanalysis were double blind, which strengthened the certainty in the evidence, and the network meta-analysis allowed coherent comparison between multiple treatments. Evidence from pair-wise analysis was of variable quality, ranging from high to very low. Drop-out rates were often high, and analysis was not always based on the intention to treat principle, leading to serious risk of bias. Much of the evidence was collected in secondary care settings outside of the UK, and there was no evidence from UK primary care settings. The Committee noted that the majority of patients with migraine would be cared for in a primary care setting, and so considered the applicability of the evidence to this setting. The Committee concluded that although there may be some differences in criteria for the initiation of prophylactic treatment across healthcare systems, the patients in the trials were likely to be broadly similar to those typically encountered in UK practice (although the Committee did not review evidence for this), and so the evidence was

generalisable. Evidence on serious adverse events was of very low quality across comparisons, largely due to the small number of serious adverse events in all study groups leading to high degrees of uncertainty in the effect estimates.

- Trade-off between benefits and harms

The review did not identify evidence of a harmful effect for any of the medicines identified. However, the evidence on serious adverse events was often absent or of very low quality. The Committee noted that side effects were likely to occur for all of the medicines identified, and that the side effect profile differed for each medicine. This, as well as the patient's co-morbidities and pregnancy potential should be taken into account when offering prophylactic treatment. Overall, the Committee considered that evidence supported the use of topiramate and propranolol as effective treatments for the prevention of migraine across a range of outcomes, and so these medicines should be offered for the prophylaxis of migraine. The Committee also judged that overall, evidence also favoured amitriptyline as a possible treatment, although the evidence was less certain. There was a single trial comparing topiramate and amitriptyline which was included in the network and pairwise analyses. Evidence from the pairwise analysis suggested that topiramate and amitriptyline had similar effectiveness, and indirect evidence suggested that amitriptyline was favoured over placebo, but with wide credible intervals that included 0. The Committee also noted that amitriptyline does not have a current marketing authorisation for migraine prophylaxis, whereas topiramate and propranolol do. The Committee therefore that the balance of evidence favoured amitriptyline less strongly that topiramate and propranolol and warranted a weaker recommendation. The topic expert members noted that topiramate, propranolol and amitriptyline had been successfully used in clinical practice for many years. They noted that the choice of medication may depend on individual patient preference and comorbidities, and the acceptability of side effects. In contrast to the evidence review for the original guideline, the current review identified evidence that gabapentin was not more effective than placebo in the prevention of migraine. The previous guideline considered a study by Di Trapani (2000) which was not included in the current review because the treatment period at the final dose was less than the 12 weeks specified in the review protocol (see the list of excluded studies in Appendix F). Two studies comparing gabapentin were included in the current review: 1 was a research report originally produced in 1990, but that only entered the public domain subsequent to the publication of the previous guideline (Feuerstein 1990), and the second was a study reported subsequent to the previous guideline (Silberstein 2013). The previous NICE guideline on headaches recommended that gabapentin was considered for migraine prophylaxis if topiramate and propranolol were ineffective or unsuitable, and this has been implemented in clinical practice. The committee therefore believed that in the light of the new evidence for the ineffectiveness of gabapentin, a specific recommendation stating that gabapentin should not be used for migraine prophylaxis should be made. The Committee considered that the evidence for levetiracetam and divalproex sodium/sodium valproate was not sufficiently strong to support a positive recommendation for these medicines. There was some evidence favouring levetiracetam, but this was from a single small study, and the outcome 'change in migraine/headache days' was not reported, so the medicine could not be included in the network meta-analysis. There was also possible evidence favouring divalproex sodium in adults (but not young people). However, it was not clear whether the evidence for a difference in effectiveness across age groups was robust, and if the data from both age groups was combined in a single analysis the evidence for a beneficial effect of divalproex sodium was much less robust, with 95% confidence intervals crossing the line of no effect. Evidence for other medicines included in the review was either absent, of low or very low quality or only included a small number of outcomes. The Committee therefore agreed that no recommendations could be made for these medicines (angiotensin II receptor blockers, angiotensin converting enzyme inhibitors, antidepressants except amitriptyline, centrally-acting alpha adrenergic receptor agonists, calcium channel blockers, betablockers except propranolol, antiepileptics except topiramate, other serotonergic modulators and NMDA receptor antagonists).

- Other considerations

The topic-expert committee members noted that many of the medicines (including topiramate, sodium valproate, gabapentin and levetiracetam) were associated with high teratogenicity which meant that they are contraindicated in pregnancy. Consequently the Committee agreed that recommendation 1 (which was unchanged from the previous version of the guideline in 2012) should continue to include specific reference to advising women of childbearing age of the risk of fetal malformations and the effect of topiramate on the effectiveness of hormonal contraception.

1.3.20 If both topiramate and propranolol [12] are unsuitable or ineffective, consider a course of up to 10 sessions of acupuncture over 5–8 weeks according to the person's preference, comorbidities and risk of adverse events. [2012, amended 2015]

- Quality of Evidence

Acupuncture: The evidence reviewed (see chapter 17) was moderate to low quality. All included studies were single blind as the person administering treatment was not blinded to treatment group, however the participants and assessors were blinded. All evidence reviewed was for traditional Chinese medicine approach to acupuncture compared to sham acupuncture. The effect size reported was good, with network meta-analysis showed acupuncture to be ranked joint second most effective treatment for reducing the number of migraine days. The economic evidence was based on an original economic model with minor limitations and direct applicability and on a published economic evaluation based on a RCT with minor limitations and partial applicability.

- Trade off between clinical benefits and harms

Acupuncture: There were very little data on serious adverse events reported in the studies included in this review (see chapter 17). Treatment reactions after acupuncture needling are common. Serious adverse events, e.g. pneumothorax can occur. This risk however is small.

1.3.21 For people who are already having treatment with another form of prophylaxis and whose migraine is well controlled, continue the current treatment as required. [2012, amended 2015]

- Relative values of different outcomes & Quality of evidence

This recommendation was based on GDG consensus opinion.

- Trade off between clinical benefits and harms

For risks associated with other forms of prophylaxis for migraine, prescribers should refer to the summary of product characteristics (SPC) or BNF looking at side effects, contraindications, dosage regimens and costs.

- Other considerations

The GDG considered that there may be other prophylactic treatments, such as amitriptyline, pizotifen, sodium valproate, lisinopril and losartan which are in regular use and are effective for some people, although no evidence was identified in this review. Pizotifen is particularly used for prophylaxis in children and young people. This was noted as an absence of evidence, not evidence that such treatments are ineffective. The GDG made research recommendations for trials to evaluate the use of amitriptyline and pizotifen and this is outlined in more detail in Appendix M. During the development of the Headaches clinical guideline the NICE technology appraisal programme has published guidance on Botox (Botulinum toxin type A for the prevention of headaches in adults with chronic migraine). This is a treatment option for people with chronic migraine.

1.3.22 Review the need for continuing migraine prophylaxis 6 months after the start of prophylactic treatment. [2012]

- Relative values of different outcomes & Quality of evidence

All evidence reviewed was for 3-6 months treatment. This recommendation was based on GDG consensus opinion.

- Trade off between clinical benefits and harms

The aim of prophylaxis is to reduce the frequency and severity of migraine. Continuing to take treatment when it is no longer required puts the patient at risk of side effects and drug interactions.

- Other considerations

The GDG experience is that people are able to stop prophylaxis after 6 months of treatment and have continued benefit from the prophylactic treatment. They considered that all people on prophylactic treatment should have their need to continue treatment reviewed at 6 months.

1.3.23 Advise people with migraine that riboflavin (400 mg [14] once a day) may be effective in reducing migraine frequency and intensity for some people. [2012]

- Relative values of different outcomes & Quality of evidence

The GDG agreed that responder rate should be considered the most important outcome. This recommendation is based on moderate quality evidence from one outcome (responder rate). No economic evidence was found on this question.

- Trade off between clinical benefits and harms

Decrease in migraine frequency and intensity and increase in responder rate needs to be balanced against the adverse events that may be attributed to riboflavin.

- Other considerations

Da eine negative Empfehlung vorliegt und keine Zulassung vorliegt, werden diese nicht dargestellt.

Combined hormonal contraceptive use by women and girls with migraine

1.3.24 Do not routinely offer combined hormonal contraceptives for contraception to women and girls who have migraine with aura. [2012]

- Relative values of different outcomes & Quality of evidence

The GDG considered the incidence of cardiovascular events (thromboembolic stroke) to be the most important outcome. GDG informal consensus was also used to form this recommendation. This recommendation was based on the consensus opinion of the GDG. There was limited evidence from this review regarding the use of hormonal contraception in women with migraine. The population in one study 34 consisted of over 70% of people with migraine with aura which is a greater proportion of people with aura than in the migraine population. No economic evidence was found on this question.

- Trade off between clinical benefits and harms

There is an increased risk of ischaemic stroke in people with migraine with aura. This is multiplied in people using combined hormonal contraception.

Menstrual-related migraine

1.3.25 For women and girls with predictable menstrual-related migraine that does not respond adequately to standard acute treatment, consider treatment with frovatriptan [15] (2.5 mg twice a day) or zolmitriptan[16] (2.5 mg twice or three times a day) on the days migraine is expected. [2012]

- Relative values of different outcomes & Quality of evidence

Responder rate was considered to be the most important outcome. Other evidence considered was based on the reduced use of acute pharmacological treatment.This recommendation is based on low quality evidence from two studies [20, 257] showing reduced acute medication use and increased responder rate with frovatriptan or zolmitriptan compared to placebo. Only one study reported responder rate [257]. Additional evidence and advice was gained from an expert advisor to inform the recommendations. The economic evidence was based on a limited cost analysis based only on the drug acquisition costs.

- Trade off between clinical benefits and harms

The risk of medication overuse headache should be considered when triptans are used for prophylaxis of menstrual migraine.

- Other considerations

Menstrual migraine and menstrual related migraine are treated with the same strategies. One of the important issues in deciding on treatment is frequency of migraine as infrequent migraine is best treated using acute treatments. Studies included in this review have shown a benefit with the use of triptans in doses of 2.5 mg with up to twice daily (with the highest dose of 2.5mg demonstrating better efficacy) dosing for long acting triptans (frovatriptan) and three times a day dosing for short acting triptans (zolmitriptan). The later trials have used longer acting triptans. This treatment is off licence and menstruation needs to be predictable to use this method. The GDG considered that peri menstrual prophylaxis is only required for a small number of people who have regular periods. The co-opted expert considered that oestrogen supplementation e.g. using gels is rarely required even in specialist practice. Women who require contraception and can safely use combined hormonal contraceptives, can manipulate their cycles to reduce the number of periods they have e.g. by tricycling combined hormonal contraception or by reducing the hormone free interval.

Treatment of migraine during pregnancy

1.3.26 Offer pregnant women paracetamol for the acute treatment of migraine. Consider the use of a triptan [9] or an NSAID after discussing the woman's need for treatment and the risks associated with the use of each medication during pregnancy. [2012]

- Relative values of different outcomes & Quality of evidence

The GDG considered all serious adverse events reported for decision making. This recommendation was also made partially on GDG informal consensus. The evidence reviewed was very low quality evidence. The use of NSAID was not reviewed as the GDG agreed this was already established. No economic evidence was identified specifically on the treatment of migraine during pregnancy

- Trade off between clinical benefits and harms

The GDG noted that many people continue to suffer migraine during pregnancy as they avoid medication due to not being certain of the risks. It was agreed that the evidence reviewed did not indicate an increased risk of the use of triptans during pregnancy and therefore people should be made aware of this to avoid suffering unnecessarily. There is not conclusive evidence of safety, but the evidence is reassuring. High doses of aspirin recommended for migraine are considered potentially harmful in pregnancy so should be avoided in pregnancy. The GDG agreed that possible risks NSAID during pregnancy are known and their use should be.

- Other considerations

The reviewed evidence was in people with mild to moderate migraine only. The relative contraindications depending on the stage of pregnancy should be considered when prescribing acute treatments. There is some evidence that migraine often resolves during pregnancy (in 70% of people) [164, 230] which may reduce the need for acute treatment in many people.

1.3.27 Seek specialist advice if prophylactic treatment for migraine is needed during pregnancy. [2012]

- Relative values of different outcomes & Quality of evidence

This recommendation was based on GDG informal consensus.

- Trade off between clinical benefits and harms

The GDG agreed that some people may require prophylaxis during pregnancy, in the absence of evidence for safety of recommended prophylactic treatment during pregnancy, a specialist should be consulted.

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4 Detaillierte Darstellung der Recherchestrategie

Cochrane Library - Cochrane Database of Systematic Reviews (Issue 2 of 12, February 2020) am 24.02.2020

#	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 2015 to present, in Cochrane Reviews

Systematic Reviews in Medline (PubMed) am 24.02.2020

#	Suchfrage
1	migraine disorders[MeSH Terms]
2	migrain*[Title/Abstract]
3	hemicrania*[Title/Abstract]
4	#1 OR #2 OR #3
5	(#4) AND (((Meta-Analysis[ptyp] OR systematic[sb] OR ((systematic review [ti] OR meta-analysis[pt] OR meta-analysis[ti] OR systematic literature review[ti] OR this systematic review[tw] OR pooling project[tw] OR (systematic review[tiab] AND review[pt]) OR meta synthesis[ti] OR meta-analy*[ti] OR integrative review[tw] OR integrative research review[tw] OR rapid review[tw] OR umbrella review[tw] OR consensus development conference[pt] OR practice guideline[pt] OR drug class reviews[ti] OR cochrane database syst rev[ta] OR acp journal club[ta] OR health technol assess[ta] OR evid rep technol assess summ[ta] OR jbi database system rev implement rep[ta]) OR (clinical guideline[tw] AND management[tw]) OR ((evidence based[ti] OR evidence-based medicine[mh] OR best practice*[ti] OR evidence synthesis[tiab]) AND (review[pt] OR diseases category[mh] OR behavior and behavior mechanisms[mh] OR therapeutics[mh] OR evaluation study[pt] OR validation study[pt] OR guideline[pt] OR pmcbook)) OR ((systematic[tw] OR systematically[tw] OR critical[tiab] OR (study selection[tw]) OR (predetermined[tw] OR inclusion[tw] AND criteri* [tw]) OR exclusion criteri*[tw] OR main outcome measures[tw] OR standard of care[tw] OR standards of care[tw]) AND (survey[tiab] OR surveys[tiab] OR overview*[tw] OR review[tiab] OR reviews[tiab] OR search*[tw] OR handsearch[tw] OR analysis[ti] OR critique[tiab] OR appraisal[tw] OR (reduction[tw] AND (risk[mh] OR risk[tw]) AND (death OR recurrence))) AND (literature[tiab] OR articles[tiab] OR publications[tiab] OR publication [tiab] OR bibliography[tiab] OR bibliographies[tiab] OR published[tiab] OR pooled data[tw] OR unpublished[tw] OR citation[tw] OR citations[tw] OR database[tiab] OR internet[tiab] OR textbooks[tiab] OR references[tw] OR scales[tw] OR papers[tw] OR datasets[tw] OR trials[tiab] OR meta-analy*[tw] OR (clinical[tiab] AND studies[tiab]) OR treatment outcome[mh] OR treatment outcome[tw] OR pmcbook)) NOT (letter[pt] OR newspaper article[pt])) OR Technical Report[ptyp]) OR (((((trials[tiab] OR studies[tiab] OR database*[tiab] OR literature[tiab] OR publication*[tiab] OR Medline[tiab] OR Embase[tiab] OR Cochrane[tiab] OR Pubmed[tiab])) AND systematic*[tiab] AND (search*[tiab] OR research*[tiab]))) OR ((((((((((HTA[tiab]) OR technology assessment*[tiab]) OR technology report*[tiab]) OR (systematic*[tiab] AND review*[tiab])) OR (systematic*[tiab] AND overview*[tiab])) OR meta-analy*[tiab]) OR (meta[tiab] AND analyz*[tiab])) OR (meta[tiab] AND analys*[tiab])) OR (meta[tiab] AND analyt*[tiab]))) OR (((review*[tiab]) OR overview*[tiab]) AND ((evidence[tiab]) AND based[tiab]))))))

6	(#5) AND ("2015/02/01"[PDAT] : "3000"[PDAT])
7	(#6) NOT "The Cochrane database of systematic reviews"[Journal]
8	(#7) NOT (retracted publication[pt] OR retraction of publication[pt])

Leitlinien in Medline (PubMed) am 24.02.2020

#	Suchfrage
1	migraine disorders[MeSH Terms]
2	migrain*[Title/Abstract]
3	hemicrania*[Title/Abstract]
4	"Headache Disorders, Primary"[Mesh:NoExp]
5	"Headache Disorders"[Mesh:NoExp]
6	headache[MeSH Major Topic]
7	headache*[Title]
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 ("2015/02/01"[PDAT] : "3000"[PDAT])
11	(#10) NOT (retracted publication[pt] OR retraction of publication[pt])

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