Gemeinsamer Bundesausschuss

Kriterien zur Bestimmung der zweckmäßigen Vergleichstherapie

und

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

Vorgang: 2020-B-055 Cenobamat

Stand: Mai 2020

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

Cenobamat
[Zusatzbehandlung fokaler Anfälle bei Erwachsenen mit 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 unter Tabelle 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	Nutzenbewertung nach § 35a SGB V • Beschluss zu Retigabin vom 03.07.2014 • 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:	
Cenobamat N03AX25 Ontozry	Ontozry® wird angewendet zur adjunktiven Behandlung fokaler Anfälle mit oder ohne sekundäre Generalisierung bei erwachsenen Patienten mit Epilepsie, die trotz einer vorangegangenen Behandlung mit mindestens 2 anti-epileptischen Arzneimitteln nicht ausreichend kontrolliert sind
Perampanel N03AX22 Fycompa®	- Fycompa ist angezeigt als **Zusatztherapie** fokaler Anfälle mit oder ohne sekundäre Generalisierung bei Epilepsiepatienten ab 12 Jahren - Fycompa wird angewendet als Zusatztherapie bei primär generalisierten tonisch-klonischen Anfällen bei Erwachsenen und Jugenlichen ab 12 Jahren mit idiopathischer generalisierter Epilepsie
Brivaracetam N03AX23 Briviact	Zusatzbehandlung fokaler Anfälle mit oder ohne sekundäre Generalisierung bei Erwachsenen, Jugendlichen und Kindern ab 4 Jahren mit Epilepsie.
Oxcarbazepin N03AF02	Zur Behandlung von fokalen Anfällen mit oder ohne sekundär generalisierten tonisch- klonischen Anfällen. Zur Monotherapie oder **Kombinationstherapie** von Erwachsenen und Kindern ab 6 Jahren.
Eslicarbazepin N03AF04 Zebinix®	Begleittherapie bei Erwachsenen mit partiellen epileptischen Anfällen mit oder ohne sekundärer Generalisierung angewendet.
Valproinsäure N03AG01	Behandlung von - generalisierten Anfällen in Form von Absencen, myoklonischen Anfällen und tonisch-klonischen Anfällen - partiellen (fokalen) Anfällen und sekundär-generalisierten Anfällen sowie zur Kombinationsbehandlung, wenn diese Anfallsformen auf die übliche antiepileptische Behandlung nicht ansprechen.
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.

Tiagabin[1] N03AG06 Gabitril®	**Zusatzbehandlung** bei Patienten mit partiellen Anfällen mit oder ohne sekundäre Generalisierung, die mit anderen Antiepileptika nicht ausreichend behandelbar sind. Dieses Arzneimittel darf nur bei Erwachsenen und Jugendlichen über 12 Jahren angewendet werden.
Lamotrigin N03AX09	Erwachsene und Jugendliche ab 13 Jahren: **Zusatz**- oder Monotherapie partieller und generalisierter Anfälle einschließlich tonisch-klonischer Anfälle Kinder und Jugendliche von 2 bis 12 Jahren: Zusatztherapie bei partiellen und generalisierten Anfällen einschließlich tonisch-klonischer Anfälle
Topiramat N03AX11	**Zusatztherapie** bei Kindern ab 2 Jahren, Jugendlichen und Erwachsenen mit fokalen Anfällen mit oder ohne sekundärer Generalisierung oder primär generalisierten tonisch-klonischen Anfällen
Gabapentin N03AX12	**Zusatztherapie** bei Erwachsenen und Kindern von 6 Jahren und älter mit partiellen Anfällen mit und ohne sekundäre Generalisierung
Levetiracetam N03AX14 Keppra®	**Zusatzbehandlung** - partieller Anfälle mit oder ohne sekundärer Generalisierung bei Erwachsenen, Kindern und Säuglingen ab 1 Monat mit Epilepsie. - primär generalisierter tonisch-klonischer Anfälle bei Erwachsenen und Jugendlichen ab 12 Jahren mit Idiopathischer Generalisierter Epilepsie
Zonisamid N03AX15 Zonegran®	**Zusatztherapie** für die Behandlung erwachsener Patienten mit partiellen Anfällen mit oder ohne sekundäre Generalisierung. Die Unbedenklichkeit und Wirksamkeit von Zonegran® bei Kindern und Jugendlichen ist bisher noch nicht nachgewiesen.
Pregabalin N03AX16 Lyrica®	Lyrica wird angewendet zur **Zusatztherapie** von partiellen Anfällen mit und ohne sekundäre Generalisierung im Erwachsenenalter..
Lacosamid N03AX18 Vimpat®	**Zusatzbehandlung** fokaler Anfälle mit oder ohne sekundäre Generalisierung bei Epilepsiepatienten ab 16 Jahren.
Clobazam N05BA09 Frisium®	**Zusatztherapie** bei Patienten mit epileptischen Anfällen, die mit einer Standardbehandlung – bestehend aus einem oder mehreren Antiepileptika – nicht anfallsfrei waren.
Clonazepam N03AE01 Clonazepam-	- Zur Behandlung von Epilepsien - besonders fokalen Anfällen - des Erwachsenen. - Zur Behandlung der Mehrheit der klinischen Formen der Epilepsie des Säuglings und des Kindes, insbesondere typischen und atypischen Petit-mal-Epilepsien, primär oder sekundär generalisierten tonisch-klonischen Krisen.

[1] Derzeit in Deutschland nicht in Verkehr (Stand: März 2020)

neuraxpharm®	
Primidon N03AA03 Liskantin®	- Epileptische Anfälle, besonders Grand-mal-Anfälle, fokale Anfälle (Jackson-Anfälle, Adversivkrämpfe, psychomotorische Anfälle u.a.), myoklonische Anfälle des Jugendalters (Impulsiv-Petit-mal) - […]

Quellen: AMIS-Datenbank, Fachinformationen

Gemeinsamer Bundesausschuss

Abteilung Fachberatung Medizin

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

Vorgang: 2020-B-055 (Cenobamat)

Auftrag von:	Abt. AM
Bearbeitet von:	Abt. FB Med
Datum:	2. April 2020

Inhaltsverzeichnis

Abkürzungsverzeichnis

AE	adverse event
AED	antiepileptic drug
AES	American Epilepsy Society
ANN	American Academy of Neurology
AWMF	Arbeitsgemeinschaft der wissenschaftlichen medizinischen Fachgesellschaften
CLB	clobazam
ECRI	ECRI Guidelines Trust
ESL	eslicarbazepine
EZG	ezogabine
FBM	felbamate
FDA	Food and Drug Administration
G-BA	Gemeinsamer Bundesausschuss
GBP	gabapentin
GE	generalized epilepsy
GIN	Guidelines International Network
GoR	Grade of Recommendations
GTC	generalized tonic-clonic
HR	Hazard Ratio
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen
JME	juvenile myoclonic epilepsy
KI	Konfidenzintervall
LCM	lacosamide
LEV	levetiracetam
LEV-XR	extended-release levetiracetam
LoE	Level of Evidence
LTG	lamotrigine
LTG-XR	extended-release lamotrigine
NICE	National Institute for Health and Care Excellence

OR	Odds Ratio
OXC	oxcarbazepine
OXC-XR	extended-release oxcarbazepine
PER	perampanel
PGB	pregabalin
PGBCR	controlled-release pregabalin
PGB-IR	immediate-release pregabalin
RFN	rufinamide
RR	Relatives Risiko
SIGN	Scottish Intercollegiate Guidelines Network
TGB	tiagabine
TPM	topiramate
TPM-XR	extended-release topiramate
TR	treatment-resistant
TRAFE	treatment-resistant adult focal epilepsy
TRIP	Turn Research into Practice Database
VGB	vigabatrin
WHO	World Health Organization
ZNS	zonisamide

1 Indikation

zur Zusatzbehandlung fokaler Anfälle mit oder ohne sekundäre Generalisierung bei Erwachsenen mit Epilepsie, die trotz vorangegangener Therapie mit mindestens zwei zuvor verschriebenen Antiepileptika nicht ausreichend kontrolliert sind.

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 13.03.2020 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 933 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.

3 Ergebnisse

3.1 G-BA Beschlüsse/IQWiG Berichte

G-BA, 2014 [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 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

Die zweckmäßige Vergleichstherapie für die Zusatztherapie fokaler Anfälle mit oder ohne 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.

Fazit / Ausmaß des Zusatznutzens

Ausmaß und Wahrscheinlichkeit des Zusatznutzens gegenüber einer individuellen antiepileptischen Zusatztherapie, soweit medizinisch indiziert und falls noch keine Pharmakoresistenz/Unverträglichkeit und Kontraindikationen bekannt sind, mit einem der oben benannten Wirkstoffe:

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 3. Juli 2014 – Retigabin.

Anwendungsgebiet

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

Zweckmäßige Vergleichstherapie

Eine individuelle antiepileptische Zusatztherapie, soweit medizinisch indiziert und falls noch keine Pharmakoresistenz/Unverträglichkeit und Kontraindikationen bekannt sind, mit einem der folgenden Wirkstoffe: Tiagabin2, 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).*

Fazit / Ausmaß des Zusatznutzens

Ausmaß und Wahrscheinlichkeit des Zusatznutzens gegenüber einer individuellen antiepileptischen Zusatztherapie, soweit medizinisch indiziert und falls noch keine Pharmakoresistenz/Unverträglichkeit und Kontraindikationen bekannt sind, mit einem der folgenden Wirkstoffe: Tiagabin, Valproinsäure oder Vigabatrin, ansonsten: Therapie nach Wahl des Arztes:

Ein Zusatznutzen gilt als nicht belegt.

G-BA, 2016 [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 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, 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 17. Januar 2019 - Brivaracetam (neues Anwendungsgebiet: Epilepsie, Patienten ab 4 Jahren).

Anwendungsgebiet

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.

Zweckmäßige Vergleichstherapie

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

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:

Eslicarbazepin[1], Gabapentin[2], Lacosamid, Lamotrigin, Levetiracetam, Oxcarbazepin[2], Perampanel[3], Topiramat, Valproinsäure[4], Zonisamid[2]

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.

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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.

Fazit / Ausmaß des Zusatznutzens

Ein Zusatznutzen ist nicht belegt.

3.2 Cochrane Reviews

Bresnahan R. et al., 2019 [1].

Topiramate add-on therapy for drug-resistant focal epilepsy.

Fragestellung

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

Methodik

Population:

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

Intervention:

- The active treatment group received treatment with topiramate in addition to conventional antiepileptic drug treatment.

Komparator:

- The control group received a matched placebo or an alternative dose of topiramate in addition to conventional antiepileptic drug treatment.

Endpunkte:

- 50% or greater reduction in seizure frequency, seizure freedom, Treatment withdrawal, Adverse effects

Recherche/Suchzeitraum:

- For the latest update of this review we searched the following databases on 2 July 2018: Cochrane Register of Studies (CRS Web), which includes the Cochrane Epilepsy Group Specialized Register and the Cochrane Central Register of Controlled Trials (CENTRAL); MEDLINE (Ovid, 1946-); ClinicalTrials.gov and the WHO International Clinical Trials Registry Platform (ICTRP)

Qualitätsbewertung der Studien:

- Cochrane approach / GRADE

Ergebnisse

Anzahl eingeschlossener Studien:

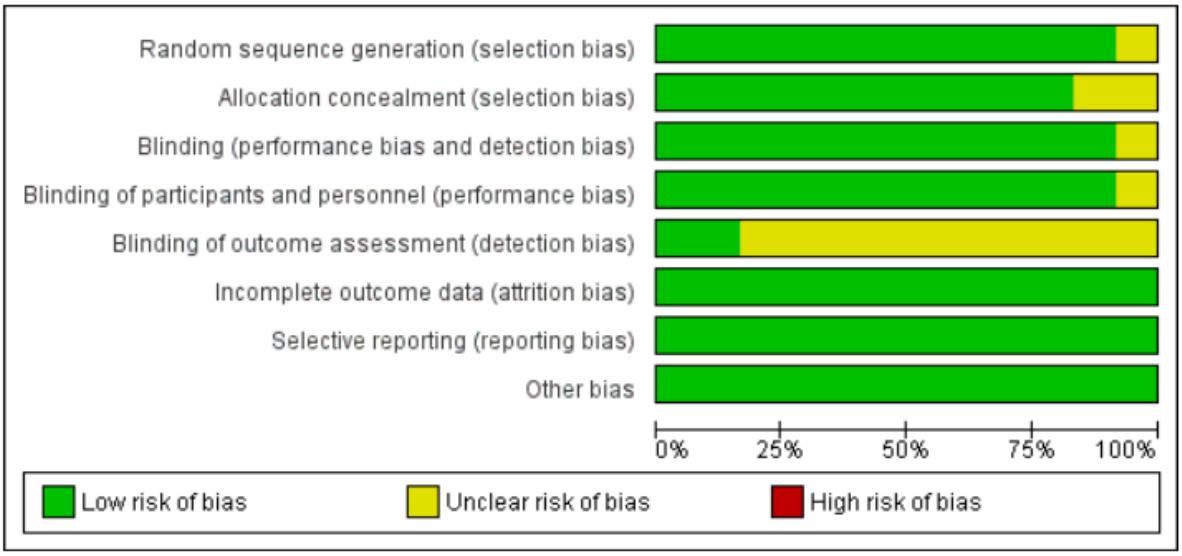
- The 12 RCTs identified by the screening process recruited a total of 1650 participants

Charakteristika der Population:

- Baseline phases ranged from four to 12 weeks and double-blind phases ranged from 11 to 19 weeks.

Qualität der Studien:

- We rated all studies included in the review as having either low or unclear risk of bias. Overall, we assessed the evidence as moderate to high certainty due to the evidence of publication bias, statistical heterogeneity and imprecision, which was partially compensated for by large effect sizes.



Studienergebnisse:

- The RR for a 50% or greater reduction in seizure frequency with add-on topiramate compared to placebo was 2.71 (95% CI 2.05 to 3.59; 12 studies; high-certainty evidence).
- The proportion of participants achieving seizure freedom was also significantly increased with add-on topiramate compared to placebo (RR 3.67, 95% CI 1.79 to 7.54; 8 studies; moderate-certainty evidence).
- Treatment withdrawal was significantly higher for add-on topiramate compared to placebo (RR 2.37, 95% CI 1.66 to 3.37; 12 studies; high-certainty evidence).
- The RRs for the following adverse effects indicate that they are significantly more prevalent with topiramate, compared to placebo: ataxia 2.29 (99% CI 1.10 to 4.77; 4 studies); concentration difficulties 7.81 (99% CI 2.08 to 29.29; 6 studies; moderate-certainty evidence); dizziness 1.52 (99% CI 1.07 to 2.16; 8 studies); fatigue 2.08 (99% CI 1.37 to 3.15; 10 studies); paraesthesia 3.65 (99% CI 1.58 to 8.39; 7 studies; moderate-certainty evidence); somnolence 2.44 (99% CI 1.61 to 3.68; 9 studies); 'thinking abnormally' 5.70 (99% CI 2.26 to 14.38; 4 studies; high-certainty evidence); and weight loss 3.99 (99% CI 1.82 to 8.72; 9 studies; low-certainty evidence).

Anmerkung/Fazit der Autoren

Topiramate has efficacy as an add-on treatment for drug-resistant focal epilepsy as it is almost three times more effective compared to a placebo in reducing seizures. The trials reviewed were of relatively short duration and provided no evidence for the long-term efficacy of topiramate. Short-term use of add-on topiramate was shown to be associated with several adverse events. The results of this review should only be applied to adult populations as only one study included children. Future research should consider further examining the effect of dose.

Kommentare zum Review

- Ausschließlich Placebo kontrollierte Studien

Panebianco M. et al., 2019 [19].

Pregabalin add-on for drug-resistant focal epilepsy.

Fragestellung

To assess the efficacy and tolerability of pregabalin when used as an add-on treatment for drug-resistant focal epilepsy.

Methodik

Population:

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

Intervention:

- The active-treatment group received pregabalin in addition to an existing AED regimen taken at time of randomisation.

Komparator:

- The control group received a matched placebo or an active comparator control in addition to an existing AED regimen taken at time of randomisation.

Endpunkte:

- 50% or greater reduction in seizure frequency, seizure freedom, Treatment withdrawal, Adverse effects

Recherche/Suchzeitraum:

- For the latest update we searched the Cochrane Register of Studies (CRS Web), which includes the Cochrane Epilepsy Group Specialized Register and the Cochrane Central Register of Controlled Trials (CENTRAL), on 5 July 2018, MEDLINE (Ovid, 1946 to 5 July 2018), ClinicalTrials.gov (5 July 2018), and the World Health Organization International Clinical Trials Registry Platform (ICTRP, 5 July 2018), and contacted Pfizer Ltd, manufacturer of pregabalin, to identify published, unpublished, and ongoing trials.

Qualitätsbewertung der Studien:

- Cochrane approach / GRADE

Ergebnisse

Anzahl eingeschlossener Studien:

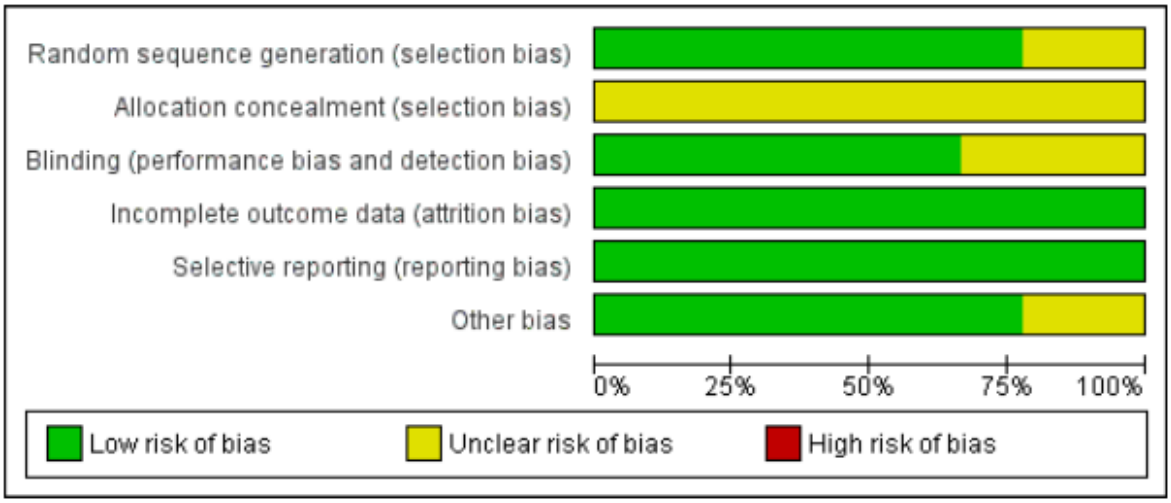
- 9 randomised controlled trials (3327 participants)
- 7 trials compared pregabalin to placebo

Charakteristika der Population:

-

Qualität der Studien:

- We rated the overall risk of bias in the included studies as low or unclear due to the possibility of publication bias and lack of methodological details provided. We rated the certainty of the evidence as very low to moderate using the GRADE approach.



Studienergebnisse:

- For the primary outcome, participants randomised to pregabalin were significantly more likely to attain a 50% or greater reduction in seizure frequency compared to placebo (RR 2.28, 95% CI 1.52 to 3.42, 7 trials, 2193 participants, low-certainty evidence).
- Pregabalin was significantly associated with seizure freedom (RR 3.94, 95% CI 1.50 to 10.37, 4 trials, 1125 participants, moderate-certainty evidence).
- Participants were significantly more likely to withdraw from pregabalin treatment than placebo for any reason (RR 1.35, 95% CI 1.11 to 1.65, 7 trials, 2193 participants, moderate-certainty evidence) and for adverse effects (RR 2.65, 95% CI 1.88 to 3.74, 7 trials, 2193 participants, moderate-certainty evidence).
- Three trials compared pregabalin to three active-control drugs: lamotrigine, levetiracetam, and gabapentin.
  - Participants allocated to pregabalin were significantly more likely to achieve a 50% or greater reduction in seizure frequency than those allocated to lamotrigine (RR 1.47, 95% CI 1.03 to 2.12, 1 trial, 293 participants) but not those allocated to levetiracetam (RR 0.94, 95% CI 0.80 to 1.11, 1 trial, 509 participants) or gabapentin (RR 0.96, 95% CI 0.82 to 1.12, 1 trial, 484 participants).
  - no significant differences between pregabalin and lamotrigine (RR 1.39, 95% CI 0.40 to 4.83) for seizure freedom, however, significantly fewer participants achieved seizure freedom with add-on pregabalin compared to levetiracetam (RR 0.50, 95% CI 0.30 to 0.85). No data were reported for this outcome for pregabalin versus gabapentin.
  - no significant differences between pregabalin and lamotrigine (RR 1.07, 95% CI 0.75 to 1.52), levetiracetam (RR 1.03, 95% CI 0.71 to 1.49), or gabapentin (RR 0.78, 95% CI 0.57 to 1.07) for treatment withdrawal due to any reason or due to adverse effects (pregabalin versus lamotrigine: RR 0.89, 95% CI 0.53 to 1.48; versus levetiracetam: RR 1.29, 95% CI 0.66 to 2.54; versus gabapentin: RR 1.07, 95% CI 0.54 to 2.11).

- o Ataxia, dizziness, somnolence, weight gain, and fatigue were significantly associated with pregabalin.

Anmerkung/Fazit der Autoren

Pregabalin, when used as an add-on drug for treatment-resistant focal epilepsy, is significantly more effective than placebo at producing a 50% or greater seizure reduction and seizure freedom. Results demonstrated efficacy for doses from 150 mg/day to 600 mg/day, with increasing effectiveness at 600 mg doses, however issues with tolerability were noted at higher doses. The trials included in this review were of short duration, and longer-term trials are needed to inform clinical decision making.

Kommentare zum Review

- All studies were industry-sponsored
- 7 trials compared pregabalin to placebo

Bresnahan R. et al., 2019 [2].

Tiagabine add-on therapy for drug-resistant focal epilepsy.

Fragestellung

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

Methodik

Population:

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

Intervention:

- treatment with tiagabine, in addition to conventional AED treatment;.

Komparator:

- matched placebo or a different add-on AED, in addition to conventional AED treatment

Endpunkte:

- 50% or greater reduction in seizure frequency, Treatment withdrawal, Adverse effects, Cognitive effects, QoL

Recherche/Suchzeitraum:

- This is an updated Cochrane review, last published in 2014. For the latest update, we searched the following databases on 22 January 2019: Cochrane Register of Studies (CRS Web), which includes the Cochrane Epilepsy Group's Specialized Register and the Cochrane Central Register of Controlled Trials, MEDLINE (Ovid, 1946 to January 21, 2019), ClinicalTrials.gov, and the WHO International Clinical Trials Registry Platform. We imposed no language restrictions. We also contacted the manufacturers of tiagabine and experts in the field to identify any ongoing or unpublished studies.

Qualitätsbewertung der Studien:

- Cochrane approach / GRADE

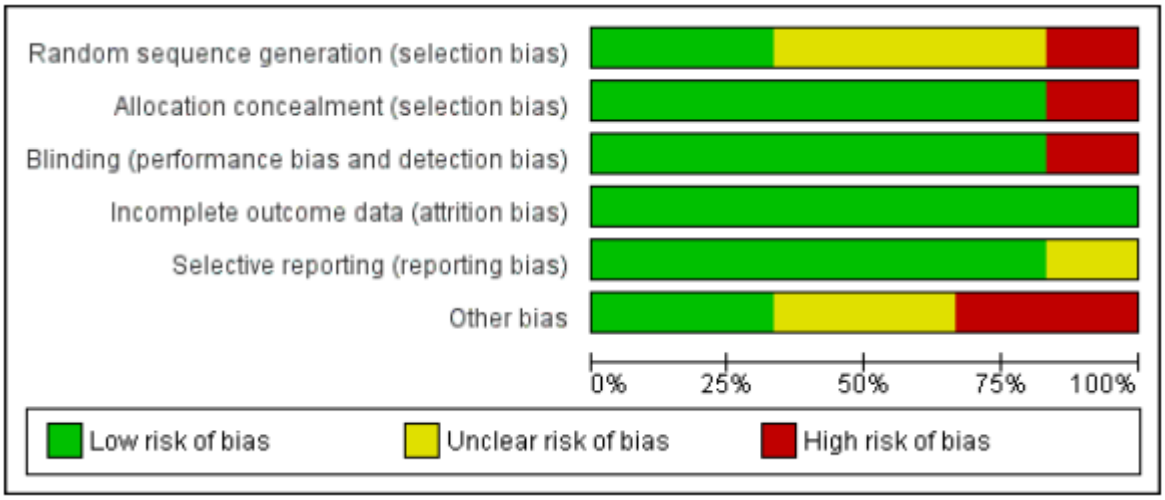
Ergebnisse

Anzahl eingeschlossener Studien:

- No further studies were added since the previous update in 2014. The review included six trials (four parallel-group and two cross-over group trials) consisting of 948 participants.
- For the main comparison, tiagabine versus placebo, all participants were aged between 12 and 77 years and the study treatment periods ranged from 12 to 22 weeks.

Qualität der Studien:

- We judged two of the six included studies to have low risk of bias, three studies to have an unclear risk of bias, and one study to have a high risk of bias. Methods for randomisation sequence generation were the least reported trial design factor and generated the most concerns regarding risk of bias. We rated the overall certainty of the evidence as largely moderate to high using the GRADE approach. We rated the evidence for two of the adverse effect outcomes, nausea and tremor, as low certainty.



Studienergebnisse:

- The overall risk ratio (RR) with 95% confidence intervals (CIs) for a 50% or greater reduction in seizure frequency (tiagabine versus placebo) was 3.16 (95% CI 1.97 to 5.07; 3 trials; 769 participants; highcertainty evidence).
- The RR for treatment withdrawal (tiagabine versus placebo) was 1.81 (95% CI 1.25 to 2.62; 3 trials, 769 participants; moderate-certainty evidence).
- Dizziness and tremor were significantly associated with tiagabine therapy.
- For cognitive and quality-of-life outcomes, the limited available data suggested no significant effects on cognition, mood, or adjustment.
- One trial comparing tiagabine with an active drug control group (tiagabine versus topiramate) found no significant differences between the two add-on drugs for a 50% or greater reduction in seizure frequency (RR 0.54, 95% CI 0.19 to 1.58; 1 trial; 41 participants) or for treatment withdrawal (RR 1.43, 95% CI 0.74 to 2.74; one trial; 41 participants).

Anmerkung/Fazit der Autoren

Tiagabine reduced seizure frequency but was associated with some adverse effects when used as an add-on treatment in people with drug-resistant focal epilepsy. The findings of the current review are mainly applicable to adults and adolescents, and may not necessarily be applicable to children as none of the trials included participants aged under 12 years. We found no significant differences between tiagabine and topiramate as add-on drugs; however, evidence was provided by a single trial and was therefore limited.

Bresnahan R. et al., 2019 [4].

Brivaracetam add-on therapy for drug-resistant epilepsy.

Fragestellung

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

Methodik

Population:

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

Intervention:

- brivaracetam in addition to an existing antiepileptic drug regimen taken at the time of randomisation.

Komparator:

- a matched placebo or active comparator in addition to an existing antiepileptic drug regimen taken at the time of randomisation

Endpunkte:

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

Recherche/Suchzeitraum:

- We searched the following databases on 9 October 2018: the Cochrane Register of Studies (CRS Web), which includes the Cochrane Epilepsy Group Specialized Register and the Cochrane Central Register of Controlled Trials (CENTRAL); Medline (Ovid) 1946 to 8 October 2018; ClinicalTrials.gov; and the World Health Organization (WHO) International Clinical Trials Registry Platform (ICTRP). Originally we also searched SCOPUS as a substitute for Embase, but this is no longer necessary, because randomised and quasi-randomised controlled trials in Embase are now included in CENTRAL.

Qualitätsbewertung der Studien:

- Cochrane approach / GRADE

Ergebnisse

Anzahl eingeschlossener Studien:

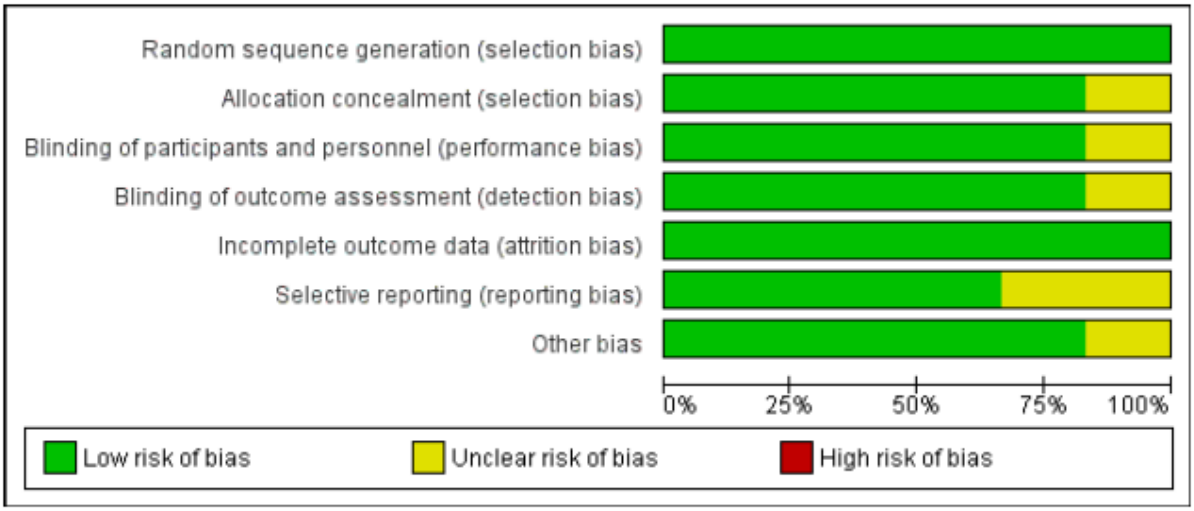
- six trials representing 2411 participants

Charakteristika der Population:

- Only one study included participants with both focal and generalised onset seizures; the other five trials included participants with focal onset seizures only
- All six studies included adult participants between 16 and 80 years old, and treatment periods ranged from 7 to 16 weeks

Qualität der Studien:

- We judged two studies to have low risk of bias and four to have unclear risk of bias. One study failed to provide details on the method used for allocation concealment, and one did not report all outcomes prespecified in the trial protocol. One study did not describe how blinding was maintained, and another noted discrepancies in reporting.



Studienergebnisse:

- Participants receiving brivaracetam add-on were significantly more likely to experience a 50% or greater reduction in seizure frequency than those receiving placebo (RR 1.81, 95% CI 1.53 to 2.14; 6 studies; moderate-quality evidence).
- Participants receiving brivaracetam were also significantly more likely to attain seizure freedom (RR 5.89, 95% CI 2.30 to 15.13; 6 studies; moderate-quality evidence).
- The incidence of treatment withdrawal for any reason (RR 1.27, 95% CI 0.94 to 1.74; 6 studies; low-quality evidence), as well as the risk of participants experiencing one or more adverse events (RR 1.08, 95% CI 1.00 to 1.17; 5 studies; moderate-quality evidence), was not significantly different following treatment with brivaracetam compared to placebo.
- However, participants receiving brivaracetam did appear to be significantly more likely to withdraw from treatment specifically because of adverse events compared with those receiving placebo (RR 1.54, 95% CI 1.02 to 2.33; 6 studies; low-quality evidence).

Anmerkung/Fazit der Autoren

Brivaracetam, when used as add-on therapy for patients with drug-resistant epilepsy, is effective in reducing seizure frequency and can aid patients in achieving seizure freedom. However, add-on brivaracetam is associated with a greater proportion of treatment withdrawals due to adverse events compared with placebo. It is important to note that only one of the eligible studies included participants with generalised epilepsy. None of the studies included participants under the age of 16, and all studies were of short duration. Consequently, these findings are mainly applicable to adult patients with drug-resistant focal epilepsy. Future research should thus focus on investigating the tolerability and efficacy of brivaracetam during longer-term follow-up, and should also assess the efficacy and tolerability of add-on brivaracetam in managing other types of seizures and its use in other age groups.

Kommentare zum Review

- Nur Placebo kontrollierte Studien
- Siehe auch: Lattanzi, S. et al., 2016 [16]

Bresnahan R. et al., 2019 [3].

Clobazam add-on therapy for drug-resistant epilepsy.

Fragestellung

To assess the efficacy, effectiveness and tolerability of clobazam as an add-on therapy for drug-resistant generalised-onset and focal-onset seizures, with or without secondary generalisation, in adults and children.

Methodik

Population:

- Children (< 16 years) or adults with drug-resistant generalised or focal-onset seizures (including simple focal, complex focal or secondary generalised seizures)

Intervention:

- clobazam in addition to their usual antiepileptic drugs (AED) treatment

Komparator:

- placebo in addition to their usual AED treatment

Endpunkte:

- Fifty per cent or greater reduction in seizure frequency, Seizure freedom, Treatment withdrawal, treatment withdrawal due to adverse events, adverse events, Quality of life

Recherche/Suchzeitraum:

- For the latest update, we searched the following databases on 9 October 2018: Cochrane Register of Studies (CRS Web), which includes the Cochrane Epilepsy Group Specialized Register and the Cochrane Central Register of Controlled Trials (CENTRAL), Medline (Ovid) 1946 to 8 October, 2018, ClinicalTrials.gov, and the WHO International Clinical Trials Registry Platform (ICTRP). For some previous updates we also searched SCOPUS, DARE,

and BIOSIS Previews, but these are no longer needed. (SCOPUS was searched as a substitute for EMBASE, but randomised and quasi-randomised controlled trials in EMBASE are now included in CENTRAL; DARE ceased operation at the end of March 2015; BIOSIS Previews yielded no relevant items that were not found in the other databases).

Qualitätsbewertung der Studien:

- Cochrane approach / GRADE

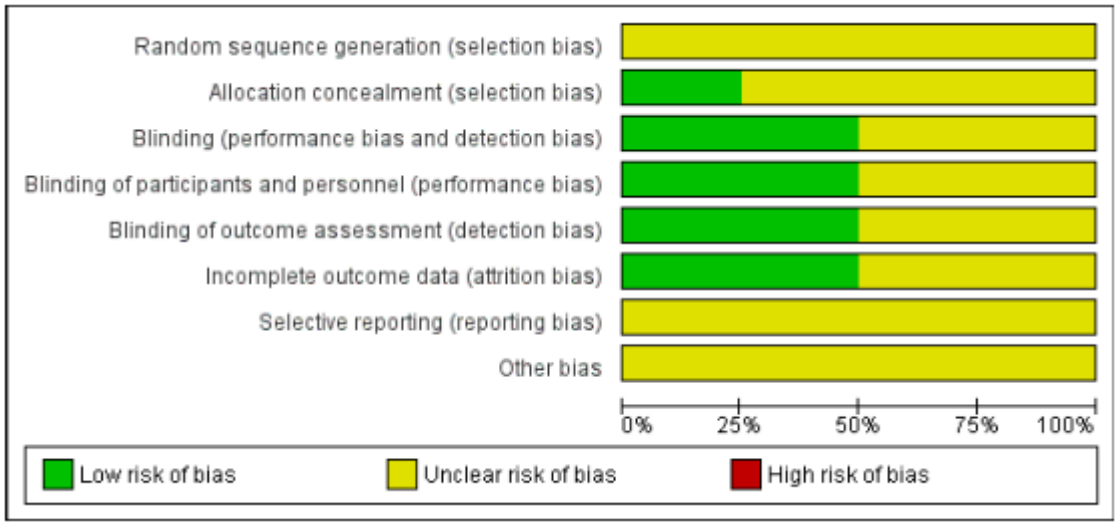
Ergebnisse

Anzahl eingeschlossener Studien:

- 4 studies / 197 people

Qualität der Studien:

- All four studies were of short duration. They used different methods, e.g. different lengths of treatment, and were of poor quality



Studienergebnisse:

- Two studies reported that more than half of the people given clobazam reached a 50% of greater reduction in the number of their seizures. Three of the studies reported how many people were seizure-free whilst taking clobazam. In total, approximately 15% of people were seizure-free when taking clobazam, compared to 0% when they were given placebo (a fake, inactive drug which should have no effect of epilepsy).
- All four studies reported how many people withdrew from treatment during the studies. Slightly more people withdrew from the studies when receiving clobazam (17 out of 197 people) than when receiving placebo (12 out of 197 people), but the rate of people withdrawing was still low overall.
- Clobazam was associated with side effects, in particular drowsiness.

Anmerkung/Fazit der Autoren

- The results suggest that clobazam reduces seizure frequency for people with drug-resistant focal epilepsy (epilepsy that originates from one area of the brain), but there were not enough data to determine whether clobazam is as effective for generalised epilepsy (epilepsy

involving the whole brain). The very low quality of the evidence provided by the four included studies means that we are very uncertain about whether the findings are accurate and, therefore, they must be taken and applied with caution.

Panebianco M. et al., 2018 [18].

Gabapentin add-on treatment for drug-resistant focal epilepsy.

Fragestellung

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

Methodik

Population:

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

Intervention:

- gabapentin in addition to conventional AED

Komparator:

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

Endpunkte:

- Reduction in seizure frequency of 50% or more, Seizure freedom, Treatment withdrawal, Adverse effects

Recherche/Suchzeitraum:

- For the latest update, we searched the Cochrane Register of Studies (CRS Web, 20 March 2018), which includes the Cochrane Epilepsy Group's Specialized Register and the Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE (Ovid, 1946 to 20 March 2018), ClinicalTrials.gov (20 March 2018) and the World Health Organization International Clinical Trials Registry Platform (ICTRP, 20 March 2018)

Qualitätsbewertung der Studien:

- Cochrane approach / GRADE

Ergebnisse

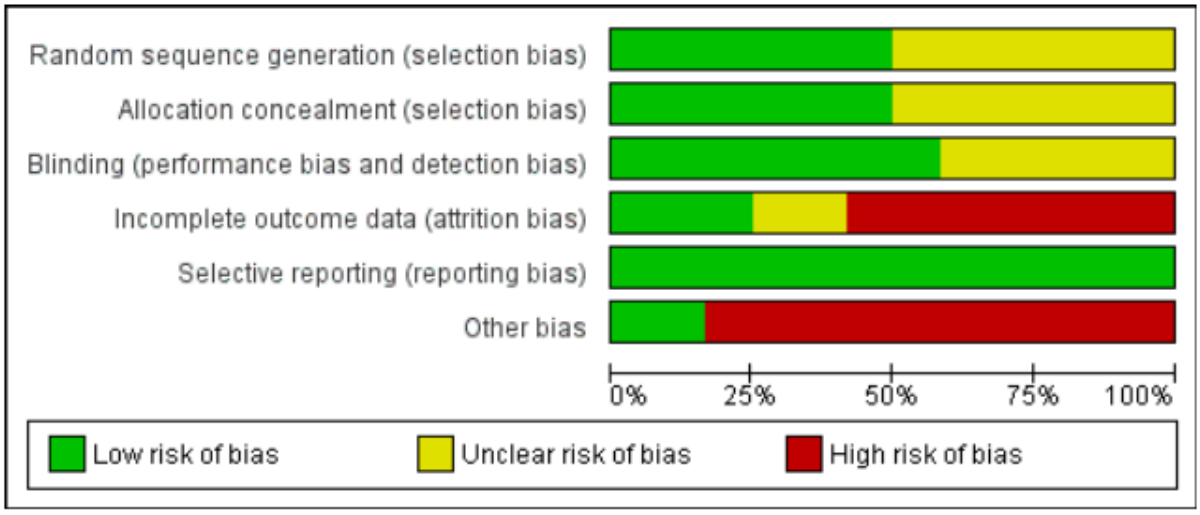
Anzahl eingeschlossener Studien:

- 12 trials representing 2607 randomised participants
- data from six trials in meta-analyses of 1206 randomised participants

Qualität der Studien:

- Overall, the studies were rated at low to unclear risk of bias due to information on each risk of bias domain not being available. We judged the overall quality of evidence (using the

GRADE approach) as low to moderate due to potential attrition bias resulting from missing outcome data and imprecise results with wide confidence intervals.



Studienergebnisse:

- Vs. Placebo:
  - The overall RR for reduction in seizure frequency of 50% or more compared to placebo was 1.89 (95% confidence interval (CI) 1.40 to 2.55; 6 trials, 1206 participants; moderate-quality evidence).
  - The RR for treatment withdrawal compared to placebo was 1.05 (95% CI 0.74 to 1.49; 6 trials, 1206 participants; moderate-quality evidence).
  - Adverse effects were significantly associated with gabapentin compared to placebo. RRs were as follows: ataxia 2.01 (99% CI 0.98 to 4.11; 3 studies, 787 participants; low-quality evidence), dizziness 2.43 (99% CI 1.44 to 4.12; 6 studies, 1206 participants; moderate-quality evidence), fatigue 1.95 (99% CI 0.99 to 3.82; 5 studies, 1161 participants; low-quality evidence) and somnolence 1.93 (99% CI 1.22 to 3.06; 6 studies, 1206 participants; moderate-quality evidence). There were no significant differences for the adverse effects of headache (RR 0.79, 99% CI 0.46 to 1.35; 6 studies, 1206 participants; moderate-quality evidence) or nausea (RR 0.95, 99% CI 0.52 to 1.73; 4 trials, 1034 participants; moderate-quality evidence).
- Gabapentin versus vigabatrin: One study compared gabapentin versus vigabatrin (Lindberger 2000).
  - Reduction in seizure frequency of 50% or more and seizure freedom: The study noted a reduction in seizure frequency of 50% or more and seizure freedom in 27/50 participants (54%) in the gabapentin group and 34/52 participants (56%) in the vigabatrin group (on an ITT basis); the 95% CIs were wide and this was not deemed statistically significant. The proportion of seizure-free participants without adverse effects was 13/50 (26%) in the gabapentin group and 18/52 (35%) participants in the vigabatrin group. This was not statistically significant. The study measured an extra variable of 'improvement rate' (proportion of participants with 50% or greater seizure reduction without adverse effects), which was 24/50 (48%) participants in the gabapentin group and 29/52 (56%) participants in the vigabatrin group. Thirteen out of 50 participants were seizure-free in the gabapentin group compared to 18/52 participants in the vigabatrin group.

- Treatment withdrawals: There were 14 withdrawals from the study as a result of adverse effects, seven in each group. In the gabapentin group they were status epilepticus, psychiatric problems, epigastric pain, diplopia, vertigo and dizziness (three participants); in the vigabatrin group they were depression, generalised seizure, rash, numbness and dizziness (three participants).
- Adverse effects: In the gabapentin group, three participants experienced serious adverse effects which were status epilepticus, pyelonephritis and psychiatric problems. In the vigabatrin group, four participants had serious adverse effects, which were agitation, depression, weight gain, mononucleosis and a secondary generalised seizure. Thirtyeight (76%) participants in the gabapentin group and 45 (86.5%) participants in the vigabatrin group experienced adverse effects of any type. The five most common adverse effects were similar in both groups (tiredness, dizziness, respiratory infection, headache and diarrhoea). Specific proportions of individual adverse effects were not provided.

- Gabapentin versus lamotrigine: One trial compared gabapentin versus lamotrigine (Sethi 2002).
  - Reduction in seizure frequency of 50% or more and seizure freedom: There was a 50% or greater reduction in seizure frequency by 77.7% of participants in the gabapentin group and 92% of participants in the lamotrigine group (ITT analysis). There was complete seizure control in 8/27 (29.6%) participants in the gabapentin group; this was not specified in the lamotrigine group.
  - Treatment withdrawals: Sethi 2002 did not report any treatment withdrawals.
  - Adverse effects: Twenty-two out of 27 (81.5%) participants in the gabapentin group and 18/25 (72%) participants in the lamotrigine group reported adverse effects. The most common adverse effects were neurotoxic: dizziness (gabapentin: 22.2%; lamotrigine: 28%), diplopia (gabapentin: 11.11%; lamotrigine: 24%), weakness (gabapentin: 14.8%; lamotrigine: 24%), headache (gabapentin: 25.9%; lamotrigine: 20%), drowsiness (gabapentin: 14.8%; lamotrigine: 12%), tiredness (gabapentin: 14.8%; lamotrigine: 4%), amnesia (gabapentin: 11.11%; lamotrigine: 12%), tingling sensation (gabapentin: 11.11%; lamotrigine: 0%) and anorexia (gabapentin: 11.11%; lamotrigine: 8%).
  - There were no serious adverse effects in the gabapentin group. In the lamotrigine group, there were two serious adverse effects (Steven Johnson's syndrome and anxiety neurosis (corresponding with an increase in seizure frequency)). There was an increase in the number of seizures in one participant receiving gabapentin 2400 mg/day. In the gabapentin group, there was a change of seizure type from focal seizures to myoclonic jerks or atypical seizures in five participants during treatment. In the lamotrigine group, seizure type changed to atypical absence (two participants) and pseudoseizures (two participants).
  - Additionally, the benefit of gabapentin was more pronounced in participants with simple focal seizures with secondary generalisation than in participants with simple and complex focal seizures without secondary generalisation, whereas all subtypes of epilepsy responded similarly in the lamotrigine group.

- Gabapentin versus pregabalin: One study compared gabapentin versus pregabalin (French 2016).
  - Reduction in seizure frequency of 50% or more and seizure freedom: There was a reduction in seizure frequency of 50% or more in 140/240 (58.3%) participants in the gabapentin group and 134/238 (56.3%) participants in the pregabalin groups (on an ITT basis); the 95% CIs were wide and this was not deemed statistically significant. The

proportion of seizure-free participants was 62/182 (34.1%) in the gabapentin group and 58/189 (30.7%) in the pregabalin group; these were not statistically significant. The study measured an extra variable of 'improvement rate' (proportion of participants with 75% or greater seizure reduction) and was 82/240 (34.2%) participants in the gabapentin group and 80/238 (33.6%) participants in the pregabalin group.

- Treatment withdrawals: There were 123 withdrawals for any reason from the study, and 31 due to adverse effects (16 in the gabapentin group and 15 in the pregabalin group). In the gabapentin group, the adverse effects were status epilepticus, psychiatric problems, epigastric pain, diplopia, vertigo and dizziness (three participants); in the vigabatrin group, they were depression, generalised seizure, rash, numbness and dizziness (three participants).
- Adverse effects: In the gabapentin group, 129/241 (53.5%) participants reported adverse effects and, in the pregabalin group, 142/241 (58.9%) participants reported adverse effects. Both groups had six (2.5%) participants with serious adverse effects. The five most common adverse effects were similar in both groups (somnolence, dizziness, headache, increased weight and dry month).

Anmerkung/Fazit der Autoren

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

Chang XC et al., 2017 [8].

Eslicarbazepine acetate add-on for drug-resistant focal epilepsy.

Fragestellung

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

Methodik

Population:

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

  In this review, we defined drug resistance as continued seizures despite treatment with one or more AEDs.

Intervention:

- ESL in addition to an existing AED regimen at the time of randomization

Komparator:

- matched placebo in addition to an existing AED regimen at the time of randomization

Endpunkte:

- 50% or greater reduction in seizure frequency, Freedom from seizures, Treatment withdrawal, Adverse effects,

Recherche/Suchzeitraum:

- The searches for the original review were run in November 2011. Subsequently, we searched the Cochrane Epilepsy Group Specialized Register (6 December 2016), the Cochrane Central Register of Controlled Trials (CENTRAL 2016, Issue 11) and MEDLINE (1946 to 6 December 2016). There were no language restrictions. We reviewed the reference lists of retrieved studies to search for additional reports of relevant studies. We also contacted the manufacturers of ESL and experts in the field for information about any unpublished or ongoing studies.

Qualitätsbewertung der Studien:

- Cochrane approach / GRADE

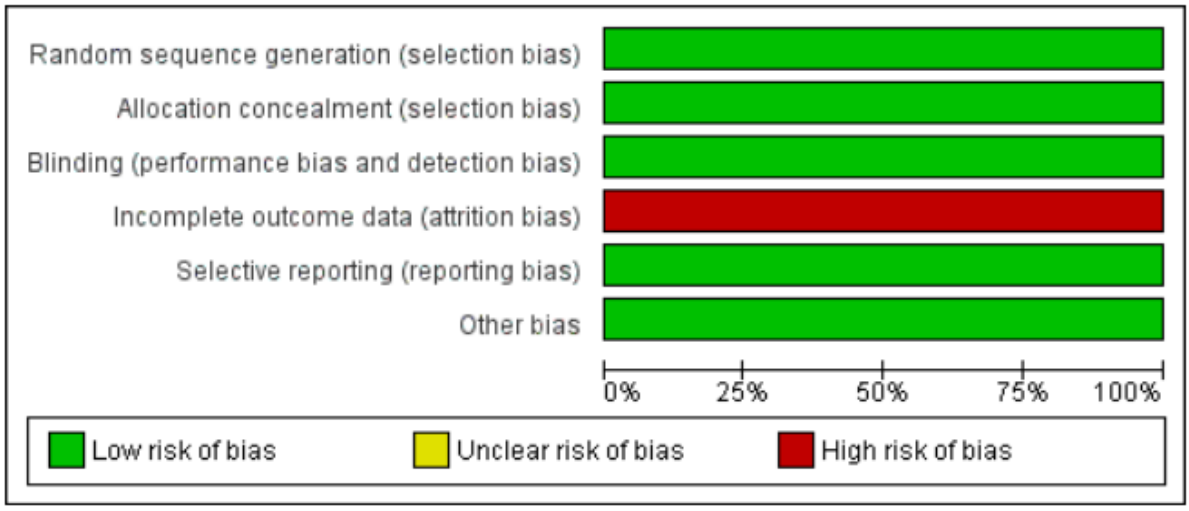
Ergebnisse

Anzahl eingeschlossener Studien:

- five trials (1799 participants)

Qualität der Studien:

- low risk of bias apart from a high risk of attrition bias; all studies were funded by BIAL.



Studienergebnisse:

- The overall risk ratio (RR) with 95% confidence interval (CI) for 50% or greater reduction in seizure frequency was 1.71 (95% CI 1.42 to 2.05).
- ESL was significantly associated with seizure freedom (RR 2.90, 95% CI 1.49 to 5.68). Participants were more likely to have ESL withdrawn for adverse effects (RR 2.66, 95% CI 1.42 to 4.96) but not for any reason (RR 1.19, 95% CI 0.86 to 1.64).
- The following adverse effects were significantly associated with ESL: dizziness (RR 2.81, 99% CI 1.86 to 4.27); nausea (RR 2.61, 99% CI 1.36 to 5.01); diplopia (RR 4.14, 99% CI 1.74 to 9.84); somnolence (RR 1.71, 99% CI 1.11 to 2.63) and vomiting (RR 3.30, 99% CI 1.34 to 8.13). Overall the quality of the evidence was rated as moderate due to a high discontinuation rate.

Anmerkung/Fazit der Autoren

ESL reduces seizure frequency when used as an add-on treatment for people with drug-resistant focal epilepsy. The trials included in this review were of short-term duration and focused on adults. One new trial has been included in this update, but the conclusions are unchanged.

Kommentare zum Review

- Ausschließlich Placebo kontrollierte Studien

Brigo F. et al., 2018 [6].

Zonisamide add-on therapy for focal epilepsy.

Fragestellung

To evaluate the efficacy and tolerability of zonisamide, when used as an add-on treatment for people with focal epilepsy uncontrolled by one or more concomitant antiepileptic drugs.

Methodik

Population:

- Participants of any age with focal epilepsy (i.e. experiencing simple focal, complex focal, or secondary generalised tonic-clonic seizures), uncontrolled by one or more concomitant antiepileptic drug.

Intervention:

- zonisamide in addition to conventional AED treatment

Komparator:

- matched placebo in addition to conventional AED treatment

Endpunkte:

- Proportion of participants with a 50% or greater reduction in seizure frequency in the treatment period compared to the pre-randomisation baseline period, adverse events

Recherche/Suchzeitraum:

- For this update, on 4 September 2017, we searched the Cochrane Epilepsy Group Specialised Register, Cochrane Register of Studies Online, MEDLINE Ovid, ClinicalTrials.gov, and the WHO International Clinical Trials Registry Platform ICTRP. We searched SCOPUS on 13 February 2013, but this is no longer necessary, because RCTs and quasi-RCTs in Embase are now included in CENTRAL. In addition, we contacted Eisai Limited (makers and licensees of zonisamide) and experts in the field to seek any ongoing or unpublished studies.

Qualitätsbewertung der Studien:

- Cochrane approach / GRADE

Ergebnisse

Anzahl eingeschlossener Studien:

- eight studies (1636 participants)

Qualität der Studien:

- Across the eight studies, we rated risk of bias domains at low or unclear risk of bias apart from two studies which we rated at high risk of attrition bias. Five of the eight studies were sponsored by the drug companies that produced zonisamide

Studienergebnisse:

- The RR for 50% reduction in seizure frequency compared to placebo for any dose of zonisamide (100 mg to 500 mg/ day) was 1.86 (95% CI 1.60 to 2.17; 7 trials, 1429 participants; moderate-quality evidence). The number needed to treat for an additional beneficial outcome was six (95% CI 4.1 to 6.8) for this outcome.
- The CIs of the following adverse effects indicated that they were significantly associated with zonisamide: ataxia RR 3.85 (99% CI 1.36 to 10.93; 4 trials, 734 participants; low-quality evidence); somnolence RR 1.52 (99% CI 1.00 to 2.31; 8 trials, 1636 participants; moderate-quality evidence); agitation RR 2.35 (99% CI 1.05 to 5.27; 4 trials, 598 participants; low-quality evidence); and anorexia RR 2.74 (99% CI 1.64 to 4.60; 6 trials, 1181 participants; low-quality evidence).

Anmerkung/Fazit der Autoren

When used as an add-on treatment in people with focal epilepsy uncontrolled by one or more concomitant antiepileptic drugs, moderatequality evidence found that zonisamide was more successful than placebo at reducing the frequency of seizures by at least 50%. We were unable to identify minimum effective and maximum tolerated doses. The included trials evaluated a maximum stable-dose phase of 18 weeks, so results cannot be used to confirm longer periods of efficacy in seizure control. The results cannot be extrapolated to monotherapy or to people with other seizure types or epilepsy syndromes

Kommentare zum Review

- Ausschließlich Placebo kontrollierte Studien

3.3 Systematische Reviews

Chen D. et al., 2019 [9].

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

Fragestellung

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

Methodik

Population:

- refractory epilepsy, regardless of age and gender

Intervention:

- add-on levetiracetam

Komparator:

- Placebo

Endpunkte:

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

Recherche/Suchzeitraum:

- Web of Science, MEDLINE (Ovid and PubMed), Cochrane Library, EMBASE, and Google Scholar from inception up to May 31, 2018

Qualitätsbewertung der Studien:

- Cochrane Collaboration's Risk of Bias tool

Ergebnisse

Anzahl eingeschlossener Studien:

- a total of 17 RCTs with 3,205 participants were included in the current meta-analysis

Charakteristika der Population:

- Fourteen trials involved adult patients and three involved children
- Of the 17 RCTs, 15 involved patients with refractory partial-onset seizures, whereas the two others were designed to assess the efficacy for patients with uncontrolled idiopathic generalized epilepsy

Qualität der Studien:

- Ten trials were considered as low risk of bias, because sequence generation and allocation method were described. The remaining seven trials were regarded as risk of selection bias, mainly because insufficient information for random list generation and allocation concealment were not reported. All trials were reported to be double-blind trials; however,

six trials did not describe the details of approaches applied to blind participants and personnel, then regarded as unclear for risk of bias. Most of the trials were viewed as low risk of bias concerning incomplete outcome data biases; nevertheless, three trials were considered as high risk of bias, for the number of patients reported after treatment was not consistent with the initial number. In general, the quality assessment for all included RCTs was not very high.

Studienergebnisse:

- Pooled estimates suggested that levetiracetam was an effective anti-epileptic drug at 1,000–3,000 mg/day (RR =2.00 for 1,000 mg/day, RR =2.68 for 2,000 mg/day, RR =2.18 for 3,000 mg/day) for adults and 60 mg/kg/day (RR =2.00) for children compared to placebo in terms of 50% reduction from baseline.
- Likewise, as for seizure freedom rate, levetiracetam had an advantage over placebo at 1,000–3,000 mg/day (RR =5.84 for 1,000 mg/day, RR =4.55 for 2,000 mg/day, RR =4.57 for 3,000 mg/day, respectively) for adults and 60 mg/kg/day (RR =4.52) for children.
- Regarding safety profile, patients treated with levetiracetam had significantly higher occurrence than placebo for somnolence, asthenia, dizziness, infection, nasopharyngitis, anxiety, and irritability; however, most studies reported that these adverse events were mild and transient.

Anmerkung/Fazit der Autoren

In summary, findings from the current meta-analysis suggested that levetiracetam at 1,000–3,000 mg/day (for children 60 mg/kg/day) is an effective AED for patients with refractory partial or generalized epilepsy, even in very young children. Moreover, levetiracetam has a favorable safety profile, and most of the AEs are mild or moderate. However, it seems that levetiracetam has a limited improvement in patients' QoL.

Kommentare zum Review

- Ausschließlich Placebo kontrollierte Studien

Hu Q. et al., 2018 [14].

Efficacy and safety of antiepileptic drugs for refractory partial-onset epilepsy: a network meta-analysis.

Fragestellung

…In our review, we included the newer AEDs to evaluate the comparative efficacy and safety of AEDs for the treatment of refractory partial-onset epilepsy.

Methodik

Population:

- patients older than 2 years of age with a clinical diagnosis of drug-resistant partial epilepsy (simple, complex, or secondarily tonic–clonic seizures)

Intervention / Komparator:

- placebo-controlled or active-controlled add-on trials

Endpunkte:

- seizure freedom and withdrawal rate due to treatment-emergent adverse effects

Recherche/Suchzeitraum:

- PubMed, EMBASE, and the Cochrane Central Register of Controlled Trials (Cochrane Library 2017, Issue 1) from their inception to February 18, 2017.

Qualitätsbewertung der Studien:

- Cochrane Collaboration's risk of bias tool

Ergebnisse

Anzahl eingeschlossener Studien & Charakteristika

- Seventy-six RCTs with 17 AEDs and 20,711 patients
- All examined AEDs included Lacosamide (LCM), Carisbamate (CRS), ESL, GBP, LTG, LEV, OXC, PER, Pregabalin (PGB), RTG, TPM, Vigabatrin (VGB), VPA, Rufinamide (RUF), Tiagabine (TGB), and Brivaracetam (BRV)
- The number of trials per antiepileptic drug (AED) was 3 for Lacosamide (LCM), 2 for Carisbamate (CRS), 4 for Eslicarbazepine acetate (ESL), 7 for Gabapentin (GBP), 4 for Lamotrigine (LTG), 12 for Levetiracetam (LEV), 3 for Oxcarbazepine (OXC), 4 for Perampanel (PER), 7 for Pregabalin (PGB), 4 for Retigabine (RTG), 9 for Topiramate (TPM), 4 for Vigabatrin (VGB), 1 for Valproate (VPA), 6 for Zonisamide (ZNS), 1 for Rufinamide (RUF), 3 for Tiagabine (TGB) and 2 for Brivaracetam (BRV).
- Three of those trials were head-to-head studies comparing LEV with PGB, VGB with VPA and PGB with LTG. Seventy-one trials were parallel-group studies, and 5 trials were crossover studies, of which 2 analyzed LTG, 1 analyzed LEV, 1 analyzed ZNS and 1 analyzed VGB.
- Sixty-eight trials evaluated adults (range, 12 to 80 years old), and eight trials evaluated children (range, 1 to 17 years old). The duration of the double-blind treatment period (maintenance+titration) was 12 to 20 weeks.

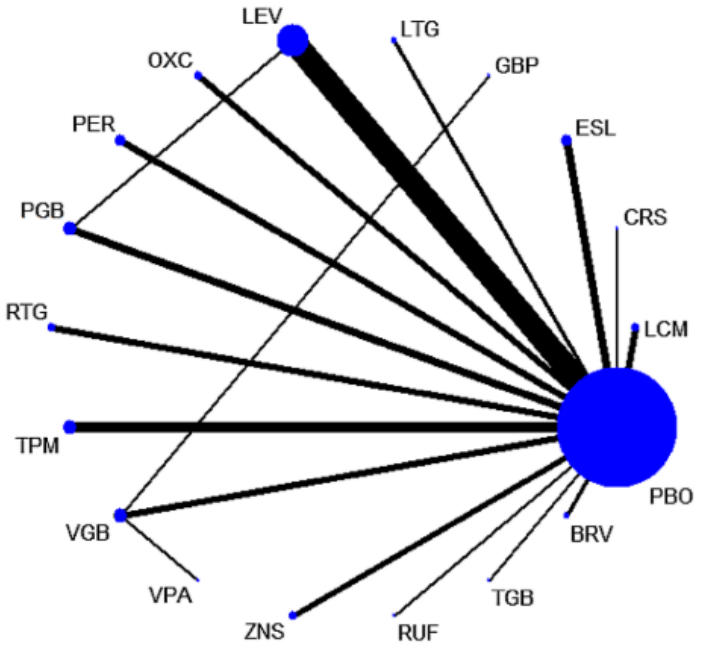
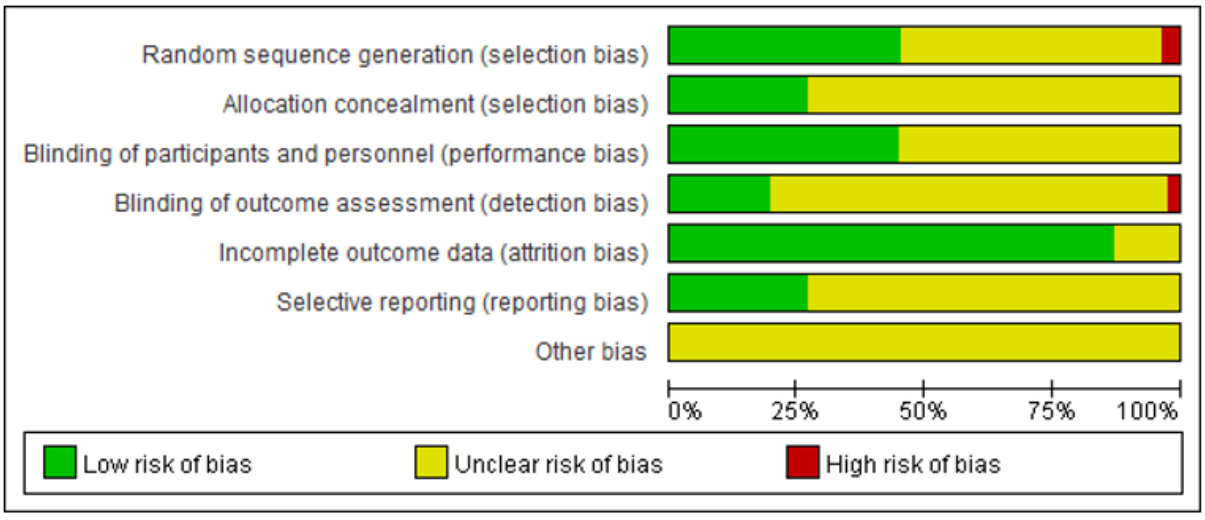


Fig. 1 Network plot of the efficacy of different inventions. The size of the nodes corresponds to the number of trials that study the treatments. Directly comparable treatments are linked with a line, the thickness of which corresponds to the number of trials that assess the comparison. *LCM* Lacosamide, *CRS* Carisbamate, *ESL* Eslicarbazepine acetate, *GBP* Gabapentin, *LTG* Lamotrigine, *LEV* Levetiracetam, *OXC* Oxcarbazepine, *PER* Perampanel, *PGB* Pregabalin, *RTG* Retigabine, *TPM* Topiramate, *VGB* Vigabatrin, *VPA* Valproate, *ZNS* Zonisamide, *RUF* Rufinamide, *TGB* Tiagabine, *BRV* Brivaracetam, *PBO* Placebo

Qualität der Studien:

- 35 trials showed random sequence generation, 21 trials provided details describing an adequate allocation concealment, and 35 trials described how blinding of interventions was achieved by providing identical capsules and tablets.



Studienergebnisse:

- Fifty-four RCTs, with a total of 15,784 patients with refractory partial-onset epilepsy, reported efficacy outcomes comparing 17 AEDs.
  - The NMA of the 'seizure free' outcomes showed that all drugs were superior to the placebo, apart from CRS, GBP, LTG, ZNS, RUF, and TGB, which showed no statistical significance.
  - Compared to other AEDs, TGB had the greatest likelihood of allowing patients to attain seizure freedom, and this result is consistent with the ranking probability for the SUCRA. BRV, TPM, LEV, OXC, VPA, and VGB which had a lower likelihood of efficacy for seizure freedom when compared to RUF. [BRV: OR = 12.64, 95% CI (1.57–129.61); TPM: OR = 9.93, 95% CI (5.54–79); LEV: OR = 11.44, 95% CI (2.20–73.46); OXC: OR = 14.27, 95% CI (2.01–121.09); VGB: OR = 8.76, 95% CI (1.24, 80.42); VPA: OR = 12.77, 95% CI (1.35, 163.66)].
  - Rank probability analysis showed that TGB had the highest probability of improving seizure freedom (SUCRA = 98.5%), followed by BRV (SUCRA = 73.8%) and VPA (SUCRA = 71.5%).

- Sixty-six RCTs including 18,989 patients with refractory partial onset reported safety outcomes.
  - LEV was associated with a lower withdrawal rate due to adverse effects than LCM [OR = 2.72, 95% CI (1.05–7.48)], ELS [OR = 2.31, 95% CI (1.02–5.48)], OXC [OR = 3.48, 95% CI (1.43–8.43)], PGB [OR = 2.16, 95% CI (1.13–4.34)], and RTG [OR = 3.27, 95% CI (1.38–7.52)]).
  - Rank probability analysis showed that PBO was best tolerated AED in terms of safety outcomes (SUCRA = 94.6%), followed by LEV (SUCRA = 84.8%), BRV (SUCRA = 70.6%), and PER (SUCRA = 58%).

Anmerkung/Fazit der Autoren

This systematic review and Bayesian NMA provided an overview of the relative efficacy and tolerability of the most common AEDs used in patients with drug-resistant partial epilepsy. The newer AEDs—BRV, LEV, OXC, RTG, VGB, and TPM—were demonstrated to be as efficacious as the older AEDs (VPA) for the treatment of partial epilepsy, while OXC, RTG, and RUF had poorer tolerability. LEV showed the best efficacy and tolerability. However, the safety of VGB and VPA remains controversial in clinical practice. To reduce this uncertainty, it is critical to perform direct RCTs and to obtain prospective data from representative cohort studies.

Li-Na Z. et al., 2018 [17].

Indirect comparison of third-generation antiepileptic drugs as adjunctive treatment for uncontrolled focal epilepsy.

Fragestellung

to indirectly compare overall efficacy and tolerability between third-generation AEDs in uncontrolled focal epilepsy.

Methodik

Population:

- Adult participants diagnosed with partial-onset epilepsy

Intervention/Komparator:

- ESL, LAC, PER, BRV vs. placebo as an add-on treatment for uncontrolled focal epilepsy

Endpunkte:

- 50% responder rate, seizure-free rate, treatment-emergent adverse events (TEAEs), withdrawal rates due to adverse events (AEs), and serious adverse events (SAEs)

Recherche/Suchzeitraum:

- Pubmed, Embase, Cochrane from the establishment of each database to July 30th, 2017.

Qualitätsbewertung der Studien:

- Cochrane approach

Ergebnisse

Anzahl eingeschlossener Studien:

- Nineteen randomized, double-blind, placebo controlled trials (5 with ESL, 4 with LAC, 4 with PER and 6 with BRV) were carefully evaluated and included in our analysis
- a total of 7245 patients: 5282 of whom were randomized to active drug and 1963 to placebo
- 5 studies performed with ESL, 1183 subjects were treated with ESL and 545 with placebo. 1296 subjects were treated with LAC and 542with placebo in the LAC study. 1088 subjects were treated with PER and 492 with placebo in the PER study. Finally, in the BRV group, 1715 participants were randomized to active drug and 684 to placebo. All studies included patients with uncontrolled partial onset seizure and treated with at least 1or 2 other AEDs at the baseline phase

Qualität der Studien:

- All studies included in our analysis were considered to have low or unclear bias risks

Studienergebnisse:

- Conventional meta-analysis
  - Efficacy: All drugs showed higher 50% responder rate than placebo, regardless of dose. Moreover, all of these drugs were associated with better seizure free rate than placebo except for the minimum effective doses of LAC and BRV and the highest effective recommended dose for PER.
  - Tolerability: For BRV, there were significant higher risk of withdrawal rates due to AEs at all doses combined compared to placebo. For ESL, we found statistically significant higher rates of TEAEs and withdrawal rates due to AEs at all dose levels compared to placebo. The highest effective recommended dose of LAC also presented more TEAEs, higher withdrawal rates due to AEs and more SAEs. Finally, PER was associated with a greater number of TEAEs and higher withdrawal rates due to AEs when used at highest dose and all doses combined. High heterogeneity in LAC studies was mainly ascribed to Hong's

study, in which the race was clearly different to others. We didn't find other obvious causes leading to the high heterogeneity, which might be mainly due to statistical heterogeneity.

- Common reference-based indirect comparisons
  - Efficacy: The indirect comparisons found no significant differences in 50% responder rates or seizure freedom rates between any of the four third-generation AEDs.
  - Tolerability: Indirect comparisons showed ESL [RD 0.10, 95% CI (0.025, 0.175)] and PER [RD 0.07,95% CI (0.003, 0.137)] had a statistically significant higher risk of TEAEs compared to BRV at all doses combined.

    According to the indirect evidence, there were significantly higher risks for withdrawal rate due to AEs in LAC [RD 0.08, 95% CI (0.027, 0.133)] and PER treatment [RD 0.11, 95% CI (0.042, 0.178] compared to BRV at the highest effective recommended daily dosages. AE-related withdrawals in ESL [RD 0.06, 95% CI (0.001, 0.119)] and LAC treatment [RD 0.08, 95% CI (0.007, 0.153)] were higher than that of BRV when all doses were combined.
  - Serious adverse events (SAEs) were reported in all trials. The number of SAEs was 89/1715 (5.2%) for subjects randomized to BRV treatment, 71/1296(5.5%) for subjects randomized to LAC, 45/ 1133 (4.0%) for subjects randomized to ESL and 57/1037(5.5%) for subjects randomized to PER respectively. Common reference-based indirect comparisons showed that the risk of experiencing AEs did not differ between these newer AEDs at any dose.

Anmerkung/Fazit der Autoren

In this meta-analysis, we found no significant differences in efficacy between third-generation AEDs at all any dose in uncontrolled focal epilepsy. Our study might suggest BRV may have the best tolerability profile and the other newer AEDs carry higher risks for intolerable adverse events. The results from these indirect comparisons should be confirmed through future trials designed to compare these drugs directly.

Zhang L. et al., 2016 [21].

Levetiracetam vs. brivaracetam for adults with refractory focal seizures: A meta-analysis and indirect comparison.

Fragestellung

to compare the efficacy and tolerability of levetiracetam (LEV) and brivaracetam (BRV) in adults with refractory focal seizures.

Methodik

Population:

- patients with RFS

Intervention/Komparator:

- LEV vs. BRV indirectly

Endpunkte:

- 50% responder rate, seizure-free rate, and adverse effects

Recherche/Suchzeitraum:

- Medline, Embase, and the Cochrane Library on November 6, 2015

Qualitätsbewertung der Studien:

- Cochrane approach

Ergebnisse

Anzahl eingeschlossener Studien:

- 13 trials that met our criteria, including 8 studies in LEV and 5 trials in BRV comparing with placebo
- In total, 8 studies in LEV and 5 studies in BRV included 1765 patients (Table 1) and 1919 patients, respectively

Charakteristika der Population:

Characteristics of the included studies of levetiracetam.

LEV study	Design	Inclusion criteria of patients	Groups (mg/d)	LEV No. (ITT)	Males, %	Age, y, (mean, SD)	Titration, w	Treatment duration, w	Duration of epilepsy, y	BSF, n/w median
Ben-Menachem [1]	RDBPCT	Having at least 2 partial seizures per month during baseline despite treatment with 1 AED	Placebo	105	49	37 (12)	4	16	19 (12)	1.8
			3000	181	48	36 (12)			19 (11)	1.7
Cereghino [13]	RDBPCT	Having partial seizures occurring monthly during baseline despite treatment with at least 2 AEDs	Placebo	95	52.6	38 (11)	4	18	–	1.8
			1000	98	63.3	38 (11)			–	2.5
			3000	101	65.3	38 (11)			–	2.0
Shorvon [16]	RDBPCT	Having seizures that persisted for at least the previous 2 years despite treatment with 1 or 2 AEDs	Placebo	112	49	37 (12)	4	12	23.2 (11.0)	2.5
			1000	106	48	36 (10)			23.8 (12.3)	2.8
			2000	106	48	37 (12)			23.6 (13.3)	2.6
Peltola [15]	RDBPCT	Having recurrent partial seizures despite receiving 1–3 AEDs	Placebo	79	59.5	32.38 (12.60)	Without	12	6.43 (11.9)	–
			1000	79	65.8	33.97 (13.41)			13.11 (10.8)	–
Tsai [17]	RDBPCT	Having partial seizures that were treatment resistant with at least 2 classic AEDs	Placebo	47	53.2	31.7 (8.2)	2	12	18.7 (10.7)	1.6
			2000	47	36.2	32.8 (10.5)			18.6 (8.5)	2.0
Wu [18]	RDBPCT	Having treatment-resistant partial seizures on 1 or 2 AEDs	Placebo	100	54.0	32.8 (11.9)	4	16	17.3 (12.1)	1.8
			3000	102	50.0	32.7 (13.4)			16.5 (12.7)	1.8
Xiao [19]	RDBPCT	Having at least 4 seizures per month despite therapy with other AEDs	Placebo	28	42.9	32.8 (11.2)	4	16	14.1 (9.4)	–
			3000	28	42.9	32.5 (11.2)			16.1 (12.5)	–
Inoue [14]	RDBPCT	Experiencing partial seizures at least twice per month when taking 1 – 3 AEDs, with a history of partial seizures for >2 years	Placebo	70	50.0	34.9 (12.56)	4	12	16.3 (11.9)	3.0
			500	71	49.3	33.2 (10.64)			16.4 (10.9)	2.7
			1000	70	41.4	32.8 (10.90)			14.5 (8.9)	2.7
			2000	70	50.0	30.4 (10.06)			13.8 (9.6)	3.2
			3000	70	52.9	33.1 (11.72)			15.2 (10.3)	2.7

LEV, levetiracetam; ITT, intent-to-treat; SD, standard deviation; BSF, baseline seizure frequency; RDBPCT, randomized, double-blind, placebo-controlled trial; AEDs, antiepileptic drugs.

Characteristics of the included studies of brivaracetam.

BRV study	Design	Inclusion criteria of patients	Group (mg/d)	BRV No. (ITT)	Patients who use LEV	Males, %	Age, y, (mean, SD)	Titration, w	Treatment duration, w	Duration of epilepsy, y	BSF, n/w median
Biton [4]	RDBPCT	Having partial seizures that are uncontrolled by 1–2 AEDs	Placebo	98	<20%	43.9	37.5 (12.6)	Without	12	24.3 (12.2)	2.6
			5	97		50.5	38.9 (11.6)			22.2 (12.1)	2.4
			25	100		52.0	37.3 (13.3)			22.9 (14.0)	2.2
			50	101		50.5	38.9 (12.3)			26.2 (12.0)	2.9
French [5]	RDBPCT	Experiencing at least 4 PS during the baseline period when taking 1 or 2 AEDs	Placebo	54	<20%	44.4	33.6 (11.3)	Without	7	21.7 (13.0)	2.2
			5	50		60.0	32.7 (12.2)			16.0 (11.5)	2.2
			20	52		53.8	35.3 (13.7)			22.9 (13.5)	2.3
			50	52		53.8	30.9 (11.6)			19.1 (10.8)	1.9
Klein [6]	RDBPCT	Having uncontrolled FS despite treatment with 1 or 2 AEDs	Placebo	259	0	51.0	39.8 (12.5)	Without	12	22.7 (13.3)	2.5
			100	252		40.3	39.1 (13.4)			22.2 (13.3)	2.3
			200	249		53.2	39.8 (12.8)			23.4 (14.6)	2.3
Ryvlin [7]	RDBPCT	Having ≥2 focal seizures per month and 8 or more FSs during baseline	Placebo	100	<20%	54.0	36.4 (13.0)	Without	12	20.4 (12.3)	2.0
			20	99		61.6	35.7 (12.5)			22.1 (13.6)	1.9
			50	99		54.5	38.9 (13.6)			22.3 (13.0)	1.8
			100	100		58.0	38.0 (13.1)			22.1 (12.8)	2.0
Van [8]	RDBPCT	Experiencing ≥4 PS during baseline despite treatment with 1 or 2 AEDs	Placebo	52	<25%	48.1	40.0 (11.7)	3	7	21.0 (12.9)	2.3
			50	53		45.3	38.2 (12.1)			25.1 (14.8)	1.8
			150	52		40.4	34.4 (10.1)			19.8 (11.6)	2.9

BRV, brivaracetam; ITT, intent-to-treat; SD, standard deviation; BSF, baseline seizure frequency; RDBPCT, randomized, double-blind, placebo-controlled trial; AEDs, antiepileptic drugs; FS, focal seizures.

Qualität der Studien:

- All of the enrolled RCTs were of high quality because the result with low risk was over 50%.

Studienergebnisse:

- The indirect comparison between LEV-treated vs. BRV-treated RFS patients shows that there were no statistical differences at all dose levels. However, most RRs at three dose levels were >1 for 50% response proportions (smallest P value 0.08).
- Adverse events
  - Adverse withdrawal events of LEV at the middle-dose level (2000 mg) and somnolence in the low- and middle-dose levels (1000–2000 mg) exhibited statistically significant differences.
  - Adverse withdrawal events of BRV at the middle-dose level (100 mg), at least one treatment-emergent adverse event at the middle-dose level (100 mg), dizziness at the high-dose level (150–200 mg), somnolence at middle- and high-dose levels (100– 200 mg), and asthenia a low- and middle-dose levels (20–100 mg) exhibited statistically significant differences.
  - The indirect comparison between LEV-treated and BRV treated RFS patients showed that only two AEs, including headache (RR 0.41, 95%CI 0.12–1.37, P = 0.02) and dizziness (RR 0.38, 95%CI 0.18–0.83, P = 0.03), exhibited statistically significant differences at the high-dose level, which is possibly because BRV had a higher incidence of headache and dizziness
  - We also found that the overall RRs of headache was 0.67 (95%CI 0.40, 1.12; P = 0.04). Nevertheless, the RRs of headache included the null value of 1, which might indicate no statistically significant difference regarding headache. There were no statistically significant differences in other AEs at the middle- and low-dose levels.

Anmerkung/Fazit der Autoren

Our results suggest that LEV may have a slightly higher efficacy with a lower probability of dizziness compared with BRV for patients with refractory focal seizures. The majority of statistically statistical differences in the AE of LEV and BRV were found at high and middle-dose levels. Therefore, the dose of LEV and BRV should be carefully selected. Further RCTs with large samples are needed to determine these findings.

Brigo F. et al., 2016 [7].

A common reference-based indirect comparison meta-analysis of eslicarbazepine versus lacosamide as add on treatments for focal epilepsy.

Fragestellung

to indirectly compare the efficacy of ESL and LCM used as add-on treatments in patients with focal epilepsy using common reference-based indirect comparison meta-analysis.

Methodik

Population:

- patients from any age group and diagnosed with focal epilepsy (simple focal, complex focal or secondary generalized tonic-clonic seizures)

Intervention/Komparator:

- add-on ESL or LCM versus placebo in the treatment of focal epilepsy

Endpunkte:

- Proportion of 50% or greater reduction in seizure frequency in the maintenance phase compared to baseline; Proportion of patients achieving seizure freedom; Proportion of patients with treatment withdrawal for any reason; Proportion of patients with 25% or greater increase in seizure frequency in the maintenance phase compared to baseline

Recherche/Suchzeitraum:

- on 18th February 2016

Qualitätsbewertung der Studien:

- Cochrane approach

Ergebnisse

Anzahl eingeschlossener Studien:

- eight studies: 5 comparing ESL with placebo and 3 comparing LCM with placebo

Charakteristika der Population:

Characteristics of included studies.

Study	Age, range (years)	Number of concomitant AEDs	Interventions	Starting dose	Titration
Double-blind randomized controlled trials comparing eslicarbazepine with placebo					
Elger et al., 2007	18–65	1–2	Placebo ESL ESL	400 mg/d	Target dose of 800 or 1200 mg achieved in 4 w
Elger et al., 2009	18–76	1–2	Placebo ESL 400 mg ESL800 mg ESL 1200 mg	400 mg/d	Target dose achieved in 2 w
Gil-Nagel et al., 2009	17–77	1–2	Placebo ESL 800 mg once/d ESL 1200 mg once/d	400 mg/d or 600 mg/d	Target dose achieved in 2 w
Ben-Menachem et al., 2010	18–69	1–3	Placebo ESL 400 mg ESL 800 mg ESL 1200 mg	400 or 800 mg/d	Patients allocated to 1200 mg/d achieved this dose in 2 w
Sperling et al., 2015	16–71	1–3	Placebo ESL 800 mg/d ESL 1200 mg/d	400 or 800 mg/d	Target dose achieved in 1 w
Double-blind randomized controlled trials comparing lacosamide with placebo					
Ben-Menachem et al., 2007	18–65	1–2	Placebo LCM 200 mg/d LCM 400 mg/d 600 mg/d	100 mg/d	Titration rate of 100 mg/w until target dose
Halász et al., 2009	16–70	1–3	Placebo LCM 200 mg/d LCM 400 mg/d	100 mg/d	Titration rate of 100 mg/w until target dose
Chung et al., 2010a,b	16–70	1–3	Placebo LCM 400 mg/d LCM 600 mg/d	100 mg/d	Titration rate of 100 mg/w until target dose

Abbreviations: d: day; ESL: eslicarbazepine acetate; LCM: lacosamide; w: week(s).

Qualität der Studien:

- All studies were double-blind RCT adopting adequate random sequence generation and allocation concealment (low risk of selection bias). Performance and detection bias were also low in each included study. No incomplete outcomes were reported in all studies (low risk of attrition bias), except one with high proportion of missing data (11/47 from the placebo group, 8/50 from the ESL once daily group, and 12/37 from the ESL twice daily group; unclear risk of attrition bias, due to lack of reasons for missing data)

Studienergebnisse:

- Conventional meta-analysis per AED

  Eslicarbazepine acetate versus placebo

  - Proportion of responders: Higher proportions of responders were found in patients treated with ESL at any dose compared with those receiving placebo (OR 2.00; 95% CI 1.56–2.55).
  - Seizure freedom: Higher proportions of seizure free patients were found in patients treated with ESL at any dose compared with those receiving placebo (OR 2.94; 95% CI 1.24–7.01).
  - Worsening of seizure frequency: A higher proportion of patients who received placebo experienced an exacerbation of seizure frequency ≥ 25% than patients treated with ESL. The difference was statistically significant for ESL at any dose (OR 0.56; 95%CI 0.38–0.82)
  - No statistical significant differences were found in treatment withdrawal (for any reason) between patients treated with ESL at any dose and those receiving placebo
- Common reference-based indirect comparisons by combining meta-analyses of AEDs
  - showed no difference for responder rate and seizure freedom, and lower withdrawal rates in patients receiving ESL than in those treated with LCM (OR 0.56; 95% CI 0.35–0.90) (Table 2).
  - showed no difference between ESL and LCM for responder rate and seizure freedom both at minimum and at highest effective recommended daily dosages.
  - Similarly, withdrawal rates adjusted for dose-effect also did not show any difference between the two drugs.
  - Only one study was available for evaluating worsening of seizures with LCM, therefore we did not carry the indirect comparison with ESL out.

  Lacosamide versus placebo

  - Higher proportions of responders were found in patients treated with LCS at any dose compared with those receiving placebo (OR 2.11; 95% CI 1.58–2.82).
  - No difference in proportion of seizure free patients was found in patients treated with LCM at any dose compared with those receiving placebo.
  - No difference in proportion of patients with 25% or greater increase in seizure frequency versus baseline was found in patients treated with LCM at any dose compared with those receiving placebo.
  - Higher withdrawal rates compared to placebo were found for LCM at any dose (OR 2.14, 95% CI 1.42–3.23).

Anmerkung/Fazit der Autoren

Our results failed to demonstrate a significant difference in efficacy between ESL and LCM, after dose-adjustments. Direct head-to-head clinical trials comparing ESL with LCM as add-on antiepileptic treatment are nonetheless required to confirm results of indirect comparisons carried out in our study. However, it is unlikely that RCTs directly comparing novel AEDs will be conducted, as drug companies would not carry the risk of performing a comparison which may prove unfavourable for the own test AED. Apart from possible differences in efficacy, other aspects including frequency of administration (unlike LCM, ESL can be administered only once

daily), pharmacokinetic properties with risk of drug interactions, tolerability profile (e.g. higher rates of hyponatremia with ESL), and patients preferences should all be taken into account when choosing between ESL and LCM. Since there is no single AED representing the “right drug” for all patients, the choice should rely on individual considerations.

Brigo F. et al., 2016 [5].

Efficacy and tolerability of brivaracetam compared to lacosamide, eslicarbazepine acetate, and perampanel as adjunctive treatments in uncontrolled focal epilepsy: Results of an indirect comparison meta-analysis of RCTs.

Fragestellung

To compare BRV with the other add-on AEDs in patients with uncontrolled focal epilepsy, estimating their efficacy and tolerability through an adjusted, common-reference based indirect comparison meta-analysis.

Methodik

Population:

- Patients from any age group and diagnosed with focal epilepsy (simple focal, complex focal or secondary generalized tonic–clonic seizures)

Intervention/Komparator:

- Add-on BRV, LCM, ESL or PER versus placebo

Endpunkte:

- 50% responder rate, defined as the proportion of patients with 50% or greater reduction in seizure frequency in the treatment period compared to the pre-randomization baseline period (“responders”);
- Proportion of patients achieving seizure freedom during treatment period;
- Proportion of patients experiencing any TEAE during treatment period;
- Proportion of patients with TEAEs leading to study/treatment discontinuation

Recherche/Suchzeitraum:

- on 13th March 2016

Qualitätsbewertung der Studien:

- Cochrane approach

Ergebnisse

Anzahl eingeschlossener Studien:

- 17 studies with a total of 4971 patients

Charakteristika der Population:

Characteristics of included studies.

Study	Age, range (years)	Number of concomitant AEDs	Interventions	Starting dose	Titration	Treatment maintenance period (weeks)
Double-blind randomized controlled trials comparing brivaracetam with placebo						
French et al. [21]	30.9 ± 11.6 to 35.3 ± 13.7	1 AED (35%) 2 AED (59%) ≥3 AED (6%)	Placebo BRV 5 mg/d BRV 20 mg/d BRV 50 mg/d	No titration	No titration	7
Van Paesschen et al. [22]	34.4 ± 10.1 to 40 ± 11.7 (16.5–65.6)	1 AED (18%) 2 AED (75%) ≥3 AED (6%)	Placebo BRV 50 mg/d BRV 150 mg/d	25 mg/d	25mg/w or 50 mg/w	7
Biton et al. [23]	37.3 ± 13.3 to 38.9 ± 12.3	1 AED (14%) 2 AED (78%) ≥3 AED (7%)	Placebo BRV 5 mg/d BRV 20 mg/d BRV 50 mg/d	No titration	No titration	12
Ryvlin et al. [24]	37.2 ± 13.1 (NR)	1 AED (17%) 2 AED (79%) ≥3 AED (4%)	Placebo BRV 20 mg/d BRV 50 mg/d BRV 100 mg/d	No titration	No titration	12
Klein et al. [25]	39.1 ± 13.4 to 39.8 ± 12.8	1 AED (28%) 2 AED (71%) ≥3 AED (0.5%)	Placebo BRV 100 mg/d BRV 200 mg/d	No titration	No titration	12
Double-blind randomized controlled trials comparing perampanel with placebo						
French et al. [27]	36 ± 14.5 (12–77)	1 AED (16%) 2 AED (56%) 3 AED (29%) >3 AED (0)	Placebo PER 8 mg/d PER 12 mg/d	2 mg/d	2 mg/w	13
Krauss et al. [28]	33.4 ± 12.6 to 34.6 ± 12.8 (NR)	1 AED (15%) 2 AED (48%) 3 AED (37%) >3 AED (0)	Placebo PER 2 mg/d PER 4 mg/d PER 8 mg/d	1 mg/d	2 mg/w	13
French et al. [29]	34.4 ± 14.4 to 36.7 ± 14.4 (NR)	1 AED (11%) 2 AED (51%) 3 AED (39%) >3 AED (0)	Placebo PER 8 mg/d PER 12 mg/d	2 mg/d	2 mg/w	13
Krauss et al. [30]	40.7 ± 11.99 to 45.5 ± 12.05 (NR)	1 AED (4%) 2 AED (65%) 3 AED (31%) >3 AED (0)	Placebo PER 12 mg/d	2 mg/d	2 mg/2 w	4
Double-blind randomized controlled trials comparing eslicarbazepine with placebo						
Elger et al. [31]	39.3 ± 11.4 to 40.4 ± 10.8 (19–61)	1 AED (NR) 2 AED (NR)	Placebo ESL 800 mg/d ESL 1200 mg/d	400 mg/d	Target dose of 800 or 1200 mg achieved in 4 w	16
Elger et al. [32]	37 ± 11.9 to 41.3 ± 12 (18–76)	1 AED (36%) 2 AED (64%) 3 AED (0.4%) >3 AED (0)	Placebo ESL 400 mg/d ESL800 mg/d ESL 1200 mg/d	400 mg/d	Target dose achieved in 2 w	12
Gil Nagel et al. [33]	36 ± 11.4 to 37.7 ± 12.1 (17–77)	1 AED (20%) 2 AED (74%) 3 AED (6%) >3 AED (0.4%)	Placebo ESL 800 mg/d ESL 1200 mg/d	400 mg/d	Target dose achieved in 2 w	12
Ben-Menachem et al. [34]	35 ± NR (18–69)	1 AED (18%) 2 AED (72%) 3 AED (37%) >3 AED (1%)	Placebo ESL 400 mg/d ESL 800 mg/d ESL 1200 mg/d	400 or 800 mg/d	Patients allocated to 1200 mg/d achieved this dose in 2 w	14
Sperling et al. [35]	48 ± NR to 39 ± NR (16–71)	1 AED (28%) 2 AED (71%) ≥3 AED (0)	Placebo ESL 800 mg/d ESL 1200 mg/d	400 or 800 mg/d	Target dose achieved in 1 w	12
Double-blind randomized controlled trials comparing lacosamide with placebo						
Ben-Menachem et al. [36]	39.9 ± 11.3 (18–65)	1 AED (16%) 2 AED (84%) 3 AED (0) >3 AED (0)	Placebo LCM 200 mg/d LCM 400 mg/d 600 mg/d	100 mg/d	Titration rate of 100 mg/w until target dose	12
Halász et al. [37]	37.8 ± 11.9 (16–70)	1 AED (13%)	Placebo	100 mg/d		12

Qualität der Studien:

- All studies were double-blind RCT adopting adequate random sequence generation and allocation concealment (low risk of selection bias). Performance and detection bias were also low in each included study. No study except one reported incomplete outcomes (low risk of attrition bias). In the one study, however, there was a high proportion of missing data (11/47 from the placebo group, 8/50 from the ESL once daily group, and 12/37 from the ESL twice daily group; unclear risk of attrition bias, due to lack of reasons for missing data).

Studienergebnisse:

- Indirect comparison reference-based meta-analysis
  - 50% responder rate: no difference between BRV and LCM, ESL or PER both at minimum and at highest effective recommended daily dosages.
  - Seizure freedom: no difference between BRV and LCM, ESL or PER both at minimum and at highest effective recommended daily dosages.
  - Treatment-emergent adverse events: statistically significant lower risk of TEAEs for BRV 50 mg compared to PER 8 mg, and for BRV 200 mg compared to ESL 1200 mg or PER 12 mg. No difference was found between BRV 200 mg and LCM 400 mg and between BRV 50 mg and LCM 200 mg or ESL 800 mg.
  - Treatment-emergent adverse events leading to study/treatment discontinuation: no difference between BRV and LCM, ESL or PER both at minimum and at highest effective recommended daily dosages in terms of TEAEs leading to study/ treatment discontinuation.

- Sensitivity analysis → to evaluate the effect of clinical heterogeneity in terms of number of concomitant AEDs.
  - All the 5 included RCTs on BRV enrolled <10% of patients on ≥3 AEDs. We therefore conducted a sensitivity analysis excluding seven trials (four PER, one ESL, and two LCM enrolling >10% of patients on ≥3 AEDs. Sensitivity analysis showed no difference between BRV and LCM or PER both at minimum and at highest effective recommended daily dosages in 50% responder rate, in seizure freedom, and in TEAEs. Brivaracetam 200 mg was associated with lower TEAEs overall, and with lower TEAEs leading to discontinuation than ESL 1200 mg; this difference was not demonstrated at minimum effective recommended daily dosage (BRV 50 mg/day versus ESL 800 mg/day).

Anmerkung/Fazit der Autoren

In conclusion, indirect comparison meta-analysis do not demonstrate a significant difference in efficacy between BRV compared to LCM, ESL or PER, and might suggest a better tolerability than ESL, and possibly also PER, when these drugs are used at the highest effective recommended dose. Although we found no clinically or methodologically relevant discrepancies or significant statistical heterogeneity across included trials, our results are based on indirect evidence which provides higher grade of uncertainty than that from direct comparison. Ideally, future direct head-to-head trials directly comparing these AEDs should be conducted to draw definite conclusions on comparative efficacy and tolerability of BRV with LCM, ESL, or PER. However, it is unlikely that RCTs directly comparing novel AEDs will be conducted, as drug companies would not carry the risk of performing a comparison which may prove unfavorable for the own test AED.

3.4 Leitlinien

Scottish Intercollegiate Guidelines Network 2015 [20].

Scottish Intercollegiate Guidelines Network (SIGN)

Diagnosis and management of epilepsy in adults.

Leitlinienorganisation/Fragestellung

This guideline updates SIGN 70: Diagnosis and management of epilepsy in adults to reflect the most recent evidence.

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, Cinahl, PsycINFO and the Cochrane Library. The year range covered was 2001–2013.
- In September 2018, this guideline was updated to take account of new drug safety advice from the Medicines and Healthcare products Regulatory Agency (MHRA), published in April 2018, relating to use of valproate medicines in women and girls of childbearing potential. Warnings have been inserted where relevant in sections 4 and 5 to reflect this advice.

LoE/GoR

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

Sonstige methodische Hinweise

- First published May 2015 Updated September 2018

Recommendations

MANAGEMENT OF DRUG-RESISTANT EPILEPSY

Drug-resistant epilepsy has been defined as failure to achieve sustained seizure freedom after trials of two tolerated and appropriate AED schedules (whether as monotherapies or in combination). The majority of patients with newly-diagnosed epilepsy respond well to AEDs. Failure to do so may be due to:

- an incorrect diagnosis of epilepsy[3, 103]
- an inappropriate choice of AED for the epilepsy syndrome[103, 104]
- failure to take the prescribed AED
- an underlying cerebral neoplasm, metabolic condition, or immune process
- concurrent drug or alcohol misuse.

1^{++}
2^{+}
4

Given a correct diagnosis of epilepsy, failure to control seizures completely with the first well-tolerated AED is a predictor of drug-resistant epilepsy.[85, 105] The choice of adjunctive AED will depend on a number of factors including sex, reproductive potential, age, concomitant medications, pre-existing or comorbid conditions, other medical or psychiatric conditions and adverse effect profiles. | 2+

Once two AEDs have failed as monotherapy the chance of seizure freedom with further monotherapy is low.[85] Improvement in seizure control may be obtained by combining AEDs.[106, 107] | 2++ 2+ 4

Once the decision has been made to use combination therapy, the patient should be established on the best combination at the optimal dose, ie one that produces best efficacy with fewest adverse effects.[108] A range of different AEDs appropriate to the epilepsy syndrome should be added as necessary in sequence, increasing the dose of each slowly to obtain the best response. Deciding on the best combination may be a matter of trial and error, although some evidence exists for enhanced efficacy of lamotrigine/sodium valproate[109] and lacosamide/non-sodium channel blocking drug.[110] | 2+ 4

Use of sodium valproate must take into account MHRA safety advice, issued in April 2018, on use of valproate medicines in women and girls of childbearing potential and the conditions of the Pregnancy Prevention Programme *(see section 5.2.0)*.[454]

The aim should be seizure freedom on the lowest number of drugs. With good response, consideration should be given to withdrawal of the baseline AED. Where an encouraging but suboptimal effect is obtained with a particular combination, it may be worthwhile trying the addition of a small dose of a third AED.

The law of diminishing returns may require patient and doctor to accept the persistence of some seizures once a range of treatment options has failed and where surgery is not an option *(see section 4.9)*. Adequacy of seizure control must be balanced with optimal quality of life. Little will be lost by carefully reducing the drug burden in a patient with continuing seizure activity aiming for the most effective combination of two or at most three AEDs. Producing less intrusive episodes, abolishing tonic-clonic seizures, preventing falls and decreasing automatisms can be acceptable end points for some patients.

C **Failure to respond to appropriate antiepileptic drugs should prompt a review of the diagnosis of epilepsy and adherence to medication.**

D **Combination therapy should be considered when treatment with two first-line antiepileptic drugs has failed or when improved control occurs during the process of phased substitution.**

A **Carbamazepine, gabapentin, lacosamide, lamotrigine, levetiracetam, oxcarbazepine, perampanel, pregabalin, topiramate, sodium valproate and zonisamide may be used in the adjunctive treatment of focal epilepsy.**

A **Lamotrigine, levetiracetam, ethosuximide, sodium valproate and topiramate may be used in the adjunctive treatment of generalised epilepsy.**

B **The choice of drugs in combination should be matched to the patient's seizure type(s) and should, where possible, be limited to two or at most three antiepileptic drugs.**

✓ Sodium valproate should not be used in women and girls of childbearing potential unless there is no suitable alternative and a Pregnancy Prevention Programme is in place.

Kanner A. M. et al., 2018 [15].

American Academy of Neurology (AAN)

Practice guideline update summary: Efficacy and tolerability of the new antiepileptic drugs II: Treatment-resistant epilepsy: Report of the Guideline Development, Dissemination, and Implementation Subcommittee of the American Academy of Neurology and the American Epilepsy Society.

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

- **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

For adult patients with TR focal epilepsy, are these AEDs effective as adjunctive therapy in reducing seizure frequency?

- For TRAFE, immediate-release PGB and PER are established as effective to reduce seizure frequency (Level A). LCM, ESL, and TPM-XR use should also be considered to decrease seizure frequency in this population (Level B). VGB and RFN should be considered established as effective for decreasing seizure frequency in TRAFE (Level A) but are not first-line agents (retinopathy risk with VGB and modest benefit with RFN). EZG use should be considered to decrease seizure frequency in this population (Level B) but carries a serious

risk of skin and retinal discoloration. CLB and OXC-XR use may be considered to decrease seizure frequency in TRAFE (Level C).

For adult patients with TR focal epilepsy, are these AEDs effective in reducing seizure frequency when used as monotherapy?

- ESL use may be considered to decrease seizure frequency as monotherapy for TRAFE (Level C).
- Data are insufficient to recommend the use ofsecond- and the other third-generation AEDs as monotherapy in TRAFE (Level U).

For adult and pediatric patients with TR GE, are these AEDs effective in reducing seizure frequency when used as adjunctive therapy (compared with no adjunctive therapy)?

- For add-on therapy for GE, immediate-release and LTG-XR use should be considered as add-on therapy to decrease seizure frequency in treating adults with TR GTC seizures secondary to GE (Level B). Levetiracetam use should be considered to decrease seizure frequency as add-on therapy for TR GTC seizures and for TR JME (Level B).

For adult and pediatric patients with LGS, are these AEDs effective as adjunctive therapy in reducing seizure frequency (compared with no adjunctive therapy)?

- For LGS, RUF use should be considered established as effective to decrease seizure frequency as add-on therapy (Level A), and CLB use should be considered (Level B).

4 Detaillierte Darstellung der Recherchestrategie

Cochrane Library - Cochrane Database of Systematic Reviews (Issue 1 of 12, January 2020) am 09.03.2020

#	Suchfrage
1	[mh epilepsy]
2	[mh "epilepsies, partial"]
3	[mh "drug resistant epilepsy"]
4	(epilep* OR seizure* OR antiepilep*):ti
5	#1 or #2 or #3 or #4
6	#5 with Cochrane Library publication date from Mar 2015 to Mar 2020

Systematic Reviews in Medline (PubMed) am 11.03.2020

#	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]
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 (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 ("2015/03/01"[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 11.03.2020

#	**Suchfrage**
1	epilepsy[mh]
2	epilepsies, partial[mh]
3	drug resistant epilepsy[mh]
4	(epilep*[ti] OR seizure*[ti] OR antiepilep*[ti] OR convuls*[ti])
5	#1 OR #2 OR #3 OR #4
6	(#5) AND (Guideline[ptyp] OR Practice Guideline[ptyp] OR guideline*[Title] OR Consensus Development Conference[ptyp] OR Consensus Development Conference, NIH[ptyp] *OR recommendation*[ti])*
7	(#6) AND ("2015/03/01"[PDAT] : "3000"[PDAT])
8	(#7) NOT ((comment[ptyp]) OR letter[ptyp])
9	(#8) NOT (animals[MeSH:noexp] NOT (Humans[mh] AND animals[MeSH:noexp]))
10	(#9) NOT (retracted publication [pt] OR retraction of publication [pt])

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2. **Bresnahan R, Martin-McGill KJ, Hutton JL, Marson AG.** Tiagabine add-on therapy for drug-resistant focal epilepsy. Cochrane Database of Systematic Reviews [online]. 2019(10):Cd001908. URL: http://dx.doi.org/10.1002/14651858.CD001908.pub4.

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