Gemeinsamer Bundesausschuss

Kriterien zur Bestimmung der zweckmäßigen Vergleichstherapie

und

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

und

Schriftliche Beteiligung der wissenschaftlich-medizinischen Fachgesellschaften und der Arzneimittelkommission der deutschen Ärzteschaft (AkdÄ) zur Bestimmung der zweckmäßigen Vergleichstherapie nach § 35a SGB V

Vorgang: 2021-B-094 Brivaracetam

Stand: Mai 2021

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

Brivaracetam (2021-B-094)
Zur Zusatzbehandlung fokaler 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.	Nicht angezeigt
Beschlüsse/Bewertungen/Empfehlungen des Gemeinsamen Bundesausschusses zu im Anwendungsgebiet zugelassenen Arzneimitteln/nicht-medikamentösen Behandlungen	*Beschlüsse in ähnlichem Anwendungsgebiet* • Beschluss zu Perampanel vom 06.11.2014 und 17.05.2018 • Beschluss zu Brivaracetam vom 04.08.2016 • Beschluss zu Brivaracetam vom 17.01.2019 • Beschluss zu Vigabatrin vom 19.12.2019
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:	
Brivaracetam ATC Code Briviact®	Geplantes neues Anwendungsgebiet laut Beratungsanforderung: „Zusatzbehandlung fokaler Anfälle mit oder ohne sekundäre Generalisierung Kindern ab 1 Monat bis 4 Jahren mit 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**.
Vigabatrin N03AG04 Sabitril®	In Kombination mit anderen Antiepileptika zur Behandlung von Patienten mit pharmakoresistenten fokalen Anfällen mit oder ohne sekundäre Generalisierung, bei denen alle anderen adäquaten Arzneimittelkombinationen nicht ausreichend wirksam waren oder nicht vertragen wurden. In FI 4.2: Dosierungsempfehlungen **für Neugeborene, Kinder** und Jugendliche.
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	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**

II. Zugelassene Arzneimittel im Anwendungsgebiet	
mg Filmtabletten	oder primär generalisierten tonisch-klonischen Anfällen und zur Behandlung von Anfällen, die mit dem Lennox-Gastaut Syndrom assoziiert sind.
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.
Carbamazepin N03AF01 z.B. Timonil®	Epilepsie – generalisierte tonisch-klonische Anfälle – **partielle Anfälle** (Aus FI 4.2: Dosierungsempfehlungen für **Kinder ab unter 1 Jahr,** Timonil® sollte zur Behandlung der Epilepsie **bevorzugt allein** (Monotherapie) angewendet werden.)
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**)
Clobazam N05BA09 Clobazam Syri Pharma® 2 mg/ml Suspension zum Einnehmen	Clobazam Syri Pharma® kann bei Epilepsie bei Erwachsenen und **Kindern über 2 Jahren als Zusatzmedikation** angewendet werden, wenn die Standardbehandlung mit einem oder mehreren Antikonvulsiva fehlgeschlagen ist. Zur Behandlung von einfacher oder komplexer partieller Epilepsie mit oder ohne sekundäre Generalisierung und zur Behandlung aller Arten von generalisierter Epilepsie (tonisch-klonisch, myoklonisch, Absencen).

Quellen: AMiCE-Datenbank, Fachinformationen

Gemeinsamer Bundesausschuss

Abteilung Fachberatung Medizin

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

Vorgang: 2021-B-094 (Brivaracetam)

Auftrag von:	Abt. AM
Bearbeitet von:	Abt. FB Med
Datum:	25. Mai 2021

Inhaltsverzeichnis

Abkürzungsverzeichnis

AE	Adverse events
AED	Anti-epileptic drugs
ADR	Adverse drug reactions
ASM	Anti-seizure medication
AWMF	Arbeitsgemeinschaft der wissenschaftlichen medizinischen Fachgesellschaften
BECTS	Benign epilepsy of childhood with centrotemporal spikes
BNFC	British National Formulary for Children
CBZ	Carbamazepine
CI	Confidence interval
CLB	Clobazam
DRE	Drug resistant epilepsy
ECTS	Epilepsy with Centrotemporal Spikes
ETS	Ethosuximide
ESL	Eslicarbazepine Acetate
FBM	Felbamate
FOS	Focal-onset seizures
G-BA	Gemeinsamer Bundesausschuss
GoR	Grade of Recommendations
GPT/GBP	Gabapentin
GTC	Generalized tonic–clonic
GVG	Vigabatrin
HLA-B	Human Leukocyte Antigen-B
HR	Hazard Ratio
ICTRP	Clinical Trials Registry Platform
ILAE	International League Against Epilepsy
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen
KI	Konfidenzintervall
LCM	Lacosamid
LTG	Lamotrigine
LEV	Levetiracetam
LoE	Level of Evidence
NHLBI	National Heart, Lung, and Blood Institute
NICE	National Institute for Health and Care Excellence
NHS	National Health Service

MHRA	Medicines and Healthcare products Regulatory Agency
NZP	Nitrazepam
NOS	Newcastle–Ottawa scale
ORBIT	Outcome Reporting Bias in Trials
OR	Odds Ratio
OXC	Oxcarbazepine
PER	Perampanel
PGB	Pregabalin
PHT	Phenytoin
PLB	Placebo
QOL	Quality of life
RFN/RUF	Rufinamide
RR	Relatives Risiko
SIGN	Scottish Intercollegiate Guidelines Network
STM	Sulthiame
STP	Stiripentol
TEAE	Treatment emergent adverse events
TGB	Tiagabin
TPM	Topiramate
TR	Treatment-resistant
VGB	Vigabatril
VNS	Vagus nerve stimulator
VPA	Valproic acid
WHO	World Health Organization
ZNS	Zonisamide

1 Indikation

Zusatzbehandlung fokaler Anfälle mit oder ohne sekundäre Generalisierung Kindern ab 1 Monat bis 4 Jahren mit Epilepsie.

2 Systematische Recherche

Es wurde eine systematische Literaturrecherche nach systematischen Reviews, Meta-Analysen und evidenzbasierten systematischen Leitlinien zur Indikation *Epilepsie* durchgeführt. Der Suchzeitraum wurde auf die letzten 5 Jahre eingeschränkt und die Recherche am 19.04.2021 abgeschlossen. Die Suche erfolgte in den aufgeführten Datenbanken bzw. Internetseiten folgender Organisationen: The Cochrane Library (Cochrane Database of Systematic Reviews), MEDLINE (PubMed), AWMF, ECRI, 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.

In einem zweistufigen Screening wurden die Ergebnisse der Literaturrecherche bewertet. Die Recherche ergab 1132 Quellen. Im ersten Screening wurden auf Basis von Titel und Abstract nach Population, Intervention, Komparator und Publikationstyp nicht relevante Publikationen ausgeschlossen. Zudem wurde eine Sprachrestriktion auf deutsche und englische Quellen vorgenommen. Im zweiten Screening wurden die im ersten Screening eingeschlossenen Publikationen als Volltexte gesichtet und auf ihre Relevanz und methodische Qualität geprüft. Dafür wurden dieselben Kriterien wie im ersten Screening sowie Kriterien zur methodischen Qualität der Evidenzquellen verwendet. Basierend darauf, wurden insgesamt 21 Quellen eingeschlossen. Es erfolgte eine synoptische Darstellung wesentlicher Inhalte der identifizierten Referenzen.

Nachträglich wurde die aktualisierte Leitlinie vom NICE vom Mai 2021 [20] identifiziert und in die Synopse aufgenommen. Desweiteren wurde die Vorgängerversion von Kanner 2018 [16] French 2004 [5] für die Auswertung herangezogen. Insgesamt ergab dies 23 Quellen, die in die synoptische Evidenz-Übersicht aufgenommen wurden

3 Ergebnisse

3.1 G-BA Beschlüsse/IQWiG Berichte

G-BA, 2019 [11].

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.

G-BA, 2019 [13].

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 19. Dezember 2019 - Vigabatrin

Anwendungsgebiet

Kigabeq wird angewendet bei Kindern im Alter ab 1 Monat bis unter 7 Jahre:

- zur Behandlung in Kombination mit anderen Antiepileptika für Patienten 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.

Kinder ab 1 Monat bis unter 7 Jahre, mit therapieresistenter partieller Epilepsie (fokale Anfälle) mit oder ohne sekundäre Generalisierung, bei denen sich alle anderen geeigneten Arzneimittelkombinationen als unzureichend erwiesen haben oder nicht vertragen wurden.

Zweckmäßige Vergleichstherapie

Eine patientenindividuelle Optimierung der antiepileptischen Therapie unter Berücksichtigung der Vortherapie.

Fazit / Ausmaß des Zusatznutzens

Der Zusatznutzen gilt als nicht belegt.

G-BA, 2019 [6].

Beschluss des Gemeinsamen Bundesausschusses über eine Änderung der Arzneimittel-Richtlinie (AM-RL): Anlage VII (Austauschbarkeit von Arzneimitteln) – Teil A (Pregabalin) vom 22. November 2019

I.

In die Tabelle in Teil A der Anlage VII wird entsprechend der alphabetischen Reihenfolge folgende Zeile eingefügt:

Wirkstoff	Wirkstoffbasen im Verhältnis	austauschbare Darreichungsformen
„Pregabalin		Hartkapseln Tabletten“

II. Die Änderung der Richtlinie tritt am 15. März 2020 in Kraft.

G-BA, 2018 [12].

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. Mai 2018 - Perampanel (Neues Anwendungsgebiet laut Zulassung vom 22.06.2015)

Anwendungsgebiet

Fycompa® wird angewendet als Zusatztherapie bei primär generalisierten tonisch-klonischen Anfällen bei Erwachsenen und Jugendlichen ab 12 Jahren mit idiopathischer generalisierter Epilepsie.

Zweckmäßige Vergleichstherapie

Die zweckmäßige Vergleichstherapie für die Zusatztherapie bei primär generalisierten tonisch-klonischen Anfällen bei Erwachsenen und Jugendlichen ab 12 Jahren mit idiopathischer generalisierter Epilepsie ist:

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

Lamotrigin, Levetiracetam, Valproinsäure, Topiramat, Clobazam

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.

Fazit / Ausmaß des Zusatznutzens

Ein Zusatznutzen ist nicht belegt.

G-BA, 2016 [9].

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 4. August 2016 - Brivaracetam

Anwendungsgebiet

Briviact wird angewendet zur Zusatzbehandlung fokaler Anfälle mit oder ohne sekundäre Generalisierung bei Erwachsenen und Jugendlichen ab 16 Jahren mit Epilepsie.

Zweckmäßige Vergleichstherapie

Eine individuelle antiepileptische Zusatztherapie, soweit medizinisch indiziert und falls noch keine Pharmakoresistenz / Unverträglichkeit und Kontraindikationen bekannt sind, mit einem der folgenden Wirkstoffe:

Eslicarbazepin oder Gabapentin oder Lacosamid oder Lamotrigin oder Levetiracetam oder Oxcarbazepin oder Pregabalin oder Topiramat oder Valproinsäure oder Zonisamid.

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

Fazit / Ausmaß des Zusatznutzens

Ein Zusatznutzen ist nicht belegt

G-BA, 2014 [10].

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 6. November 2014 - Perampanel

Anwendungsgebiet

Perampanel (Fycompa®) ist angezeigt als Zusatztherapie fokaler Anfälle mit oder ohne sekundäre Generalisierung bei Epilepsiepatienten ab 12 Jahren.

Zweckmäßige Vergleichstherapie

sekundäre Generalisierung bei Epilepsiepatienten ab 12 Jahren ist eine individuelle antiepileptische Zusatztherapie, soweit medizinisch indiziert und falls noch keine Pharmakoresistenz/Unverträglichkeit und Kontraindikationen bekannt sind, mit einem der folgenden Wirkstoffe:

Eslicarbazepin1 oder Gabapentin oder Lacosamid2 oder Lamotrigin oder Levetiracetam oder Oxcarbazepin oder Pregabalin1 oder Topiramat oder Valproinsäure oder Zonisamid.

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 Präparate ist zu beachten.

1 Für Erwachsene.

2 Für Patienten ab 16 Jahren.

Fazit / Ausmaß des Zusatznutzens

Ein Zusatznutzen ist nicht belegt.

G-BA, 2014 [8].

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 3. Juli 2014 - Retigabin

Anwendungsgebiet

Retigabin (Trobalt®) ist angezeigt als Zusatztherapie für pharmakoresistente fokale Krampfanfälle mit oder ohne sekundäre Generalisierung bei Patienten mit Epilepsie im Alter von 18 Jahren oder älter, bei denen andere geeignete Arzneimittelkombinationen unzureichend wirkten oder nicht vertragen wurden.[1]

1 European Public Assessment Report (EPAR) – Zusammenfassung der Merkmale des Arzneimittels (Anhang I) von Trobalt® (Retigabin); Stand: Mai 2014; http://www.ema.europa.eu/docs/de_DE/document_library/EPAR_-_Product_Information/human/001245/WC500104835.pdf; Zugriff am 17. Juni 2014.

Zweckmäßige Vergleichstherapie

Eine individuelle antiepileptische Zusatztherapie, soweit medizinisch indiziert und falls noch keine Pharmakoresistenz/Unverträglichkeit und Kontraindikationen bekannt sind, mit einem der folgenden Wirkstoffe: Tiagabin[2], Valproinsäure* oder Vigabatrin, ansonsten: Therapie nach Wahl des Arztes in Abhängigkeit der Basis- und Vortherapie(n) und unter Berücksichtigung des Grundes für den Therapiewechsel und etwaig einhergehender Nebenwirkungen. Die jeweilige Zulassung der Präparate ist zu beachten.

*Anmerkung: Valproinsäure ist üblicherweise Bestandteil der Vortherapie, die Angemessenheit des Einsatzes als Zusatztherapie ist in Hinblick auf diese zu beurteilen (z. B. Nebenwirkungen von Valproinsäure).

2 Außer Handel; Stand Lauer-Taxe: 15. Juni 2014.

Fazit / Ausmaß des Zusatznutzens

Ein Zusatznutzen gilt als nicht belegt.

G-BA, 2012 [7].

Beschluss des Gemeinsamen Bundesausschusses über eine Änderung der Richtlinie Methoden vertragsärztliche Versorgung: Neuropsychologische Therapie vom 24. November 2011

Der Gemeinsame Bundesausschuss hat in seiner Sitzung am 24. November 2011 beschlossen, die Richtlinie zu Untersuchungsund Behandlungsmethoden der vertragsärztlichen Versorgung (Richtlinie Methoden vertragsärztliche Versorgung) in der Fassung vom 17. Januar 2006 (BAnz. S. 1523), zuletzt geändert am 20. Oktober 2011 (BAnz. 2012 S. 535), wie folgt zu ändern:

I.

In der Anlage I „Anerkannte Untersuchungs- oder Behandlungsmethoden“ wird nach Nummer 18 die folgende Nummer 19 angefügt:

„**19. Neuropsychologische Therapie**

3.2 Cochrane Reviews

Bresnahan R et al., 2020 [2].

Oxcarbazepine add-on for drug-resistant focal epilepsy (Review)

Fragestellung

To assess the efficacy and tolerability of oxcarbazepine as an addon treatment for people with drug-resistant focal epilepsy.

Methodik

Population:

- Adults and children with drug-resistant focal epilepsy, as defined by the International League Against Epilepsy (ILAE 2009). We included participants who had undergone other interventions to treat epilepsy, such as surgery, vagal nerve stimulation or ketogenic diet.

Intervention:

- The active treatment group received therapy with oxcarbazepine, in addition to their usual treatment.
- Oxcarbazepine (600 mg/d, 1200 mg/d, 2400 mg/d, 10 mg/kg/d, and 60 mg/kg/d)

Komparator:

- The control group received placebo, an alternative antiepileptic drug or a different dose of oxcarbazepine, in addition to their usual treatment.

Endpunkte:

- Primary outcomes (1) Median percentage seizure reduction per 28 days, (2) 50% or greater reduction in seizure frequency, (3) Adverse effects
- Secondary outcomes (1) Seizure freedom, (2) Treatment withdrawal, (3) Cognitive effects, (4) Quality of life

Recherche/Suchzeitraum:

We ran the first searches for this review in July 2014. We ran subsequent searches in December 2016; and we ran the most recent searches on 24 September 2018, when we searched the following databases. There were no language restrictions.

1. Cochrane Register of Studies (CRS Web), which includes the Cochrane Epilepsy Group Specialized Register and the Cochrane Central Register of Controlled Trials (CENTRAL)

2. MEDLINE (Ovid) 1946 to 21 September 2018

3. ClinicalTrials.gov using the search strategy set out in Appendix 3. 4. WHO International Clinical Trials Registry Platform (ICTRP)

Qualitätsbewertung der Studien:

- Cochrane 'Risk of bias' tool
- I2 statistic and a Chi2 test, where applicable, to assess statistical heterogeneity. We judged a Chi2 P value of less than 0.10 or I2 greater than 50% to indicate statistical heterogeneity.
- Reporting bias using the ORBIT matrix system.

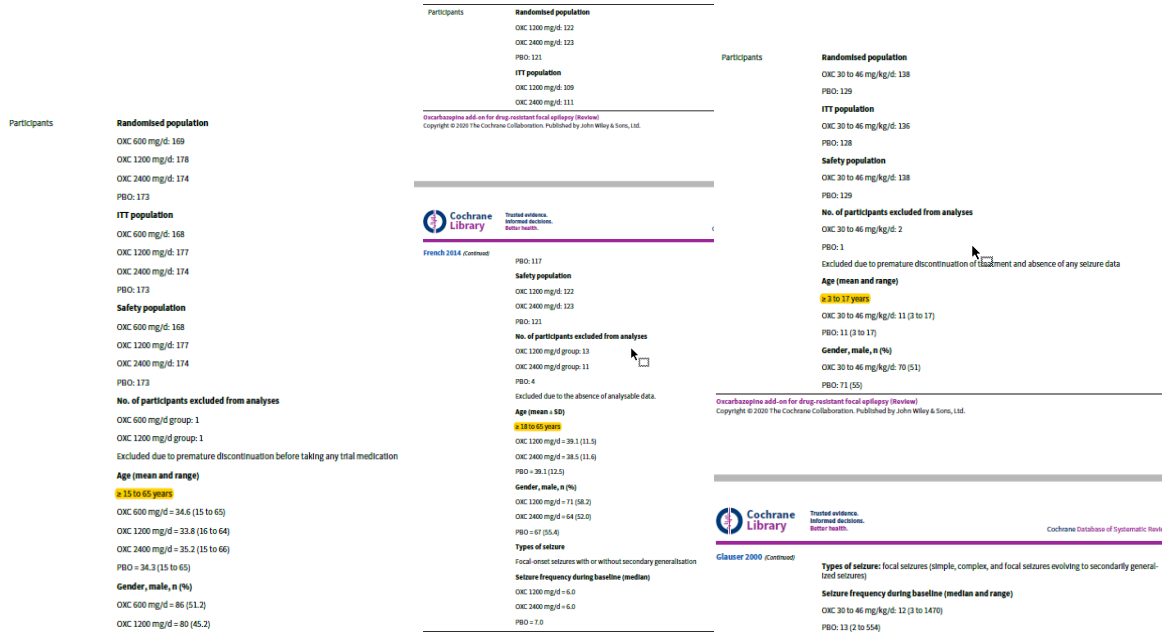
- To examine publication bias, we searched for unpublished data. We also looked for small-study effects to establish the likelihood of publication bias.
- Where possible, we stratified subgroup analysis by type of control group, age group (adults or children), duration of treatment, and experimental treatment dose.
- We did not conduct any sensitivity analyses as part of this review.

Ergebnisse

Anzahl eingeschlossener Studien:

- The 20 records related to six individual trials (Barcs 2000; Glauser 2000; Kraiprab 2005; Pina-Garza 2005; NCT00975715; French 2014). We extracted the data from these six studies and included them in the subsequent meta-analysis.
- The six included studies were all randomised, controlled trials with parallel group design. Four of the included studies were placebo-controlled (Barcs 2000; Glauser 2000; French 2014; NCT00975715); whilst two of the studies were alternative-dose-controlled (Kraiprab 2005; Pina-Garza 2005)

Charakteristika der Population:



Participants

Randomised population
OXC 600 mg/d: 169
OXC 1200 mg/d: 178
OXC 2400 mg/d: 174
PBO: 173
ITT population
OXC 600 mg/d: 168
OXC 1200 mg/d: 177
OXC 2400 mg/d: 174
PBO: 173
Safety population
OXC 600 mg/d: 168
OXC 1200 mg/d: 177
OXC 2400 mg/d: 174
PBO: 173
No. of participants excluded from analyses
OXC 600 mg/d group: 1
OXC 1200 mg/d group: 1
Excluded due to premature discontinuation before taking any trial medication
Age (mean and range)
≥ 15 to 65 years
OXC 600 mg/d = 34.6 (15 to 65)
OXC 1200 mg/d = 33.8 (16 to 64)
OXC 2400 mg/d = 35.2 (15 to 66)
PBO = 34.3 (15 to 65)
Gender, male, n (%)
OXC 600 mg/d = 86 (51.2)
OXC 1200 mg/d = 80 (45.2)

Participants

Randomised population
OXC 1200 mg/d: 122
OXC 2400 mg/d: 123
PBO: 121
ITT population
OXC 1200 mg/d: 109
OXC 2400 mg/d: 111

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French 2014 (Continued)

PBO: 117
Safety population
OXC 1200 mg/d: 122
OXC 2400 mg/d: 123
PBO: 121
No. of participants excluded from analyses
OXC 1200 mg/d group: 13
OXC 2400 mg/d group: 11
PBO: 4
Excluded due to the absence of analysable data.
Age (mean ± SD)
≥ 18 to 65 years
OXC 1200 mg/d = 39.1 (11.5)
OXC 2400 mg/d = 38.5 (11.6)
PBO = 39.1 (12.5)
Gender, male, n (%)
OXC 1200 mg/d = 71 (58.2)
OXC 2400 mg/d = 64 (52.0)
PBO = 67 (55.4)
Types of seizure
Focal-onset seizures with or without secondary generalisation
Seizure frequency during baseline (median)
OXC 1200 mg/d = 6.0
OXC 2400 mg/d = 6.0
PBO = 7.0

Participants

Randomised population
OXC 30 to 46 mg/kg/d: 138
PBO: 129
ITT population
OXC 30 to 46 mg/kg/d: 136
PBO: 128
Safety population
OXC 30 to 46 mg/kg/d: 138
PBO: 129
No. of participants excluded from analyses
OXC 30 to 46 mg/kg/d: 2
PBO: 1
Excluded due to premature discontinuation of treatment and absence of any seizure data
Age (mean and range)
≥ 3 to 17 years
OXC 30 to 46 mg/kg/d: 11 (3 to 17)
PBO: 11 (3 to 17)
Gender, male, n (%)
OXC 30 to 46 mg/kg/d: 70 (51)
PBO: 71 (55)

Oxcarbazepine add-on for drug-resistant focal epilepsy (Review)
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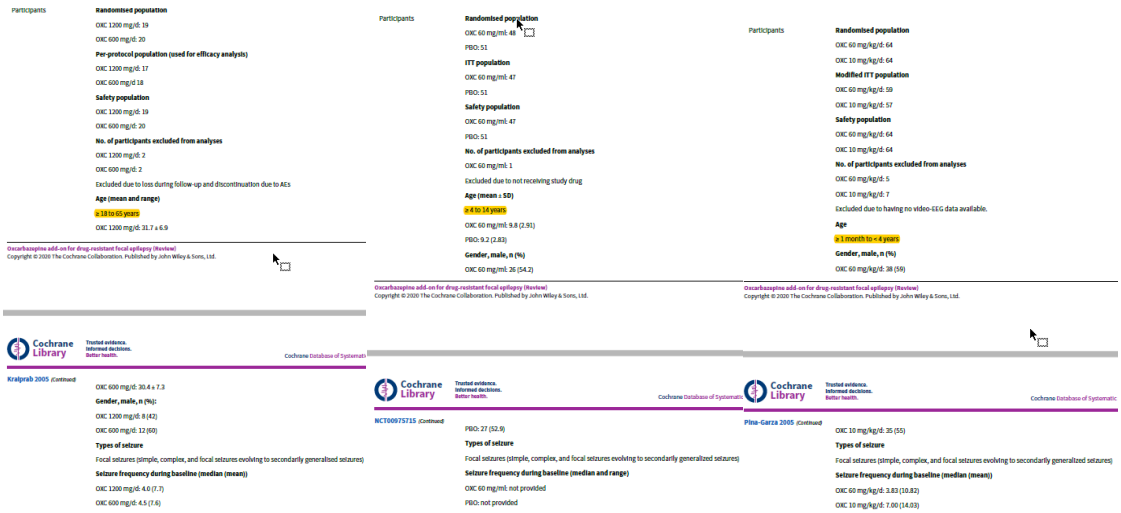
Glauser 2000 (Continued)

Types of seizure: focal seizures (simple, complex, and focal seizures evolving to secondarily generalized seizures)
Seizure frequency during baseline (median and range)
OXC 30 to 46 mg/kg/d: 12 (3 to 1470)
PBO: 13 (2 to 554)

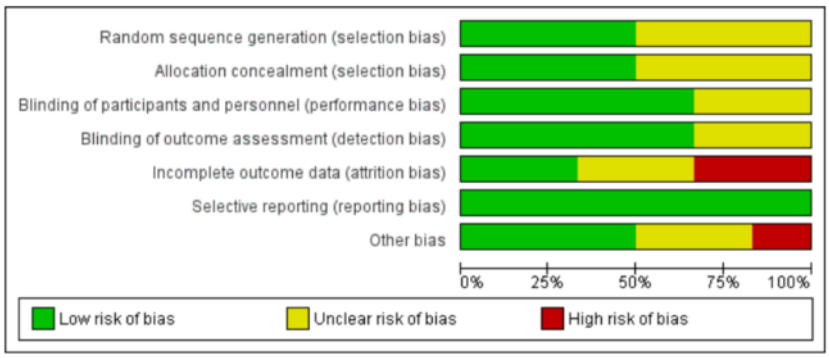


Qualität der Studien:

- We judged that three of the included studies were at an unclear risk of bias overall (Glauser 2000; Kraiprab 2005; NCT00975715), and rated that the remaining three studies were at a high risk of bias (Barcs 2000; Pina-Garza 2005; French 2014).

Figure 2. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.

Figure 3. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.



Studienergebnisse:

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI for efficacy outcomes and 99% CI for adverse effects)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with control	Risk with Oxcarbazepine				
Median percentage seizure reduction per 28 days Follow-up: 9 days to 26 weeks	The values reported ranged from 7.6% to 28.7% seizure reduction with 2 of the 3 studies specifically reporting percentage reductions of less than 10%. The median percentage seizure reduction for participants randomised to experimental oxcarbazepine treatment ranged from 26% to 83.3%. Importantly, for each study that described this outcome, the median percentage seizure reduction reported was consistently higher in experimental oxcarbazepine treatment group than in the control group.		-	**1494** (5 RCTs)	⊕⊕⊕◯ **MODERATE**[a]	Oxcarbazepine likely increases the median percentage seizure reduction per 28 days attained by participants.
50% or greater reduction in seizure frequency Follow-up: 9 days to 26 weeks	**Study population** 217 per 1000	390 per 1000 (275 to 555)	**RR 1.80** (1.27 to 2.56)	**1593** (6 RCTs)	⊕⊕◯◯ **LOW**[a,b]	Oxcarbazepine may increase the number of participants achieving a 50% or greater reduction in seizure frequency but we are uncertain.
Ataxia Follow-up: 9 days to 26 weeks	**Study population** 50 per 1000	128 per 1000 (43 to 380)	**RR 2.54** (0.86 to 7.54)	**1227** (5 RCTs)	⊕⊕⊕◯ **MODERATE**[a,b,d]	Oxcarbazepine likely increases the incidence of ataxia.
Hyponatraemia	**Study population**[#] 0 per 558	5 per 1035	**RR 2.53** (0.27 to 23.85)	**1593** (6 RCTs)	⊕⊕⊕◯ **MODERATE**[a,c,d]	Oxcarbazepine likely increases the incidence of hyponatraemia.
Follow-up: 9 days to 26 weeks						
Somnolence Follow-up: 9 days to 26 weeks	**Study population** 120 per 1000	244 per 1000 (140 to 425)	**RR 2.03** (1.17 to 3.54)	**1593** (6 RCTs)	⊕⊕◯◯ **LOW**[a,b,c,d]	Oxcarbazepine may increase the incidence of somnolence but we are uncertain.
Seizure freedom Follow-up: 9 days to 26 weeks	**Study population** 36 per 1000	102 per 1000 (42 to 244)	**RR 2.86** (1.19 to 6.87)	**1494** (5 RCTs)	⊕⊕◯◯ **LOW**[a,b,c,d]	Oxcarbazepine may increase the incidence of seizure freedom amongst participants but we are uncertain.
Treatment withdrawal Follow-up: 9 days to 26 weeks	**Study population** 167 per 1000	292 per 1000 (240 to 355)	**RR 1.75** (1.44 to 2.13)	**1593** (6 RCTs)	⊕⊕⊕◯ **MODERATE**[a]	Oxcarbazepine likely increases treatment withdrawal.

*The risk in the intervention group (and its 95% CI for efficacy outcomes, including treatment withdrawal, and 99% CI for adverse effects) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI for efficacy outcomes, including treatment withdrawal, and 99% CI for adverse effects).

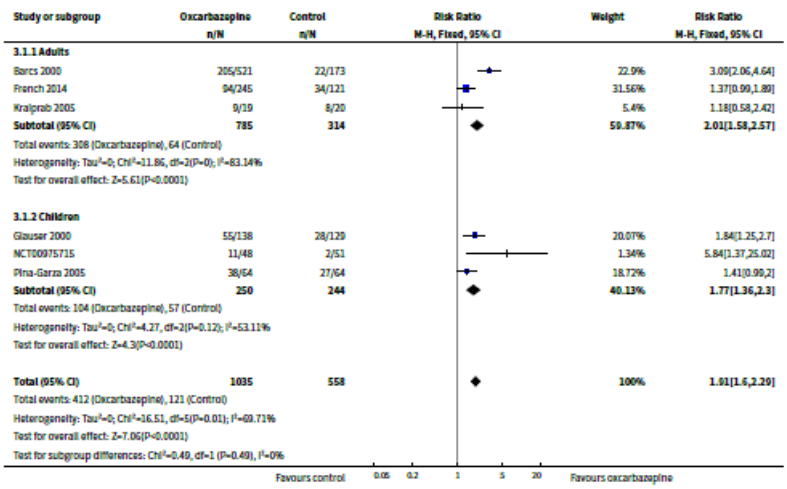
For the adverse event, **Hyponatraemia**, we have reported the **Number of events recorded per number of randomised participants** rather than the **Anticipated absolute effects**. Under the circumstances, this measure was considered more informative.

CI: Confidence interval; **RR:** Risk ratio

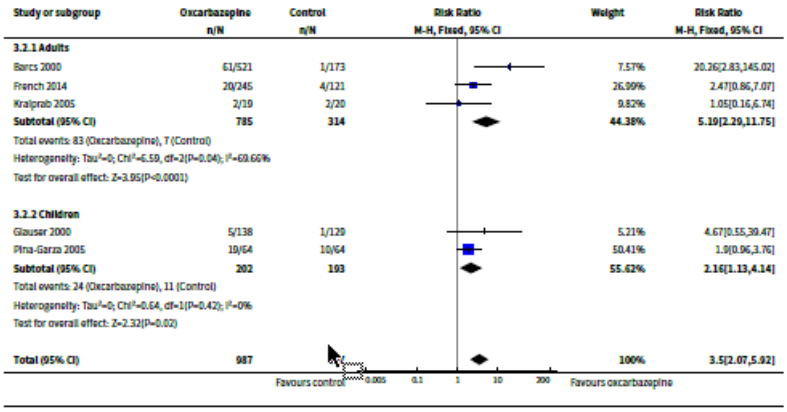
- **50% or greater reduction in seizure frequency**: Subgroup analysis stratified by the age of participants did not reveal a significant subgroup effect (P = 0.49).
- **Seizure freedom**: Subgroup analysis stratified by age of study population (P = 0.10) did not display a significant subgroup effect.

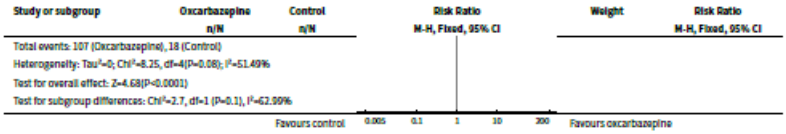
- **Treatment withdrawal**: Subgroup analysis stratified by the age of the clinical sample (P = 0.29) did not display a significant subgroup effects.

Analysis 3.1. Comparison 3 Oxcarbazepine vs. control (Subgroup analysis - Age group), Outcome 1 50% or greater reduction in seizure frequency.

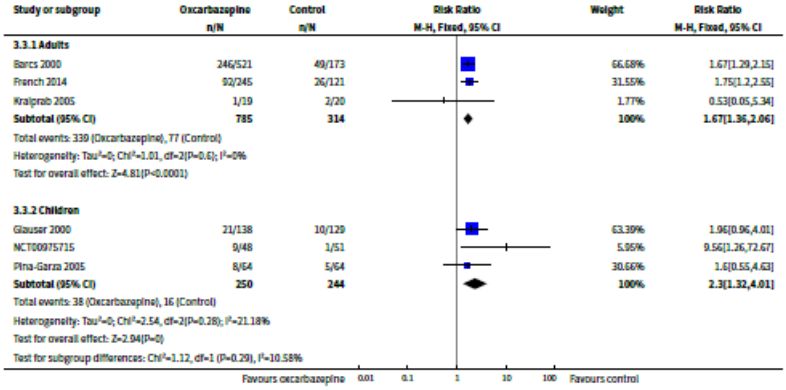


Analysis 3.2. Comparison 3 Oxcarbazepine vs. control (Subgroup analysis - Age group), Outcome 2 Seizure freedom.





Analysis 3.3. Comparison 3 Oxcarbazepine vs. control (Subgroup analysis - Age group), Outcome 3 Treatment withdrawal.



Anmerkung/Fazit der Autoren

Oxcarbazepine might be effective at reducing seizure frequency when used as an add-on for drug-resistant focal epilepsy. The efficacy outcomes — 50% or greater seizure reduction and seizure freedom — were derived from low-certainty evidence. We are, therefore, uncertain whether the estimated effect size is representative of the true effect. In contrast, the evidence for median percentage seizure reduction and treatment withdrawal were of moderate certainty: thus, we are fairly certain of the effect estimates' reliability. Overall, we are unsure of the true efficacy of oxcarbazepine, but have concerns about its tolerability.

Mbizvo GK et al., 2020 [19].

Levetiracetam add-on for drug-resistant focal epilepsy (Review)

Fragestellung

To evaluate the effectiveness of levetiracetam when used as an addon treatment for people with drug-resistant focal epilepsy.

Methodik

Population:

- Participants had to meet all of the following criteria.
  - Any age, gender, and ethnic background
  - Experiencing drug-resistant focal epilepsy

Intervention:

- The active treatment group received treatment with levetiracetam in addition to conventional AED treatment.

Komparator:

- The control group received matched placebo in addition to conventional AED treatment.

Endpunkte:

- Primary outcomes: 1.) 50% or greater reduction in focal seizure frequency, 2.) Treatment withdrawal, 3.) Adverse effects.
- Secondary outcomes: 1.) Cognitive effects, 2.) Quality of life.

Recherche/Suchzeitraum:

- The first searches for the original review were in 2000. Subsequent searches were in September 2002, July 2005, January 2010, February 2011, April 2011, August 2012, March 2014, February 2015, March 2017, October 2017, and 26 November 2018. For the latest update, we searched the following databases. There were no language restrictions:
  - Cochrane Register of Studies (CRS Web, 26 November 2018)
  - MEDLINE (Ovid, 1946 to November 21, 2018)
  - ClinicalTrials.gov (26 November 2018)
  - WHO International Clinical Trials Registry Platform (ICTRP; apps.who.int/trialsearch/; 26 November 2018)
  - CRS Web includes the Cochrane Epilepsy Group Specialized
  - Register and the Cochrane Central Register of Controlled Trials

Qualitätsbewertung der Studien:

- Selection bias, Performance bias, Detection bias, Attrition bias, Reporting bias
- Statistical heterogeneity between trials was checked for each outcome using a Chi 2 test for heterogeneity and the I2 statistic.
  - Subgroup analyses separating adult and paediatric trials.
- reporting biases:
  - We assessed the consistency of the measurements and outcomes planned by the original investigators during the trial with those reported within the published paper by comparing the trial protocols.
  - Where there were 10 or more studies for any comparison or outcome, we investigated the presence of publication bias by inspecting a funnel plot for asymmetry.

Ergebnisse

Anzahl eingeschlossener Studien:

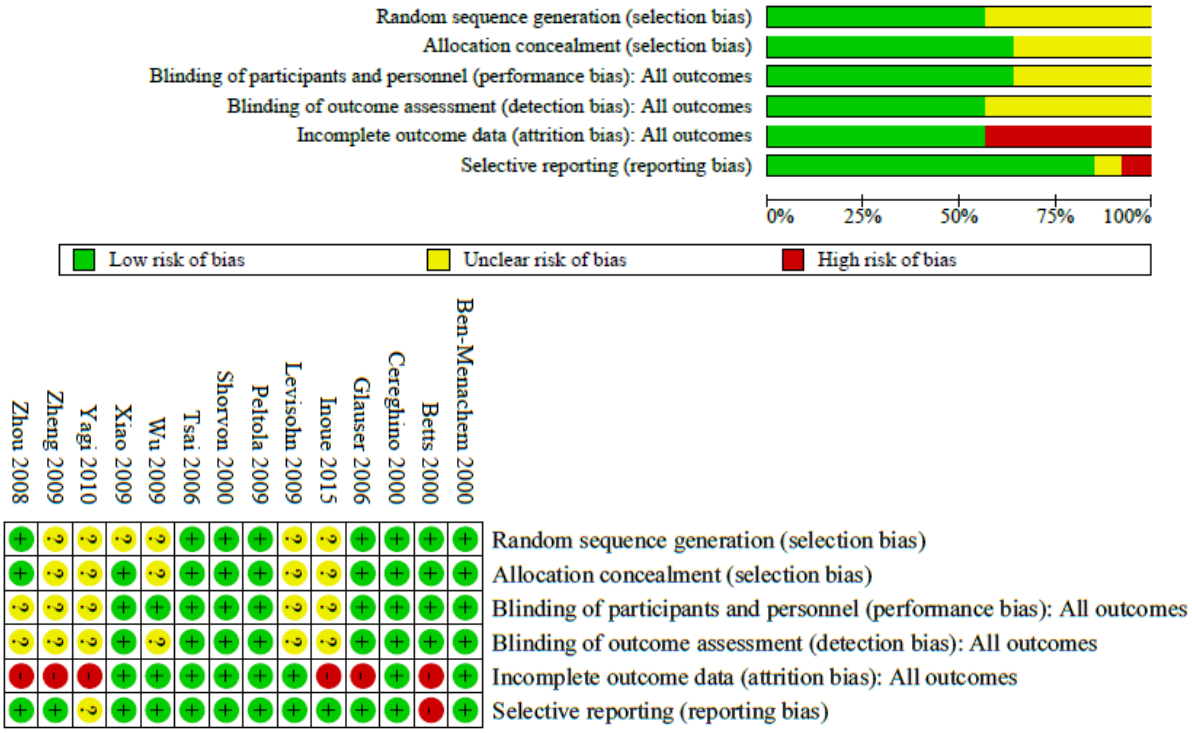
- This update included 14 trials (2455 participants), seven of which were published subsequent to the original 2001 review.
- Aside from one cross-over trial (Shorvon 2000), all trials were parallel design.

Charakteristika der Population:

- Participants were 296 children in two trials (**age range four to 16 years**) (Glauser 2006; Levisohn 2009). The remaining trials included 2159 adults aged over 16 years.

Qualität der Studien:

Figure 2. 'Risk of bias' graph: review authors' judgements about each 'Risk of bias' item presented as percentages across all included studies (shown above).



Studienergebnisse:

Summary of findings 1. Levetiracetam compared to placebo for drug-resistant focal epilepsy

Levetiracetam compared to placebo for drug-resistant focal epilepsy

Patient or population: drug-resistant focal epilepsy
Setting: outpatients
Intervention: levetiracetam
Comparison: placebo

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI) (99% CI for adverse events)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with placebo	Risk with levetiracetam				
50% or greater reduction in focal seizure frequency (responders) intention to treat – all doses	**Study population** 172 per 1000	404 per 1000 (344 to 473)	**RR 2.37** (2.02 to 2.78)	2455 (14 RCTs)	⊕⊕⊕⊖ **Moderate** a,b	The odds of response (50% reduction in seizure frequency) was increased by nearly 40% (OR 1.39, 95% CI 1.23 to 1.58) for each 1000 mg increase in dose of levetiracetam.
Treatment withdrawal – all doses	**Study population** 114 per 1000	127 per 1000 (101 to 160)	**RR 1.11** (0.89 to 1.40)	2428 (13 RCTs)	⊕⊕⊕⊕ **High** b	There was no effect on the odds of withdrawal of treatment (OR 0.99, 95% CI 0.85 to 1.15) for each 1000 mg increase in dose of levetiracetam.
Adverse effects: 5 most common adverse effects (any age) – somnolence	**Study population** 97 per 1000	158 per 1000 (116 to 214)	**RR 1.62** (1.19 to 2.20)	2423 (13 RCTs)	⊕⊕⊕⊖ **Moderate** c	—
Adverse effects: 5 most common adverse effects (any age) – headache	**Study population** 87 per 1000	74 per 1000 (52 to 106)	**RR 0.85** (0.60 to 1.21)	2423 (13 RCTs)	⊕⊕⊖⊖ **Low** a,c	—
Adverse effects: 5 most common adverse effects (any age) – dizziness	**Study population** 49 per 1000	76 per 1000 (49 to 119)	**RR 1.54** (0.99 to 2.42)	2423 (13 RCTs)	⊕⊕⊕⊖ **Moderate** c	—
Adverse effects: 5 most common adverse effects (any age) – fatigue (asthenia)	**Study population** 45 per 1000	69 per 1000 (44 to 107)	**RR 1.53** (0.98 to 2.38)	2423 (13 RCTs)	⊕⊕⊕⊖ **Moderate** c	—
Adverse effects: 5 most common adverse effects (any age) – accidental injury	**Study population** 74 per 1000	53 per 1000 (36 to 78)	**RR 0.72** (0.49 to 1.06)	2423 (13 RCTs)	⊕⊕⊖⊖ **Low** a,c	—

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

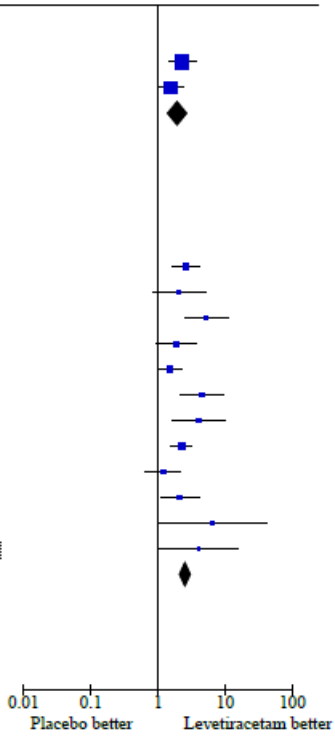
CI: confidence interval; **OR:** odds ratio; **RCT:** randomised controlled trial; **RR:** risk ratio.

- **Subgroup analysis: adult trials compared to paediatric trials.**

  For the two trials that recruited children, the results were sufficiently similar to be combined to give a pooled RR for 50% or greater reduction in seizure frequency of 1.91 (95% CI 1.38 to 2.63; P < 0.0001; Chi2 = 1.58, df = 1 (P = 0.21); I2 = 37%). 52% of children responded to levetiracetam (95% CI 44% to 59%), with a placebo response of 25% (95% CI 18% to 34%). Overall, there was no statistically significant difference in the results of trials recruiting adults (all levetiracetam doses) and trials recruiting children (test for subgroup differences: Chi2 = 2.01, df = 1 (P = 0.16); I2 = 50.3%).

Analysis 1.3. Comparison 1: Levetiracetam versus placebo, Outcome 3: ≥ 50% reduction in focal seizure frequency: (intention to treat): subgroup analysis by age

Study or Subgroup	Levetiracetam Events	Levetiracetam Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Fixed, 95% CI
1.3.1 Children						
Glauser 2006	45	101	19	97	51.5%	2.27 [1.44 , 3.60]
Levisohn 2009	40	64	14	34	48.5%	1.52 [0.97 , 2.37]
Subtotal (95% CI)		**165**		**131**	**100.0%**	**1.91 [1.38 , 2.63]**
Total events:	85		33			
Heterogeneity: Chi² = 1.58, df = 1 (P = 0.21); I² = 37%						
Test for overall effect: Z = 3.94 (P < 0.0001)						
1.3.2 Adults (all doses)						
Ben-Menachem 2000	76	181	17	105	15.4%	2.59 [1.62 , 4.14]
Betts 2000	21	80	5	39	4.8%	2.05 [0.83 , 5.02]
Cereghino 2000	76	199	7	95	6.8%	5.18 [2.49 , 10.80]
Inoue 2015	59	281	8	70	9.1%	1.84 [0.92 , 3.66]
Peltola 2009	34	79	23	79	16.4%	1.48 [0.96 , 2.27]
Shorvon 2000	59	212	7	112	6.5%	4.45 [2.10 , 9.42]
Tsai 2006	20	47	5	47	3.6%	4.00 [1.64 , 9.77]
Wu 2009	57	103	26	103	18.6%	2.19 [1.51 , 3.19]
Xiao 2009	13	28	11	28	7.9%	1.18 [0.64 , 2.17]
Yagi 2010	38	144	9	72	8.6%	2.11 [1.08 , 4.12]
Zheng 2009	13	18	1	9	1.0%	6.50 [1.00 , 42.17]
Zhou 2008	8	14	2	14	1.4%	4.00 [1.03 , 15.50]
Subtotal (95% CI)		**1386**		**773**	**100.0%**	**2.49 [2.08 , 2.99]**
Total events:	474		121			
Heterogeneity: Chi² = 21.83, df = 11 (P = 0.03); I² = 50%						
Test for overall effect: Z = 9.80 (P < 0.00001)						
Test for subgroup differences: Chi² = 2.01, df = 1 (P = 0.16), I² = 50.3%						



- **Behavioural adverse effects**:
  - One trial provided outcome data for cognitive as well as behavioural and emotional effects in children (Levisohn 2009)
  - Changes in behaviour were negligible in adults (1% affected; RR 1.79, 99% CI 0.59 to 5.41), but significant in children (23% affected; RR 1.90, 99% CI 1.16 to 3.11). Levetiracetam had a positive effect on some aspects of cognition and QoL in adults and worsened certain aspects of child behaviour.

Anmerkung/Fazit der Autoren

Overall, this review update finds that in both adults and children with drug-resistant focal epilepsy, levetiracetam added on to usual care is more effective than placebo at reducing seizure frequency, it is unlikely to be stopped by patients, and it has minimal adverse effects outside of potential worsening behaviour in children. These findings are unchanged from the previous review update in 2012. This review update contributes two key additional findings: 1. a 500 mg daily dose of levetiracetam is no more effective than placebo at reducing seizures; and 2. the odds of response (50% reduction in seizure frequency) are increased by nearly 40% for each 1000 mg increase in dose of levetiracetam.

It seems reasonable to continue the use of levetiracetam in both adults and children with drug-resistant focal epilepsy.

Kommentare zum Review

- Studien schließen keine Kinder <4 Jahre ein.

3.3 Systematische Reviews

Gerstl et al., 2021 [14].

A systematic review of seizure-freedom rates in patients with benign epilepsy of childhood with centrotemporal spikes receiving antiepileptic drugs

Fragestellung

To evaluate seizure remission rates in patients with benign epilepsy of childhood with centrotemporal spikes (BECTS) receiving antiepileptic drugs.

Methodik

Die Studie wird ergänzend dargestellt erfüllt jedoch die methodischen Anforderungen nicht. Keine Qualitätsbeurteilung der Studien.

Population:

- Children and adolescents with a diagnosis of BECTS where anticonvulsive treatment was performed are included

Intervention/Komparator:

- 1 or several treatment arms as well as studies where a part of the children received placebo or no treatment

Endpunkte:

- Seizure-freedom rates
- Adverse events (drop-outs)

Recherche/Suchzeitraum:

- PubMed and Web of Science for studies published until May 2017

Qualitätsbewertung der Studien:

- Keine Qualitätsbeurteilung vorgenommen

Ergebnisse

Anzahl eingeschlossener Studien:

- In the end, 19 publications met the inclusion criteria, 6 of which covered RCTs

Charakteristika der Population:

- Keine genaue Information zu Epilepsieform

TABLE 2. Randomized controlled trials

Author	Study Design	Medication	Seizure Freedom	Observation Period, mo	Mean Age, y
Kwon et al[14]	RCT (blinded)	OXC (n = 13) Once daily (n = 4) Twice daily (n = 9) No treatment (n = 16)	OXC: 54% (n = 7) Once daily: 50% (n = 2) Twice daily: 56% (n = 5) No treatment: 50% (n = 8)	6	8.2 (SD, 2.3; 5–15)
Borggraefe et al[15]	RCT (blinded)	STM (n = 21) LEV (n = 22)	STM: 91% (n = 19) LEV: 81% (n = 18) (not significant)	6	LEV: 8.7 (SD, 1.7; 6–12) STM: 9.0 (SD, 1.5; 6–12)
Rating et al[16]	RCT (blinded)	STM (n = 31) Placebo (n = 35)	STM: 87% (n = 27) Placebo: 40% (n = 14)	6	All children: 8.3 (3–10) STM: 8.2 (3.9–10.7) Placebo: 8.4 (3.1–10.3)
Andrade et al[19]	RCT (open)	CLB (n = 18) CBZ (n = 25)	CLB: 89% (n = 16) CBZ: 84% (n = 21)	24	7.7 (SD, 4.4; 5–12.1)
Coppola et al[17]	RCT (open)	LEV (n = 21) OXC (n = 18)	LEV: 91% (n = 19) OXC: 72% (n = 13)	18.5	All children: 10.7 LEV: 10.5 (5–13) OXC: 8.4 (3.3–14)
Kang et al[18]	RCT (open)	TPM (n = 45) CBZ (n = 43)	TPM: 69.6% (n = 31) CBZ: 70.0% (n = 30) (P = 0.968)	12	All children: 8.7 (5–15) TPM: 8.7 (SD, 1.9) CBZ: 8.7 (SD, 2.0)

TABLE 3. Non–randomized controlled trials

Year	Author	Study Design	N*	Medication	Seizure Freedom	Observation Period	Mean Age, y
2016	Liu et al[13]	Prospective study	85	TPM 2 mg/kg nightly (n = 44) TPM daily 4 mg/kg (n = 41)	TPM nightly: 90.9% (n = 27) TPM daily: 92.5% (n = 27)	12 mo	Group A: 8.6 Group B: 7.9 All: 8.26
2014	Xiao et al[20]	Retrospective study	56	LEV (n = 33) VPA (n = 23)	LEV: 57.5% (n = 19; 6 Monate), 81.8% (n = 27; 12Monate), 100% (n = 33; 18 Monate) VPA: 60.9% (n = 14; 6 Monate), 73.9% (n = 17; 12Monate), 100% (n = 23; 18 Monate)	6, 12, and 18 mo (using data for 6 mo)	VPA: 8.6 LEV: 8.3 All children: 8.42
2012	Pavlou et al[21]	Prospective study	55	CBZ/OXC (n = 24) VPA (n = 31)	CBZ/OXC: 71% (n = 17) VPA: 65% (n = 20)	12 or 24 Seizure freedom after 1 or 2 y; no further discrimination	7.5 (2.5–13)
2010	Stülpnagel et al[22]	Retrospective study	4	LEV (n = 4)	LEV: 50%	3 mo	10.6 (4–14)
2008	Wirrell et al[23]	Retrospective study	6	STM (n = 6)	STM: 100% (n = 6)	6 mo	9.1
2007	Kossof et al[24]	Retrospective study	6	LEV (n = 6)	LEV: 67% (n = 4)	6 mo	8.5 (4.6–11.2)
2007	Verrotti et al[25]	Retrospective study	21	1. LEV as initial monotherapy (n = 9); 2. LEV as monotherapy after conversion from another drug (n = 12)	1. LEV: 89% (n = 8) 2. LEV: 75% (n = 9)	12 mo	7.7 (SD, 4.4)

TABLE 3. *(Continued)*

Year	Author	Study Design	N*	Medication	Seizure Freedom	Observation Period	Mean Age, y
2005	Tzitiridou et al[26]	Prospective open trial	70	OXC (n = 70)	OXC: 53% (n = 37)	18 mo	8.4 (SD, 1.2; 5.2–11.6)
2004	Ben-Zeev et al[27]	Retrospective multicenter study	39	STM (n = 39)	STM: 74% (n = 29)	2–12 y	Range of 3–18
2003	Bello-Espinosa and Roberts[28]	Retrospective case series	3	LEV (n = 3)	LEV: 100% (n = 3)	3 mo (2000–2003)	6.83
2003	Engler et al[29]	Retrospective study	16	STM (n = 16)	STM: 63% (n = 10)	3–6 mo, 7–12 mo, 1–2 y, 2–3 y	7.1
2002	Kramer et al[6]	Prospective open trial	56	STM (n = 18) CBZ (n = 38)	STM: 67% (n = 12) CBZ: 74% (n = 28) (not significant)	2 y	No age
1995	Gross-Selbeck[10]	Retrospective analysis	42	STM (n = 17) CBZ (n = 16) PRM or PHE (n = 2) No treatment (n = 7)	STM: 88% (n = 17) CBZ: 56% (n = 16) PRM or PHE:50% (n = 1) No treatment: 57% (n = 4)	1.5–11 y	No age

TABLE 1. Patient Counts From the RCTs

Study	Treatment 1		Treatment 2		Follow-up, mo
Borggraefe et al[15]	Sulthiame	(n = 21)	Levetiracetam	(n = 22)	6
Rating et al[16]	Sulthiame	(n = 31)	Placebo	(n = 35)	6
Coppola et al[17]	Levetiracetam	(n = 21)	Oxcarbazepine	(n = 18)	18.5
Kwon et al[14]	Oxcarbazepine	(n = 13)	No treatment	(n = 16)	6
Kang et al[18]	Carbamazepine	(n = 43)	Topiramate	(n = 45)	12
Andrade et al[19]	Carbamazepine	(n = 25)	Clobazam	(n = 18)	24

Qualität der Studien:

- Keine Qualitätsbeurteilung vorgenommen

Studienergebnisse:

- Seizure-freedom rates:

  The seizure-freedom rates in those patients who did not receive any treatment respectively who were “treated” with placebo were significantly lower than those in the compound group of all patients receiving AEDs. Based on the treatment success rates, the patients receiving levetiracetam, sulthiame, and clobazam were aggregated into 1 group and compared with the children treated with oxcarbazepine, carbamazepine, or topiramate. The patients in the former group had a significantly higher success rate than those in the latter one.

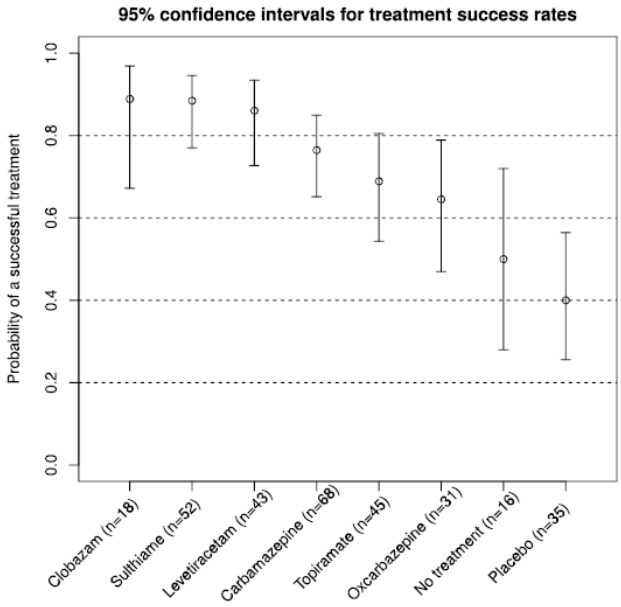


FIGURE 2. Seizure-freedom rates for the different treatment agents. A, Data from the RCTs. *B*, All available data.

TABLE 4. Results of Fisher Exact Test Comparing the Grouped Patients From the RCTs

Selection	*P*
Treatment vs no treatment/placebo	<0.0001
LEV/STM/CLB vs OXC/CBZ/TPM	0.0021

CBZ, carbamazepine; CLB, clobazam; LEV, levetiracetam; OXC, oxcarbazepine; STM, sulthiame; TPM, topiramate.

- Adverse events and drop outs:

TABLE 5. Dropouts Because of Adverse Effects in the RCTs, by Medication

	Dropouts	
Sulthiame	1.9%	(1/52)
Oxcarbazepine	3.2%	(1/31)
Clobazam	5.5%	(1/18)
Levetiracetam	14%	(6/43)
Carbamazepine	14%	(12/86)
Topiramate	29%	(13/45)
Total	12%	(34/275)

Anmerkung/Fazit der Autoren

As far as the low amount of available data permits those conclusions, the analyses performed here show that a treatment with sulthiame, clobazam, or levetiracetam leads to a both statistically and clinically significant higher degree of seizure freedom in children with BECTS when compared with oxcarbazepine, carbamazepine, and topiramate. The

adverse effects profile of the former treatment agents appears to be favorable with the lowest incidence of therapy-limiting adverse effects reported in the use of sulthiame.

Kommentare zum Review

- Die Studie wird ergänzend dargestellt erfüllt jedoch die methodischen Anforderungen nicht. Keine Qualitätsbeurteilung der Studien.

Widjaja et al., 2020 [23].

Seizure outcome of pediatric epilepsy surgery: Systematic review and meta-analyses

Fragestellung

This systematic review and meta-analyses assessed seizure outcome following pediatric epilepsy surgery

The aim of this systematic review and meta-analysis was to estimate effects on seizure outcomes following pediatric epilepsy surgery, including long-term seizure outcome and seizure outcome by different surgery locations, pathologies, nonlesional epilepsy, and incomplete resection in children with DRE.

Methodik

Population:

- The population included children with DRE undergoing epilepsy surgery.

Intervention:

- Resective epilepsy surgery

Komparator:

- Medical therapy with AEDs

Endpunkte:

- The outcome was seizure freedom on follow-up at 12 months or longer.

Recherche/Suchzeitraum:

- MEDLINE, EMBASE, and Cochrane databases were searched systematically (on November 9, 2017)

Qualitätsbewertung der Studien:

- The Newcastle-Ottawa Quality Assessment Scale was used to assess the quality of observational studies.
- The quality of RCT was assessed using the Cochrane risk-of-bias tool.
- Sensitivitätsanalyse

Ergebnisse

Anzahl eingeschlossener Studien:

- All studies were observational studies, except for 1 RCT. There were 244 (95%) retrospective studies and 11 (4%) controlled studies. (*Hier fehlen zwei Studien)*

Charakteristika der Population:

Heterogene Pathologien

Table 1 Meta-analyses for seizure-free outcome for mixed pathologies and surgery locations, surgery locations, pathologies, and nonlesional epilepsy

	No. of studies	Total no. of seizure-free	Total no. of patients	Seizure-free percentage (95% CI)	*p* Value	I^2
Pathologies						
Tumor	42	932	1,170	79.8% (74.8%–84.0%)	<0.001	66.3
Malformations of cortical development	40	780	1,379	57.1% (52.8%–61.2%)	0.001	53.4
Mesial temporal sclerosis	15	268	348	77.9% (68.5%–85.1%)	<0.001	60.2
Encephalomalacia	13	187	337	60.8% (49.7%–70.8%)	0.055	68.2
Rasmussen encephalitis	10	125	174	71.7% (58.3%–82.1%)	0.002	55.0
Hemimegalencephaly	6	52	88	59.4% (47.0%–70.8%)	0.135	17.9
Hypothalamic hamartoma	4	31	68	45.9% (30.7%–61.9%)	0.621	35.0
Tuberous sclerosis	18	188	344	55.0% (48.8%–61.6%)	0.115	10.6
Nonlesional epilepsy	19	266	523	51.5% (44.1%–58.8%)	0.697	55.9

Abbreviation: CI = confidence interval.
[a] Included 1 randomized controlled trial; no. = number.

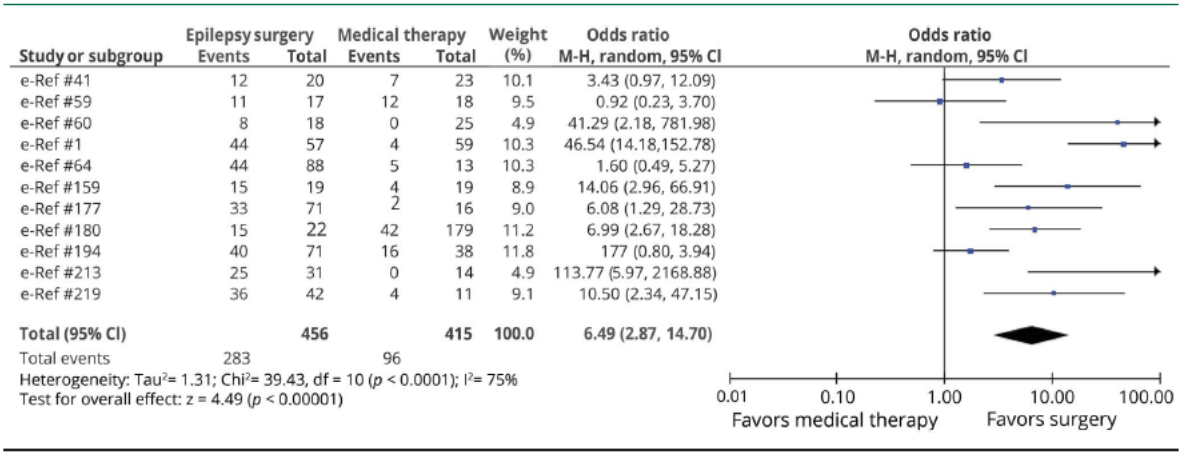
Qualität der Studien:

- Quality of observational studies, the mean score for selection was 3.0 stars (SD 0.2), for comparability was 1.2 stars (SD 0.8), for outcome was 2.6 stars (SD 0.6), and the mean total score was 6.8 stars (SD 1.0). The studies were on average considered as good quality because a selection score of 3 or 4 stars. a comparability score of 1 or 2 stars, and an outcome score of 2 or 3 stars were considered as good.
- For the quality of RCT, the risks of selection bias related to randomized sequence or allocation concealment, reporting bias, performance bias, detection bias, attrition bias, and other bias were low.

Studienergebnisse:

- 11 studies compared epilepsy surgery with medical therapy, with a total of 456 patients in the surgical group and 415 patients in the medical group, and the range of follow-up was 1–13.5 years.
- The odds of seizure-free outcome were higher for surgery compared with medical therapy (OR = 6.49 [95% CI: 2.87–14.70], p < 0.001) (figure 2).
- The funnel plot showed evidence of publication bias, with fewer studies on the right of the funnel plot with smaller effect size. The observed effect size (OR = 6.49) was higher than the imputed effect size (OR = 3.11) if there were more studies on the right of the funnel plot.

Figure 2 Forest plot from meta-analysis comparing surgery (n = 456) with medical therapy (n = 415), showing higher odds for seizure-free outcome after surgery compared with medical therapy



Anmerkung/Fazit der Autoren

In summary, the findings from this systematic review and meta-analyses support the benefits of epilepsy surgery in children with DRE compared with medical therapy. This study demonstrated the nuance of pediatric epilepsy surgery outcomes based on surgery locations, pathologies, nonlesional epilepsy, and incomplete resection. The findings suggest that epilepsy surgery should be the treatment of choice among children with focal DRE who are eligible for surgery, particularly those with lesional epilepsy, such as tumor and mesial temporal sclerosis, where seizure freedom could be achieved in greater than 70% of patients.

Kommentare zum Review

- Sehr heterogene Pathologien in zugrundeliegenden Studien

Cao Y et al., 2019 [3].

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 (1763 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

Table 1 Characteristics of prospective studies

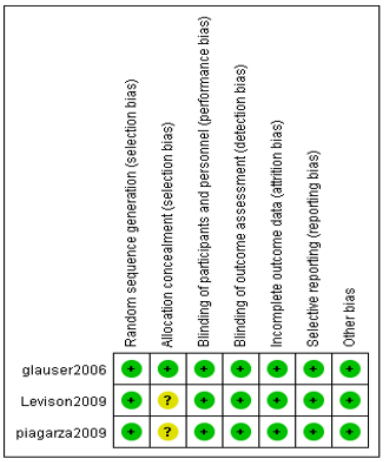
References	Trial design	NO. ITT	Age (years)	baseline drug
Glauser et al.2002(Glauser et al., 2002c)	MC, P, OL, NC	23	6-12y	CBZ, LTG, VPA, TPM, FEM, GBM, PRM
Wheless et al.2002(Wheless and Ng, 2002a)	OL, P, NC	25	≤16y	NR
Grosso et al.2005(Grosso et al., 2005)	MC, P, NC	53	6m-16y	VPA, CBZ, VBA, TPM, CPM, LTG, PBA, DAP
Lagae et al.2003(Lagae et al., 2003a) ENREF_32	OL, P	10	6m-14y	VPA, GVG, LTG, BZP, TOP, GBP, CBZ, TGB, PB, PHT
Lagae et al.2005(Lagae et al., 2005)	P, NC	31	6m-16y	NR
Callenbach et al.2008(Callenbach et al., 2008)	P, MC, OL, NC	31	4-16y	NR
Tonekaboni et al.2010(Tonekaboni et al., 2010)	P, NC	8	⩽16y	BZP, PB, PRM, TOP, VPA, LTG, CBZ, VGB, GBP, OBP, EOM, PHT

Continue·table·1¶

References¤	Trial·↵ design¤	NO.¶ ITT¤	Age¶ (years)¤	baseline·drug¤
Kanemura·et·al.2013(Kanemura·et·al.,·2013b)¤	P,·NC¤	48¤	16m-18y¤	NR¤
Chhun·et·al.2011(Chhun·et·al.,·2011)¤	P,·OL,·NC¤	36¤	6m-15y¤	VPA,·LTG,·CBZ,·VBA,·TPM¤
Posar·et·al.2014(Posar·et·al.,·2014)¤	P,·OL,·NC¤	8¤	6y-16y¤	VPA,·ESM,·LTG¤
Delgado·et·al.2012(Schiemann-Delgado·et·al.,·2012)¤	P,·MC,·OL,·NC,·E¤	103¤	4-16y¤	OCBZ,·CBZ,·LTG,·VPA,·TPM¤
PinaGarza··et·al.2010(Piña-Garza·et·al.,·2010)¤	P,·OL,·MC,·E¤	152¤	1m-4y¤	PB,·VPA,·TPM,·OCBZ,·DZP,·CZP,·VBA,·CBZ,·LTG¤
Fountain·et·al.2007(Fountain·et·al.,·2007a)¤	P,·OL,·MC,·PM¤	21¤	4-12y¤	CBZ,·VPA¤
Iwasaki2015(Iwasaki·et·al.,·2015a)¤	P,·OL¤	24¤	0.7-16.7y¤	CBZ,·PBA,·ZAM,·CZP,·CBM,·GBP,·TPM,·LTG¤

Qualität der Studien:

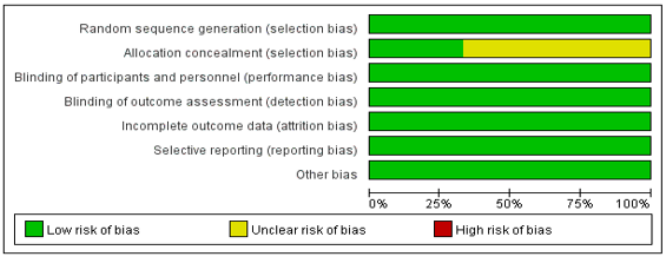
- RCTs: low risk



Caption

Risk of bias summary: review authors' judgements about each risk of bias item for each included study. ¶

Figure·1· 'Risk·of·bias'·summary·for·RCTs¶



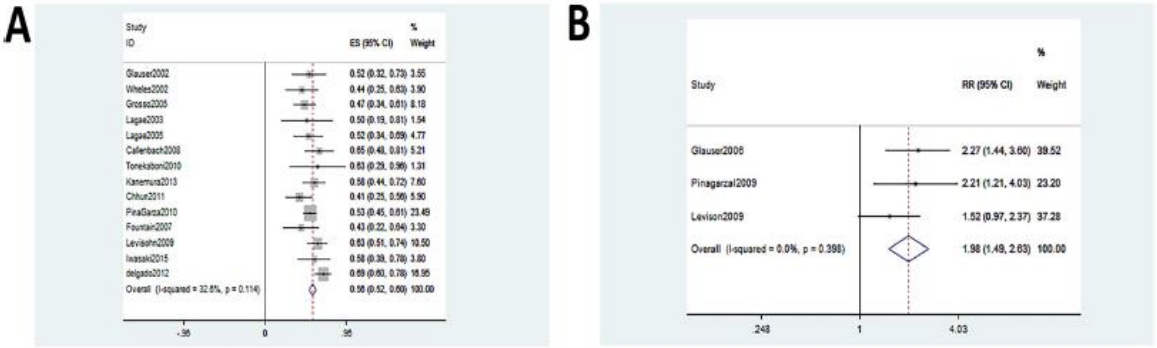
Caption

Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies. ¶

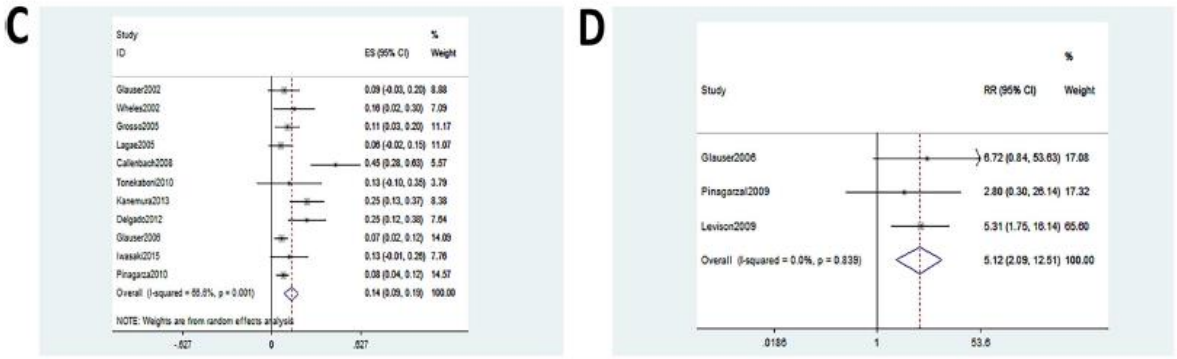
Figure· 2· 'Risk· of· bias'· graph· for· RC

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 (Fig. 2B)
- The fixed-effect model was adopted, showing the ORR was 56% (95% CI: 52%–60%) for the 50% responder rate (Fig. 2A).



- **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 (Fig. 2D)



- **median percentage reduction rate**:
  - The chi2 test indicates statistically significant heterogeneity between trials (chi2 = 96.16, I2=95.8%, p=0.000), and a random-effects model was adopted. The ORR was 55% (95% CI: 31%–79%) in the pooled analysis for overall median percentage reduction rate (Fig. 2E).
  - A sensitivity analysis was performed, one prospective self-controlled study was removed, and indicated a slight decrease in the rate of the median percentage reduction rate with a pooled ORR of 55% (95% CI: 31%–79%). 568 patients (LEV=298; placebo=260) from head-to head trials were included in meta-analysis. The chi2 test showed no statistically significant heterogeneity between trials, (chi2 = 2.64, I2 = 0.0%, p=0.451), and the fixed-effect model was chosen. The overall RR was 3.19 (95% CI: 2.37–4.31) between these two groups (Fig. 2F).

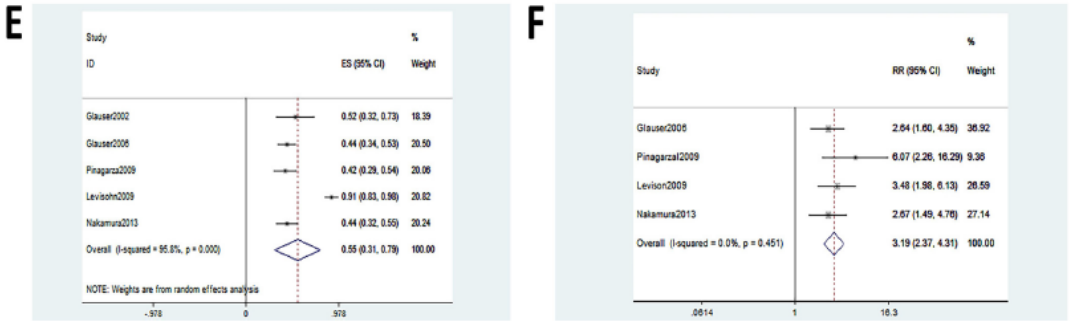


Fig. 2. Meta-analysis of the efficacy of add-on levetiracetam (LEV) in children with focal-onset seizures (FOS): (A) Overall response rate of the 50% responder for LEV group; (B) Risk ratio of the 50% responder for LEV group vs. placebo group;(C) Overall response rate of seizure freedom rate for LEV group; (D) Risk ratio of seizure freedom rate for LEV group vs. placebo group;(E) Overall response rate of the median percentage reduction rate for LEV group; (F) Risk ratio of the median percentage reduction rate for LEV group vs. placebo group.

- **Treatment emergent adverse events (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 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.

Rosati et al., 2018 [22].

Comparative efficacy of antiepileptic drugs in children and adolescents: A network meta-analysis

Fragestellung

To estimate the comparative efficacy among antiepileptic drugs in the pediatric population (0-18 years).

Methodik

Population:

- pediatric age (0-18 years)
- RCTs conducted on mixed populations were included only when the outcome efficacy was available for pediatric age or the mean age of patients enrolled was <18 years.

Intervention/Komparator:

22 antiepileptic drugs and placebo

- The molecules considered were adrenocorticotropic hormone (ACTH), prednisolone, prednisone
- firstgeneration (carbamazepine [CBZ], clobazam [CLB], ethosuximide [ETS], nitrazepam [NZP], phenobarbital [PB], phenytoin [PHT], sulthiame [STM], valproic acid [VPA]),
- second-generation (felbamate [FBM], gabapentin

- [GPT], lamotrigine [LTG], levetiracetam [LEV], oxcarbazepine [OXC], topiramate [TPM], vigabatrin [GVG], zonisamide [ZNS])
- third-generation AEDs (perampanel [PER], rufinamide [RUF], stiripentol [STP]).

Endpunkte:

- Seizure freedom, when reported, or ≥50% seizure reduction from baseline to the last evaluation was considered as the efficacy outcome. If necessary (inhomogeneous outcome data across studies), seizure freedom was used as a proxy of ≥50% seizure reduction.

Recherche/Suchzeitraum:

- The NICE search strategy was updated in the Embase and MEDLINE databases up to February 24, 2017

Qualitätsbewertung der Studien:

- Study-level quality was assessed using the items reported in the Cochrane risk-of-bias tool (random sequence generation, allocation concealment, blinding of participants, outcome assessment, incomplete data, and selective reporting).

Ergebnisse

Anzahl eingeschlossener Studien:

- 46 RCTs were included in the qualitative synthesis; 43 articles were analyzed for efficacy outcome
- The 46 studies enrolled 5652 individuals (aged from 0 months to 42 years) randomized to 22 AEDs or placebo (PLB), and followed for a minimum of 7 days to a maximum of 4 years (<1 year of follow-up in 39/46 studies).

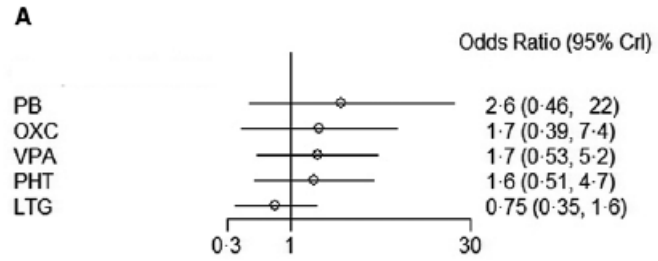
Charakteristika der Population:

- Six studies included newly diagnosed epilepsy with focal or generalized seizures, and 10 RCTs were conducted in refractory focal epilepsy. According to the syndromic classification, 2 RCTs were included on ECTS, 14 on infantile spasms–West syndrome, 6 on Lennox-Gastaut syndrome, 5 on childhood absence epilepsy and juvenile absence epilepsy, 1 on Dravet syndrome, and 2 on juvenile myoclonic epilepsy.

Qualität der Studien:

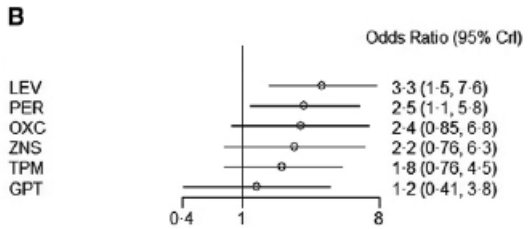
- Attrition bias was the most frequent bias observed (28 studies were judged to be high risk), followed by performance (19 studies), and detection bias (15 studies). Allocation concealment and random sequence generation were the more poorly reported domains, with 14 and 8 studies, respectively, being judged to have an unclear level of risk. Selective reporting or other quality domains were judged to have a low risk of bias.

Studienergebnisse:



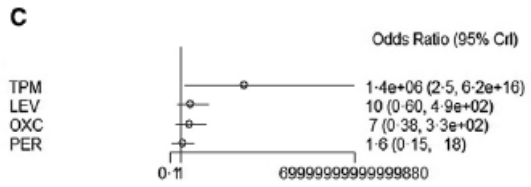
Forest plot of antiepileptic drugs compared to: carbamazepine in newly diagnosed focal epilepsy (seizure freedom outcome, A)

- Direct comparisons showed that all AEDs with the exception of TPM and GPT were more effective than PLB in terms of ≥50% seizure reduction. Only LEV (OR = 3.3, 95% CrI = 1.3-7.6) and PER (OR = 2.5, 95% CrI = 1.1-5.8) were more effective compared to PLB in mixed comparisons (Figure B)



Forest plot of antiepileptic drugs compared to: PLB in refractory focal epilepsy (≥50% seizure reduction outcome, B)

- Considering seizure freedom outcome, none among the AEDs analyzed (TPM, LEV, OXC, and PER) was better than PLB in direct comparison, whereas in mixed comparisons only TPM showed a superiority compared to PLB (Figure C). No evidence of heterogeneity or inconsistency was found. Attrition bias was the most frequently observed bias



Forest plot of antiepileptic drugs compared to: PLB in refractory focal epilepsy (seizure freedom, C)

Anmerkung/Fazit der Autoren

The point estimates of carbamazepine and lamotrigine efficacy showed their superiority with respect to all comparator antiepileptic drugs for the treatment of newly diagnosed focal epilepsy. In refractory focal epilepsy, levetiracetam (odds ratio [OR] = 3.3, 95% credible interval [CrI] = 1.3-7.6) and perampanel (OR = 2.5, 95% CrI = 1.1-5.8) were more effective compared to placebo.

Kommentare zum Review

- 2 RCTs were included on ECTS, 14 on infantile spasms–West syndrome, 6 on Lennox-Gastaut syndrome, 5 on childhood absence epilepsy and juvenile absence epilepsy, 1 on Dravet syndrome, and 2 on juvenile myoclonic epilepsy

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Maragkos G et al., 2018 [18].

Quality of Life After Epilepsy Surgery in Children: A Systematic Review and Meta-Analysis

Fragestellung

To estimate the quality of life (QOL) long-term outcomes after surgery for intractable epilepsy in pediatric patients.

Methodik

Population:

- Epilepsy surgery in pediatric patients (≤18 years old)

Intervention:

- Epilepsy surgery

Komparator:

- Medical controls (if any)

Endpunkte:

- Primary Outcome: Postoperative QOL
- Secondary outcomes: postoperative IQand Engel score.

Recherche/Suchzeitraum:

- The PubMed bibliographical database and the Cochrane Library were screened for eligible studies on March 20, 2018.

Qualitätsbewertung der Studien:

- For nonrandomized cohort studies, quality assessment was performed using the Newcastle–Ottawa scale (NOS), with a score of≥6 denoting high quality.
- For case series, study quality was assessed with the National Heart, Lung, and Blood Institute (NHLBI) tool. The NHLBI scale ranges from 1 to 9, with a score of 1-3 denoting poor quality, 4-6 fair, and 7-9 good quality
- Publication or small-study bias was assessed with funnel plots and Begg's tests.
- Between-study heterogeneity assessment was conducted using the Cochran Q statistic and I2. High heterogeneity was confirmed with a significance level of $P < .05$ and $I2 \geq 50\%$.
- Sensitivity analysis

Ergebnisse

Anzahl eingeschlossener Studien:

- 18 studies satisfied the predetermined search criteria and were included in this systematic review

Charakteristika der Population:

TABLE 1. Characteristics of Included Studies

Study	Study design	Surgical patients	Age, years, mean ± SD (range)	Surgery type, N	Quality of life question-naire	Follow-up, months, mean ± SD (range)
Hosoyama et al, 2017 [22]	RC	85	<16	N/A	*	185 ± 60
Panigrahi et al, 2016 [11]	RC	21	0.9 to 5.1	VPH: 16, PIH: 5	QOLIE	24 to 27
Downes et al, 2015 [18]	RC	14	6.2 ± 1.4	MST: 14	PedsQL	>18
Puka et al, 2015 [16]	RC	71	12.3 ± 4.3	LES: 14, COR: 17, LOB: 40	QOLIE	81 ± 26
Chen et al, 2014 [9]	RC	30	1.7 to 17	LES: 26	ABAS-II	N/A
Liang et al, 2014 [26]	PC	23	7.3 to 11.7	CAL: 23	QOLIE	24
Titus et al, 2013 [23]	RC	28	12.7 ± 2.6	MST: 1, PIH: 1, LES: 8, COR: 2, ATL: 11, LOB: 3, CAL: 2	QOLCE	12 ± 4
Liang et al, 2012 [21]	RC	206	11.3 ± 2.4	LES: 89, ATL: 60, AHT: 11, LOB: 18, CAL: 28	QOLIE	60
Ciliberto et al, 2012 [17]	RC	7	0.4 to 16.4	PIH: 7	QOLCE	24 to 64
Dagar et al, 2011 [12]	RC	118	9.8 ± 4.3	ATL: 43; VPH: 35; LOB: 25; CAL 5; VNS: 1	QOLIE	47 ± 23
Skirrow et al, 2011 [10]	RC	42	13.3 ± 3.1	N/A	QOLIE	60 to 180
Mikati et al, 2010 [15]	RC	19	12 ± 3.9	VPH: 2, ATL: 6, LOB: 11	QOLCE	46 ± 27
Mikati et al, 2008 [20]	RC	17	11.2 ± 1	ATL: 8, LOB: 9	QOLCE	29 ± 3
Griffiths et al, 2007 [13]	RC	56	12.9 ± 4.6	VPH: 26, ATL: 17, LOB: 13	HARCES	N/A
Sabaz et al, 2006 [14]	PC	35	6 to 18	N/A	QOLCE	18
van Empelen et al, 2005 [24]	PC	21	6.2 to 16.8	PIH: 6, ATL: 10, LES: 5	HAY-P	24
Keene et al, 1997 [19]	RC	64	12.2 ± 4.8	PIH: 4, ATL: 44, LOB: 16	QOLIE	91 ± 46
Gilliam et al, 1997 [25]	RC	33	4 to 14	VPH: 3, ATL: 18, LOB: 12	CHQ	7 to 72

Abbreviations: RC, retrospective cohort; PC, prospective cohort; SD, standard deviation; MST, multiple subpial transection; VPH, vertical parasagittal hemispherotomy; PIH, lateral peri-insular functional hemispherotomy; LES, lesionectomy; COR, corticectomy; ATL, anterior temporal lobectomy; AHT, amygdalohippocampectomy; LOB, other lobectomy; CAL, anterior corpus callosotomy; VNS, vagal nerve stimulation; QOLIE, quality of life in epilepsy; QOLCE, quality of life in childhood epilepsy; PedsQL, pediatric quality of life; ABAS-II, adaptive behavior assessment system; HARCES, Hague restrictions in childhood epilepsy scale; HAY-P, How Are You Pediatric; CHQ, child health questionnaire; N, number of procedures; SD, standard deviation; N/A, not applicable.
*The authors used a questionnaire devised for the purposes of their study.

Qualität der Studien:

- Mean NHLBI score for the 12 case series included in this review was 7.0 ± 1.1 (high quality: 8 studies; fair quality: 4 studies). The mean NOS score for the 6 retrospective cohort studies was 6.8 ± 1.2 (high quality: 4 studies; fair quality: 2 studies).
- No significant publication bias was identified using funnel plots and Begg's tests for any of the analyses.

Studienergebnisse:

- **QOL**: I^2 of0% (P= .60); The forest plot (Figure 2) showed that QOL was significantly better in surgically treated patients, compared to matched patients treated medically, and the pooled mean difference between the 2 groups was 12.42 (WMD: 12.42, 95% CI: 6.25-18.58, P< .001)

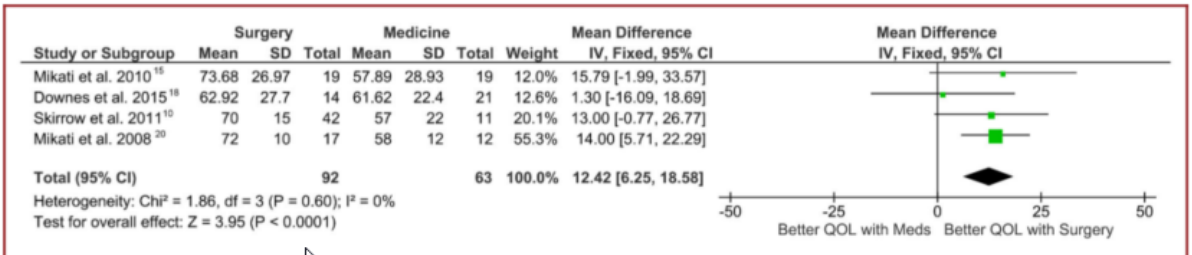

FIGURE 2. *Forest plot for the comparison between postoperative QOL and QOL after the same time period on antiepileptic medications. Abbreviations: SD, standard deviation; CI, confidence interval; QOL, quality of life.*

- **Intelligence Quotient**: I^2 = 0%; The pooled mean difference in IQ was 1.61 (95% CI: 4.10-17.12, P = .001), which was statistically significant in favor of the surgically treated patients.

- **Odds for IQ improvement of 10 or more**: (I2 = 0%), The pooled odds ratio for IQ improvement was 9.51 (95% CI: 2.51-36.07, P < .001), which was statistically significant in favor of surgically treated patients.

- **Seizure Outcome**: I2 = 64%; The pooled odds ratio for seizure freedom was 6.17 (95% CI: 1.65-23.08, P = .007), which was found statistically significant in favor of surgical treatment.

Anmerkung/Fazit der Autoren

Pediatric epilepsy surgery improves QOL in children with debilitating and medically recalcitrant seizures, likely due to higher postoperative seizure-freedom rates compared to medical management. Postoperative QOL outcomes were found to be better than both the preoperative state of each patient and matched medically managed controls.

Kommentare zum Review

- Keine Interessenskonflikte
- A number of studies did not report on all outcomes of interest; therefore, summary estimates were calculated based on available data.

Pindrik J et al., 2018 [21].

Preoperative evaluation and surgical management of infants and toddlers with drug-resistant epilepsy

Fragestellung

Despite perioperative risks, epilepsy surgery represents a legitimate curative or palliative treatment approach for children with drug-resistant epilepsy (DRE). Several factors characterizing infants and toddlers with DRE create unique challenges regarding optimal evaluation and management.

Methodik

Population:

- Children < 3 years of age undergoing surgical treatment of DER.

Intervention:

- surgery

Endpunkte:

- Seizure outcomes

Recherche/Suchzeitraum:

- PubMed database, the study team searched for articles published from January 1985 through May 2018

Qualitätsbewertung der Studien:

- All selected studies represented retrospective reviews, observational studies, and uncontrolled case series, representing low quality of evidence.

- Keine weitere Qualitätsbeurteilung vorgenommen

Ergebnisse

Anzahl eingeschlossener Studien:

- 20 eligible studies were identified.
- All selected studies represented retrospective reviews, observational studies, and uncontrolled case series, representing low quality of evidence.
- The studies varied widely regarding number of patients, with a range of 5 to 116.

Charakteristika der Population:

- 465 individuals who underwent resective or disconnective surgery (18 studies, 444 individuals total) or vagus nerve stimulator (VNS) insertion (2 studies, 21 individuals total) (Tables 1 and 2).
- Among these studies, patient age at surgery ranged between 28 days and 36 months, with a mean of 16.8 months.

TABLE 1. Summary of reported series of intracranial epilepsy surgery in children under 3 years of age

Authors & Year	No. of Pts	Age at Surgery (mean)	Etiology	Surgical Operation
Duchowny et al., 1990	5	2–11 mos (7.3 mos)	Gliosis, 2 (40%); neoplasm, 1 (20%); TSC, 1 (20%); idiopathic, 1 (20%)	Multilobar resection, 1 (20%); lobar/focal resection, 3 (60%); palliative/focal resection, 1 (20%)
Chugani et al., 1993	20	6–33 mos (14.1 mos)	MCD, 11 (55%); gliosis, 4 (20%); hemimeg, 2 (10%); cystic malformation, 2 (10%); TSC, 1 (5%)	Hemispherotomy, 8 (40%); multilobar resection, 11 (55%); lobar/focal resection, 1(5%)
Wyllie et al., 1996	12	2.5–29 mos (15.3) mos	MCD, 5 (42%); neoplasm, 3 (25%); SWS, 3 (25%); hemimeg, 1 (8%)	Hemispherotomy, 5 (42%); multilobar resection, 2 (17%); lobar/focal resection, 5 (42%)
Duchowny et al., 1998	31	0.9–36 mos (18.3 mos)	MCD, 18 (58%); neoplasm, 6 (19%); SWS, 2 (6%); hemimeg, 1 (3%); TSC, 1 (3%); other, 3 (9%)	Hemispherotomy, 14 (45%); multilobar resection, 3 (10%); lobar/focal resection, 14 (45%)
Sugimoto et al., 1999	20	3–34 mos (15.3 mos)	MCD, 8 (35%); neoplasm, 3 (13%); SWS, 5 (22%); hemimeg, 3 (13%); peri-/postnatal infarction, 2 (9%); hippocampal sclerosis, 1 (4%); other, 1 (4%)	Hemispherotomy, 11 (48%); multilobar resection, 3 (13%); lobar/focal resection, 9 (39%)
Bittar et al., 2002	11	5–33 mos (15.0 mos)	Peri-/postnatal infarction, 3 (27%); neoplasm, 2 (18%); hemimeg, 2 (18%); MCD, 1 (9%); SWS, 1 (9%); TSC, 1 (9%); vascular malformations, 1 (9%); hippocampal sclerosis, 1 (9%)	Hemispherotomy, 7 (64%); lobar/focal resection, 4 (36%)
Kang et al., 2006	9	4–35 mos (19.5 mos)	MCD, 7 (78%); TSC, 2 (22%)	Lobar/focal resection, 6 (67%); functional disconnection, 3 (33%)
Battaglia et al., 2006	26	4–33 mos (8.5 mos)	MCD, 10 (38%); hemimeg, 7 (27%); neoplasm, 6 (23%); peri-/postnatal infarct, 2 (8%); SWS, 1 (4%)	Hemispherotomy, 7 (30%); multilobar resection, 8 (35%); lobar/focal resection, 8 (35%)
Lodden-kemper et al., 2007	24	3–33 mos (14 mos)	MCD, 12 (50%); hemimeg, 7 (29%); SWS, 2 (8%); neoplasm, 2 (8%); TSC, 1 (4%)	Hemispherotomy, 14 (58%); multilobar resection, 6 (25%); lobar/focal resection, 4 (17%)

» CONTINUED FROM PAGE 3

TABLE 1. Summary of reported series of intracranial epilepsy surgery in children under 3 years of age

Authors & Year	No. of Pts	Age at Surgery (mean)	Etiology	Surgical Operation
Maton et al., 2008	13	6–33 mos (14 mos)	Neoplasm, 6 (46%); MCD, 4 (31%); peri-/postnatal infarction, 1 (8%); gliosis, 1 (8%); encephalitis, 1 (8%)	Lobar/focal resection, 13 (100%)
Steinbok et al., 2009	116	1–35 mos (15.8 mos)	MCD, 57 (49%); neoplasm, 22 (19%); SWS, 19 (16%); hemimeg, 8 (7%); peri-/postnatal infarction, 1 (1%); TSC, 1 (1%); gliosis, 1 (1%); other, 10 (9%); encephalitis, 1 (1%)	Hemispherotomy, 40 (34%); lesionectomy, 35 (30%); cortical resection, 33 (28%); temporal lobectomy, 7 (6%); corpus callosotomy, 1 (1%)
Gowda et al., 2010	15	1.5–6 mos (4 mos)	MCD, 8 (53%); hemimeg, 6 (40%); TSC, 1 (7%)	Hemispherectomy, 11 (73%); multilobar resection, 3 (20%); lobar/focal resection, 1 (7%)
Dunkley et al., 2011	42	3–36 mos (20 mos)	MCD, 26 (62%); hemimeg, 5 (12%); SWS, 5 (12%); neoplasm, 2 (5%); peri-/postnatal infarction, 1 (2%); TSC, 1 (2%); hippocampal sclerosis, 1 (2%)	Hemispherotomy, 27 (23%); multilobar resection, 4 (3%); lobar/focal resection, 11 (9%)
Iwatani et al., 2012	6	5–26 mos (15.5 mos)	MCD, 4 (66%); hemimeg, 1 (17%); PVL, 1 (17%)	Hemispherotomy, 2 (33%); cortical resection, 2 (50%); multilobar dissection, 1 (17%); corpus callosotomy, 1 (33%)
Ramantani et al., 2013	30	5–33.5 mos (20 mos)	MCD, 18 (60%); hemimeg, 6 (20%); neoplasm, 3 (10%); peri-/postnatal infarction, 3 (10%)	Hemispherotomy, 16 (47%); multilobar resection, 7 (21%); lobar/focal resection, 11 (32%)
Kumar et al., 2015	25	11 days–11.5 mos (4.7 mos)	MCD, 10 (40%); hemimeg, 8 (32%); peri-/postnatal infarction, 2 (8%); neoplasm, 1 (4%); SWS, 1 (4%); TSC, 1 (4%); gliosis, 1 (4%); other, 1 (4%)	Hemispherotomy, 16 (64%); grid-based resection, 7 (28%); lobar/focal resection, 9 (36%)
Jenny et al., 2016	19	5–36 mos	MCD, 7 (37%); neoplasm, 3 (16%); hemimeg, 2 (11%); peri-/postnatal infarction, 1 (5%); SWS, 1 (5%); TSC, 3 (16%); hippocampal sclerosis, 1 (5%); hamartoma, 1 (5%)	Hemispherotomy, 4 (21%); lobar/focal resection, 15 (79%)

» CONTINUED FROM PAGE 4

TABLE 1. Summary of reported series of intracranial epilepsy surgery in children under 3 years of age

Authors & Year	No. of Pts	Age at Surgery (mean)	Etiology	Surgical Operation
Gröppel et al., 2018	20	3–32 mos (16.2 mos)	MCD, 10 (50%); peri-/postnatal infarction, 5 (25%); neoplasm, 2 (10%); SWS, 2 (10%); gliosis, 1 (5%)	Hemispherotomy, 11 (55%); lobar/focal resection, 9 (45%)
Combined total	444	28 days–36 mos (16.8 mos)	MCD, 220 (50%); neoplasm, 62 (14%); SWS, 41 (9%); hemimeg, 59 (13%); peri-/postnatal infarction, 22 (5%); TSC, 14 (3%); gliosis, 10 (2%); cystic malformations, 2 (<1%); vascular malformations, 1 (<1%); hippocampal sclerosis, 4 (1%); other, 18 (4%)	Hemispherotomy, 186 (42%); multilobar resection, 50 (11%); lobar/focal resection, 200 (45%); corpus callosotomy, 4 (1%)

Qualität der Studien:

- All selected studies represented retrospective reviews, observational studies, and uncontrolled case series, representing low quality of evidence.

Studienergebnisse:

- Retrospective studies have demonstrated greater rates of seizure freedom in children 3 years of age or younger compared to patients 4–17 years of age.Reported rates of seizure freedom following epilepsy surgery in infants and toddlers range between 48% and 89.5%, including 65%–85% following hemispherotomy or hemispherectomy.

Anmerkung/Fazit der Autoren

Preoperative evaluation and surgical management of infants and toddlers with DRE offer substantial opportunities for favorable outcomes regarding seizure frequency and neurocognitive development. Young chronological and developmental age, physiological immaturity, small body size, and low blood volumes present nuances and unique challenges in the assessment and management of this young population. Epilepsy surgery represents a safe and effective treatment strategy for infants and toddlers with DRE, but requires modifications in evaluation and management from multiple disciplines.

Kommentare zum Review

- Suche erfolgte in nur einer Datenbank
- Keine Qualitätsbeurteilung der Studien (nur retrospective studies)
- Die Studie erfüllt die methodischen Anforderungen nicht ausreichend , sie wird nur ergänzend für die Altersgruppe <4 Jahre dargestellt.

3.4 Leitlinien

National Institute for Health and Care Excellence (NICE), 2012[20].

Clinical guideline [CG137] Published: 11 January ***2012 Last updated: 12 Mai 2021***

Epilepsies: diagnosis and management

Zielsetzung/Fragestellung

The guideline covers diagnosing, treating and managing epilepsy and seizures in children, young people and adults in primary and secondary care. It offers best practice advice on managing epilepsy to improve health outcomes so that people with epilepsy can fully participate in daily life.

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 über Appendices dargestellt; Die Aktualität der Appendices entspricht nicht dem Update der LL und es fehlt eine eindeutige Verbindung der Evidenz zu den Empfehlungen.
- Regelmäßige Überprüfung der Aktualität gesichert. Die aktuelle Version ist das Ergebnis der zweijährlichen Überprüfung (siehe „Surveillance report 2018 – Epilepsies: diagnosis and management (2012) NICE guideline CG137“); überarbeitete LL erwartet für März 2022

Recherche/Suchzeitraum:

- Cochrane reviews published between 11 September 2013 and 19 December 2017

Update Information:

- This guidance updates and replaces NICE guideline CG20. This guideline also updates and replaces NICE technology appraisal guidance 76 (2004) and NICE technology appraisal guidance 79 (2004).

LoE/GoR

- • GRADE-Systematik

Grading:	***1++***	***High-quality meta-analyses, systematic reviews of RCTs, or RCTs with a very low risk of bias***
Grading:	***1+***	***Well-conducted meta-analyses, systematic reviews of RCTs, or RCTs with a low risk of bias***
Grading:	***1-***	***Meta-analyses, systematic reviews of RCTs, or RCTs with a high risk of bias****

Sonstige methodische Hinweise

- Zusammenhang zwischen Grading und Wording über (Evidence to recommendation Table) ist nicht hinterlegt.
- Wording: NICE verzichtet auf die Auszeichnung der Stärke der Empfehlung, sondern realisiert das über die Formulierung
  - must/must not
  - should/should not
  - could/could not
  - For reccomendations on interventions that should be used (strong) use direct instructions rather than using the word „should". Use verbs such as „**offer**", „refer", „advise", and „discuss"

Empfehlungen

1.9 Pharmacological treatment

- In February 2020 we strengthened warnings that valproate must not be used in women and girls of childbearing potential (including young girls who are likely to need treatment into their childbearing years), unless alternative treatments are not suitable. Women and girls of childbearing potential must be fully informed about the risks of taking valproate during pregnancy, and only take valproate if they have a pregnancy prevention programme in place, in line with the MHRA safety advice on valproate.
- Valproate must not be used in pregnant women. See update informationfor more details.
- Recommendations in this section offer alternative prescribing options for this group and provide additional specific information of relevance when considering prescribing anti-epileptic drugs (AEDs) to women and girls of childbearing potential.

1.9.3 Pharmacological treatment of focal seizures

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

1.9.3.1 For first-line treatment of newly diagnosed focal seizures:

- Offer lamotrigine to women and girls of childbearing potential (including young girls who are likely to need treatment into their childbearing years).
- Offer lamotrigine or carbamazepine to boys, men and women who are not of childbearing potential. [2012, amended 2021] [2012, amended 2021]

1.9.3.2 If carbamazepine or lamotrigine are unsuitable or not tolerated for newly diagnosed focal seizures:

- Offer levetiracetam to women and girls of childbearing potential (including young girls who are likely to need treatment into their childbearing years). If levetiracetam is ineffective, offer oxcarbazepine. Advise that oxcarbazepine can impair the effectiveness of hormonal contraceptives.
- Do not offer sodium valproate to women and girls of childbearing potential (including young girls who are likely to need treatment into their childbearing years) with focal seizures, unless other options are ineffective or not tolerated and the pregnancy prevention programme is in place. Follow the MHRA safety advice on valproate use by women and girls.

- Offer levetiracetam, oxcarbazepine or sodium valproate to boys, men and women who are not of childbearing potential. If the first AED tried is ineffective, offer an alternative from these AEDs.
  - Levetiracetam is not cost effective at June 2011 unit costs. (Estimated cost of a 1,500mg daily dose was £2.74 at June 2011. Cost taken from theNational Health Service Drug Tariff for England and Wales.) It may be offered 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. [amended 2020] [amended 2020].

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

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

- In January 2012, the use of clobazam, gabapentin, eslicarbazepine acetate, pregabalin and zonisamide in recommendations 1.9.3.4 and 1.9.3.5 was off label (see the BNFor BNFCfor details). See NICE's information on prescribing medicines.
- Recommendations 1.9.3.4 and 1.9.3.5: As of 1 April 2019, gabapentin is a Class C controlled substance (under the Misuse of Drugs Act 1971) and scheduled under the Misuse of Drugs Regulations 2001 as Schedule 3. Evaluate patients carefully for a history of drug abuse before prescribing and observe patients for development of signs of abuse and dependence (MHRA, Drug Safety Update April 2019).

1.9.3.4 If first-line treatments (see recommendations1.9.3.1 and 1.9.3.2) for children, young people and adults with focal seizures are ineffective or not tolerated:

- Offer lamotrigine, levetiracetam, carbamazepine, clobazam, gabapentin, oxcarbazepine or topiramate as adjunctive treatment to women and girls of childbearing potential (including young girls who are likely to need treatment into their childbearing years). Follow the MHRA safety advice on antiepileptic drugs in pregnancy. Advise that topiramate and oxcarbazepine can impair the effectiveness of hormonal contraceptives.
- Do not offer sodium valproate to women and girls of childbearing potential (including young girls who are likely to need treatment into their childbearing years) with focal seizures, unless the other options are ineffective or not tolerated and the pregnancy prevention programme is in place. Follow the MHRA safety advice on valproate use by women and girls.
- Offer carbamazepine, clobazam, gabapentin, lamotrigine, levetiracetam, oxcarbazepine, sodium valproate or topiramate as adjunctive treatment to boys, men and women who are not of childbearing potential. [amended 2021]

Hinweis:

Die Empfehlung 1.9.3.4 stellt eine Aktualisierung der Empfehlung Nr. 88 („Offer carbamazepine, clobazam, gabapentin, lamotrigine, levetiracetam, oxcarbazepine, sodium valproate or topiramate as adjunctive treatment of children, young people and adults with focal seizures if first-line treatments (see recommendations 85 and 86) are ineffective or not tolerated. Be aware of teratogenic risks of sodium valproate (see recommendation 83). [new 2012]") dar.

Die Aktualisierung, die sich vorrangig auf die Entfernung der Empfehlung zur Behandlung mit Valproinsäure bezieht, wird folgendermaßen begründet:

- **May 2021:** We amended recommendations on carbamazepine, gabapentin, lamotrigine, levetiracetam, oxcarbazepine, phenobarbital, phenytoin, pregabalin, topiramate and zonisamide in line with updated MHRA safety advice on antiepileptic drugs in pregnancy.
- **February 2020: We amended recommendations in line with the MHRA guidance on valproate use by women and girls**. The MHRA states that valproate must not be used in women and girls of childbearing potential (including young girls who are likely to need treatment into their childbearing years), unless other options are unsuitable and the pregnancy prevention programme is in place. We did this by:
  - moving cautions and links to the MHRA's latest advice on sodium valproate into the recommendations
  - adding bullet points to some recommendations to clarify that sodium valproate is not an option for women and girls of childbearing potential, but is an option for men, boys and women who are not of childbearing potential.

  Medicines containing valproate taken in pregnancy can cause malformations in 11% of babies and developmental disorders in 30% to 40% of children after birth. Valproate treatment must not be used in girls and women including in young girls below the age of puberty, unless other treatments are unsuitable and the terms of the European Medicines Agency's pregnancy prevention programmeare met. This programme includes: assessment of patients for the potential of becoming pregnant; pregnancy tests; counselling patients about the risks of valproate treatment; explaining the need for effective contraception throughout treatment; regular (at least annual) reviews of treatment by a specialist, and completion of a risk acknowledgement form. In pregnancy, valproate is contraindicated and an alternative treatment should be decided on, with appropriate specialist consultation. See the MHRA toolkit to ensure female patients are better informed about the risks of taking valproate during pregnancy.

Für die aktualisierte Empfehlung 1.9.3.4 liegt keine aktuelle und detaillierte Darstellung der zugrundeliegenden Evidenz vor. Da sich die Änderung der Empfehlung 88 aber vor allem auf den Ausschluss von Valproinsäure bezieht und die restlichen Wirkstoffe der Empfehlung weiterhin empfohlen werden, wird nachfolgend die Zusammenfassung der Evidenz zur Formulierung der Empfehlung Nr. 88 extrahiert.

Hintergrund:

Evidenzextraktion: Clinical guideline (CG137) Published 11. Januar 2012. Last updated May 2021; bezieht sich auf NCGC (National Clinical Guideline Centre) *The Epilepsies; The diagnosis and management of epilepsies in adults and children in primary and secondary care* (Recommendation 88).

Relative values of different outcomes	In children, young people and adults, the achievement of seizure freedom or at least a 50% reduction in seizure frequency were considered to be the most clinically relevant outcomes. Tolerability, as measured by withdrawals due to adverse events, was also considered important.
Trade off between clinical benefits and harms	The evidence for adults showed that significantly more participants receiving clobazam, levetiracetam, levetiracetam extended-release, oxcarbazepine and topiramate achieved seizure freedom than placebo. Significantly more on gabapentin, oxcarbazepine, lamotrigine, levetiracetam and topiramate experienced at least a 50% reduction in seizure frequency when compared to placebo. From the evidence for children, significantly more participants on lamotrigine and oxcarbazepine compared to placebo experienced at least a 50% reduction in seizure frequency. More people on oxcarbazepine (adults and children) achieved seizure freedom than those on placebo in a refractory population on monotherapy. In children, significantly more participants on levetiracetam compared to placebo experienced at least a 50% reduction in seizure frequency.
	The drugs recommended above had unfavourable adverse events profiles, but the GDG found this unsurprising given that they were being evaluated as combination treatment in a refractory population. Many of the adverse events observed in the trials were dose related and in clinical practice these can be mitigated through careful dose titration. Significantly more participants receiving gabapentin, lamotrigine, topiramate and oxcarbazepine withdrew due to adverse events compared to placebo. Gabapentin had higher incidence of somnolence, dizziness and ataxia and aggravation of seizures when compared to placebo. There was no significant difference between levetiracetam and placebo for withdrawal due to adverse events although incidence of adverse events was significantly higher in the levetiracetam arm. No specific adverse events were reported in the trial for clobazam, but the GDG considered its tendency to have sedative side effects and its efficacy can wane over extended use. Oxcarbazepine and lamotrigine had a less favourable adverse events profile compared to placebo. Topiramate had higher incidence of headache when compared with lamotrigine. In children taking lamotrigine the incidence of dizziness, tremor, nausea and ataxia were higher

* At the time of publication (Janaury 2012), this drug did not have UK marketing authorisation for this indication and/or population (see appendix K for details). Informed consent should be obtained and documented.

	compared to to placebo. A decision model was built to weigh up the clinical benefits of each adjunctive AED, measured by seizure control and seizure reduction, compared to the harms from adverse events as measured by withdrawals from treatment due to adverse events. For the drugs recommended here, the treatment benefits outweighed the harms for the average patient and the QALYs gained justified the additional costs over placebo (no adjunctive AED).

Quality of evidence	For adults, the majority of the evidence was placebo controlled and there were few head to head comparisons. All of the studies were randomised controlled trials, the majority of which were double-blind. Most of the studies gave unclear details of their methods of randomisation, allocation concealment and blinding. The statistically significant results for 50% reduction in seizure frequency were from the placebo-controlled studies. Few of the drugs which were compared to drugswere statistically significant and where this did occur there was uncertainty in the magnitude of clinical effect. The quality overall was generally low or very low. The published economic evidence varied had problems of methodological quality and applicability to the decision-making context of the guideline. Some had out of date costs that could change the study's conclusions or did not include all of the relevant comparators. The original decision models undertaken for the guideline aimed to overcome these limitations, but still had some of their own. Limitations of the original analyses, particularly where assumptions had to be made, relate to the lack of data availability on longer term effectiveness and discontinuation, limited health-state utility data and limited to no data to inform estimates of NHS resource use.
Other considerations	The drugs recommended above are older and therefore there is long-term experience with them. Eslicarbazepine acetate, lacosamide, pregabalin, and zonisamide showed efficacy but were not included for first-line adjunctive treatment as they are newer drugs and the GDG felt that there needed to be more long-term evidence of their efficacy and cost-effectiveness for adjunctive treatment. There is limited evidence for tiagabine being effective. Gabapentin was included as first-line adjunctive drug option, but based on the clinical experience of the GDG was regarded as less effective than the other AEDs. The GDG considered the addition of oxcarbazepine without trying carbamazepine as unusual but may be considered, as it is less enzyme inducing. The GDG were aware that in clinical practice a second AED is added to the first. They also agreed with published literature which states that if the latter helps the first may be taken away if the patient agrees.[287] GDG discussion centred around some key issues. Namely, care should be taken with clobazam when withdrawing and a slow withdrawal of clobazam over/up to 4-6mg in view of the risk of withdrawal seizures. They noted that sodium valproate inhibits the metabolism of lamotrigine and this needs to be taken into consideration when introducing or withdrawing either medication. Clinical experience led the GDG to believe that on withdrawal of sodium valproate, lamotrigine levels may drop and this may be ther reason for breakthrough seizures. They also noted that there should be a concomitant increase in the lamotrigine dose but did not wish to make a specific recommendation. Topiramate may affect phenytoin levels.

	NICE has also issued guidance on the use of retigabine as an option for the adjunctive treatment of partial (focal has been used in this guideline) onset seizures with or without secondary generalisation in adults aged 18 years and older with epilepsy in 'Retigabine for the adjunctive treatment of partial onset seizures in epilepsy' (NICE technology appraisal guidance 232).

Referenzen:

189 Koeppen D, Baruzzi A, Capozza M et al. Clobazam in therapy-resistant patients with partial epilepsy: a double-blind placebo-controlled crossover study. *Epilepsia.* 1987; 28(5):495-506.

190 Elger C, Bialer M, Cramer JA et al. Eslicarbazepine acetate: a double-blind, add-on, placebocontrolled exploratory trial in adult patients with partial-onset seizures. *Epilepsia.* 2007; 48(3):497-504.

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1.9.3.5 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, lacosamide, phenobarbital, phenytoin, pregabalin , tiagabine, vigabatrin and zonisamide. Follow the MHRA safety advice on antiepileptic drugs in pregnancy.
- Carefully consider the risk–benefit ratio when using vigabatrin because of the risk of an irreversible effect on visual fields. [2012, amended 2021] [2012, amended 2021]

Kanner AM et al., 2018 [15,17] und Clinical Practice Guideline Process Manual [1].

American Academy of Neurology (AAN)

Practice guideline update summary: efficacy and tolerability of the new antiepileptic drugs I: treatment of new-onset epilepsy and II: treatment-resistant epilepsy

Leitlinienorganisation/Fragestellung

To update the 2004 American Academy of Neurology guideline for managing treatment resistant (TR) epilepsy with second- and third-generation antiepileptic drugs (AEDs).

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 explizit dargestellt;
- Regelmäßige Überprüfung der Aktualität gesichert.

Recherche/Suchzeitraum:

- MEDLINE, EMBASE, Scientific Citation Index (using Web of Science), and Cochrane databases. An initial search was conducted from January 2004 to March 2009 for the 8 AEDs reviewed in the 2004 guidelines and the newer AEDs approved since the 2004 publications. A second search was conducted to include studies published to November 2015. For CLB and VGB, a search was conducted from 1980 to 2014.

LoE/GoR

Criteria for Rating Therapeutic Studies:

- **Class I** A randomized controlled clinical trial of the intervention of interest with masked or objective outcome assessment, in a representative population. Relevant baseline characteristics are presented and substantially equivalent among treatment groups or there is appropriate statistical adjustment for differences. The following are also required:

  a. concealed allocation

  b. primary outcome(s) clearly defined

  c. exclusion/inclusion criteria clearly defined

  d. adequate accounting for dropouts (with at least 80% of enrolled subjects completing the study) and crossovers with numbers sufficiently low to have minimal potential for bias.

  e. For noninferiority or equivalence trials claiming to prove efficacy for one or both drugs, the following are also required*: 1. The authors explicitly state the clinically meaningful difference to be excluded by defining the threshold for equivalence or noninferiority. 2. The standard treatment used in the study is substantially similar to that used in previous studies establishing efficacy of the standard treatment (e.g., for a drug, the mode of administration, dose and dosage adjustments are similar to those previously shown to be effective). 3. The inclusion and exclusion criteria for patient selection and the outcomes of patients on the standard treatment are comparable to those of previous studies establishing efficacy of the standard treatment. 4. The interpretation of the results of the study is based upon a per-protocol analysis that takes into account dropouts or crossovers.
- **Class II** A randomized, controlled clinical trial of the intervention of interest in a representative population with masked or objective outcome assessment that lacks one criteria a–e above (see Class I) or a prospective matched cohort study with masked or objective outcome assessment in a representative population that meets b-e above (see Class I). Relevant baseline characteristics are presented and substantially equivalent among treatment groups or there is appropriate statistical adjustment for differences.

- **Class III** All other controlled trials (including well-defined natural history controls or patients serving as own controls) in a representative population, where outcome is independently assessed, or independently derived by objective outcome measurement.**
- **Class IV** Studies not meeting Class I, II, or III criteria, including consensus or expert opinion. * Note that numbers 1–3 in Class Ie are required for Class II in equivalence trials. If any one of the three is missing, the class is automatically downgraded to Class III. *Objective outcome measurement: an outcome measure that is unlikely to be affected by an observer's (patient, treating physician, investigator) expectation or bias (e.g., blood tests, administrative outcome data).

Classification of recommendations

A = Established as effective, ineffective, or harmful (or established as useful/predictive or not useful/predictive) for the given condition in the specified population. (Level A rating requires at least two consistent Class I studies.)*

B = Probably effective, ineffective, or harmful (or probably useful/predictive or not useful/predictive) for the given condition in the specified population. (Level B rating requires at least one Class I study or two consistent Class II studies.)

C = Possibly effective, ineffective, or harmful (or possibly useful/predictive or not useful/predictive) for the given condition in the specified population. (Level C rating requires at least one Class II study or two consistent Class III studies.)

U = Data inadequate or conflicting; given current knowledge, treatment (test, predictor) is unproven. *In exceptional cases, one convincing Class I study may suffice for an "A" recommendation if 1) all criteria are met, 2) the magnitude of effect is large (relative rate improved outcome > 5 and the lower limit of the confidence interval is > 2).

Recommendations

Aus I:

Monotherapy in children with new-onset epilepsy with either focal epilepsy or unclassified GTC seizures

Empfehlung:

- Although the data from this study would suggest that TPM monotherapy is possibly more efficacious at 400 mg/d than at 50 mg/d for treating children and adolescents with new-onset focal epilepsy or generalized-onset GTC seizures (1 Class II study), no recommendations can be made regarding TPM use at the studied doses, particularly in new-onset epilepsy and pediatric patients.

Hintergrund: TPM monotherapy at 400mg/d is possibly more effective than at 50 mg/d in treating children and adolescents with new-onset focal seizures or generalized-onset GTC seizures (1 Class II study). The higher dose is associated with more AEs and is not used in these patients in clinical practice. Of note, this study was done for regulatory and not clinical purposes, and the doses used are not clinically relevant. Therefore, the study data are nonapplicable to clinical practice.

Aus II:

For pediatric patients with TR focal epilepsy, are these AEDs effective as adjunctive therapy in reducing seizure frequency (compared with no adjunctive therapy)?

In the 2004 guideline, GBP, LTG, OXC, and TPM were found to be effective as add-on therapy in treating TR focal epilepsy in children (Evidenz aus LL 2004 siehe unten). Since then, 4 studies have been published: 2 on LEV, 1 on OXC, and 1 on ZNS.

Empfehlung:

- For add-on therapy for TR focal epilepsy, LEV use should be considered to decrease seizure frequency (**Level B for ages 1 month to 16 years**), ZNS use should be considered to decrease seizure frequency (**Level B for ages 6–17 years**), and OXC use should be considered to decrease seizure frequency (**Level B for ages 1 month to 4 years**).

Data are unavailable on the efficacy of CLB, ESL, LCM, PER, PGB, RFN, TGB, or VGB as add-on therapy for the treatment of these children or adolescents (**Level U**).

Hintergrund:

- **Levetiracetam:** LEV is probably effective as add-on therapy for TR focal epilepsy in children and adolescents (1 Class I study). Moreover, LEV is probably effective as add-on therapy in TR focal epilepsy in infants and children aged <4 years (1 Class I study).
  - One Class I multicenter double-blind RCT was conducted in 198 children aged 4–16 years, who were randomized to placebo or an initial dose of LEV of 20 mg/kg/d to reach a target dose of 60 mg/kg/d over 6 weeks.[e52] A significantly greater median reduction in seizure frequency per week and > 50% seizure frequency reduction per week were found for LEV than placebo. LEV was associated with more frequent AEs than placebo, including somnolence, accidental injury, vomiting, anorexia, rhinitis, hostility, increased cough, pharyngitis, and nervousness. AE-related withdrawal from the study was higher among children randomized to placebo (9.3%) than to LEV (5.5%).
  - The second Class I study was a multicenter double-blind RCT in 116 children aged 1 month to < 4 years who were randomized to placebo or LEV at a dose of 40 mg/kg/d (if aged 1 to < 6 months) or 50 mg/kg/d (if aged ≥6 months to < 4 years).[e53] The study included a 48-hour inpatient baseline video electroencephalography and a 5-day inpatient treatment period with oneday up-titration and a 48-hour evaluation with video electroencephalography in the last 2 days. Children randomized to LEV had a significantly greater responder rate in average daily seizure frequency and greater median percent reduction from baseline in the average of daily seizure frequency with LEV. Five children were withdrawn from the study. The most frequently reported AEs related to LEV included somnolence and irritability.
- **Oxcarbazepine**: OXC is probably effective as add-on therapy in infants and young children with TR focal epilepsy (1 Class I study). Given the study's short duration, however, generalizability may be limited.
  - One Class I single (rater)–blind, multicenter, randomized, parallel-group study of 128 children aged 1 month to < 4 years compared the efficacy and tolerability of 2 doses of OXC, 10 mg/kg/d and 60 mg/kg/d, given as add-on therapy in an oral suspension.[e54] The primary outcome was absolute change in the frequency of focal seizures per 24 hours during 3 days of continuous treatment-phase video electroencephalography compared with baseline seizure frequency.
  - Children on the higher OXC dose experienced a significantly greater seizure frequency reduction than those on the low dose and a greater median percent reduction in seizure frequency per 24 hours. Children in the high-dose group also experienced more frequent AEs than those in the low-dose group (31.3% vs 4.7%), which included somnolence, ataxia, and vomiting. Five patients, 2 in the low-dose group and 3 in the high-dose group, discontinued because of AEs.

- **Zonisamide:** ZNS is probably effective as add-on therapy for TR focal epilepsy in children and adolescents (1 Class I study). Data are unavailable on the efficacy of CLB, ESL, LCM, PER, PGB, RFN, TGB, or VGB as add-on therapy for this group.
  - One Class I double-blind, multicenter, randomized, placebo-controlled trial of 207 children and adolescents aged 6–17 years compared the efficacy and tolerability of ZNS at a dose of 8 mg/kg/d with placebo. [e55] Patients were started on 1 mg/kg/d, with titration over an 8-week period. The primary outcome was the responder rate during a 12-week maintenance period, which was found to be significantly higher for the patients randomized to ZNS. The incidence of AEs did not differ between the 2 groups, including serious AEs (3.7% for ZNS vs 2% for placebo), although AEs leading to withdrawal were higher in the placebo group (3% for ZNS vs 0.9% for placebo). The AEs reported with a higher frequency in the ZNS group included decreased appetite, decreased weight, somnolence, vomiting, and diarrhea.

Clinical context

- A pharmacokinetic: pharmacodynamic analysis performed comparing adults with children receiving approved AEDs showed that, in each case where the serum concentrations were similar, there was similar seizure reduction for the 2 groups. On the basis of these data, the FDA has determined that efficacy of AEDs for focal seizures in adults can be extrapolated downwardto children 4 years of age. [e56] However, trials in pediatric populations are very important toestablish efficacy in this and in other pediatric-specific epilepsy syndromes, to evaluate efficacyin children younger than 2 years of age, to identify specific safety issues, and to characterize thedosing and pharmacokinetic properties. Further, it is essential to assess safety issues in the entirepediatric population.

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AAN LL 2004: Efficacy and tolerability of the new antiepileptic drugs II: Treatment of refractory epilepsy2004 [5]

Diese Leitlinie wird ergänzend für die Evidenzlage zur Empfehlung für GBP, LTG, OXC, and TPM dargestellt.

Treatment of refractory epilepsy in children.

- Question 4: What is the evidence that the new AEDs are effective in refractory partial epilepsy as adjunctive therapy in children?
  - *Gabapentin.* There is one study with class I evidence[68] that evaluated the efficacy of gabapentin in 247 children whose age ranged between **3 and 12 years** in a 12-week doubleblind placebo-controlled trial. Gabapentin was titrated up to a dose of 23 to 35 mg/kg/day. The outcome variable in this study was the percentage change in frequency of complex partial and secondarily generalized tonic-clonic seizures. Children randomized to gabapentin had a median drop of 35% of complex partial and 28% of secondarily generalized tonic-clonic seizures, while those on placebo had a 12% median reduction and 13% increase, respectively. The discontinuation rate was

5% for children on gabapentin and 2% for those on placebo. The five most frequent adverse events were viral infection, fever, hostility, fatigue, and weight gain.

- *Lamotrigine.* There is one study[69] with class I evidence that evaluated the efficacy of lamotrigine versus placebo in 199 children aged **2 to 16 years**. The lamotrigine target doses varied according to the type of AED the child was taking at the time of randomization: 1 to 3 mg/kg in the presence of valproic acid only, 1 to 5 mg/kg if an enzyme inducing AED (phenytoin, carbamazepine, phenobarbital) in combination with valproic acid, and 5 to 15 mg/kg if the child was on enzyme inducing AED only. The responder rate was 45% among children randomized to lamotrigine and 25% for those on placebo. Children on lamotrigine had a significantly higher drop in weekly seizure frequency (44%) compared to those on placebo (12.8%). The discontinuation rate caused by adverse events was 5% for children on lamotrigine and 6% for those on placebo. The five most frequent adverse events included ataxia, dizziness, tremor, nausea, and asthenia. One patient had a severe rash presenting as Stevens Johnson syndrome.
- *Topiramate.* There is one study with class I evidence that evaluated the efficacy of topiramate versus placebo in 86 children aged 2 to 16 years during a 16-week trial.[70] The topiramate dose was titrated to 125 to 400 mg/day, according to weight. Starting dose was 25 mg/day. The 50% responder rate was 39% for children on topiramate and 20% for those on placebo. Children on topiramate had a median reduction in seizures of 33% versus 10.5% for those on placebo. No child on topiramate and two children on placebo were discontinued from the study. The five most frequent adverse events included emotional lability, difficulty concentrating, fatigue, memory deficits, and weight loss. There were no cases of hypohidrosis in clinical trials. A case series has been published reporting three children, aged 17 months, 9 years, and 16 years, who developed hypohidrosis while receiving topiramate monotherapy.[71]
- *Oxcarbazepine.* There is one study with class I evidence that evaluated the efficacy of oxcarbazepine in 267 children, aged 3 to 17 years, in a double-blind placebo controlled study.[72] The maximal doses of oxcarbazepine ranged between 30 and 46 mg/kg/day. A 50% responder rate of 41% was found among children on oxcarbazepine and 22% of children on placebo. A median reduction in seizure frequency of 35% was observed among children on oxcarbazepine versus 8.9% on placebo. The discontinuation rate related to adverse events was 10% for children on oxcarbazepine and 3% for those on placebo. The five most common adverse events were somnolence, headache, dizziness, vomiting, and nausea. Rash rates were 4% on oxcarbazepine and 5% on placebo.
- *Levetiracetam.* There is one study with class IV evidence[73] that evaluated the efficacy of levetiracetam in 24 children in an open trial at a maximal dose of 40 mg/kg, titrated over a 6-week period. A responder rate of 52% was obtained. None of the children were discontinued from the study because of adverse events. The most frequent adverse events included somnolence, ataxia, headache, anorexia, and nervousness. Adverse events reported in other open trials have included behavioral problems, depression, and psychosis.
- *Zonisamide.* No studies have specifically studied efficacy of zonisamide in pediatric patients with partial seizures. A single case has been reported of hypohidrosis caused by zonisamide.[74]

- Summary of evidence:
  - Refractory partial seizures — pediatric. Gabapentin (23 to 35 mg/kg/day), lamotrigine 1 to 5 mg/kg/day with enzyme inducers (1 to 3 mg/kg/day in regimens including

valproate), oxcarbazepine 30 to 46 mg/kg/day, and topiramate 125 to 400 mg/day are effective in reducing seizure frequency as adjunctive therapy in children with refractory partial seizures.

- To date, there is a lack of class I or II evidence regarding the efficacy of levetiracetam, tiagabine, or zonisamide. Based on class III and IV evidence, there are specific safety concerns in children when using these drugs, specifically serious rash with lamotrigine, and hypohidrosis with zonisamide and topiramate.

- Recommendations:
  - 1. Gabapentin, lamotrigine, oxcarbazepine, and topiramate may be used as adjunctive treatment of children with refractory partial seizures (Level A) (table 2).
  - 2. There is insufficient evidence to recommend levetiracetam, tiagabine, or zonisamide as adjunctive treatment of children with refractory partial seizures (Level U) (table 2).

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Epilepsy Technical Advisory Group

Paediatric Neurology Clinical Network

New Zealand League Against Epilepsy

Epilepsy: guidelines and pathways for children and young people

Zielsetzung/Fragestellung

Define best practice for epilepsy care for New Zealand 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 explizit dargestellt;
- Regelmäßige Überprüfung der Aktualität gesichert.

Recherche/Suchzeitraum:

- Siehe NICE guideline

LoE/GoR

- Siehe NICE guideline

Sonstige methodische Hinweise

- The guideline was adapted from the NICE paediatric epilepsy guidelines (NICE, 2016) and are evidence based where evidence exists. Its purpose is to define best practice for epilepsy care for New Zealand children.
- Diese Leitlinie wird nur ergänzend dargestellt für die **Special considerations for children under 3 years of age**

Empfehlungen

Focal Epilepsies

Childhood Epilepsy with Centrotemporal Spikes and Panayiotopoulos Syndrome

- Discuss with the child and their family and/or carers, whether ASM treatment for Self-limited Epilepsy with Centrotemporal Spikes or Panayiotopoulos Syndrome is indicated.
- If therapy is required offer lamotrigine or carbamazepine as first-line treatment to children with Self-limited Epilepsy with Centrotemporal Spikes or Panayiotopoulos syndrome.
- Consider levetiracetam as first line treatment if lamotrigine or carbamazepine are contraindicated.
- Be aware that carbamazepine and oxcarbazepine may exacerbate or unmask continuous spike and wave during slow sleep, which may occur in some children with Childhood Epilepsy with Centrotemporal Spikes. Clinically this may present with learning and/or behavioural difficulties or more seizures.
- Negative effects on the fetus needs to be discussed with girls and their families considering using ASMs. Avoid sodium valproate in focal epilepsies if possible in females. It is essential that appropriate contraception advice is given to all girls that might become sexually active.

Note

Children of South East Asian origin should be screened for HLA-B*1502 haplotype via the Blood Bank prior to the initiation of carbamazepine - positive children should not receive carbamazepine.

Special considerations for children under 3 years of age

Efficacy of ASMs

- There is very limited evidence to support any of the current agents for use in infants with seizures. Recent recommendations by the ILAE Commission of Paediatrics gives a strong recommendation for the use of levetiracetam in children of this age group who have focal seizures (Wilmhurst, et al., 2015).

Special warning

Given potential fatal liver toxicity that can be unmasked by sodium valproate in children under three years of age with certain metabolic disorders (e.g. mitochondrial disorders), sodium valproate should not be used first-line in children in this age group if the aetiology is unclear, until the results of their metabolic screen make any of these disorders unlikely.

Kinetics of ASMs

There is evidence that infants metabolise ASMs at different rates to older children. This needs to be considered when dosing.

- Carbamazepine – increased clearance
- Phenytoin – increased clearance
- Topiramate – increased clearance
- Levetiracetam –decreased clearance.

Wilmhurst, J. M., Gaillard, W. D., Vinayan, K. P., Tsuchida, T. N., Plouin, P., Van Bogaert, P., Cross, J. H. (2015). Summary of recommendations for the management of infantile seizures: Task Force Report for the ILAE Commission of Paediatrics. Epilepsia 56(8), 1185-97.Referenzen aus Leitlinien

4 Detaillierte Darstellung der Recherchestrategie

Cochrane Library - Cochrane Database of Systematic Reviews (Issue 04 of 12, April 2021) am 13.04.2021

#	Suchfrage
1	[mh epilepsy]
2	(epilep* OR seizure* OR antiepilep* OR convuls*):ti
3	(#1 OR #2)
4	#3 in Cohrane Reviews publication date from Apr 2016 to Apr 2021

Systematic Reviews in Medline (PubMed) am 13.04.2021

#	Suchfrage
1	epilepsies, partial[mh]
2	drug resistant epilepsy[mh]
3	epilep*[tiab] OR seizure*[tiab]
4	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] OR "secondarily generalized"[tiab] OR "secondarily generalised"[tiab] OR (childhood[tiab] AND benign[tiab]) OR “psychic equivalent”[tiab] OR roland*[tiab] OR sylvian[tiab] OR centrotemporal[tiab] OR centralopathic[tiab] OR "temporal-central" [tiab] OR BCECTS[tiab] OR BECTS[tiab]
5	drug resistan*[tiab] OR medication resistan*[tiab] OR treatment resistan*[tiab] OR intractable[tiab] OR pharmacoresistan*[tiab] OR refractory[tiab] OR "inadequately controlled"[tiab] OR uncontrolled[tiab] OR FBTCS[tiab]
6	#3 AND (#4 OR #5)
7	#1 OR #2 OR #6
8	(#7) 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 study[pt] OR validation study[pt] OR guideline[pt] OR pmcbook)) OR ((systematic[tw] OR systematically[tw] OR critical[tiab] OR (study selection[tw]) OR

#	Suchfrage
	(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]))))))
9	(#8) AND ("2016/04/01"[PDAT] : "3000"[PDAT])
10	(#9) NOT "The Cochrane database of systematic reviews"[Journal]
11	(#10) NOT (animals[MeSH:noexp] NOT (Humans[mh] AND animals[MeSH:noexp]))
12	(#11) NOT (retracted publication [pt] OR retraction of publication [pt])

Leitlinien in Medline (PubMed) am 13.04.2021

#	Suchfrage
1	epilepsy[mh]
2	(epilep*[ti] OR seizure*[ti] OR antiepilep*[ti] OR convuls*[ti])
3	#1 OR #2
4	(#3) AND (Guideline[ptyp] OR Practice Guideline[ptyp] OR guideline*[Title] OR Consensus Development Conference[ptyp] OR Consensus Development Conference, NIH[ptyp] OR recommendation*[ti])
5	(#4) AND ("2016/04/01"[PDAT] : "3000"[PDAT])
6	(#5) NOT (retracted publication [pt] OR retraction of publication [pt])

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Beteiligung von AkdÄ und Fachgesellschaften nach §35a Abs. 7 SGB V i.V.m. VerfO 5. Kapitel § 7 Abs. 6

2021-B-094

Kontaktdaten

Arzneimittelkommission der deutschen Ärzteschaft (AkdÄ), Herbert-Lewin-Platz 1, 10623 Berlin (www.akdae.de); Stand: 06.05.2021

Indikation gemäß Beratungsantrag

Zusatzbehandlung fokaler Anfälle mit oder ohne sekundäre Generalisierung bei Erwachsenen, Jugendlichen und Kindern ab 1 Monat mit Epilepsie

Was ist der Behandlungsstandard in o. g. Indikation bei Kindern ab 1 Monat - < 4 Jahren unter Berücksichtigung der vorliegenden Evidenz? Wie sieht die Versorgungspraxis in Deutschland aus?

Es gibt nur wenige Studien, die die Wirksamkeit und Verträglichkeit von Antiepileptika bei Kindern < 4 Jahre untersucht haben; es gibt kaum Evidenz. Entsprechend sind nur recht alte und eher nebenwirkungsreiche Substanzen wie Carbamazepin, Phenytoin, Phenobarbital und Valproinsäure zugelassen, die diesen Status erreicht haben, bevor strikte randomisierte kontrollierte Studien die Voraussetzung zur Zulassung waren. Im Alltag werden primär Substanzen gegeben, die für Kinder < 4 Jahre nicht zugelassen, aber besser verträglich sind als die alten Substanzen. Dazu gehören Oxcarbazepin, Eslicarbazepinacetat, Lamotrigin, Levetiracetam und Lacosamid. Lediglich für Levetiracetam liegen Daten vor, die die Wirksamkeit im Säuglingsalter nachgewiesen haben. Levetiracetam ist auch das bei Kindern < 4 Jahre mit fokaler Epilepsie am häufigsten eingesetzte Antiepileptikum.

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Gibt es Kriterien für unterschiedliche Behandlungsentscheidungen bei der Behandlung „fokaler Anfälle mit oder ohne sekundäre Generalisierung bei Kindern ab 1 Monat - < 4 Jahre mit Epilepsie**“, die regelhaft berücksichtigt werden? Wenn ja, welche sind dies und was sind in dem Fall die Therapieoptionen?**

Da es in Bezug auf die Wirksamkeit keine relevanten Unterschiede zwischen zugelassenen und den im klinischen Alltag eingesetzten, oftmals nicht zugelassenen Antiepileptika gibt, entscheidet in der Regel das Kriterium der Verträglichkeit. Und hier sind die neueren, seit 1990 verfügbaren Substanzen besser verträglich als die älteren (siehe oben).

Selten kann die selbstlimitierende fokale Epilepsie mit zentrotemporalen Spikes („Rolando-Epilepsie“) vor dem 4. Lebensjahr beginnen. Wenn überhaupt eine Indikation zur antiepileptischen Therapie gesehen wird, kommt in Deutschland (international eher nicht üblich) die Substanz Sultiam zum Einsatz.

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