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-156-z Vigabatrin

Stand: August 2019

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

Vigabatrin (2019-B-156-z)
Zur Zusatzbehandlung therapieresistenter partieller Epilepsie

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.	ggf. Epilepsiechirurgie
Beschlüsse/Bewertungen/Empfehlungen des Gemeinsamen Bundesausschusses zu im Anwendungsgebiet zugelassenen Arzneimitteln/nicht-medikamentösen Behandlungen	*Beschlüsse in ähnlichem Anwendungsgebiet* – *D-371 Brivaracetam (Beschluss vom 17.01.2019)* – *D-325 Perampanel (nAWG, Beschluss vom 17.05.2018)* – *D-208 Brivaracetam (Beschluss vom 04.08.2016)* – *D-106 Perampanel (Beschluss vom 06.11.2014)* – *D-089 Retigabin (Beschluss vom 03.07.2014)*
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:	
Vigabatrin N03AG04 Kigabeq®	Zugelassenes Anwendungsgebiet: Zur Kombinationsbehandlung mit anderen Antiepileptika von Kindern im Alter ab 1 Monat bis unter 7 Jahre mit therapieresistenter partieller Epilepsie (fokale Anfälle) mit oder ohne sekundäre Generalisierung, wenn alle anderen geeigneten Arzneimittelkombinationen sich als unzureichend erwiesen haben oder nicht vertragen wurden.
Oxcarbazepin[1] N03AF02 z.B. Oxcarbazepin HEXAL 60, 150, 300, 600 mg Filmtabletten	Zur Behandlung von **fokalen Anfällen mit oder ohne sekundär generalisierten tonisch-klonischen Anfällen**. Zur Monotherapie oder Kombinationstherapie von Erwachsenen, Jugendlichen und **Kindern ab 6 Jahren**.
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.

[1] Im AWG nur für Kinder im Alter von 6 Jahren zugelassen

II. Zugelassene Arzneimittel im Anwendungsgebiet	
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.
Gabapentin[1] N03AX12 z.B. Gabapentin - 1A Pharma® 100, 300 und 400 mg Hartkapseln	Zusatztherapie bei Erwachsenen und **Kindern von 6 Jahren und älter** mit **partiellen Anfällen mit und ohne sekundäre Generalisierung** indiziert.
Levetiracetam N03AX14 Keppra®	Indiziert zur Zusatzbehandlung **partieller Anfälle mit oder ohne sekundärer Generalisier**ung bei Erwachsenen, Jugendlichen, **Kindern und Säuglingen ab 1 Monat** mit Epilepsie.
Zonisamid[1] N03AX15 Zonegran®	Zusatztherapie für die Behandlung von **fokalen Anfällen mit oder ohne sekundäre Generalisierung** bei Erwachsenen, Jugendlichen und **Kindern ab 6 Jahren**. Aus FI 4.2: Die Sicherheit und Wirksamkeit von Zonegran® bei Kindern unter 6 Jahren oder einem Körpergewicht unter 20 kg ist bisher noch nicht erwiesen. Für Patienten mit einem Körpergewicht unter 20 kg liegen nur eingeschränkte Daten aus klinischen Studien vor. Daher ist bei der Behandlung von Kindern ab 6 Jahren mit einem Körpergewicht unter 20 kg Vorsicht geboten.
Lacosamid N03AX18 Vimpat®	Indiziert zur Monotherapie und Zusatzbehandlung **fokaler Anfälle mit oder ohne sekundäre Generalisierung** bei Erwachsenen, Jugendlichen und **Kindern ab 4 Jahren** mit Epilepsie.
Clobazam[1] 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**)
Brivaracetam N03AX23 Briviact®	Zusatzbehandlung **fokaler Anfälle mit oder ohne sekundäre Generalisierung** bei Erwachsenen, Jugendlichen und **Kindern ab 4 Jahren** mit Epilepsie.

II. Zugelassene Arzneimittel im Anwendungsgebiet	
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**)

Quellen: AMIS-Datenbank, Fachinformationen (Stand Juli 2019)

Gemeinsamer Bundesausschuss

Abteilung Fachberatung Medizin

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

Vorgang: 2019-B-156z (Vigabatrin)

Auftrag von:	Abt. AM
Bearbeitet von:	Abt. FB Med
Datum:	14. August 2019

Inhaltsverzeichnis

Abkürzungsverzeichnis

AWMF	Arbeitsgemeinschaft der wissenschaftlichen medizinischen Fachgesellschaften
G-BA	Gemeinsamer Bundesausschuss
GIN	Guidelines International Network
GoR	Grade of Recommendations
HR	Hazard Ratio
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
RR	Relatives Risiko
SIGN	Scottish Intercollegiate Guidelines Network
TRIP	Turn Research into Practice Database
WHO	World Health Organization
AED	antiepileptic drug
(S)AE	(serious) adverse events
AED	antiepileptic drug
BMI	body mass index
KD	ketogenic diet
MAD	modified Atkins diet

1 Indikation

Zur Kombinationsbehandlung mit anderen Antiepileptika von Kindern im Alter ab 1 Monat bis unter 7 Jahre mit therapieresistenter partieller Epilepsie (fokale Anfälle) mit oder ohne sekundäre Generalisierung, wenn alle anderen geeigneten Arzneimittelkombinationen sich als unzureichend erwiesen haben oder nicht vertragen wurden.

2 Systematische Recherche

Es wurde eine systematische Literaturrecherche nach systematischen Reviews, Meta-Analysen und evidenzbasierten systematischen Leitlinien zur Indikation fokale Anfälle/Epilepsie durchgeführt. Der Suchzeitraum wurde auf die letzten 5 Jahre eingeschränkt und die Recherche am 28.05.2019 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 632 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 16 Quellen, die in die synoptische Evidenz-Übersicht aufgenommen wurden.

3 Ergebnisse

3.1 G-BA Beschlüsse/IQWiG Berichte

G-BA, 2019 [4].

Richtlinie über die Verordnung von Arzneimitteln in der vertragsärztlichen Versorgung (AM-RL); Anlage XII: (Frühe) Nutzenbewertung nach § 35a SGB V; Geltende Fassung zum Beschluss vom 17. Januar 2019 - Brivaracetam (neues Anwendungsgebiet: Epilepsie, Patienten ab 4 Jahren)

Neues Anwendungsgebiet (laut Zulassung vom 11. Juli 2018):

Briviact® wird angewendet zur Zusatzbehandlung fokaler Anfälle mit oder ohne sekundäre Generalisierung bei Erwachsenen, Jugendlichen und Kindern ab 4 Jahren mit Epilepsie.

Das neu zu bewertende Anwendungsgebiet umfasst die Patientenpopulation der Kinder und Jugendlichen von 4 bis <16 Jahren.

Kinder und Jugendliche im Alter von 4 bis <16 Jahren mit fokalen epileptischen Anfällen mit und ohne sekundäre Generalisierung in der Zusatztherapie:

Zweckmäßige Vergleichstherapie

Eine patientenindividuelle antiepileptische Zusatztherapie, soweit medizinisch indiziert und falls jeweils noch keine Pharmakoresistenz (im Sinne eines nicht ausreichenden Ansprechens), Unverträglichkeit und Kontraindikationen bekannt sind, mit einem der folgenden Wirkstoffe:

Eslicarbazepin1, Gabapentin2, Lacosamid, Lamotrigin, Levetiracetam, Oxcarbazepin2, Perampanel3, Topiramat, Valproinsäure4, Zonisamid2

Die Therapie soll nach Wahl des Arztes in Abhängigkeit der Basis- und Vortherapie(en) und unter Berücksichtigung des Grundes für den Therapiewechsel und etwaig einhergehender Nebenwirkungen erfolgen.

Die jeweilige Zulassung der Arzneimittel ist zu berücksichtigen.

1 Zulassung für Kinder über 6 Jahre
2 Zulassung für Kinder ab 6 Jahren
3 Zulassung für Jugendliche ab 12 Jahren
4 Valproinsäure kommt für die Zusatzbehandlung fokaler Anfälle mit oder ohne sekundäre Generalisierung bei Kindern und Jugendlichen im Alter von 4 bis <16 Jahren aufgrund von potentiell auftretenden Leberschäden und der Teratogenität nicht regelhaft in Frage. Im Rahmen einer patientenindividuellen Therapie kann die Zusatzbehandlung mit Valproinsäure jedoch eine mögliche Option darstellen.

Ausmaß und Wahrscheinlichkeit des Zusatznutzens von Brivaracetam gegenüber der zweckmäßigen Vergleichstherapie:

Ein Zusatznutzen ist nicht belegt.

3.2 Cochrane Reviews

Krishnaiah B et al., 2018 [6].

New search for studies and content updated (no change to conclusions)

Subpial transection surgery for epilepsy

Fragestellung

To assess the effects of subpial transection for focal-onset seizures and generalised tonic-clonic seizures in children and adults.

Methodik

Population:

Children or adults with refractory focal-onset seizures (simple focal, complex focal or secondary generalised tonic-clonic seizures) or generalised-onset tonic-clonic seizures (with or without other generalised seizure types).

Intervention:

- Subpial transection versus antiepileptic drug therapy (monotherapy or multi-drug therapy)
- Subpial transection versus another type of epilepsy surgery or vagal nerve stimulation
- Subpial transection versus sham surgery

Komparator: keine Angabe

Endpunkte:

- Seizure outcomes at one year, two years and five years after surgery: free of disabling seizures, completely seizure-free, improved, not improved
- Time to achieve one- or two-year seizure remission
- Quality of life outcomes, assessed by generic and disease specific validated scales
- Employment outcomes: postoperative unemployment, underemployment, employment
- Activities of daily living and driving
- Medication - postsurgical requirement of antiepileptic medication: increased, decreased, stopped, monotherapy or polytherapy
- Changes in cognitive function and behaviour following surgery (assessed by validated scales)
- Mortality
- Morbidity: infection, new neurological deficits and other surgical complications

Recherche/Suchzeitraum:

- on 7 August 2018

Qualitätsbewertung der Studien:

- Cochrane risk of bias tool

Ergebnisse

We found no relevant studies.

Anmerkung/Fazit der Autoren

We found no evidence to support or refute the use of subpial transection surgery for patients with medically refractory epilepsy. Well designed randomised controlled trials are needed to guide clinical practice.

Martin-McGill KJ et al. 2018 [7].

New search for studies and content updated (no change to conclusions)

Ketogenic diets for drug-resistant epilepsy

Fragestellung

To assess the effects of KDs for drug-resistant epilepsy by reviewing the evidence from randomised controlled trials.

Methodik

Population:

- Adults and children with a diagnosis of drug-resistant epilepsy irrespective of their seizure type or epilepsy syndrome.

Intervention:

- Any diet that is designed to produce ketones. There are several KDs that have been used depending upon the proportion of the different types of lipids. The main types of diet are classical KD, medium-chain triglyceride (MCT) KD, modified Atkins diet (MAD) and low glycaemic index treatment (LGIT).
- We will also include studies which compare different types of KDs or different KD regimes (fasting versus gradual initiation).

Komparator:

- Placebo/usual/sham diet given as a standard treatment that is thought to have no effect on epilepsy. Any treatment with known antiepileptic properties.

Endpunkte:

- Primary outcomes
  - Seizure freedom (100% reduction in seizure frequency)
  - Seizure reduction (50% or greater reduction in seizure frequency)
  - Adverse effects
- Secondary outcomes
  - Cognitive and behaviour outcomes, as measured by validated rating scales
  - Quality of life, as measured by validated rating scales
  - Attrition rate

Recherche/Suchzeitraum:

- Searches were run for the original review in March 2005 and subsequent searches were run in July 2007, January 2010, June 2011, March 2015, and April 2017.

Qualitätsbewertung der Studien:

- Cochrane risk of bias tool

Ergebnisse

Anzahl eingeschlossener Studien:

- 11 randomised controlled trials (RCTs) identified: recruited 778 patients (66 adults)

Charakteristika der Population (nur Ergebnisse für Kinder):

- 712 children and adolescents
  - aged 4 months to 18 years
  - all seizure types included
  - drug-resistant epilepsy

Qualität der Studien:

- all trials applied an intention-to-treat analysis with varied randomisation methods
- all 11 studies at low to unclear risk of bias for the following domains: random sequence generation, allocation concealment and selective reporting
- other domains (blinding, incomplete outcome data, other bias): assessments varied (low, unclear and high risk of bias)
- We could not conduct a meta-analysis due to the heterogeneity of the studies and the quality of the evidence was low to very low (GRADE ratings)

Studienergebnisse (nur Ergebnisse für Kinder):

- **seizure freedom**
  - rates reached as high as 55% in a classical 4:1 KD group after three months
  - seizure reduction reached as high as 85% in a classical 4:1 KD group after three months (GRADE rating low).
  - no significant difference between fasting-onset and gradual-onset KD for rates of seizure freedom, and seizure reduction in the gradual-onset KD group
  - efficacy of the MAD: seizure freedom rates of up to 25% and seizure reduction rates of up to 60% in children.
  - simplified MAD (sMAD): seizure freedom rates of 15% and seizure reduction rates of 56% in children
- **Adverse effects** of the dietary interventions experienced in all studies
  - most commonly reported: gastrointestinal syndromes
  - adverse effects reason for participants dropping out of trials (GRADE rating low)
  - Other reasons for dropout: lack of efficacy and non-acceptance of the diet (GRADE rating low)
  - classical 4:1 KD was consistently associated with more adverse effects
- One study assessed the effect of dietary interventions on **quality of life, cognition and behavioural functioning**, reporting participants in the KD group to be more active, more productive and less anxious after four months, compared to the control group.
  - no significant difference found in quality-adjusted life years (QALYs) between the KD group and control group at four or 16 months (GRADE rating very low)

Anmerkung/Fazit der Autoren

The RCTs discussed in this review show promising results for the use of KDs in epilepsy. However, the limited number of studies, small sample sizes and the limited studies in adults, resulted in a low to very low overall quality of evidence.

There were adverse effects within all of the studies and for all KD variations, such as short-term gastrointestinal-related disturbances and increased cholesterol. However, study periods were short, therefore the long-term risks associated with these adverse effects is unknown. Attrition rates remained a problem with all KDs and across all studies; reasons for this being lack of observed efficacy and dietary tolerance.

Only one study reported the use of KDs in adults with epilepsy; therefore further research would be of benefit.

Other more palatable but related diets, such as the MAD, may have a similar effect on seizure control as the classical KD, but this assumption requires more investigation. For people who have medically intractable epilepsy or people who are not suitable for surgical intervention, KDs remain a valid option; however, further research is required.

Panebianco M et al., 2018 [13].

New search for studies and content updated (no change to conclusions)

Gabapentin add-on treatment for drug-resistant focal epilepsy

Fragestellung

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

Methodik

Population:

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

Intervention:

- gabapentin in addition to conventional AED

Komparator:

- matched placebo, different dose of gabapentin or alternative AED in addition to conventional AED

Endpunkte:

- reduction in seizure frequency of 50% or more, seizure freedom, treatment withdrawal, adverse effects

Recherche/Suchzeitraum:

- Cochrane Register of Studies (CRSWeb, 20March 2018), MEDLINE (Ovid, 1946 to 20 March 2018), ClinicalTrials.gov (20 March 2018) and the World Health Organization International Clinical Trials Registry Platform (ICTRP, 20 March 2018)

Qualitätsbewertung der Studien:

- Cochrane risk of bias tool

Ergebnisse

Anzahl eingeschlossener Studien:

- 12 trials representing 2 607 randomised participants
- one trial recruited children only (Appleton 1999): parallel trial compared gabapentin to a placebo, children aged less than 12 years with a minimum of four seizures during the six weeks baseline period, treatment period of 12 weeks, 128 participants received placebo and 119 participants received gabapentin dose dependent on body weight
- one Indian trial included 52 children and adults aged 10 – 60 years (notes: as no clear baseline period, excluded from meta-analysis)

Referenzen aus dem Review:
Appleton R, et al. and the Gabapentin Paediatric Study Group. Gabapentin as add-on therapy in children with refractory partial seizures: a 12 week, multicentre, double blind placebo controlled study. Epilepsia 1999;40(8): 1147–54.
Sethi A, et al. Gabapentin and lamotrigine in Indian patients of partial epilepsy refractory to carbamazepine. Neurology India 2002;50(3):359–63.

Charakteristika der Population:

- all participants (adults and children) were previously taking at least one antiepileptic medicine and were continuing to have seizures

Qualität der Studien:

- studies rated at low to unclear risk of bias due to information on each risk of bias domain not being available
- overall quality of evidence (using the GRADE approach) as low to moderate due to potential attrition bias:
  - missing outcome data,
  - imprecise results with wide confidence intervals

Studienergebnisse:

- overall RR for reduction in seizure frequency of 50% or more compared to placebo: 1,89 (95% confidence interval (CI) 1,40 to 2,55; 6 trials, 1 206 participants; moderate-quality evidence)
- RR for treatment withdrawal compared to placebo: 1,05 (95% CI 0,74 to 1,49; 6 trials, 1 206 participants; moderate-quality evidence)
- Adverse effects significantly associated with gabapentin compared to placebo (RRs as follows):
  - ataxia 2.01 (99% CI 0.98 to 4.11; 3 studies, 787 participants; low-quality evidence),
  - dizziness 2.43 (99% CI 1.44 to 4.12; 6 studies, 1206 participants; moderate-quality evidence),
  - fatigue 1.95 (99% CI 0.99 to 3.82; 5 studies, 1161 participants; low-quality evidence) and
  - somnolence 1.93 (99% CI 1.22 to 3.06; 6 studies, 1206 participants; moderate quality evidence)
- no significant differences for adverse effects of headache or nausea
- **Appleton 1999:** seizure reduction was low
  - data not included in dose regression models, as participants were not randomised to a specific daily dose
  - 3/119 participants receiving gabapentin seizure-free compared to 1/128 participants receiving placebo
- no important heterogeneity identified - no subgroup analysis conducted

Anmerkung/Fazit der Autoren

Gabapentin has efficacy as an add-on treatment in people with drug-resistant focal epilepsy. However, the trials reviewed were of relatively short duration and provide no evidence for the long-term efficacy of gabapentin beyond a three-month period. The results cannot be extrapolated to monotherapy or to people with other epilepsy types.

Ramaratnam S et al., 2016 [14].

Edited (no change to conclusions)

Lamotrigine add-on for drug-resistant partial epilepsy

Fragestellung

To determine the effects of lamotrigine on (1) seizures, (2) adverse effect profile, and (3) cognition and quality of life, compared to placebo controls, when used as an add-on treatment for people with refractory partial epilepsy.

Methodik

Population:

- individuals of any age with partial epilepsy (i.e. experiencing simple partial, complex partial, or secondarily generalized tonic-clonic seizures) who had failed to respond to at least one AED (drug-resistant epilepsy)

Intervention:

- lamotrigine in addition to conventional antiepileptic drug (AED) treatment

Komparator:

- conventional AED treatment plus a matched placebo, or 'no treatment' control

Endpunkte:

- greater than 50% reduction in seizure frequency, treatment withdrawal, adverse effects, cognitive effects, quality of life

Recherche/Suchzeitraum (for this update):

- Cochrane Epilepsy Group Specialized Register (28 May 2015), CENTRAL (The Cochrane Library 2015, Issue 4), MEDLINE (Ovid, 1946 toMay 2015), and reference lists of articles, the manufacturers of lamotrigine (GlaxoSmithKline) contacted

Qualitätsbewertung der Studien:

- Cochrane risk of bias tool

Ergebnisse

Anzahl eingeschlossener Studien:

- no new studies for this update identified, results are unchanged
- five parallel add-on studies and eight cross-over studies plus
- one parallel add-on study with a responder-enriched design in infants (Piña-Garza JE, et al. 2008)
- total: 1 958 participants (38 infants, 199 children, and 1 721 adults)
- Duchowny 1999 recruited only children (27% less than 6 years old, 60% between 6 to 12 years and 11% over 12 years age)
- Piña-Garza 2008 enrolled only infants aged one to 24 months of age

Referenzen aus dem Review:

Duchowny M, et al. A placebo-controlled trial of lamotrigine add-on therapy for partial seizures in children. Neurology 1999;53(8):1724–31.
Piña-Garza JE, et al. Adjunctive lamotrigine for partial seizures in patients aged 1 to 24 months. Neurology 2008;70:2099–108.

- Baseline phases ranged from 4 to 12 weeks; treatment phases from 8 to 36 weeks.

Charakteristika der Population:

- adults or children with refractory focal epilepsy

Qualität der Studien:

- eleven studies (1 243 participants) with low risk of bias
- three (715 participants) with unclear risk of bias due to lack of reported information around study design
- effective blinding reported in three studies (504 participants)
- overall: high to moderate quality of evidence, due to incomplete data for some outcomes

Studienergebnisse (for children):

- 50% or greater reduction in **seizure frequency**
    - RR was 2.64; 95% CI 1.59 to 4.38 (Duchowny 1999), indicating that lamotrigine significantly more effective than placebo in reducing seizure frequency
    - no responder rates for the infants in Piña-Garza 2008 calculated: primary end point was exit due to treatment failure
- **treatment withdrawal** (for any reason)
    - 14 participants withdrew from treatment and 18 from control groups in a parallel study in children (Duchowny 1999)
    - 11 participants withdrew from treatment and 16 withdrew from control groups in a parallel study in infants (Piña-Garza 2008)
- **adverse events** significantly associated with lamotrigine in children: dizziness
    - more often reported with lamotrigine: ataxia, fatigue, nausea, somnolence
- limited data precluded conclusions about effects on **cognition** and **quality of life**
- no important heterogeneity between studies for any of the outcomes

Anmerkung/Fazit der Autoren

Lamotrigine as an add-on treatment for partial seizures appears to be effective in reducing seizure frequency, and seems to be fairly well tolerated. However, the trials were of relatively short duration and provided no evidence for the long-term. Further trials are needed to assess the long-term effects of lamotrigine, and to compare it with other add-on drugs.

Since we did not find any new studies, our conclusions remain unchanged.

Michaelis R et al. 2017 [9].

Psychological treatments for people with epilepsy

Edited (no change to conclusions)

Fragestellung

To assess the effects of psychological treatments for people with epilepsy on HRQoL outcomes.

Methodik

Population:

- men, women, children of any age, with any type of epilepsy, treatment-responsive or treatment-resistant,with orwithout learning disabilities or intellectual disabilities, whether or not they were taking antiepileptic drugs (AEDs)

Intervention:

- For the operational definition of 'psychological treatments', we included a broad range of treatments that were designed to improve health-related quality of life (HRQoL), seizure frequency and severity, and reduce psychological and psychiatric comorbidities. We explained these different streams of psychological treatments in detail in the Description of the intervention:
  1. Psychological interventions
  2. Self-management
  3. Adherence interventions
  4. Educational interventions
  5. A combination of the above

Komparator:

- comparison of two or more of the above treatments, and comparisons to 'wait-list control' and 'treatment as usual'

Endpunkte:

- Primary outcomes: Mean of change from baseline, or comparisons of post intervention scores from validated HRQoL measures.
- Secondary outcomes
  - Comparisons of post-intervention scores from validated measures of psychiatric comorbidities, such as depressive and anxiety symptoms.
  - Comparisons of post-intervention data from validated seizure-related outcome measures.

Recherche/Suchzeitraum (for this update):

- on 20 September 2016

Qualitätsbewertung der Studien:

- Cochrane risk of bias tool

Ergebnisse (nur für Kinder)

Anzahl eingeschlossener Studien:

- 24 completed RCTs, with a total of 2 439 participants
- 11 studies investigated psychological interventions: cognitive, behavioral, and mindfulness-based interventions
- educational interventions (N = 7), self-management interventions (N = 3), adherence interventions (N = 1), mixed interventions (N = 2)
- 2 studies investigated interventions for children and adolescents

Referenzen aus dem Review
Jantzen S, et al. FLIP&FLAP-a training programme for children and adolescents with epilepsy, and their parents. Seizure 2009;18(7):478–86.
Rau J, et al. [Education of children with epilepsy and their parents by the modular education program epilepsy for families (FAMOSES)--results of an evaluation study]. Rehabilitation 2006;45(1):27–39.

Charakteristika der Population:

- Janzen et al. 2009: diagnosis of epilepsy, taking antiepileptic drugs, sufficient German literacy, willingness of the child and at least one career to participate in the education programme, age range: 6 to 17 years
- Rau et al. 2006: children with epilepsy, able to read and write in German, parents of children with epilepsy, whether or not they could read and write German, age: 8 to 13 years

Qualität der Studien:

- Quality of the evidence (GRADE): moderate

Studienergebnisse:

- interventions were geared towards the education of children, adolescents, and their parents
- **HRQoL** outcome measures:
    - **Jantzen 2009** reported that children and adolescents in the treatment group showed a significant increase in the social exclusion subscale in DISABKIDS, indicating better quality of life, based on post-intervention scores [P value was not provided; d = 0.3 (Cohen)
    - The three remaining studies did not report a significant post-intervention difference in meanQoL scores between groups. **Rau 2006** used the self-reported German questionnaire, Gesundheitsbezogene Lebensqualität und psychosoziale Auswirkungen der Epilepsie, (HRQoL and psychosocial consequences of epilepsy (intervention mean 70.62 (SD 13.29) versus wait-list control mean 77.25 (SD 15.0); P = 0.075).

Anmerkung/Fazit der Autoren

Implications for practice: Psychological interventions and self-management interventions improved QoL, and emotional well-being, and reduced fatigue in adults and adolescents with epilepsy. Adjunctive use of psychological treatments for adults and adolescents with epilepsy may provide additional benefits to QoL in those who incorporate patient-centered management.

Implications for research: Authors should strictly adhere to the CONSORT guidelines to improve the quality of reporting on their interventions. A thorough description of the intervention protocol is necessary to ensure reproducibility.

When researching psychological treatments for people with epilepsy, the use of Quality of Life in Epilepsy Inventories (QOLIE-31, QOLIE-31-P, and QOLIE-89) would increase comparability. There is a critical gap in pediatric RCTs for psychological treatments, particularly those that use an epilepsy-specific measure of HRQoL.

Finally, in order to increase the overall quality of study designs, adequate randomization with allocation concealment and blinded outcome assessment should be pursued when conducting RCTs. As attrition is often high in research that requires active participant participation, an intention-to-treat analysis should be carried out.

West S et al., 2015 [15].

Surgery for epilepsy

New, published in Issue 7, 2015

Fragestellung

The primary objective is to assess the overall outcome of epilepsy surgery according to evidence from randomised controlled trials.

The secondary objectives are to assess the overall outcome of epilepsy surgery according to non-randomised evidence and to identify the factors that correlate to remission of seizures postoperatively.

Methodik

Population:

- children, adolescents and adults considered surgical candidates, having drug-resistant partial seizures and secondarily generalised seizures of temporal or extratemporal origin, i.e. seizures that continue despite treatment with anticonvulsant medication

Intervention:

- surgical treatment

Komparator:

- medical treatment or no treatment, or comparisons of different surgical techniques

Endpunkte:

- Seizure outcome (proportion achieving a good outcome from surgery)
- Seizure outcome according to prognostic factors of interest: Pre-operative factors, Operative factors, Postoperative factors

Recherche/Suchzeitraum (for this update):

- up to 4 July 2013

Qualitätsbewertung der Studien:

- Cochrane risk of bias tool for RCTs
- Effective Public Health Practice Project (EPHPP) tool for non-randomised studies
- Quality in Prognostic Studies (QUIPS) tool for multivariate analyses

Ergebnisse

Anzahl eingeschlossener Studien:

- 177 studies (16 253 participants)
- 4 studies were RCTs (including one that randomised participants to surgery or medical treatment)
- All other studies were of a non-randomised design and did not include a control group in the study design.

- 21 studies included children only (12% of total studies, 1147 participants) and 103 studies included both adults and children (58% of total studies, 10 374 participants)

Charakteristika der Population:

- Anmerkung: keine Extraktion wegen der großen Informationsmenge

Qualität der Studien:

- The risk of bias in the RCTs was unclear or high, limiting our confidence in the evidence that addressed the primary review objective.
- most of the remaining 173 non-randomised studies had a retrospective design; were of variable size, were conducted in a range of countries, recruited a wide demographic range of participants, used a wide range of surgical techniques and used different scales used to measure outcomes: provided moderate or weak evidence
- For 29 studies reporting multivariate analyses we determined that very few studies were at low risk of bias across the domains.

Studienergebnisse

- Anmerkung: Die Autorengruppe beschreibt keine Ergebnisse für die Subgruppe der Kinder.

Anmerkung/Fazit der Autoren

The study design issues and limited information presented in the included studies mean that our results provide limited evidence to aid patient selection for surgery and prediction of likely surgical outcome. Future research should be of high quality, have a prospective design, be appropriately powered and focus on specific issues related to diagnostic tools, the site-specific surgical approach and other issues such as the extent of resection. Prognostic factors related to the outcome of surgery should be investigated via multivariable statistical regression modelling, where variables are selected for modelling according to clinical relevance and all numerical results of the prognostic models are fully reported. Protocols should include pre- and postoperative measures of speech and language function, cognition and social functioning along with a mental state assessment. Journal editors should not accept papers where adverse events from a medical intervention are not recorded. Improvements in the development of cancer care over the past three to four decades have been achieved by answering well-defined questions through the conduct of focused RCTs in a step-wise fashion. The same approach to surgery for epilepsy is required.

3.3 Systematische Reviews

Chen D et al., 2019 [3].

A meta-analysis of levetiracetam for randomized placebo-controlled trials in patients with refractory epilepsy

Fragestellung

The objective of this study was to investigate the efficacy and safety profile of levetiracetam as add-on therapy in patients with refractory epilepsy.

Methodik

Population:

- refractory epilepsy, regardless of age and gender

Intervention:

- levetiracetam

Komparator:

- k.A.

Endpunkte:

- responder or seize freedom rate, adverse events (AEs) including dropouts owing to AEs and SAEs

Recherche/Suchzeitraum:

- from inception up to May 31, 2018: EMBASE, MEDLINE, Web of Science, Cochrane Library PubMed, Google Scholar, Chinese National Knowledge Infrastructure and Wanfang Data databases

Qualitätsbewertung der Studien:

- Cochrane Collaboration's Risk of Bias tool

Ergebnisse

Anzahl eingeschlossener Studien:

- 17 RCTs with 3 205 participants included in current meta-analysis
- three involved children [10,26,28] with age ranging from 1 month

Referenzen aus dem Review:
10. Piña-Garza JE, et al. Adjunctive levetiracetam in infants and young children with refractory partial-onset seizures. Epilepsia. 2009;50(5):1141–1149.
26. Glauser TA, et al. Double-blind placebocontrolled trial of adjunctive levetiracetam in pediatric partial seizures. Neurology. 2006;66(11):1654–1660.
28. Levisohn PM, et al, N01103 Levetiracetam Study Group. Neurocognitive effects of adjunctive levetiracetam in children with partial-onset seizures: a randomized, double-blind, placebo-controlled, noninferiority trial. Epilepsia. 2009;50(11): 2377–2389.

- two used maximum dosage of 60 mg/kg/day [26,28], the remaining one used slightly less, at a maximum of 50 mg/kg/day [27]

- trial of Piña-Garza et al only lasted 7 days, which may bring about potential risk of bias for outcomes

Charakteristika der Population:

- 15 RCTs involved patients with refractory partial-onset seizures

Qualität der Studien:

- all to be double-blind trials, quality assessment for all not very high
- Glauser TA, et al.2006: low risk of bias, because sequence generation and allocation method described
- Piña-Garza JE, et al. 2009 und Levisohn PM, et al, 2009: risk of selection bias, mainly because insufficient information for random list generation and allocation concealment not reported
- Piña-Garza JE, et al. 2009: high risk of bias, for the number of patients reported after treatment was not consistent with the initial number
- no potential publication bias across included studies

Studienergebnisse (subgroup analysis based on age <16 years vs. >16 years):

- **50% reduction from baseline**: adult patients treated with levetiracetam had a slightly better efficacy of responder rate than children (RR =2.08, 95% CI 1.83–2.34 and RR =1.94, 95% CI 1.46–2.57).
- **Seizure freedom** from baseline: no statistically significant difference between groups of age
- **SAE and side effects leading to withdrawal**: no statistically significant difference between children and adults
- **most common AEs**:
  - somnolence, asthenia (fatigue): no statistically significant difference between children and adults, even though children had a higher occurrence
  - other side effects: dizziness, infection, nasopharyngitis, nausea, anxiety, irritability

Anmerkung/Fazit der Autoren

Levetiracetam is an effective anti-epileptic drug for both adults and children with generalized or partial-onset refractory seizures at 1,000–3,000 or 60 mg/kg/day, with a favorable adverse event profile.

Kommentare zum Review

- *The authors report no conflicts of interest in this work.*
- *Keine Informationen zur Finanzierung der Arbeit*
- *There were only three trials that involved children and one of them had a study period of only 7 days - results for children should be regarded with caution.*
- *Subgruppenanalyse "Kinder vs. Erwachsene" beantwortet nur indirekt die Fragstellung.*
- *In der Subgruppe der Erwachsenen sind verschiedene Epilepsieformen summiert.*

Cao Y et al., 2019 [2].

Efficacy and safety of Levetiracetam as adjunctive treatment in children with focal onset seizures: A systematic review and meta-analysis

Fragestellung

To assess the efficacy and safety of levetiracetam (LEV) as adjunctive treatment in children (0–18 years) with focal-onset seizures (FOS) with a larger dataset.

Methodik

Population:

- children (0–18 years) with partial epilepsy, of any gender, ethnicity, and seizure severity

Intervention:

- LEV in additional to conventional AEDs treatment (LEV group)

Komparator:

- placebo in addition to conventional AEDs treatment (placebo group)

Endpunkte:

- 50% responder rate, seizure freedom rate, median percentage reduction rate, treatment-emergent adverse event, withdrawal rate

Recherche/Suchzeitraum:

- PubMed (Medline), Web of Science, Cochrane Central Register of Controlled Trials, US NIH Clinical Trials Registry (http://www.clinicaltrials.gov), last search was performed in January 2018

Qualitätsbewertung der Studien:

- Cochrane Collaboration's tool and Methodological index for non-randomized studies (MINORS)

Ergebnisse

Anzahl eingeschlossener Studien:

- 31 articles (1 763 patients): 18 prospective self-controlled studies and 13 retrospective studies
  - 3 RCTs (Glauser et al., 2006; Levisohn et al., 2009; Pina-Garza et al., 2009)

Charakteristika der Population:

- characteristics of the included studies summarized in Supplementary 1 (Anmerkung: liegt nicht vor)

Qualität der Studien:

- RCTs: low risk

Studienergebnisse (nur RCTs):

- **50% responder rate**: 412 patients (LEV, n=225; placebo, n=187), no statistically significant heterogeneity, Fixed-effect model RR=1.98 (95% CI: 1.49–2.63), LEV group significantly more effective than placebo group
- **seizure freedom rate**: LEV, n=250; placebo, n=212; no statistically significant heterogeneity, fixed-effect model RR=5.12 (95% CI: 2.09–12.51), LEV group significantly more effective than placebo group
- **median percentage reduction rate**: keine Meta-Analyse aus den RCTs
- **TEAE** rate: RR=1.03 (95% CI: 0.93–1.13), favoring LEV treatment associated with a significant higher incidence of TEAEs
- **adverse drug reactions (ADR) related treatment emergent adverse events (TEAE)** rate: RR=1.45 (95% CI: 1.13–1.86), favoring LEV treatment associated with a significant higher incidence of TEAEs
- **withdrawal** rate and **ADR-related withdrawal** rate compared LEV group and placebo group, no statistically significant heterogeneity, no statistical significant differences

Anmerkung/Fazit der Autoren

The meta-analysis suggested that add-on LEV can significantly reduce seizure frequency and fairly tolerated compared to placebo.

Kommentare zum Review

- *study supported by National Natural Science Foundation of China …, Natural Science Foundation of Guangdong Province, China …, Fundamental Research Funds for the Central Universities …*
- *research conducted in absence of any commercial or financial relationships that could be construed as a potential conflict of interest*
- *Qualitätsbewertung der Studien positiver als bei Chen D, et al. 2019*
- *Quellenangaben der eingeschlossenen Studien entsprechen Chen D, et al. 2019 (siehe oben)*

Boon P et al., 2018 [1].

Neurostimulation for drug-resistant epilepsy: a systematic review of clinical evidence for efficacy, safety, contraindications and predictors for response

Fragestellung

In this study, we systematically reviewed each of these neurostimulation modalities. For each neurostimulation modality, we addressed two primary questions: is the treatment efficacious? Is the treatment well tolerated?

We further addressed the following two secondary questions: are there contraindications for the treatment? Are there predictors for response to the treatment?

Methodik

Population:

- patients with drug-resistant epilepsy (DRE), unsuitable surgery candidates

Intervention:

- Neurostimulation modalities: vagus nerve stimulation (VNS), deep brain stimulation (DBS), responsive neurostimulation (RNS), transcutaneous vagus nerve stimulation (tVNS), transcranial magnetic stimulation (TMS), trigeminal nerve stimulation (TNS), transcranial direct current stimulation (tDCS)

Komparator:

- k.A.

Endpunkte:

- seizure outcome data (change in seizure frequency and responder rates (≥50% reduction in seizure frequency), quality of life (QoL) data, adverse events

Recherche/Suchzeitraum:

- MEDLINE database searched (14/2–2017)

Qualitätsbewertung der Studien:

- Preexisting systematic reviews were only selected if they fulfilled the following eight criteria:
  - clearly defined questions or objectives with provided answers to at least one of the primary questions;
  - methodologically transparent with systematic data collection and literature evaluation according to a clearly specified protocol;
  - the collection and evaluation of literature performed by more than one independent investigator;
  - application of the GRADE scoring system for evaluation of the quality of the evidence reviewed;
  - excluding case report evidence, retrospective evidence or prospective studies with less than 10 patients;
  - including the most recently published RCTs for the relevant neurostimulation modality;
  - the focus of the systematic review on neurostimulation for epilepsy.

- RCTs were critically appraised with regard to bias risks according to the GRADE procedure

Ergebnisse (nur Ergebnisse zu Kindern)

Anzahl eingeschlossener Studien:

- primary questions regarding efficacy and safety of VNS
  - two systematic reviews [7,8] used

Referenzen aus dem Review
7. Panebianco M, et al. Vagus nerve stimulation for partial seizures. Cochrane Database Syst Rev 2015; CD002896.
8. Chambers A, Bowen JM. Electrical stimulation for drug-resistant epilepsy: an evidence-based analysis. Ont Health Technol Assess Ser 2013; 13:1–37.

- secondary questions regarding contraindications and predictors for response
  - three prospective studies [19,26,27] and
  - 11 registry studies [6,46,47,50,52,54–57,59,60]

Charakteristika der Population :

- Chambers A, eta l. 2013: three RCTs in adults [40,42,43] and one RCT in children (<18 years) [39] with focal DRE

Referenzen aus dem Review
39. Klinkenberg S, et al. Vagus nerve stimulation in children with intractable epilepsy: a randomized controlled trial. Dev Med Child Neurol 2012; 54:855–861.

- Panebianco M, et al. 2015: four RCTs [37,39,42,43] in both children and adults with partial epilepsies

Referenzen aus dem Review
37. Michael JE,et al. Vagus nerve stimulation for intractable seizures: one year follow-up. J Neurosci Nurs 1993; 25:362–366.
39. Klinkenberg S, et al. Vagus nerve stimulation in children with intractable epilepsy: a randomized controlled trial. Dev Med Child Neurol 2012; 54:855–861.
42. Handforth A, et al. Vagus nerve stimulation therapy for partial-onset seizures: a randomized active-control trial. Neurology 1998; 51:48–55.
43. [No authors listed]. A randomized controlled trial of chronic vagus nerve stimulation for treatment of medically intractable seizures. The Vagus Nerve Stimulation Study Group. Neurology 1995; 45:224–230.

Qualität der Studien:

- for efficacy outcome
  - Chambers A, et al. 2013: RCT in children [39], rated as low-quality evidence
  - Panebianco M, et al. 2015: evidence was rated as moderate in quality
- for safety outcomes
  - Panebianco M, et al. 2015: moderate and low in evidence quality

Studienergebnisse:

- Chambers A, eta l. 2013: effectiveness of VNS in children not demonstrated
- Panebianco M, et al. 2015:
  - Seizure reduction: OR of 1.73 (95% CI: 1.13–2.64) in favor of the high-stimulation paradigm (assumed therapeutic dose) over a low-stimulation paradigm (assumed subtherapeutic dose)
  - safety of VNS by conducting meta-analyses to estimate the relative risk (RR) of adverse events between the high stimulation group and low-stimulation groups.
    - voice alteration or hoarseness: RR of 2.17 (99% CI: 1.47–3.17) - three RCTs [37,42,43]

    - cough: RR of 1.09 (99% CI: 0.74–1.62) - three RCTs [37,42,43]
    - dyspnea: RR of 2.45 (99% CI: 1.07–5.60) - two RCTs [42,43]
    - pain and paresthesias: RRs of 1.01 (99% CI: 0.60–1.68) and 0.78 (99% CI: 0.39–1.53) - two RCTs [42,43]
    - nausea: RR of 0.89 (99% CI: 0.42–1.90)
    - headache: RR of 0.90 (0.48–1.69)
- Chambers A, eta l. 2013: no meta-analyses on safety outcomes, but similar adverse events reported in the safety review of VNS in both children and adults
- report on rare adverse events: two cases of vocal cord paralysis, two cases of lower facial muscle paresis, three cases of postsurgical infection, one case of fluid accumulation over the pulse generator, which required intervention

Anmerkung/Fazit der Autoren

In conclusion, there is low-to-moderate quality evidence that VNS is well tolerated in both children and adults with drug-resistant partial epilepsies, whereas there is moderate quality evidence for the effectiveness of VNS in adults with drug-resistant partial epilepsies.

Head-to-head comparison of treatment modalities such as VNS, DBS and RNS across different epileptic syndromes are required to decide which treatment modality is the most effective for a given patient scenario. Such studies are challenging and it is unlikely that data will be available in the near future. Additional data collection on potentially promising noninvasive neurostimulation modalities like tVNS, TMS, TNS and tDCS is warranted to get a more precise estimate of their therapeutic benefit and long-term safety.

Kommentare zum Review

- *Für die weiteren Verfahren liegen keine Daten aus Studien mit Kindern vor.*
- *Register of interest: P.B. has received consultancy and speaker fees from UCB Pharma, LivaNova, Medtronic and Eisai. E.D.C. has a loan agreement with a distributor of Soterix Medical. E.T. has received research funding from UCB, Biogen-Idec, Red Bull, Merck, Novartis. E.T. has received consultancy fees from Eisai, Ever Pharma, Novartis, Biogen Idec, Medtronic, LivaNova, Bial and UCB Pharma and speaker fees from Bial, Eisai, GL Pharma, Boehringer, Newbridge and UCB Pharma. P.B. has received free devices for research studies in normal volunteers and preclinical studies from LivaNova, Cerbomed, Neurosigma, Medtronic.*
- *P.B. is supported by grants of the 'Fonds voor Wetenschappelijk Onderzoek' (FWO) Flanders, the Ghent University Research Fund (BOF), Ghent University Hospital and E-Epilepsy (EU). E.D.C. is supported by a grant of the Ghent Institute of Neuroscience. A.M. is supported by an 'Aspirant' grant of the 'Fonds voor Wetenschappelijk Onderzoek' (FWO) Flanders. E.T. has received research funding from the European Union, FWF Österreichischer Fond zur Wissenschaftsförderung, and the Bundesministerium für Wissenschaft und Forschung.*

Mohd-Tahir NA et al., 2018 [10].

Meta-analyses of newer antiepileptic drugs as adjunct for treatment of focal epilepsy in children

Fragestellung

This study conducted a systematic review evaluating the effectiveness of newer antiepileptic drugs (AEDs) (namely, lamotrigine, levetiracetam, topiramate, vigabatrin, zonisamide, oxcarbazepine, perampanel, gabapentin, and stiripentol) as add-on for treatment of focal epilepsy in children.

Methodik

Population:

- children aged less than 18 years old with diagnosis and seizure outcome of focal seizure

Intervention:

- newer AEDs was used as adjunct treatment

Komparator:

- placebo or older AEDs treatment

Endpunkte:

- responder rate (more than 50% seizure reduction from baseline) or seizure free events, withdrawal rate due to adverse events and ineffective treatment, and total numbers of treatment-emergent adverse events (TEAE), adverse events of somnolence, nausea and/or vomiting, aggressive behaviour, dizziness, headache, rhinitis and rash

Recherche/Suchzeitraum:

- Embase, Medline, and Cochrane Library, from inception to January 2016

Qualitätsbewertung der Studien:

- based on the recommendations from the Cochrane review

Ergebnisse

Anzahl eingeschlossener Studien:

- 12 articles fulfilled the inclusion criteria

Study	Comparative treatment	Study design	n	Age ranges (years)
1 Appleton et al. (1999)	GBP vs PCB	6 weeks baseline, 12 weeks treatment	247	3–12
2 Chiron et al. (1996)	VGB vs PCB	8 weeks baseline, 16 weeks treatment	28	1.5–18.5
3 Chiron et al. (2006)	STP vs PCB	8 weeks	32	2.2–15.3
4 Duchowny et al. (1999)	LTG vs PCB	8 weeks baseline, 18 weeks treatment	199	2–16
5 Elterman et al. (1999)	TPM vs PCB	8 weeks baseline, 16 weeks treatment	86	2–16
6 Glauser et al. (2000)	OXC vs PCB	56 days baseline, 112 days treatment	267	3–17
7 Glauser et al. (2006)	LEV vs PCB	8 weeks baseline, 14 weeks treatment	198	4–16
8 Guerrini et al. (2013)	ZNS vs PCB	8 weeks baseline, 12 weeks treatment	207	6–17
9 Novotny et al. (2010)	TPM vs PCB	20 days treatment	149	1–24 mth
10 Pina-Garza et al. (2008)	LTG vs PCB	48 weeks treatment (maximum treatment duration)	204	1–24 mth
11 Pinea-Garza et al. (2009)	LEV vs PCB	2 days baseline, 5 days treatment	116	1 mth to<4 years
12 Rosenfeld et al. (2015)	PMP vs PCB	6 weeks titration, 13 weeks maintenance	143	12–17

GBP: Gabapentin; LTG: Lamotrigine; LEV: Levetiracetam; n: No. of children; OXC: Oxcarbazepine; PCB: placebo; PMP: Perampanel; STP: Stiripentol; TPM: Topiramate; VGB: Vigabatrin; ZNS: Zonisamide;mth: month(s)

- median number of participants: 174 (range 28–267)
- median treatment duration: 147 days (range 7–336 days)

Charakteristika der Population:

- children with inadequate control of epilepsy
- age ranged from 0 to 18 years old
  - two studies specifically evaluated the effectiveness of AEDs in infants (i.e 1–24 months old) and one study in children less than four years old respectively (Pina-Garza et al., 2008; Pinea-Garza et al., 2009; Novotny et al., 2010)
  - much younger than the other studies, also analysed separately to check for difference in treatment effect, result showed no significant difference from the main analysis where these studies were included

Qualität der Studien:

- Heterogeneity and quality of the included studies were considered acceptable with about 40–50% of studies reporting low risk of bias
- Appleton et al. (1999): high risk of bias as it recruited patients based on the availability of interventions, not randomly generated
- most studies did not adequately describe the process of blinding of outcome assessment (65% of studies), and the amount, nature or handling of incomplete data (75% of studies) resulting in unclear risk of detection and attrition bias respectively
- most studies (60%) did not adequately report all the primary or secondary outcomes

Studienergebnisse:

- OR for responder=2.15 (95%CI:1.72, 2.69)
- OR for seizure-free=1.99 (95%CI:0.72, 5.48)
- OR for withdrawal rates=0.69 (95%CI:1.13, 2.39)
- Adverse events comparatively higher than placebo (OR:1.64, 95%CI:1.13, 2.39)

Anmerkung/Fazit der Autoren

In our updated review, newer AEDs as adjunct therapy for focal epilepsy in children have trends of better effectiveness compared to placebo. Newer AEDs are associated with statistically more children with>50% seizure reduction, and a trend of better seizure freedom. Their tolerability would also be considered acceptable with the observed low withdrawal rate. However, the relative lack of well-conducted RCTs evaluating their effectiveness against other active AED treatment in children would not facilitate evidence-based practice.

This highlights the knowledge gap and the need for more well-conducted RCTs against active treatments to ascertain the long term effectiveness and the role of newer AEDs in managing epilepsy in children.

Kommentare zum Review

- *Stiripentol und Perampanel für die Fragestellung der Evidenzsynopse nicht relevant wegen fehlender Zulassung im Anwendungsgebiet (je 1 Studie)*
- *no conflicts of interests to declare with regard to the content of this article*
- *research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors*

Jobst BC et al., 2015 [5].

Resective epilepsy surgery for drug-resistant focal epilepsy: a review

Fragestellung

To review resective surgery outcomes for focal epilepsy, to identify which patients benefit the most, and to discuss why epilepsy surgery may not be universally accepted.

Methodik

Population:

- patients with focal seizures who do not respond to appropriate antiepileptic drug therapy consisting of 2 or more medications

Intervention:

- epilepsy surgery: resection of the medial structures of the temporal lobe, including the amygdala, hippocampus, and entorhinal cortex and may also involve resection of the temporal neocortex or the resection of neocortex in the remainder of the brain. Resections of the cortex are guided by imaging results and intracranial electroencephalography

Komparator:

- k.A.

Endpunkte:

- seizure activity, seizure freedom, cognitive, psychiatric, quality-of-life, and psychosocial outcomes

Recherche/Suchzeitraum:

- from January 1993 toJune2014

Qualitätsbewertung der Studien:

- systematic reviews assessed by the Assess the Methodological Quality of Systematic Reviews (AMSTAR) tool
- quantitative studies assessed using the Quality Assessment Tool for Quantitative Studies Measurement (EPHPP) tool

Ergebnisse (nur für Kinder)

Anzahl eingeschlossener Studien:

- Three meta-analyses reported on epilepsy surgery outcomes for children.

18. Englot DJ, et al. Seizure outcomes after temporal lobectomy in pediatric patients. J Neurosurg Pediatr. 2013;12(2):134-141.
19. Englot DJ, et al. Seizure outcomes after resective surgery for extra-temporal lobe epilepsy in pediatric patients. J Neurosurg Pediatr. 2013;12(2):126-133.
20. Ansari SF, et al. Surgery for extratemporal nonlesional epilepsy in children: ameta-analysis. Childs Nerv Syst. 2010;26(7):945-951.

- Englot et al, 2013 (18)
  - No. of Studies Included: 36
  - Pooled No. of Patients: 1318
- Englot et al, 2013 (19)

  - No. of Studies Included: 36
  - Pooled No. of Patients: 1259
- Ansari et al, 2010
  - No. of Studies Included: 17
  - Pooled No. of Patients: 95

Charakteristika der Population:

- Englot et al, 2013 (18)
  - Inclusion Criteria: temporal lobe epilepsy (TLE only)
- Englot et al, 2013 (19)
  - Inclusion Criteria: extratemporal, neocortical epilepsy (XTL only)
- Ansari et al, 2010
  - Inclusion Criteria: extratemporal, neocortical epilepsy (XTL only)

Qualität der Studien:

- Quality ratings of all included studies are reported in eTable 1 in the Supplement. (wird beschafft)

Studienergebnisse:

- on average, seizure-free outcomes of
  - 76% for temporal lobe epilepsy and
  - 34% to 56% for extra temporal lobe epilepsy
- Englot et al, 2013 (18)
  - Mean (Range), y
    - Follow-up Duration: >1 (NR)
    - Duration of Epilepsy: 5.4 (NR)
  - Seizure Free, No. (%): 1002 (76)
- Englot et al, 2013 (19)
  - Mean (Range), y
    - Follow-up Duration: >1 (NR)
    - Duration of Epilepsy: 7.1 (NR)
  - Seizure Free, No. (%): 705 (56)
- Ansari et al, 2010
  - Mean (Range), y
    - Follow-up Duration: >1 (NR)
    - Duration of Epilepsy: 6.4 (NR)
  - Seizure Free, No. (%): 32 (33.7)
- The long-term effect of performing epilepsy surgery at a younger age or soon after the onset of the seizure disorder is unknown as compared with performing surgery at a later age or later in the course of the disease.
- Epilepsy duration is not a consistent predictor of success, (17,18,27) although 1 RCT showed that early surgery is more successful. (Anmerkung: Quelle unklar)

17. McIntosh AM, et al. Seizure outcome after temporal lobectomy: current research practice and findings. Epilepsia. 2001;42 (10):1288-1307.
27. Englot DJ, et al. Factors associated with seizure freedom in the surgical resection of glioneuronal tumors. Epilepsia. 2012;53(1):51-57.

- The mean duration of epilepsy was greater than 5 years showing that surgical referrals occur late in the disease.
- Several single-center studies found improved quality of life for children undergoing epilepsy surgery.

59. Mikati MA, et al. Quality of life after surgery for intractable partial epilepsy in children: a cohort study with controls. Epilepsy Res. 2010;90(3):207-213.

- Temporary neurologic complications occur in about 10% of patients and are more likely in children and in patients undergoing extratemporal resections.

50. Téllez-Zenteno JF, et al. Long-term outcomes in epilepsy surgery: antiepileptic drugs, mortality, cognitive and psychosocial aspects. Brain. 2007; 130(pt 2):334-345.

- Discontinuation of Antiepileptic Medication After Surgery: The TimeToStop study, a retrospective study of 15 centers performing epilepsy surgery in children, found no difference in seizure outcome related to the time in which antiepileptic medications were discontinued after surgery.

66. Boshuisen K, et al; TimeToStop study group. Timing of antiepileptic drug withdrawal and long-term seizure outcome after paediatric epilepsy surgery (TimeToStop): a retrospective observational study. Lancet Neurol. 2012;11(9):784-791.

Anmerkung/Fazit der Autoren

Epilepsy surgery reduced seizure activity in randomized clinical trials when compared with continued medical therapy. Long-term cognitive, psychiatric, psychosocial, and quality-of-life outcomes were less well defined. Despite good outcomes from high-quality clinical trials, referrals of patients with seizures refractory to medical treatment remain infrequent.

Kommentare zum Review

- *Conflict of Interest Disclosures: All authors have completed and submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Dr Jobst reported receiving research support from the National Institutes of Health, Centers for Disease Control and Prevention, the American Epilepsy Society, Pfizer Inc, Neuropace Inc, UCB Inc, Upsher-Smith, and Lunbeck; serving on the scientific advisory committee of Neuropace Inc; and receiving royalties for medical writing from Medlink Inc. None of these activities represent a significant conflict of interest regarding the content of this review. Dr Cascino reported receiving research support from the National Institutes of Health; serving as an associate editor for the journal Neurology (American Academy of Neurology); receiving honoraria from the American Epilepsy Society and American Academy of Neurology for educational activities; and receiving royalty from theMayo Foundation (Mayo Medical Ventures).*

Mbizvo GK et al., 2014 [8].

The adverse effects profile of levetiracetam in epilepsy: a more detailed look

Fragestellung

By highlighting the common and uncommon adverse effects of levetiracetam and their relative importance in terms of statistical significance we update the information available on the adverse effects profile of levetiracetam.

Methodik

Population:

- partial-onset seizures (with or without secondary generalisation) that were refractory to one to three AEDs

Intervention:

- levetiracetam in addition to conventional AED drug treatment

Komparator:

- matched placebo pills in addition to conventional AED drug treatment

Endpunkte:

- adverse effects

Recherche/Suchzeitraum:

- Databases EMBASE (1974–April 2015), MEDLINE (1946–April 2015), PubMed and the Cochrane library

Qualitätsbewertung der Studien:

- keine

Ergebnisse

Anzahl eingeschlossener Studien:

- 10 trials included in review (1 831 participants)
  - 2 trials included children: 198 (children) Glauser 2006 [11], 98 (children) Levisohn 2009 [12]

Charakteristika der Population:

- nicht näher beschrieben

Qualität der Studien:

- adverse effects published if greater than 5% or 10% of the participants in any treatment group had been affected
- treatment period durations ranged between 12 and 24 weeks between the trials
  - titration ranging from zero to four weeks
  - maintenance ranging from 8 to 12 weeks
- Levetiracetam tested at a 60 mg/kg/d dose in paediatric trials

Studienergebnisse:

- adverse effects (in decreasing order of frequency): somnolence; headache; asthenia; accidental injury; dizziness; infection; pharyngitis; pain; rhinitis; abdominal pain; flu syndrome; vomiting; diarrhoea; convulsion; nausea; increased cough; anorexia; upper respiratory tract infection; hostility; personality disorder; urinary tract infection; nervousness; depression; aggression; back pain; agitation; emotional liability; psychomotor hyperactivity; pyrexia; rash; ECG abnormalities; decreased appetite; nasal congestion; irritability; abnormal behaviour; epistaxis; insomnia; altered mood; anxiety; bloody urine; diplopia; dissociation; memory impairment; pruritis; increased appetite; acne; and stomach discomfort
- **Significant adverse effects** (analysis levetiracetam vs. placebo restricted to 296 children only)
  - none of the adverse effects (including those of words pertaining to infection) retained statistical significance
- **Behavioural effects** (across children)
  - these affected 40.6% and 21.4% on levetiracetam and placebo, respectively (RR 1.90, CI 1.16–3.11, Chi2 p = 0.64), demonstrating significance

Anmerkung/Fazit der Autoren

This review updates the adverse effects profile data on levetiracetam use by empirically reporting its common and uncommon adverse effects and analysing their relative importance statistically using data from a group of trials that posses low Risk of Bias and high Quality of Evidence GRADE scores.

Kommentare zum Review

- *Pete Dixon was funded jointly by UCB and Eisai through their support of the National Audit of Seizure management in Hospitals (NASH). Gashirai Mbizvo and Tony Marson are employees of the National Health Service (NHS). Pete Dixon is employed by The University of Liverpool. Jane Hutton is employed by The University of Warwick. The views and opinions expressed within this article do not necessarily reflect those of the NHS, the HTA, or the Department of Health. The researchers are independent from the funders.*
- *Quellenangaben der eingeschlossenen Studien entsprechen Chen D, et al. 2019 (siehe oben)*

3.4 Leitlinien

National Institute for Health and Care Excellence (NICE), 2012 [11].

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 indirekt 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“ [12])

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.
- 1.9.3 Pharmacological treatment of focal seizures
  - Impact statements: The new evidence supports the current recommendations concerning the use of vigabatrin, lacosamide, eslicarbazepine acetate, gabapentin, lamotrigine, levetiracetam, pregabalin, tiagabine, topiramate and zonisamide as adjunctive treatments for refractory focal seizures. The guideline does not recommend felbamate or stiripentol as adjunctive treatments and current evidence does not indicate that this would change. The evidence concerning the effectiveness and safety profile of losigamone and brivaracetam (which are not currently recommended) as an adjunctive treatment for focal seizures could be considered in an update, however losigamone is not currently available in the UK.

- Evidence concerning the use of perampanel as a first-line and adjunctive treatment should be considered during the update of this section. - New evidence identified that may change current recommendations.

- 1.11 Psychological interventions
  - Impact statement: The guideline makes broad recommendations concerning interventions to improve psychological difficulties associated with epilepsy including recommending relaxation and cognitive behaviour therapy; and recognises the psychological impact of epilepsy and that it should be identified and addressed. The evidence supports the current recommendation, and the findings of the most recent Cochrane review [116] may provide additional intervention details that could be reflected in the recommendation content. This section of the guideline should be updated.

116. Michaelis R, Tang V, Wagner JL, Modi AC, LaFrance JWC, Goldstein LH, Lundgren T, Reuber M: Psychological treatments for people with epilepsy. In: Cochrane Database of Systematic Reviews. John Wiley & Sons, Ltd; 2017.

  - New evidence identified that may change current recommendations.

- 1.13 Vagus nerve stimulation (VNS)
  - Impact statement: This section of the guideline should be updated. Evidence indicates that for focal seizures VNS appears to be effective and well tolerated and that VNS stimulation using a high stimulation paradigm is significantly better than low stimulation in reducing frequency of seizures, however there was limited information available 'so important differences between high and low stimulation cannot be excluded'. VNS is recommended in the guideline for people with refractory epilepsy and focal seizures but there is no mention of low versus high stimulation, as such the evidence in the review may impact on the recommendation.
  - 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. Perampanel hat eine Zulassung für Kinder ab 12 Jahren, Eslicarbazepin für Kinder über 6 Jahre. Alter der Kinder in den Studien zu nichtmedikamentösen Therapien unklar.

1.9.3 Pharmacological treatment of focal seizures

First-line treatment in children, young people and adults with newly diagnosed focal seizures

Empfehlung 1.9.3.1 (Empfehlungsgrad: siehe Formulierung)

Offer carbamazepine or lamotrigine as first-line treatment to children, young people and adults with newly diagnosed focal seizures. [new 2012]

Empfehlung 1.9.3.2 (Empfehlungsgrad: siehe Formulierung)

Levetiracetam is not cost effective at June 2011 unit costs[13]. Offer levetiracetam, oxcarbazepine or sodium valproate (provided the acquisition cost of levetiracetam falls to at least 50% of June 2011 value documented in the National Health Service Drug Tariff for England and Wales) if carbamazepine and lamotrigine are unsuitable or not tolerated. If the first AED tried is ineffective, offer an alternative from these five AEDs. Follow the MHRA safety advice on sodium valproate. [2018]

Empfehlung 1.9.3.3 (Empfehlungsgrad: siehe Formulierung)

Consider adjunctive treatment if a second well-tolerated AED is ineffective (see recommendations 1.9.3.1 and 1.9.3.2). [new 2012]

Adjunctive treatment in children, young people and adults with refractory focal seizures

Empfehlung 1.9.3.4 (Empfehlungsgrad: siehe Formulierung)

Offer carbamazepine, clobazam[14], gabapentin[15], lamotrigine, levetiracetam, oxcarbazepine, sodium valproate or topiramate as adjunctive treatment to children, young people and adults with focal seizures if first-line treatments (see recommendations 1.9.3.1 and 1.9.3.2) are ineffective or not tolerated. Follow the MHRA safety advice on sodium valproate. [2018]

Empfehlung 1.9.3.5 (Empfehlungsgrad: siehe Formulierung)

If adjunctive treatment (see recommendation 1.9.3.4) is ineffective or not tolerated, discuss with, or refer to, a tertiary epilepsy specialist. Other AEDs that may be considered by the tertiary epilepsy specialist are eslicarbazepine acetate[15], lacosamide, phenobarbital, phenytoin, pregabalin[15], tiagabine, vigabatrin and zonisamide[15]. Carefully consider the risk–benefit ratio when using vigabatrin because of the risk of an irreversible effect on visual fields. [new 2012]

[13] Estimated cost of a 1500 mg daily dose was £2.74 at June 2011. Cost taken from the National Health Service Drug Tariff for England and Wales.
[14] At the time of publication (January 2012), this drug did not have UK marketing authorisation for this indication and/or population (see appendix E for details). Informed consent should be obtained and documented.
[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.

1.11 Psychological interventions

Empfehlung 1.11.2 (Empfehlungsgrad: siehe Formulierung)

Psychological interventions (relaxation, cognitive behaviour therapy) may be used in children and young people with drug-resistant focal epilepsy. [2004]

Empfehlung 1.11.3 (Empfehlungsgrad: siehe Formulierung)

Psychological interventions may be used as adjunctive therapy. They have not been proven to affect seizure frequency and are not an alternative to pharmacological treatment. [2004]

1.12 Ketogenic diet

Empfehlung 1.12.1 (Empfehlungsgrad: siehe Formulierung)

Refer children and young people with epilepsy whose seizures have not responded to appropriate AEDs to a tertiary paediatric epilepsy specialist for consideration of the use of a ketogenic diet. [new 2012]

1.13 Vagus nerve stimulation (VNS)

Empfehlung 1.13.2 (Empfehlungsgrad: siehe Formulierung)

Vagus nerve stimulation is indicated for use as an adjunctive therapy in reducing the frequency of seizures in children and young people who are refractory to antiepileptic

medication but who are not suitable for resective surgery. This includes children and young people whose epileptic disorder is dominated by focal seizures[20] (with or without secondary generalisation) or generalised seizures[20]. [2004, amended 2012]

[20] Evidence from Vagus nerve stimulation for refractory epilepsy in children, NICE interventional procedure guidance 50 (2004).

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] this term only
2	MeSH descriptor: [Epilepsies, Partial] explode all trees
3	(epilep* OR seizure* OR convulsion*):ti
4	#1 OR #2 OR #3
5	#4 with Cochrane Library publication date from May 2014 to present, in Cochrane Reviews

Systematic Reviews in Medline (PubMed) am 06.05.2019

#	Suchfrage
1	Epilepsies, Partial[mh]
2	(epilep*[tiab] OR seizure*[tiab] OR convulsion*[tiab])
3	((((((((((((partial[tiab] OR focal[tiab])) OR (benign[tiab] AND occipital[tiab])) OR (gelastic[tiab] OR amygdalo-hippocampal[tiab] OR rhinencephalic[tiab])) OR ("occipital lobe"[tiab])) OR ("temporal lobe"[tiab])) OR "lateral temporal"[tiab]) OR ("frontal lobe"[tiab])) OR (cingulate[tiab] OR opercular[tiab] OR "orbito frontal"[tiab] OR "supplementary motor"[tiab])) OR (abdominal[tiab] OR digestive[tiab] OR subclinical[tiab] OR uncinate[tiab])) OR ("localization related"[tiab] OR "localisation related"[tiab])) OR psychomotor[tiab]) OR (versive[tiab])) OR (sensory[tiab] OR gustatory[tiab] OR olfactory[tiab] OR vertiginous[tiab])
4	#2 AND #3
5	#1 OR #4
6	(#5) 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]))))))
7	(#6) AND ("2014/05/01"[PDAT] : "3000"[PDAT])

Leitlinien in Medline (PubMed) am 06.05.2019

#	**Suchfrage**
1	Epilepsy[mh:noexp]
2	Epilepsies, Partial[mh]
3	(epilep*[ti] OR seizure*[ti] OR convulsion*[ti])
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*[ti])
6	(#5) AND ("2014/05/01"[PDAT] : "3000"[PDAT])

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