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-022 Fremanezumab

Stand: Mai 2017

Gemeinsamer Bundesausschuss

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

Fremanezumab zur 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: 08.06.2016): Off-Label Indikation für Valproinsäure: Migräneprophylaxe im Erwachsenenalter (Beschluss des G-BA vom 16. September 2010) • Anlage VII zum Abschnitt M der Arzneimittel-Richtlinie - Regelungen zur Austauschbarkeit von Arzneimitteln (aut idem): Valproinsäure in der Darreichungsform Retardtabletten (auch als Natriumvalproat und Valproinsäure in Kombination mit Natriumvalproat): Ausschluss einer Ersetzung durch ein wirkstoffgleiches Arzneimittel (Beschluss des G-BA vom 21. April 2016)
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:	
Fremanezumab kein ATC-Code	
Metoprolol C07AB02 (generisch)	– Migräneprophylaxe (Metoprolol Succinat-CT 47,5 mg/ 95 mg/190 mg Retardtabletten)
Propranololhydrochlorid C07AA05 (generisch)	– Migräneprophylaxe (Propranolol-GRY® 40 mg Tabletten)
Flunarizin N07CA03 (generisch)	Zur Prophylaxe bei diagnostisch abgeklärter, einfacher und klassischer Migräne bei Patienten mit häufigen und schweren Migräneanfällen, wenn die Behandlung mit Beta-Rezeptorenblockern kontraindiziert ist oder keine ausreichende Wirkung gezeigt hat.
Topiramat N03AX11 (generisch)	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® Allergan	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).

Quellen: AMIS-Datenbank, Fachinformationen

Gemeinsamer Bundesausschuss

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

Inhalt

Systematische Recherche:

Es wurde eine systematische Literaturrecherche nach systematischen Reviews, Meta-Analysen, HTA-Berichten und Evidenz-basierten systematischen Leitlinien zur Indikation Migräneprophylaxe durchgeführt. Der Suchzeitraum wurde auf die letzten 5 Jahre eingeschränkt und die Recherche am 16.03.2016 abgeschlossen. Die Suche erfolgte in folgenden 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 642 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 17 Quellen, die in die synoptische Evidenz-Übersicht aufgenommen wurden.

Indikation:

Prophylaxe von Kopfschmerzen bei Erwachsenen mit chronischer oder episodischer Migräne, die auf prophylaktische Medikation nur unzureichend angesprochen oder diese nicht vertragen haben

Abkürzungen:

AE	Unerwünschte Ereignisse (Adverse Events)
AED	Antiepileptika (Anti-Epileptic-Drugs)
AWMF	Arbeitsgemeinschaft der wissenschaftlichen medizinischen Fachgesellschaften
BoNT	Botulinum-Neurotoxin
CI	Konfidenzintervall (Confidence Interval)
CM	Chronische Migräne
CrI	Credible Interval
EM	Episodische Migräne
G-BA	Gemeinsamer Bundesausschuss
GIN	Guidelines International Network
GoR	Grade of Recommendation
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen
LoE	Level of Evidence
MAM	Menstrually Associated Migraine
MD	Mean Difference
MIDAS	Migraine Disability Assessment
MSQ	Migraine-Specific Quality of Life Questionnaire
NGC	National Guideline Clearinghouse
NICE	National Institute for Health and Care Excellence
NMA	Netzwerk-Metaanalyse
OnaBoNT	Onabotulinumtoxin
OR	Odds Ratio
QoL	Lebensqualität
RR	Relatives Risiko
SEM	Standardfehler (Standard Error of the Mean)
SIGN	Scottish Intercollegiate Guidelines Network
TRIP	Turn Research into Practice Database
UE	Unerwünschte Ereignisse
VAS	Visuelle Analogskala (Visual Analogue Scale)
WHO	World Health Organization

Gemeinsamer Bundesausschuss (G-BA), 2010 [2]. 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), 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 [1]. 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.“

Linde M et al., 2013 [8].

Topiramate for the prophylaxis of episodic migraine in adults.

Cochrane Database of Systematic Reviews

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

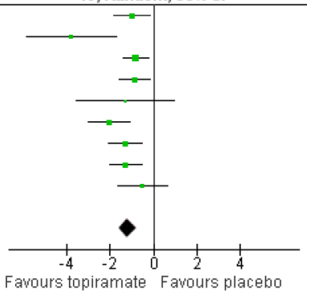
9 RCTs mit hohem Risk of Bias

Topiramat vs. Placebo

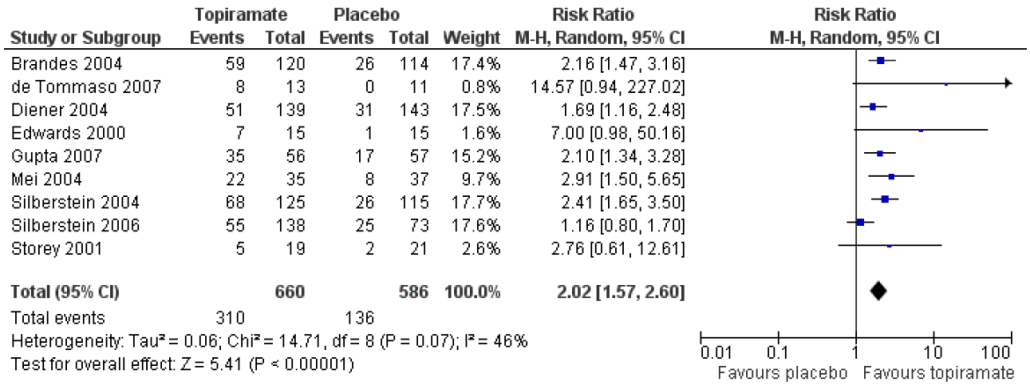
Kopfschmerzhäufigkeit (9 Studien, 1737 Patienten): statistisch signifikanter Unterschied zugunsten von Topiramat vs. Placebo (mean difference (MD) -1.20; 95% confidence interval (CI) -1.59 to -0.80; I^2=39%). Statistisch signifikanter Vorteil für alle Dosierungen (50mg-200mg)

	Topiramate			Placebo				Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	IV, Random, 95% CI
Brandes 2004	3.5	3.5	120	4.5	2.9	114	13.1%	-1.00 [-1.82, -0.18]	
de Tommaso 2007 (1)	4.5	1.5	13	8.3	3.2	11	3.3%	-3.80 [-5.86, -1.74]	
Diener 2004 (2)	-1.6	2.6	139	-0.8	2.5	143	18.0%	-0.80 [-1.40, -0.20]	
Diener 2007 (3)	4.97	3.85	253	5.82	4.36	257	15.2%	-0.85 [-1.56, -0.14]	
Edwards 2000	2.63	2.54	9	3.92	2.63	11	2.7%	-1.29 [-3.56, 0.98]	
Gupta 2007	-4.21	2.63	56	-2.16	2.71	57	10.5%	-2.05 [-3.03, -1.07]	
Lipton 2011	-6.6	3.5	159	-5.3	3.6	171	14.2%	-1.30 [-2.07, -0.53]	
Silberstein 2004	3.3	2.9	125	4.6	3	115	14.5%	-1.30 [-2.05, -0.55]	
Storey 2001	3.31	1.65	19	3.83	2.06	21	8.5%	-0.52 [-1.67, 0.63]	
Total (95% CI)			**893**			**900**	**100.0%**	**-1.20 [-1.59, -0.80]**	

Heterogeneity: Tau² = 0.13; Chi² = 13.16, df = 8 (P = 0.11); I² = 39%
Test for overall effect: Z = 5.95 (P < 0.00001)



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)



Study or Subgroup	Topiramate Events	Total	Placebo Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Brandes 2004	59	120	26	114	17.4%	2.16 [1.47, 3.16]
de Tommaso 2007	8	13	0	11	0.8%	14.57 [0.94, 227.02]
Diener 2004	51	139	31	143	17.5%	1.69 [1.16, 2.48]
Edwards 2000	7	15	1	15	1.6%	7.00 [0.98, 50.16]
Gupta 2007	35	56	17	57	15.2%	2.10 [1.34, 3.28]
Mei 2004	22	35	8	37	9.7%	2.91 [1.50, 5.65]
Silberstein 2004	68	125	26	115	17.7%	2.41 [1.65, 3.50]
Silberstein 2006	55	138	25	73	17.6%	1.16 [0.80, 1.70]
Storey 2001	5	19	2	21	2.6%	2.76 [0.61, 12.61]
Total (95% CI)		**660**		**586**	**100.0%**	**2.02 [1.57, 2.60]**
Total events	310		136			

Heterogeneity: Tau² = 0.06; Chi² = 14.71, df = 8 (P = 0.07); I² = 46%
Test for overall effect: Z = 5.41 (P < 0.00001)

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

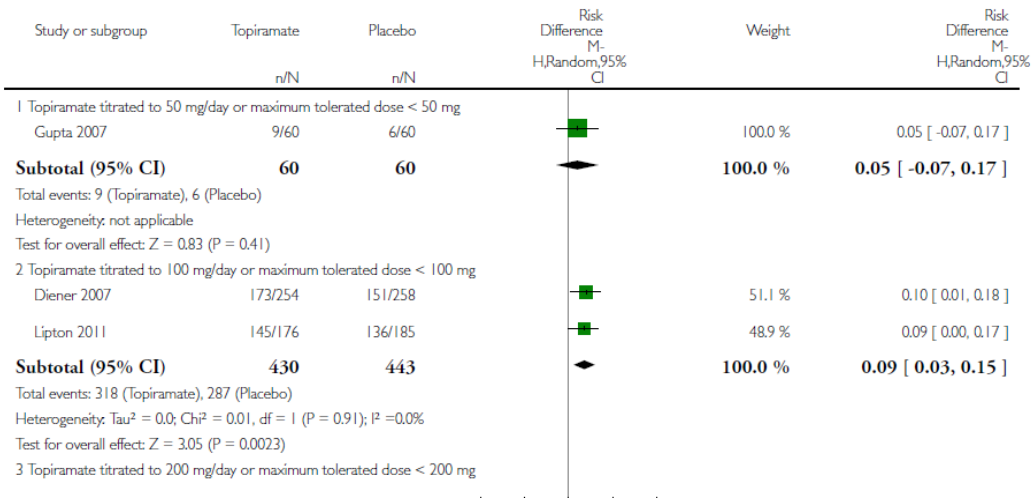
Sieben Studien verglichen Topiramat vs. einen aktiven Komparator**:**

- 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*)

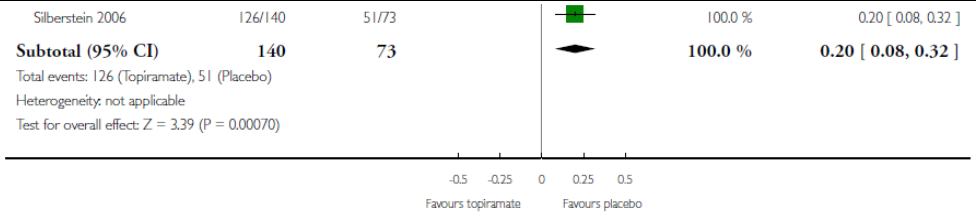
Kopfschmerzhäufigkeit und Ansprechen: kein statisch signifikanter Unterschied zu Amitriptylin, Flunarizin, Propranolol; Statistisch signifkanter Vorteil von Topiramat vs. Valproinsäure (MD -0.90; 95% CI -1.58 to -0.22; I²=0%).

Sicherheit

Jedes UE:



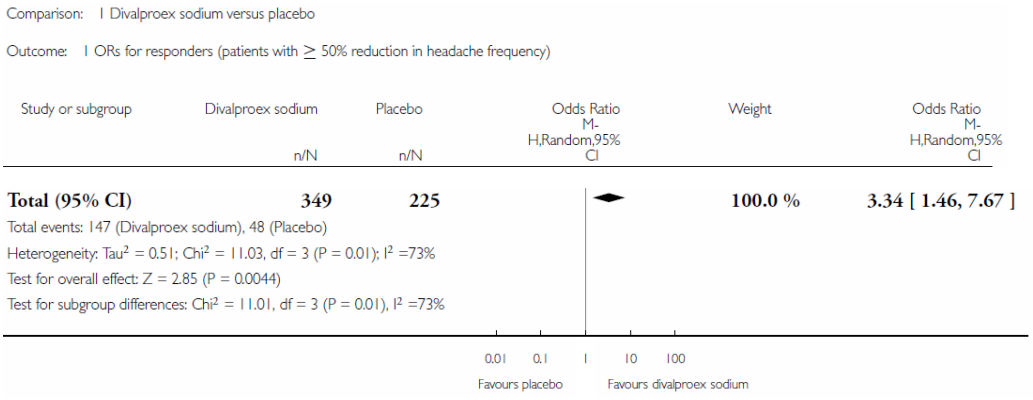
Study or subgroup	Topiramate n/N	Placebo n/N	Risk Difference M-H,Random,95% CI	Weight	Risk Difference M-H,Random,95% CI
1 Topiramate titrated to 50 mg/day or maximum tolerated dose < 50 mg					
Gupta 2007	9/60	6/60		100.0 %	0.05 [-0.07, 0.17]
Subtotal (95% CI)	**60**	**60**		**100.0 %**	**0.05 [-0.07, 0.17]**
Total events: 9 (Topiramate), 6 (Placebo)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.83 (P = 0.41)					
2 Topiramate titrated to 100 mg/day or maximum tolerated dose < 100 mg					
Diener 2007	173/254	151/258		51.1 %	0.10 [0.01, 0.18]
Lipton 2011	145/176	136/185		48.9 %	0.09 [0.00, 0.17]
Subtotal (95% CI)	**430**	**443**		**100.0 %**	**0.09 [0.03, 0.15]**
Total events: 318 (Topiramate), 287 (Placebo)					
Heterogeneity: Tau² = 0.0; Chi² = 0.01, df = 1 (P = 0.91); I² =0.0%					
Test for overall effect: Z = 3.05 (P = 0.0023)					
3 Topiramate titrated to 200 mg/day or maximum tolerated dose < 200 mg					

	 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 [9]. Valproate (valproic acid or sodium valproate or a combination of the two) for the prophylaxis of episodic migraine in adults. Cochrane Database of Systematic Reviews	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.
	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** <u>Divalproex sodium:</u>

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.

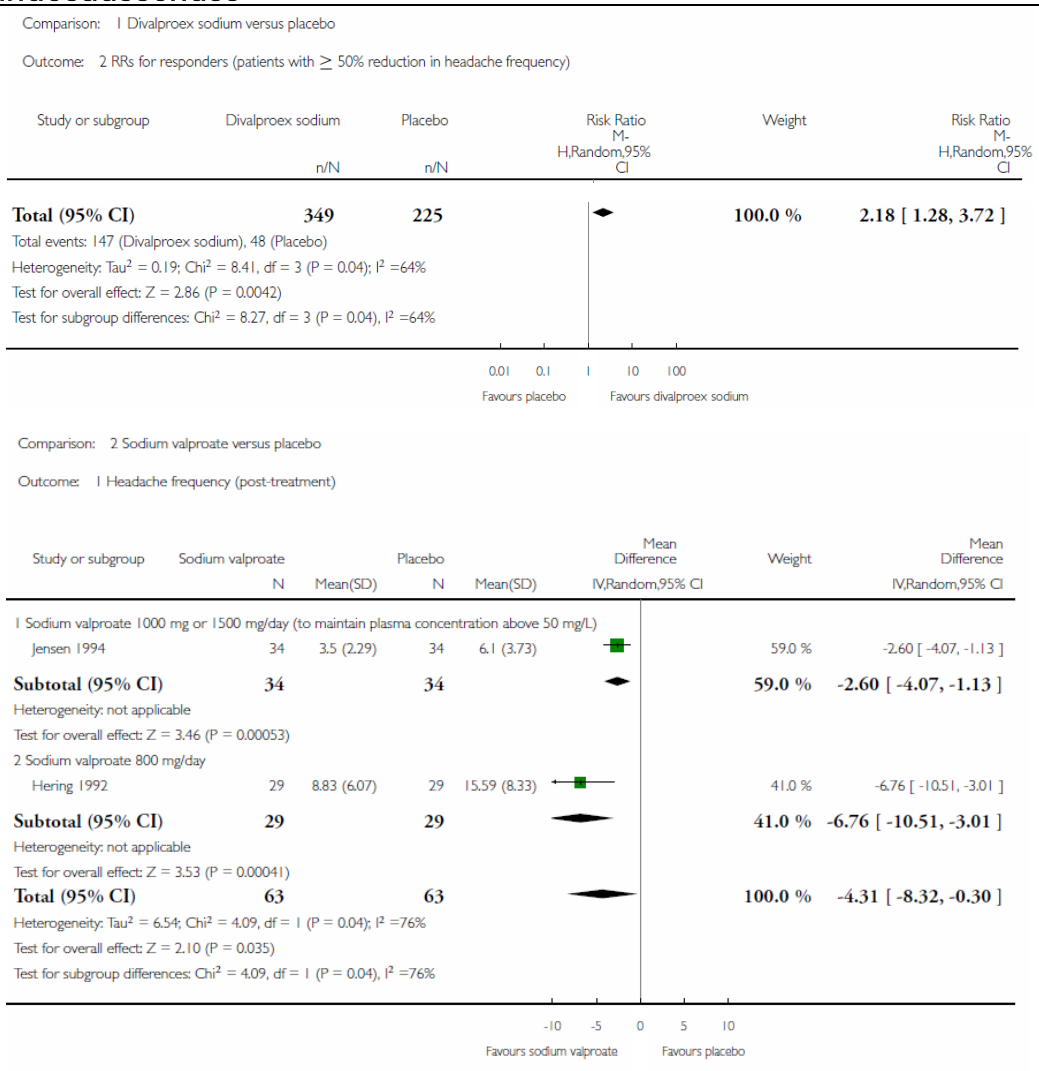


Sodium valproate

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).



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).

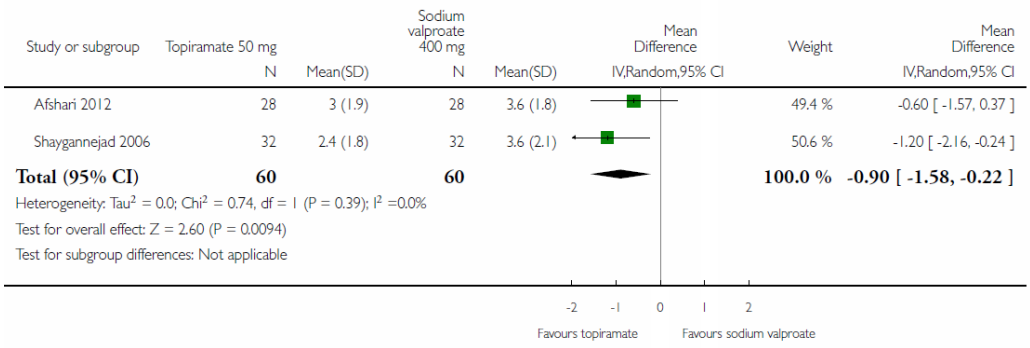
Divalproex sodium versus propranolol

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

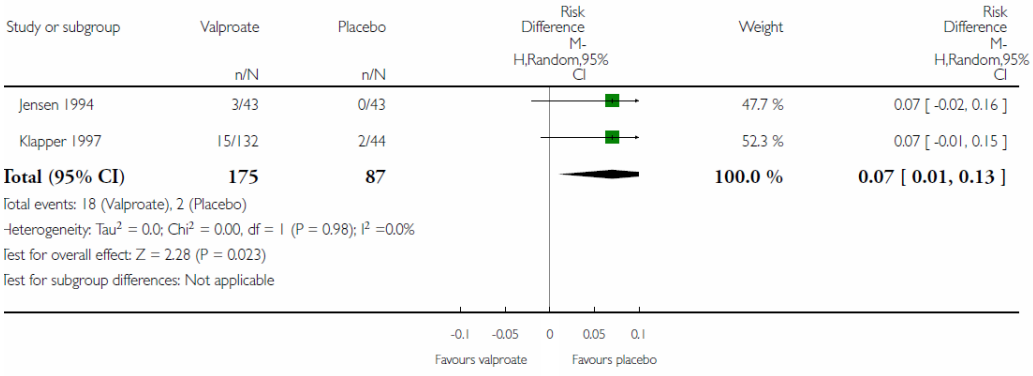
frequency of approximately one headache per 28 days with topiramate versus sodium valproate. The median baseline headache frequency in the topiramate groups of the two trials was 6.1 headaches per 28 days (mean 6.1; range: 5.4 to 6.8). It should be noted that the doses used in these two studies are not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



Safety

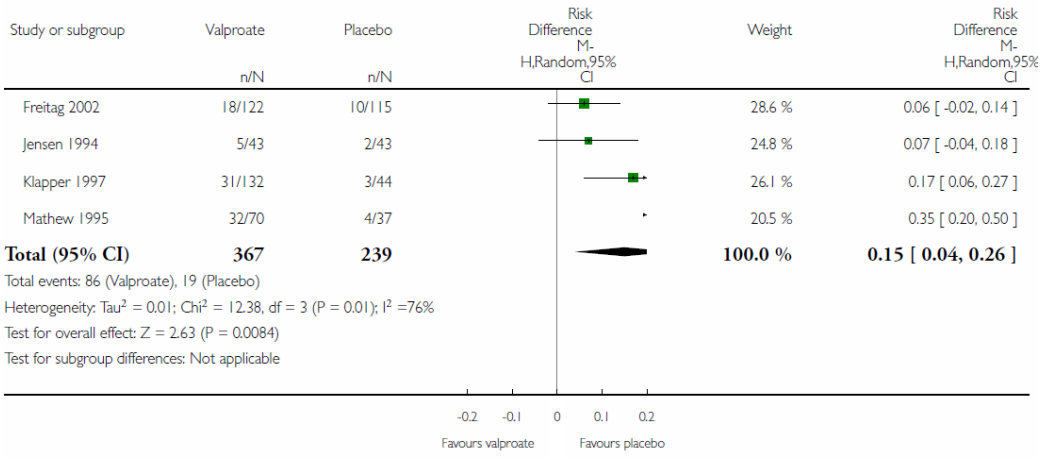
Comparison: 7 Safety of sodium valproate and divalproex sodium versus placebo

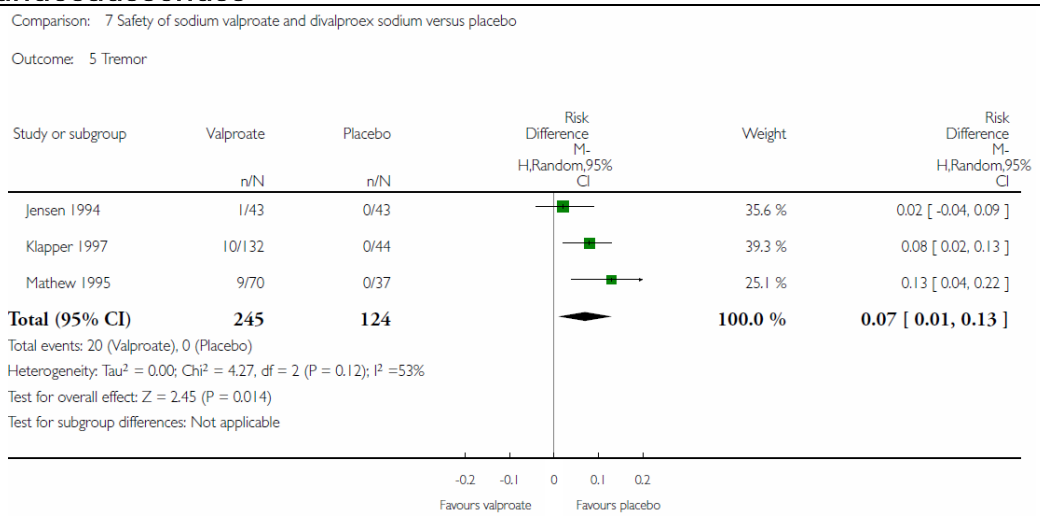
Outcome: 3 Dizziness/vertigo



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

Outcome: 4 Nausea





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.

Guo Y et al., 2012 [3].

Meta-analysis of efficacy of topiramate in migraine prophylaxis

1. Fragestellung

To evaluate the treatment effects and safety of topiramate in migraine prophylaxis.

2. Methodik

Population: Migraine patients diagnosed by the criteria of ICHD-I (diagnose criteria 1.2.3 Treatment)
Intervention: topiramate 100–200 mg per day
Komparator: placebo
Endpunkte: Efficacy: responder rate (response defined as at least a 50% reduction in average monthly migraine frequency) and change in mean monthly number of migraine days. Adverse events: number of subjects exhibiting at least one adverse event.
Suchzeitraum (Aktualität der Recherche): 1995 – 05/2011
Anzahl eingeschlossene Studien/Patienten (Gesamt): 8 (k.A.)
Qualitätsbewertung der Studien: Jadad scores

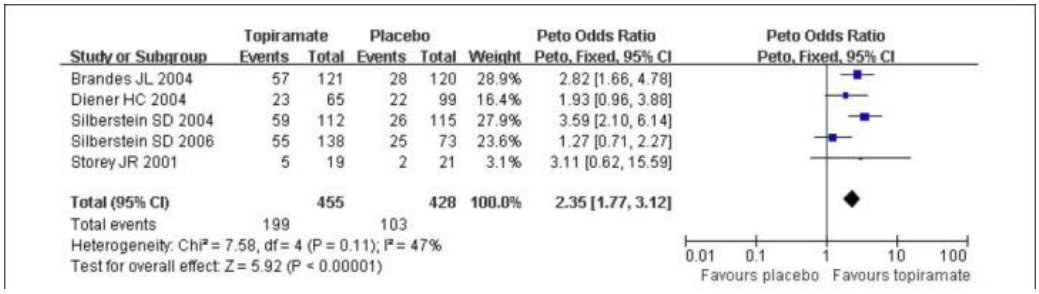
3. Ergebnisdarstellung

Studies	Subjects	Treatment	Dosage[a] (oral administration)	Course (week)	Number (T/C)[b]	Age (T/C)	Index
Brandes *et al* (2004) [4]	Migraine with/without aura	T/C	100/200 mg/d	26	121/120	12–65	Responder rate, change of mean monthly migraine days
Silberstein *et al* (2004) [5]	Migraine	T/C	100/200 mg/d	26	117/117	12–65	Responder rate
Silberstein *et al* (2007) [6]	Chronic migraine	T/C	100 mg/d	16	153/153	18–65	Change of mean monthly migraine days, adverse events
Silberstein *et al* (2006) [10]	Migraine with/without aura	T/C	200 mg/d	20	138/73	18–64	Responder rate
Storey *et al* (2001) [11]	Migraine with/without aura	T/C	200 mg/d	16	19/21	19–62	Responder rate
Diener *et al* (2004) [12]	Migraine with/without aura	T/C	100/200 mg/d	26	143/143	12–65	Responder rate, change of mean monthly migraine days
Diener *et al* (2007) [13]	Chronic migraine	T/C	100 mg/d	16	32/27	18–65	Change of mean monthly migraine days, adverse events
Silberstein *et al* (2009) [14]	Migraine with/without aura	T/C	100 mg/d	16	153/154	18–74	Adverse events

a: target dose: patients were started on topiramate or placebo 25 mg per day, and the daily dose was increased by 25 mg weekly until patients reached the target dose or their maximum tolerated dose. b: T: experimental group (topiramate); C: control group (placebo).

Comparison of effects of topiramate 200 mg/d and placebo on responder rate

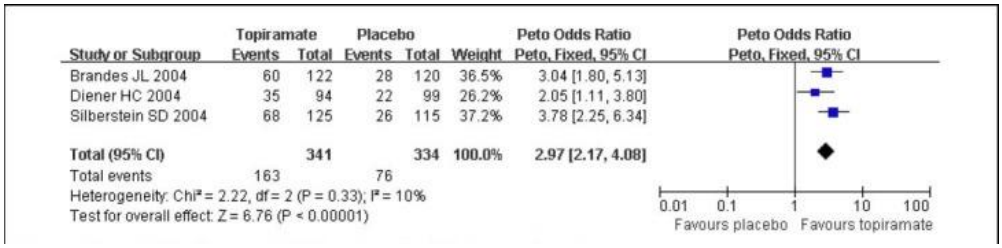
Regarding the comparison of topiramate 200 mg/d with placebo, five studies reported outcomes for responder rate. There was no significant heterogeneity among the studies (I^2 = 47%), and the data were calculated using a fixed effects model. Topiramate 200 mg/d was clearly superior to placebo with OR for a responder rate of 2.35 (95% CI: 1.77–3.12, P < 0.01; Figure 2).



Comparison of topiramate 100 mg/d with placebo on responder rate

Three studies reported outcomes for responder rate. There was no significant heterogeneity among the studies (I^2 = 10%, P = 0.33), and the data were calculated using the fixed effects model. Topiramate 100 mg/d was significantly superior to placebo

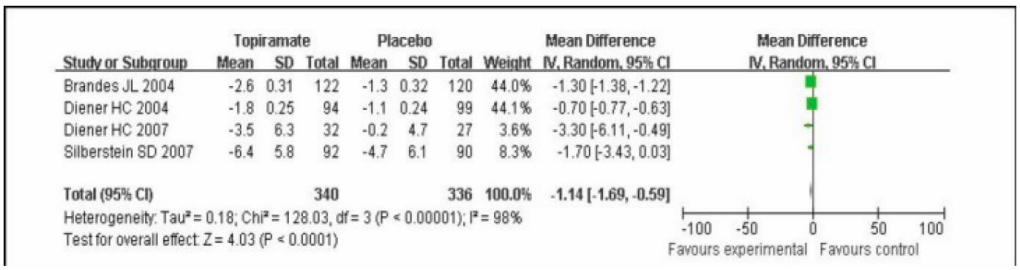
with OR for a responder rate of 2.97 (95% CI: 2.17–4.08, P < 0.01; Figure 3).



Mean monthly migraine days after topiramate prophylaxis

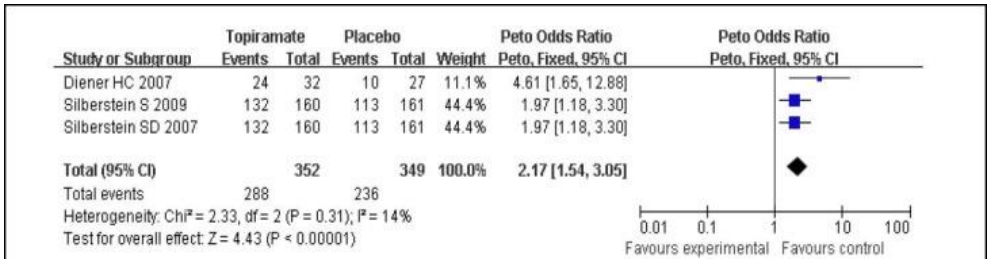
Regarding comparison of topiramate 100 mg/d with placebo, four studies reported outcomes for the change in mean monthly migraine days. The data were calculated using a random effects model because of significant heterogeneity among the studies (I^2 = 98%, P < 0.01). Topiramate 100 mg/d was significantly superior to placebo with MD for reduction of mean monthly migraine days (P < 0.01;Figure 4).

Figure 4



Adverse events

Regarding the comparison of topiramate (100 mg/d) with placebo, three studies reported the total incidence rate of adverse events. There was no significant heterogeneity among the studies (I^2 = 14%, P = 0.31), and the data were calculated using a fixed effects model. The total incidence rate of adverse events of topiramate 100 mg/d was higher than that of placebo (P < 0.01). The most common adverse events in the topiramate group were paresthesia, nausea, anorexia, weight loss, upper respiratory tract infection, and fatigue.



4. Anmerkungen/Fazit der Autoren

In conclusion, the results revealed that topiramate is effective in migraine prophylaxis. The responder rate and reduction in mean monthly number of migraine days were found to be better in the treatment than in the placebo group, and the drug was found to be generally safe. As the number of included studies was small, and there was heterogeneity among studies, the conclusion requires confirmation in future. More high-quality randomized controlled clinical trials are needed to provide more robust evidence for the efficacy of topiramate in migraine prophylaxis.

5. Kommentare zum Review

	Die empfohlene Dosierung laut Fachinformation liegt bei 25-100mg
Mulleners WM et al., 2015 [10]. 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]	

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]	

Quality of life	*Daily dose titrated up to*		
	50 mg/d (MD (95% CI))	100 mg/d (MD (95% CI))	200 mg/d (MD (95% CI))
MSQ-role function restrictive	5.83 (2.25, 9.41)	10.08 (6.55, 13.60)	10.36 (6.68, 14.04)
MSQ-role function preventive	ns	6.39 (3.37, 9.41)	5.06 (1.87, 8.25)
MSQ-emotional function	4.58 (0.61, 8.54)	10.22 (6.31, 14.14)	8.45 (4.38, 12.52)
SF-36 role physical	ns	ns	8.59 (0.65, 16.52)
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 mg/d (NNH (95% CI))
Any AE	ns	11 (7, 33)	5 (3, 12)
Anorexia	ns	17 (10, 50)	12 (8, 20)
Fatigue	ns	25 (17, 100)	12 (8, 25)
Memory problems	ns	25 (17, 100)	12 (9, 17)
Nausea	ns	ns	17 (9, 50)
Paresthesia	ns	3 (2, 6)	2 (2, 3)
Taste disturbance	7 (5, 14)	14 (8, 100)	7 (5, 11)
Weight loss	25 (14, 100)	17 (11, 33)	11 (8, 14)
Withdrawals due to AE	2%–17%	8%–29%	11%–44%

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

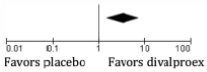
Valproat

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.

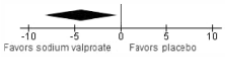
Efficacy

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.

5. Kommentare zum Review

Heterogenität unzureichend dargestellt

Jackson JL et al., 2012 [6].

Botulinum toxin A for prophylactic

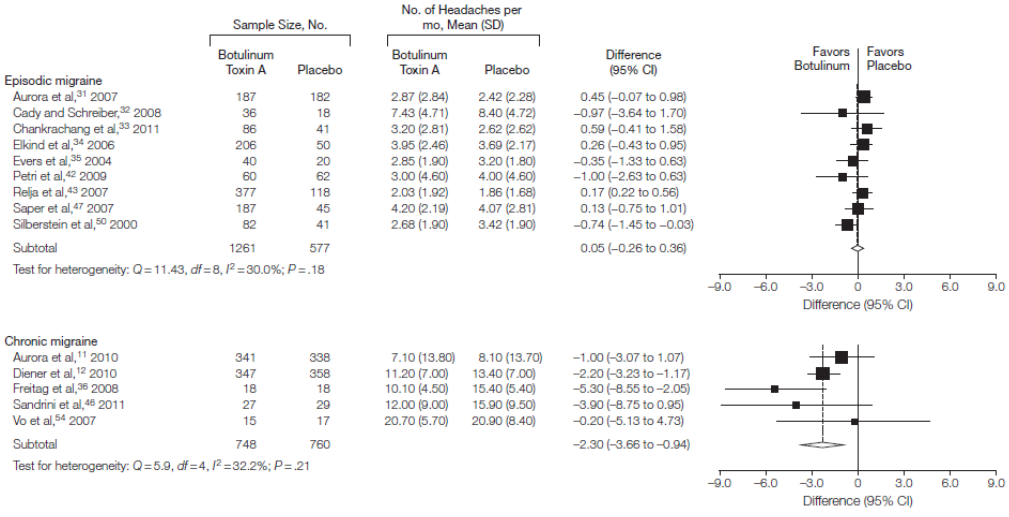
1. Fragestellung

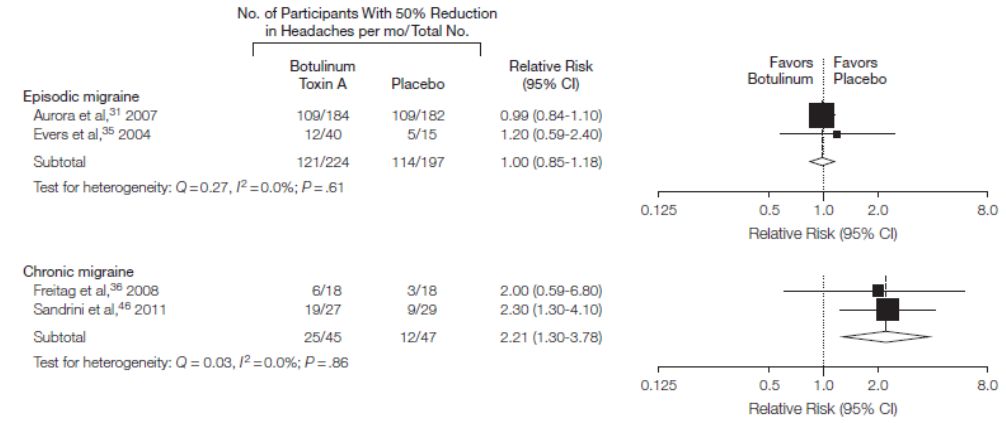
To assess botulinum toxin A for the prophylactic treatment of headaches in adults.

- Es werden nachfolgend nur die Ergebnisse für Migräne dargestellt -

2. Methodik

Population: Erwachsene Patienten mit episodischer oder chronischer Migräne oder

treatment of migraine and tension headaches in adults: a meta-analysis. **Siehe auch:** **Kim M et al., 2014 [7].** Botulinum toxin type A for prophylactic treatment of chronic migraine	Spannungskopfschmerz. Ergebnisse wurden separat für episodische und chronische Migräne dargestellt. **Intervention**: Botulinum Toxin A in Mono- oder Kombinationstherapie mit anderen Analgetika **Komparator**: Placebo, keine Intervention, andere aktive pharmakologische Intervention, nicht pharmakologische Intervention **Endpunkte**: Belastung durch Kopfschmerzen (definiert als die Häufigkeit der Kopfschmerzen mit der Intensität), Häufigkeit, Intensität, Schwere, Dauer, Verbesserung um ≥50% des Kopfschmerzes, UE **Suchzeitraum** (Aktualität der Recherche): Medline, Embase und Cochrane Datenbank bis 2012 **Anzahl eingeschlossene Studien/Patienten** (Gesamt): Für episodische Migräne: 10 (1938 Patienten); für chronische Migräne 7 Studien (795 Patienten für Placebo-Vergleich, 300 für Topiramat-Vergleich, 250 für Amitriptylin-Vergleich) **Qualitätsbewertung der Studien**: Cochrane Risk of Bias und Jadad Tool
	3. Ergebnisdarstellung **Botulinum Toxin A vs. Placebo** <u>Reduktion der Kopfschmerztage pro Monat:</u> *Chronische Migräne (9 Studien):* statistisch signifikanter Unterschied zugunsten von Botulinum Toxin A vs. Placebo (MD −2.30 headaches per month; 95% CI, −3.66 to −0.94; Q=5.9, df=4, I^2=32.2%; P=.21). *Episodische Migräne (5 Studien):* Kein statistisch signifikanter Unterschied  <u>Rückgang der Migränehäufigkeit um ≥50% (4 Studien):</u> *Chronische Migräne (2 Studien):* statistisch signifikanter Unterschied zugunsten von Botulinum Toxin A vs. Placebo (RR, 2.21; 95% CI, 1.30-3.78; Q=0.03, I^2=0.0%; P=.86) *Episodische Migräne (5 Studien):* Kein statistisch signifikanter Unterschied



Botulinum Toxin A vs. aktiven Komparator

Chronische Migräne: kein statistisch signifikanter Unterschied im Vergleich zu Amitriptylin, Topiramat oder Valproat

Sensitivitätsanalyse hinsichtlich Studienqualität:

There was no relationship between total Jadad score and outcomes or between Jadad scores of more than 3 vs 3 or less and study outcomes.

There was no relationship between the outcomes and intention-to-treat analysis (P=.74), concealed allocation (P = .40), adequacy of sequence generation (P=.17), industry sponsorship (P=.16), blinding (P=.37), or dropouts (P=.40).

Sicherheit (zusammen berichtet für Spannungskopfschmerz und Migräne)

Botulinum Toxin A führte statistisch signifikant häufiger zu UE, aber nicht zu höheren Abbruchraten.

Statistisch signifikant häufiger traten Blepharoptosis (RR 9,5; 95% CI, 4,7 bis 18,9), Muskelschwäche (RR 8,9; 95% CI, 2,5 bis 30,9), Nackenschmerzen (RR 4,7; 95% CI, 3,2 bis 6,9), Nackensteifigkeit (RR 3,2; 95% CI, 1,9 bis 5,6), Parästhesien (RR 3,3; 95% CI, 1,3 bis 7,9), und Spannen der Haut (RR 3,6; 95% CI, 1,6 bis 8,3).

	No./Total No. of Participants		Relative Risk	Heterogeneity		
Adverse Effect	Botulinum Toxin A	Placebo	(95% CI)	Q	df	I^2, %
Any adverse effect	1672/2955	1268/2756	1.25 (1.14-1.36)	61.9	24	61.2
Withdrawals, any cause	1843/4630	1456/4606	1.04 (0.85-1.27)	16.74	22	0
Blepharoptosis	136/1797	13/1300	9.5 (4.7-18.9)	16.07	12	25.3
Bruising	8/784	12/757	0.73 (0.27-2.00)	5.44	6	0
Dizziness	24/1038	13/769	1.15 (0.55-2.43)	5.28	8	0
Injection site pain	66/1651	42/1334	1.00 (0.72-1.54)	14.56	15	0
Muscle weakness	358/1706	25/1077	8.9 (2.5-30.9)	77.28	11	85.8
Nausea	11/646	5/426	1.72 (0.55-5.40)	0.80	4	0
Neck pain	230/1205	30/828	4.7 (3.2-6.9)	5.09	5	1.8
Neck stiffness	56/395	16/372	3.2 (1.9-5.6)	1.30	3	0
Parasthesia	54/1794	18/1316	3.3 (1.3-7.9)	29.15	12	0
Skin tightness	30/580	7/508	3.6 (1.6-8.3)	0.93	4	0

4. Anmerkungen/Fazit der Autoren

Our analyses suggest that botulinum toxin A may be associated with improvement in the frequency of chronic migraine and chronic daily headaches, but not with improvement in the frequency of episodic migraine. However, the association of botulinum toxin A with clinical benefit was small. Botulinum toxin A was associated with a reduction in the number of headaches per month from 19.5 to 17.2 for chronic migraine. There does not appear to be a difference in outcomes when botulinum toxin A is injected in a fixed schedule, when certain muscle groups are injected, or when botulinum toxin A is injected using a follow-the-pain method. We found no differences in outcomes between injecting once or performing 3 injections at 90-day intervals. There was no difference in the

	number of muscle groups injected or the total botulinum toxin A dose used and study outcomes.
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. Amitriptyline
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

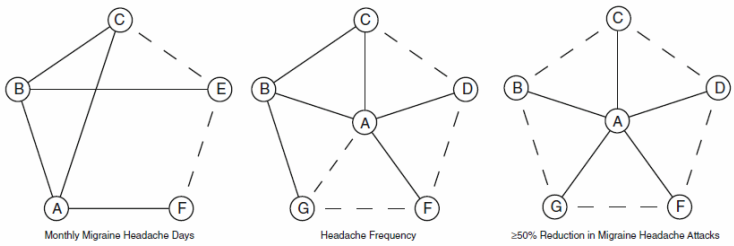


Fig. 2 Network plots of eligible comparisons of migraine intervention (monthly migraine headache days; headache frequency; ≥50% reduction in migraine headache attacks). *A*: Placebo; *B*: Topiramate; *C*: Propranolol; *D*: Gabapentin; *E*: Amitriptyline; *F*: Divalproex; *G*: Valproate. Direct comparisons 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	Withdrawal	Withdrawal due to AEs
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 (0.91, 1.21)	**2.08 (1.56, 2.78)**
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 (0.76, 1.51)	**1.87 (1.09, 3.19)**
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 (0.82, 1.77)	1.57 (0.86, 2.88)
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)	-	2.00 (0.17, 22.93)
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 (0.92, 2.82)	1.67 (0.70, 3.98)
Placebo vs Valproate	-	-	-	-	3.00 (0.59, 15.37)	-	2.00 (0.36, 11.26)	0.88 (0.29, 2.62)	0.97 (0.26, 3.56)
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 (0.44, 0.99)**	**0.58 (0.37, 0.91)**
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 (0.70, 1.50)	1.14 (0.69, 1.88)
Topiramate vs Valproate	-	-	-	1.22 (0.54, 2.76)	1.00 (0.29, 3.48)	1.30 (0.44, 3.84)	-	0.67 (0.24, 1.88)	2000 (0.58, 18.16)
Propranolol vs Divalproex	-	-	-	1.36 (0.58, 3.16)	3.50 (0.67, 18.15)	-	1.00 (0.19, 5.33)	-	4.00 (0.42, 37.78)

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, 1.31)	-
	Propranolol	**−0.98 (−1.86, −0.07)**	0.22 (−0.67, 1.30)	**Propranolol**	-	0.13 (−2.02, 2.33)	0.31 (−1.05, 1.83)	-
	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, 2.53)	-
	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	-	-	-	-	-	-	**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, 2.42)	0.84 (−0.81, 2.48)
	Topiramate	**4.28 (1.35, 14.70)**	**Topiramate**	0.21 (−0.88, 1.33)	0.05 (−2.20, 2.28)	-	−0.56 (−2.53, 1.39)	−0.32 (−1.76, 1.10)
	Propranolol	1.65 (0.25, 11.29)	0.38 (0.04, 3.70)	**Propranolol**	−0.17 (−2.45, 2.15)	-	−0.76 (−2.90, 1.32)	−0.53 (−2.33, 1.23)
	Gabapentin	1.59 (0.41, 6.93)	0.37 (0.06, 2.43)	0.96 (0.10, 10.96)	**Gabapentin**	-	−0.61 (−3.39, 2.12)	−0.36 (−3.01, 2.38)
	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**	0.24 (−2.21, 2.67)
	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, 52.31)	**Valproate**
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, 0.85)**	-
	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)	**Valproate**
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, 13.06)	2.16 (0.25, 17.88)
	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, 13.03)	1.56 (0.24, 10.53)
	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, 10.90)	0.80 (0.04, 10.81)
	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)	0.80 (0.05, 11.62)
	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, 20.34)	0.97 (0.05, 15.68)
	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**	0.73 (0.06, 10.84)
	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, 15.46)	**Valproate**

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 (1.14, 3.67)**	1.29 (0.48, 2.68)
	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 (0.96, 3.36)	1.14 (0.42, 2.46)
	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 (1.11, 4.52)**	1.51 (0.49, 3.69)
	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 (0.74, 3.37)	1.02 (0.33, 2.38)
	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 (0.74, 3.73)	1.08 (0.35, 2.33)
	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)	**Divalproex**	0.68 (0.22, 1.83)
	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 (0.23, 4.28)	**Valproate**

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

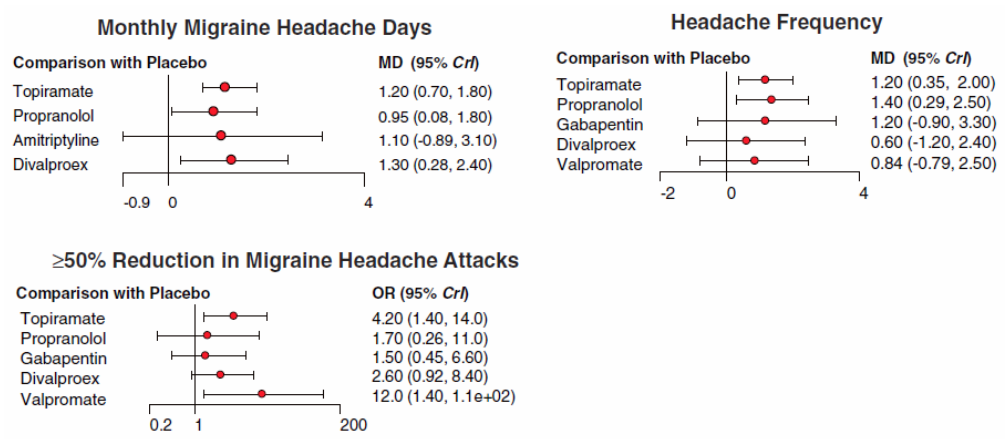


Fig. 5 Forest plots of summary effects (NMA) with respect to monthly migraine headache days, headache frequency and at least 50% reduction in migraine attacks

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

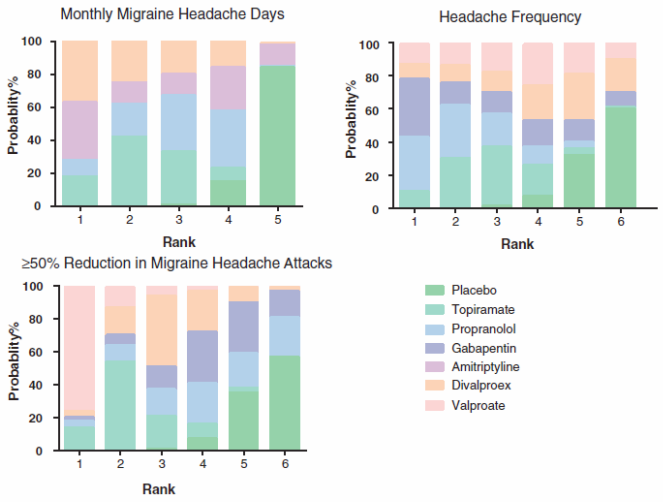


Fig. 8 Probability ranking plot of monthly migraine headache days, headache frequency and at least 50% reduction in migraine attacks

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/Patienten** (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%.

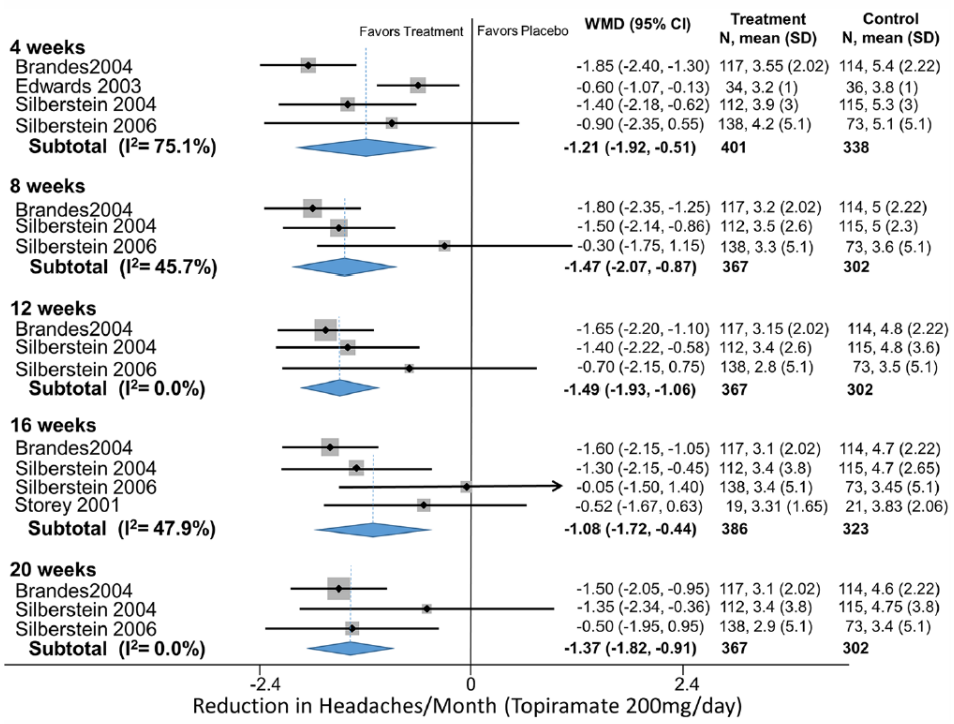


Fig 4. Topiramate compared to placebo for episodic migraine headaches.

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%.

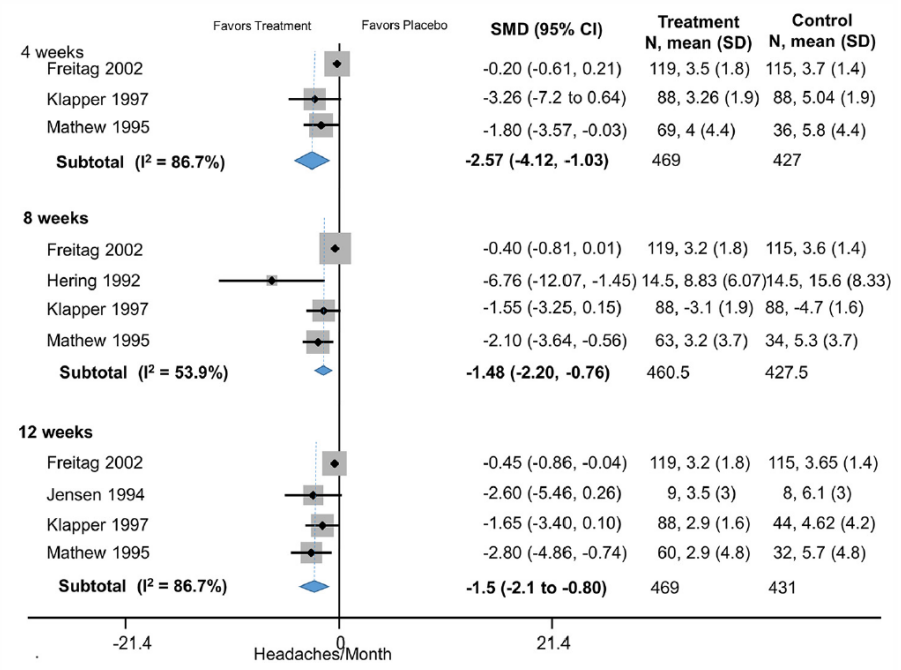


Fig 5. Valproate compared to placebo for episodic migraine headaches.

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.

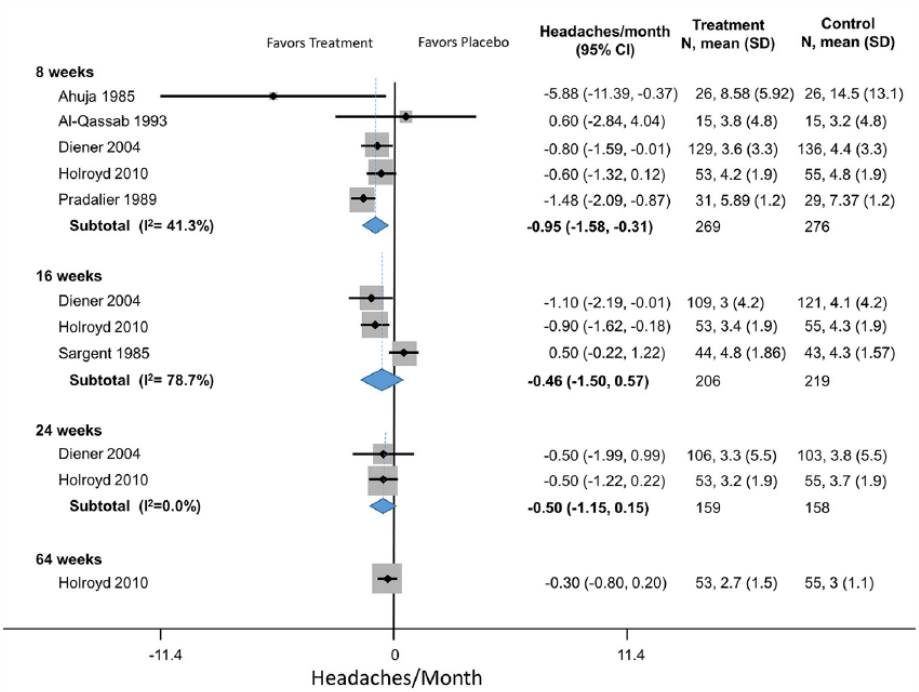


Fig 7. Propranolol compared to placebo for episodic migraine headaches.

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.

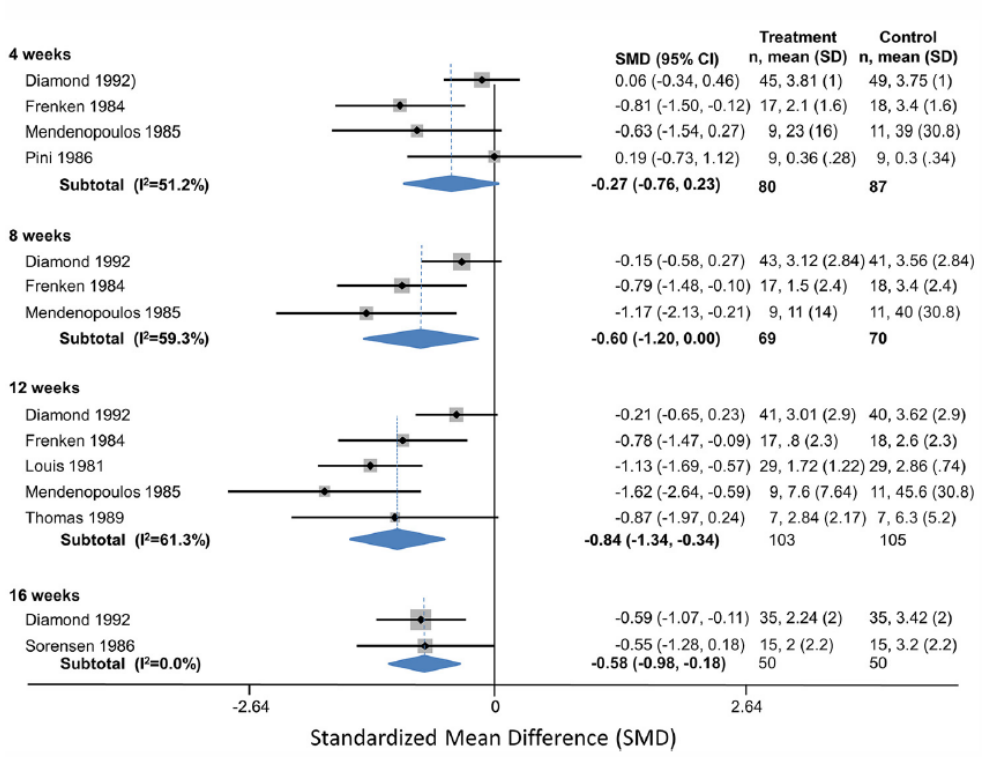


Fig 8. Flunarizine compared to placebo for episodic migraine headaches.

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.

Shamliyan TA et al., 2013 [15].

Migraine in Adults: Preventive Pharmacologic Treatments.

1. Fragestellung
Systematic review of preventive pharmacologic treatments for community-dwelling adults with episodic migraine

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.

3. Ergebnisdarstellung
Pharmakologische Prophylaxe vs. Placebo

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

Active Preventive Treatment	Outcome	Sample	Relative Risk (95% CI)	Absolute Risk Difference (95% CI)	Strength of Evidence (Reasons for Lowering SOE)
Metoprolol for episodic migraine	**≥50% decrease in migraine frequency**	**225**	**2.0 (1.3 to 3.2)**	**0.20 (0.09 to 0.3)**	**Low (medium ROB, imprecision)**
Nimodipine for episodic migraine	**≥50% decrease in migraine frequency**	**126**	**4.5 (0.5 to 40.1)**	**0.23 (0.06 to 0.39)**	**Low (medium ROB, imprecision)**
Magnesium for episodic migraine	**≥50% decrease in migraine frequency**	137	1.3 (0.7 to 2.3)	0.08 (-0.09 to 0.26)	Low (inconsistency, imprecision)

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 [14].

Preventive pharmacologic treatments for episodic migraine in adults.

1. Fragestellung

Weitere Analyse der Daten aus Shamliyan 2013 [15]

Systematic literature review of the comparative effectiveness and tolerability of the available preventive medications for episodic 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

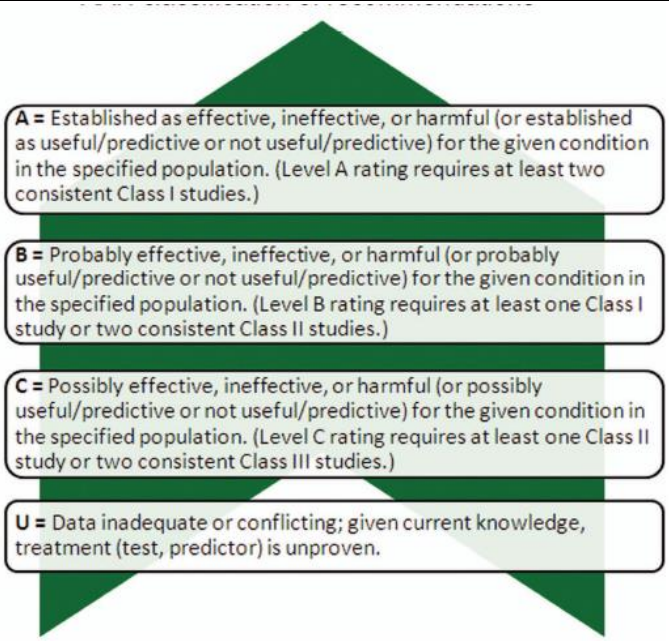
	Endpunkte: ≥50 % reduction in frequency of migraine attack from baseline, complete cessation of migraine attacks, migraine-related disability, and quality of life **Suchzeitraum** (Aktualität der Recherche): through May 20, 2012 **Anzahl eingeschlossene Studien/Patienten** (Gesamt): 215 RCTs, 76 non-RCTs (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.

Silberstein SD et al., 2012 [16]. Evidence-based guideline update: pharmacologic treatment for episodic migraine prevention in adults: report of the Quality Standards Subcommittee of the American Academy of Neurology and the American Headache Society.	Leitlinie der American Academy of Neurology **Zielpopulation**: Patienten mit episodischer Migräne. Patienten mit chronischer Migräne sind nicht Teil der Zielpopulation
	Methodik Grundlage der Leitlinie: systematische Literatursuche in MEDLINE, Psyc-INFO, CINAHL und Panel Diskussion – Update Recherche zu einer LL aus dem Jahr 2000 – Suchzeitraum: 1999-2007 – Nur Klasse 1 und Klasse 2 Evidenz hinzugezogen – Alle Aussagen mit Literaturstellen verknüpft – Evidenz bei >20% Dropoutrate wird herabgestuft – Leitlinie der Evidenzstufe S2e (AWMF) **LoE** Class I**.** A randomized, controlled clinical trial of the intervention of interest with masked or objective outcome assessment, in a representative population. Class II. A randomized controlled clinical trial of the intervention of interest in a representative population with masked or objective outcome assessment that lacks one criteria a–e above or a prospective matched cohort study with masked or objective outcome assessment in a representative population that meets b–e above. Class III**.** All other controlled trials (including well-defined natural history controls or patients serving as their own controls) in a representative population, where outcome is independently assessed, or independently derived by objective outcome measurement. Class IV**.** Studies not meeting Class I, II, or III criteria including consensus or expert opinion. **GoR**



Empfehlungen

Topiramate

Four Class I studies and 7 Class II studies report topiramate (50–200 mg/day) is effective in migraine prevention. In a Class I placebo-controlled study (mean topiramate dose 125 mg/day [range 25–200 mg/day]), patients given topiramate experienced a significantly lower 28-day migraine frequency vs with placebo (3.31 +/- 1.7 vs 3.83 +/- 2.1; p=0.002). In a second placebo-controlled Class I double-crossover study, topiramate was more effective than placebo and lamotrigine for primary efficacy measures. In the topiramate groups, 15% of patients experienced AEs, most commonly paresthesias, sleepiness, and gastrointestinal intolerance. The placebo group reported gastrointestinal intolerance (3%) and anorexia (3%).

Two additional Class I studies report topiramate is as effective as propranolol or sodium valproate, drugs previously established as effective for migraine prevention. In the first study, subjects given topiramate 50 mg/day had reduced mean migraine frequency (episodes/ month) from baseline (6.07 +/- 1.89 to 1.83 +/- 1.39; p<0.001) at 8 weeks, decreased headache intensity VAS score from 7.1 +/- 1.45 to 3.67 +/- 2.1 (p<0.001), and decreased headache duration from 16.37 +/- 7.26 hours to 6.23 +/- 5.22 hours (p<0.001). Subjects given topiramate reported paresthesias (23%), weight loss (16%), and somnolence (13%). In patients treated with propranolol 80 mg/day, mean headache frequency (episodes/month) decreased from 5.83 +/- 1.98 to 2.2 +/- 1.67 (p<0.001) at 8 weeks, headache intensity VAS score decreased from 6.43 +/- 1.6 to 4.13 +/- 1.94 (p<0.001), and headache duration decreased from 15.10 +/- 6.84 hours to 7.27 +/- 6.46 hours (p<0.001). Although monthly headache frequency, intensity, and duration decreased in both groups, the topiramate group reported significantly greater mean reduction (topiramate frequency decrease 4.23 +/- 1.2 vs propranolol 3.63 +/- 0.96 [p=0.036; CI 0.39 +/- 1.16]; topiramate intensity decrease 3.43 +/- 1.38 vs propranolol 2.3 +/- 1.2 [p<0.001; CI 0.46 –1.8]; topiramate duration decrease 10.1

+/- 4.3 vs propranolol 7.83 +/- 4.5 [p<0.048; CI 0.17– 4.6]).

In a crossover Class I trial (2-month washout between therapies) comparing topiramate 50 mg/day with sodium valproate 400 mg/day, both groups showed improvement from baseline in headache frequency, intensity, and duration. Average monthly migraine frequency decreased by 1.8 times with sodium valproate (baseline 5.4 +/- 2.5; posttreatment 3.6 +/- 2.1; CI 1.0 –2.6; p<0.001), as compared with a 3-time reduction with topiramate (baseline 5.4 +/- 2.0; posttreatment 2.4 +/- 2.4; CI 2.1–3.9; p<0.001). Headache intensity decreased by 3.7 with sodium valproate (baseline 7.7 +/- 1.2; treatment 4.0 +/- 2.1; CI 2.9–4.6; p<0.001), as compared with a reduction of 3.6 with topiramate (baseline 6.9 +/- 1.2, treatment phase 3.3 +/- 1.5; CI 2.9–4.3; p<0.001). The average headache episode duration decreased by 13.4 hours from baseline with sodium valproate (baseline 21.3 +/- 14.6; treatment 7.9 +/- 7.7; CI 7.5– 19.3; p<0.001) as compared with an 11.9-hour reduction with topiramate (baseline 17.3 +/- 8.4; treatment 5.4 +/- 6.4; CI 8.2–15.6; p<0.001). The overall analysis of repeated-measures analysis of variance demonstrated no differences in monthly headache frequency, intensity, or duration after the first or second treatment rounds. Topiramate Aes were weight loss (18.8%), paresthesias (9.4%), or both (25%). Sodium valproate Aes were weight gain (34.5%), hair loss (3.1%), and somnolence (3.1%).

Results of 5 Class II studies support those of the Class I studies showing topiramate as effective for migraine prevention.

Gupta P, Singh S, Goyal V, Shukla G, Behari M. Lowdose topiramate versus lamotrigine in migraine prophylaxis (the Lotolamp study). Headache 2007;47:402– 412.

Ashtari F, Shaygannejad V, Akbari M. A double-blind, randomized trial of low-dose topiramate vs propranolol in migraine prophylaxis. Acta Neurol Scand 2008;118:301– 305.

Shaygannejad V, Janghorbani M, Ghorbani A, Ashtary F, Zakizade N, Nasr V. Comparison of the effect of topiramate and sodium valproate in migraine prevention: a randomized blinded crossover study. Headache 2006;46:642– 648.

Storey JR, Calder CS, Hart DE, Potter DL. Topiramate in migraine prevention: a double-blind, placebo-controlled study. Headache 2001;41:968 –975.

Brandes JL, Saper JR, Diamond M, et al; MIGR-002 Study Group. Topiramate for migraine prevention: a randomized controlled trial. JAMA 2004;291:965–973.

Diener HC, Matias-Guiu J, Hartung E, et al. Topiramate in migraine prophylaxis–results from a placebo-controlled trial with propranolol as an active control. J Neurol 2004; 251:943–950.

Dodick DW, Freitag F, Banks J, et al; CAPSS-277 Investigator Group. Topiramate versus amitriptyline in migraine prevention: a 26-wk, multicenter, randomized, doubleblind, double-dummy, parallel-group noninferiority trial in adult migraineurs. Clin Ther 2009;31:542–559.

Keskinbora K, Aydinli I. A double-blind randomized controlled trial of topiramate and amitriptyline either alone or in combination for the prevention of migraine. Clin Neurol Neurosurg 2008;110:979 –984.

Mei D, Capuano A, Vollono C, et al. Topiramate in migraine prophylaxis: a randomised double-blind versus placebo study. Neurol Sci 2004;25:245–250.

Silberstein SD, Neto W, Schmitt J, Jacobs D; MIGR-001 Study Group. Topiramate in migraine prevention: results of a large controlled trial. Arch Neurol 2004;61:490–495.

Milla´n-Guerrero RO, Isais-Milla´n R, Barreto-Vizcaíno S, et al. Subcutaneous histamine versus topiramate in migraine prophylaxis: a double-blind study. Eur Neurol 2008;59:237–242.

Silberstein SD, Hulihan J, Karim MR, et al. Efficacy and tolerability of topiramate 200 mg/d in the prevention of migraine with/without aura in adults: a randomized, placebo-controlled, double-blind, 12-week pilot study. Clin Ther 2006;28:1002–1011.

B-Blocker (Metoprolol, Propranolol)

The original guideline concluded metoprolol was probably effective in migraine prevention. We reclassified these studies as Class I using the revised AAN criteria. One new Class II study reported metoprolol (200 mg/day) was more effective than aspirin (300 mg/day) in achieving 50% migraine frequency reduction (responder

rate metoprolol=45.2%; aspirin=29.6%; mean difference 15.65; CI 4.43–26.88). Attack frequencies (attacks/month) at placebo run-in and week 20 are 3.36 to 2.37, respectively, for aspirin and 3.55 to 1.82, respectively, for metoprolol. No significant Aes were reported. A small Class II study reported metoprolol (47.5–142.5 mg/day) had similar efficacy to nebivolol 5 mg/day for migraine prevention (assessed by a decrease in mean migraine attacks).

The original guideline concluded propranolol was established as effective for migraine prevention. In a Class II study, propranolol (80 mg/day) was more effective than placebo and as effective as cyproheptadine (4 mg/day) in reducing migraine frequency, duration, and attack severity. The difference in attack frequency reduction was significant between treatments: propranolol -2.85 +/- 0.2 (SEM) vs cyproheptadine -3.09 +/- 0.31 vs combination 3.12 +/- 0.1 vs placebo -1.77 +/- 0.44 (all $p<0.05$ vs placebo). For attack frequency reduction, combination therapy was more effective than monotherapy ($p<0.05$). Aes were drowsiness, sleep disturbance, weight gain, fatigue, and dry mouth; percentages of patients affected were not reported.

Conclusions. Metoprolol is established as effective for migraine prevention (2 Class I studies) and is possibly as effective as nebivolol or aspirin for migraine prevention (1 Class II study each). Propranolol is established as effective for migraine prevention (multiple Class I studies) and is possibly as effective as cyproheptadine for migraine prevention (1 Class II study).

Diener HC, Hartung E, Chrubasik J, et al. A comparative study of oral acetylsalicylic acid and metoprolol for the prophylactic treatment of migraine: a randomized, controlled, double-blind, parallel group phase III study. Cephalalgia 2001;21:120 –128.

Schellenberg R, Lichtenthal A, Wo¨hling H, Graf C, Brixius K. Nebivolol and metoprolol for treating migraine: an advance on beta-blocker treatment? Headache 2008;48: 118–125.

Rao BS, Das DG, Taraknath VR, Sarma Y. A double blind controlled study of propranolol and cyproheptadine in migraine prophylaxis. Neurol India 2000;48:223–226.

Antiepileptic drugs (Divalproex, Valproinsäure)

The original guideline found strong, consistent support (5 studies) for the efficacy of divalproex sodium and its corresponding compound, sodium valproate, for migraine prevention. Since the 2000 publication, 1 double-blind, randomized, Class I placebo-controlled 12-week trial showed extended-release (ER) divalproex sodium 500–1,000 mg/day had a mean reduction in 4-week migraine headache rate from 4.4/week (baseline) to 3.2/week (-1.2 attacks/week) in the ER divalproex sodium group and from 4.2/week to 3.6/week (-0.6 attacks/week) in the placebo group (CI 0.2–1.2; p=0.006). No significant differences were detected between groups in the number of treatment-emergent Aes.

Clinical context. In most headache trials, patients taking divalproex sodium or sodium valproate reported no more Aes than those on placebo. However, weight gain has been clinically observed with divalproex sodium long-term use. Treatment with these agents requires careful follow-up and testing because of pancreatitis, liver failure, and teratogenicity risks.

Freitag FG, Collins SD, Carlson HA, et al. A randomized trial of divalproex sodium extended-release tablets in migraine prophylaxis. Neurology 2002;58:1652–1659.

Silberstein SD, Collins SD. Safety of divalproex sodium in migraine prophylaxis: an open-label, long-term study: long-term safety of Depakote in Headache Prophylaxis Study Group. Headache

	1999;39:633– 643.
	
	RECOMMENDATIONS Level A. The following medications are established as effective and should be offered for migraine prevention:
	• Antiepileptic drugs (AEDs): divalproex sodium, sodium valproate, topiramate
	• β-Blockers: metoprolol, propranolol, timolol
	• Triptans: frovatriptan for short-term MAMs prevention
	
	Level B. The following medications are probably effective and should be considered for migraine prevention:
	• Antidepressants: amitriptyline, venlafaxine
	• β-Blockers: atenolol, nadolol
	• Triptans: naratriptan, zolmitriptan for short-term MAMs prevention
	
	Level C. The following medications are possibly effective and may be considered for migraine prevention:
	• ACE inhibitors: lisinopril
	• Angiotensin receptor blockers: candesartan
	• α-Agonists: clonidine, guanfacine
	• AEDs: carbamazepine
	• β-Blockers: nebivolol, pindolol
	
	Level U. Evidence is conflicting or inadequate to support or refute the use of the following medications for migraine prevention:
	• AEDs: gabapentin
	• Antidepressants
	  • Selective serotonin reuptake inhibitor/selective serotonin-norepinephrine reuptake inhibitors: fluoxetine, fluvoxamine
	  • Tricyclics: protriptyline
	• Antithrombotics: acenocoumarol, Coumadin, picotamide
	• β-Blockers: bisoprolol
	• Calcium-channel blockers: nicardipine, nifedipine, nimodipine, verapamil
	• Acetazolamide
	• Cyclandelate

Simpson DM et al., 2016 [17]. Practice guideline	Leitlinie der American Academy of Neurology
	Methodik Grundlage der Leitlinie: systematische Literatursuche in MEDLINE, Psyc-INFO, CINAHL und Panel Diskussion

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.	– 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 [16]
	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 studies[12,13], 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 report[14] 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 study[15] 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. <u>Recommendations</u>: 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 study[16] 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; 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.

National Clinical Guideline Centre (NCGC), 2012 [11].

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

NICE Clinical Guideline; Band 150

Vielfältige Fragestellungen zur Kopfscherzdiagnostik und –behandlung; hier relevant:

Chapter	Review questions	Outcomes
Management: **Prophylactic**	In migraine with or without aura and chronic migraine, what is the clinical evidence and cost-effectiveness for	• Change in patient-reported headache days, frequency and intensity
pharmacological treatment of migraine	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?	• 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.

Commissioned by the National Institute for Health and Clinical Excellence

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: 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.
Pringsheim T et al., 2012 [12]. Canadian Headache Society guideline for migraine prophylaxis.	Leitlinie der Canadian Headache Society Zielpopulation: This guideline is focused on patients with episodic migraine (headache on ≤ 14 days a month) who: 1. Suffer a significant degree of disability as a result of their migraine, and for whom acute medication treatment has not proved sufficient to minimize this disability. 2. May be responding well to their symptomatic medications, but in whom a high frequency of acute medication use may place them at risk for medication overuse headache or significant systemic side effects. Although it is likely that physicians may extrapolate from the evidence presented here and use it for the care of patients with higher migraine frequencies, the literature reviewed for these guidelines did not include patients with chronic migraine (headache on > 14 days a month).
	Methodik Grundlage der Leitlinie: systematische Literatursuche nach prospektiven doppelblinden RCT bei erwachsenen Patienten in Medline, Embase, Cochrane Datenbank. Zusätzlich Konsensusprozess und Expertenpanels

Primärer Endpunkt für die LL: Kopfschmerzhäufigkeit

- Suchzeitraum: initial 1950-2007, Update bis 2011
- Qualität der Studien wurde untersucht: assembly of comparable groups, adequate randomization, allocation concealment, confounders distributed equally, maintenance of comparable groups, absence of overall high or important differential loss to follow-up, measurement instruments are acceptable and applied equally, masking of outcome assessment, clear definition of interventions, all important outcomes considered and intention to treat analysis performed.
- Empfehlungen basieren auf GRADE System
- Alle Aussagen mit Literaturstellen verknüpft
- Leitlinie der Evidenzstufe S3 (AWMF)

LoE

Level of Evidence	Definition
High	We are confident that the true effect lies close to the estimate given by the evidence available.
Moderate	We are moderately confident in the effect estimate, but there is a possibility it is substantially different.
Low	Our confidence in the effect estimate is limited. The true effect may be substantially different.
Very low	We have little confidence in the effect estimate.

GoR

Recommendation Grade	Benefits versus Risks	Clinical Implication
Strong – high quality evidence	Benefits clearly outweigh risks and burdens for most patients	Can apply to most patients in most circumstances
Strong – moderate quality evidence	Benefits clearly outweigh risks and burdens for most patients	Can apply to most patients, but there is a chance the recommendation may change with more research
Strong – Low quality evidence	Benefits clearly outweigh risks and burdens for most patients	Can apply to most patients, but there is a good chance the recommendation could change with more research
Weak – high quality evidence	Benefits are more closely balanced with risks and burdens for many patients	Whether a medication is used will depend upon patient circumstances
Weak – Moderate quality evidence	Benefits are more closely balanced with risks and burdens for many patients	Whether a medication is used will depend upon patient circumstances, but there is less certainly about when it should be used
Weak – low quality evidence	Benefits are more closely balanced with risks and burdens	There is considerable uncertainty about when to use this medication

Empfehlungen

Divalproex sodium / sodium valproate

Weak recommendation, high quality evidence: While there is high quality evidence that divalproex sodium 500 to 1500 mg per day is effective for migraine prophylaxis, a weak recommendation was made based on the risk benefit profile of

	this medication for many patients. Divalproex sodium often promotes weight gain and may cause reversible tremor and hair loss. It is usually avoided in women with child bearing potential. When considered for this patient group, it should be given with folic acid, and caution should be exercised with careful consideration of birth control status due to the potential risk for teratogenicity. **Topiramat** *Strong recommendation, high quality evidence*: We recommend that clinicians offer topiramate to eligible patients for migraine prophylaxis. We found high quality evidence that topiramate provides a reduction in migraine frequency, though side effects from treatment are common. Due to the high number of adverse events and withdrawals on the 200 mg dose of topiramate, and the high quality evidence for a therapeutic benefit on the 100 mg dose, the recommended target dosage of topiramate for migraine prophylaxis is 100 mg per day. As was done in the clinical trials, the dosage should be increased gradually. **Propranolol** *Strong recommendation, high quality evidence*: We recommend that clinicians offer propranolol at a target dose of 80 to 160 mg per day to eligible patients for migraine prophylaxis. Studies comparing propranolol to calcium channel blockers (mainly flunarizine), and metoprolol suggest comparative efficacy between treatments. **Metoprolol** *Strong recommendation, high quality evidence*: We recommend that clinicians offer metoprolol (100 to 200 mg daily) to eligible patients for migraine prophylaxis. **Flunarizine** *Weak recommendation, high quality evidence*: While there is high quality evidence that flunarizine 10 mg per day is effective for migraine prophylaxis, a weak recommendation was made because treatment is often limited by side effects, including depression and weight gain. **Botulinum Toxin Typ A** *Strong recommendation, high quality evidence*: We recommend against providing botulinum toxin type A for the prophylaxis of episodic migraine in patients with less than 15 headache days per month. The evidence indicates that botulinum toxin type A is no better than placebo for the prophylaxis of migraine in such patients. **Additional monotherapy drug strategies: EXPERT CONSENSUS** i. Topiramate is a useful migraine prophylactic drug. Although used for first time prophylaxis by some clinicians, it is not included here in the “First time” strategies because of its side effect profile. An exception is when it is used as part of the increased body mass index strategy. ii. Divalproex sodium is a useful migraine prophylactic drug in patients when other prophylactic drugs have failed. Given its teratogenicity, it should generally be avoided in women with child bearing potential and if used, should only be used

	when the benefits are felt to outweigh the risks, and with appropriate contraception in place. iii. Gabapentin can be considered in patients when other prophylactics have failed. It has the advantage of few drug interactions. Evidence for efficacy is less strong than for some other prophylactics. iv. Flunarizine can be a useful prophylactic when other prophylactics have failed, but should be avoided in patients with a significant history of depression. Patients on flunarizine should be monitored for onset of depression. **Refractory patient strategy: EXPERT CONSENSUS** i. The simultaneous use of more than one prophylactic drug may be of benefit in patients with migraine refractory to prophylactic monotherapy. ii. The following drug combinations may be useful in patients with refractory migraine, based primarily on non-randomized trials and clinical experience: beta-blockers and topiramate, beta-blockers and divalproex sodium, beta-blockers and amitriptyline, and amitriptyline and topiramate. iii. Patients requiring prophylactic polypharmacy should be considered for specialist referral. 26. Schulman EA, Lake III AE, Goadsby PJ, et al. Defining Refractory Migraine and Refractory Chronic Migraine: Proposed Criteria From the Refractory Headache Special Interest Section of the American Headache Society. Headache. 2008;48:778-82. 27. Lipton RB, Silberstein SD, Saper JR, Bigal ME, Goadsby PJ. Why headache treatment fails. Neurology. 2003;60:1064-70. 28. Evans RW, Pascual J, Lainez, MJA, Leira R. Bending the Rule of Monotherapy for Migraine Prevention? Headache. 2005;45: 748-50. 29. Peterlin BL, Calhoun AH, Siegel S, Mathew NT. Rational Combination Therapy in Refractory Migraine. Headache. 2008; 48:805-19. 30. Pascual1 J, RivasMT, Leira R. Testing the combination beta-blocker plus topiramate in refractory migraine. Acta Neurol Scand. 2007: 15:81-3. 31. Martínez HR, Londoño O, Cantú-Martínez L, del Carmen Tarín L, Castillo CD. Topiramate as an adjunctive treatment in migraine prophylaxis. Headache. 2003 Nov-Dec;43(10):1080-4. 32. Pascual J, Leira R, Láinez JM. Combined therapy for migraine prevention? Clinical experience with a b-blocker plus sodium valproate in 52 resistant migraine patients. Cephalalgia. 2003;23: 961-2. 33. Keskinbora K,Aydinli I. A double-blind randomized controlled trial of topiramate and amitriptyline either alone or in combination for the prevention of migraine. Clin Neurol Neurosurg. 2008;110: 979-84.
Sarchielli P et al., 2012 [13]. Italian guidelines for primary headaches: 2012 revised version.	Leitlinie der Italian Society for the Study of Headaches Zielpopulation: Patienten mit chronischer oder episodischer Migräne
	Methodik Grundlage der Leitlinie: systematische Literatursuche in MEDLINE und Panel Diskussion – Update einer LL von 2001 – Suchzeitraum: 2001-2011 – RCTs und Meta-Analysen eingeschlossen. Nur wenn RCT nicht vorhanden wurden auch Studien schlechterer Qualität eingeschlossen – Leitlinie der Evidenzstufe S2e (AWMF) **LoE**

Table 1 Levels of evidence

Level A: Two or more clinically controlled, randomize, double-blind studies carried out according to good clinical practice (GCP) versus placebo or versus an active drug for which there is proven evidence of efficacy
Level B: One clinically controlled study according to GCP or more than one controlled case–control study/ies or Cohort study/ies
Level C: Favourable judgement of two-thirds of the Ad Hoc Committee, historical controls, non-randomized studies, case reports

GoR

Table 4 Levels of recommendation for the pharmacological treatment of primary headaches

Level I	Drugs with high efficacy supported by statistically significant data (evidence of at least two controlled, randomized studies versus placebo or versus active drugs of proven efficacy) or very high clinical benefit for patients (clinical effectiveness +++) and with no severe adverse events
Level II	Drugs whose value of efficacy is statistically of lower significance compared to drugs of group I and with a less significant clinical benefit for patients (clinical effectiveness ++) and no severe adverse events
Level III	Drugs showing efficacy from a statistical point of view but not from a clinical point of view (contrasting results or evidence is not conclusive). The drugs belonging to this group were further subdivided into two subgroups: (a) Drugs with no severe adverse events (b) Unsafe drugs or with complex indications for use (e.g. special diets) or important pharmacological interactions
Level IV	Drugs of proven efficacy but with frequent and severe adverse events or drugs whose efficacy has not been proven from a clinical or statistical point of view (no difference with respect to placebo). Drugs with unknown clinical patient benefit or statistical significance of efficacy (data unavailable or insufficient)

Assessment of the clinical effectiveness of treatments

Preventive drugs

+++	The majority (≥50 %) of the patients experienced a reduction, of at least 50 %, in the frequency (and intensity) of attacks
++	Many patients (from ≥30 to <50 %) experienced a reduction, of at least 50 %, in the frequency (and intensity) of attacks
+	Some of the patients (from ≥20 to <30 %) experienced a reduction, of at least 50 %, in the frequency (and intensity) of attacks
0	Less than 20 % of the treated patients received a clinical benefit
?	The members of the Ad Hoc Committee were unable to express any judgement on effectiveness based on their personal clinical impressions

Anmerkung zur Leitlinie: unklar, ob eine Level I Empfehlung zwangsläufig mit hoher Evidenzstufe verbunden ist, oder ob ein hoher klinischer Effekt gezeigt unter geringerer Studienqualität ausreicht.

Empfehlungen

1. A good response to prophylactic treatment is obtained if there is at least a 50 % reduction in the frequency and severity of migraine attacks and a significant improvement in the quality of life is reached.

2. To minimize side effects and improve patient's compliance, the most appropriate drug should be taken at the lowest dosage, preferentially as a monotherapy. Doses can be slowly increased until therapeutic goals are achieved without side effects.

3. Prophylactic treatment should be maintained for at least 3 months. Clinical benefit may take some time to be obtained.

4. Prophylactic drugs should be chosen based on patient's comorbidities.

5. Particular attention should be devoted to drug–drug and drug–food interactions.

6. Most preventive drugs may have a teratogenic effect. Women should use a safe contraception.

7. Prophylactic treatment during pregnancy should be limited to special situations, and in these cases drugs with lowest risk for the foetus should be preferred.

Drugs for the preventive treatment of migraine with a level of recommendation I and II

Drug (by oral route)	Daily dosage (mg)	Level of recommendation	Comments
Beta-blockers			
Propranolol	80–240	I	Useful in patients with hypertension, anxiety and panic disorders. It can exacerbate depression. Do not use with ergotamine. Increase doses gradually. Particularly useful in patients with essential tremor. Most frequent adverse events are fatigue, mood disorders, nightmares. Other side effects are bradicardia, orthostatic hypotension, impotence, hallucinations, weight gain
Metoprolol	50–200	I	Same indications and side effects as for propranolol, excluding essential tremor
Atenolol	100	I	Same indications and side effects as for propranolol, excluding essential tremor
Bisoprolol	5–10	II	Same indications and side effects as for propranolol, excluding essential tremor
Nadolol	40–240	II	
Calcium channel blockers			
Flunarizine	5–10	I	Use administration schedules with periodic suspensions (i.e. 5 days/week or 3 weeks/month), to avoid the accumulation of the drug Most frequent side effects are weight gain, sedation and depression. Extrapyramidal symptoms may be observed in elderly patients. The recommended dose to reduce adverse events is 5 mg
Cinnarizine	75–150	II	Most frequent side effects are weight gain and drowsiness
Antidepressants tricyclic			
Amitriptyline	10–75	I	Dosages tested in clinical trials, the majority of them dated, are in general higher than those usually used in clinical practice for prophylactic treatment of migraine A progressive increase in doses is recommended until maintenance doses are reached in order to reduce adverse events Most frequent side effects are drowsiness, weight gain and anticholinergic symptoms. Particularly useful in patients with depression, concurrent migraine and tension-type headache. Higher doses should be used in patients with comorbid depression
Antiepileptic drugs			
Sodium valproate	500–1,500	I	Controlled release formulations are available with a better tolerability profile. Recommended for patients with prolonged or atypical migraine aura. Not recommended in patients with liver disease and haemorrhagic diathesis. A progressive increase in doses is recommended. Frequent adverse events include nausea, asthenia, somnolence. Other side effects include weight gain, hair loss and tremor. Teratogenic potential
Topiramate	50–100	I	Gradual increase of dosage is recommended. Frequent, not serious adverse events include paresthesiae, memory and concentration disturbances, nausea, weight loss and drowsiness. Rare serious adverse events include kidney stones, narrow-angle glaucoma
Gabapentin	900–2,400	II	Recommended for elderly patients. Well tolerated
5HT-antagonists			
Pizotifen	1.5	II	Frequent adverse events include weight gain and somnolence
Other drugs			
Dihydroergotamine	10	II	Do not use within 6 h after triptan administration. Useful for intermittent or short-term prophylaxis. Withdrawal could be associated with rebound headache
Dihydroergocriptine	20	II	Mild side effects. Withdrawal could be associated with rebound headache
Onabotulinum toxin type A	155–195 U[a]	IV (episodic migraine)	The majority of controlled studies have not provided conclusive results in episodic migraine
		I (chronic migraine)	It is effective in chronic migraine. Costs are comparable to topiramate 100 mg for a period of treatment of 3 months and lower than topiramate for a period of 4 months

Cochrane Library **(Cochrane Database of Systematic Reviews, Health Technology Assessment Database) am 13.03.2017**

#	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 2012 to 2017, in Cochrane Reviews (Reviews only) and Technology Assessments

SR, HTAs in Medline (PubMed) am 13.03.2017

#	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 Filters: Publication date from 2012/03/01 to 2017/03/13

Leitlinien in Medline (PubMed) am 13.03.2017

#	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 guideline*[Title] OR Consensus Development Conference[ptyp] OR Consensus Development Conference, NIH[ptyp] OR recommendation*[Title])
6	#5 Filters: Publication date from 2012/03/01 to 2017/03/13

Literatur:

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