Gemeinsamer Bundesausschuss

Kriterien zur Bestimmung der zweckmäßigen Vergleichstherapie

und

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

Vorgang: 2017-12-01-D-325 Perampanel

Stand: Dezember 2017

I. Zweckmäßige Vergleichstherapie: Kriterien der VerfO

Zusatztherapie bei primär generalisierten tonisch-klonischen Anfällen bei Erwachsenen und Jugendlichen ab 12 Jahren mit idiopathischer generalisierter Epilepsie.

Kriterien gemäß 5. Kapitel § 6 Absatz 3 Satz 2 VerfO

Sofern als Vergleichstherapie eine Arzneimittelanwendung in Betracht kommt, muss das Arzneimittel grundsätzlich eine Zulassung für das Anwendungsgebiet haben.	*Siehe unter 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.*
Als Vergleichstherapie sollen bevorzugt Arzneimittel-anwendungen oder nicht-medikamentöse Behandlungen herangezogen werden, deren patientenrelevanter Nutzen durch den Gemeinsamen Bundesausschuss bereits festgestellt ist.	*Nicht angezeigt.*
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 Beratungsanforderung/Fachinformation)
Zu bewertendes Arzneimittel	
Perampanel **N03AX22** **Fycompa®**	Zusatztherapie bei primär generalisierten tonisch-klonischen Anfällen bei Erwachsenen und Jugendlichen ab 12 Jahren mit idiopathischer generalisierter Epilepsie.
Valproinsäure N03AG01 Valproinsäure-ratiopharm	Zur Behandlung von: - generalisierten Anfällen in Form von Absencen, myoklonischen Anfällen und tonisch-klonischen Anfällen - […]
Phenobarbital N03AA02 Phenobarbital-neuraxpharm®	Verschiedene Formen der Epilepsie (Grand-mal, Impulsiv-Petit-mal).
Phenytoin N03AB02 Phenytoin AWD	Fokal eingeleitete generalisierende und generalisierte tonisch-klonische Anfälle (Grand mal) sowie einfache (z.B. Jackson-Anfälle) und komplexe Partialanfälle (z.B. Temporallappenanfälle).
Lamotrigin N03AX09 Lamotrigin Desitin®	<u>Erwachsene und Jugendliche ab 13 Jahren:</u> Zusatz- oder Monotherapie partieller und generalisierter Anfälle einschließlich tonisch-klonischer Anfälle.
Topiramat N03AX11 Topiramat Desitin	Zusatztherapie bei Kindern ab 2 Jahren, Jugendlichen und Erwachsenen mit fokalen Anfällen mit oder ohne sekundärer Generalisierung oder primär generalisierten tonisch-klonischen Anfällen […].
Levetiracetam N03AX14 Levetiracetam Abz	Zusatzbehandlung - […] - primär generalisierter tonisch-klonischer Anfälle bei Erwachsenen und Jugendlichen ab 12 Jahren mit Idiopathischer Generalisierter Epilepsie.

Clobazam N05BA09 Frisium®	Zusatztherapie bei Patienten mit epileptischen Anfällen, die mit einer Standardbehandlung – bestehend aus einem oder mehreren Antiepileptika – nicht anfallsfrei waren.
Clonazepam N03AE01 Clonazepam-neuraxpharm®	- Zur Behandlung der Mehrheit der klinischen Formen der Epilepsie des Säuglings und des Kindes, insbesondere typischen und atypischen Petit-mal-Epilepsien, primär oder sekundär generalisierten tonisch-klonischen Krisen. - Zur Behandlung von Epilepsien - besonders fokalen Anfällen - des Erwachsenen.
Primidon N03AA03 Liskantin®	- Epileptische Anfälle, besonders Grand-mal-Anfälle, fokale Anfälle (Jackson-Anfälle, Adversivkrämpfe, psychomotorische Anfälle u.a.), myoklonische Anfälle des Jugendalters (Impulsiv-Petit-mal) - […]

Quellen: AMIS-Datenbank, Fachinformationen

Gemeinsamer Bundesausschuss

Abteilung Fachberatung Medizin

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

Vorgang: 2017-B-264z (Perampanel nAWG)

Auftrag von:	Abt. AM
bearbeitet von:	Abt. FB Med
Datum:	28.11.2017

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 evidenzbasierten systematischen Leitlinien zur Indikation *tonisch-klonischer Krampfanfall*/*Epilepsie* durchgeführt. Der Suchzeitraum wurde auf die letzten 5 Jahre eingeschränkt und die Recherche am 15.11.2017 abgeschlossen. Die Suche erfolgte in den aufgeführten Datenbanken bzw. Internetseiten folgender Organisationen: The Cochrane Library (Cochrane Database of Systematic Reviews, Health Technology Assessment Database), MEDLINE (PubMed), AWMF, Clinical Evidence, DAHTA-Datenbank, 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 90 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 3 Quellen, die in die synoptische Evidenz-Übersicht aufgenommen wurden.

Indikation:

Zusatztherapie bei primär generalisierten tonisch-klonischen Anfällen bei Erwachsenen und Jugendlichen ab 12 Jahren mit idiopathischer generalisierter Epilepsie

Abkürzungen:

AED	Anti-epileptic drug
AWMF	Arbeitsgemeinschaft der wissenschaftlichen medizinischen Fachgesellschaften
DAHTA	Datenbank der Deutsche Agentur für Health Technology Assessment
G-BA	Gemeinsamer Bundesausschuss
GIN	Guidelines International Network
GRADE	Grading of Recommendations Assessment, Development and Evaluation
GTC	Generalized tonic-clonic
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen
NGC	National Guideline Clearinghouse
NHS CRD	National Health Services Center for Reviews and Dissemination
NICE	National Institute for Health and Care Excellence
SIGN	Scottish Intercollegiate Guidelines Network
TRIP	Turn Research into Practice Database
WHO	World Health Organization

IQWiG Berichte/G-BA Beschlüsse

Es wurden keine relevanten Quellen identifiziert.

Cochrane Reviews

Es wurden keine relevanten Quellen identifiziert.

Systematische Reviews

Cross JH, 2015 [1]. **Epilepsy (generalised seizures)**	1. Fragestellung What are the effects of additional treatments in people with drug-resistant epilepsy characterised by generalised seizures?
	2. Methodik Population: people with generalised seizures (excluding status epilepticus) or where a subgroup analysis was carried out in people with generalised epilepsy (mehr Details, sofern verfügbar im Ergebnisteil) Intervention: lamotrigine, levetiracetam, lacosamide, perampanel, zonisamide Komparator: placebo or other antiepileptic drugs Endpunkt: Seizure frequency percentage reduction in seizure frequency, proportion of responders (response defined as at least 50% reduction in seizure frequency); quality of life; adverse effects. Recherche: The following databases were used to identify studies for this systematic review: Medline 1966 to April 2014, Embase 1980 to April 2014, and The Cochrane Database of Systematic Reviews 2014, issue 4 (1966 to date of issue). Additional searches were carried out in the the Database of Abstracts of Reviews of Effects (DARE) and Health Technology Assessment (HTA) database. Anzahl eingeschlossene Studien/Patienten (Gesamt): siehe Ergebnisteil Qualitätsbewertung der Studien: keine Qualitätsbewertung der Studien, aber Einschätzung des Evidenzgrades mittels GRADE
	3. Ergebnisdarstellung

TABLE GRADE evaluation of interventions for Epilepsy (generalised seizures)

Important outcomes	Seizure frequency, quality of life, adverse effects								
Number of studies (participants)	Outcome	Comparison	Type of evidence	Quality	Consistency	Directness	Effect size	GRADE	Comment
What are the effects of additional treatments in people with drug-resistant epilepsy characterised by generalised seizures?									
3 (296) [22] [23] [24]	Seizure frequency	Adding lamotrigine *v* adding placebo	4	−1	0	0	0	Moderate	Quality point deducted for incomplete reporting of results
2 (284) [28]	Seizure frequency	Adding levetiracetam *v* adding placebo	4	−1	0	0	0	Moderate	Quality point deducted for incomplete reporting of results (adults/children)

Type of evidence: 4 = RCT; 2 = Observational.
Consistency: similarity of results across studies.
Directness: generalisability of population or outcomes.
Effect size: based on relative risk or odds ratio.

ADDITION OF LACOSAMIDE COMPARED WITH ADDING PLACEBO IN PEOPLE WITH DRUG-RESISTANT EPILEPSY CHARACTERISED BY GENERALISED SEIZURES.

- No RCTs and no systematic review identified

Clinical Guide

Lacosamide is available to be used as an add-on agent where existing anti-epileptic drugs have failed. Individuals initiated on this medication should be under on-going review by an epilepsy specialist.

ADDITION OF LAMOTRIGINE COMPARED WITH ADDING PLACEBO IN PEOPLE WITH DRUG-RESISTANT EPILEPSY CHARACTERISED BY GENERALISED SEIZURES

Seizure frequency

Adding lamotrigine seems more effective than adding placebo at decreasing the frequency of generalised tonic clonic seizures and at increasing the proportion of people with a 50% or greater reduction in generalised seizures (moderate-quality evidence).

Benefits:

- Based on one systematic review (search date 2010, 2 RCTs, 143 people, aged 2–55 years, 51% men) and one subsequent RCT (153 people, aged at least 13 years, 51% male)
- each trial reported significant advantage of lamotrigine vs placebo in patients with primary generalised tonic clonic seizures:
    - o 50% or greater reduction in seizure rate: 50-75 % with lamotrigine vs 32-49 % with placebo

Harms:

- Rash (one study: 7/26 [27%] with lamotrigine v 0/26 [0%] with placebo; significance assessment not reported)
- higher rates of dizziness, nausea, and somnolence with adding lamotrigine compared with adding placebo to usual care (one study: dizziness: 5% with lamotrigine v 2% with placebo; nausea: 5% with lamotrigine v 3% with placebo; somnolence: 5% with lamotrigine v 2% with placebo; absolute results and significance assessment not reported)

	Clinical guide Lamotrigine has been demonstrated to be an effective medication in add-on therapy to first-line anti-epileptic drugs. It has been demonstrated to be effective in most epilepsies characterised by generalised seizures, although the clinician should note it may aggravate myoclonic seizures. Although there is an early risk of rash on initiation, in the longer term the medication appears to have a beneficial safety profile. The risk is highest when introduced with sodium valproate, although synergistic action may be seen on this combination. Although its safety profile for use in pregnancy appears favourable, adjustment in dose is likely to be required in some women through pregnancy and postpartem. ADDITION OF LEVETIRACETAM COMPARED WITH ADDITION OF PLACEBO IN PEOPLE WITH DRUG-RESISTANT EPILEPSY CHARACTERISED BY GENERALISED SEIZURES Seizure frequency Adding levetiracetam seems to be more effective than adding placebo at increasing the proportion of responders (defined by at least a 50% reduction in seizure frequency) and seems to be more effective at increasing the proportion of people who are seizure-free at 16 and 24 weeks (moderate-quality evidence). Benefits - based on one systematic review (search date 2012, 2 RCTs, 284 people with primary generalised seizure, one RCT in patients with generalised tonic clonic seizures (164 people, aged 4–65 years [mean age 29 years], 44% male), one RCT in patients with myoclonic seizures (120 people, aged 12–65 years, 36% male,)) - significantly increased proportion of responders (defined as at least a 50% reduction in seizure frequency per week from baseline) compared with placebo at 16 or 24 weeks (50% reduction in weekly seizure frequency: 93/140 [66%] with levetiracetam v 52/144 [36%] with placebo; OR 3.70, 95% CI 2.24 to 6.12, P <0.00001) - significantly increased proportion of people seizure-free compared with placebo at 16 to 24 weeks (37/140 [26%] with levetiracetam v 11/144 [8%] with placebo; OR 4.59, 95% CI 2.20 to 9.56, P <0.00001) Harms - no significant difference in rates of adverse drug reactions between levetiracetam and placebo in both RCTs. - review of 13 RCTs of levetiracetam in various different population groups: o adverse effects of somnolence, agitation, dizziness, asthenia, and infection more often in the levetiracetam group o serious adverse reactions such as kidney and liver functional abnormality, rash, and decreases in white blood cells

	occurred rarely in both drug and placebo groups Clinical guide - Levetiracetam has been shown to be an effective as an add-on to existing treatment in epilepsy characterised by generalised tonic clonic seizures. - Lack of interactions with other medications can put levetiracetam ahead of lamotrigine in the treatment of individuals with epilepsy characterised by generalised seizures. ADDITION OF <u>ZONISAMIDE</u> COMPARED WITH THE ADDITION OF PLACEBO IN PEOPLE WITH DRUG-RESISTANT EPILEPSY CHARACTERISED BY GENERALISED SEIZURE - No RCTs and no systematic review identified Comment - Zonisamide is increasingly used as add-on therapy where other medication has failed. Somnolence and loss of appetite are noticed in clinical practice. There is little evidence of aggravation of seizures. Clinical Guide - Zonisamide is available to be used as an add-on agent where existing anti-epileptic drugs have failed. Individuals initiated on this medication should be under on-going review by an epilepsy specialist.
	4. Anmerkungen/Fazit der Autoren Adding lamotrigine or levetiracetam seems to be more effective than adding placebo at reducing seizure frequency in people with drug-resistant epilepsy characterised by generalised seizures. We don’t know about the benefits of adding lacosamide, perampanel, or zonisamide compared to adding placebo, as we found no systematic reviews or RCTs. 5. *<u>Kommentare zum Review</u>: systematisches Review zu Levetiracetam enthielt auch eine Studie mit Patienten mit myoklonischen Anfällen*

Leitlinien

<table>
<tr>
<td>Scottish Intercollegiate Guidelines Network (SIGN), 2015 [3].

Diagnosis and management of epilepsy in adults. A national clinical guideline</td>
<td>Fragestellung/Zielsetzung: This guideline provides recommendations based on current evidence for best practice in the diagnosis and management of epilepsy in adults.</td>
</tr>
<tr>
<td></td>
<td>Methodik

Grundlage der Leitlinie

- Update of a previous version (SIGN 70) of the guideline: Where no new evidence was identified to support an update, text and recommendations are reproduced verbatim from SIGN 70. The original supporting evidence was not reappraised by the current guideline development group.
- systematic review of the literature (Medline, Embase, Cinahl, PsycINFO and the Cochrane Library) search period: 2001–2013
- systematic quality assessment of identified studies
- developed by multidisciplinary groups of practising healthcare professionals using a standard methodology (AGREE II Standard)
- guideline is considered for review in three years

LoE / GoR

<table>
<tr><th colspan="2">KEY TO EVIDENCE STATEMENTS AND GRADES OF RECOMMENDATIONS</th></tr>
<tr><td colspan="2">LEVELS OF EVIDENCE</td></tr>
<tr><td>1++</td><td>High-quality meta-analyses, systematic reviews of RCTs, or RCTs with a very low risk of bias</td></tr>
<tr><td>1+</td><td>Well-conducted meta-analyses, systematic reviews, or RCTs with a low risk of bias</td></tr>
<tr><td>1-</td><td>Meta-analyses, systematic reviews, or RCTs with a high risk of bias</td></tr>
<tr><td>2++</td><td>High-quality systematic reviews of case-control or cohort studies
High-quality case-control or cohort studies with a very low risk of confounding or bias and a high probability that the relationship is causal</td></tr>
<tr><td>2+</td><td>Well-conducted case-control or cohort studies with a low risk of confounding or bias and a moderate probability that the relationship is causal</td></tr>
<tr><td>2-</td><td>Case-control or cohort studies with a high risk of confounding or bias and a significant risk that the relationship is not causal</td></tr>
<tr><td>3</td><td>Non-analytic studies, eg case reports, case series</td></tr>
<tr><td>4</td><td>Expert opinion</td></tr>
<tr><td colspan="2">GRADES OF RECOMMENDATION</td></tr>
<tr><td colspan="2">Note: The grade of recommendation relates to the strength of the evidence on which the recommendation is based. It does not reflect the clinical importance of the recommendation.</td></tr>
<tr><td>A</td><td>At least one meta-analysis, systematic review, or RCT rated as 1++,
and directly applicable to the target population; or
A body of evidence consisting principally of studies rated as 1+,
directly applicable to the target population, and demonstrating overall consistency of results</td></tr>
<tr><td>B</td><td>A body of evidence including studies rated as 2++,
directly applicable to the target population, and demonstrating overall consistency of results; or
Extrapolated evidence from studies rated as 1++ or 1+</td></tr>
<tr><td>C</td><td>A body of evidence including studies rated as 2+,
directly applicable to the target population and demonstrating overall consistency of results; or
Extrapolated evidence from studies rated as 2++</td></tr>
<tr><td>D</td><td>Evidence level 3 or 4; or
Extrapolated evidence from studies rated as 2+</td></tr>
<tr><td colspan="2">GOOD PRACTICE POINTS</td></tr>
<tr><td>✓</td><td>Recommended best practice based on the clinical experience of the guideline development group</td></tr>
</table>

<u>Empfehlungen</u>

<u>4.3.2 drug -resistant generalised or unclassified epilepsy</u></td>
</tr>
</table>

	RCTs have shown that lamotrigine,[97] levetiracetam,[97,111] sodium valproate and topiramate[87] are all effective in the adjunctive treatment of generalised epilepsy. Ethosuximide remains useful in patients with absence seizures. Drop attacks in patients with Lennox-Gastaut syndrome may respond to rufinamide.[116] 1++ Lamotrigine acts synergistically with sodium valproate to produce a better therapeutic outcome.[109] Lacosamide was shown to be effective and well tolerated. Treatment response was good regardless of type of concomitant AED but when lacosamide was used in combination with a non-sodium channel blocker response rates were higher and adverse events less frequent.[110] 2+ A **Lamotrigine, levetiracetam, ethosuximide, sodium valproate and topiramate may be used in the adjunctive treatment of generalised epilepsy.** B **The choice of drugs in combination should be matched to the patient's seizure type(s) and should, where possible, be limited to two or at most three antiepileptic drugs.** Referenzen: 87. Marson AG, Al-Kharusi AM, Alwaidh M, Appleton R, Baker GA, Chadwick DW, et al. The SANAD study of effectiveness of valproate, lamotrigine, or topiramate for generalised and unclassifiable epilepsy: an unblinded randomised controlled trial. Lancet 2007;369(9566):1016-26. 97. Maguire M, Marson AG, Ramaratnam S. Epilepsy (generalised). Clinical Evidence 2012;02:1201. 109. Brodie MJ, Yuen AW. Lamotrigine substitution study: evidence for synergism with sodium valproate? 105 Study Group. Epilepsy Res 1997;26(3):423-32. 110. V illanueva V, Lopez-Gomariz E, Lopez-Trigo J, Palau J, Garcia M, Villarroya T, et al. Rational polytherapy with lacosamide in clinical practice: results of a Spanish cohort analysis RELACOVA. Epilepsy Behav 2012;23(3):298-304. 111. Lo BW, Kyu HH, Jichici D, Upton AM, Akl EA, Meade MO. Metaanalysis of randomized trials on first line and adjunctive levetiracetam. Can J Neurol Sci 2011;38(3):475-86. *<u>Kommentare zur Leitlinie:</u> keine spezifischen Empfehlungen für Zusatztherapie bei primär generalisierten tonisch-klonischen Anfälle, sondern allgemein für generalisierte Epilepsie; Zielpopulation: Erwachsene*
National Institute for Health and Care Excellence (NICE), 2012 [2]. Epilepsies: diagnosis and management	Clinical guidelines are defined as 'systematically developed statements to assist practitioner and patient decisions about appropriate healthcare for specific clinical circumstances'. This guideline is a partial update of the 2004 guideline and offers best practice advice on the treatment and management of the epilepsies in children and adults.
	Methodik Grundlage der Leitlinie: - Repräsentatives Gremium - Formulierung von PICO-Fragen - Systematische Literaturrecherche in mehreren Datenbanken (bis 3 Juni 2010), Datenextraktion, Qualitätsbewertung der identifizierten Literatur - Ein regelmäßiger Abgleich der Empfehlung mit neuer Evidenz findet statt (letztmalig 10 September 2013 – Evidence Update 53). Im Bezug zur Indikation wurde keine neue Evidenz identifiziert, die zu einer Änderung der bisherigen Empfehlungen führen könnte. - Bewertung der Evidenz und Stärke der Empfehlung nach GRADE - keine direkte Verknüpfung der Empfehlungen mit der Evidenz
	<u>10.5.7 Adjunctive therapy for the treatment of generalised tonic-clonic</u>

	seizures Summary of Clinical Evidence Clobazam versus placebo (1 RCT: Aucamp, 1985) - Significantly more participants taking clobazam adjunctive therapy were seizure free compared to placebo (7/9 (77.8%) vs. 1/9 (11.1%)). However, there is uncertainty about the magnitude of the clinical effect. (VERY LOW QUALITY (limited number of events, Cross-over RCT with unclear randomistaion and allocation concealment) Lamotrigine versus placebo (1 RCT: Biton, 2005) - Significantly more participants in lamotrigine adjunctive therapy achieved at least a 50% reduction in seizure frequency compared to placebo. (37/58 (63.8%) vs 23/59 (39%); LOW QUALITY, unclear randomisation method and allocation concealment. High drop-out rate.) - No significant difference between lamotrigine adjunctive therapy and placebo for the proportion of seizure free participants. (22/58 - (37.9%) vs. 14/59 (23.7%); VERY LOW QUALITY, Unclear randomisation method and allocation concealment. High drop-out rate. Confidence interval crossed both MID points) - No significant difference between lamotrigine adjunctive therapy and placebo for the proportion of participants having their treatment withdrawn due to adverse events. (5/58 (8.6%) vs. 2/59 (3.4%); VERY LOW QUALITY, Unclear randomisation method and allocation concealment. High drop-out rate. Limited number of events. Confidence interval crossed both MID points) Lamotrigine extended-release versus placebo - Significantly more participants taking lamotrigine extended-release adjunctive therapy were seizure free compared to participants taking placebo. (MODERATE QUALITY) - Significantly more participants taking lamotrigine extended-release adjunctive therapy achieved at least a 50% reduction in seizure frequency compared to participants taking placebo. (MODERATE QUALITY) - No significant difference between lamotrigine extended-release adjunctive therapy and placebo for the proportion of participants having treatment withdrawn due to adverse events. (VERY LOW QUALITY) - No significant difference between lamotrigine extended-release adjunctive therapy and placebo for the incidence of the following adverse events: headache & vomiting Levetiracetam versus placebo (1 RCT: Berkovic, 2007)

	- Significantly more participants taking levetiracetam adjunctive therapy were seizure free compared to participants taking placebo. (27/80 (33.8%) vs. 9/84 (10.7%), HIGH QUALITY) - Significantly more participants taking levetiracetam adjunctive therapy achieved at least a 50% reduction in seizure frequency compared to participants taking placebo. (57/80 (71.3%), 38/84 (45.2%); HIGH QUALITY) - No significant difference between levetiracetam adjunctive therapy and placebo for the proportion of participants having treatment withdrawn due to lack of efficacy. (0/80 (0%) vs. 3/84 (3.6%), LOW QUALITY) - No significant difference between levetiracetam adjunctive therapy and placebo for the proportion of participants having treatment withdrawn due to adverse events. (1/80 (1.3%) vs. 4/84 (4.8%), LOW QUALITY) - No significant difference between levetiracetam adjunctive therapy and placebo for the incidence of the following adverse events: o nasopharyngitis (11/80 (13.8%) vs. 4/84 (4.8%), MODERATE QUALITY) o headache (8/80 (10%) vs. 10/84 (11.9%), LOW QUALITY), o fatigue (8/80 (10%) vs. 7/84 (8.3%); LOW QUALITY), o aggravation of seizures (8/80 (10%) vs. 13/84 (15.5%), LOW QUALITY) - No statistically significant difference between levetiracetam adjunctive therapy and placebo in achieving a greater improvement in the quality of life. (18/47 (38.3%) vs. 16/56 (28.6%), LOW QUALITY) <u>Topiramate versus placebo (2 RCTs: Biton 1999, Barrett 1997 (unpublished))</u> - Significantly more participants taking topiramate adjunctive therapy compared to placebo achieved at least 50% reduction in seizure frequency. (22/39 (56.4%) vs. 8/41 (19.5%); VERY LOW QUALITY) - No significant difference between topiramate adjunctive therapy and placebo in achieving a greater proportion of seizure-free participants. (5/39 (12.8%) vs. 2/41 (4.9%); VERY LOW QUALITY) - No significant difference between topiramate adjunctive therapy and carbamazepine monotherapy for the proportion of participants who withdrew due to adverse events (1/39 (2.6%) vs. 1/41 (2.4%), VERY LOW QUALITY) - No statistically significant difference between topiramate adjunctive therapy and placebo for the incidence for adverse events (VERY LOW QUALITY) **Recommendation:**

	Offer clobazam, lamotrigine, levetiracetam, sodium valproate, or topiramate as adjunctive treatment to children, young people and adults with GTC seizures if first-line treatments (see recommendations 90, 91 and 92) are ineffective or not tolerated. Be aware of teratogenic risks of sodium valproate (see recommendation 83). [new 2012] Relative values of different outcomes: The most important outcomes were adverse effects and 50% reduction in seizure frequency. Trade off between clinical benefits and harms: Lamotrigine, levetiracetam and topiramate as adjunctive therapies all significantly reduced seizure frequency by at least 50% when compared to placebo. There was significantly more seizure freedom with clobazam and levetiracetam compared to placebo but lamotrigine and topiramate showed no difference compared to placebo. There was no significant difference for any adverse event, withdrawal due to adverse events or lack of efficacy for lamotrigine, levetiracetam and topiramate adjunctive therapies when compared to placebo. Quality of evidence: Diagnostic, demographic and dosing considerations must be taken into consideration. There was a lack of power in the studies particularly with regard to side-effects. The overall quality of evidence was low: some had no details of randomisation or allocation concealment, high drop-out rate or a very small sample size. Other considerations There is a pharmacodynamic interaction between levetiracetam and carbamazepine and between lamotrigine and carbamazepine so side effects may be enhanced. Sodium valproate inhibits the metabolism of lamotrigine and this must be taken into consideration when introducing or withdrawing either medication. On withdrawal of sodium valproate, lamotrigine levels may drop and this may be the reason for breakthrough seizures. There should be a concomitant increase in lamotrigine dose. Care should be taken when withdrawing clobazam with a slow withdrawal up to 4-6 months in view of the risk of withdrawal seizures. Topiramate may affect phenytoin levels. Referenzen: Aucamp AK. Clobazam as adjunctive therapy in uncontrolled epileptic patients. Current Therapeutic Research, Clinical & Experimental. 1985; 37:1098-1103. Biton V, Sackellares JC, Vuong A et al. Double-blind, placebo-controlled study of lamotrigine in primary generalized tonic-clonic seizures. Neurology. 2005; 65(11):1737-1743. Berkovic SF, Knowlton RC, Leroy RF et al. Placebo-controlled study of levetiracetam in

	idiopathic generalized epilepsy. Neurology. 2007; 69(18):1751-1760. Biton V, Montouris GD, Ritter F et al. A randomized, placebo-controlled study of topiramate in primary generalized tonic-clonic seizures. Topiramate YTC Study Group. Neurology. 1999; 52(7):1330-1337. *<u>Anmerkung:</u> Quelle für Barrett 1997 (unpublished) konnte im Literaturverzeichnis nicht gefunden werden*

Detaillierte Darstellung der Recherchestrategie

Cochrane Library (Cochrane Database of Systematic Reviews, Health Technology Assessment Database) am 14.11.2017

#	Suchfrage
1	[mh “Epilepsy, Tonic-Clonic”]
2	(epilep* or seizure* or convulsion*):ti,ab,kw
3	(Grand next Mal):ti,ab,kw or (“Tonic-Clonic” or (tonic next clonic)):ti,ab,kw
4	#1 or (#2 and #3)
5	#4 Publication Date from 2012-2017

SR, HTAs in Medline (PubMed) am 14.11.2017

#	Suchfrage
1	Epilepsy, Tonic-Clonic[mh]
2	epilep*[tiab] or seizure*[tiab] OR convulsion*[tiab]
3	„Grand Mal“[tiab] OR “Tonic-Clonic”[tiab] OR (Tonic[tiab] and Clonic[tiab])
4	#1 OR (#2 AND #3)
5	(#4) 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]))))
6	((#5) AND ("2012/11/01"[PDAT] : "2017/11/30"[PDAT]) NOT "The Cochrane database of systematic reviews"[Journal]) NOT (animals[MeSH:noexp] NOT (Humans[MesH] AND animals[MeSH:noexp]))

Leitlinien in Medline (PubMed) am 14.11.2017

#	**Suchfrage**
1	(Epilepsy, Tonic-Clonic[mh]) OR Epilepsy, Generalized[mh:noexp]
2	epilep*[tiab] OR seizure*[tiab] OR convulsion*[tiab]
3	„Grand Mal“[tiab] OR “Tonic-Clonic”[tiab] OR (Tonic[tiab] AND Clonic[tiab])
4	#1 OR (#2 AND #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) AND ("2012/11/01"[PDAT] : "2017/11/30"[PDAT])) NOT (animals[MeSH:noexp] NOT (Humans[MesH] AND animals[MeSH:noexp])) NOT ("The Cochrane database of systematic reviews"[Journal]))

Literatur

1. **Cross JH.** Epilepsy (generalised seizures). BMJ Clin Evid 2015;2015:pii1201.

2. **National Institute for Health and Care Excellence (NICE).** Epilepsies: diagnosis and management [online]. 02.2016. London (GBR): NICE; 2012. [Zugriff: 15.11.2017]. (Clinical guideline; Band 137). URL: https://www.nice.org.uk/guidance/cg137/evidence/full-guideline-pdf-6664855034.

3. **Scottish Intercollegiate Guidelines Network (SIGN).** Diagnosis and management of epilepsy in adults. A national clinical guideline [online]. 05.2015. Edingburgh (GB),: SIGN; 2015. [Zugriff: 15.11.2017]. (SIGN publication; Band 143). URL: http://www.sign.ac.uk/pdf/SIGN143.pdf.