Gemeinsamer Bundesausschuss

# Kriterien zur Bestimmung der zweckmäßigen Vergleichstherapie

# und

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

# und

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

## Vorgang: 2023-B-352 Cannabidiol

Stand: März 2023

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

**Cannabidiol**
**[Krampfanfälle im Zusammenhang mit Tuberöser Sklerose]**

| **Kriterien gemäß 5. Kapitel § 6 VerfO** | |
|---|---|
| Sofern als Vergleichstherapie eine Arzneimittelanwendung in Betracht kommt, muss das Arzneimittel grundsätzlich eine Zulassung für das Anwendungsgebiet haben. | Siehe Übersicht „II. Zugelassene Arzneimittel im Anwendungsgebiet“. |
| Sofern als Vergleichstherapie eine nicht-medikamentöse Behandlung in Betracht kommt, muss diese im Rahmen der GKV erbringbar sein. | Epilepsiechirurgische Maßnahmen |
| Beschlüsse/Bewertungen/Empfehlungen des Gemeinsamen Bundesausschusses zu im Anwendungsgebiet zugelassenen Arzneimitteln/nicht-medikamentösen Behandlungen | Für Krampfanfälle im Zusammenhang mit Tuberöser Sklerose:<br>• Beschluss zu Cannabidiol am 04.11.2021 (TCS)<br>Im Anwendungsgebiet Epilepsie:<br>• Beschluss zu Cannabidiol am 15.04.2021 (LGS, DS)<br>• Beschluss zu Cenobamat vom 19.11.2021<br>• Beschluss zu Vigabatrin vom 19.12.2019<br>• Beschluss zu Brivaracetam vom 04.08.2016, 17.01.2019 und 01.09.2022<br>• Beschluss zu Perampanel vom 06.11.2014, 17.05.2018 und 03.06 2021<br>• Beschluss zu Retigabin vom 03.07.2014 |
| Die Vergleichstherapie soll nach dem allgemein anerkannten Stand der medizinischen Erkenntnisse zur zweckmäßigen Therapie im Anwendungsgebiet gehören. | Siehe systematische Literaturrecherche |

## II. Zugelassene Arzneimittel im Anwendungsgebiet

| **Wirkstoff**<br>**ATC-Code**<br>**Handelsname** | **Anwendungsgebiet**<br>(Text aus Fachinformation) |
|---|---|
| Zu bewertendes Arzneimittel: | |
| Cannabidiol<br>N03AX2<br>Epidylex® | „Epidyolex wird als Zusatztherapie von Krampfanfällen im Zusammenhang mit Tuberöser Sklerose (TSC) bei Patienten ab 2 Jahren angewendet.” |
| **Zulassung für Tuberöse Sklerose** | |
| Everolimus<br>L01EG02<br>Votubia®<br>Tabletten<br>zur Herstellung<br>einer Suspension<br>zum Einnehmen | Refraktäre Krampfanfälle in Zusammenhang mit einer tuberösen Sklerose (tuberous sclerosis complex, TSC)<br>Votubia wird als Begleittherapie bei Patienten ab 2 Jahren mit refraktären partiellen Krampfanfällen, mit oder ohne sekundäre Generalisierung, in Zusammenhang mit TSC angewendet. |
| **Zulassung für die Behandlung epileptischer Anfälle** | |
| Perampanel<br>N03AX22<br>Fycompa® | Fycompa (Perampanel) wird angewendet als Zusatztherapie bei<br>– fokalen Anfällen mit oder ohne sekundäre(r) Generalisierung bei Patienten ab 4 Jahren.<br>– primär generalisierten tonisch-klonischen Anfällen bei Patienten ab 7 Jahren mit idiopathischer generalisierter Epilepsie (IGE). |
| Brivaracetam<br>N03AX23<br>Briviact | Briviact wird angewendet zur Zusatzbehandlung fokaler Anfälle mit oder ohne sekundäre Generalisierung bei Erwachsenen, Jugendlichen und Kindern ab 2 Jahren mit Epilepsie. |
| Oxcarbazepin<br>N03AF02 | Zur Behandlung von fokalen Anfällen mit oder ohne sekundär generalisierten tonisch- klonischen Anfällen.<br>Zur Monotherapie oder Kombinationstherapie von Erwachsenen und Kindern ab 6 Jahren. |

| II. Zugelassene Arzneimittel im Anwendungsgebiet | |
|---|---|
| Eslicarbazepin<br>N03AF04<br>Zebinix® | – Monotherapie zur Behandlung partieller epileptischer Anfälle mit oder ohne sekundärer Generalisierung bei Erwachsenen mit neu diagnostizierter Epilepsie.<br>– Begleittherapie bei Erwachsenen, Jugendlichen und Kindern über 6 Jahren mit partiellen epileptischen Anfällen mit oder ohne sekundärer Generalisierung. |
| Carbamazepin<br>N03AF01 | Epilepsie<br>– Einfache partielle Anfälle (fokale Anfälle)<br>– Komplexe partielle Anfälle (psychomotorische Anfälle)<br>– Grand mal, insbesondere fokaler Genese (Schlaf-Grand mal, diffuses Grand mal)<br>– gemischte Epilepsieformen |
| Valproinsäure<br>N03AG01 | Behandlung von<br>– generalisierten Anfällen in Form von Absencen, myoklonischen Anfällen und tonisch-klonischen Anfällen<br>– fokalen und sekundär-generalisierten Anfällen und zur Kombinationsbehandlung bei anderen Anfallsformen, z. B. fokalen Anfällen mit einfacher und komplexer Symptomatologie sowie fokalen Anfällen mit sekundärer Generalisation, wenn diese Anfallsformen auf die übliche antiepileptische Behandlung nicht ansprechen. |
| Vigabatrin<br>N03AG04<br>Sabril® | 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]<br>N03AG06<br>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<br>N03AX09 | Erwachsene und Jugendliche ab 13 Jahren:<br>– Zusatz- oder Monotherapie partieller und generalisierter Anfälle einschließlich tonisch-klonischer Anfälle<br>Kinder und Jugendliche von 2 bis 12 Jahren:<br>– Zusatztherapie bei partiellen und generalisierten Anfällen einschließlich tonisch-klonischer Anfälle sowie […] |

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

| II. Zugelassene Arzneimittel im Anwendungsgebiet | |
|---|---|
| | – Monotherapie typischer Absencen. |
| Topiramat<br>N03AX11 | – Monotherapie bei Erwachsenen, Jugendlichen und Kindern ab 6 Jahren mit fokalen Krampfanfällen mit oder ohne sekundär generalisierten Anfällen und primär generalisierten tonisch-klonischen Anfällen.<br>– Zusatztherapie bei Kindern ab 2 Jahren, Jugendlichen und Erwachsenen mit fokalen Anfällen mit oder ohne sekundärer Generalisierung oder primär generalisierten tonisch-klonischen Anfällen und zur Behandlung von Anfällen, die mit dem Lennox-Gastaut-Syndrom assoziiert sind. |
| Gabapentin<br>N03AX12 | – Zusatztherapie bei Erwachsenen und Kindern von 6 Jahren und älter mit partiellen Anfällen mit und ohne sekundäre Generalisierung<br>– Monotherapie bei Erwachsenen und Jugendlichen von 12 Jahren und älter mit partiellen Anfallen mit und ohne sekundäre Generalisierung indiziert. |
| Levetiracetam<br>N03AX14<br>Keppra® | 1. Zur Monotherapie<br>– partieller Anfälle mit oder ohne sekundäre Generalisierung bei Erwachsenen und Jugendlichen ab 16 Jahren mit neu diagnostizierter Epilepsie.<br>2. Zusatzbehandlung<br>– partieller Anfälle mit oder ohne sekundärer Generalisierung bei Erwachsenen, Kindern und Säuglingen ab 1 Monat mit Epilepsie.<br>– primär generalisierter tonisch-klonischer Anfälle bei Erwachsenen und Jugendlichen ab 12 Jahren mit Idiopathischer Generalisierter Epilepsie |
| Zonisamid<br>N03AX15<br>Zonegran® | – Monotherapie für die Behandlung von fokalen Anfällen mit oder ohne sekundäre Generalisierung bei Erwachsenen mit neu diagnostizierter Epilepsie<br>– Zusatztherapie für die Behandlung von fokalen Anfällen mit oder ohne sekundäre Generalisierung bei Erwachsenen, Jugendlichen und Kindern ab 6 Jahren. |
| Pregabalin<br>N03AX16<br>Lyrica® | Lyrica wird angewendet zur Zusatztherapie von partiellen Anfällen mit und ohne sekundäre Generalisierung im Erwachsenenalter. |
| Lacosamid<br>N03AX18<br>Vimpat® | Indiziert zur Monotherapie und Zusatzbehandlung fokaler Anfälle mit oder ohne sekundäre Generalisierung bei Erwachsenen, Jugendlichen und Kindern ab 4 Jahren mit Epilepsie. |

| II. Zugelassene Arzneimittel im Anwendungsgebiet | |
|---|---|
| Clobazam<br>N05BA09<br>Frisium® | Zusatztherapie bei Patienten mit epileptischen Anfällen, die mit einer Standardbehandlung – bestehend aus einem oder mehreren Antiepileptika – nicht anfallsfrei waren.<br><br>(Aus FI 4.2: Dosierungsempfehlungen für Kinder ab 6 Jahren) |
| Clonazepam<br>N03AE01<br>Clonazepam-neuraxpharm® | Clonazepam neuraxpharm ist als Zusatztherapie oder in Fällen von Nichtansprechen auf andere Arzneimittel zur Behandlung der meisten Formen der Epilepsie, insbesondere von Absencen, einschließlich atypischen Absencen, Lennox-Gastaut-Syndrom sowie myoklonischen und atonischen Anfällen indiziert. |
| Primidon<br>N03AA03<br>Liskantin® | - 1. Epileptische Anfälle, besonders Grandmal-Anfälle, fokale Anfälle (Jackson-Anfälle, Adversivkrämpfe, psychomotorische Anfälle u.a.), myoklonische Anfälle des Jugendalters (Impulsiv-Petit-mal).<br>- 2. Bei Absencen und anderen kindlichen Petit-mal-Epilepsien ist Primidon bei entsprechenden EEG-Anzeichen als Grand-mal-Prophylaxe indiziert.<br>[…]<br><br>*[Aus FI 5.3.:*<br>*Wenn die Behandlung mit einem anderen Antikonvulsivum allein nicht ausreicht […], erhalten die Patienten […]]* |
| Phenytoin<br>N03AB02<br>z.B. Phenhydan® | - 1. Fokal eingeleitete generalisierende und generalisierte tonisch-klonische Anfälle (Grand mal) sowie einfache (z.B. Jackson-Anfälle) und komplexe Partialanfälle (z.B. Temporallappenanfälle).<br>- 2. Prophylaxe von Krampfanfällen, z.B. bei neurochirurgischen Eingriffen.<br>[…] |
| Phenobarbital<br>N03AA02<br>Luminal® | - Verschiedene Formen der Epilepsie (Grand mal, Impulsiv-Petit-mal); Grand mal-Schutz bei Petit mal-Anfällen im Kindesalter. |
| Ethosuximid<br>N03AD01 | - Pyknoleptische Absencen sowie komplexe und atypische Absencen.<br>- Myoklonisch-astatisches Petit mal und myoklonische Anfälle des Jugendlichen (Impulsiv-Petit-mal), wenn andere Arzneimittel nicht wirksam waren und/oder nicht vertragen wurden. |

| II. Zugelassene Arzneimittel im Anwendungsgebiet | |
|---|---|
| Ethosuximid-neuraxpharm | |
| Mesuximid<br>N03AD03<br>Petinutin® | - Bei Petit Mal im Rahmen gemischter Epilepsien.<br>- Bei Absencen, deren Behandlung mit anderen Antiepileptika nicht zum gewünschten Erfolg geführt hat. |
| Cenobamat<br>N03AX25<br>Ontozry Tabletten | - 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 antiepileptischen Arzneimitteln nicht ausreichend kontrolliert sind. |
| **Zulassung für die Behandlung infantiler Spasmen** | |
| Vigabatrin<br>N03AG04<br>Sabril® | Als Monotherapie zur Behandlung infantiler Spasmen (West-Syndrom). |
| Tetracosactidhexa acetat<br>H01AA02<br>Synacthen-Depot ® und Synacthen ® | Synacthen-Depot®<br>**West-Syndrom**<br><br>Synacthen®<br>Therapeutisch beim **West-Syndrom** anstelle von Synacthen Depot 1 mg, wenn die i.v. Gabe einer i.m.Injektion vorzuziehen ist. |
| Prednison<br>H02AB07<br>z.B. Cutason® 5, 20 und 50 mg Tabletten | Neurologie (DS: a)<br>– **BNS-Krämpfe** |
| Prednisolon<br>H02AB06 | Neurologie (DS a)<br>Myasthenia gravis (Mittel der 1. Wahl ist Azathioprin), chronisches Guillain-Barré-Syndrom, Tolosa-Hunt-Syndrom, Polyneuropathie bei monoklonaler Gammopathie, Multiple Sklerose (zum oralen Ausschleichen nach hochdosierter parenteraler Glukokortikoidgabe im Rahmen eines akuten Schubes), **BNS-Krämpfe**. |

| II. Zugelassene Arzneimittel im Anwendungsgebiet | |
|---|---|
| z.B. Dermosolon® 5, 10 und 20 mg Tabletten | |
| Clonazepam N03AE01 Clonazepam-neuraxpharm® | Bei **infantilen Krampfanfällen (inklusive des West-Syndroms)** und tonisch-klonischen Anfällen ist Clonazepam neuraxpharm ausschließlich als Zusatztherapie oder bei Nichtansprechen auf andere Arzneimittel indiziert. |
| Nitrazepam N05CD02 z.B. Nitrazepam-neuraxpharm 5 und 10 mg Tabletten | – Behandlung von **BNS-Krämpfen (West-Syndrom)** des Säuglings und Kleinkindes. |

Quellen: AMice-Datenbank, Fachinformationen

Gemeinsamer Bundesausschuss

## Abteilung Fachberatung Medizin

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

# Vorgang: 2022-B-352 (Cannabidiol)

| | |
|---|---|
| Auftrag von: | Abt. AM |
| Bearbeitet von: | Abt. FB Med |
| Datum: | 13. März 2023 |

# Inhaltsverzeichnis

# Abkürzungsverzeichnis

| | |
|---|---|
| AWMF | Arbeitsgemeinschaft der wissenschaftlichen medizinischen Fachgesellschaften |
| CBD | Cannabidiol |
| DS | Dravet syndrome |
| G-BA | Gemeinsamer Bundesausschuss |
| GoR | Grade of Recommendations |
| HR | Hazard Ratio |
| IQWiG | Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen |
| ISS | infantile spasm syndrome |
| KI | Konfidenzintervall |
| LGS | Lennox-Gataut syndrome |
| LoE | Level of Evidence |
| NICE | National Institute for Health and Care Excellence |
| OR | Odds Ratio |
| RR | Relatives Risiko |
| SIGN | Scottish Intercollegiate Guidelines Network |
| TRIP | Turn Research into Practice Database |
| TSC | Tuberöse Sklerose |
| WHO | World Health Organization |

# 1 Indikation

Epidyolex wird als Zusatztherapie von Krampfanfällen im Zusammenhang mit Tuberöser Sklerose (TSC) bei Patienten ab 2 Jahren angewendet.

*Hinweis zur Synopse: Informationen hinsichtlich nicht zugelassener Therapieoptionen sind über die vollumfängliche Darstellung der Leitlinienempfehlungen dargestellt.*

# 2 Systematische Recherche

Es wurde eine systematische Literaturrecherche nach systematischen Reviews, Meta-Analysen und evidenzbasierten systematischen Leitlinien zur Indikation *Tuberöser Sklerose (TSC)* durchgeführt und nach PRISMA-S dokumentiert [A]. Die Recherchestrategie wurde vor der Ausführung anhand der PRESS-Checkliste begutachtet [B]. Es erfolgte eine Datenbankrecherche ohne Sprachrestriktion in: The Cochrane Library (Cochrane Database of Systematic Reviews), PubMed. Die Recherche nach grauer Literatur umfasste eine gezielte, iterative Handsuche auf den Internetseiten von Leitlinienorganisationen. Ergänzend wurde eine freie Internetsuche (*https://www.google.com/*) unter Verwendung des privaten Modus, nach aktuellen deutsch- und englischsprachigen Leitlinien durchgeführt.

Der Suchzeitraum wurde auf die letzten fünf Jahre eingeschränkt und die Recherche am 12.01.2023 abgeschlossen. Die detaillierte Darstellung der Recherchestrategie inkl. verwendeter Suchfilter sowie eine Angabe durchsuchter Leitlinienorganisationen ist am Ende der Synopse aufgeführt. Mit Hilfe von EndNote wurden Dubletten identifiziert und entfernt. Die Recherche ergab 120 Referenzen.

In einem zweistufigen Screening wurden die Ergebnisse der Literaturrecherche bewertet. 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 Referenzen 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 5 Referenzen eingeschlossen. Es erfolgte eine synoptische Darstellung wesentlicher Inhalte der identifizierten Referenzen.

# 3 Ergebnisse

## 3.1 Cochrane Reviews

Es wurden keine relevanten Cochrane Reviews identifiziert.

## 3.2 Systematische Reviews

Es wurden keine relevanten Systematischen Reviews identifiziert.

## 3.3 Leitlinien

**National Institute for Health and Care Excellence (NICE), 2022 [3].**

Epilepsies in children, young people and adults

**Zielsetzung/Fragestellung**

This guideline covers diagnosing and managing epilepsy in children, young people and adults in primary and secondary care. It aims to improve diagnosis and treatment for different seizure types and epilepsy syndromes, and reduce the risks for people with epilepsy.

**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:

- Medical Literature Analysis and Retrieval System Online (MEDLINE) and MEDLINE-in-Process, Embase, Cochrane Central Register of Controlled Trials (CCTR), Cochrane Database of Systematic Reviews (CDSR), Database of Abstracts of Reviews of Effects (DARE) and Health Technology Assessments (HTA).
- All searches were updated on April 2021

LoE/GoR

- Cochrane RoB2 / GRADE
- Anmerkung FBMed: NICE verzichtet in der Regel auf die Auszeichnung der Stärke der Empfehlung, sondern realisiert das über die Formulierung (Wording):
  - must/must not
  - should/should not
  - could/could not
  - For recommendations on interventions that should be used (strong) use direct instructions rather than using the word „should“. Use verbs such as „offer“, „refer“, „advise“, and „discuss“

**Empfehlungen**

*Anmerkung: Die Empfehlungen des NICE zur Tuberösen Sklerose beziehen sich überwiegend auf die Infantilen Spasmen bei Kindern < 2 Jahren (Abschnitt 6.3 in der Leitlinie). Für die Behandlung von Personen > 2 Jahren wurden die Empfehlungen nach Anfallsart aufgeführt. Die Darstellung der Hintergrundinformationen aus der Leitlinie beschränkt sich auf die Empfehlungen, die sich explizit auf die Tuberöse Sklerose beziehen.*

Principles of treatment, safety, monitoring and withdrawal

- 4.1.3 Use a single antiseizure medication (monotherapy) to treat epilepsy whenever possible.
- 4.1.4 Review the diagnosis of epilepsy if seizures continue despite an optimal dose of a first-line antiseizure medication.
- 4.1.5 If first-line monotherapy is unsuccessful and epilepsy diagnosis remains confirmed, try monotherapy with another antiseizure medication, using caution during the changeover period:
    - Increase the dose of the second medicine slowly while maintaining the dose of the first medicine.
    - If the second medicine is successful, slowly taper off the dose of the first medicine.
    - If the second medicine is unsuccessful, slowly taper off the dose of the second medicine and consider an alternative.
- 4.1.6 If monotherapy is unsuccessful, consider trying an add-on treatment.
- 4.1.7 When starting an add-on treatment, carefully titrate the additional medicine and review treatment frequently, including monitoring for adverse effects such as sedation.
- 4.1.8 If trials of add-on treatment do not result in a reduction in seizures, use the regimen that provides the best balance between effectiveness and tolerability of side effects.

5.1 Generalised tonic-clonic seizures

**Monotherapy**

- 5.1.1 Offer sodium valproate as first-line monotherapy for generalised tonic-clonic seizures in:
    - boys and men
    - girls aged under 10 years and who are unlikely to need treatment when they are old enough to have children
    - women who are unable to have children.
- 5.1.2 Offer lamotrigine or levetiracetam as first-line monotherapy for generalised tonic-clonic seizures in women and girls able to have children (including young girls who are likely to need treatment when they are old enough to have children). If the first choice is unsuccessful, offer the other of these options. In April 2022, these were off-label uses of lamotrigine in children under 13 years and levetiracetam in adults and children. See NICE's information on prescribing medicines.
- 5.1.3 If first-line monotherapy with sodium valproate is unsuccessful for generalised tonic-clonic seizures, offer lamotrigine or levetiracetam as second-line monotherapy treatment. If the first choice is unsuccessful, try the other of these options. In April 2022, these were off-label uses of lamotrigine in children under 13 years and levetiracetam in adults and children. See NICE's information on prescribing medicines.
- 5.1.4 Do not offer sodium valproate monotherapy for generalised tonic-clonic seizures in women and girls able to have children (including young girls who are likely to need treatment when they are old enough to have children), unless:
    - other treatment options are unsuccessful

  - the risks and benefits have been fully discussed, including the risks to an unborn child
  - the likelihood of pregnancy has been taken into account and a pregnancy prevention programme put in place, if appropriate.
- Follow the MHRA safety advice on valproate use by women and girls.

**Add-on treatment**

For guidance on safe prescribing and managing withdrawal of clobazam in adults, see NICE's guideline on medicines associated with dependence or withdrawal symptoms.

- 5.1.5 If monotherapy is unsuccessful in people with generalised tonic-clonic seizures, consider 1 of the following first-line add-on treatment options:
  - clobazam
  - lamotrigine
  - levetiracetam
  - perampanel
  - sodium valproate, except in women and girls able to have children
  - topiramate
  - If the first choice is unsuccessful, consider the other first-line add-on options. In April 2022, these were off-label uses of clobazam as add-on therapy in children under 6 months, lamotrigine in children under 2 years, levetiracetam in children under 12 years, perampanel in children under 7 years, and topiramate in children under 2 years. See NICE's information on prescribing medicines.
- 5.1.6 If first-line add-on treatments tried are unsuccessful in people with generalised tonic-clonic seizures, consider 1 of the following second-line add-on treatment options:
  - brivaracetam
  - lacosamide
  - phenobarbital
  - primidone
  - zonisamide
  - If the first choice is unsuccessful, consider the other second-line add-on options. In April 2022, these were off-label uses of brivaracetam in adults and children, lacosamide in children under 4 years, and zonisamide in adults and children. See NICE's information on prescribing medicines.
- 5.1.7 Do not offer sodium valproate as an add-on treatment for generalised tonic-clonic seizures in women and girls able to have children (including young girls who are likely to need treatment when they are old enough to have children), unless:
  - other treatment options are unsuccessful
  - the risks and benefits have been fully discussed, including the risks to an unborn child
  - the likelihood of pregnancy has been taken into account and a pregnancy prevention programme put in place, if appropriate.
  - Follow the MHRA safety advice on valproate use by women and girls.

**Other treatment considerations**

5.1.8 Be aware that the following antiseizure medications may exacerbate seizures in people with absence or myoclonic seizures, including in juvenile myoclonic epilepsy:

  - carbamazepine

- gabapentin
- lamotrigine (for myoclonic seizures)
- oxcarbazepine
- phenytoin
- pregabalin
- tiagabine
- vigabatrin.

5.2 Focal seizures with or without evolution to bilateral tonic-clonic seizures

**Monotherapy**

- 5.2.1 Consider lamotrigine or levetiracetam as first-line monotherapy for people with focal seizures. If the first choice is unsuccessful, consider the other of these options.
  - In April 2022, these were off-label uses of lamotrigine in children under 13 years, and levetiracetam in children and young people under 16 years. See NICE's information on prescribing medicines.
- 5.2.2 If first-line monotherapies are unsuccessful in people with focal seizures, consider 1 of the following second-line monotherapy options:
  - carbamazepine
  - oxcarbazepine
  - zonisamide.
  - If the first choice is unsuccessful, consider the other second-line monotherapy options. In April 2022, these were off-label uses of oxcarbazepine in children under 6 years, and zonisamide in children. See NICE's information on prescribing medicines.
- 5.2.3 If second-line monotherapies tried are unsuccessful in people with focal seizures, consider lacosamide as third-line monotherapy.
  - In April 2022, this was an off-label use of lacosamide in children under 4 years. See NICE's information on prescribing medicines.

**Add-on treatment**

For guidance on safe prescribing of pregabalin in adults, see NICE's guideline on medicines associated with dependence or withdrawal symptoms.

- 5.2.4 If monotherapy is unsuccessful in people with focal seizures, consider 1 of the following first-line add-on treatment options:
  - carbamazepine
  - lacosamide
  - lamotrigine
  - levetiracetam
  - oxcarbazepine
  - topiramate
  - zonisamide
  - If the first choice is unsuccessful, consider the other first-line add-on options.
  - In April 2022, these were off-label uses of lacosamide in children under 4 years, lamotrigine in children under 2 years, levetiracetam in children under 4 years, oxcarbazepine in children under 6 years, topiramate in children under 2 years, and zonisamide in children under 6 years. See NICE's information on prescribing medicines.

5.2.5 If first-line add-on treatments tried are unsuccessful in people with focal seizures, consider 1 of the following second-line add-on treatment options:

- brivaracetam
- cenobamate (in line with NICE's technology appraisal guidance on cenobamate for treting focal onset seizures in epilepsy)
- eslicarbazepine acetate
- perampanel
- pregabalin
- sodium valproate, except in women and girls able to have children. If the first choice is unsuccessful, consider the other second-line add-on options.
- In April 2022, these were off-label uses of brivaracetam in children under 4 years, eslicarbazepine acetate in children under 6 years, perampanel in children under 4 years, and pregabalin in children. See NICE's information on prescribing medicines.

- 5.2.6 If second-line add-on treatments tried are unsuccessful in people with focal seizures, consider 1 of the following third-line add-on treatment options:
  - phenobarbital
  - phenytoin
  - tiagabine
  - vigabatrin. If the first choice is unsuccessful, consider the other third-line add-on options.
  - In April 2022, this was an off-label use of tiagabine in children under 12 years. See NICE's information on prescribing medicines.
- 5.2.7 Do not offer sodium valproate as an add-on treatment for focal seizures in women and girls able to have children (including young girls who are likely to need treatment when they are old enough to have children), unless:
  - other treatment options are unsuccessful
  - the risks and benefits have been fully discussed, including the risks to an unborn child
  - the likelihood of pregnancy has been taken into account and a pregnancy prevention programme put in place, if appropriate.
  - Follow the MHRA safety advice on valproate use by women and girls.

5.3 Absence seizures

**Absence seizures (including childhood absence epilepsy)**

- 5.3.1 Offer ethosuximide as first-line treatment for absence seizures.
- 5.3.2 If first-line treatment is unsuccessful, offer sodium valproate as second-line monotherapy or add-on treatment for absence seizures in:
  - boys of all ages
  - girls aged under 10 years and who are unlikely to need treatment when they are old enough to have children
  - women who are unable to have children.
- 5.3.3 If second-line treatment is unsuccessful for absence seizures, consider lamotrigine or levetiracetam as a third-line monotherapy or add-on treatment options. If the first choice is unsuccessful, consider the other of these options.

  - In April 2022, these were off-label uses of lamotrigine in children under 2 years and levetiracetam in adults and children. See NICE's information on prescribing medicines.
- 5.3.4 Be aware that the following antiseizure medications may **exacerbate** seizures in people with absence seizures:
  - carbamazepine
  - gabapentin
  - oxcarbazepine
  - phenobarbital
  - phenytoin
  - pregabalin
  - tiagabine
  - vigabatrin.

**Absence seizures with other seizure types**

- 5.3.5 Consider sodium valproate as first-line treatment for absence seizures with other seizure types (or at risk of these) in:
  - boys and men
  - girls aged under 10 years and who are unlikely to need treatment when they are old enough to have children
  - women who are unable to have children.
- 5.3.6 Consider lamotrigine or levetiracetam as first-line treatment options in women and girls able to have children (including young girls who are likely to need treatment when they are old enough to have children) with absence seizures and other seizure types (or at risk of these). If the first choice is unsuccessful, consider the other of these options. In April 2022, these were off-label uses of levetiracetam as monotherapy for adults and children, and as an add-on therapy for children under 12 years. See NICE's information on prescribing medicines.
- 5.3.7 Do not offer sodium valproate for absence seizures with other seizure types (or at risk of these) in women and girls able to have children (including young girls who are likely to need treatment when they are old enough to have children), unless:
  - other treatment options are unsuccessful
  - the risks and benefits have been fully discussed, including the risks to an unborn child
  - the likelihood of pregnancy has been taken into account and a pregnancy prevention programme put in place, if appropriate.
  - Follow the MHRA safety advice on valproate use by women and girls.
- 5.3.8 If first-line treatments tried are unsuccessful for absence seizures and other seizure types (or at risk of these), consider:
  - lamotrigine or levetiracetam as a second-line monotherapy or add-on treatment options or
  - ethosuximide as a second-line add-on treatment. If the first choice is unsuccessful, consider the other second-line options.
  - In April 2022, these were off-label uses of lamotrigine in children under 2 years, and levetiracetam in adults and children. See NICE's information on prescribing medicines.

- 5.3.9 Be aware that the following antiseizure medications may exacerbate seizures in people with absence seizures and other seizure types (or at risk of these):
  - carbamazepine
  - gabapentin
  - oxcarbazepine
  - phenobarbital
  - phenytoin
  - pregabalin
  - tiagabine
  - vigabatrin

5.4 Myoclonic seizures

**First-line treatment**

- 5.4.2 Offer sodium valproate as first-line treatment for myoclonic seizures in:
  - boys and men
  - girls aged under 10 years and who are unlikely to need treatment when they are old enough to have children
  - women who are unable to have children.
- 5.4.3 Offer levetiracetam as first-line treatment for myoclonic seizures in women and girls able to have children (including young girls who are likely to need treatment when they are old enough to have children).
  - In April 2022, this was an off-label use of levetiracetam. See NICE's information on prescribing medicines.

**Second- and third-line treatments**

For guidance on safe prescribing and managing withdrawal of clobazam and clonazepam in adults, see NICE's guideline on medicines associated with dependence or withdrawal symptoms.

- 5.4.4 If sodium valproate is unsuccessful as first-line treatment for myoclonic seizures, offer levetiracetam as a second-line monotherapy or add-on treatment.
  - In April 2022, these were off-label uses of levetiracetam as monotherapy for adults and children, and as an add-on therapy for children under 12 years. See NICE's information on prescribing medicines.
- 5.4.5 If levetiracetam is unsuccessful for myoclonic seizures, consider 1 of the following as monotherapy or add-on treatment options:
  - brivaracetam
  - clobazam
  - clonazepam
  - lamotrigine
  - phenobarbital
  - piracetam
  - topiramate
  - zonisamide.
  - If the first choice is unsuccessful, consider any other of these options.

  - In April 2022, these were off-label uses for brivaracetam in adults and children, clobazam as monotherapy in adults and children, clobazam as add-on therapy in children under 6 months, clonazepam solution in children, lamotrigine as monotherapy for children under 13 years and add-on therapy for children under 2 years, piracetam in children, topiramate in adults and children, and zonisamide in adults and children. See NICE's information on prescribing medicines.

- 5.4.6 Do not offer sodium valproate for myoclonic seizures in women and girls able to have children (including young girls who are likely to need treatment when they are old enough to have children), unless:
  - other treatment options are unsuccessful
  - the risks and benefits have been fully discussed, including the risks to an unborn child
  - the likelihood of pregnancy has been taken into account and a pregnancy prevention programme put in place, if appropriate.
  - Follow the MHRA safety advice on valproate use by women and girls.

**Other treatment considerations**

- 5.4.7 Be aware that lamotrigine can occasionally exacerbate myoclonic seizures.
- 5.4.8 Do not use any of the following antiseizure medications in people with myoclonic seizures because they may exacerbate seizures:
  - carbamazepine
  - gabapentin
  - oxcarbazepine
  - phenytoin
  - pregabalin
  - tiagabine
  - vigabatrin

5.5 Tonic or atonic seizures

**First-line treatment**

- 5.5.2 Offer sodium valproate as first-line treatment for tonic or atonic seizures in:
  - boys and men
  - girls aged under 10 years and who are unlikely to need treatment when they are old enough to have children
  - women who are unable to have children.
- 5.5.3 Consider lamotrigine as first-line treatment for tonic or atonic seizures in women and girls able to have children (including young girls who are likely to need treatment when they are old enough to have children). In April 2022, this was an off-label use of lamotrigine in children under 13 years. See NICE's information on prescribing medicines.

**Second- and third-line treatments**

For guidance on safe prescribing and managing withdrawal of clobazam in adults, see NICE's guideline on medicines associated with dependence or withdrawal symptoms.

- 5.5.4 If sodium valproate is unsuccessful as first-line treatment for tonic or atonic seizures, consider lamotrigine as a second-line monotherapy or add-on treatment. In April 2022, this was an off-label use of lamotrigine as monotherapy in children under 13 years and add-on therapy in children under 2 years. See NICE's information on prescribing medicines.

- 5.5.5 If lamotrigine is unsuccessful for treating tonic or atonic seizures, consider 1 of the following as monotherapy or add-on treatment options:
  - clobazam
  - rufinamide
  - topiramate
  - If the first choice is unsuccessful, consider any other of these options.
  - In April 2022, these were off-label uses for clobazam as monotherapy in adults and children, clobazam as add-on therapy in children under 6 months, rufinamide, and topiramate as monotherapy in children under 6 years, and topiramate as add-on therapy in children under 2 years. See NICE's information on prescribing medicines
- 5.5.6 Do not offer sodium valproate for tonic or atonic seizures in women and girls able to have children (including young girls who are likely to need treatment when they are old enough to have children), unless:
  - other treatment options are unsuccessful
  - the risks and benefits have been fully discussed, including the risks to an unborn child
  - the likelihood of pregnancy has been taken into account and a pregnancy prevention programme put in place, if appropriate.
  - Follow the MHRA safety advice on valproate use by women and girls.

**Further treatment options**

- 5.5.7 If third-line treatment is unsuccessful for tonic or atonic seizures in children, consider a ketogenic diet as an add-on treatment under the supervision of a ketogenic diet team.
- 5.5.8 If all other treatment options for tonic or atonic seizures are unsuccessful, consider felbamate as an add-on treatment under the supervision of a neurologist with expertise in epilepsy.
  - In April 2022, felbamate was not licensed for use in the UK. See NICE's information on prescribing medicines.

**Other treatment considerations**

- 5.5.9 Be aware that the following antiseizure medications may exacerbate seizures in people with tonic or atonic seizures:
  - carbamazepine
  - gabapentin
  - oxcarbazepine
  - pregabalin
  - tiagabine
  - vigabatrin

5.6 Idiopathic generalised epilepsies

**First-line treatment**

- 5.6.1 Offer sodium valproate as first-line treatment for idiopathic generalised epilepsies in:
  - boys and men
  - girls aged under 10 years and who are unlikely to need treatment when they are old enough to have children
  - women who are unable to have children.

- 5.6.2 Offer lamotrigine or levetiracetam as first-line treatment for idiopathic generalised epilepsies in women and girls able to have children (including young girls who are likely to need treatment when they are old enough to have children). If the first choice is unsuccessful, offer the other of these options. In April 2022, these were off-label uses of lamotrigine in children under 13 years, and levetiracetam in adults and children. See NICE's information on prescribing medicines.

**Second-line treatment**

- 5.6.3 If first-line treatments are unsuccessful for idiopathic generalised epilepsies, consider lamotrigine or levetiracetam as a second-line monotherapy or add-on treatment options. If the first choice is unsuccessful, consider the other of these options. In April 2022, these were off-label uses of lamotrigine as monotherapy in children under 13 years and add-on therapy for children under 2 years, and levetiracetam as monotherapy in adults and children and add-on therapy for children under 12 years.
- 5.6.4 If second-line treatments tried are unsuccessful for idiopathic generalised epilepsies, consider perampanel or topiramate as third-line add-on treatment options. If the first choice is unsuccessful, consider the other of these options.
  - In April 2022, this was an off-label use of perampanel for children under 7 years. See NICE's information on prescribing medicines.
- 5.6.5 Do not offer sodium valproate for idiopathic generalised epilepsies in women and girls able to have children (including young girls who are likely to need treatment when they are old enough to have children), unless:
  - other treatment options are unsuccessful
  - the risks and benefits have been fully discussed, including the risks to an unborn child
  - the likelihood of pregnancy has been taken into account and a pregnancy prevention programme put in place, if appropriate. Follow the MHRA safety advice on valproate use by women and girls.

[…]

6.3 Infantile spasms syndrome

**First-line treatment**

- […]
- 6.3.6 **Offer vigabatrin alone as first-line treatment for infantile spasms due to tuberous sclerosis. If vigabatrin is ineffective after 1 week, add high-dose oral prednisolone.**
  - In April 2022, this was an off-label use of vigabatrin in combination with prednisolone. See NICE's information on prescribing medicines.
- 6.3.7 Before starting oral prednisolone for infantile spasms: discuss the possible side effects of steroid treatment with parents and carers test whether the child has antibodies to the varicella zoster virus give the parents and carers a steroid card and information about when to seek medical help for side effects.
- 6.3.8 When using oral prednisolone to treat infantile spasms, follow the advice in the BNF for children on prednisolone dosages. Monitor blood pressure and urinary glucose weekly during treatment.
- 6.3.9 When using vigabatrin to treat infantile spasms, increase the dose as outlined in the BNF for children on vigabatrin. Discuss further dose increases with a tertiary paediatric neurologist if the spasms do not stop (clinically and on EEG).

**Hintergrund** (aus [2])
Based on evidence, the committee agreed that children with infantile spasms due to tuberous sclerosis should be offered vigabatrin as a first-line treatment. Tuberous sclerosis is a major cause of infantile spasms, and these children are particularly refractory to treatment. Trials have shown spasms freedom in a short period of time with vigabatrin in children with infantile spasms due to tuberous sclerosis, however, due to the high risk of neurodevelopmental problems in these babies, the committee agreed, based on evidence, that high-dose oral prednisolone should be added if vigabatrin is ineffective after 1 week. The study that assessed the effectiveness of high-dose oral prednisolone and vigabatrin did not include children with tuberous sclerosis, however the committee agreed that it was appropriate to extrapolate from this study due to the similar pathophysiology between both groups.
Prednisolone lowers the immune system, therefore the committee agreed that the possible side effects of steroid treatment should be discussed with the parents or carers of the baby with infantile spasms. The risk of immunosuppression continues up to 3 months after starting treatment, and parents and carers need to be made aware of the increased risk of infection. However, the committee were in agreement that, in the majority of cases, the risks of a short course of steroids do not outweigh the benefits. Children should also be tested for antibodies for varicella zoster virus as, if they get infected while taking prednisolone, it can have severe and occasionally life-threatening consequences due to the supressed immune system. In line with current clinical practice, the committee also noted that a steroid card and information about where to seek medical advice for side effects should be provided to parents or carers.
The committee agreed the dosage of prednisolone given should be in line with advice in the BNF for children. Based on their experience and expertise, they also noted that monitoring blood pressure and urinary glucose weekly would help identify possible risks of infection in a timely manner.
The committee agreed the dosage of vigabatrin should be in line with advice in the BNF for children, and they noted that, in some cases, it may be necessary to go above these recommended doses if there is a sub-optimal response, in which case, any adjustment should be undertaken with guidance from a specialist, to ensure optimal treatment benefit.

**Second-line treatment**

- 6.3.10 If first-line treatment for infantile spasms is unsuccessful, discuss further treatment with a tertiary paediatric epilepsy specialist.
- 6.3.11 Consider the following as a second-line monotherapy or add-on treatment options for infantile spasms, guided by a ketogenic diet team or tertiary paediatric epilepsy specialist, as appropriate:
  - ketogenic diet
  - levetiracetam
  - nitrazepam
  - sodium valproate
  - topiramate.

  If the first choice is unsuccessful, consider the other second-line options. In April 2022, these were off-label uses of levetiracetam, nitrazepam and topiramate. See NICE's information on prescribing medicines.

**Hintergrund** (aus [2])
The committee did not think the evidence for second-line therapy allowed them to make any firm recommendations. Based on their experience and expertise, the committee provided some treatments that are successfully used in clinical practice and emphasised that any treatment should be individually tailored and only prescribed in consultation with a tertiary paediatric epilepsy specialist. This is due to the long-term risk of adverse neurodevelopmental outcomes associated with treatment resistant cases of infantile spasms and the complexity of the presentation.

## 7 Treating status epilepticus, repeated or cluster seizures, and prolonged seizures

### 7.1 Status epilepticus

**Initial treatment for generalised convulsive status epilepticus**

- 7.1.1 Provide resuscitation and immediate emergency treatment for children, young people and adults who have convulsive status epilepticus (seizures lasting 5 minutes or more).
- 7.1.2 If the person with convulsive status epilepticus has an individualised emergency management plan that is immediately available, administer medication as detailed in the plan.
- 7.1.3 If the person with convulsive status epilepticus does not have an individualised emergency management plan immediately available:
  - give a benzodiazepine (buccal midazolam or rectal diazepam) immediately as first-line treatment in the community or
  - use intravenous lorazepam if intravenous access and resuscitation facilities are immediately available.
- 7.1.4 Be aware of the possible underlying causes of status epilepticus, including hypoglycaemia, eclampsia and alcohol withdrawal, which may need to be treated with additional medication.
- 7.1.5 Be alert to non-adherence to antiseizure medication, which can also be a cause of status epilepticus.
- 7.1.6 Be aware that non-epileptic seizures (dissociative seizures) can be similar in presentation to convulsive status epilepticus.

**Management if initial treatment is unsuccessful**

- 7.1.7 If convulsive status epilepticus does not respond to the first dose of benzodiazepine:
  - call emergency services in the community or
  - seek expert guidance in hospital.
- 7.1.8 Continue to follow the person's individualised emergency management plan, if this is immediately available, or give a second dose of benzodiazepine if the seizure does not stop within 5 to 10 minutes of the first dose.
- 7.1.9 If convulsive status epilepticus does not respond to 2 doses of a benzodiazepine, give any of the following medicines intravenously as a second-line treatment:
  - levetiracetam
  - phenytoin
  - sodium valproate.
  - Take into account that levetiracetam may be quicker to administer and have fewer adverse effects than the alternative options.
  - In April 2022, this was an off-label use of levetiracetam. See NICE's information on prescribing medicines. Follow the Medicines and Healthcare products Regulatory Agency (MHRA) safety advice on valproate use by women and girls.
- 7.1.10 If convulsive status epilepticus does not respond to a second-line treatment, consider trying an alternative second-line treatment option under expert guidance.
- 7.1.11 If convulsive status epilepticus does not respond to the second-line treatment options tried, consider the following third-line options under expert guidance:
  - phenobarbital or
  - general anaesthesia.
- 7.1.12 After an episode of convulsive status epilepticus, agree an emergency management plan with the person if they do not already have one and there is concern that status epilepticus may recur.

7.2 Repeated seizures or cluster seizures

- 7.2.1 Manage repeated or cluster seizures (typically 3 or more self-terminating seizures in 24 hours) as a medical emergency.
- 7.2.2 If a person has repeated or cluster seizures:
  - follow their individualised emergency management plan, if this is immediately available or
  - consider giving a benzodiazepine, such as clobazam or midazolam, immediately if they do not have an individualised emergency management plan immediately available.
- 7.2.3 Seek expert guidance if the person has further episodes of repeated or cluster seizures.
- 7.2.4 Agree an individualised emergency management plan with the person after repeated or cluster seizures if they do not have one already and there is concern that repeated or cluster seizures may recur.

7.3 Prolonged seizures

For convulsive seizures that continue for 5 minutes or more, follow the recommendations in the section on status epilepticus.

- 7.3.1 Manage prolonged convulsive seizures (any convulsive seizure that continues for more than 2 minutes longer than a person's usual seizure) as a medical emergency.
- 7.3.2 If a person has a prolonged convulsive seizure:
  - follow their individualised emergency management plan if this is immediately available or
  - consider giving a benzodiazepine, such as midazolam or clobazam, immediately if they do not have an individualised emergency management plan immediately available.
- 7.3.3 After a prolonged convulsive seizure, agree an emergency management plan with the person if they do not already have one and there is concern that prolonged convulsive seizures may recur.
- 7.3.4 After a prolonged non-convulsive seizure (a non-convulsive seizure that continues for more than 2 minutes longer than a person's usual seizure), agree an emergency management plan with the person if they do not already have one and there is concern that prolonged non-convulsive seizures may recur.

8.1 Ketogenic diet

- 8.1.1 Consider a ketogenic diet under the guidance of a tertiary epilepsy specialist, in people with:
  - certain childhood-onset epilepsy syndromes (see also the section on treating childhood-onset epilepsies), for example:
  - glucose transporter type 1 deficiency syndrome (GLUT1 deficiency syndrome)
  - epilepsy associated with pyruvate dehydrogenase deficiency
  - infantile spasms syndrome
  - epilepsy with myoclonic-atonic seizures (Doose syndrome)

    - Dravet syndrome
    - Lennox–Gastaut syndrome
  - drug-resistant epilepsy if other treatment options have been unsuccessful or are not appropriate.

8.2 Resective epilepsy surgery

- 8.2.1 Discuss the options for assessment for resective epilepsy surgery with people who have drug-resistant epilepsy, and their families or carers if appropriate. Explain what the process of surgical assessment involves as well as the benefits and risks associated with surgical procedures.
- 8.2.2 Refer people with drug-resistant epilepsy, including those without identified MRI abnormalities, for consideration of assessment for resective epilepsy surgery:
  - For adults, this should be to a tertiary epilepsy service.
  - For children and young people, this should be to a tertiary paediatric neurology service for consideration of referral to a children's epilepsy service surgery centre.
  - 8.2.3 For **people with MRI abnormalities that indicate a high risk of drug-resistant epilepsy, consider early referral to a tertiary epilepsy service for assessment, including an evaluation for resective epilepsy surgery if appropriate**. Examples of specific lesions seen on MRI may include, but are not limited to, the following:
  - hippocampal sclerosis
  - malformations of cortical development
  - epilepsy-associated low-grade tumours
  - hypothalamic hamartomas
  - neuronal migrational disorders
  - **tuberous sclerosis complex**
  - vascular malformations, including Sturge–Weber syndrome
  - cerebral contusions from previous head injury.

  Full details of the evidence and the committee's discussion are in evidence review 13: referral and surgical interventions [2].

**Hintergrund:**
The evidence on surgical interventions showed that resective epilepsy surgery is the most clinically effective treatment for children, young people and adults with drug-resistant focal epilepsy. This was based on the evidence showing better quality of life and lower rates of recurrence after surgery compared with medical care. The committee also considered the relative harms of surgery, such as higher rates of postoperative cognitive deficits and other adverse events. The benefits of surgery were agreed to outweigh these harms, because in many cases, the cognitive effects did not cause significant dysfunction in everyday life, and many of the other adverse events (perioperative infection, bleeding and postoperative changes in mood) were self-limiting. In addition, the committee noted that the risk of harm from surgery needed to be balanced against the risks of ongoing seizures, which include injury, head injury and sudden unexpected death in epilepsy (SUDEP). The committee accepted that the risk of harm may increase as the surgical complexity increases, but agreed that the overall balance in favour of a benefit is likely to apply across most types of epilepsy surgery for both children and adults.
[…]
No evidence was found on the most effective criteria for referral. However, the committee agreed that because benefits from surgery would outweigh harms across all the populations considered, including improvement in seizure control, potential seizure freedom, better quality of life and reduced risk of epilepsy-related death, all people with drug-resistant epilepsy would benefit from a referral to a tertiary centre for consideration of resective surgery, including those without identified MRI abnormalities.
The committee also discussed whether there were other groups that might benefit from a referral for consideration of surgery. The committee agreed, by consensus, that people with specific MRI

abnormalities that might indicate future resistance to antiseizure medication, should be referred to a tertiary centre at diagnosis, rather than waiting until treatment is unsuccessful.
In addition, the committee discussed that, in their experience, people with genetic abnormalities or learning disabilities can sometimes be excluded from referral to a tertiary centre for consideration of surgery. This may happen because it is thought that surgery is not suitable for them, or they might be erroneously considered unable to cope with surgical assessment. The committee agreed they should have treatment in the same way as other people with epilepsy and be referred if indicated.

## 8.3 Vagus nerve stimulation

- 8.3.1 If resective epilepsy surgery is not suitable for a person with drug-resistant seizures, consider vagus nerve stimulation as an add-on treatment to antiseizure medication. See also NICE's interventional procedures guidance on vagus nerve stimulation for refractory epilepsy in children.
- 8.3.2 Discuss with the person with epilepsy, and their family or carers if appropriate, the benefits and risks of vagus nerve stimulation before making a shared decision about having this procedure.

**Scottish Intercollegiate Guidelines Network (SIGN), 2021 [5].**

Epilepsies in children and young people: investigative procedures and management

**Zielsetzung/Fragestellung**

- This evidence-based guideline covers specific aspects of investigation and management of epilepsies in children and young people aged from 1 month to 19 years if they remain in secondary education.
- The guideline does not cover seizures in newborn babies, infants under 1 month of age, referral for diagnosis of epilepsy or the management of non-epileptic seizures. Emergency management of seizures, including status epilepticus, is also excluded […].
- Although surgery for epilepsy is addressed, this guideline does not cover specific surgical treatment, as this is managed on a case-by-case basis.

**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
- 2007–2017, with a search for RCTs updated to 2020

LoE / GoR

Key to evidence statements and 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<br>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 |

Recommendations

Some recommendations can be made with more certainty than others. The wording used in the recommendations in this guideline denotes the certainty with which the recommendation is made (the 'strength' of the recommendation).

The 'strength' of a recommendation takes into account the quality (level) of the evidence. Although higher-quality evidence is more likely to be associated with strong recommendations than lower-quality evidence, a particular level of quality does not automatically lead to a particular strength of recommendation.

Other factors that are taken into account when forming recommendations include: relevance to the NHS in Scotland; applicability of published evidence to the target population; consistency of the body of evidence; and the balance of benefits and harms of the options.

**R** For 'strong' recommendations on interventions that 'should' be used, the guideline development group is confident that, for the vast majority of people, the intervention (or interventions) will do more good than harm. For 'strong' recommendations on interventions that 'should not' be used, the guideline development group is confident that, for the vast majority of people, the intervention (or interventions) will do more harm than good.

**R** For 'conditional' recommendations on interventions that should be 'considered', the guideline development group is confident that the intervention will do more good than harm for most patients. The choice of intervention is therefore more likely to vary depending on a person's values and preferences, and so the healthcare professional should spend more time discussing the options with the patient.

**Empfehlungen**

*Anmerkung: Die Empfehlungen des SIGN zur Tuberösen Sklerose beziehen sich überwiegend auf die Infantilen Spasmen bei Kindern < 2 Jahren (Abschnitt 5.6 in der Leitlinie). Für die Behandlung von Personen > 2 Jahren wurden die Empfehlungen nach Anfallsart aufgeführt. Die Darstellung der Hintergrundinformationen aus der Leitlinie beschränkt sich auf die Empfehlungen, die sich explizit auf die Tuberöse Sklerose beziehen.*

5 Pharmacological management

5.2 Focal epilepsy

**5.2.1 First-line treatment**

R | **Carbamazepine or lamotrigine could be considered for children and young people with focal epilepsy.**

R | **Levetiracetam, oxcarbazepine or sodium valproate could be considered for children and young people with focal epilepsy if carbamazepine and lamotrigine are not suitable or tolerated.**

✓ | Sodium valproate should not be used in girls of childbearing potential unless there is no suitable alternative and a pregnancy prevention programme is in place.

**5.2.2 Adjunctive treatment**

R | **Carbamazepine, clobazam, gabapentin, lamotrigine, levetiracetam, oxcarbazepine, sodium valproate, topiramate or zonisamide** (over 6 years of age) **can be considered as adjunctive therapies in children and young people with focal epilepsy if first-line therapies are ineffective or not tolerated.**

✓ | Sodium valproate should not be used in girls of childbearing potential unless there is no suitable alternative and a pregnancy prevention programme is in place.

R | **Perampanel could be considered as adjunctive therapy in adolescents from 12 years of age with focal epilepsy.**

5.3 Generalised epilepsy

5.3.1 Absence seizures

R | **Ethosuximide should be considered as first-line monotherapy for the treatment of patients with childhood absence epilepsy. Sodium valproate should also be considered, but has a higher risk of adverse events.**

R | **Lamotrigine could be considered for patients with childhood absence epilepsy if ethosuximide and sodium valproate are ineffective, not suitable or not tolerated.**

R | **A combination of two or three AEDs could be considered if two first-line AEDs are ineffective. If treatment is still ineffective, advice should be sought from, or the patient should be referred to, a tertiary epilepsy specialist to consider the use of clobazam, clonazepam, levetiracetam, topiramate or zonisamide.**

✓ | 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.

## 5.6 Tuberous sclerosis

One RCT was identified examining the efficacy of adjuvant everolimus therapy (low or high exposure) in 366 patients, age range 2–65 years, with tuberous sclerosis complex (TSC) and treatment-resistant focal-onset seizures.[127] The median age was 10.1 years and 82% of participants were under 18 years of age. Adjunctive everolimus treatment significantly reduced seizure frequency in patients with TSC and intractable epilepsy. The median percentage reduction in seizure frequency was 14.9% (95% CI 0.1% to 21.7%) with placebo versus 29.3% with low-exposure everolimus (95% CI 18.8% to 41.9%) and 39.6% with high-exposure everolimus (95% CI 35.0% to 48.7%). 1++

A post-hoc analysis of this trial separately considered the results for the 299 paediatric participants, splitting the results into two age groups (under 6 years and 6 to under 18 years).[128] Adjunctive everolimus therapy resulted in sustained reductions in seizure frequency after 1 year and was well tolerated in paediatric patients with treatment-refractory seizures associated with TSC. The younger participants appeared to receive greater benefit than older participants. 3

Everolimus was not found to improve cognitive functioning, autism or neuropsychological functioning.[129] 1++

Everolimus showed immunosuppressive properties in the full study cohort. The most common adverse events were stomatitis, diarrhoea, nasopharyngitis, pyrexia and upper respiratory tract infection.[127] In the post-hoc analysis of patients under 18, grade 3 or 4 adverse events were reported in 45% of participants under 6 years of age (commonly pneumonia) and 38% in older participants (commonly pneumonia and stomatitis). Two deaths were reported during the extension phase, one due to pneumonia which was suspected to be treatment related.[128] 1++ 3

Everolimus requires dose titration according to blood levels and close monitoring for potential adverse effects, and therefore may necessitate frequent hospital visits.

Everolimus is accepted for use in Scotland by SMC for children aged 2 years and over with refractory seizures associated with TSC (*see section 11.4*).

Whilst there is no QoL data from studies concerning everolimus, its beneficial effect on seizure frequency may allow patients to manage their condition more effectively and in so doing potentially increase independence and participation in school and family life, and reduce carer responsibilities.

The side-effect profile for everolimus, while not insignificant, appears tolerable in the light of the severity of the condition and its associated risk of mortality.

One underpowered RCT reported that sirolimus did not significantly reduce seizure frequency in children with TSC and intractable epilepsy.[129] 1-

There is insufficient evidence to indicate using sirolimus to treat refractory seizures in children with TSC.

R **Everolimus could be considered as an adjunctive treatment for children** (age 2 years and older) **with refractory seizures associated with tuberous sclerosis complex, when other treatments have failed. Children prescribed everolimus should be closely monitored for adverse events.**

**Referenzen**

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128 Curatolo P, Franz D, Lawson J, Yapici Z, Ikeda H, Polster T, et al. Adjunctive everolimus for children and adolescents with treatment-refractory seizures associated with tuberous sclerosis complex: post-hoc analysis of the phase 3 EXIST-3 trial. Lancet child and adolescent health 2018;2(7):495-504.
129 Overwater IE, Rietman AB, Bindels-de Heus K, Looman CW, Rizopoulos D, Sibindi TM, et al. Sirolimus for epilepsy in children with tuberous sclerosis complex: A randomized controlled trial. Neurology 2016;87(10):1011-8.

5.6.1 Infantile spasms with tuberous sclerosis

NICE recommends offering vigabatrin as first-line treatment to infants with infantile spasms due to tuberous sclerosis.[42] If vigabatrin is ineffective, a steroid (prednisolone or ACTH) should be offered, with careful consideration of the risk–benefit ratio. This was based on low-quality evidence, which found that vigabatrin was more effective at stopping infantile spasms than steroids. There was also resolution of hypsarrhythmia in the patients taking vigabatrin. — 4

A Cochrane review of the treatment of infantile spasms identified two small, underpowered studies which found vigabatrin to be more effective than hydrocortisone at stopping spasms.[117] — 1++

Vigabatrin is associated with significant adverse events and needs careful counselling and monitoring.[42] — 4

R **Vigabatrin should be considered as first-line treatment in infantile spasms for children with tuberous sclerosis. Children prescribed vigabatrin should be closely monitored for adverse events.**

**Referenzen**

42 National Institute for Health and Care Excellence. Epilepsies: diagnosis and management. London: NICE 2012. [cited 23 Sep 2020]. Available from url: https://www.nice.org.uk/guidance/cg137

117 Hancock Eleanor C, Osborne John P, Edwards Stuart W. Treatment of infantile spasms. Cochrane Database of Systematic Reviews 2013, Issue 6.

## 6 Non-pharmacological management

### 6.1 Ketogenic diet

R **A ketogenic diet should be offered as a treatment option in children with drug-resistant epilepsy.**

R **A ketogenic diet should be considered after a child has failed to respond to two antiepileptic drugs.**

R **A ketogenic diet should be tried for at least 3 months in children with drug-resistant epilepsy to assess efficacy, with consideration of continuation of the ketogenic diet based on risk and benefits at each visit and after 2 years of continuous use.**

### 6.2 Surgery for drug-resistant epilepsy

R **Children with drug-resistant epilepsy who fulfil referral criteria for assessment for surgery should be identified early.**

✓ Children who are candidates for surgery should be referred to a comprehensive epilepsy surgery programme.

### 6.3 Vagus nerve stimulation

R **Vagus nerve stimulation could be considered as an adjunctive treatment for children with drug-resistant epilepsy who are not candidates for surgery, under the specialist guidance of a consultant paediatric neurologist.**

**Northrup, H et al 2021 [4].**

Updated International Tuberous Sclerosis Complex Diagnostic Criteria and Surveillance and Management Recommendations

*Die Leitlinie erfüllt nicht ausreichend die methodischen Anforderungen. Aufgrund limitierter Evidenz hinsichtlich der Fragestellung zur Therapie von Krampfanfällen speziell bei TSC bei Patientinnen und Patienten ab 2 Jahren wird die LL jedoch ergänzend dargestellt.*

**Zielsetzung/Fragestellung**

- To update recommendations for diagnosis and clinical management of patients affected by TSC

**Methodik**

Grundlage der Leitlinie

- Repräsentatives Gremium – trifft zu;
- Interessenkonflikte und finanzielle Unabhängigkeit dargelegt – trifft zu;
- Systematische Suche, Auswahl und Bewertung der Evidenz – trifft teilweise zu (die Bewertung der Primärstudien mittels National Comprehensive Cancer Network Clinical Guidelines framework ermöglicht keine umfassende Einschätzung des Verzerrungspotenzials);
- Formale Konsensusprozesse und externes Begutachtungsverfahren dargelegt – trifft zu;
- Empfehlungen der Leitlinie sind eindeutig und die Verbindung zu der zugrundeliegenden Evidenz ist explizit dargestellt – trifft zu;
- Regelmäßige Überprüfung der Aktualität gesichert – unklar.

Recherche/Suchzeitraum:

- Update einer Recherche aus 2012 in PUBMED and SCOPUS
- bis Mai 2018

LoE / GoR

- National Comprehensive Cancer Network Clinical Guidelines framework

**TABLE 1.**
Recommendation Categories and Descriptions

| Category | Description | Supporting Evidence |
|---|---|---|
| 1 | Based upon high-level evidence, there is uniform consensus that the intervention is appropriate | At least one convincing class I study<br>OR at least two convincing and consistent class II studies<br>OR at least three convincing and consistent class III studies |
| 2A | Based upon lower-level evidence, there is uniform consensus that the intervention is appropriate | At least one convincing class II study<br>OR at least two convincing and consistent class III studies |
| 2B | Based upon lower-level evidence, there is consensus that the intervention is appropriate | At least one convincing class III study<br>OR at least two convincing and consistent class IV studies |
| 3 | Based upon any level of evidence, a consensus on appropriate intervention cannot be reached | Class I-IV studies that are conflicting or inadequate to form a consensus |

Class definitions for supporting evidence:
Class I: evidence provided by a prospective, randomized controlled clinical trial with masked outcome assessment, in a representative population.
Class II: evidence provided by a prospective matched group cohort study in a representative population with masked outcome assessment.
Class III: evidence provided by all other controlled trials (including well-defined natural history controls or patients serving as own controls) in a representative population, where outcome assessment is independent of patient treatment.
Class IV: evidence provided by uncontrolled studies, case series, case reports, or expert opinion.

## Empfehlungen

Hintergrund
The majority of infants with TSC will experience their first seizure before age one year,[97] and seizure control should be considered a medical emergency in infants with TSC because refractory epilepsy is strongly correlated with poor developmental and cognitive outcomes [31,32,97,98] and earlier recognition and treatment of epilepsy in infancy is associated with better long-term neurological outcomes.[31,33] Routine EEG in asymptomatic infants with TSC should be obtained every six weeks up to age 12 months and every three months up to age 24 months, as abnormal EEG very commonly precedes onset of clinical seizures,[29,30] allowing for the earliest possible intervention (Category 1).
It should be noted that the first seizure types to occur in TSC can be infantile spasms, focal seizures, or both, and infantile spasms in TSC are frequently not accompanied by hypsarrhythmia.[30]

- Vigabatrin is the recommended first-line therapy for infantile spasms. ACTH, synthetic ACTH, or prednisolone can be used if treatment with full-dose vigabatrin for 2 weeks has not correlated with clinical and EEG improvement.

There is strong evidence for the efficacy of vigabatrin for the treatment of infantile spasms associated with TSC31,[33,99,100]; therefore, we recommend vigabatrin as the first-line treatment. The prescriber should be aware of the possible side effects, particularly potential retinal toxicity associated with peripheral vision loss, and how to monitor for these. While the risk of retinal toxicity or abnormalities on brain MRI may correlate with total cumulative dose,[101,102] improved control of infantile spasms also correlates with dose.[103,104] Therefore, the relative risks of uncontrolled epilepsy and treatment-related adverse effects should be discussed and weighed by health care providers and parents/ caregivers together. Vigabatrin should be titrated rapidly up to 100 to 150 mg/kg/day. If resolution of the hypsarrhythmia pattern on EEG (when present) and abatement of infantile spasms does not occur within two weeks, adrenocorticotropic hormone (ACTH), synthetic adrenocorticotropic hormone, or prednisolone can be added as second-line therapy[105] (Category 1).
The recently completed EPISTOP study found that preventative vigabatrin treatment resulted in reduced risk of seizures, infantile spasms, and drug-resistant epilepsy; however, there was no difference in the prevalence of developmental delay or autism at age two years.[34,35] These results are promising, but the consensus committee determined that additional evidence is needed before preventative treatment with vigabatrin can be recommended for all infants with TSC universally. The PREVeNT clinical trial (NCT02849457), with results expected in the next year, should address this need.

- Routine EEG is recommended in individuals with known or suspected seizure activity, but frequency should be determined by clinical need rather than a specifically defined interval. Prolonged (24 hours or longer) video-EEG is appropriate when seizure occurrence is unclear or when unexplained sleep, behavioural changes, or other alteration in cognitive or neurological function is present (Category 2A).

- Other than infantile spasms, antiseizure medications for other seizure types in TSC should generally follow that of other epilepsies.

Seizures in adults with TSC can begin at any age, can worsen, or can abate over the individual's lifespan. Also, seizure semiology can change in adults with TSC (i.e., focal seizures with impaired awareness may become bilateral, tonic-clonic seizures). Any adult with TSC presenting with new-onset seizures or changed seizure semiology should be examined for non-TSC-related events, which can occur with or without TSC (e.g., glioma, subarachnoid hemorrhage, stroke, etc.).

- Everolimus and a specific cannabidiol formulation are approved by regulatory authorities for treatment of seizures associated with TSC. No comparative effectiveness

data exist to recommend antiseizure medications, everolimus, cannabidiol, or dietary therapies over one another in specific subsets of patients.

Other than for infantile spasms, antiseizure medication or dietary therapy selection in TSC should generally follow that of other epilepsies. The mTOR inhibitor everolimus[83] and a specific formulation of cannabidiol[106] have been specifically evaluated in randomized controlled clinical trials to treat seizures in TSC and found to be effective and well-tolerated (Category 1). Both are now approved by many regulatory authorities for adjunctive treatment of seizures associated with TSC. However, no comparative effectiveness data exist to recommend specific antiseizure medications, everolimus, or cannabidiol over one another in a particular patient. Clinicians should be aware that both everolimus[107] and cannabidiol[108] have important drug interactions with other antiseizure medications, including with each other.[109,110]

- Epilepsy surgery should be considered for TSC patients with refractory seizures, seizures, particularly after failing three medications. [114-116] Special consideration should be given to children at younger ages experiencing neurological regression, [117,118] and evaluation for surgery should be performed at centers with experience and expertise in TSC (Category 2A).

- Dietary interventions, including a ketogenic diet [111,112] or low-glycemic index treatment,[113] may be an effective nonpharmacological therapy for patients with TSC with intractable epilepsy, including infantile spasms refractory to vigabatrin and hormonal therapies.

- Vagus nerve stimulation can be used in TSC for medically refractory epilepsy if surgery is unsuccessful or not an option.[119] There are early data suggesting that responsive neurostimulation may be effective in select adults with TSC and intractable seizures.[120]

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**Gesellschaft für Neuropädiatrie, 2021 [1].**
Therapie der Blitz-Nick-Salaam Epilepsie (West-Syndrom), aktualisierte Version 3.0.

*Die Leitlinie bezieht sich auf die Therapie der BNS-Epilepsie („infantile Spasmen“) und betrifft damit laut Leitlinie Kinder im Alter „vorwiegend unter 2 Jahre“. Aufgrund limitierter Evidenz hinsichtlich der Fragestellung zur Therapie von Krampfanfällen speziell bei TSC bei Patientinnen und Patienten ab 2 Jahren wird die LL jedoch ergänzend dargestellt.*

**Zielsetzung/Fragestellung**

Die vorliegende Leitlinie bezieht sich ausschließlich auf die Therapie der akuten, neu aufgetretenen BNS-Epilepsie bzw. des West-Syndroms. Die Therapie anderer Anfallstypen, die vor, zeitgleich oder im Verlauf der BNS-Epilepsie auftreten, werden in der Leitlinie nicht berücksichtigt.

[…]

Ziel der Leitlinie ist es, Therapieziele zu formulieren und die Wirkungsnachweise und Nebenwirkungen der verschiedenen Therapieoptionen darzulegen. […]. Die Leitlinie bezieht sich auf die Therapie der BNS-Epilepsie („infantile spasms“) im oben definierten Sinne, unabhängig von ihrer jeweiligen Ätiologie.

**Methodik**

Grundlage der Leitlinie

- Repräsentatives Gremium – trifft teilweise zu (keine Patientenvertreter);
- Interessenkonflikte und finanzielle Unabhängigkeit dargelegt – trifft zu;
- Systematische Suche, Auswahl und Bewertung der Evidenz – trifft zu;
- Formale Konsensusprozesse und externes Begutachtungsverfahren dargelegt – trifft zu;
- Empfehlungen der Leitlinie sind eindeutig und die Verbindung zu der zugrundeliegenden Evidenz ist explizit dargestellt – trifft zu;
- Regelmäßige Überprüfung der Aktualität gesichert – trifft zu.

Recherche/Suchzeitraum:

- Cochrane, PubMed
- internationalen Datenbank für medizinische Leitlinien (https://g-i-n.net)
- 01.01.2014 bis 02.07.2020

LoE / GoR

- SIGN

| | |
|---|---|
| 1++ | Hochwertige Meta-Analysen, systematische Reviews von randomisierten, kontrollierten Studien (RCT) oder RCT mit einem sehr niedrigen Bias-Risiko. |
| 1+ | Gut durchgeführte Meta-Analysen, systematische Reviews von randomisierten, kontrollierten Studien (RCT) oder RCT mit einem niedrigen Bias-Risiko. |
| 1- | Meta-Analysen, systematische Reviews von randomisierten, kontrollierten Studien (RCT) oder RCT mit einem hohen Bias-Risiko. |
| 2++ | Hochwertige systematische Reviews von Fallkontroll- oder Kohortenstudien, hochwertige Fallkontroll- oder Kohortenstudien mit einem sehr niedrigen Risiko für Confounder-Effekt, Bias oder Zufall und mit der hohen Wahrscheinlichkeit für eine kausale Beziehung. |
| 2+ | Gut durchgeführte Fallkontroll- oder Kohortenstudien mit einem niedrigen Risiko für Confounder-Effekt, Bias oder Zufall und mit der mittleren Wahrscheinlichkeit für eine kausale Beziehung. |
| 2- | Fallkontroll- oder Kohortenstudien mit einem hohen Risiko für Confounder-Effekt, Bias oder Zufall und mit einem signifikanten Risiko, dass die dargestellte Beziehung nicht kausal ist. |
| 3 | Nicht-analytische Studien, z. B. Einzelfallberichte, Fallserien. |
| 4 | Expertenmeinung. |

| Qualität der Evidenz | Empfehlungsformulierung | Symbolik |
|---|---|---|
| hoch<br>in der Regel EK 1++ und EK 1+, in begründeten Fällen auch EK 2++ oder EK 2+ | Patienten sollen ..... | ⇑⇑ |
| mittel<br>in der Regel EK 2++ und EK 2+, in begründeten Ausnahmen auch EK 3 oder abgewertete EK 1++ oder EK 1+ | Patienten sollten ..... | ⇑ |
| schwach<br>in der Regel EK 3, in begründeten Ausnahmefällen auch abgewertete EK 2++ oder EK 2+ | Patienten können ..... | ⇔ |

## Empfehlungen

*Anmerkung: Die Darstellung der Hintergrundinformationen aus der Leitlinie beschränkt sich auf die Empfehlungen, die explizit für Kinder mit Tuberöser Sklerose formuliert sind oder für die Evidenz aus Studien mit Kindern mit Tuberöser Sklerose zitiert wird. Alle anderen Empfehlungen werden ohne Hintergrundinformation dargestellt.*

### 6.3 Empfehlung Medikamente

| Evidenz | Empfehlung 6 | Empfehlungsgrad |
|---|---|---|
| Hoch | Kinder mit einer BNS-Epilepsie sollen primär mit Hormonen (ACTH oder Prednisolon) oder mit einer Kombination von Hormonen mit Vigabatrin behandelt werden. | ⇑⇑ |
| Literatur: Go et al., 2012; Hancock et al., 2013; Lux et al., 2004a, 2005a; O'Callaghan et al., 2017, 2018; sowie Tabellen 1-3 | | |
| Konsensstärke: >75% | | |

**Hintergrundinformation**
**5.2 ACTH**
**5.1.2 Besondere Indikationen**
[…]. **In einer retrospektiven Studie wurden 80% der kryptogenen und 59% der symptomatischen Fälle, sowie 73% von 22 Kindern mit Tuberöse Sklerose Komplex nach ACTH anfallsfrei (Riikonen and Simell, 1990). Die Rezidivrate betrug 30%, 31% und 62%.** Daniels et al. 2019 (Daniels et al., 2019) verglichen bei Kindern mit Down Syndrom retrospektiv ACTH (n=18) mit anderen Medikamenten (u. a. Vigabatrin, Valproat, Zonisamid, Topiramat, n=17) und ermittelten für ACTH eine Responderrate von 81% und eine von 19% für die anderen Medikamente.

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| Evidenz | Empfehlung 7 | Empfehlungsgrad |
|---|---|---|
| Hoch | Kinder mit Tuberöse Sklerose Komplex und Kinder, bei denen Gründe vorliegen, die gegen eine Hormontherapie sprechen, sollen primär mit Vigabatrin behandelt werden | ⇑⇑ |
| Literatur: Chiron et al., 1997; Hancock and Osborne, 1999; sowie Tabellen 8-11 | | |
| Konsensstärke: >95% | | |

**Hintergrundinformation**
**Kommentar zu Empfehlung 7:**
Tuberöse Sklerose Komplex ist eine häufige Ursache der BNS-Epilepsie (1-33%, im Durchschnitt 11%) (Frost and Hrachovy, 2003). In allen Studien konnte eine gute Wirkung von Vigabatrin bei BNS-Epilepsie im Zusammenhang mit Tuberöse Sklerose Komplex aufgezeigt werden.
Vigabatrin ist neben ACTH/Glucocorticoiden eine Therapieoption 1. Wahl. Die Wirksamkeit von Vigabatrin wurde in mehreren EK 1 Studien (Elterman et al., 2001; Lux et al., 2004, 2005; Vigevano and Cilio, 1997) nachgewiesen. Zwei EK 1 Studien (Lux et al., 2004, 2005; Vigevano and Cilio, 1997) zeigen aber auch, dass die Hormontherapie (ACTH oder Prednisolon) im Vergleich zu Vigabatrin in der Wirksamkeit überlegen ist.

Auch die amerikanische Guideline zur Behandlung der BNS-Epilepsie erwähnt eine Überlegenheit von ACTH gegenüber Vigabatrin (Go et al., 2012).
In den meisten Studien wird Vigabatrin in Dosen von 75-150 mg/kg verabreicht. Meist erfolgt die initiale Einstellung in 1 bis 2 Schritten auf 75-100 mg/kg und nach einer Woche eine Anhebung auf 100-150 mg/kg, wenn der Therapieerfolg ausbleibt. Bei Nicht- oder unzureichendem Ansprechen sollte Vigabatrin wegen der potentiellen Gefahr von späteren Gesichtsfeldeinschränkungen rasch wieder abgesetzt werden. Aus dem gleichen Grund sollte die Behandlung mit Vigabatrin bei unkompliziertem Verlauf möglichst nach 6 Monaten abgeschlossen sein.

**Zur Datenlage (body of evidence) siehe Kapitel 5.3.2.**

**5.3.2 Besondere Indikationen**

Patienten mit **Tuberöse Sklerose Komplex (TSC)** sprechen signifikant besser auf Vigabatrin an als Patienten mit BNS-Epilepsie anderer Ätiologie. In 3 prospektiv randomisierten (Chiron et al., 1997; Elterman et al., 2010; Vigevano and Cilio, 1997) (EK 1+/EK 1-), 4 prospektiven (Covanis et al., 1998; Fejerman et al., 2000; Vles et al., 1993; Wohlrab et al., 1998) (EK 2-/+) und 4 retrospektiven Studien (Aicardi et al., 1996; Camposano et al., 2008; Granström et al., 1999; Kankirawatana et al., 2002) (EK 3) zeigten Patienten mit TSC eine hohe Responderrate von 57% bis 100%. Eine Studie (Chiron et al., 1997) verglich Vigabatrin in einem cross-over Design mit Hydrocortison. Alle initial (11/11) mit Vigabatrin behandelten und 6/11 im cross-over Design (unter Hydrocortison nicht anfallsfrei) behandelte Kinder waren Responder. Oft sind die Fallzahlen in den zitierten Studien jedoch klein (zwischen 1 und 42). In einem Review stellten Hancock & Osborne (Hancock and Osborne, 1999) in den damals vorliegenden Daten eine Responderrate von 95% fest (73/77).
Im Rahmen einer präventiven Studie (Jóźwiak et al., 2011) (EK 2-) wurden 14 noch anfallsfreie Kinder mit TSC präventiv mit Vigabatrin behandelt, sobald Epilepsiepotentiale im EEG erkennbar waren. In der vergleichenden Standardgruppe bekamen 31 Kinder mit TSC erst Vigabatrin, wenn Anfälle auftraten. BNS-Anfälle entwickelten 35% (11/31) in der Standardgruppe und 14% (2/14) in der Präventiv-Gruppe (p=0.151). Anfälle traten in den 24 Beobachtungsmonaten bei 71% (22/31) der Standardgruppe und 43% (6/14) der präventiv behandelten Gruppe auf (p=0.072). Im Langzeitverlauf nach 7-11 Jahren (Jóźwiak et al., 2019) (EK 2-) war die Anzahl anfallsfreier Patienten in beiden Gruppen mit 55% (6/11) und 54% (13/24) gleich. Die Entwicklung aber war nach 24 Monaten und im Langzeit-Verlauf in der präventiv behandelten Gruppe besser. Die Ergebnisse sind Grundlage zweier laufender Studien zum präventiven Einsatz von Vigabatrin bei TSC: EPISTOP (clinicaltrials.gov #NCT02098759) randomisiert und PREVent (clinicaltrials.gov #NCT02849457) randomisiert, placebokontrolliert. Die Resultate von EPISTOP werden demnächst erwartet, PREVent rekrutiert noch.

**5.4.11 Everolimus bei Tuberöse Sklerose Komplex (G. Kurlemann)**

Samueli et al. (Samueli et al., 2018) behandelten 4 männliche Säuglinge mit TCS (Alter 6-12 Monate) mit Everolimus zusätzlich zu Levetiracetam, Vigabatrin oder ketogener Diät, nachdem Vigabatrin, ACTH und ketogene Diät wirkungslos waren. Primärer Endpunkt: Anfallsfreiheit und EEG-Sanierung am Tag 14. Die Tagesdosis lag im Mittel bei 2,57 mg (2,5-5 mg) und die Serumkonzentration bei 6,9 ng/ml (4,5-7.5 ng/ml). 2/4 Kindern waren nach 14 Tagen anfallsfrei und ohne Hypsarrhythmie, keine Rezidive in der Nachbeobachtung über 18 Monate.

**5.7 Zusammenfassende Beurteilung aller Therapien**

[…] Für Kinder mit TSC bleibt Vigabatrin Mittel der 1. Wahl (EK 1+). Für die anderen Substanzen (Sultiam, Benzodiazepine, Immunglobuline, Levetiracetam, Pyridoxin, Pyridoxalphosphat, Topiramat, Felbamat, Valproat, Zonisamid und ketogene Diät) ist eine Wirksamkeit in Studien mit kleinen Fallzahlen oder offenen Studien mitgeteilt worden. **Bezüglich Tetrahydrocannabinol/Cannabidiol oder Everolimus bei TSC ist die Datenlage für eine Aussage bislang unzureichend**. Epilepsiechirurgie ist eine Therapieoption, wenn Therapieresistenz vorliegt und verschiedene Untersuchungsverfahren auf einen resezierbaren Ursprungsherd hinweisen.

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| Evidenz | Empfehlung 8 | Empfehlungsgrad |
|---|---|---|
| Hoch | Folgende Therapieschemata sind wirksam und sollten angewendet werden:<br>➢ Prednisolon 40-60 mg/Tag per os: Dauer jeweils 2 Wochen + 2 Wochen schrittweise Beendigung<br>*oder*<br>➢ Depot ACTH (Tetracosactide): 40-60 IE i. m. für 2 Wochen, jeweils alle 2 Tage + 2 Wochen schrittweise Beendigung über Prednisolon per os<br>*oder*<br>➢ Vigabatrin 100-150 mg/kg/Tag: 3 Monate + 1 Monat schrittweise Beendigung | ⇑ |
| Literatur:<br>Prednisolon-Schema: (EK 1+): Lux et al., 2004a, 2005a; O'Callaghan et al., 2017, 2018; Wanigasinghe et al., 2015, 2017; Yi et al., 2019<br>ACTH Depot-Schema: (EK 1+): Lux et al., 2004a, 2005a; O'Callaghan et al., 2017, 2018; Wanigasinghe et al., 2015, 2017<br>Vigabatrin-Schema: (EK 1+): Lux et al., 2004a, 2005a; O'Callaghan et al., 2017, 2018; Vigevano and Cilio, 1997; Wanigasinghe et al., 2015, 2017, sowie EK 2 und EK 3 in Tabelle 8-11 | | |
| Konsensstärke: >95% | | |

| Evidenz | Empfehlung 9 | Empfehlungsgrad |
|---|---|---|
| Schwach | Wenn Medikamente der ersten Wahl keine Wirkung zeigen, sollen andere Therapieoptionen wie zum Beispiel ketogene Diät, Sultiam, Topiramat, Valproat, Zonisamid oder Benzodiazepine eingesetzt werden. | ⇑⇑ |
| Literatur: EK 1-, EK 2 und EK 3 (Tabelle 14-20) | | |
| Konsensstärke: >75% | | |

| Evidenz | Empfehlung 10 | Empfehlungsgrad |
|---|---|---|
| Schwach | Bei Kindern, die nicht auf eine medikamentöse Therapie der ersten Wahl ansprechen, sollte früh die Möglichkeit eines epilepsiechirurgischen Vorgehens, insbesondere bei sichtbaren fokalen ZNS-Läsionen, geprüft werden. | ⇑ |
| Literatur: zahlreiche EK 3 Studien (siehe Kapitel 5.6. der Langfassung) | | |
| Konsensstärke: >95% | | |

# 4 Detaillierte Darstellung der Recherchestrategie

**Cochrane Library - Cochrane Database of Systematic Reviews (Issue 01 of 12, January 2022) am 12.01.2023**

| # | Suchfrage |
|---|---|
| 1 | [mh "Tuberous Sclerosis"] |
| 2 | [mh "Tuberous Sclerosis Complex 1 Protein"] |
| 3 | [mh "Tuberous Sclerosis Complex 2 Protein"] |
| 4 | ((Tuberos* OR tuberous*) AND scleros*):ti,ab,kw |
| 5 | (Cerebral NEXT scleros*):ti,ab,kw |
| 6 | (Bourneville* OR Epiloia):ti,ab,kw |
| 7 | #1 OR #2 OR #3 OR #4 OR #5 OR #6 |
| 8 | #7 with Cochrane Library publication date from Jan 2018 to present |

**Systematic Reviews in PubMed am 12.01.2023**

verwendete Suchfilter:
*Konsentierter Standardfilter für Systematische Reviews (SR), Team Informationsmanagement der Abteilung Fachberatung Medizin, Gemeinsamer Bundesausschuss, letzte Aktualisierung am 02.01.2020.*

| # | Suchfrage |
|---|---|
| 1 | Tuberous Sclerosis [mh] |
| 2 | "Tuberous Sclerosis Complex 1 Protein"[mh] |
| 3 | "Tuberous Sclerosis Complex 2 Protein"[mh] |
| 4 | (Tuberos*[tiab] OR tuberous*[tiab]) AND scleros*[tiab] |
| 5 | Cerebral scleros*[tiab] |
| 6 | Bourneville*[tiab] OR Epiloia[tiab] |
| 7 | #1 OR #2 OR #3 OR #4 OR #5 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 |

| # | Suchfrage |
|---|---|
| | 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])))))) |
| 10 | (#8) AND ("2018/01/01"[PDAT] : "3000"[PDAT]) |
| 11 | (#9) NOT "The Cochrane database of systematic reviews"[Journal] |
| 12 | (#10) NOT (retracted publication [pt] OR retraction of publication [pt]) |

**Leitlinien in PubMed am 12.01.2023**

verwendete Suchfilter:
*Konsentierter Standardfilter für Leitlinien (LL), Team Informationsmanagement der Abteilung Fachberatung Medizin, Gemeinsamer Bundesausschuss, letzte Aktualisierung am 21.06.2017.*

| # | Suchfrage |
|---|---|
| 1 | Tuberous Sclerosis [mh] |
| 2 | "Tuberous Sclerosis Complex 1 Protein"[mh] |
| 3 | "Tuberous Sclerosis Complex 2 Protein"[mh] |
| 4 | (Tuberos*[tiab] OR tuberous*[tiab]) AND scleros*[tiab] |
| 5 | Cerebral scleros*[tiab] |
| 6 | Bourneville*[tiab] OR Epiloia[tiab] |
| 7 | #1 OR #2 OR #3 OR #4 OR #5 OR #6 |
| 8 | (#7) AND (Guideline[ptyp] OR Practice Guideline[ptyp] OR guideline*[Title] OR Consensus Development Conference[ptyp] OR Consensus Development Conference, NIH[ptyp] *OR* recommendation*[ti]) |
| 9 | (#8) AND ("2018/01/01"[PDAT] : "3000"[PDAT]) |
| 10 | (#9) NOT (retracted publication [pt] OR retraction of publication [pt]) |

**Iterative Handsuche nach grauer Literatur, abgeschlossen am 12.01.2023**

- Arbeitsgemeinschaft der Wissenschaftlichen Medizinischen Fachgesellschaften (AWMF)
- Leitlinienprogramm Onkologie (Deutsche Krebsgesellschaft, Deutsche Krebshilfe, AWMF)
- Nationale VersorgungsLeitlinien (NVL)

- National Institute for Health and Care Excellence (NICE)
- Scottish Intercollegiate Guideline Network (SIGN)
- World Health Organization (WHO)

- Dynamed / EBSCO
- Trip Medical Database

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2. **National Guideline Alliance.** Epilepsies in children, young people and adults: effectiveness of antiseizure therapies for infantile spasms; evidence reviews underpinning recommendations 6.3.1-6.3.11 [online]. London (GBR): NICE; 2022. [Zugriff: 12.01.2023]. (NICE guidelines; Band NG217). URL: https://www.ncbi.nlm.nih.gov/books/n/niceng217er36/pdf/.

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[B] **McGowan J, Sampson M, Salzwedel DM, Cogo E, Foerster V, Lefebvre C.** PRESS Peer Review of Electronic Search Strategies: 2015 Guideline Statement. J Clin Epidemiol 2016;75:40-46. https://doi.org/10.1016/j.jclinepi.2016.01.0

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

Verfahrens-Nr.: 2022-B-352

| **Verfasser** | |
|---|---|
| Name der Institution | |
| Namen aller beteiligten Sachverständigen | Gesellschaft für Neuropädiatrie und Gesellschaft für Epileptologie |
| Datum der Erstellung | 21. Februar 2023 |

*(Bei mehreren beteiligten Fachgesellschaften bitte mit entsprechenden Angaben.)*

| **Indikation** |
|---|
| Zusatztherapie von Krampfanfällen im Zusammenhang mit Tuberöser Sklerose (TSC) bei Patienten ab 2 Jahren |
| **Fragen zur Vergleichstherapie** |
| Was ist der Behandlungsstandard in o.g. Indikation unter Berücksichtigung der vorliegenden Evidenz? Wie sieht die Versorgungspraxis in Deutschland aus?<br>*(Bitte begründen Sie Ihre Ausführungen; geben Sie ggf. zitierte Quellen in einer Referenzliste an.)* |
| Die Standardbehandlung epileptischer Anfälle bei TSC hängt vom Zeitpunkt der Manifestation ab.<br>1) Manifestation im Säuglingsalter als West Syndroms gemäß aktueller S2 Leitlinie (nicht relevant aufgrund des Alters aufgrund der o.g. Fragestellung): Ersttherapie mit Vigabatrin, Zusatztherapie Prednisolon oder ACTH (1).<br><br>2) Therapie ab 2 Jahren: Behandlung wie eine fokale/multifokale Epilepsie (2, 3). In einer aktuellen Analyse in Deutschland, wurden folgende anfallssupprimierende Medikamente in absteigender bei TSC eingesetzt (in Klammern die Rate von Patienten mit ≥ 50% Anfallsreduktion (3)): Valproat (70%), Lamotrigin (79%), Oxcarbazepin (67%), Levetiracetam (40%), Lacosamid (48%), Topiramat (keine Daten zur Responderraten bei TSC), Clobazam (69%) und Carbamazepin (67%). Vigabatrin wird vorwiegend bei Kindern < 2 Jahren eingesetzt und wird daher hier nicht erwähnt. Es muss bemerkt werden, dass sich die Studien in ihrem Design und Fallzahl z.T. deutlich unterschieden haben. Aufgrund der Tatsache, dass die Patienten in dem Alter von 2 Jahren oft nicht naiv auf anfallssupprimierende Medikamente sind (Ersttherapie aufgrund im jungen Alters wie oben angemerkt oft mit Vigabatrin ggf. +Steroide), ist in dem Fall als erste Zusatztherapie Lamotrigin oder Oxcarbazepin der aktuelle Behandlungsstandard. Für Patienten, die vor dem 2. Lebensjahr noch keine Epilepsie hatten, stellt die Therapie mit Lamotrigin oder Oxcarbazepin die gängige Ersttherapie da. Als Standard in der Zusatztherapie sind dann Levetiracetam und Lacosamid (bzw. Lamotrigin oder Oxcarbazepin, je nachdem, welches Medikament in der Ersttherapie schon verwendet wurde). |
| Gibt es Kriterien für unterschiedliche Behandlungsentscheidungen in der o.g. Indikation, die regelhaft berücksichtigt werden? Wenn ja, welche sind dies und was sind in dem Fall die Therapieoptionen?<br>*(Bitte begründen Sie Ihre Ausführungen; geben Sie ggf. zitierte Quellen in einer Referenzliste an.)* |

Die zwei unten genannten „neuen“ Medikamente werden regelhaft in der Zusatztherapie der TSC ab 2 Jahren berücksichtigt. Beide Medikamente verfügen über neuartige zelluläre Wirkmechanismen, die sich sowohl untereinander als auch von allen oben genannten (1. Frage des GBA) anfallssupprimierenden Medikamente signifikant unterscheiden. Die Prüfung der drei folgenden Medikamente erfolgte ausnahmslos an einer therapierefraktären Kohorte (die meisten Patienten hatten im Median vor der Studienmedikation 7 oder mehr anfallssupprimierende Medikamente) in randomisierten, doppelblinden Placebostudien.

1) Everolimus: Everolimus wirkt über die Hemmung des mTOR Pathways, der bei TSC durch Mutation im *TSC-1* bzw. *TSC-2* disinhibiert wird. Everolimus gilt daher auch als sogenannte Präzisionstherapie bei TSC. Responderraten (≥50% Anfallsreduktion) lagen je nach Studie bei 28 bzw. 40% (vs. 15% in der Placebogruppe (4)). Langzeitdaten über 2 Jahre zeigen eine Responderrate von 57% (5). Aufgrund des einzigartigen Wirkmechanismus und dem Aspekt der Responderraten an einer hochtherapierefraktären Patientengruppe stellt Everolimus eine sinnvolle, Präzisionsmedizin basierte Alternative zur Zusatztherapie von epileptischen Anfällen bei TCS ab 2 Jahren da.
2) Cannabidiol: Cannabidiol wirkt über die Hemmung neuronaler Exzitabilität durch Inhibition von GPR55 and TRPV1 Rezeptoren und der Modulation Adenosin vermittelter Signalwege (6). Responderraten (≥50% Anfallsreduktion) lagen je nach Dosis bei 36 bzw. 40% (vs. 22% in der Placebogruppe (7)). Langzeitdaten über 2 Jahre zeigen eine Responderrate von 61% nach einem Jahr (8). Aufgrund des einzigartigen Wirkmechanismus und dem Aspekt der Responderraten an einer hochtherapierefraktären Patientengruppe stellt Cannabidiol eine sinnvolle Alternative zur Zusatztherapie von epileptischen Anfällen bei TCS ab 2 Jahren da.

*Referenzliste:*


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