Gemeinsamer Bundesausschuss

Kriterien zur Bestimmung der zweckmäßigen Vergleichstherapie

und

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

Vorgang: 2019-B-090 Perampanel

Stand: Juni 2019

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

Perampanel (2019-B-090)
Zur Behandlung der idiopathischen generalisierten Epilepsie (primär generalisierte tonisch-klonische Anfälle)

Kriterien gemäß 5. Kapitel § 6 VerfO	
Sofern als Vergleichstherapie eine Arzneimittelanwendung in Betracht kommt, muss das Arzneimittel grundsätzlich eine Zulassung für das Anwendungsgebiet haben.	*Siehe Übersicht „II. Zugelassene Arzneimittel im Anwendungsgebiet“.*
Sofern als Vergleichstherapie eine nicht-medikamentöse Behandlung in Betracht kommt, muss diese im Rahmen der GKV erbringbar sein.	*„nicht angezeigt“*
Beschlüsse/Bewertungen/Empfehlungen des Gemeinsamen Bundesausschusses zu im Anwendungsgebiet zugelassenen Arzneimitteln/nicht-medikamentösen Behandlungen	*Beratungen* – *2017-B-264-z Perampanel (UA am 12.12.2017)* – *2015-B-016 Perampanel (Antwortschreiben)* *Beschlüsse* – *D-325 Perampanel (nAWG, Beschluss vom 17.05.2018)*
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:	
Perampanel N03AX22 Fycompa® 2, 4, 6, 8, 10 und 12 mg Filmtabletten	Primär generalisierte tonisch-klonische Anfälle: Zusatztherapie bei pädiatrischen Patienten im Alter von 7 bis 11 Jahren mit idiopathischer generalisierter Epilepsie.
Valproinsäure N03AG01 z.B. Convulex® 300 und 500mg magensaftresistente Kapsel	Zur Behandlung von: – **Generalisierten Anfällen** in Form von Absencen, myoklonischen Anfällen und tonisch-klonischen Anfällen, – fokalen und sekundär-generalisierten Anfällen- und zur Kombinationsbehandlung bei anderen Anfallsformen, z. B. fokalen Anfällen mit einfacher und komplexer Symptomatologie sowie fokalen Anfällen mit sekundärer Generalisation, wenn diese Anfallsformen auf die übliche antiepileptische Behandlung nicht ansprechen. *Hinweis:* **Bei Kleinkindern sind valproinsäurehaltige Arzneimittel nur in Ausnahmefällen Mittel erster Wahl**; Convulex sollte nur unter besonderer Vorsicht nach strenger Nutzen-Risiko-Abwägung und möglichst als Monotherapie angewendet werden. Aus FI 4.2: Dosierungsempfehlungen für **Kinder ab 3 Monaten**.
Lamotrigin N03AX09 z.B. Lamotrigin acis 25, 50, 100 und 200 mg Tabletten	Kinder und Jugendliche von **2 bis 12 Jahren** – Zusatztherapie bei partiellen und **generalisierten Anfällen einschließlich tonisch-klonischer Anfälle** sowie bei Anfällen in Zusammenhang mit dem Lennox-Gastaut-Syndrom. – Monotherapie typischer Absencen.
Topiramat N03AX11 z.B. Topamax® 25, 50, 100 und 200 mg Filmtabletten	Monotherapie bei Erwachsenen, Jugendlichen und **Kindern ab 6 Jahren** mit fokalen Krampfanfällen mit oder ohne sekundär generalisierten Anfällen und **primär generalisierten tonisch-klonischen Anfällen.** Zusatztherapie bei **Kindern ab 2 Jahren**, Jugendlichen und Erwachsenen mit fokalen Anfällen mit oder ohne sekundärer Generalisierung oder **primär generalisierten tonisch-klonischen Anfällen** und zur Behandlung von Anfällen, die mit dem Lennox-Gastaut Syndrom assoziiert sind.

II. Zugelassene Arzneimittel im Anwendungsgebiet	
Clobazam N05BA09 Frisium®	Zusatztherapie bei **Patienten mit epileptischen Anfällen**, die mit einer Standardbehandlung – bestehend aus einem oder mehreren Antiepileptika – nicht anfallsfrei waren. (Aus FI 4.2: Dosierungsempfehlungen für **Kinder ab 6 Jahren**)
Clonazepam N03AE01 Rivotril® 0,5, 2 und 2,5 mg Tabletten	Als Zusatztherapie oder in Fällen von Nichtansprechen auf andere Arzneimittel zur Behandlung der meisten Formen der Epilepsie, insbesondere von Absencen, inklusive atypischen Absencen, Lennox-Gastaut-Syndrom sowie myoklonischen und atonischen Anfällen indiziert. Bei infantilen Krampfanfällen (inklusive des West-Syndroms) und **tonisch-klonischen Anfällen** ist Rivotril ausschließlich als Zusatztherapie oder bei Nichtansprechen auf andere Arzneimittel indiziert. (Aus FI 4.2: Dosierungsempfehlungen für Patienten **ab 0 Monaten**)
Carbamazepin N03AF01 z.B. Carbadura® 200, 300, 400 und 600 mg Retardtabletten	Epilepsie – **generalisierte tonisch-klonische Anfälle** – partielle Anfälle (Aus FI 4.2: Dosierungsempfehlungen für **Kinder ab unter 1 Jahr**)
Primidon N03AA03 z.B. Primidon Holsten 250 mg Tabletten	Partielle Anfälle mit und ohne Generalisation zu tonisch-klonischen Anfällen, **primär generalisierende tonisch-klonische Anfälle**, Absencen, myoklonische Anfälle des Jugendlichen. (Aus FI 4.2: Dosierungsempfehlungen für **Kinder ab 6 Monaten**)
Phenytoin N03AB02 z.B. Phenhydan®	Fokal eingeleitete generalisierende und **generalisierte tonisch-klonische Anfälle** (Grand mal) sowie einfache (z.B. Jackson Anfälle) und komplexe Partialanfälle(z.B. Temporallappenanfälle). Prophylaxe von Krampfanfällen, z.B. bei neurochirurgischen Eingriffen. Neurogene Schmerzzustände vom Typ des Tic-douloureux und andere zentrale oder periphere neurogene Schmerzzustände, wenn andere Therapiemaßnahmen nicht erfolgreich waren oder nicht durchführbar sind. (Aus FI 4.2: Dosierungsempfehlungen bereits für **Kinder unter 6 Jahren**)
Phenobarbital N03AA02 z.B. Phenobarbital-neuraxpharm 15 und 100 mg	– Verschiedene Formen der Epilepsie (**Grand-mal**, Impulsiv-Petit-mal) – Grand-mal-Schutz bei Petit-mal-Anfällen im Kindesalter (Aus FI 4.2: Dosierungsempfehlungen für Kinder und Erwachsene ohne Altersangaben)

II. Zugelassene Arzneimittel im Anwendungsgebiet	
Tabletten	

Quellen: AMIS-Datenbank, Fachinformationen, Stand Mai 2019.

Gemeinsamer Bundesausschuss

Abteilung Fachberatung Medizin

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

Vorgang: 2019-B-090 (Perampanel)

Auftrag von:	Abt. AM
Bearbeitet von:	Abt. FB Med
Datum:	28. Mai 2019

Inhaltsverzeichnis

Abkürzungsverzeichnis

AED	anti-epileptic drugs
AWMF	Arbeitsgemeinschaft der wissenschaftlichen medizinischen Fachgesellschaften
G-BA	Gemeinsamer Bundesausschuss
GIN	Guidelines International Network
GoR	Grade of Recommendations
HR	Hazard Ratio
IGE	idiopathic generalised epilepsy
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen
KI	Konfidenzintervall
LoE	Level of Evidence
NICE	National Institute for Health and Care Excellence
OR	Odds Ratio
PGTCS	primary generalised tonic clonic seizures
RR	Relatives Risiko
SIGN	Scottish Intercollegiate Guidelines Network
TRIP	Turn Research into Practice Database
WHO	World Health Organization

1 Indikation

Primär generalisierte tonisch-klonische Anfälle: Zusatztherapie bei pädiatrischen Patienten im Alter von 2 bis 11 Jahren mit idiopathischer generalisierter Epilepsie

2 Systematische Recherche

Es wurde eine systematische Literaturrecherche nach systematischen Reviews, Meta-Analysen und evidenzbasierten systematischen Leitlinien zur Indikation tonisch-klonische Anfälle/Epilepsie durchgeführt. Der Suchzeitraum wurde auf die letzten 5 Jahre eingeschränkt und die Recherche am 22.05.2019 abgeschlossen. Die Suche erfolgte in den aufgeführten Datenbanken bzw. Internetseiten folgender Organisationen: The Cochrane Library (Cochrane Database of Systematic Reviews), MEDLINE (PubMed), AWMF, G-BA, GIN, NICE, TRIP, SIGN, WHO. Ergänzend erfolgte eine freie Internetsuche nach aktuellen deutschen und europäischen Leitlinien. Die detaillierte Darstellung der Suchstrategie ist am Ende der Synopse aufgeführt.

Die Recherche ergab 94 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 5 Quellen, die in die synoptische Evidenz-Übersicht aufgenommen wurden.

3 Ergebnisse

3.1 G-BA Beschlüsse/IQWiG Berichte

Zur Fragestellung konnten keine relevanten G-BA Beschlüsse/IQWiG Berichte identifiziert werden.

3.2 Cochrane Reviews

Bresnahan R et al., 2019 [1].

New, published in Issue 3, 2019.

Brivaracetam add-on therapy for drug-resistant epilepsy

Fragestellung

To evaluate the efficacy and tolerability of brivaracetam when used as add-on treatment for people with drug-resistant epilepsy.

Methodik

Population:

- People of any age with drug-resistant focal-onset seizures (simple focal, complex focal, or secondary generalised tonic-clonic seizures) or generalised-onset seizures.

Intervention:

- brivaracetam in addition to an existing antiepileptic drug regimen

Komparator:

- matched placebo or active comparator in addition to an existing antiepileptic drug regimen

Endpunkte:

- 50% or greater reduction in seizure frequency (responder rate)
- Seizure freedom, Treatment withdrawal, Adverse events, Drug interactions

Recherche/Suchzeitraum:

- Cochrane Register of Studies (CRS Web); Medline (Ovid) 1946 to 8 October 2018; ClinicalTrials.gov; World Health Organization (WHO) International Clinical Trials Registry Platform (ICTRP)

Qualitätsbewertung der Studien:

- Cochrane RoB-tool

Ergebnisse

Anzahl eingeschlossener Studien:

- six studies that included a total of 2 411 participants

Charakteristika der Population:

- aged 16 to 80
- most participants had focal epilepsy (i.e. epilepsy that originates in one area of the brain)

Qualität der Studien:

- evidence was of moderate quality
- Evidence regarding the tolerability of brivaracetam, for example, the number of people who withdrew from these studies and the number of people who experienced side effects,

however, was of low quality. This means that we cannot be sure that trial findings are completely accurate, and that more research is needed to fully investigate the tolerability of brivaracetam.

Studienergebnisse:

- with brivaracetam in addition to normal antiepileptic medication a 50% or greater reduction in the frequency of seizures is almost twice as likely
- nearly six times more likely to achieve freedom from all seizures
- more likely to withdraw from studies due to side effects, but not actually more likely to experience side effects

Anmerkung/Fazit der Autoren

… we can be fairly certain that study findings showing that brivaracetam is effective in reducing the frequency of seizures in drug-resistant epilepsy are accurate. Evidence regarding the tolerability of brivaracetam, for example, the number of people who withdrew from these studies and the number of people who experienced side effects, however, was of low quality. This means that we cannot be sure that trial findings are completely accurate, and that more research is needed to fully investigate the tolerability of brivaracetam. All study participants were adults, and most had focal epilepsy. As a result, the review cannot inform us about how effective brivaracetam is in children or in individuals with other types of epilepsy, for example, generalised epilepsy, which is epilepsy that involves the whole brain.

Kommentare zum Review

- *Direkte Aussagen zu Kindern und allgemein Menschen mit primär generalisierten Anfällen nicht möglich.*

Song L et al., 2018 [5].

New, published in Issue 5, 2018

Clonazepam add-on therapy for refractory epilepsy in adults and children

Fragestellung

To assess the efficacy and tolerability of clonazepam when used as an add-on therapy for adults and children with refractory focal onset or generalised onset epileptic seizures, when compared with placebo or another antiepileptic agent.

Methodik

Population:

- children (< 16 years) or adults with drug-resistant generalised or focal onset epileptic seizures, people with eclampsia, mood disorders, schizophrenia, disorders with psychotic features, and alcohol-related disorders excluded

Intervention:

- clonazepam in addition to their regular antiepileptic drug therapy

Komparator:

- placebo or another antiepileptic agent in addition to their regular antiepileptic drug therapy

Endpunkte:

- 50% or greater reduction in seizure frequency
- total cessation of seizures
- treatment withdrawn during the course of the treatment period (due to adverse effects, lack of efficacy, or a combination of both)

Recherche/Suchzeitraum:

- Cochrane Epilepsy Group Specialized Register, Cochrane Central Register of Controlled Trials (CENTRAL) via Cochrane Register of Studies Online (CRSO), MEDLINE (Ovid 1946 to 14 September 2017), ClinicalTrials.gov, WHO International Clinical Trials Registry Platform (ICTRP)

Qualitätsbewertung der Studien:

- Cochrane RoB-tool

Ergebnisse

Anzahl eingeschlossener Studien:

- No double-blind randomised controlled trials met the inclusion criteria.

Anmerkung/Fazit der Autoren

There is no evidence from double-blind randomised controlled trials for or against the use of clonazepam as an add-on therapy for adults and children with refractory focal or generalised onset epileptic seizures.

3.3 Systematische Reviews

Colleran N et al., 2017 [2].

Anti epileptic drug trials for patients with drug resistant idiopathic generalised epilepsy: A meta-analysis

Fragestellung

What is the impact of anti-epileptic drugs for all patients with drug resistant IGE?

Methodik

Population:

- patients with drug resistant Idiopathic generalised epilepsy (IGE)

Intervention:

- various anti-epileptic drugs (AED) treatments options

Komparator:

- with each other or placebo

Endpunkte:

- efficacy (reduction in seizures, seizure freedom) and tolerability (Adverse events)

Recherche/Suchzeitraum:

- Medline, Cumulative Index to Nursing an Allied Health Literature (CINAHL), Cochrane Epilepsy Group Central Specialised Register, Cochrane Central Register of controlled Trials (CENTRAL), Embase and Lenus and Health Technology Assessment (HTA) database

Qualitätsbewertung der Studien:

- Cochrane risk of bias assessment from the Review Manager

Ergebnisse

Anzahl eingeschlossener Studien:

- 9 studies, 921 participants

Charakteristika der Population:

- Four of the trials included a total 106 children, <16 years of age [20]; 2–12 years of age [21]; <16 years of age [19] and (2–12 years of age) [24].

Referenzen aus dem Review
[19] Berkovic SF, et al. Placebo-controlled study of levetiracetam in idiopathic generalised epilepsy. Neurology 2007;69:1751–9.
[20] Biton V, et al. A randomized, placebo-controlled study of topiramate in primary generalized tonic clonic seizures. Neurology 1999;52:1330–7.
[21] Biton V, et al. Double-blind, placebo-controlled study of lamotrigine in primary generalized tonic-clonic seizures. Neurology 2005;65:1737–43.
[24] Trevathan E, et al. Lamotrigine adjunctive therapy among children and adolescents with primary generalised tonic clonic seizures. Pediatrics 2008;118:e371–8.

- Berkovic et al. 2017: Randomised double blinded placebo controlled parallel group trial of **levetiracetam** in idiopathic generalised epilepsy
  - Participants: 164 adults and children 4 to 65 years of age, >20 kg, mean age 28,75 (17 of 164 patients <16 years old), on 1–2 other AED's
  - Outcomes: Primary outcome was percentage reduction in PGTCS frequency per week over the 24 week treatment period. Secondary outcome was percentage reduction in seizure days per week (all seizures) in terms of PGTCS frequency per week and seizure days per week from prospective baseline period defined as more than 50% reduction; percentage of seizure free patients (all seizures) during the evaluation and treatment periods. Adverse events.
- Bias
  - Allocation concealment (Selection bias): not stated - Unclear risk
  - Selective reporting (Reporting bias): High rate of placebo seizure freedom, perhaps due to lifestyle changes while enrolled in a clinical trial. - High risk
  - Other bias: No standardisation of IGE diagnosis between the different recruiting centres, patients with partial in addition to generalised seizures as part of an IgE syndrome were NOT excluded, short titration time 4 weeks, patient or carer entered data in a seizure diary which may be subjective. - High risk
- Biton et al. 1999: Randomised double blind parallel-group, placebo controlled multi centre trial of **topiramate** in PGTCS
  - Participants: 80 patients, 3–59 years of age, weighed more than 25kg's, who experienced PGTCS with or without other generalised seizure types. EEG findings consistent with generalised seizures. On 1–2 other AED's.
  - Interventions: Topiramate versus placebo
  - Outcomes: Percentage reduction in PGTC seizure rate during the double blind phase, % reduction in all generalised seizures in double blind phase, proportion of patients with 50% or more, 75% or more, 100% reduction in PGTCS and all generalised seizures and safety evaluations including adverse events.
- Bias
  - Allocation concealment (Selection bias): Not stated - Unclear risk
  - Other bias: Patient or carer entered data in a seizure diary which may be subjective - High risk
- Biton et al. 2005: Randomised, double blind, placebo controlled trial of **lamotrigine** in PGTC seizures.
  - Participants: 117 participants, aged 2–55 years of age with a diagnosis of epilepsy with PGTC seizures who were receiving one or two AED's at study entry.
  - Interventions: Lamotrigine versus placebo
  - Outcomes Percentage change in PGTCS frequency from baseline, percentage change in other generalised seizure types monthly. Median seizure counts, Proportion of people greater than 25% reduction, 50% reduction,75% reduction or 100% reduction in frequencies of PGTCS and all generalised seizures. Withdrawal from study for any reason. Adverse effects.
- Bias

- Random sequence generation (Selection bias): Unclear just randomized 1:1 to receive either **LTG** or Placebo - Unclear risk
- Allocation concealment (Selection bias): not stated - Unclear risk
- Blinding of participants and personnel (Performance bias): not stated - Unclear risk
- Blinding of outcome assessment (Detection bias): not stated - Unclear risk
- Selective reporting (Reporting bias): 39/117 patients had no generalised discharges on routine EEG therefore not definite IGE and some had seizures not typical of IGE eg. tonic seizures. - High risk
- Other Bias: Patient or carer entered data in a seizure diary which may be subjective. Seizure counts of PGTC seizures not stated if 28/30 day month. Absence seizures were counted which can introduce bias as some may be missed and difficult to count – high risk

- Trevathan et al. 2006: Randomised, double blinded, parallel controlled clinical trial of **lamotrigine** adjunctive therapy among children and adolescents with Primary generalised tonic clonic seizures
  - Participants: 45 children and adolescents 2–20 years of age in total randomly assigned on 1–2 other AED's. Evidence of PGTC seizure on EEG, no historical or EEG evidence of partial seizures however patients with a normal interictal EEG were included if their clinical history was believed to be clinically consistent with PGTCS. On 1–2 current AED's
  - Interventions: Lamotrigine versus placebo
  - Outcomes Primary outcome was the median reduction in the frequency of PGTCS from baseline. The median percentage change from the baseline in the average monthly seizure frequency for other Generalised seizure types and the percentage of patients who had a reduction of >25%, >50%, >75% 0r 100% in frequency of PGTCS and all other generalised seizures. Adverse events.
- Bias
  - Allocation concealment (Selection bias): Not stated – unclear risk
  - Blinding of participants and personnel (Performance bias): Double blinded. Otherwise nothing else stated – unclear risk
  - Blinding of outcome assessment (Detection bias): not stated – unclear risk
  - Selective reporting (Reporting bias): Risk of reporting bias as did not present data for all secondary efficacy endpoints ie. 50% reduction in seizure frequency Other bias High risk This is a post hoc analysis of the pediatric population and adolescent population form a larger RCT and as such has its limitations. It was estimated that 150 patients (adults and children >2 years of age) would need to enrolled to randomly assign 104 patients required to satisfy the power calculations. This clinical trial was not specifically powered for this post subanalysis of the children and adolescents (2–20 years of age). High placebo response in the subgroup analysis is not likely to be because of small sample size as high placebo response was similar to overall clinical trial, atonic and tonic seizures and not likely in IGE. Of the 45 children randomly assigned, 74% had generalised spike, polyspike, and/or generalized spike and wave discharges on routine EEG, 26% had no clear EEG findings. Patients or legal guardians recorded seizures therefore subjective. – High risk

Qualität der Studien:

- Siehe Studienbeschreibung

Studienergebnisse:

- The first paediatric only data from a placebo controlled trial was reported [24]
  - o did not present findings for ≥50% **reduction in PGTC seizures** in children and adolescents which was one of their outcomes
  - o report is a post hoc analysis of the paediatric population in a bigger trial, limitations as the trial was not powered for this subgroup analysis
  - o percentage reduction of PGTC seizures among children who received lamotrigine was significant and not likely due to chance ($p = 0.044$)
- **adverse effects:** in two lamotrigine trials similar rates for dizziness, somnolence and nausea [21,22], in each was one withdrawal in the lamotrigine groups due to non serious rash
  - o subgroup analysis of children: headache most common adverse event, no reports of rash

Anmerkung/Fazit der Autoren

This systematic review demonstrated efficacy of adjunctive anti-epileptic drugs with regard to 50% reduction and seizure freedom. Adverse events are identified in all of the studies in the drug treatment groups but are consistent with previous studies of these drugs. Additional adequately powered studies with long term follow up needs to be conducted to unequivocally establish the long term efficacy and tolerability of anti-epileptic drug's for patients with drug resistant idiopathic generalised epilepsy.

Kommentare zum Review

- *Suchzeitraum nicht identifiziert*
- *wenige oder keine Informationen aus den Subgruppen für Kinder vorhanden*
- *Conflicts of interest: None.*
- *Keine Angaben zur Finanzierung*

Cross HJ, 2015 [3].

BMJ Clinical Evidence reviews: Epilepsy (generalised seizures)

Fragestellung

What are the effects of additional treatments in people with drug-resistant epilepsy characterised by generalised seizures?

Methodik

Population:

- people with drug-resistant epilepsy characterised by generalised seizures

Intervention:

- additional treatments

Komparator:

- k.A.

Endpunkte:

- seizure frequency, proportion of responders (response defined as at least 50% reduction in seizure frequency); quality of life; adverse effects

Recherche/Suchzeitraum:

- 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 in the the Database of Abstracts of Reviews of Effects (DARE)
- and Health Technology Assessment (HTA) database

Qualitätsbewertung der Studien:

- GRADE-Systematik (Ergebnis im Volltext abgebildet)

Ergebnisse

Anzahl eingeschlossener Studien:

- four studies

Charakteristika der Population:

- siehe Studienergebnisse

Qualität der Studien:

- moderate-quality evidence

Studienergebnisse:

OPTION: ADDITION OF LAMOTRIGINE COMPARED WITH ADDING PLACEBO IN PEOPLE WITH DRUGRESISTANT EPILEPSY CHARACTERISED BY GENERALISED SEIZURES (Likely to be beneficial)

Seizure frequency

- Adding lamotrigine compared with adding placebo 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: Adding lamotrigine versus adding placebo:
  - one systematic review [21] of two RCTs: without pooling of data due to differences in study design between the two RCTs (one crossover RCT [23], one parallel RCT [24])
  - one subsequent RCT [22] comparing addition of lamotrigine with addition of placebo in people who had not responded to usual drug treatment

Referenzen aus Leitlinien
21. Tjia-Leong E, Leong K, Marson AG. Lamotrigine adjunctive therapy for refractory generalized tonic-clonic seizures. In: The Cochrane Library, Issue 4, 2014. Chichester, UK: John Wiley & Sons, Ltd. Search date 2010.

- second RCT: parallel design, 121 people with primary generalised tonic clonic seizures, aged 2–55 years [mean age about 26 years], 53% men
  - compared adding lamotrigine (maximum 200–400 mg/day) with adding placebo to usual drug treatment (up to 2 drugs allowed)

24. Biton V, Sackellares JC, Vuong A, et al. Double-blind, placebo-controlled study of lamotrigine in primary generalized tonic-clonic seizures. Neurology 2005;65:1737–1743.

  - included a dose-escalation phase (lamotrigine dose titrated to target dose over 7 weeks for people aged 12 years or more, or over 12 weeks for children aged 2–12 years, versus placebo), followed by a maintenance phase (target lamotrigine dose versus placebo for 12 weeks)
  - proportion of people with a 50% or greater reduction in primary generalised tonic clonic seizures over both dose-escalation and maintenance phases: 64% with lamotrigine v 39% with placebo; P <0.05; over maintenance phase only: 72% with lamotrigine v 49% with placebo; P <0.05; absolute numbers not reported; intention-to-treat analysis
  - high proportion of people (34/121 [28%]) did not complete the study (data on all randomised people who received at least one dose of study medication (117 people) in its intention-to-treat analysis included)

Anmerkung/Fazit der Autoren

Few RCTs have compared second-line drugs directly with each other. The RCTs did not report outcomes separately for adults and children. It was noted that rash was more prevalent with lamotrigine, and this risk is higher when the medication is added to sodium valproate; although, the risk can be minimised by a slow cautious introduction.

Some anti-epileptic drugs (AEDs) are associated with an increased risk for congenital malformations in the unborn child in women taking AEDs while pregnant. The risk appears low with lamotrigine monotherapy. There has also been increasing concern about the effects of valproate on longer term cognition and behaviour in children born to mothers taking valproate during pregnancy. However, lamotrigine does not appear to be implicated.

Kommentare zum Review

- *Competing interests: JHC is on the advisory board to Eisai, Vitaflo, Nutricia, and Viropharma, for which remuneration is made to the Clinical Neurosciences department at UCLInstitute of Child Health. JHC is also a speaker for Nutricia and Viropharma; remuneration is made to above-mentioned department at UCL.*

3.4 Leitlinien

National Institute for Health and Care Excellence (NICE), 2012 [4].

Epilepsies: diagnosis and management

Fragestellung

16. What AED treatment should be used in adults and children?

Methodik

Grundlage der Leitlinie

- Repräsentatives Gremium;
- Interessenkonflikte und finanzielle Unabhängigkeit dargelegt;
- Systematische Suche, Auswahl und Bewertung der Evidenz;
- Formale Konsensusprozesse und externes Begutachtungsverfahren dargelegt;
- Empfehlungen der Leitlinie sind eindeutig und die Verbindung zu der zugrundeliegenden Evidenz ist dargestellt;
- Regelmäßige Überprüfung der Aktualität gesichert: aktuelle Version ist Ergebnis der zweijährlichen Überprüfung (siehe „Surveillance report 2018 – Epilepsies: diagnosis and management (2012) NICE guideline CG137“)

Recherche/Suchzeitraum:

- for Cochrane reviews between 11 September 2013 and 19 December 2017
- relevant ongoing research, National Institute for Health Research (NIHR) signals, policy and guidance documents

LoE/GoR

- GRADE-Systematik

Sonstige methodische Hinweise

- Overall decision
  - After considering the guideline content, all the evidence and views of topic experts, the surveillance team recommend that NICE guideline CG137 on epilepsies: diagnosis and management requires a full update.
- 1.9.12 Pharmacological treatment of idiopathic generalised epilepsy (IGE)
- 1.9.14 Pharmacological treatment of epilepsy with generalised tonic–clonic (GTC) seizures only
  - Impact statements: This section of the guideline should be updated as safety concerns about sodium valproate in women have suggested the need to review the recommendations for sodium valproate and its place in the management of the epilepsies. New evidence identified that may change current recommendations.

Anmerkung: Alle Informationen zur Evidenzbasis sind in Anhängen der Leitlinie enthalten. Unklar bleibt der Extrapolationsprozess für die Empfehlungen für Kinder.

1.9.12 Pharmacological treatment of idiopathic generalised epilepsy (IGE)

First-line treatment in children, young people and adults with IGE

Empfehlung 1.9.12.1 (Empfehlungsgrad: siehe Formulierung)

Offer sodium valproate as first-line treatment to children, young people and adults with newly diagnosed IGE, particularly if there is a photoparoxysmal response on EEG. Follow the MHRA safety advice on sodium valproate. [2018]

Empfehlung 1.9.12.2 (Empfehlungsgrad: siehe Formulierung)

Offer lamotrigine[15] if sodium valproate is unsuitable or not tolerated. Be aware that lamotrigine can exacerbate myoclonic seizures. If JME is suspected see recommendations 1.9.13.1 and 1.9.13.2. Follow the MHRA safety advice on sodium valproate

Empfehlung 1.9.12.3 (Empfehlungsgrad: siehe Formulierung)

Consider topiramate[15] but be aware that it has a less favourable side-effect profile than sodium valproate and lamotrigine. Follow the MHRA safety advice on sodium valproate. [2018]

Adjunctive treatment in children, young people and adults with IGE

Empfehlung 1.9.12.4 (Empfehlungsgrad: siehe Formulierung)

Offer lamotrigine[15], levetiracetam[15], sodium valproate or topiramate[15] as adjunctive treatment to children, young people and adults with IGE if first-line treatments (see recommendations 1.9.12.1, 1.9.12.2 and 1.9.12.3) are ineffective or not tolerated. Follow the MHRA safety advice on sodium valproate. [2018]

Empfehlung 1.9.12.5 (Empfehlungsgrad: siehe Formulierung)

If adjunctive treatment (see recommendation 1.9.12.4) is ineffective or not tolerated, discuss with, or refer to, a tertiary epilepsy specialist and consider clobazam[15], clonazepam or zonisamide[15]. [new 2012]

Empfehlung 1.9.12.6 (Empfehlungsgrad: siehe Formulierung)

Do not offer carbamazepine, gabapentin, oxcarbazepine, phenytoin, pregabalin, tiagabine or vigabatrin. [new 2012]

1.9.14 Pharmacological treatment of epilepsy with generalised tonic–clonic (GTC) seizures only

First-line treatment in children, young people and adults with epilepsy with GTC seizures only

Empfehlung 1.9.14.1 (Empfehlungsgrad: siehe Formulierung)

Offer lamotrigine or sodium valproate as first-line treatment to children, young people and adults with epilepsy with GTC seizures only. If they have suspected myoclonic seizures, or are suspected of having JME, offer sodium valproate first, unless it is unsuitable. Follow the MHRA safety advice on sodium valproate. [2018]

Empfehlung 1.9.14.2 (Empfehlungsgrad: siehe Formulierung)

Consider carbamazepine and oxcarbazepine[15] but be aware of the risk of exacerbating myoclonic or absence seizures. [new 2012]

Adjunctive treatment in children, young people and adults with epilepsy with GTC seizures only

Empfehlung 1.9.14.3 (Empfehlungsgrad: siehe Formulierung)

Offer clobazam[15], lamotrigine, levetiracetam, sodium valproate or topiramate as adjunctive treatment to children, young people and adults with epilepsy with GTC seizures only, if first-line treatments (see recommendations 1.9.14.1 and 1.9.14.2) are ineffective or not tolerated. Follow the MHRA safety advice on sodium valproate. [2018]

[15] Treatment with AEDs is associated with a small risk of suicidal thoughts and behaviour; available data suggest that the increased risk applies to all AEDs and may be seen as early as 1 week after starting treatment.

MHRA advice on valproate: In April 2018, we added warnings that valproate treatment must not be used in girls and women including in young girls below the age of puberty, unless alternative treatments are not suitable and unless the conditions of the pregnancy prevention programme are met. Valproate must not be used in pregnant women. See also the MHRA toolkit to ensure female patients are better informed about the risks of taking valproate during pregnancy. See update information for more details.

Referenzen aus Leitlinien

182 Guerreiro MM, Vigonius U, Pohlmann H et al. A double-blind controlled clinical trial of oxcarbazepine versus phenytoin in children and adolescents with epilepsy. Epilepsy Res. 1997; 27(3):205-213.

3.5 Ergänzende Dokumente anderer Organisationen zu möglichen Komparatoren

Zur Fragestellung konnten keine relevanten ergänzenden Dokumente anderer Organisationen zu möglichen Komparatoren identifiziert werden.

4 Detaillierte Darstellung der Recherchestrategie

Cochrane Library - Cochrane Database of Systematic Reviews (Issue 5 of 12, May 2019) am 06.05.2019

#	Suchfrage
1	MeSH descriptor: [Epilepsy, Generalized] this term only
2	MeSH descriptor: [Epilepsy, Tonic-Clonic] explode all trees
3	(epilep* OR seizure* OR convulsion*):ti,ab,kw
4	(grand NEXT mal):ti,ab,kw OR (“tonic-clonic” OR (tonic NEXT clonic) OR generalized):ti,ab,kw
5	#1 OR #2 OR (#3 AND #4)
6	#5 with Cochrane Library publication date from May 2014 to present, in Cochrane Reviews

Systematic Reviews in Medline (PubMed) am 06.05.2019

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

	OR (meta[tiab] AND analyt*[tiab])))) OR (((review*[tiab]) OR overview*[tiab]) AND ((evidence[tiab]) AND based[tiab]))))))
6	(#5) AND ("2014/05/01"[PDAT] : "3000"[PDAT])
7	(#6) NOT "The Cochrane database of systematic reviews"[Journal]
8	(#7) NOT (animals[MeSH:noexp] NOT (Humans[mh] AND animals[MeSH:noexp]))
9	(#8) NOT retracted publication[ptyp]

Leitlinien in Medline (PubMed) am 06.05.2019

#	**Suchfrage**
1	Epilepsy, Generalized[mh:noexp]
2	Epilepsy, Tonic-Clonic[mh]
3	epilep*[tiab] OR seizure*[tiab] OR convulsion*[tiab]
4	„grand mal“[tiab] OR “tonic-clonic”[tiab] OR (tonic[tiab] AND clonic[tiab]) OR generalized[tiab]
5	#1 OR #2 OR (#3 AND #4)
6	(#5) AND (Guideline[ptyp] OR Practice Guideline[ptyp] OR guideline*[Title] OR Consensus Development Conference[ptyp] OR Consensus Development Conference, NIH[ptyp] OR recommendation*[ti])
7	(#6) AND ("2014/05/01"[PDAT] : "3000"[PDAT])
8	(#7) NOT (animals[MeSH:noexp] NOT (Humans[mh] AND animals[MeSH:noexp]))
9	(#8) NOT retracted publication[ptyp]

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1. **Bresnahan R, Panebianco M, Marson AG.** Brivaracetam add-on therapy for drug-resistant epilepsy. Cochrane Database of Systematic Reviews [online]. 2019(3):CD011501. URL: http://dx.doi.org/10.1002/14651858.CD011501.pub2.
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5. **Song L, Liu F, Liu Y, Zhang R, Ji H, Jia Y.** Clonazepam add-on therapy for refractory epilepsy in adults and children. Cochrane Database of Systematic Reviews [online]. 2018(5):CD012253. URL: http://dx.doi.org/10.1002/14651858.CD012253.pub2.