Gemeinsamer Bundesausschuss

Kriterien zur Bestimmung der zweckmäßigen Vergleichstherapie

und

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

Vorgang: 2017-B-299 Galcanezumab

Stand: Januar 2018

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

Galcanezumab [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	Anlage VI zum Abschnitt K der Arzneimittel-Richtlinie – Verordnungsfähigkeit von zugelassenen Arzneimitteln in nicht zugelassenen Anwendungsgebieten (Stand: 07.12.2017): Nicht zugelassenes Anwendungsgebiet (Off-Label-Indikation) für Valproinsäure: Migräneprophylaxe von Erwachsenen ab 18 Jahren, wenn eine Behandlung mit anderen dafür zugelassenen Arzneimitteln nicht erfolgreich war oder kontraindiziert ist.
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:	
Galcanezumab	Geplantes Anwendungsgebiet laut Zulassungsantrag: Prophylaxe der Migräne in erwachsenen Patienten
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).
Amitryptilin N06AA09 Saroten®	– zur prophylaktischen Behandlung von Migräne bei Erwachsenen.

Quellen: AMIS-Datenbank, Fachinformationen. Stand: Januar 2018.

Gemeinsamer Bundesausschuss

Abteilung Fachberatung Medizin

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

Vorgang: 2017-B-299 (Galcanezumab)

Auftrag von:	Abt. AM
bearbeitet von:	Abt. FB Med
Datum:	25.01.2018

Recherche und Synopse der Evidenz zur Bestimmung der zweckmäßigen Vergleichstherapie (zVT):

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Systematische Recherche:

Es wurde eine systematische Literaturrecherche nach systematischen Reviews, Meta-Analysen, HTA-Berichten und evidenzbasierten systematischen Leitlinien zur Indikation *Migräneprophylaxe* durchgeführt. Der Suchzeitraum wurde auf die letzten 5 Jahre eingeschränkt und die Recherche am 08.01.2018 abgeschlossen. Die Suche erfolgte in den aufgeführten Datenbanken bzw. Internetseiten folgender Organisationen: The Cochrane Library (Cochrane Database of Systematic Reviews, Health Technology Assessment Database), MEDLINE (PubMed), AWMF, Clinical Evidence, DAHTA, G-BA, GIN, IQWiG, NGC, 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.

Die Recherche ergab 676 Quellen, die anschließend in einem zweistufigen Screening-Verfahren nach Themenrelevanz und methodischer Qualität gesichtet wurden. Zudem wurde eine Sprachrestriktion auf deutsche und englische Quellen vorgenommen. Insgesamt ergab dies 14 Quellen, die in die synoptische Evidenz-Übersicht aufgenommen wurden.

Indikation:

Prophylaxe der Migräne in erwachsenen Patienten.

Abkürzungen:

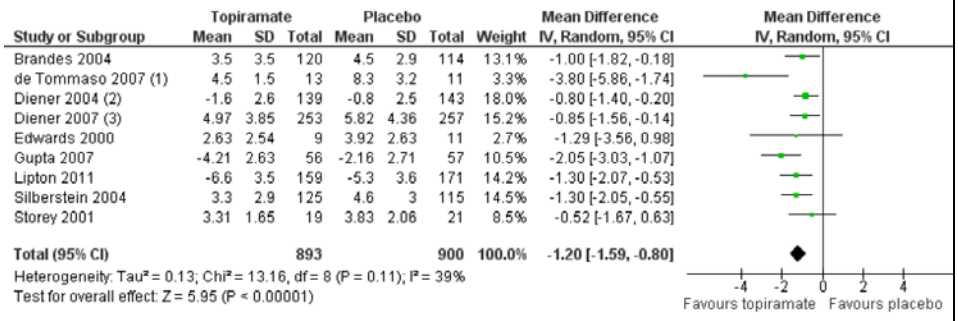
Akdae	Arzneimittelkommission der deutschen Ärzteschaft
AWMF	Arbeitsgemeinschaft der wissenschaftlichen medizinischen Fachgesellschaften
DAHTA	DAHTA-Datenbank
G-BA	Gemeinsamer Bundesausschuss
GIN	Guidelines International Network
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen
NGC	National Guideline Clearinghouse
NICE	National Institute for Health and Care Excellence
SIGN	Scottish Intercollegiate Guidelines Network
TRIP	Turn Research into Practice Database
WHO	World Health Organization

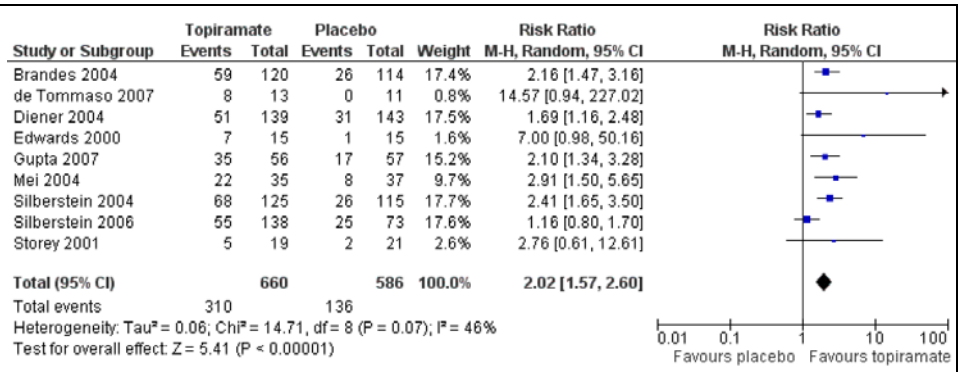
IQWiG Berichte/G-BA Beschlüsse

Gemeinsamer Bundesausschuss (G-BA), 2010 [3]. Zusammenfassende Dokumentation zum Beschluss des Gemeinsamen Bundesausschusses über eine Änderung der Arzneimittel-Richtlinie: Anlage VI (Off-Label-Use) Valproinsäure bei der Migräneprophylaxe im Erwachsenenalter vom 16. September 2010 **Gemeinsamer Bundesausschuss (G-BA), 2017 [1].** Siehe Anlage VI zum Abschnitt K der Arzneimittel-Richtlinie: Verordnungsfähigkeit von zugelassenen Arzneimitteln in nicht zugelassenen Anwendungsgebieten (sog. Off-Label-Use); Teil A Ziffer V;, Valporinsäure bei der Migräneprophylaxe im Erwachsenenalter; letzte Änderung in Kraft getreten am: 07.12.2017	Gemeinsamer Bundesausschuss (G-BA), 2010 [1]. Der Gemeinsame Bundesausschuss hat in seiner Sitzung am 16. September 2010 die Änderung der Richtlinie über die Verordnung von Arzneimitteln in der vertragsärztlichen Versorgung (Arzneimittel-Richtlinie) in der Fassung vom 18. Dezember 2008 / 22. Januar 2009 (BAnz. Nr. 49a vom 31. März 2009), zuletzt geändert am 11. November 2010 (BAnz. S. 4 003), beschlossen: I. Die Anlage VI wird im Teil A wie folgt ergänzt: „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. 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. e) Patienten, die nicht behandelt werden sollten: Gegenanzeigen entsprechen denen der Fachinformation. - Schwangere Frauen sind in jedem Fall von der Behandlung auszunehmen.

Gemeinsamer Bundesausschuss (G-BA), 2015 [2]. Beschluss des G-BA über eine Änderung der Arzneimittel-Richtlinie (AM-RL): Anlage VI – Off-Label-Use Teil A Ziffer V. Valproinsäure bei der Migräneprophylaxe im Erwachsenenalter	Beschluss vom 27.11.2015 I. Ziffer V. des Teil A der Anlage VI wird wie folgt geändert: 1. Der Nummer 1 Buchstabe a) „Nicht zugelassenes Anwendungsgebiet (Off-Label- Indikation):“ wird der Satz „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).“ angefügt. 2. Nummer 1 Buchstabe d) „Spezielle Patientengruppe:“ wird wie folgt geändert: a) Dem Wortlaut werden folgende Sätze vorangestellt: „Vor Beginn einer Therapie mit Valproinsäure muss eine Schwangerschaft ausgeschlossen sein. Da Valproinsäure eine erhebliche teratogene Wirkung und ein erhöhtes Risiko für Entwicklungsstörungen sowie autistischen Störungen bei Einnahme während einer Schwangerschaft hat, muss darüber umfassend aufgeklärt und die Aufklärung dokumentiert werden.“ b) Nach dem Wort „Missbildungen“ werden die Angaben “, Entwicklungsstörungen und autistischen Störungen“ eingefügt. c) Nach dem Satz endend auf die Wörter „eine effektive Methode der Kontrazeption erforderlich ist.“ wird der Satz „Falls keine wirksame Methode der Kontrazeption angewendet wird, ist der Einsatz von Valproinsäure kontraindiziert.“ eingefügt. 3. Nummer 1 Buchstabe e) „Patienten, die nicht behandelt werden sollten:“ wird wie folgt gefasst: „- Gegenanzeigen entsprechen denen der Fachinformation. - 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.“

Cochrane Reviews

Linde M et al., 2013 [6]. Topiramate for the prophylaxis of episodic migraine in adults.	1. Fragestellung To describe and assess the evidence from controlled trials on the efficacy and tolerability of topiramate for preventing migraine attacks in adult patients with episodic migraine.
	2. Methodik **Population:** Erwachsene Patienten mit episodischer Migräne. Patienten mit chronischer Migräne ausgeschlossen **Intervention:** Topiramat Monotherapie, Dosis zwischen 50-200mg **Komparator:** Placebo, keine Intervention, andere aktive pharmakologische Intervention, nicht pharmakologische Intervention, Dosisvergleich **Endpunkte:** Kopfschmerzhäufigkeit, Ansprechen (definiert als ≥50% Reduktion der Kopfschmerzhäufigkeit), QoL, UE **Suchzeitraum** (Aktualität der Recherche): Suche in Cochrane Datenbank, Medline, Embase bis Januar 2013 **Anzahl eingeschlossene Studien/Patienten** (Gesamt): 17 **Qualitätsbewertung der Studien:** Cochrane Risk of Bias Tool
	3. Ergebnisdarstellung 9 RCTs mit hohem Risk of Bias Topiramat vs. Placebo Kopfschmerzhäufigkeit (9 Studien, 1737 Patienten): statistisch signifikanter Unterschied zugunsten von Topiramat vs. Placebo (mean difference (MD) -1.20; 95% confidence interval (CI) -1.59 to -0.80; I^2=39%). Statistisch signifikanter Vorteil für alle Dosierungen (50mg-200mg)  Ansprechen (definiert als ≥50% Reduktion der Kopfschmerzhäufigkeit (9 Studien, 1190 Patienten): statistisch signifikanter Unterschied zugunsten von Topiramat vs. Placebo (OR 3.18; 95% CI 2.10 to 4.82; I^2=46%). Statistisch singifkanter Vorteil für alle Dosierungen (50mg-200mg)



Lebensqualität (2 Studien): Topiramat 50mg (463 Patienten): statistisch signifkanter Unterschied zugunsten von Topiramat im Vergleich zu Placebo für Migraine Specific Questionnaire (MSQ) sowie SF-36 körperliche Schmerzen; Topiramat 100mg (474 Patienten): statistisch signifkanter Unterschied zugunsten von Topiramat im Vergleich zu Placebo für MSQ; Topiramat 200mg (458 Patienten): statistisch signifkanter Unterschied zugunsten von Topiramat im Vergleich zu Placebo für MSQ und SF-36

Topiramat Dosisvergleich

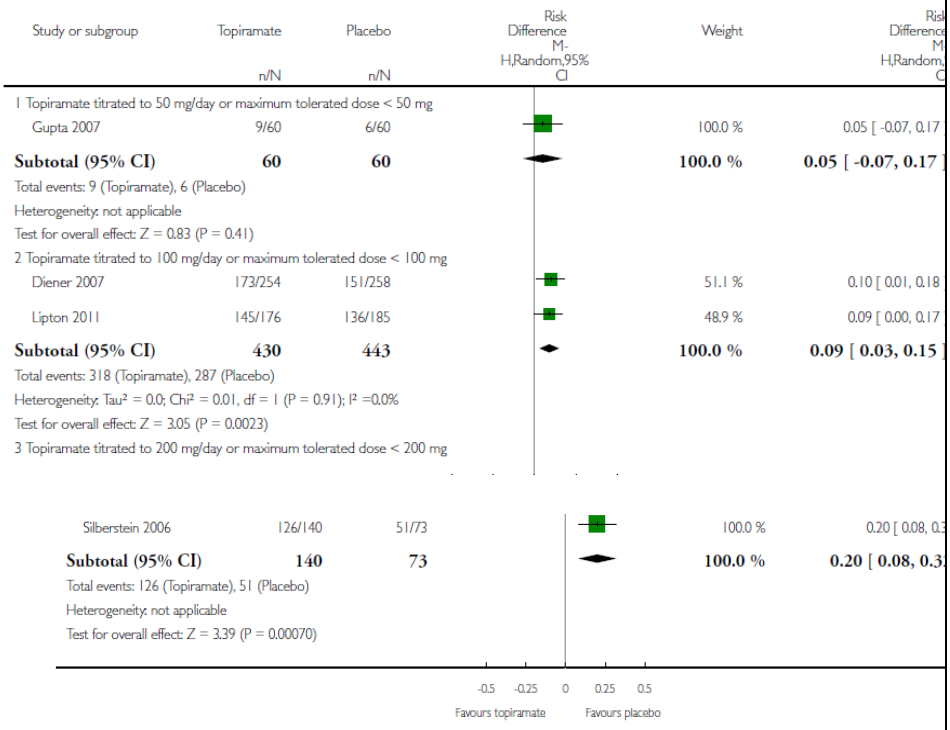
Kopfschmerzhäufigkeit und Ansprechen: statistisch signifkanter Unterschied zugunsten von Topiramat 100mg und 200mg im Vergleich zu 50mg. Kein Unterschied zwischen 100mg und 200mg.

Topiramat vs. aktiven Komparator

Sieben Studien verglichen Topiramat vs. einen aktiven Komparator:

- Amitriptylin (eine Studie, 330 Patienten);
- Flunarizin (eine Studie, 83 Patienten);
- Propranolol (zwei Studien, 342 Patienten);
- Sodium valproate (zwei Studien, 120 Patienten);
- Relaxation (eine Studie, 61 Patienten) (nicht zugelassen)

Kopfschmerzhäufigkeit und Ansprechen: kein statisch signifikanter Unterschied zu Amitriptylin, Flunarizin, Propranolol; Statistisch signifkanter Vorteil von Topiramat vs. Valproinsäure (MD -0.90; 95% CI -1.58 to -0.22; I^2=0%).

	Sicherheit Jedes UE:  Statistisch signifikant häufiger traten in den Topiramat-Armen Geschmacksstörungen, Gewichtsverlust, Gedächtnisstörungen und Fatigue auf.
	4. Anmerkungen/Fazit der Autoren It can be concluded from this review that topiramate is of proven efficacy in migraine prevention and is suitable for routine clinical use. It must be stressed, however, that this review does not provide definite evidence for the efficacy of topiramate in the management of other aspects of the condition (eg, prodromal symptoms, aura symptoms). Likewise, the conclusions in this review cannot be extrapolated to chronic migraine, transformed migraine, or chronic daily headache. None of these conditions was considered for this review, as properly validated definitions are as yet lacking. Although adverse events were reported by a large proportion of study participants treated with topiramate, these were usually mild and of a non-serious nature. Thus it can be concluded that topiramate is reasonably well-tolerated.
Linde M et al., 2013 [7]. Valproate (valproic acid or sodium	1. Fragestellung To describe and assess the evidence from controlled trials on the efficacy and tolerability of valproate (valproic acid or sodium valproate or a combination of the two) for preventing migraine attacks in adult patients with episodic migraine.

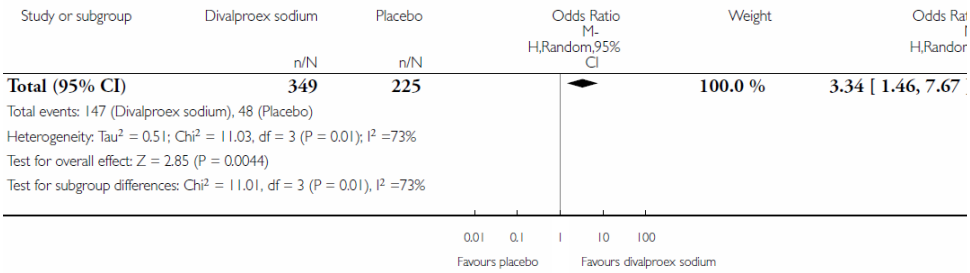
valproate or a combination of the two) for the prophylaxis of episodic migraine in adults.	2. Methodik **Population:** Study participants were required to be adults (at least 16 years of age) and to meet reasonable criteria designed to distinguish migraine from tension-type headache **Intervention:** Included studies were required to have at least one arm in which valproate (valproic acid or sodium valproate or combination of the two, without concomitant use of other migraine prophylactic treatment) was given regularly **Komparator:** placebo, no intervention, active drug treatment (ie, with proven efficacy, not experimental), the same drug treatment with a clinically relevant different dose, and nonpharmacological therapies with proven efficacy in migraine **Endpunkte:** headache frequency, responders (patients with ≥ 50%reduction in headache frequency), quality of life, and adverse events. **Suchzeitraum** (Aktualität der Recherche): 15 January 2013 **Anzahl eingeschlossene Studien/Patienten** (Gesamt): 10 RCTs **Qualitätsbewertung der Studien:** Cochrane risk of bias tool
	3. Ergebnisdarstellung Of 60 risk of bias items scored for the 10 studies, the majority of ratings were either 'unclear' (23 (38%)) or 'low' (20 (33%)) (Figure 1; Figure 2); we judged seven studies (Afshari 2012;Hering 1992; Jensen 1994; Kaniecki 1997; Kinze 2001; Klapper 1997; Mitsikostas 1997) as having a 'high' risk of bias for at least one item (Figure 2). One of these studies (Kinze 2001) was judged as having a high risk of bias for all six items assessed. Valproate versus placebo Divalproex sodium: None of the four trials comparing divalproex sodium with placebo (Freitag 2002; Kaniecki 1997; Klapper 1997; Mathew 1995) reported sufficient data for us to calculate mean differences (MDs) for headache frequency, our preferred outcome measure. All four trials did, however, report data on responders. Analysis of these data showed, overall, that active treatment was significantly superior to placebo for this outcome (odds ratio (OR) 3.34; 95% confidence interval (CI) 1.46 to 7.67; 542 patients (one crossover study had 32 patients); Analysis 1.1). In clinical terms, the observed effect suggests that patients are approximately twice as likely to experience a 50% reduction in headache frequency with divalproex sodium as with placebo. Details are as follows: • The proportion of responders with divalproex sodium was 42% (147/349; range: 30% to 66%);

- The proportion of responders with placebo was 21% (48/ 225; range 14% to 24%);
- the risk ratio (RR) for divalproex sodium versus placebo was 2.18 (95% CI 1.28 to 3.72; Analysis 1.2);
- The number needed to treat (NNT) for divalproex sodium versus placebo was 4 (95% CI 2 to 11).

It is notable that the largest of the four studies analysed (Freitag 2002; 234 patients) found no significant difference between active treatment and placebo.

Comparison: 1 Divalproex sodium versus placebo

Outcome: 1 ORs for responders (patients with ≥ 50% reduction in headache frequency)



Sodium valproate

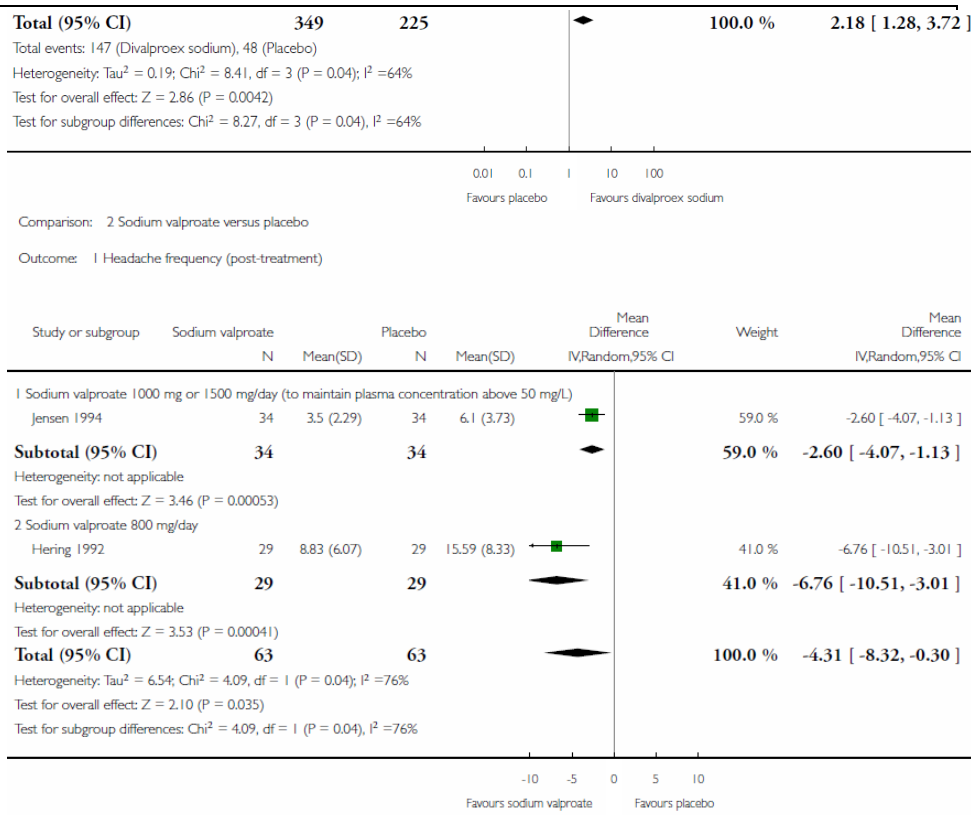
Two cross-over trials of sodium valproate (Hering 1992; Jensen 1994; 63 patients) showed a significant reduction in headache frequency (per 28-day period) in the active group compared to the placebo group (MD -4.31; 95% CI -8.32 to -0.30; Analysis 2.1). In clinical terms, the observed effect corresponds to a reduction in headache frequency of approximately four headaches per 28 days. The mean baseline headache frequency in the valproate group (reported only by Jensen 1994, and only for completers) was 6.1 headaches per 28 days.

One cross-over trial (Jensen 1994; 34 patients) reported data on responders; these showed that sodium valproate was significantly superior to placebo for this outcome (OR 4.67; 95% CI 1.54 to 14.14; Analysis 2.2). In clinical terms, the observed effect suggests that patients are nearly three times as likely to experience a ≥ 50% reduction in headache frequency with sodium valproate as with placebo. Details are as follows:

- The proportion of responders with sodium valproate was 50% (17/34);
- The proportion of responders with placebo was 18% (6/34);
- The RR for sodium valproate versus placebo was 2.83 (95% CI 1.27 to 6.31; Analysis 2.3);
- The NNT for sodium valproate versus placebo was 3 (95% CI 2 to 9).

Comparison: 1 Divalproex sodium versus placebo

Outcome: 2 RRs for responders (patients with ≥ 50% reduction in headache frequency)



Sodium valproate versus flunarizine

- One parallel-group trial (Mitsikostas 1997) compared sodium valproate with flunarizine. There was no significant difference between sodium valproate and flunarizine in the proportion of responders (OR 1.07; 95% CI 0.28 to 4.12; 41 patients).

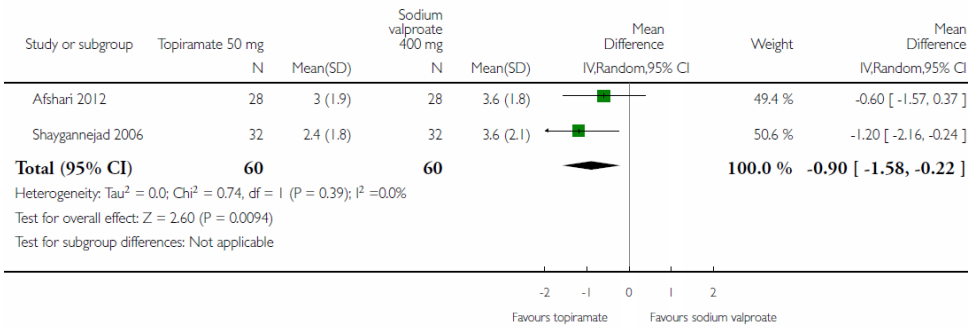
Divalproex sodium versus propranolol

- A further (cross-over) trial using an active comparator examined divalproex sodium versus propranolol (Kaniecki 1997). There was no significant difference between treatments in the proportion of responders (OR 1.15; 95% CI 0.41 to 3.18; 32 patients).

Sodium valproate versus topiramate

- Two fairly small studies compared topiramate 50 mg with sodium valproate 400 mg. Afshari 2012 did not demonstrate a significant difference in mean headache frequency during treatment (MD -0.60; 95%CI -1.57 to 0.37; 56 participants).On the basis of their statistical analysis, the authors of Shaygannejad 2006 found no significant differences in efficacy between the two drugs. However, our analysis of post-treatment mean headache frequencies demonstrated a slight but significant advantage for topiramate over valproate (MD -1.20; 95%CI -2.16 to -0.24; 32 (cross-over) participants). The pooled results of these two studies indicate a significant difference between topiramate and sodium valproate, in favour of topiramate, for this outcome (MD -0.90; 95% CI -1.58 to -0.22). In clinical terms, the observed effect corresponds to a

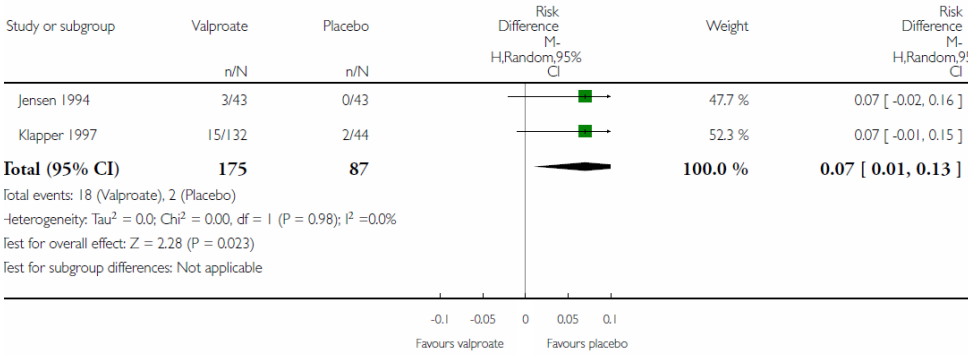
reduction in headache frequency of approximately one headache per 28 days with topiramate versus sodium valproate. The median baseline headache frequency in the topiramate groups of the two trials was 6.1 headaches per 28 days (mean 6.1; range: 5.4 to 6.8). It should be noted that the doses used in these two studies are not those used in routine clinical practice for the management of migraine.



Safety

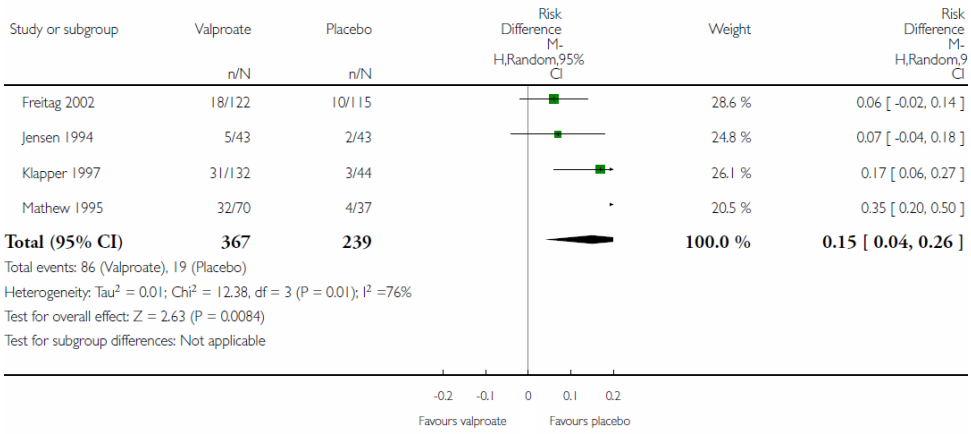
Comparison: 7 Safety of sodium valproate and divalproex sodium versus placebo

Outcome: 3 Dizziness/vertigo



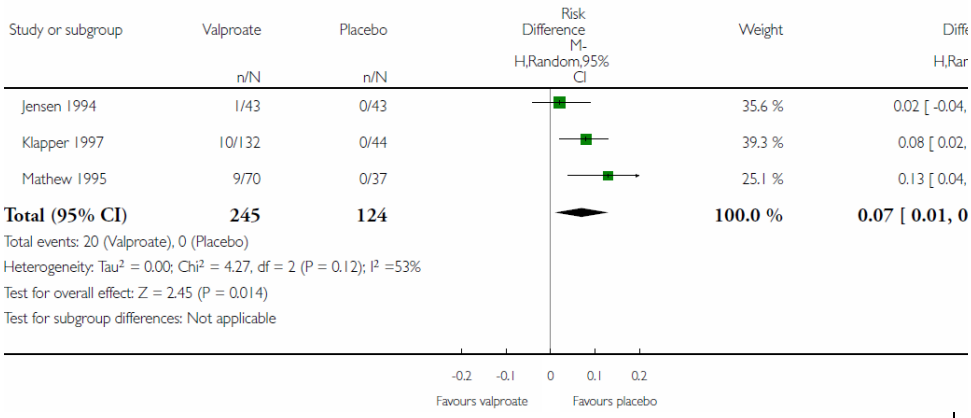
Comparison: 7 Safety of sodium valproate and divalproex sodium versus placebo

Outcome: 4 Nausea



Comparison: 7 Safety of sodium valproate and divalproex sodium versus placebo

Outcome: 5 Tremor



4. Anmerkungen/Fazit der Autoren

Valproate has been investigated in 10 independent clinical trials, the results of which are generally consistent. It can be concluded from this review that valproate is of proven efficacy in migraine prevention and is suitable for routine clinical use. Although adverse events were reported by a large proportion of migraine patients treated with valproate, these were usually mild and of a non-serious nature. Thus it can be concluded that valproate is reasonably well tolerated. One important caveat should be noted: valproate is known to be teratogenic (Morrell 2003), and appropriate caution must accordingly be used when prescribing to women of childbearing age.

Systematische Reviews

Xu XM et al., 2017 [14]. Tricyclic antidepressants for preventing migraine in adults	1. Fragestellung We reviewed all randomized controlled trials that assigned adults with a clinical diagnosis of migraine to TCAs or other treatments (placebo or other antidepressants).
	2. Methodik **Population:** adults (≥18 years) with a primary diagnosis ofmigraine, described in theAdHocCommittee on the Classification of Headache or the International Headache Society. **Intervention:** Tricyclic antidepressant, amitriptyline **Komparator:** Placebo, serotonin reuptake inhibitors (SSRIs) **Endpunkt:** Reduction in migraine frequency or index and response rates to treatment were defined as the efficacy outcomes. Rates of dropout due to adverse effects were defined as the tolerability outcomes. **Recherche:** 07/2016 **Anzahl eingeschlossene Studien/Patienten** (Gesamt): 12/1006 patients (9 trials compared TCAs with placebo, and the other 3 compared amitriptyline with selective serotonin reuptake inhibitors (SSRIs) or serotonin norepinephrine reuptake inhibitors (SNRIs)) **Qualitätsbewertung der Studien:** Risk of bias" tool developed by the Cochrane Collaboration.
	3. Ergebnisdarstellung Qualität der Studien: Most studies were at unclear risk with respect to the methods of randomization and allocation concealment. Besides, information on blinding of participants, investigators, and outcome assessment was described in less than half of the trials. Amitriptyline versus other antidepressants (SSRIs or SNRIs): • In a limited number of trials the efficacy between amitriptyline and SSRIs (SMD = .16; 95% CI = -0.32 to 0.63; P=.52) or SNRIs (SMD = -.13; 95% CI = -0.51 to 0.25; P=.51) did not demonstrate diffenrences for migraine prevention in adults (SMD=-.01; 95% CI=-0.31 to 0.28; P=.94), with no heterogeneity presented (I^2=0%; P=.38) • No significant difference in respnce rates betzween SSRIs and

	amitriptyline was found on the only one available study (RR=1.08; 95% CI=0.41-2.83; P=.87) - patients receiving amitriptyline were more likely to withdraw from treatment due to adverse effects than those treated with SSRIs or SNRIs (SMD = 2.85; 95% CI = 0.97–8.41; P=.06) with low heterogeneity (I^2 = 0%; P=.54)
	4. Anmerkungen/Fazit der Autoren This research reveals that TCAs were more effective than placebo, but no more than SSRI or SNRI in ameliorating the headache burden in adults with migraine. However, TCAs appeared to be less tolerated than placebo and SSRIs or SNRIs for some side effects. 5. *Kommentare zum Review* - Zulassung der untersuchten AM im SR beachten
He A et al., 2017 [4]. Unveiling the relative efficacy, safety and tolerability of prophylactic medications for migraine: pairwise and network-meta analysis	1. Fragestellung We compared several preventative medications for migraine patients by using the approach of network meta-analysis (NMA).
	2. Methodik **Population:** migraine patients **Intervention:** Nicht spezifiziert, siehe Tabelle in der Ergebnisdarstellung **Komparator:** Nicht spezifiziert **Endpunkte**: monthly migraine headache days, headache frequency, the percentages of patients with at least 50% reductions in migraine attacks (efficacy), the number of patients with all adverse events such as nausea, somnolence or dizziness (safety) and the number of patients who withdrew from studies (tolerability). **Suchzeitraum** (Aktualität der Recherche): nicht angegeben **Anzahl eingeschlossene Studien/Patienten** (Gesamt): 32 RCTs (n = 6052) **Qualitätsbewertung der Studien:** Jaded scale
	3. Ergebnisdarstellung As suggested by both the node splitting method (P-value > 0.05) and net heat plots, there is no significant inconsistency between direct and indirect evidence for the majority of comparisons. Therefore, we concluded that the consistency model is valid in our NMA.

Table 1 Studies identified for the NMA with interventions and outcomes evaluated

Author, Year	Center	Design	Blind	Mechanism of action	Intervention
Silberstein et al., 2013 [42]	Multi	RCT	Double	Anticonvulsants	Gabapentin vs. Placebo
Afshari et al., 2012 [41]	Mono	RCT	Double	Anticonvulsants	Topiramate vs. Valproate
Lipton et al., 2011 [40]	Multi	RCT	Double	Anticonvulsants	Topiramate vs. Placebo
Holroyd et al., 2010 [39]	Multi	RCT	Double	β blocker	Propranolol vs. Placebo
Dodick et al., 2009 [38]	Multi	RCT	Double	Anticonvulsants	Topiramate vs. Amitriptylin
Ashtari et al., 2008 [37]	Mono	RCT	Double	Anticonvulsants	Topiramate vs. Propranolol
Silberstein et al., 2007 [36]	Multi	RCT	Double	Anticonvulsants	Topiramate vs. Placebo
Gupta et al., 2007 [35]	Mono	Crossover	Double	Anticonvulsants	Topiramate vs. Placebo
Diener et al., 2007 [33, 34]	Multi	RCT	Double	Anticonvulsants	Topiramate vs. Placebo
Diener et al., 2007 [33, 34]	Multi	RCT	Double	Anticonvulsants	Topiramate vs. Placebo
Tommaso et al., 2007 [32]	Mono	RCT	Double	Anticonvulsants	Topiramate vs. Placebo
Silberstein et al., 2006 [31]	Multi	RCT	Double	Anticonvulsants	Topiramate vs. Placebo
Shaygannejad et al., 2006 [30]	Mono	Crossover	Double	Anticonvulsants	Topiramate vs. Valproate
Brandes et al., 2006 [29]	Multi	RCT	Double	Anticonvulsants	Topiramate vs. Placebo
Silberstein et al., 2004 [28]	Multi	RCT	Double	Anticonvulsants	Topiramate vs. Placebo
Mei et al., 2004 [27]	Mono	RCT	Double	Anticonvulsants	Topiramate vs. Placebo
Diener et al., 2004 [26]	Multi	RCT	Double	Anticonvulsants	Topiramate vs. Propranolol
Brandes et al., 2004 [25]	Multi	RCT	Double	Anticonvulsants	Topiramate vs. Placebo
Freitag et al., 2002 [24]	Multi	RCT	Double	Anticonvulsants	Divalproex vs. Placebo
Storey et al., 2001 [23]	Mono	RCT	Double	Anticonvulsants	Topiramate vs. Placebo
Mathew et al., 2001 [22]	Multi	RCT	Double	Anticonvulsants	Gabapentin vs. Placebo
Klapper, 1997 [21]	Multi	RCT	Single	Anticonvulsants	Divalproex vs. Placebo
Kaniecki, 1997 [20]	Mono	RCT	Single	Anticonvulsants	Divalproex vs. Propranolol
Diener et al, 1996 [19]	Multi	RCT	Double	β blocker	Propranolol vs. Placebo
Bendtsen et al., 1996 [18]	Mono	Crossover	Double	Antidepressive	Amitriptyline vs. Placebo
Mathew et al., 1995 [17]	Multi	RCT	Double	Anticonvulsants	Divalproex vs. Placebo
Hering and Kuritzky, 1992 [16]	Mono	Crossover	Double	Anticonvulsants	Valproate vs. Placebo
Pradalier et al., 1989 [15]	Multi	RCT	Double	β blocker	Propranolol vs. Placebo
Mikkelsen et al., 1986 [14]	Mono	Crossover	Double	β blocker	Propranolol vs. Placebo
Sadeghian andMotiei-Langroudi, 2015 [45]	Mono	RCT	Double	Anticonvulsants	Valproate vs. Placebo
Sarchielli et al., 2014 [44]	Multi	RCT	Double	Anticonvulsants	Valproate vs. Placebo
Nofal et al., 2014 [43]	Moni	RCT	Double	Anticonvulsants	Gabapentin vs. Placebo

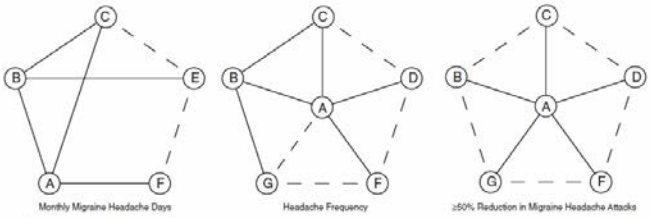


Fig. 2 Network plots of eligible comparisons of migraine intervention (monthly migraine headache days; headache frequency; ≥50% reduction in migraine headache attacks). *A*: Placebo; *B*: Topiramate; *C*: Propranolol; *D*: Gabapentin; *E*: Amitriptyline; *F*: Divalproex; *G*: Valproate. Direct comparisons were connected by solid lines whereas indirect comparisons were connected by dashed lines

Pairwise comparison using conventional meta-analysis

- A total of ten direct comparisons with respect to each endpoint were produced by using pairwise meta-analysis. Patients with topiramate exhibited significantly less average headache days, less headache frequency, a higher likelihood of at least 50% reduction compared to those with placebo (migraine headache days: −0.28, 95% CI = −0.53 to −0.03; headache frequency: −0.31, 95% CI = −0.45 to −0.17; ≥ 50% reduction: OR = 2.33, 95% CI = 1.58–3.42). However, patients with topiramate appeared to have significantly higher risk of all-adverse events and withdrawal due to adverse events compared to those with placebo (all-adverse events: OR = 1.35, 95% CI = 1.06–1.73, withdrawal due to adverse events: OR = 2.08, 95% CI = 1.56–2.78). Patients with propranolol exhibited a significantly less

average headache days but higher risk of all-adverse events, somnolence and withdrawal due to adverse events compared to those with placebo (migraine headache days: −0.29, 95% CI = −0.49 to −0.09; all-adverse events: OR = 2.02, 95% CI = 1.05–4.08, somnolence: OR = 4.33, 95% CI = 1.21 to 15.53, withdrawal due to adverse events: OR = 1.87, 95% CI = 1.09 to 3.09).

- Patients treated with amitriptyline or divalproex exhibited a reduced headache days or headache frequency as well as a better performance in at least 50% reduction in headache attacks compared to those with placebo (amitriptyline: headache frequency: −0.36, 95% CI = −0.62 to −0.10; ≥ 50% reduction: OR = 1.81, 95% CI = 1.03–3.20; divalproex: migraine headache days: −0.40, 95% CI = −0.61 to −0.18; ≥ 50% reduction: OR = 4.27, 95% CI = 1.30–13.99), however, this was offset by an increased risk of all-adverse events or nausea (amitriptyline: all-adverse events: OR = 2.20, 95% CI = 1.04–4.66; divalproex: nausea: OR = 2.23, 95% CI = 1.21–4.10). Besides that, we were not able to identify any significant results between direct comparisons produced by conventional meta-analysis.

Table 2 Relative treatment efficacy, safety and tolerability produced by pairwise meta-analysis

Comparison	Migraine headache days	Headache frequency	≥50% Reduction	All-adverse events	Nausea	Somnolence	Dizziness	Withdra
Placebo vs Topiramate	**−0.28 (−0.53, −0.03)**	**−0.31 (−0.45, −0.17)**	**2.33 (1.58, 3.42)**	**1.35 (1.06, 1.73)**	1.31 (0.97, 1.76)	1.38 (0.70, 2.74)	1.07 (0.54, 2.13)	1.05 (0.9 1.21)
Placebo vs Propranolol	**−0.29 (−0.49, −0.09)**	−1.17 (−2.89, 0.55)	1.37 (0.69, 2.70)	**2.02 (1.05, 4.08)**	1.64 (0.78, 3.47)	**4.33 (1.21, 15.53)**	1.27 (0.20, 8.08)	1.07 (0.7 1.51)
Placebo vs Gabapentin	−0.09 (−0.29, 0.10)	−0.34 (−0.69, 0.01)	1.36 (0.63, 2.95)	1.15 (0.87, 1.51)	0.92 (0.52, 1.64)	**2.23 (1.11, 4.46)**	**3.13 (1.73, 5.66)**	1.21 (0.8 1.77)
Placebo vs Amitriptyline	-	**−0.36 (−0.62, −0.10)**	**1.81 (1.03, 3.20)**	**2.20 (1.04, 4.66)**	0.33 (0.03, 3.34)	-	1.75 (0.47, 6.45)	-
Placebo vs Divalproex	**−0.40 (−0.61, −0.18)**	-	**4.27 (1.30, 13.99)**	0.98 (0.71, 1.34)	**2.23 (1.21, 4.10)**	1.92 (0.32, 11.63)	-	1.61 (0.9 2.82)
Placebo vs Valproate	-	-	-	-	3.00 (0.59, 15.37)	-	2.00 (0.36, 11.26)	0.88 (0.2 2.62)
Topiramate vs Propranolol	−0.12 (−0.32, 0.08)	0.18 (−0.45, 0.81)	-	**0.57 (0.36, 0.90)**	0.81 (0.45, 1.45)	1.42 (0.68, 2.99)	-	**0.66 (0.4 0.99)**
Topiramate vs Amitriptyline	0.01 (−0.20, 0.22)	-	-	1.03 (0.76, 1.41)	0.70 (0.33, 1.49)	1.50 (0.82, 2.72)	1.26 (0.61, 2.57)	1.02 (0.7 1.50)
Topiramate vs Valproate	-	-	-	1.22 (0.54, 2.76)	1.00 (0.29, 3.48)	1.30 (0.44, 3.84)	-	0.67 (0.2 1.88)
Propranolol vs Divalproex	-	-	-	1.36 (0.58, 3.16)	3.50 (0.67, 18.15)	-	1.00 (0.19, 5.33)	-

Including both direct and indirect evidence in the NMA

- Results produced by NMA are displayed in Table 3 which determined the relative efficacy, safety and tolerability of prophylactic migraine interventions by using both direct and indirect evidence. Patients with three interventions exhibited significantly less average migraine headache days compared with those treated by placebo (topiramate: −1.20, 95% CrI = −1.83 to −0.70; propranolol: −0.98, 95% CrI = −1.86 to −0.07; divalproex: −1.28, 95% CrI = −2.44 to −0.27; Table 3, Fig. 5). Moreover, patients with topiramate and valproate exhibited a significantly increased likelihood of at least 50% reduction in migraine headache attacks compared to those with placebo

(topiramate: OR = 4.28, 95% CrI = 1.35 to 14.70; valproate: 11.38, 95% CrI = 1.31 to 111.11; Table 3, Fig. 5). Patients with topiramate or propranolol also exhibited significantly reduced headache frequency compared to those with placebo (topiramate: −1.17, 95% CrI = −1.98 to −0.35; propranolol: −1.37, 95% CrI = −2.49 to 0.29; Table 3, Fig. 5).

Table 3 Relative efficacy, safety and tolerability of migraine interventions produced by NMA

Migraine Headache Days	**Placebo**	**Placebo**	1.20 (0.70, 1.83)	0.98 (0.07, 1.86)	-	1.09 (−0.89, 3.13)	1.28 (0.27, 2.44)
	Topiramate	**−1.20 (−1.83, −0.70)**	**Topiramate**	−0.22 (−1.30, 0.67)	-	−0.10 (−2.03, 1.81)	0.09 (−1.16, 13
	Propranolol	**−0.98 (−1.86, −0.07)**	0.22 (−0.67, 1.30)	**Propranolol**	-	0.13 (−2.02, 2.33)	0.31 (−1.05, 18
	Gabapentin	-	-	-	**Gabapentin**	-	-
	Amitriptyline	−1.09 (−3.13, 0.89)	0.10 (−1.81, 2.03)	−0.13 (−2.33, 2.02)	-	**Amitriptyline**	0.21 (−2.08, 25
	Divalproex	**−1.28 (−2.44, −0.27)**	−0.09 (−1.31, 1.16)	−0.31 (−1.83, 1.05)	-	−0.21 (−2.53, 2.08)	**Divalproex**
	Valproate	-	-	-	-	-	-
Headache Frequency							
≥50% Reduction in Migraine Headache Attacks	**Placebo**	**Placebo**	**1.17 (0.35, 1.98)**	**1.37 (0.29, 2.49)**	1.20 (−0.87, 3.28)	-	0.60 (−1.18, 24
	Topiramate	**4.28 (1.35, 14.70)**	**Topiramate**	0.21 (−0.88, 1.33)	0.05 (−2.20, 2.28)	-	−0.56 (−2.53, 1
	Propranolol	1.65 (0.25, 11.29)	0.38 (0.04, 3.70)	**Propranolol**	−0.17 (−2.45, 2.15)	-	−0.76 (−2.90, 1
	Gabapentin	1.59 (0.41, 6.93)	0.37 (0.06, 2.43)	0.96 (0.10, 10.96)	**Gabapentin**	-	−0.61 (−3.39, 2
	Amitriptyline	-	-	-	-	**Amitriptyline**	-
	Divalproex	2.63 (0.91, 8.79)	0.62 (0.12, 3.11)	1.58 (0.18, 14.74)	1.67 (0.26, 9.65)	-	**Divalproex**
	Valproate	**11.38 (1.31, 111.11)**	2.66 (0.22, 32.35)	7.00 (0.37, 128.51)	7.19 (0.51, 94.89)	-	4.30 (0.38, 52.3
All Adverse Events							
Nausea	**Placebo**	**Placebo**	**2.44 (1.55, 3.88)**	1.09 (0.47, 2.54)	1.66 (0.70, 4.01)	**4.66 (1.74, 12.93)**	1.13 (0.51, 2.57)
	Topiramate	1.37 (0.99, 1.94)	**Topiramate**	0.45 (0.18, 1.07)	0.69 (0.25, 1.89)	1.92 (0.72, 5.20)	0.46 (0.19, 1.15)
	Propranolol	1.13 (0.56, 2.24)	0.81 (0.44, 1.59)	**Propranolol**	1.53 (0.45, 5.26)	**4.29 (1.24, 15.39)**	1.04 (0.39, 2.75)
	Gabapentin	0.91 (0.47, 1.86)	0.67 (0.32, 1.43)	0.82 (0.32, 2.06)	**Gabapentin**	2.80 (0.75, 10.80)	0.68 (0.20, 2.19)
	Amitriptyline	0.80 (0.32, 1.84)	0.58 (0.24, 1.37)	0.71 (0.23, 1.89)	0.85 (0.27, 2.50)	**Amitriptyline**	**0.24 (0.07, 0.8**
	Divalproex	**3.04 (1.72, 6.47)**	**2.24 (1.13, 4.93)**	**2.79 (1.19, 6.48)**	**3.31 (1.31, 9.25)**	**3.83 (1.40, 12.81)**	**Divalproex**
	Valproate	2.05 (0.75, 5.65)	1.53 (0.54, 4.07)	1.88 (0.53, 5.59)	2.27 (0.55, 7.43)	2.63 (0.63, 10.29)	0.67 (0.20, 2.32)
Somnolence							
Dizziness	**Placebo**	**Placebo**	1.36 (0.48, 3.76)	2.68 (0.39, 21.57)	2.68 (0.55, 14.14)	2.20 (0.20, 23.60)	2.95 (0.55, 13.0
	Topiramate	1.17 (0.48, 2.71)	**Topiramate**	1.98 (0.31, 15.33)	1.96 (0.32, 14.39)	1.58 (0.19, 14.47)	2.18 (0.31, 13.0
	Propranolol	1.40 (0.11, 17.00)	1.20 (0.09, 17.20)	**Propranolol**	1.01 (0.07, 12.38)	0.81 (0.04, 13.07)	1.09 (0.07, 10.9
	Gabapentin	**3.69 (1.17, 9.63)**	3.21 (0.74, 11.22)	2.64 (0.19, 35.35)	**Gabapentin**	0.83 (0.04, 12.96)	1.12 (0.10, 8.96)
	Amitriptyline	1.63 (0.46, 6.07)	1.40 (0.44, 5.06)	1.17 (0.08, 18.83)	0.44 (0.10, 2.67)	**Amitriptyline**	1.43 (0.07, 20.3
	Divalproex	1.37 (0.05, 34.88)	1.18 (0.04, 35.19)	0.94 (0.11, 9.66)	0.38 (0.01, 11.64)	0.84 (0.02, 27.74)	**Divalproex**
	Valproate	0.44 (0.04, 2.98)	0.37 (0.03, 3.27)	0.30 (0.01, 7.28)	0.12 (0.01, 1.13)	0.26 (0.02, 2.72)	0.29 (0.01, 15.4
Withdrawal							
Withdrawal due to AEs	**Placebo**	**Placebo**	1.10 (0.95, 1.38)	0.81 (0.63, 1.29)	1.17 (0.80, 2.08)	1.19 (0.68, 2.14)	**1.68**
	Topiramate	**2.33 (1.55, 3.45)**	**Topiramate**	0.71 (0.54, 1.15)	1.04 (0.67, 1.87)	1.09 (0.60, 1.82)	1.48
	Propranolol	1.51 (0.78, 2.94)	0.64 (0.32, 1.34)	**Propranolol**	1.54 (0.78, 2.63)	1.56 (0.68, 2.56)	**2.09**
	Gabapentin	1.81 (0.71, 4.58)	0.78 (0.28, 2.18)	1.21 (0.38, 3.72)	**Gabapentin**	1.03 (0.43, 1.95)	1.34
	Amitriptyline	2.69 (0.93, 7.57)	1.16 (0.43, 3.12)	1.80 (0.51, 5.84)	1.49 (0.35, 5.96)	**Amitriptyline**	1.32
	Divalproex	**2.25 (1.01, 5.49)**	0.96 (0.41, 2.57)	1.50 (0.57, 4.26)	1.25 (0.38, 4.49)	0.83 (0.24, 3.40)	**Diva**
	Valproate	2.20 (0.68, 6.92)	0.96 (0.30, 2.97)	1.50 (0.39, 5.28)	1.25 (0.26, 5.38)	0.85 (0.17, 3.58)	0.99

Row treatments were compared to column treatments in the lower diagonal whereas column treatments were compared to row treatments in the upper diagonal

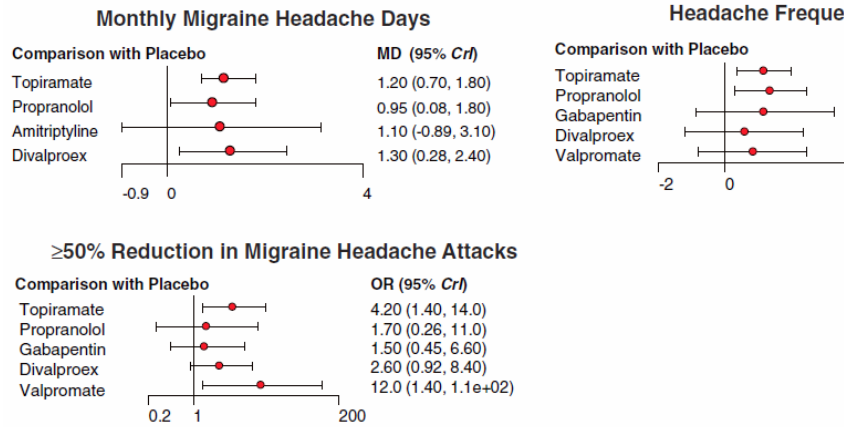


Fig. 5 Forest plots of summary effects (NMA) with respect to monthly migraine headache days, headache frequency and at in migraine attacks

- Propranolol, topiramate and gabapentin exhibited the largest three SUCRA values with respect to headache frequency. Moreover, valproate, topiramate and divalproex were more

preferable than other interventions with respect to the endpoint of at least 50% reduction in migraine attacks. Overall, propranolol seemed to be the most desirable intervention when several endpoints were simultaneously considered

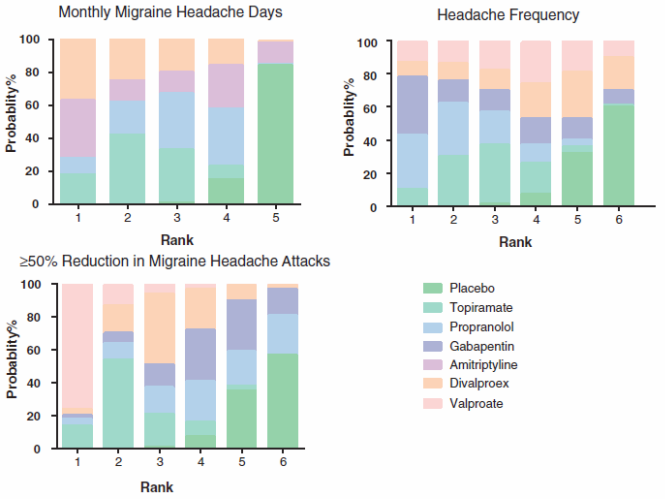


Fig. 8 Probability ranking plot of monthly migraine headache days, headache frequency and at least 50% reduction in

4. Anmerkungen/Fazit der Autoren

Results of our NMA indicated that three interventions may be particularly efficacious for reducing the corresponding symptoms of migraine: divalproex, propranolol and valproate. In our study, divalproex ranked the highest with respect to the reduction of monthly headache days whereas propranolol appeared to be the most preferable intervention for reducing headache frequency. Moreover, our study also suggested that valproate exhibited superior performance with respect to at least 50% reduction in headache attacks.

Despite that some new findings have been suggested by our study, it is essential to discuss several key issues that may have impact on our conclusions. Firstly, we include both RCTs and crossover studies in our NMA; this may significantly increase the heterogeneity resulted from the design and implantation of different studies. Furthermore, the inclusion of crossover studies produced some extra confounding factors that were not presented in RCTs. For instance, a wash-out period between interventions is often used in crossover studies and the duration of the wash-out period may have significant impact on medication compliance as well as on the corresponding endpoints.

Jackson JL et al., 2015 [5]. A Comparative Effectiveness Meta-Analysis of Drugs for the Prophylaxis of Migraine Headache.	1. Fragestellung To compare the effectiveness and side effects of migraine prophylactic medications. network meta-analysis
	2. Methodik **Population:** adults with migraine headaches of at least 4 weeks in duration. episodic migraines (< 15 headaches/ month), chronic migraine (>15 headaches/month) and chronic daily headache **Intervention:** nicht spezifiziert (migraine prophylactic medications) **Komparator:** Placebo oder aktive Kontrolle **Endpunkt:** nicht vorab spezifiziert **Suchzeitraum** (Aktualität der Recherche): bis 05/2014 **Anzahl eingeschlossene Studien/Patie**nten (Gesamt): 179 Placebo-kontrollierte Studien (n = 15.493), 53 nicht Placebo-kontrollierte, vergleichende Studien **Qualitätsbewertung der Studien:** JADAD and Cochrane Risk of Bias instruments - Nachfolgend werden nur Ergebnisse für in Deutschland zugelassene Wirkstoffe dargestellt. -
	3. Ergebnisdarstellung Studienqualität: By Jadad criteria, 34% of studies had scores ≤ 3.0, suggesting low quality, 39% had scores between 3 and 5 consistent with modest quality and only 37% had scores ≥ 5 suggesting high quality. Only 36% used an intention to treat analysis, 27% assessed compliance, 26% had concealed allocation, and 51% had adequate blinding. There was no difference in the overall effect sizes for placebo controlled trials using Jadad criteria as a scale (p = 0.44) or when coded as high, modest or low quality (p = 0.37), or when assessed by most of the specific Jadad or Cochrane Risk of Bias quality characteristics (compliance p = 0.59; blinding p = 0.36; adequacy of blinding p = 0.50, industry sponsorship p = 0.52; incomplete outcome reporting p = 0.96, reporting of withdrawals p = 0.24). **Topiramate** Topiramate has been evaluated in twelve placebo-controlled trials that reported outcomes at numerous time points and different doses (50, 100 and 200mg). Pooled results suggest that topiramate was more effective than placebo at all time points (4–24 weeks) and at all doses assessed. There was evidence that higher doses of topiramate was more effective than lower ones,

with a stepwise increase as the dose increased from 50 to 100 to 200mg. For chronic migraine, 2 studies of topiramate suggested effectiveness for up to 16 weeks. In several studies (n = 8) topiramate was also demonstrated to be more effective than placebo at reducing migraine by more than 50%.

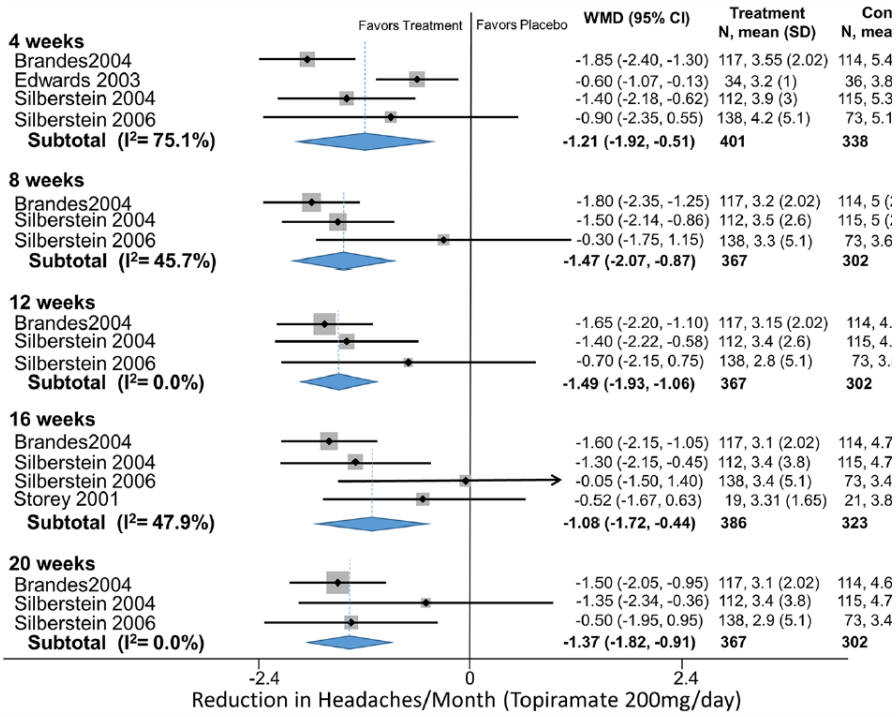


Fig 4. Topiramate compared to placebo for episodic migraine headaches.

Valproate

Valproate also had been compared to placebo in six trials with multiple time points and varying doses (500-1500mg). Valproate was found to be more effective than placebo for episodic migraine at all time points assessed including 4, 8 and 12 weeks. However, unlike topiramate there was no evidence of a difference in response to increased doses (dose-response p = 0.83). Valproate was also found in numerous trials (n = 5) to reduce headaches by more than 50%.

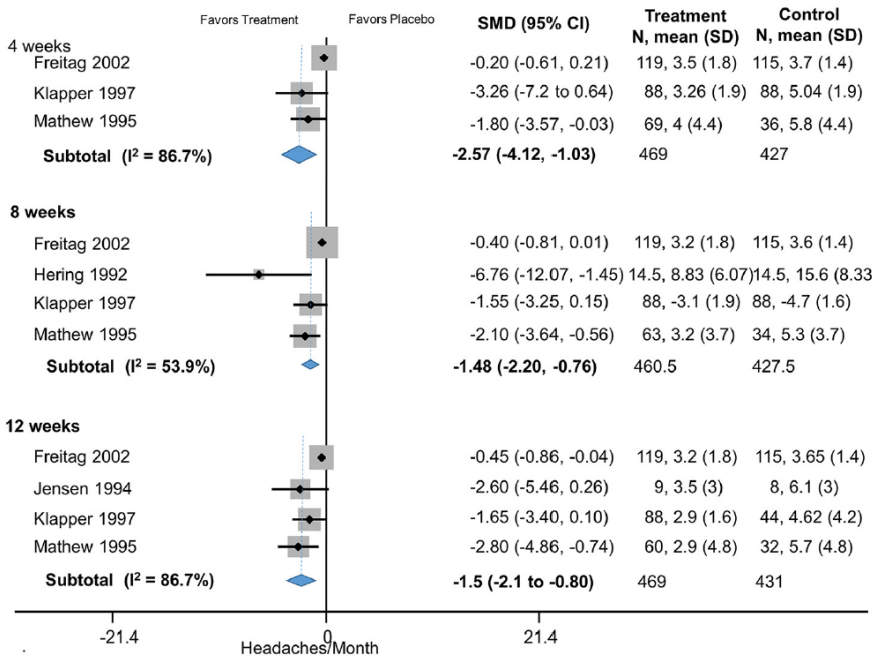


Fig 5. Valproate compared to placebo for episodic migraine headaches.

Beta Blockers

There were 38 trials comparing beta-blockers to placebo with a total of 2019 participants, 37 focusing on episodic and 1 on chronic migraine headaches. The average rate of withdrawals was 18%. Study duration averaged 11 weeks (range 4–64) with a mean of 64 participants (range 20–568). The majority (82%) reported headache frequency four trials used headache index, and one duration. There were a variety of beta-blockers tested including acebutolol (n = 1), alprenolol (n = 1), atenolol (n = 3), bisoprolol (n = 1), metoprolol (n = 4), oxprenolol (n = 1), pindolol (n = 2), propranolol (n = 19) and timolol (n = 4). Beta blockers no more effective than placebo included acebutolol, alprenolol, bisoprolol, oxprenolol and pindolol. Beta-blockers superior to placebo for episodic migraine headaches included atenolol, metoprolol, propranolol and timolol. Seven studies found that propranolol reduced headache by 50% (Table 7). Neither atenolol (1 study) nor propranolol (2 studies) were effective for chronic migraine.

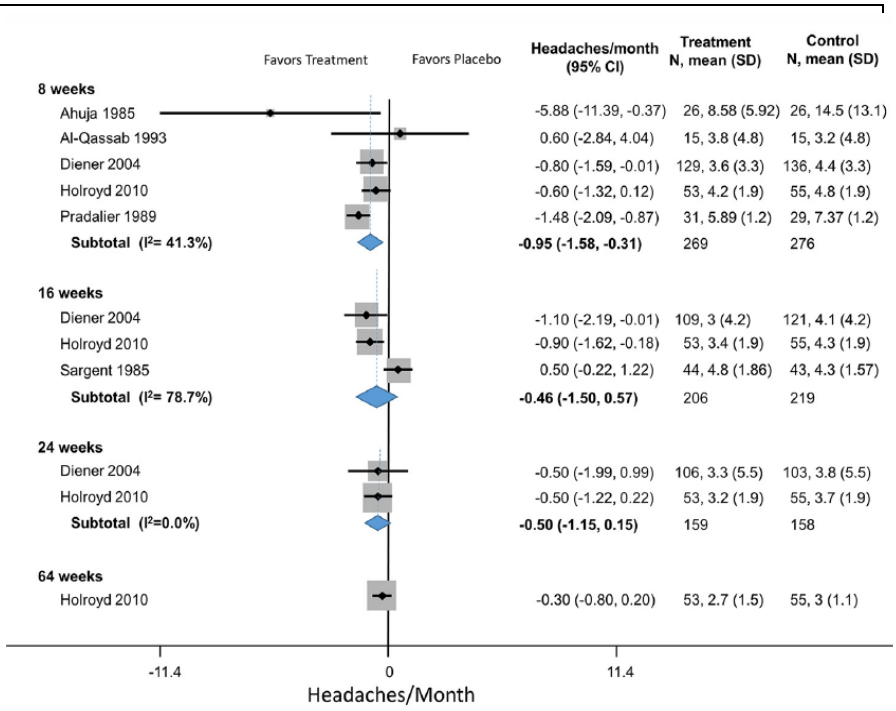


Fig 7. Propranolol compared to placebo for episodic migraine headaches.

Flunarizine

While classified as a calcium channel blocker, flunarizine has no influence on blood pressure and its side effect profile suggests that its site of action is on cellular receptors other than the calcium channel. Flunarizine is not available in the United States. There were 7 studies of episodic migraines, totaling 332 participants. Studies averaged 47 participants, 36.4 years in age, 77% women, 12.5 weeks in duration and 9% dropouts. Four studies reported headache frequency and three reported headache outcomes based on a headache index. Flunarizine was superior to placebo at 8 and 12 weeks, though not at 4 weeks. Only a single trial reported the likelihood of a 50% reduction in headache with flunarizine with insignificant results.

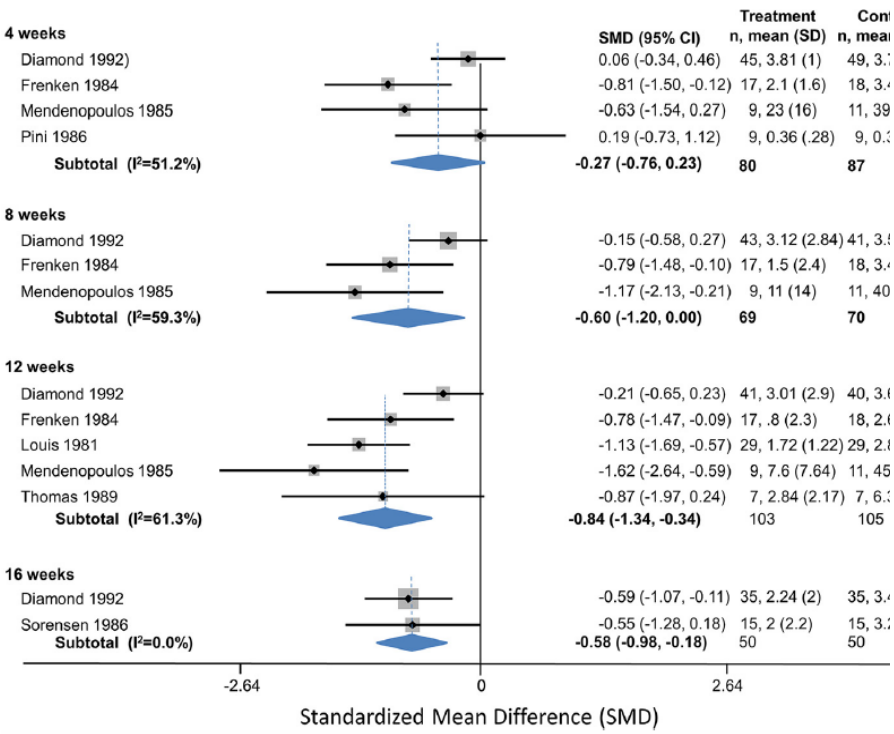


Fig 8. Flunarizine compared to placebo for episodic migraine headaches.

Comparative Effective Trials

Among beta-blockers, metoprolol was superior to clonidine, flunarizine and nifedipine and propranolol was better than femoxitine. Propranolol was equivalent to metoprolol, atenolol, nadolol as well as to flunarizine and topiramate. Among the anticonvulsants, topiramate was equivalent to flunarizine, lamotrigine and to valproate and valproate was equivalent to flunarizine.

Network Meta-analysis

Candidate drugs for the network meta-analysis were those drugs found effective for treatment of episodic migraine headaches with at least 3 randomized clinical trials. These included eleven different drugs used in prophylaxis of episodic migraine headaches. Indirect comparisons of these eleven individual drugs using meta-regression suggested that amitriptyline was more effective than several of the other drugs including candesartan (p = 0.04), fluoxetine (p = 0.03), propranolol (p = 0.009), topiramate (p = 0.005) and valproate (p = 0.009, Fig 12), and no different than atenolol (p = 0.20), flunarizine (p = 0.06), clomipramine (p = 0.15) or metoprolol (p = 0.15). The network meta-analysis found no differences between the other drugs in the relative effectiveness in the prophylaxis against migraine headaches. (p = 0.21).

4. Anmerkungen/Fazit der Autoren

Our data suggests that the current practice of tailoring prophylactic

	medication according to patient characteristics and expected side effects is a good approach. Patients with migraine headaches and hypertension should consider trials with a beta blocker. Patients with depression may benefit from either SSRI or TCA. Patients with restless leg syndrome or another indication for an anticonvulsant may benefit from topiramate or valproate. Our analysis suggests that amitryptyline is more effective than the other medications, this has not been confirmed in the limited number of direct comparative effectiveness trials that have been conducted. The placebo effect, that lasts through at least 12 weeks in our study, suggests that non-placebo controlled trials should not be performed. Nearly all studies of headache treatment were 24 weeks or less in duration, this is an important limitation since migraine is a chronic condition. **5. Kommentare zum Review** In der Netzwerk-Metanalyse sind auch Wirkstoffe eingeschlossen, die auf dem deutschen Markt keine Zulassung haben.
Mulleners WM et al., 2015 [8]. Antiepileptics in migraine prophylaxis: an updated Cochrane review.	1. Fragestellung The efficacy of several antiepileptics in the preventive treatment of episodic migraine in adults has been systematically reviewed. Because many trial reports have been published since then, an updated systematic review was warranted.
	2. Methodik **Population**: prevention of migraine; adults 16 years or older **Intervention**: Only drugs used for the treatment of epilepsy or status epilepticus, commercially available and suitable for outpatient use in either Europe or the United States (US) were considered. **Komparator**: placebo, no intervention, active drug or non-pharmacological treatments (with proven efficacy), and same drug treatments with a clinically relevant different dose. **Endpunkte**: headache frequency (both in continuous and dichotomous format), quality of life and adverse, events (AEs), obtained directly from patients, were collected. **Suchzeitraum** (Aktualität der Recherche): 1966 - 01/2013 **Anzahl eingeschlossene Studien/Patienten** (Gesamt): **Qualitätsbewertung der Studien**: durchgeführt und Ergebnisse dargestellt, jedoch Instrument nicht benannt
	3. Ergebnisdarstellung **Topiramat** The combined analysis of nine trials showed a significant reduction

	in headache frequency in the active group compared to placebo of about one attack per 28 days. Likewise, patients were twice as likely to experience a ≥50% reduction in frequency with topiramate as with placebo. The 100 and 200mg target doses were significantly superior to 50 mg in both outcomes, but did not differ from each other. The combined analyses of two studies found favorable results of topiramate across dose ranges for quality of life on various domains of the disease-specific MSQ, but the generic SF-36 was more equivocal (only two of 24 analyses pointed in this direction). Seven trials examined several doses of topiramate against active comparators (amitriptyline 50–100mg), flunarizine 5mg , propranolol 80mg and 160mg, sodium valproate 400mg and relaxation therapy. Mean headache frequencies demonstrated a slight but significant advantage for topiramate over valproate, and relaxation was superior in change from baseline in MSQ. It should be noted that most of these studies were probably not powered to detect superiority of any compound, and that the doses in some studies were lower than those used in routine clinical management.

Table 2. Topiramate main outcomes.

Efficacy against placebo			
Responders (OR (95% CI))	3.18 (2.10, 4.82)		
Frequency (MD (95% CI))	−1.20 (−1.59, −0.80)		
Dose ranges vs placebo			
Responders (OR (95% CI))			
daily dose titrated up to			
50 mg	100.0 %	2.35 [1.60, 3.44]	
100 mg	100.0 %	3.49 [2.23, 5.45]	
200 mg	100.0 %	2.49 [1.61, 3.87]	
	0.01 0.1 1 10 100		
	Favors placebo Favors topiramate		
Frequency (MD (95% CI))			
daily dose titrated up to			
50 mg	100.0 %	-0.95 [-1.95, 0.04]	
100 mg	100.0 %	-1.15 [-1.58, -0.71]	
200 mg	100.0 %	-0.94 [-1.53, -0.36]	
	-4 -2 0 2 4		
	Favors topiramate Favors placebo		
Quality of life			
	Daily dose titrated up to		
	50 mg/d (MD (95% CI))	100 mg/d (MD (95% CI))	200 n (MD
MSQ-role function restrictive	5.83 (2.25, 9.41)	10.08 (6.55, 13.60)	10.36
MSQ-role function preventive	ns	6.39 (3.37, 9.41)	5.06
MSQ-emotional function	4.58 (0.61, 8.54)	10.22 (6.31, 14.14)	8.45
SF-36 role physical	ns	ns	8.59
SF-36 bodily pain	4.35 (0.04, 8.66)	ns	ns
AEs			
	Daily dose titrated up to		
	50 mg/d (NNH (95% CI))	100 mg/d (NNH (95% CI))	200 n (NNI
Any AE	ns	11 (7, 33)	5 (3,
Anorexia	ns	17 (10, 50)	12 (8
Fatigue	ns	25 (17, 100)	12 (8
Memory problems	ns	25 (17, 100)	12 (9
Nausea	ns	ns	17 (9
Paresthesia	ns	3 (2, 6)	2 (2,
Taste disturbance	7 (5, 14)	14 (8, 100)	7 (5,
Weight loss	25 (14, 100)	17 (11, 33)	11 (8
Withdrawals due to AE	2%–17%	8%–29%	11%–

MSQ: Migraine-Specific Quality of Life Questionnaire; MD: mean difference; OR: odds ratio; CI: confidence interval; SF-36: Medical C 36-item Short-Form Health Survey; NNH: numbers-needed-to-harm; AE: adverse event; ns: not significant.

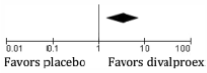
Valproat

Two cross-over trials of sodium valproate showed a significant reduction in headache frequency in the active compared to the placebo group of approximately four headaches per 28 days. Four placebo-controlled divalproex sodium trials showed that with active treatment patients are twice as likely to experience a >50% reduction in headache frequency. One trial found that sodium valproate was significantly superior to placebo for this outcome. We have not identified any placebo-controlled studies reporting quality-of-life outcome measures. Comparisons with flunarizine and propranolol were not significantly different between treatments.

Table 3. Valproate main outcomes.

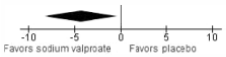
Efficacy

Responders (OR (95% CI))



100% 3.34 [1.46, 7.67]

Frequency (MD (95% CI))



100% −4.31 [−8.32, −030]

Dose ranges: no pooled data

Quality of life

No pooled data

AEs

	NNH (95% CI)
Any AE	ns
Asthenia/fatigue	ns
Dizziness/vertigo	14 (8, 100)
Nausea	7 (4, 25)
Tremor	14 (8, 100)
Weight gain	ns
Withdrawal due to AE	8%–19%

MD: mean difference; OR: odds ratio; CI: confidence interval; NNH: numbers-needed-to-harm; AE: adverse event; ns: not significant.

AE rates for sodium valproate and divalproex sodium were higher than for placebo and resulted in withdrawal rates between 8% and 19%.

4. Anmerkungen/Fazit der Autoren

Both sodium valproate and topiramate significantly reduce mean monthly headache frequency approximately four and one days, respectively. Patients are more than twice as likely to have a >50% reduction in headache frequency with divalproex sodium or topiramate than with placebo. Topiramate significantly improves quality of life compared to placebo

It can be concluded from this review that sodium valproate, divalproex sodium, and topiramate are of proven efficacy in migraine prevention and are suitable for routine clinical use. Convincing evidence for efficacy differences with amitriptyline, flunarizine, propranolol or relaxation is lacking, although topiramate may be marginally better than valproate. One important caveat should be noted: These drugs are known to or may be teratogenic, and appropriate caution must be used when prescribing to women of child-bearing age.

Although AEs are reported by a large proportion of migraine patients treated with sodium valproate/divalproex sodium or topiramate, these are usually mild and of a non-serious nature. On a case-to-case basis, rational prescriber preferences may be appreciated because of differences in side effect profiles.

<table>
<tr><td></td><td>5. Kommentare zum Review

Heterogenität unzureichend dargestellt</td></tr>
<tr><td rowspan="3">Shamliyan TA et al., 2013 [11].

Migraine in Adults: Preventive Pharmacologic Treatments.</td><td>1. Fragestellung

Systematic review of preventive pharmacologic treatments for community-dwelling adults with episodic migraine.</td></tr>
<tr><td>2. Methodik

Population: Erwachsene mit episodischer oder chronischer Migräne
Intervention: pharmakologische und nicht-pharmakologische Prophylaxemaßnahmen
Komparator: Placebo, aktive Kontrolle, keine Kontrolle
Endpunkt: Reduktion der Migränehäufigkeit um ≥50%, QoL, Nebenwirkungen
Suchzeitraum (Aktualität der Recherche): Suche in Medline, Cochrane Library und SCIRUS bis Mai 2012
Anzahl eingeschlossene Studien/Patienten (Gesamt): 245 RCTs, 76 nicht randomisierte Studien
Qualitätsbewertung der Studien: Bewertung der Studienqualität mittels Cochrane Risk of Bias Tool.</td></tr>
<tr><td>3. Ergebnisdarstellung

Pharmakologische Prophylaxe vs. Placebo

<table>
<tr><th>Active Preventive Treatment</th><th>Outcome</th><th>Sample</th><th>Relative Risk (95% CI)</th><th>Absolute Risk Difference (95% CI)</th><th>Strength o (Reasons f SO</th></tr>
<tr><td>Onabotulinumtoxin A for chronic migraine</td><td>≥50% decrease in migraine frequency</td><td>459</td><td>1.5 (1.2 to 1.8)</td><td>0.17 (0.08 to 0.26)</td><td>Low (medium RO imprecision)</td></tr>
<tr><td>Topiramate 50 to 200mg/day for episodic migraine</td><td>100% decrease in migraine frequency</td><td>1,299</td><td>1.9 (1.0 to 3.4)</td><td>0.02 (-0.01 to 0.05)</td><td>Low (medium RO inconsistency</td></tr>
<tr><td>Topiramate for episodic migraine</td><td>≥75% reduction in monthly migraine days</td><td>1,086</td><td>1.9 (1.1 to 3.1)</td><td>0.10 (-0.01 to 0.20)</td><td>Moderate (imprecision)</td></tr>
<tr><td>Topiramate 50 to 200mg for episodic migraine</td><td>≥50% reduction in monthly migraine days</td><td>1,145</td><td>1.7 (1.0 to 2.9)</td><td>0.18 (0.08 to 0.28)</td><td>Moderate (imprecision</td></tr>
<tr><td>Topiramate 50 to 200mg/day for episodic migraine</td><td>≥50% reduction in monthly migraine frequency</td><td>1,422</td><td>2.0 (1.5 to 2.7)</td><td>0.29 (0.18 to 0.40)</td><td>Moderate (medium RO</td></tr>
<tr><td>Divalproex for episodic migraine</td><td>≥50% decrease in migraine frequency</td><td>405</td><td>2.2 (1.1 to 4.2)</td><td>0.24 (0.10 to 0.38)</td><td>Low (medium RO imprecision)</td></tr>
<tr><td>Propranolol for episodic migraine</td><td>≥50% decrease in migraine frequency</td><td>541</td><td>2.0 (1.5 to 2.7)</td><td>0.22 (0.14 to 0.30)</td><td>Low (medium RO imprecision)</td></tr>
<tr><td>Timolol for episodic migraine</td><td>≥50% decrease in migraine frequency</td><td>276</td><td>2.1 (1.5 to 3.1)</td><td>0.27 (0.15 to 0.38)</td><td>Low (medium RO imprecision)</td></tr>
<tr><td>Gabapentin for episodic migraine</td><td>≥50% decrease in migraine frequency</td><td>270</td><td>1.5 (1.1 to 2.0)</td><td>0.17 (0.06 to 0.27)</td><td>Low (medium RO imprecision)</td></tr>
</table>
</td></tr>
</table>

	<table><tr><th>Active Preventive Treatment</th><th>Outcome</th><th>Sample</th><th>Relative Risk (95% CI)</th><th>Absolute Risk Difference (95% CI)</th><th>Strength o (Reasons f SO</th></tr><tr><td>Metoprolol for episodic migraine</td><td>≥50% decrease in migraine frequency</td><td>225</td><td>2.0 (1.3 to 3.2)</td><td>0.20 (0.09 to 0.3)</td><td>Low (medium RO imprecision)</td></tr><tr><td>Nimodipine for episodic migraine</td><td>≥50% decrease in migraine frequency</td><td>126</td><td>4.5 (0.5 to 40.1)</td><td>0.23 (0.06 to 0.39)</td><td>Low (medium RO imprecision)</td></tr><tr><td>Magnesium for episodic migraine</td><td>≥50% decrease in migraine frequency</td><td>137</td><td>1.3 (0.7 to 2.3)</td><td>0.08 (-0.09 to 0.26)</td><td>Low (inconsistenc imprecision)</td></tr></table> CI = confidence interval; NS = Not significant; ROB = risk of bias; SOE = strength of evidence Bold = significant effects of drugs on treatment response when 95% CI of attributable events per 1,000 treated do not include 0. Number needed to treat and number of attributable events were calculated for statistically significant differences. **Pharmakologische Prophylaxe vs. pharmakologische Kontrolle** Kein statistisch signifikanter Unterschied für Metoprolol vs. Propranolol **Nebenwirkungen:** Statistisch signifikant höhere Abbruchrate im Vergleich zu Placebo bei Topiramat, Propranolol, Amitriptylin. Kein statistisch signifkanter Unterschied der Abbruchrate im Vergleich zu Placebo bei Valproinsäure
	4. Anmerkungen/Fazit der Autoren • For chronic migraine, onabotulinumtoxin A was more effective than placebo in reducing monthly chronic migraine attacks by ≥50 percent with inconsistent improvement in quality of life. • For episodic migraine, all approved drugs (topiramate, divalproex, propranolol, and timolol) were better than placebo in reducing monthly migraine frequency by ≥50 percent (clinical response). • Relative effect of drugs was moderate: drugs would result in clinical response in 200 to 400 patients per 1,000 treated. • Strength of evidence was low due to medium risk of bias and imprecise estimates. • Low-strength evidence from individual RCTs suggested a dose-responsive increase in migraine prevention with higher doses of onabotulinumtoxin A and topiramate (from 50 to100 mg with no additional benefits with 200 mg/day). Individual RCTs provided low-strength direct evidence about the comparative effectiveness of drugs and demonstrated few significant differences between drugs.
Shamliyan TA et al., 2013 [10]. Preventive pharmacologic	1. Fragestellung Weitere Analyse der Daten aus Shamliyan 2013 [11] Systematic literature review of the comparative effectiveness and tolerability of the available preventive medications for episodic

treatments for episodic migraine in adults.	migraine in adults in outpatient settings to inform treatment and policy decisions. The topic, research questions, and eligible interventions were nominated and posted for public comments on the Effective Healthcare website. We chose not to synthesize studies of the drug flunarizine (commonly used for adults in Europe) because the FDA has not approved it. Efficacy of non-pharmacologic preventive treatments and prevention of chronic migraine are beyond the scope of this paper.
	2. Methodik **Population**: community-dwelling adults with episodic migraine **Intervention**: preventive medications for episodic migraine. Nicht weiter deifniert **Komparator**: Nicht definiert **Endpunkte**: ≥50 % reduction in frequency of migraine attack from baseline, complete cessation of migraine attacks, migraine-related disability, and quality of life **Suchzeitraum** (Aktualität der Recherche): through May 20, 2012 **Anzahl eingeschlossene Studien/Patienten** (Gesamt): 215 RCTs, 76 non-RCTs (nicht in Analyse einbezogen): topiramate (9 RCTs), divalproex (3 RCTs), timolol (3 RCTs), and propranolol (4 RCTs), beta blockers metoprolol (4 RCTs), atenolol (1 RCT), nadolol (1 RCT), and acebutolol (1 RCT); angiotensin-converting enzyme inhibitors captopril (1 RCT) and lisinopril (1 RCT); and angiotensin II receptor blocker candesartan (1 RCT) **Qualitätsbewertung der Studien**: We evaluated the risk of bias in individual studies of benefits and harms according to: (1) random allocation of subjects to the treatment groups; (2) masking the treatment status to the participants and investigators; (3) adequacy of allocation concealment; (4) adequacy of randomization as estimated based on similarity of the subjects in treatment groups by demographics and by frequency and severity of migraine; (5) planned and executed intention-to-treat principles; and 6) selective outcome reporting when compared with the articles' protocols (when available) and methods sections. We assumed a low risk of bias when RCTs met all risk of-bias criteria, a medium risk of bias if one criterion was not met, and a high risk of bias if two or more criteria were not met. We concluded an unknown risk of bias for studies with poorly reported risk-of-bias criteria.
	3. Ergebnisdarstellung More than half of the RCTs had a medium risk of bias

Enrolled patients were mostly overweight and had an average of five monthly migraine attacks with or without aura. Almost half of enrolled subjects were naïve to migraine-preventive drugs.

Efficacy for Prevention of Episodic Migraine

All approved drugs were better than placebo in reducing monthly migraine frequency by ≥50 % in individual patients (clinical response). Drugs would achieve a clinical response in 200 to 400 patients per 1,000 treated. We analyzed dose–response associations and found that an increase in target topiramate dose from 50 to 100 mg/day but not from 100 to 200 mg/ day resulted in a higher response rate (≥50 % reduction in monthly migraine frequency).

Migraine Prevention with Approved Pharmacologic Preventive Treatments vs. Placebo in Adults, Results from Randomized Controlled Clinical Trials (Random Effects Models)

Active drug	References	Sample	% with outcome with active drug [placebo]	Relative risk (95 % CI)
Antiepileptics				
Divalproex >50 % reduction on migraine frequency	**Pooled**[79,115,116]	**405**	**43.0 [23.3]**	**2.2 (1.1 to 4.2)**
	P value			**0.12**
	I squared			**0.52**
Topiramate on >50 % reduction on migraine frequency	**Pooled**[72,82,95,117–120]	**1422**	**49.6 [25.1]**	**2.0 (1.5 to 2.7)**
	P value			**0.04**
	I squared			**0.56**
Topiramate on >50 % reduction on migraine days	**Pooled**[77,82,121]	**1145**	**42.2 [23.3]**	**1.7 (1.0 to 2.9)**
	P value			**0.01**
	I squared			**0.77**
Topiramate on ≥75 % reduction in migraine days	Pooled[82,121]	1086	22.3 [11.0]	1.9 (1.1 to 3.1)
	P value			0.12
	I squared			0.58
Beta-blockers				
Propranolol >50 % reduction on migraine frequency	**Pooled**[122–125]	**541**	**45.1 [22.3]**	**2.0 (1.5 to 2.7)**
	P value			**1.00**
	I squared			**0**
Timolol ≥50 % reduction in migraine frequency	**Pooled**[122,125,126]	**276**	**49.4 [23.3]**	**2.1 (1.5 to 3.1)**
	P value			**0.73**
	I squared			**0**
Beta-blockers				
Metoprolol	**Pooled**[130–133]	**225**	**39.9 [19.4]**	**2.0 (1.3 to 3.2)**
	P value			**0.42**
	I squared			**0**

4. Anmerkungen/Fazit der Autoren

We conclude that approved drugs and off-label angiotensin-

	inhibiting drugs (lisinopril, captopril, and candesartan) or off-label beta-blockers (metoprolol, acebutolol, atenolol, and nadolol) were effective in preventing episodic migraine in adults.

Leitlinien

Simpson DM et al., 2016 [13]. Practice guideline update summary: Botulinum neurotoxin for the treatment of blepharospasm, cervical dystonia, adult spasticity, and headache: Report of the Guideline Development Subcommittee of the American Academy of Neurology.	Leitlinie der American Academy of Neurology
	Methodik Grundlage der Leitlinie: systematische Literatursuche in MEDLINE, Psyc-INFO, CINAHL und Panel Diskussion – Update Recherche zu einer LL aus dem Jahr 2008 – Suchzeitraum: 2007 - 2015 – Alle Aussagen mit Literaturstellen verknüpft – Evidenz bei >20% Dropoutrate wird herabgestuft – Leitlinie der Evidenzstufe S2e (AWMF) LoE und GoR siehe Silberstein SD et al., 2012 [12]
	Empfehlungen **Chronic migraine** The 2008 guideline found inconsistent results from 4 Class II studies comparing onaBoNT-A with placebo, resulting in insufficient evidence to support or refute a benefit of BoNT for treatment of CM.3 Comparison of BoNT with placebo. Two Class I placebo-controlled studies12,13, published since the 2008 guideline met inclusion criteria. In one study, onaBoNT-A was ineffective for changes from baseline for total headache episodes but was effective for the secondary endpoint of change in frequency of total headache days/28 days (mean intergroup difference 21.4 days, 95% CI 22.4 to 20.40). In the second study, onaBoNT-A was effective for reducing total headache days/28 days from baseline to weeks 21–24 post-treatment. Nine fewer headache days were seen in the BoNT-A group, with 6.7 in the placebo group (p, 0.001). In both studies the placebo response was high. Several follow-up reports describing pooled analyses of both Class I studies have been published. One Class I follow-up report14 described significant reduction in headache impact and improvement in health-related QOL after 24 weeks of double-blind treatment (proportion of patients with severe Headache Impact Test scores 67.6% of patients given BoNT vs 78.2% of patients given placebo, p , 0.001). Comparison of BoNT with other headache preventive treatments. One Class III study15 demonstrated similar efficacy for onaBoNT-A and topiramate in CM. No other studies comparing oral preventive medications with BoNT injections met inclusion criteria. There also are no studies comparing different BoNT serotypes in headache. AEs of onaBoNT-A included neck pain and muscle weakness. Conclusions. OnaBoNT-A is established as safe and effective for reducing the number of headache days in CM (2 Class I studies) and probably effective for improving health-related QOL (1 Class I study). There is insufficient evidence to compare the effectiveness of BoNT with that of oral prophylactic topiramate. No Class I or II studies of

	other formulations of BoNT in CM have been published. **Recommendations:** OnaBoNT-A should be offered as a treatment option to patients with CM to increase the number of headache-free days (Level A) and should be considered to reduce headache impact on health-related QOL (Level B). Clinical context. Although the reduction of headache days with onaBoNT-A was statistically superior to placebo in 2 Class I studies, the magnitude of the difference is small (1.7 and 2.3). Naumann M, So Y, Argoff CE, et al; for the Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology. Assessment: botulinum toxin in the treatment of autonomic disorders and pain (an evidence-based review): report of the Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology. Neurology 2008;70:1707–1714. Aurora SK, Dodick DW, Turkel CC, et al.; PREEMPT 1 Chronic Migraine Study Group. OnabotulinumtoxinA for treatment of chronic migraine: results from the double-blind, randomized, placebo-controlled phase of the PREEMPT 1 trial. Cephalalgia 2010;30:793-803. Diener HC, Dodick DW, Aurora SK, et al.; PREEMPT 2 Chronic Migraine Study Group. OnabotulinumtoxinA for treatment of chronic migraine: results from the double-blind, randomized, placebo-controlled phase of the PREEMPT 2 trial. Cephalalgia 2010;30:804-814. Lipton RB, Varon SF, Grosberg B, et al. OnabotulinumtoxinA improves quality of life and reduces impact of chronic migraine. Neurology 2011;77;1465-1472. Cady RK, Schreiber CP, Porter JA, Blumenfeld AM, Farmer KU. A multi-center double-blind pilot comparison of onabotulinumtoxinA and topiramate for the prophylactic treatment of chronic migraine. Headache 2011;51: 21-32. **Episodic migraine** The 2008 guideline conclusion,3 based on 2 Class I and 2 Class II studies, indicates onaBoNT-A injection is probably ineffective for treatment of EM. One Class I study16 published since the 2008 guideline compared onaBoNT-A at doses of 75 U, 150 U, and 225 U with placebo, using 3 treatment cycles 3 months apart. OnaBoNT-A was ineffective for reducing migraine frequency from baseline to day 180. Conclusion. OnaBoNT-A is ineffective for the treatment of EM (3 Class I studies, 2 from the 2008 report). **Recommendation:** OnaBoNT-A should not be offered as a treatment for EM (Level A). Relja M, Poole AC, Schoenen J, Pascual J, Lei X, Thompson C;

<table>
<tr><td></td><td>European BoNTA Headache Study Group. A multicentre, double-blind, randomized, placebo-controlled, parallel group study of multiple treatments of botulinum toxin type A (BoNTA) for the prophylaxis of episodic migraine headaches. Cephalalgia 2007;27:492-503.</td></tr>
<tr><td rowspan="2">National Clinical Guideline Centre (NCGC), 2012 [9].

Headaches: Diagnosis and management of headaches in young people and adults

NICE Clinical Guideline; Band 150

Last update: 2015</td><td>Vielfältige Fragestellungen zur Kopfscherzdiagnostik und –behandlung; hier relevant:

<table>
<tr><th>Chapter</th><th>Review questions</th><th>Outcomes</th></tr>
<tr><td>Management:

Prophylactic</td><td>In migraine with or without aura and chronic migraine, what is the clinical evidence and cost-effectiveness for</td><td>• Change in patient-reported headache days, frequency and intensity</td></tr>
<tr><td>pharmacological treatment of migraine</td><td>prophylactic pharmacological treatment with: ACE inhibitors and angiotensin II receptor antagonists (ARBs), antidepressants (SNRIs, SSRIs, tricyclics), beta blockers, calcium channel blockers, antiepileptics and other serotonergic modulators?</td><td>• Responder rate
• Functional health status and health-related quality of life Headache specific quality of life
• Resource use
• Use of acute pharmacological treatment
• Incidence of serious adverse events.</td></tr>
</table>

Commissioned by the National Institute for Health and Clinical Excellence</td></tr>
<tr><td>Methodik

A multidisciplinary Guideline Development Group (GDG) comprising professional group members and consumer representatives of the main stakeholders developed this guideline (see section on Guideline Development Group Membership and acknowledgements). The National Institute for Health and Clinical Excellence funds the National Clinical Guideline Centre (NCGC) and thus supported the development of this guideline.

The group met every 5-6 weeks during the development of the guideline. At the start of the guideline development process all GDG members declared interests including consultancies, fee-paid work, share-holdings, fellowships and support from the healthcare industry. At all subsequent GDG meetings, members declared arising conflicts of interest, which were also recorded (Appendix B).

Staff from the NCGC provided methodological support and guidance for the development process. The team working on the guideline included a project manager, systematic reviewers, health economists and information scientists. They undertook systematic searches of the literature, appraised the evidence, conducted meta-analysis and cost effectiveness analysis where appropriate and drafted the guideline in collaboration with the GDG.

Literatursuche bis 03/2012

GoR:</td></tr>
</table>

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.

Empfehlungen

Fragestellung: In people with migraine with or without aura, what is the clinical evidence and cost-effectiveness for prophylactic pharmacological treatment with: ACE inhibitors and ARBs; antidepressants; beta blockers; calcium channel blockers; antiepileptics; and other serotonergic modulators?

Recommendations	**Offer topiramate[hh] or propranolol 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 both topiramate[hh] and propranolol are unsuitable or ineffective, consider a course of up to 10 sessions of acupuncture over 5–8 weeks or gabapentin[ii] (up to 1200 mg per day) according to the person's preference, comorbidities and risk of adverse events.**

Topiramat

- Six studies with 1886 people with migraine showed that topiramate is more clinically effective than placebo at increasing responder rate at 26 week follow-up. [Low quality].
- Six studies with 2058 people with migraine showed that topiramate is more effective than placebo in reducing migraine days at 26 weeks follow-up, but the effect size is too small to be clinically important. [Moderate quality].

	• Four studies with 1345 people with migraine suggested that topiramate may be more effective than placebo in reducing migraine frequency at 26 weeks follow-up, but the effect size is too small to be clinically important, and there is considerable uncertainty. [Low quality]. • One study with 107 people with migraine showed that there is no difference between topiramate and placebo in reducing migraine intensity at 26 week follow-up. [High quality]. • Two studies with 713 people with migraine suggested that topiramate may be more effective than placebo in reducing MIDAS score at 26 week follow-up, but the effect size is too small to be clinically important and there is some uncertainty. [Moderate quality]. • Two studies with 713 people with migraine suggested that fewer adverse events occur with topiramate than placebo, but there is considerable uncertainty. [Low quality]. • Four studies with 1497 people with migraine showed that topiramate is more effective than placebo in reducing the use of acute medication at 26 week follow-up, but the effect size is too small to be clinically important. [Low quality]. • No studies reported outcome data for functional health status or resource use. **Divalproex** • One study with 305 people with migraine showed that there is no difference between divalproex and placebo in reducing the mean number of migraine days per month when assessed at 12 weeks follow-up. [Low quality]. • One study with 305 people with migraine showed that there is no difference between divalproex and placebo in reducing the mean number of migraines per month when assessed at 12 weeks follow-up. [Low quality]. • Three studies with 588 people with migraine suggested that divalproex may be more clinically effective than placebo at increasing responder rate in people with migraine when assessed at 12 weeks follow-up, but there is some uncertainty. [Very low quality]. • One study with 239 people with migraine suggested that fewer serious adverse events occur with divalproex than placebo when assessed at 12 weeks follow-up, but there is considerable uncertainty. [Very low quality]. • No studies reported outcome data for change in patient-reported migraine intensity, functional health status and health-related quality of life, resource use or use of acute pharmacological treatment.

	Topiramate vs sodium valproate • One study with 76 people suggested that there is no difference between topiramate and sodium valproate in reducing migraine severity at 12 weeks follow-up, but there is considerable uncertainty. [Low quality]. • One study with 76 people suggested that topiramate may be more clinically effective than sodium valproate in reducing migraine severity at 12 weeks follow-up, but there is considerable uncertainty. [Low quality]. • No studies reported outcome data for responder rate, change in patient-reported migraine days, functional health status and health-related quality of life, resource use, use of acute pharmacological treatment or incidence of serious adverse events. **Beta-Blockers / Propranolol** • One study with 290 people with migraine suggested that beta blockers may be more clinically effective than placebo at improving responder rate at 26 weeks follow-up, but there is some uncertainty. [Moderate quality] • In one study with 108 people with migraine there is too much uncertainty to determine whether there is a difference between beta blocker and placebo in responder rate at 10 months follow-up. [Low quality]. • One study with 290 people with migraine suggested that beta blockers may be more effective than placebo in reducing the number of migraine days at 26 weeks follow-up, but the effect size is too small to be clinically important and there is some uncertainty. [Low quality]. • One study with 108 people with migraine suggested that beta blockers may be more effective than placebo in reducing the number of migraine days at 10 months follow-up, but the effect size is too small to be clinically important and there is some uncertainty. [Moderate quality]. • One study with 108 people with migraine suggested that there is no difference between beta blockers and placebo may in reducing the number of migraine days at 16 months follow-up, but there is some uncertainty. [Moderate quality]. • Three studies with 590 people with migraine showed that beta blockers are more effective than placebo in reducing migraine frequency at 12 and 26 weeks follow-up. [Low quality]. • One study with 108 people with migraine showed that there is no difference between beta blockers and placebo in reducing migraine frequency at 10 months follow-up. [High quality]. • One study with 108 people with migraine showed that there is no difference between beta blockers and placebo in reducing migraine frequency at 16 months follow-up. [High quality].

	• One study with 108 people with migraine showed that there is no difference between beta blockers and placebo in improving migraine specific quality of life (assessed by MSQL) at 10 months follow-up. [High quality]. • One study with 108 people with migraine showed that there is no difference between beta blockers and placebo in improving migraine specific quality of life (assessed by MSQL) at 16 months follow-up. [High quality]. • No studies reported outcome data for change in patient reported migraine intensity, resource use, use of acute pharmacological treatment or incidence of serious adverse events. **Topiramate vs beta blocker (propranolol)** • One study with 575 people with migraine suggested that there is no difference between beta blockers and topiramate at increasing responder rate at 26 weeks follow-up, but there is some uncertainty. [Low quality]. • One study with 575 people with migraine showed that there is no difference between beta blockers and topiramate in reducing the number of migraine days at 26 weeks follow-up, but there is some uncertainty. [Moderate quality]. • One study with 575 people with migraine showed that there is no difference between beta blockers and topiramate in reducing migraine frequency at 26 weeks follow-up. [Moderate quality]. • One study with 575 people with migraine showed that there is no difference between beta blockers and topiramate in reducing the use of rescue medication at 26 weeks follow-up. [Moderate quality]. • No studies reported outcome data for change in patient reported migraine intensity, functional health status or health-related quality of life, resource use or incidence of serious adverse events. **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]** • 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]** • 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]** • 1.3.19 Do not offer gabapentin for the prophylactic treatment of migraine. **[new 2015]** • 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]** • 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]** • 1.3.22 Review the need for continuing migraine prophylaxis 6 months after the start of prophylactic treatment. **[2012]** • 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]**

Detaillierte Darstellung der Recherchestrategie

Cochrane Library (Cochrane Database of Systematic Reviews, Health Technology Assessment Database) am 04.01.2018

#	**Suchfrage**
1	MeSH descriptor: [Migraine Disorders] explode all trees
2	migrain*:ti,ab,kw (Word variations have been searched)
3	#1 or #2
4	#3 Publication Year from 2013 to 2018, in Cochrane Reviews (Reviews only) and Technology Assessments

SR, HTAs in Medline (PubMed) am 04.01.2018

#	**Suchfrage**
1	migraine disorders[MeSH Terms]
2	migrain*[Title/Abstract]
3	#1 OR #2
4	(#3) AND ((Meta-Analysis[ptyp] OR systematic[sb] OR Technical Report[ptyp]) OR (((((trials[Title/Abstract] OR studies[Title/Abstract] OR database*[Title/Abstract] OR literature[Title/Abstract] OR publication*[Title/Abstract] OR Medline[Title/Abstract] OR Embase[Title/Abstract] OR Cochrane[Title/Abstract] OR Pubmed[Title/Abstract])) AND systematic*[Title/Abstract] AND (search*[Title/Abstract] OR research*[Title/Abstract]))) OR ((((((((((HTA[Title/Abstract]) OR technology assessment*[Title/Abstract]) OR technology report*[Title/Abstract]) OR (systematic*[Title/Abstract] AND review*[Title/Abstract])) OR (systematic*[Title/Abstract] AND overview*[Title/Abstract])) OR meta-analy*[Title/Abstract]) OR (meta[Title/Abstract] AND analyz*[Title/Abstract])) OR (meta[Title/Abstract] AND analys*[Title/Abstract])) OR (meta[Title/Abstract] AND analyt*[Title/Abstract]))) OR (((review*[Title/Abstract]) OR overview*[Title/Abstract]) AND ((evidence[Title/Abstract]) AND based[Title/Abstract]))))
5	(#4) AND ("2013/01/01"[PDAT] : "2018/01/04"[PDAT])

Leitlinien in Medline (PubMed) am 04.01.2018

#	Suchfrage
1	migraine disorders[MeSH Terms]
2	headache disorders, primary[MeSH Major Topic]
3	migrain*[Title/Abstract]
4	#1 OR #2 OR #3
5	(#4) AND ((Guideline[ptyp] OR Practice Guideline[ptyp] OR Consensus Development Conference[ptyp] OR Consensus Development Conference, NIH[ptyp]) OR ((guideline*[Title] OR recommendation*[Title]) NOT (letter[ptyp] OR comment[ptyp])))
6	(#5) AND ("2013/01/01"[PDAT] : "2018/01/04"[PDAT])

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