A report for Universitätsklinikum Schleswig-Holstein/Campus Kiel on shared decision making for epilepsy

Kleijnen Systematic Reviews Ltd

December 2018

Kleijnen Systematic Reviews Ltd
Unit 6, Escrick Business Park
Riccall Road
Escrick
York
YO19 6FD
United Kingdom
Telephone: +44 (0)1904 727980
Fax: +44 (0)1904 720429
Email: robert@systematic-reviews.com
Website: www.systematic-reviews.com

Heike Raatz
Nigel Armstrong
Thea Drachen
Vanesa Huertas Carrera
Debra Fayter
Kate Misso
Jos Kleijnen
Robert Wolff

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF ABBREVIATIONS

AE	Adverse event
AED	Anti epileptic drug
AEP	Adverse events profile
BNF	British National Formulary
CADTH	Canadian Agency for Drugs and Technologies in Health
CBZ	carbamazepine
CBZ-CR	controlled-release carbamazepine
CDSR	Cochrane Database of Systematic Reviews
CENTRAL	Cochrane Central Register of Controlled Trials
CH	Switzerland
CI	Confidence interval
CrI	Credible interval
DARE	Database of Abstracts of Reviews of Effects
DE	Germany
DGfE	Deutsche Gesellschaft für Epileptologie
ESL	Eslicarbazepine-Acetate
EQ-5D	European Quality of Life-5 Dimensions
EURAP	European and International Registry of Antiepileptic Drugs in Pregnancy
FAQ	Frequently asked question
GIN	Guidelines International Network
GQoL	Global quality of life
GRADE	Grading of Recommendations, Assessment, Development and Evaluation
HRQoL	Health-related quality of life
HTA	Health technology assessment
ILAE	International League Against Epilepsy
KSR	Kleijnen Systematic Reviews Ltd
LCM	Lacosamide
LEV	Levetiracetam
LTG	Lamotrigine
MN	Minnesota
NAAPR	North American Antiepileptic Drug and Pregnancy Registry
NICE	National Institute for Health and Care Excellence
NMA	network meta-analysis
NMBR	Medical Birth Registry of Norway

No.	number
OR	Odds ratio
OXC	Oxcarbazepine
PICOS	Participants, intervention, comparators, outcomes and study design
QoL	Quality of life
QOLIE-10	Quality of Life in Epilepsy 10 questionnaire
RCT	Randomised controlled trial
SD	standard deviation
SDM	Shared decision making
SMBR	Swedish Medical Birth Register
SMR	Standardised Mortality Ratio
SR	Systematic review
SUDEP	Sudden unexpected death in epilepsy
TEAEs	Treatment-emergent adverse events
TPM	Topiramate
UK	United Kingdom
UKIre	UK and Irish Epilepsy and Pregnancy Registers
USA	United States of America
VPA	Valproic acid
ZNS	Zonisamide

1. PROJECT OBJECTIVE

One aim of the research project “Making SDM a reality” is to create interactive websites to inform patients as part of shared decision making (SDM).

For a range of topics, Kleijnen Systematic Reviews Ltd (KSR) will prepare an evidence table of treatment options and an evidence report with a synthesis of the literature underpinning the evidence table.

2. METHODS

2.1 INCLUSION CRITERIA

The research question underpinning the literature searches for this topic was developed in conjunction with clinical departments at Universitätsklinikum Schleswig-Holstein/Campus Kiel. The question was framed in terms of participants, intervention, comparators and outcomes (PICOS), see Table 1.

As detailed below, literature searches were carried out using a stepwise approach to identify relevant studies according to study design. In the first step, searches aimed to identify relevant systematic reviews and guidelines. For this project, no further searches were conducted as relevant results were extracted from the identified literature.

Table 1: Inclusion criteria for searches

PICOS	
Patients	Patients with first occurrence of epilepsy or in the early stage of treatment with monotherapy, respectively
Interventions	Eslicarbazepine acetate (ESL) Lacosamide (LCM) Lamotrigine (LTG) Levetiracetam (LEV) Oxcarbazepine (OXC) Topiramate (TPM) Valproic acid* (VPA) Zonisamide (ZNS)
Control	Comparisons between interventions and with no pharmaceutical therapy
Outcomes	**Primary**: Impact on (patient-reported) seizure frequency, number of hospitalisations, adverse events **Secondary**: Attitude towards therapy, adherence, patient satisfaction
Study design	Systematic reviews and guidelines

ESL = Eslicarbazepine acetate; LCM = Lacosamide; LEV = Levetiracetam; LTG = lamotrigine; OXC = oxcarbazepine; TPM = topiramate; UK = United Kingdom; VPA = valproic acid; ZNS = zonisamide

* Valproic acid and sodium valproate are two forms of the same medication with a difference in the preparation method. For the purposes of this report, both the evidence for sodium valproate and valproic acid will be referred to as for valproic acid (VPA).

In consultation with the commissioner, questions frequently asked by patients in conjunction with outcomes identified in the literature were developed into an evidence table outline.

Classification of epilepsy types and seizures have changed over the years, the German guideline[1] outlines three classification systems from the International League Against Epilepsy (ILAE) in 1989[2], Berg et al. 2010[3] and Scheffer 2017[4] (see Tables in Appendix 2). The newest ILAE classification, which is not yet finalised, still has some limitations according to the authors of the German guideline and therefore the Berg 2010[3] classification is used for this report.

2.2 FREQUENTLY ASKED QUESTIONS

The following research questions were identified as frequently asked questions (FAQs):

- FAQ 1: What does it involve?
  - Dosing frequency
  - Potential interactions with other medications?
  - Potential contraindications?
- FAQ 2: Will my symptoms get better?
  - Seizure control/frequency
- FAQ 3: Will it affect my life expectancy?
- FAQ 4: Will it affect my quality of life?
- FAQ 5: Which side effects / complications might be related to treatment?
  - Potential side effects
  - Adverse Events
- FAQ 6: How will it impact my daily life?

2.3 LITERATURE SEARCHES

Literature searches were carried out using a stepwise approach to identify relevant studies according to study design:

1. Systematic reviews and guidelines
2. Randomised controlled trials
3. Observational studies
4. Supplementary searches

Only in the event of no relevant systematic reviews or guidelines being identified were further searches to be conducted to identify randomised controlled trials (RCTs; Step 2.), and only if no RCTs were identified, searches would have been undertaken to identify observational studies (Step 3.).

The search strategies were developed specifically for each database and the keywords adapted according to the configuration of each database. Searches were limited by date range for systematic reviews and guidelines 2012-2018. Where appropriate, searches were limited to remove animal studies. Searches were not limited by language or publication status.

Handling of citations

Identified references from the bibliographic database searches were downloaded into EndNote bibliographic management software for further assessment and handling. Individual records within the EndNote libraries were tagged with searching information, such as searcher, date searched, database host, database searched, strategy name and iteration, theme or search question. This enabled the information specialist to track the

origin of each individual database record, and its progress through the screening and review process.

Quality assurance within the search process

For all searches undertaken by the KSR Information team, the main Embase strategy was independently peer reviewed by a second KSR Information Specialist. Strategy peer review was informed by items based on the Canadian Agency for Drugs and Technologies in Health (CADTH) checklist.[5]

2.4 SEARCH SOURCES

1. Systematic reviews and guidelines

The following systematic review specific databases were searched from 2012 to present:

- KSR Evidence (Internet): up to 2018/02/26 (https://ksrevidence.com/)
- Cochrane Database of Systematic Reviews (CDSR) (Wiley): issue 2 of 12, February 2018
- Database of Abstracts of Reviews of Effects (DARE) (Wiley): issue 2 of 4, April 2015
- Health Technology Assessment (HTA) database (Wiley): issue 4 of 4, October 2016

The following guidelines resources were searched from 2012 to present:

- Guidelines International Network (GIN) (Internet): up to 2018/02/26 (http://www.g-i-n.net/library/international-guidelines-library)
- NICE Evidence (Internet): up to 2018/02/26 (www.evidence.nhs.uk/)

Full details of all search strategies are presented in Appendix 1.

2. RCTs

As the search for secondary sources was sufficient no additional searches for primary studies were undertaken.

3. Observational studies

As the search for secondary sources was sufficient no additional searches for observational studies were undertaken.

4. Supplementary searches

In addition to the formal searches documented above, a targeted search was conducted to identify studies with health-related quality of life data relating to the following drug interventions: eslicarbazepine acetate, lacosamide, levetiracetam, valproic acid, and zonisamide. Details of the search strategies used for this targeted search for health-related quality of life data are presented in Appendix 1. Reviewers also conducted supplementary hand searches to identify potentially relevant references, e.g. guidance specific to Germany and websites of patient organisations. The bibliographies of included studies and review articles were also checked for additional relevant articles.

2.5 METHODS OF STUDY SELECTION, QUALITY ASSESSMENT AND DATA EXTRACTION

Study selection

Two reviewers independently inspected the title and abstract of each reference identified by the search and determined the potential relevance of each article. For potentially relevant articles, or in cases of disagreement, the full article was obtained, independently inspected, and inclusion criteria applied. Any disagreements were resolved through discussion.

Data extraction

An evidence hierarchy was used to select the most appropriate study(ies) to populate the evidence table. Where more than one study could provide evidence for the table the most relevant studies were extracted using the following criteria: recency (most recent preferred), quality (highest quality preferred), representativeness (populations representative of the general target population preferred). Where there were gaps in the evidence table (no systematic review or guideline available), as described before, relevant RCTs would have been searched for and extracted, and where no RCTs would have been identified, observational studies would have been used.

For each study, data were extracted by one reviewer and checked by another. Any disagreements were resolved by consensus.

3. RESULTS

3.1 LITERATURE SEARCHES AND INCLUSION ASSESSMENT

For this evidence report, systematic searches for systematic reviews and guidelines were supplemented by hand searches.

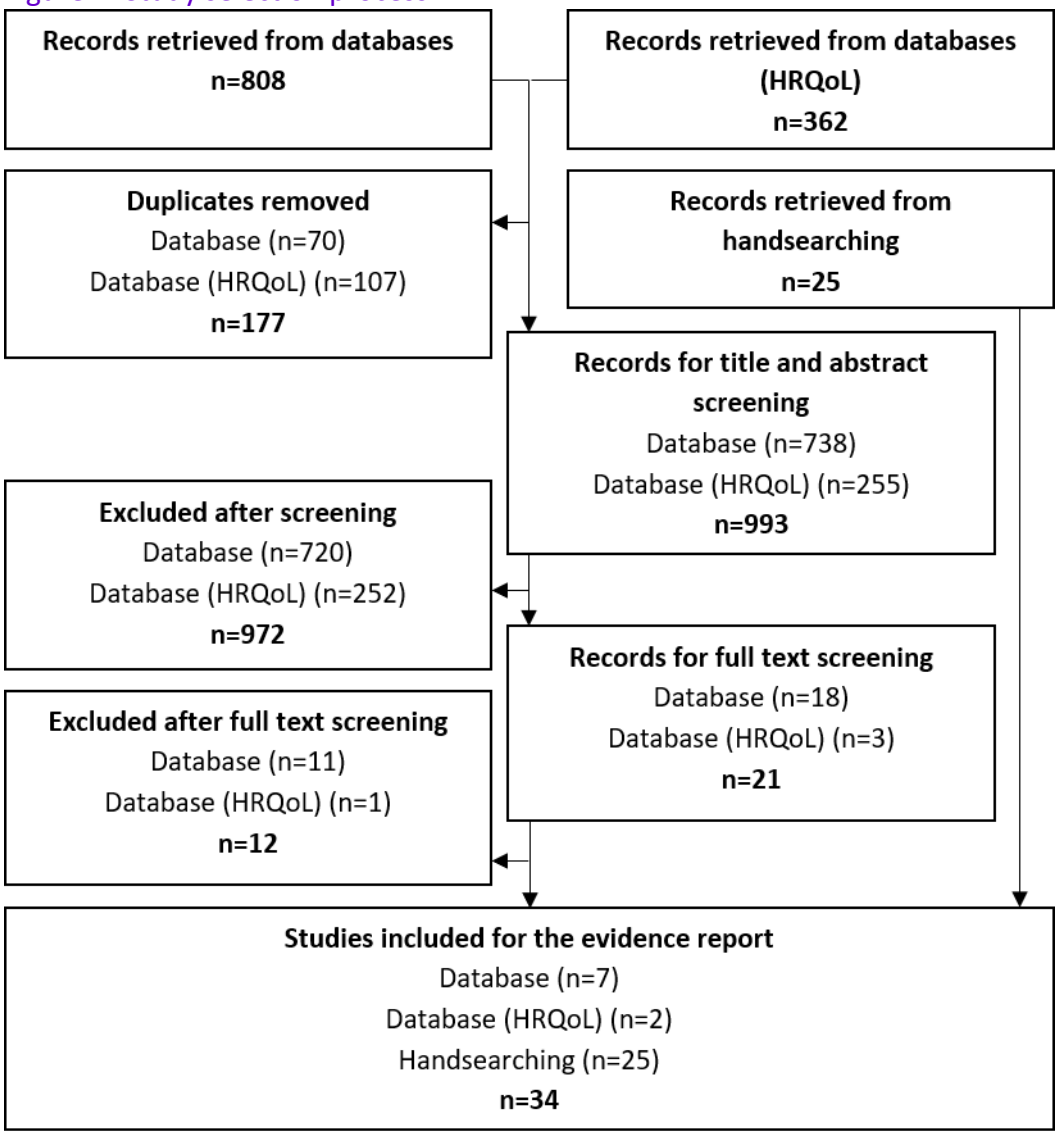
Systematic searches were conducted on 26 February 2018 to identify relevant questions (frequently asked questions; FAQs) and to answer the clinical questions focusing on systematic reviews, meta-analyses and evidence-based guidelines. A total of 808 references were retrieved from literature searches. After de-duplication, 738 titles and abstracts were screened by two reviewers. Full papers were obtained for 20 citations. After further review, a total of 12 were excluded.

To answer the more descriptive FAQs, handsearching, concentrating on patient organisations which identified patient-driven arguments and prioritisations, was performed. Thus this handsearch identified supporting evidence from non-standard sources. It also picked up a very new network meta-analysis which had not been published at the date of the systematic searches. The handsearches and reference checking identified an additional 24 publications and web-based sources of supportive evidence.

A summary of the study selection process according to modified PRISMA reporting guidelines is reported in Figure 1.

Reference checking identified 26 primary studies used in a subset of the eight included reviews, systematic reviews and network meta-analyses found in the systematic searches (not included in the PRISMA figure, but presented in table 3).

Figure 1: Study selection process



3.2 OVERVIEW OF THE EVIDENCE

The information identified to answer the patient questions is given below organised by question and the underpinning evidence in Tables 2 and 3.

Table 2: Evidence sources

Study ID	What does it involve?	Will my symptoms get better?	Will it affect my life expectancy?	Will it affect my quality of life?	Which side effects/complications?	How will it impact my daily life?
BNF[6]	x				x	x
BNF: Epilepsy[7]	x					
Campos 2016[8]				x		
DeGiorgio 2018[9]			x			
DGfE 2013[10]	x					
Elger 2017[1]	x					
Epilepsy prediction tools[11]		x				
Hampel 2017[12]			X			
Jacoby 2015[13]				x		
Kwan 2004[14]		x				
Lamberink 2017[15]		x				
Lattanzi 2018[16]		x			x	x
Maguire 2016[17]			x			
Marson 2007[18]				x		
Nevitt 2017[19]		x			x	x
patient.info/medicine[20]	x					
Rosenow 2012[21]				x		
Ryvlin 2011[22]			x			
SIGN 2015[23]			x			
Strozzi 2015[24]		x				
sudep.org[25]			x			
Thurman 2017[26]			x			
Tomson 2015[27]	x					
www.bast.de[28]					x	x
www.ema.europa.eu[29]	x					
Rote Liste[53]	x					
www.informedhealth.org[30]	x					
www.pharmawiki.ch[31]	x					
epilepsysociety.org.uk[55]	x					

BNF = British National Formulary; CH = Switzerland; DE = Germany; DGfE = Deutsche Gesellschaft für Epileptologie; UK = United Kingdom

Table 3: Primary studies used in some of the reviews, SRs and NMAs of Table 2

Study ID	What does it involve?	Will my symptoms get better?	Will it affect my life expectancy?	Will it affect my quality of life?	Which side effects/complications?	How will it impact my daily life?
Alexandre 2011[32]				x[a]		
Benn 2008[33]			x[b]			
Campbell 2014[34]	x[c]					
Cockerell 1997[35]			x[b]			
Granbichler 2015[36]			x[b]			
Guekht 2007[37]				x[d]		
Hauser 1980[38]			x[b]			
Hernandez-Diaz 2012[39]	x[c]					
Hesdorffer 2011[40]			X[e]			
Hesdorffer 2012[41]			x[e]			
Hunt 2008[42]	x[c]					
Lamberts 2012[43]			x[e]			
Lhatoo 2001[44]			x[b]			
Liebenthal 2015[45]			x[e]			
Lindsten 2000[46]			x[b]			
Mawhinney 2013[47]	x[c]					
Mohanraj 2006[48]			x[b]			
Morgan 2002[49]			x[b]			
Neligan 2011[50]			x[b]			
Nilsson 1997[51]			x[b]			
Olafsson 1998[52]			x[b]			
Rakitin 2011[53]			x[b]			
Tomson 2011[54]	x[c]					
Tomson 2012[55]	x[c]					
Trinka 2013[56]			x[b]			
Veiby 2014[57]	x[c]					

Reported in a) Campos 2016[8], b) Thurman 2017[26], c) Tomson 2015[27], d) Rosenow 2012[21], e) Hampel 2017[12]

FAQ 1: What does it involve?

Table 4 and 5 present details of the eight treatments. Table 6 presents numbers for the teratogenic effects of some of the anti epileptic drugs (AEDs).

Please note that information on AED authorisation is not included in the FAQ 1 table. The reason for this is mainly that information on AEDs is continually updated and authorisation is typically dependant on type of epilepsy, which can be intractable, particularly as types can be overlapping.

Issue of interest: Due to the variable bioavailability and the associated risk of relapse (e.g. fitness to drive) especially for patients free from seizures, a careful evaluation of the risks and information of the patient are necessary before changing to a generic brand. This particularly applies to a change between two generics as the difference in bioavailability can be up to 25%. In those instances where the manufacturer of the original drug also offers a generic with the identical formulation an exchange is possible without problems though. (Deutsche Gesellschaft für Epileptologie 2013[10]; British National Formulary: Epilepsy[7]).

Table 4: Description, dosing frequency, indications, contraindications and potential co-medication interactions

	Eslicarbazepine acetate (ESL)	**Lacosamide (LCM)**	**Lamotrigine (LTG)**	**Levetiracetam (LEV)**	**Oxcarbazepine (OXC)**	**Topiramate (TPM)**	**Valproic Acid (VPS)**	**Zonisamide (ZNS)**
Administration form	Tablets, oral liquid	Tablets, oral liquid, IV injectable	Tablets, dispersible tablets (to produce oral liquid)	Tablets, oral liquid, sachets of granules to be taken with liquids	Tablets	Tablets	Tablets, oral liquid medicine	Capsules
Administration frequency	1x/day	2x/day	1-2x/day	2x/day	2x/day	2x/day	2-4/day possible	1-2x/day
Administration rules	For most anti-epileptic drugs it is important to start with low doses and follow the dose escalation advice. Similarly, when you intend to finish treatment with a drug, you have to slowly reduce doses and follow the drug withdrawal advice.							
	Regardless of meals	Regardless of meals	Regardless of meals	Regardless of meals	Regardless of meals	Regardless of meals but with plenty of liquid	Tablets: one hour before meals with water (no gas) Liquid: with meals and with a liquid containing sugar	Regardless of meals
Co-medication interaction potential	Most anti-epileptic drugs may interact with other drugs to a differing extent and e.g. increase or decrease their efficacy, or the efficacy of the anti-epileptic drug may be impacted by other drugs. Patients should inform their treating physician about their co-medication intake. For further information on potential drug interactions see Table 5.							

	Eslicarbazepine acetate (ESL)	Lacosamide (LCM)	Lamotrigine (LTG)	Levetiracetam (LEV)	Oxcarbazepine (OXC)	Topiramate (TPM)	Valproic Acid (VPS)	Zonisamide (ZNS)
Women of childbearing age	Contraceptives may influence the efficacy of your anti-epileptic medication or the anti-epileptic medication may decrease the efficacy of your contraceptives. Talk to your physician about the best contraceptive or alternative ways of contraception. Plasma drug concentrations need to be carefully monitored.							
	Influences the efficiency of oral contraceptives Other reliable contraception should be used.	Non-enzyme-inducing, i.e. unlikely to interact with oral contraceptives.	Hormonal contraceptives reduce plasma levels of LTG. Appropriate dose escalation/ reduction might be needed. Contraceptives without pill-free week or alternative contraception recommended.	Non-enzyme-inducing, i.e. unlikely to interact with oral contraceptives.	Influences the efficiency of oral contraceptives Other reliable contraception should be used.	May influence the efficiency of oral contra-ceptives and may impact/ increase menstrual bleeding ; Test for pregnancy before treatment initiation due to teratogenic drug effects; Use effective contraception.	VPA is not recommended to girls and women of childbearing age, only if alternative treatment options have failed. Test for pregnancy before treatment initiation. Need to use effective - contraception. No interaction with oral contraceptives, however, contraception that is not dependent on user should be preferred.	Need to use effective contraception when using the drug and for one month after last dose.

	Eslicarbazepine acetate (ESL)	Lacosamide (LCM)	Lamotrigine (LTG)	Levetiracetam (LEV)	Oxcarbazepine (OXC)	Topiramate (TPM)	Valproic Acid (VPS)	Zonisamide (ZNS)
Pregnancy	Women of childbearing age intending to get pregnant should talk to their physician as early as possible. Anti-epileptic treatment may be harmful to the unborn child. Treatment should be carefully reconsidered with your physician but should never be stopped abruptly. Monotherapy and lowest possible dosing based on plasma levels and clinical advice (especially in first trimester of pregnancy) are recommended. Women should be well informed about the risks of congenital malformations and possibilities of prenatal diagnostics. Women taking anti-epileptics have a 2-3 fold higher risk of congenital malformations compared to the general population, especially when taking multiple [anti-]epileptics. In the general population, about 2-3 out of 100 unborn children have congenital malformations. Folic acid intake as early as possible may increase your chances to give birth to a healthy child.							
	Risk in humans not known. Careful risk-benefit assessment with physician is needed. Supplementation with vitamin K in last weeks of pregnany/ newborn child potentially needed.	Risk in humans not known. Careful risk-benefit assessment with physician is needed.	Limited data in humans do not suggest an increased risk for congenital malformations. Monitoring of plasma-drug concentration recommended to avoid seizures or side effects due to pregnancy-related physiological changes.	Limited data in humans do not suggest an increased risk for congenital malformations. Monitoring of plasma-drug concentration recommended to avoid seizures or side effects due to pregnancy-related physiological changes.	Close monitoring of plasma-drug concentration recommended to avoid seizures or side effects due to pregnancy-related physiological changes. Supplementation with vitamin K in last weeks of pregnany/ newborn child potentially needed.	Increased risk of congenital malformations following exposure during the first trimester, consider alternative treatment options. If used during first trimester, do careful prenatal, fetal, and post-natal monitoring.	High risk of congenital malformations and neurological disorders/ developmental retardation. Do not use or only in strict cooperation with your physician.	Risk in humans not known. However, limited data suggest increase in low-birth weight/small for gestational age infants. Careful risk-benefit assessment with physician is needed.

	Eslicarbazepine acetate (ESL)	Lacosamide (LCM)	Lamotrigine (LTG)	Levetiracetam (LEV)	Oxcarbazepine (OXC)	Topiramate (TPM)	Valproic Acid (VPS)	Zonisamide (ZNS)
Breastfeeding women	Risk to breastfed child can not be excluded, avoid breastfeeding	Risk to breastfed child can not be excluded, avoid breastfeeding	Risk to breastfed child can not be excluded, avoid breastfeeding, limited data suggest no harmful effect on infant	Risk to breastfed child can not be excluded, avoid breastfeeding	Risk to breastfed child can not be excluded, avoid breastfeeding	Risk to breastfed child possible, avoid breastfeeding or consider alternative treatment	Avoid breastfeeding due to risk of haematological disorders in breast-fed infants	Risk to breastfed child can not be excluded, avoid breastfeeding for 4 weeks after last dose
BNF[6], patient.info/medicine[20], Epilepsy Society[55]								

Table 5: Description, dosing frequency, indications, contraindications and potential co-medication interactions

Eslicarbazepine acetate (ESL)
• ESL is related to Carbamazepine (CBZ). Its effects are due to the inhibition of voltage-gated sodium channels. • Co-medication interactions: ESL is an inducer of CYP3A4 and an inhibitor of CYP2C19 (both of these are enzymes involved in the metabolism of different drugs, inducing one and inhibiting another can mean that for some drugs the rate of metabolism is increased, resulting in reduced effect, for others it is decreased resulting in increased effect). Interactions possible with e.g. some anti-epileptics, contraceptives, simvastatin, warfarin (close INR monitoring recommended), mono-amino-oxidase-inhibitors. • Other special warnings and precautions: close monitoring for suicidal thoughts/suicidality, dizziness/fatique might increase risk for falls or accidents, severe skin reactions possible • Contraindications: hypersensitivity; second or third degree atrioventricular block; renalimpairment – dif CL_{CR} less than 30 mL/minute drug not recommended; severe liver impairment
PharmaWiki.ch[31], BNF[6], please see more information on Rote Liste[53] via https://flexikon.doccheck.com/de/Eslicarbazepinacetat
Lacosamide (LCM)
• The LCM effects are due to the enhancement of the slow inactivation of the voltage-dependent sodium channels • Co-medication interactions: LCM has a low interaction potential, however, caution to use in combination with some other anti-epileptic medication or class I antiarrhythmics • The dose should be monitored carefully during pregnancy and after birth, and adjustments be made on a clinical basis • Other special warnings and precautions: not indicated in patients with certain types of cardiac arrhythmia; severe cardiac disease; close monitoring

for suicidal thoughts/behaviour; dizziness might increase risk for falls or accidents • Contraindications: hypersensitivity; second or third degree atrioventricular block;
www.informedhealth.org[30], PharmaWiki.ch[31], patient.info/medicine[20], BNF[6], please see more information on Rote Liste[53] via https://flexikon.doccheck.com/de/Lacosamid
Lamotrigine (LTG)
• LTG's effects are mainly due to the blockade of voltage-dependent sodium channels and the inhibition of the release of excitatory neurotransmitters such as glutamate. • Co-medication interactions: LTG is conjugated by UDP-glucuronyltransferases. Corresponding and further drug interactions are possible. The drug does not interact with CYP450. Caution: Hormonal contraceptives reduce plasma levels of lamotrigine. • Other special warnings and precautions: close monitoring for suicidal thoughts/behaviour, (severe) skin reactions possible Contraindications: Hypersensitivity; Severe renal insufficiency; LTG can cause blood disorders and severe skin reactions and the doctor should be contacted straightaway if high temperature or swollen gland, extreme tiredness, unexplained bruising or bleeding, or a severe skin rash occur.
PharmaWiki.ch[31], patient.info/medicine[20], BNF[6], please see more information on Rote Liste[53] via https://flexikon.doccheck.com/de/Lamotrigin
Levetiracetam (LEV)
• LEV is bio transformed by enzymatic hydrolysis of the acetamide group. Its effects are attributed to binding to the synaptic vesicle protein 2A. This leads to a reduced release of neurotransmitters in the central nervous system. • Co-medication interactions: LEV has a low potential for drug interactions. It does not interact with CYP (cytochrome P450) or UGT (Uridine 5'-diphospho-glucuronosyltransferase) isoenzymes. • Special warnings and precautions: special precautions when decreased renal or liver function, close monitoring for suicidal thoughts/suicidality, dizziness/somnolence might decrease ability to drive/work on machines Contraindications: Hypersensitivity
www.informedhealth.org[30], PharmaWiki.ch[31], patient.info/medicine[20], BNF[6], please see more information on Rote Liste[53] via https://flexikon.doccheck.com/de/Levetiracetam
Oxcarbazepine (OXC)
• OXC is a derivative of Carbamazepine (CBZ) and is a prodrug that is bio transformed in the body to the active 10-monohydroxymetabolite. May be taken as a slow-release form. The effects of OXC are based primarily on the inhibition of voltage-sensitive sodium channels. • Co-medication interactions: CYP2C19 inhibitor; unlike Carbamazepine (CBZ) weak inducer of CYP3A (involved in the metabolism of different drugs, leading to changed efficiency); interactions have been reported with oral contraceptives, calcium channel blockers, other antiepileptic drugs and lithium. • Special warnings and precautions: Hypersensitivity; Severe skin reactions; Metabolic/Blood/Renal/Liver diseses (caution in severe hepatic impairment, dose adjustments in renal impairment); Cardiac conduction disorders; Heart failure; Contraindications: Hypersensitivity
PharmaWiki.ch[31], patient.info/medicine[20], BNF[6], please see more information on Rote Liste[53] via https://flexikon.doccheck.com/de/Oxcarbazepin
Topiramate (TPM)

• TPM is an AED with anticonvulsant, neuroprotective, appetite-suppressing and teratogenic properties. The blockade of voltage-dependent sodium and calcium channels reduces the generation and number of action potentials and thus the frequency of seizures. • Co-medication interactions: TPM has a high potential for drug interactions. In high plasma concentrations, topiramate inhibits the isoenzyme CYP2C19 and weakly induces CYP3A4. If given with phenytoin it can increase the phenytoin concentration in some patients, it reduces the systemic availability of lithium and risperidone. When given together with valproic acid there is a risk of a pathologically increased level of ammonia in the blood. It should never be taken together with other drugs that increase the risk of kidney stones. Caution is warranted when TPM is given together with drugs that affect body temperature and sweating. • Special warnings, precautions and patient groups: Favourable for obese patients as it is appetite-suppressing, adjust in patients with renal impairment (risk of metabolic acidosis, risk of nephrolithiasis (ensure adequate hydration) • Contraindications: Hypersensitivity; Used with caution in patients with moderate to severe liver disorders as plasma clearance may be reduced. Avoid in acute porphyria patients.
PharmaWiki.ch[31], patient.info/medicine[20], BNF[6], please see more information on Rote Liste[53] via https://flexikon.doccheck.com/de/Topiramat
Valproic Acid (VPA)
VPA is not recommended to girls and women in the childbearing age, only if alternative treatment options have failed. Female patients need to be informed about the risks of the treatment and the use of an effective contraception. • Co-medication interactions: High potential for interactions, also with non-prescription medicines and herbal remedies and alcohol • Special warnings and precautions: Should not be used in women/teenagers at childbearing age, pregnant or breastfeeding women, not in women trying get pregnant (as doses over 1g daily are associated with increased risk of teratogenicity and developmental retardations in unborn children exposed to valproid acid throughout pregnancy as well as risk of haematological disorders in breast-fed infants); Women/teenagers at childbearing age should use effective contraception when treated with valproic acid; close monitoring for suicidal thoughts/suicidality;dizziness/somnolence might decrease ability to drive/work on machines. –Contraindications: Hypersensitivity, Kidney/Liver problems; Systemic lupus erythematosus; Acute porphyria; Mitochondrial disorders; Personal or family history of severe hepatic disfunction; Urea cycle disorder.
PharmaWiki.ch[31], patient.info/medicine[20], BNF[6], BNF: Epilepsy[7], Elger 2017[1], please see more information on Rote Liste[53] via https://flexikon.doccheck.com/de/Valproins%C3%A4ure and via https://flexikon.doccheck.com/de/Valproat
Zonisamide (ZNS)
• The effects of ZNS are attributed to interaction with voltage-dependent sodium and calcium channels. • Co-medication interactions: ZNS is a substrate of CYP3A4 (involved in the metabolism of different drugs) • Special warnings and precautions: (severe) skin reactions possible; caution is warranted in elderly, low body weight or poor appetite (monitor weight as fatal cases of weight loss reported in children), monitor serum bicarbonate concentration in children and those with risk factors for metabolic acidosis and consider dose reduction or discontinuation if metabolic acidosis develops); increased risk of kidney stones; overheating or dehydration possible; close monitoring for suicidal thoughts/suicidality • Contraindications: Hypersensitivity to ZNS or sulphonamides; Theoretically associated with antiepileptic hypersensitivity syndrome; Renal

impairment; Keep an eye on fluid balance (ensure adequate hydration); Hepatic impairment; Taking carboanhydrate inhibitors, since ZNS inhibits carbonic anhydrase, which can trigger further side effects;
PharmaWiki.ch[31], BNF[6], please see more information on Rote Liste[53] via https://flexikon.doccheck.com/de/Zonisamid
More in depth information on co-medication interactions can be found via www.ema.europa.eu[29] under product information for each AED. AED = anti epilepsy drug; ESL = Eslicarbazepine acetate; LCM = Lacosamide; LEV = Levetiracetam; LTG = lamotrigine; OXC = oxcarbazepine; TPM = topiramate; UK = United Kingdom; VPA = valproic acid; ZNS = zonisamide

Table 6: Overall frequencies of major congenital malformations for specific monotherapies

Data source Referenced	Lamotrigine (LTG)	Levetiracetam (LEV)	Oxcarbazepine (OXC)	Topiramate (TPM)	Valproic Acid (VPA)
EURAP[a]	2.9% (37/1280)	1.6% (2/126)	3.3% (6/184)	6.8% (5/73)	9.7% (98/1010)
NAAPR[b]	1.9% (31/1562)	2.4% (11/450)	2.2% (4/182)	4.2% (15/359)	9.3% (30/323)
UKIre[c,d,e]	2.3% (49/2098)	0.7% (2/304)	-	4.3% (3/70)	6.7% (82/1220)
NMBR[f]	3.4% (28/833)	1.7% (2/118)	1.8% (1/57)	4.2% (2/48)	6.3% (21/333)
SMBR[g]	2.9% (32/1100)	0% (0/61)	3.7% (1/27)	7.7% (4/52)	4.7% (29/619)

From Tomson 2015[27] Table 2
a) Tomson 2011[54]; b) Hernandez-Diaz 2012[39]; c) Campbell 2014[34]; d) Mawhinney 2013[47]; e) Hunt 2008[42]; f) Veiby 2014[57]; g) Tomson 2012[55]
EURAP = European and International Registry of Antiepileptic Drugs in Pregnancy; LTG = lamotrigine; LEV = Levetiracetam; NAAPR = North American Antiepileptic Drug and Pregnancy Registry; NMBR = Medical Birth Registry of Norway; OXC = oxcarbazepine; SMBR = Swedish Medical Birth Register; TPM = topiramate; UKIre = UK and Irish Epilepsy and Pregnancy Registers; VPA = valproic acid

FAQ 2: Will my symptoms get better?

Your symptoms will get better with the proper anti-epileptic drug (AED). Approximately 50% stop having seizures or have fewer seizures after taking the first drug they try. Overall, about 70% have no more seizures when they use AED. However, some 30% will still have seizures despite different treatments and polytherapy. In some cases seizures can stop without AED, you can do a risk estimation but there is no way to reliably predict whether a particular person will have more seizures. (Maguire 2016[17] and www.informedhealth.org[30])

Patients that have been seizure-free for a few years, might want to stop treatment with anti-epileptics at some point in time. Studies do not provide clear evidence regarding when treatment could or should best be stopped[24]. However, one epidemiologic review suggests that in 3 of 10 people that did not have any more seizures since starting treatment could stop taking medication after a couple of years without risking to have new seizures[14]. The decision to stop treatment, however, should depend on the patient's individual situation and should be discussed and evaluated together with the physician. A recent meta-analysis assessed the risk of seizure after stopping AED treatment [15]. The main predictors with higher seizure risk were found to be >10 seizures before remission, generalised tonic–clonic seizures, remote symptomatic causes, developmental delay, while patients with self-limiting epilepsy syndrome patient have a lower risk of seizures after stopping AED treatment than average. A risk calculator based on the meta-analysis is available[11].

The clinical evidence is presented in Tables 7-20. This evidence comes from two sources Nevitt 2017[19] and Lattanzi 2018,[16] both systematic reviews and network meta-analyses. Between them they cover all the eight treatments. Nevitt 2017[19] presents data on both focal and generalised seizures, Lattanzi 2018[16] only on focal seizures, thus there is a gap of

evidence for some of the AEDs for generalised seizures. The Lattanzi 2018[16] protocol mentions presenting time to first seizure, but the paper 1) does not actually present evidence, and 2) mentions that per protocol, LCM and ESL were not considered as they were note licensed and used in clinical practice as monotherapy at the time of publication of the protocol. They do mention intention to treat numbers and results for other outcomes though.

Most of the AEDs do not show a significant difference between them, neither with regards to time to first seizure or time to six- or 12-month seizure freedom or part of patients seizure free at six and 12 months. The only significant differences are found in:

- Time to first seizure for individuals with generalised tonic-clonic seizures, where VPA is preferable to TPM (Table 10)
- Time to six-month seizure freedom for individuals with generalised tonic-clonic seizures, where VPA is preferable to LTG (Table 15)
- Time to 12-month seizure freedom for individuals with focal seizures, where OXC is preferable to LEV (Table 18)

Table 7: List of tables for FAQ 2

Outcome	Type of seizures	AEDs	Table	Extra information
Time to first seizure				
Time to first seizure	Focal	LTG, LEV, OXC, TPM, VPA, ZNS	Table 8	Table 9
Time to first seizure	Generalised	LTG, LEV, OXC, TPM, VPA, ZNS	Table 10	Table 11
6-month seizure freedom				
Proportion of patients free of seizures	focal-onset with or without secondarily generalisation	ESL, LCM, LEV, ZNS	Table 12	-
Time to seizure freedom	Focal	LTG, LEV, OXC, TPM, VPA, ZNS	Table 13	Table 14
Time to seizure freedom	Generalised	LTG, LEV, OXC, TPM, VPA, ZNS	Table 15	Table 16
12-month seizure freedom				
Proportion of patients free of seizures	focal-onset with or without secondarily generalisation	ESL, LCM, LEV, ZNS	Table 17	-
Time to seizure freedom	Focal	LTG, LEV, OXC, TPM, VPA, ZNS	Table 18	Table 19
Time to seizure freedom	Generalised	LTG, LEV, OXC, TPM, VPA, ZNS	Table 20	Table 21

Table 8: Time to first seizure for individuals with focal seizures

	Lamotrigine (LTG)	Levetiracetam (LEV)	Oxcarbazepine (OXC)	Topiramate (TPM)	Valproic Acid (VPA)	Zonisamide (ZNS)
	HR (95% CI) Direct evidence %					
LTG	-	1.14 (0.96, 1.33) 15.9	1.19 (0.97, 1.45) 5.5	1.15 (0.99, 1.33) 2.3	1.07 (0.92, 1.24) 10	0.99 (0.74, 1.35) 0
LEV	0.88 (0.75, 1.04) 15.9	-	1.05 (0.83, 1.32) 0	1.01 (0.83, 1.23) 0	0.94 (0.77, 1.15) 31	0.88 (0.64, 1.2) 0
OXC	0.84 (0.69, 1.03) 5.5	0.95 (0.76, 1.2) 0	-	0.97 (0.79, 1.19) 5.4	0.90 (0.72, 1.14) 0	0.84 (0.59, 1.19) 0
TPM	0.87 (0.75, 1.01) 2.3	0.99 (0.81, 1.2) 0	1.03 (0.84, 1.27) 5.4	-	0.93 (0.77, 1.13) 70.2	0.87 (0.63, 1.19) 0
VPA	0.93 (0.81, 1.09) 10	1.06 (0.87, 1.3) 31	1.11 (0.88, 1.39) 0	1.08 (0.88, 1.3) 70.2	-	0.93 (0.68, 1.28) 0
ZNS	1.01 (0.74, 1.36) 0	1.14 (0.83, 1.57) 0	1.19 (0.84, 1.69) 0	1.15 (0.84, 1.59) 0	1.08 (0.78, 1.48) 0	-

From Nevitt 2017[19] figure 10.
HR < 1 indicates an advantage to the AED in the row over the column. None of the results were significantly different between AEDs
CI = confidence interval, LEV = Levetiracetam; LTG = lamotrigine; OXC = oxcarbazepine; TPM = topiramate; VPA = valproic acid; ZNS = zonisamide

Table 9: Time to first seizure for individuals with focal seizures, extra information

Intervention	Comparison	No of participants (studies) with direct evidence	Relative effect HR (95% CI) fixed-effect analyses		Proportion of direct evidence	Quality of the evidence (GRADE)
			Direct evidence Heterogeneity: I^2	Direct + indirect evidence NMA		
Lamotrigine (LTG)	Carbamazepine (CBZ)	2252 (9 studies)	0.98 (0.75 to 1.27) I^2 = 0%	**1.29 (1.17 to 1.42)**	40.7%	Not reported*
Levetiracetam (LEV)	Carbamazepine (CBZ)	1552 (3 studies)	1.18 (0.85 to 1.65) I^2 = 0%	1.14 (0.99 to 1.30)	26.2%	Not reported*
Oxcarbazepine (OXC)	Carbamazepine (CBZ)	555 (2 studies)	1.47 (0.57 to 3.81) I^2 = 57.3%	1.09 (0.89 to 1.32)	4.8%	Not reported*
Topiramate (TPM)	Carbamazepine (CBZ)	925 (2 studies)	1.03 (0.51 to 2.08) I^2 = 69.3%	1.12 (0.97 to 1.29)	1.5%	Not reported*
Valproic Acid (VPA)	Carbamazepine (CBZ)	813 (5 studies)	1.01 (0.86 to 1.19) I^2 = 32%	**1.20 (1.06 to 1.37)**	34.6%	Not reported*
Zonisamide (ZNS)	Carbamazepine (CBZ)	581 (1 study)	1.30 (0.97 to 1.73) I^2 = NA	1.30 (0.97 to 1.73)	100%	Not reported*

From Nevitt 2017[19] Table 14 + figure 10

HR = hazard ratio; HR < 1 indicates an advantage to the intervention rather than the comparison; results highlighted in bold are statistically significant; HRs and 95% CIs are calculated from fixed-effect analyses (pairwise and network meta-analysis); where substantial heterogeneity was present (I2 > 50%), random-effects meta-analysis was also conducted

NA - heterogeneity is not applicable as only one study contributed direct evidence

Direct evidence (%) is the proportion of the estimate contributed by direct evidence and the box size is proportional to the number of participants contributing direct evidence

*Not reported, but likely to be high, since for the outcomes in Nevitt where GRADE was reported were all high risk ("Time to 12-month seizure freedom for individuals with focal seizures" and "Time to withdrawal of treatment for individuals with focal seizures"), and since the studies contributing to those also contributed to the outcomes in this table.

CI = confidence interval; GRADE = Grading of Recommendations, Assessment, Development and Evaluation; LEV = Levetiracetam; LTG = lamotrigine; OXC = oxcarbazepine; TPM = topiramate; VPA = valproic acid; ZNS = zonisamide

Table 10: Time to first seizure for individuals with generalised tonic-clonic seizures

	Lamotrigine (LTG)	Levetiracetam (LEV)	Oxcarbazepine (OXC)	Topiramate (TPM)	Valproic Acid (VPA)
	HR (95% CI) Direct evidence %				
LTG	-	0.82 (0.48, 1.41) 0	0.89 (0.29, 2.78) 12.2	0.85 (0.56, 1.28) 13.1	1.11 (0.77, 1.6) 31.3
LEV	1.22 (0.71, 2.1) 0	-	1.09 (0.33, 3.62) 0	1.04 (0.63, 1.71) 0	1.35 (0.86, 2.13) 34
OXC	1.12 (0.36, 3.48) 12.2	0.92 (0.28, 3.03) 0	-	0.95 (0.31, 2.94) 13.6	1.24 (0.4, 3.84) 0
TPM	1.17 (0.78, 1.77) 13.1	0.96 (0.58, 1.59) 0	1.05 (0.34, 3.24) 13.6	-	**1.3 (1.01, 1.68)** 21
VPA	0.9 (0.63, 1.3) 31.3	0.74 (0.47, 1.16) 34	0.81 (0.26, 2.5) 0	**0.77 (0.6, 0.99)** 21	-

From Nevitt 2017[19] figure 11.
HR < 1 indicates an advantage to the AED in the row over the column; results highlighted in bold are statistically significant
CI = confidence interval, LEV = Levetiracetam; LTG = lamotrigine; OXC = oxcarbazepine; TPM = topiramate; VPA = valproic acid

Table 11: Time to first seizure for individuals with generalised tonic-clonic seizures, extra information

Intervention	Comparison	No of participants (studies) with direct evidence	Relative effect HR (95% CI) fixed-effect analyses		Proportion of direct evidence	Quality of the evidence (GRADE)
			Direct evidence Heterogeneity: I^2	Direct + indirect evidence NMA		
Lamotrigine (LTG)	Carbamazepine (CBZ)	302 (7 studies)	1.49 (0.94 to 2.35) I^2 = 0%	0.98 (0.70 to 1.37)	0.3%	Not reported*
Levetiracetam (LEV)	Carbamazepine (CBZ)	251 (2 studies)	1.04 (0.65 to 1.64) I^2 = 0%	1.19 (0.78 to 1.83)	44.9%	Not reported*
Oxcarbazepine (OXC)	Carbamazepine (CBZ)	9 (1 studies)	1.55 (0.38 to 6.31) I^2 = NA	1.09 (0.36 to 3.36)	9.0%	Not reported*
Topiramate (TPM)	Carbamazepine (CBZ)	101 (2 studies)	1.19 (0.56 to 2.50) I^2 = 62%	1.15 (0.89 to 1.48)	9.0%	Not reported*
Valproic Acid (VPA)	Carbamazepine (CBZ)	411 (4 studies)	1.37 (0.98 to 1.92) I^2 = 84.1%	0.88 (0.76 to 1.03)	10.4%	Not reported*

From Nevitt 2017[19] Table 15 + figure 11

HR = hazard ratio; HR < 1 indicates an advantage to the intervention rather than the comparison; none of the results were statistically significant; HRs and 95% CIs are calculated from fixed-effect analyses (pairwise and network meta-analysis); where substantial heterogeneity was present (I2 > 50%), random-effects meta-analysis was also conducted

NA - heterogeneity is not applicable as only one study contributed direct evidence

Direct evidence (%) is the proportion of the estimate contributed by direct evidence and the box size is proportional to the number of participants contributing direct evidence.

*Not reported, but likely to be high, since for the outcomes in Nevitt where GRADE was reported were all high risk ("Time to 12-month seizure freedom for individuals with focal seizures" and "Time to withdrawal of treatment for individuals with focal seizures"), and since the studies contributing to those also contributed to the outcomes in this table.

CI = confidence interval; GRADE = Grading of Recommendations, Assessment, Development and Evaluation; LEV = Levetiracetam; LTG = lamotrigine; OXC = oxcarbazepine; TPM = topiramate; VPA = valproic acid; ZNS = zonisamide

Table 12: Proportion of patients free of seizures at six months for individuals with focal-onset seizures with or without secondarily generalisation

	Eslicarbazepine acetate (ESL)	Lacosamide (LCM)	Levetiracetam (LEV)	Zonisamide (ZNS)	Carbamazepine CR (CBZ-CR)
No. of seizure free patients/all patients	284/401 (70.8%)	327/444 (73.6%)	190/285 (66.7%)	195/281 (69.4%)	305/412 (74.0%) (vs ESL) 308/442 (69.7%) (vs LCM) 194/291 (66.7%) (vs LEV) 224/300 (74.7%) (vs ZNS)
	OR (95% CrI)				
ESL	-	0.72 (0.46, 1.08)	0.87 (0.54, 1.35)	1.14 (0.69, 1.78)	0.86 (0.62, 1.16)
LCM	1.4 (0.93, 2.19)	-	1.25 (0.77, 1.92)	1.63 (1, 2.53)	1.23 (0.91, 1.63)
LEV	1.15 (0.74, 1.87)	0.8 (0.52, 1.3)	-	1.26 (0.79, 2.13)	1.02 (0.71, 1.41)
ZNS	0.88 (0.56, 1.46)	0.61 (0.4, 1)	0.79 (0.47, 1.27)	-	0.78 (0.53, 1.1)

From Lattanzi 2018[16] Table 3 and 2. All included studies were deemed to be of low risk of bias (selection, performance, detection, attrition, reporting, funding)
OR > 1 indicates an advantage to the AED in the row over the column. None of the results were significantly different between AEDs
CBZ-CR = controlled-release carbamazepine; CrI = credible interval, ESL = eslicarbazepine acetate; LCM = lacosamide, LEV = levetiracetam; No. = number; OR = odds ratio; ZNS = zonisamide

Table 13: Time to six-month seizure freedom for individuals with focal seizures

	Lamotrigine (LTG)	Levetiracetam (LEV)	Oxcarbazepine (OXC)	Topiramate (TPM)	Valproic Acid (VPA)	Zonisamide (ZNS)
	HR (95% CI) Direct evidence %					
LTG	-	1.06 (0.91, 1.25) 17.8	1.14 (0.93, 1.37) 2.4	1 (0.85, 1.18) 1.7	1.02 (0.85, 1.22) 32.1	1.11 (0.89, 1.41) 0
LEV	0.94 (0.8, 1.1) 17.8	-	1.06 (0.86, 1.31) 0	0.94 (0.79, 1.12) 0	0.95 (0.8, 1.14) 40.5	1.05 (0.84, 1.3) 0
OXC	0.88 (0.73, 1.07) 2.4	0.94 (0.76, 1.16) 0	-	0.88 (0.72, 1.08) 3.3	0.9 (0.72, 1.12) 0	0.99 (0.76, 1.28) 0
TPM	1 (0.85, 1.17) 1.7	1.06 (0.89, 1.27) 0	1.13 (0.93, 1.38) 3.3	-	1.02 (0.83, 1.24) 61.7	1.11 (0.88, 1.41) 0
VPA	0.98 (0.82, 1.18) 32.1	1.05 (0.88, 1.25) 40.5	1.11 (0.89, 1.39) 0	0.98 (0.81, 1.2) 61.7	-	1.1 (0.88, 1.39) 0
ZNS	0.9 (0.71, 1.12) 0	0.95 (0.77, 1.19) 0	1.01 (0.78, 1.32) 0	0.9 (0.71, 1.14) 0	0.91 (0.72, 1.14) 0	-

From Nevitt 2017[19] figure 10.
HR < 1 indicates an advantage to the AED in the row over the column; results highlighted in bold are statistically significant
CI = confidence interval, LEV = Levetiracetam; LTG = lamotrigine; OXC = oxcarbazepine; TPM = topiramate; VPA = valproic acid; ZNS = zonisamide

Table 14: Time to six-month seizure freedom for individuals with focal seizures, extra information

Intervention	Comparison	No of participants (studies) with direct evidence	Relative effect HR (95% CI) fixed-effect analyses		Proportion of direct evidence	Quality of the evidence (GRADE)
			Direct evidence Heterogeneity: I^2	Direct + indirect evidence NMA		
Lamotrigine (LTG)	Carbamazepine (CBZ)	1535 (7 studies)	1.15 (0.89 to 1.48) I^2 = 0%	1.11 (0.98 to 1.27)	26.4%	Not reported*
Levetiracetam (LEV)	Carbamazepine (CBZ)	1567 (3 studies)	1.06 (0.84 to 1.33) I^2 = 37.9%	1.04 (0.93 to 1.16)	20.4%	Not reported*
Oxcarbazepine (OXC)	Carbamazepine (CBZ)	555 (2 studies)	1.15 (0.65 to 2.04) I^2 = 0%	0.98 (0.82 to 1.18)	16.6%	Not reported*
Topiramate (TPM)	Carbamazepine (CBZ)	925 (2 studies)	1.05 (0.64 to 1.72) I^2 = 0%	1.11 (0.96 to 1.28)	8.8%	Not reported*
Valproic Acid (VPA)	Carbamazepine (CBZ)	816 (5 studies)	1.06 (0.90 to 1.25) I^2 = 56.5%	1.10 (0.96 to 1.25)	16.6%	Not reported*
Zonisamide (ZNS)	Carbamazepine (CBZ)	582 (1 study)	1.00 (0.82 to 1.20) I^2 = NA	1.00 (0.82 to 1.20)	100%	Not reported*

From Nevitt 2017[19] Table 12 + figure 10

HR = hazard ratio; HR < 1 indicates an advantage to the intervention rather than the comparison; none of the results were statistically significant; HRs and 95% CIs are calculated from fixed-effect analyses (pairwise and network meta-analysis); where substantial heterogeneity was present (I2 > 50%), random-effects meta-analysis was also conducted.

NA - heterogeneity is not applicable as only one study contributed direct evidence.

*Not reported, but likely to be high, since for the outcomes in Nevitt where GRADE was reported were all high risk ("Time to 12-month seizure freedom for individuals with focal seizures" and "Time to withdrawal of treatment for individuals with focal seizures"), and since the studies contributing to those also contributed to the outcomes in this table.

CI = confidence interval; GRADE = Grading of Recommendations, Assessment, Development and Evaluation; LEV = Levetiracetam; LTG = lamotrigine; OXC = oxcarbazepine; TPM = topiramate; VPA = valproic acid; ZNS = zonisamide

Table 15: Time to six-month seizure freedom for individuals with generalised tonic-clonic seizures

	Lamotrigine (LTG)	Levetiracetam (LEV)	Oxcarbazepine (OXC)	Topiramate (TPM)	Valproic Acid (VPA)
	HR (95% CI) Direct evidence %				
LTG	-	1.06 (0.75, 1.52) 0	0.93 (0.3, 2.86) 7.6	1.09 (0.73, 1.61) 10	**1.27 (1.06, 1.56)** 43.5
LEV	0.94 (0.66, 1.34) 0	-	0.88 (0.27, 2.79) 0	1.02 (0.65, 1.61) 0	1.18 (0.86, 1.63) 48.6
OXC	1.07 (0.35, 3.3) 7.6	1.14 (0.36, 3.7) 0	-	1.16 (0.38, 3.57) 9.4	1.35 (0.44, 4.17) 0
TPM	0.92 (0.62, 1.37) 10	0.98 (0.62, 1.54) 0	0.86 (0.28, 2.62) 9.4	-	1.16 (0.81, 1.68) 12.9
VPA	**0.79 (0.64, 0.94)** 43.5	0.85 (0.61, 1.16) 48.6	0.74 (0.24, 2.27) 0	0.86 (0.6, 1.23) 12.9	-

From Nevitt 2017[19] figure 11.
HR < 1 indicates an advantage to the AED in the row over the column; results highlighted in bold are statistically significant
CI = confidence interval, LEV = Levetiracetam; LTG = lamotrigine; OXC = oxcarbazepine; TPM = topiramate; VPA = valproic acid

Table 16: Time to six-month seizure freedom for individuals with generalised tonic-clonic seizures, extra information

Intervention	Comparison	No of participants (studies) with direct evidence	Relative effect HR (95% CI) fixed-effect analyses		Proportion of direct evidence	Quality of the evidence (GRADE)
			Direct evidence Heterogeneity: I^2	Direct + indirect evidence NMA		
Lamotrigine (LTG)	Carbamazepine (CBZ)	254 (5 studies)	0.58 (0.25 to 1.32) I^2 = 0%	1.20 (0.99 to 1.49)	0.1%	Not reported*
Levetiracetam (LEV)	Carbamazepine (CBZ)	251 (2 studies)	1.00 (0.72 to 1.37) I^2 = 57.9%	1.14 (0.85 to 1.52)	26.7%	Not reported*
Oxcarbazepine (OXC)	Carbamazepine (CBZ)	9 (1 studies)	0.79 (0.17 to 3.56) I^2 = NA	1.30 (0.42 to 4.00)	4.6%	Not reported*
Topiramate (TPM)	Carbamazepine (CBZ)	101 (2 studies)	1.00 (0.55 to 1.79) I^2 = 0%	1.11 (0.78 to 1.59)	32.8%	Not reported*
Valproic Acid (VPA)	Carbamazepine (CBZ)	412 (4 studies)	1.11 (0.81 to 1.53) I^2 = 29.9%	0.95 (0.84 to 1.09)	30.7%	Not reported*

From Nevitt 2017[19] Table 13 + figure 11

HR = hazard ratio; HR < 1 indicates an advantage to the intervention rather than the comparison; none of the results were statistically significant; HRs and 95% CIs are calculated from fixed-effect analyses (pairwise and network meta-analysis); where substantial heterogeneity was present (I2 > 50%), random-effects meta-analysis was also conducted

NA - heterogeneity is not applicable as only one study contributed direct evidence

Direct evidence (%) is the proportion of the estimate contributed by direct evidence and the box size is proportional to the number of participants contributing direct evidence.

*Not reported, but likely to be high, since for the outcomes in Nevitt where GRADE was reported were all high risk ("Time to 12-month seizure freedom for individuals with focal seizures" and "Time to withdrawal of treatment for individuals with focal seizures"), and since the studies contributing to those also contributed to the outcomes in this table.

CI = confidence interval; GRADE = Grading of Recommendations, Assessment, Development and Evaluation; LEV = Levetiracetam; LTG = lamotrigine; OXC = oxcarbazepine; TPM = topiramate; VPA = valproic acid; ZNS = zonisamide

Table 17: Proportion of patients free of seizures at 12 months for individuals with focal-onset seizures with or without secondarily generalisation

	Eslicarbazepine acetate (ESL)	Lacosamide (LCM)	Levetiracetam (LEV)	Zonisamide (ZNS)	Carbamazepine CR (CBZ-CR)
No. of seizure free patients/all patients	256/388 (63.8%)	264/444 (59%)	142/285 (49.8%)	157/281 (55.9%)	283/397 (68.7%) (vs ESL) 262/442 (59%) (vs LCM) 155/291 (53.3%) (vs LEV) 187/300 (62.3%) (vs ZNS)
	OR (95% CrI)				
ESL	-	0.81 (0.54, 1.19)	0.95 (0.59, 1.43)	1.08 (0.68, 1.64)	0.81 (0.6, 1.08)
LCM	1.23 (0.84, 1.87)	-	1.19 (0.76, 1.77)	1.36 (0.86, 2.04)	1.02 (0.78, 1.32)
LEV	1.06 (0.7, 1.69)	0.84 (0.57, 1.31)	-	1.11 (0.72, 1.83)	0.88 (0.63, 1.21)
ZNS	0.92 (0.61, 1.48)	0.74 (0.49, 1.16)	0.9 (0.55, 1.39)	-	0.77 (0.54, 1.06)

From Lattanzi 2018[16] Table 3 and 2. All included studies were deemed to be of low risk of bias (selection, performance, detection, attrition, reporting, funding)
OR > 1 indicates an advantage to the AED in the row over the column. None of the results were significantly different between AEDs
CBZ-CR = controlled-release carbamazepine; CrI = credible interval, ESL = eslicarbazepine acetate; LCM = lacosamide, LEV = levetiracetam; No. = number; OR = odds ratio; ZNS = zonisamide

Table 18: Time to 12-month seizure freedom for individuals with focal seizures

	Lamotrigine (LTG)	Levetiracetam (LEV)	Oxcarbazepine (OXC)	Topiramate (TPM)	Valproic Acid (VPA)	Zonisamide (ZNS)
	HR (95% CI) Direct evidence %					
LTG	-	0.85 (0.68, 1.08) 26.6	1.18 (0.93, 1.52) 2.8	1.08 (0.87, 1.33) 2.5	1.1 (0.88, 1.37) 39.9	1.1 (0.81, 1.49) 0
LEV	1.17 (0.93, 1.46) 26.6	-	**1.38 (1.05, 1.79)** 0	1.25 (0.96, 1.64) 0	1.28 (0.97, 1.67) 34.7	1.28 (0.92, 1.79) 0
OXC	0.85 (0.66, 1.08) 2.8	**0.72 (0.56, 0.95)** 0	-	0.91 (0.69, 1.2) 3.7	0.93 (0.7, 1.23) 0	0.93 (0.66, 1.32) 0
TPM	0.93 (0.75, 1.15) 2.5	0.8 (0.61, 1.04) 0	1.1 (0.83, 1.45) 3.7	-	1.02 (0.8, 1.3) 67.8	1.03 (0.76, 1.39) 0
VPA	0.91 (0.73, 1.14) 39.9	0.78 (0.6, 1.03) 34.7	1.08 (0.81, 1.43) 0	0.98 (0.77, 1.25) 67.8	-	1.01 (0.75, 1.37) 0
ZNS	0.91 (0.67, 1.23) 0	0.78 (0.56, 1.09) 0	1.07 (0.76, 1.51) 0	0.97 (0.72, 1.31) 0	0.99 (0.73, 1.34) 0	-

From Nevitt 2017[19] figure 8.
HR < 1 indicates an advantage to the AED in the row over the column; results highlighted in bold are statistically significant
CI = confidence interval, LEV = Levetiracetam; LTG = lamotrigine; OXC = oxcarbazepine; TPM = topiramate; VPA = valproic acid; ZNS = zonisamide

Table 19: Time to 12-month seizure freedom for individuals with focal seizures, extra information

Intervention	Comparison	No of participants (studies) with direct evidence	Relative effect HR (95% CI) fixed-effect analyses		Proportion of direct evidence	Quality of the evidence (GRADE)*
			Direct evidence Heterogeneity: I^2	Direct + indirect evidence NMA		
Lamotrigine (LTG)	Carbamazepine (CBZ)	891 (2 studies)	1.02 (0.69 to 1.50) I^2 = 0%	1.16 (0.98 to 1.37)	17.5%	High
Levetiracetam (LEV)	Carbamazepine (CBZ)	1567 (3 studies)	1.08 (0.81 to 1.42) I^2 = 60.8%	**1.35 (1.09 to 1.69)**	14.2%	High**
Oxcarbazepine (OXC)	Carbamazepine (CBZ)	555 (2 studies)	1.13 (0.62 to 2.05) I^2 = 0%	0.98 (0.78 to 1.25)	21%	High
Topiramate (TPM)	Carbamazepine (CBZ)	925 (2 studies)	0.94 (0.48 to 1.83) I^2 = 0%	1.08 (0.92 to 1.27)	7.2%	High
Valproic Acid (VPA)	Carbamazepine (CBZ)	816 (5 studies)	1.03 (0.85 to 1.25) I^2 = 46.4%	1.05 (0.89 to 1.25)	27.6%	High
Zonisamide (ZNS)	Carbamazepine (CBZ)	582 (1 study)	1.05 (0.85 to 1.30) I^2 = NA	1.05 (0.81 to 1.35)	100%	High

From Nevitt 2017[19] Table 10 + figure 8 + additional summary of findings p52

HR = hazard ratio; HR < 1 indicates an advantage to the intervention rather than the comparison; results highlighted in bold are statistically significant; HRs and 95% CIs are calculated from fixed-effect analyses (pairwise and network meta-analysis); where substantial heterogeneity was present (I2 > 50%), random-effects meta-analysis was also conducted

NA - heterogeneity is not applicable as only one study contributed direct evidence

*Several trials contributing direct evidence or contributing to the network meta-analysis were at high risk of bias for at least one domain; sensitivity analyses were performed in the case of particular sources of bias or inconsistencies within individual participant data provided. Results of sensitivity analyses showed similar numerical results and no changes to conclusions, therefore any risks of bias within the trials included in these analyses have not influenced the overall results (no downgrade of quality of evidence). No indication of inconsistency between direct evidence and network meta-analysis results (no downgrade of quality of evidence).

**Large amount of heterogeneity present in pairwise meta-analysis; no change to conclusions when analysis was repeated with random-effects, and heterogeneity likely due to difference in trial designs (e.g. age of participants). Despite heterogeneity, numerical results from direct evidence and from network results are similar and conclusions the same (no downgrade of quality of evidence)

Table 20: Time to 12-month seizure freedom for individuals with generalised tonic-clonic seizures

	Lamotrigine (LTG)	Levetiracetam (LEV)	Oxcarbazepine (OXC)	Topiramate (TPM)	Valproic Acid (VPA)
	HR (95% CI) Direct evidence %				
LTG	-	0.95 (0.36, 2.5) 0	0.75 (0.18, 3.03) 9.2	1.21 (0.51, 2.86) 15.1	1.35 (0.57, 3.17) 35.7
LEV	1.05 (0.4, 2.8) 0	-	0.78 (0.2, 3.09) 0	1.26 (0.68, 2.33) 0	1.42 (0.83, 2.42) 55.2
OXC	1.34 (0.33, 5.41) 9.2	1.28 (0.32, 5) 0	-	1.61 (0.44, 5.88) 11.4	1.81 (0.5, 6.58) 0
TPM	0.83 (0.35, 1.98) 15.1	0.79 (0.43, 1.47) 0	0.62 (0.17, 2.26) 11.4	-	0.12 (0.83, 1.51) 10.6
VPA	0.74 (0.32, 1.75) 35.7	0.7 (0.41, 1.2) 55.2	0.55 (0.15, 2) 0	8.33 (0.66, 1.2) 10.6	-

From Nevitt 2017[19] figure 9
HR < 1 indicates an advantage to the AED in the row over the column; results highlighted in bold are statistically significant
CI = confidence interval, LEV = Levetiracetam; LTG = lamotrigine; OXC = oxcarbazepine; TPM = topiramate; VPA = valproic acid

Table 21: Time to 12-month seizure freedom for individuals with generalised tonic-clonic seizures, extra information

Intervention	Comparison	No of participants (studies) with direct evidence	Relative effect HR (95% CI) fixed-effect analyses		Proportion of direct evidence	Quality of the evidence (GRADE)
			Direct evidence Heterogeneity: I^2	Direct + indirect evidence NMA		
Lamotrigine (LTG)	Carbamazepine (CBZ)	9 (1 studies)	1.33 (0.29 to 6.03) I^2 = NA	1.28 (0.54 to 3.03)	7.0%	Not reported*
Levetiracetam (LEV)	Carbamazepine (CBZ)	251 (2 studies)	1.02 (0.65 to 1.59) I^2 = 77.4%	1.33 (0.81 to 2.22)	16.6%	Not reported*
Oxcarbazepine (OXC)	Carbamazepine (CBZ)	9 (1 studies)	0.77 (0.15 to 3.89) I^2 = NA	1.72 (0.47 to 6.25)	5.6%	Not reported*
Topiramate (TPM)	Carbamazepine (CBZ)	101 (2 studies)	1.15 (0.52 to 2.53) I^2 = 0%	1.06 (0.78 to 1.45)	27.2%	Not reported*
Valproic Acid (VPA)	Carbamazepine (CBZ)	412 (4 studies)	1.01 (0.72 to 1.43) I^2 = 0%	0.94 (0.79 to 1.14)	51.1%	Not reported*

From Nevitt 2017[19] Table 11 + figure 9, please note there is a minor discrepancy between the Nevitt Table and figure, we have reported from the table. The discrepancy between the two is very minor and deemed to be an effect of rounding and inversing, they are very minor.

HR = hazard ratio; HR < 1 indicates an advantage to the intervention rather than the comparison; none of the results were significant; HRs and 95% CIs are calculated from fixed-effect analyses (pairwise and network meta-analysis); where substantial heterogeneity was present (I2 > 50%), random-effects meta-analysis was also conducted

NA - heterogeneity is not applicable as only one study contributed direct evidence

Direct evidence (%) is the proportion of the estimate contributed by direct evidence and the box size is proportional to the number of participants contributing direct evidence.

*Not reported, but likely to be high, since for the outcomes in Nevitt where GRADE was reported were all high risk ("Time to 12-month seizure freedom for individuals with focal seizures" and "Time to withdrawal of treatment for individuals with focal seizures"), and since the studies contributing to those also contributed to the outcomes in this table.

CI = confidence interval; GRADE = Grading of Recommendations, Assessment, Development and Evaluation; LEV = Levetiracetam; LTG = lamotrigine; OXC = oxcarbazepine; TPM = topiramate; VPA = valproic acid; ZNS = zonisamide

FAQ 3: Will it affect my life expectancy?

Epileptic patients have a risk of sudden unexpected death where the death is premature and no reason is found (SUDEP)[25].

As a general group, people with epilepsy have about a 0.1 % risk of SUDEP per year[25,9]. The Scottish epilepsy guideline[23] mentions there is "no convincing evidence that SUDEP is caused by any single or combination of AEDs". Different factors will increase that risk, but be aware that the findings around some of these risk factors are not consistent[23]. Several studies suggest that good medical control of generalized seizures might be one of the most effective measures to prevent SUDEP[22,9].

Below we are presenting studies on SUDEP risks confirmed and disproved (Table 22), some precautions that may be taken to decrease risk of SUDEP (Table 23), and the overall mortality risk among people with epilepsy (Table 24).

Table 22: SUDEP risk factors

Risk factor		Hampel 2017	Sudep.org	Maguire 2016	SIGN 2015	Ryvlin 2011
Tonic-clonic seizures	1-2 per year	OR 5.5 [a]	5 times increase in risk of SUDEP	Confirmed	Confirmed	-
	≥ 3 per year	OR 6.4 [a]	can increase risk up to 15 times			-
Absence or myoclonic seizures		-	No Increased SUDEP risk proven	-	-	-
Very frequent seizures		-	SUDEP rate estimated to be between 1-2%	-	-	-
Nocturnal seizures		OR 2.6 [b]	Confirmed	-	-	-
Duration of epilepsy ≥15 years		OR 2 [c]	-	Confirmed	-	-
Epilepsy start before the age of 16 years		OR 1.7 [c]	-	Confirmed	-	-
Male gender		OR 1.4 [c]	-	Confirmed	-	-
Prone position		73% of the cases of SUDEP [d]	-	-	-	-
AED polytherapy		-	-	-	Increased SUDEP risk disproved	Reduced risk of SUDEP with efficaceous adjunctive AED doses

Hampel 2017[12] (review) Table 2 expanded with information from Maguire 2016[17] (Cochrane systematic review), sudep.org[25] (UK registered charity with clinician input), SIGN 2015[23] (guideline), and Ryvlin 2011[22] (meta-analysis)
a) Hesdorffer 2012[41]; b) Lamberts 2012[43]; c) Hesdorffer 2011[40]; d) Liebenthal 2015[45]
AED = anti-epileptic drug; OR = odds ratio; SUDEP = sudden unexpected death in epilepsy

Table 23: Precautions for decreasing the risk of SUDEP?

No of Participants (studies)	Number of deaths due to SUDEP / No. of participants		Relative effect (95%CI)	Anticipated absolute effect	Quality of the evidence (GRADE)*
	Intervention	Comparison			
Nocturnal supervision					
468 (1 study)	34 / 190	109 / 278	OR 0.34 (0.22 to 0.53)	212 fewer per 1000 (from 137 fewer to 268 fewer)	VERY LOW
Special precautions					
331 (1 study)	11 / 53	109 / 278	OR 0.41 (0.20 to 0.82)	183 fewer per 1000 (from 46 fewer to 278 fewer)	VERY LOW

From Maguire 2016[17] summary of findings table
Assumed and corresponding risks not calculated due to study design (case-control)
* Due to observation design and serious risk of bias, mainly due to a large amount of missing data in the control group
CI = confidence interval; GRADE = Grading of Recommendations, Assessment, Development and Evaluation; No. = number; OR = Odds Ratio; SUDEP = sudden unexpected death in epilepsy

Please note that as the study reported was a case-control with a large amount of missing data, the information in this table translates into "limited, low-quality evidence that supervision at night prevents SUDEP". In addition, it seems special precautions (such as regular checking throughout the night or a listening device) can also have a preventative effect, although "Further research is needed to identify if other treatments, such as seizure detection devices, safety pillows, and drug interventions working on serotonin, adenosine, and opiate levels in the brain are effective in preventing SUDEP in people with epilepsy" (Maguire 2016).[17]

Table 24: Overall mortality risk among people with epilepsy: all age or adult only populations

Locality	Population characteristics	Study quality*	Cohort size [1]	Follow-up (years)	SMR** (95% CI)
Population- or community-based studies					
England and Wales, UK [a]	Incident cohort, all ages	1	792	11.8 [2]	2.1 (1.8-2.4)
Vasterbotten County, Sweden [b]	Incident cases, adult cohort	1	107	10	2.5 (1.2-3.2)
Rochester, MN, USA [c]	Incident cases, all ages	1	618	13.3 [2]	2.3 (1.9-2.6)
Northern Manhattan, USA [d]	Incident epilepsy or unprovoked seizures, all ages	2	209	2.9 [2]	1.7 (1.1-2.3)
UK [e]	Incident cases, all ages	2	792	≤9	3.0 (2.5-3.7)
UK [f]	Incident cases, all ages (extended follow-up of above)	2	564	22.8	2.6 (2.2-3.0)
Cardiff and Glamorgan, UK [g]	Prevalent cases, all ages	2	3007	≤4	2.1 (1.7-2.6)
Iceland [h]	Incident unprovoked seizures, all ages	2	224	≤30	1.6 (1.2-2.2)
Estonia [i]	Incident cases, age ≥20 years	2	81	12.5 [2]	2.6 (1.8-3.5)
Clinic-based studies					
Stockholm, Sweden [j]	Previously hospitalised for epilepsy	3	9061	≤17	3.6 (3.5-3.7)
Glasgow, UK [k]	Incident clinic referral cases	3	890	7 [2]	1.4 (1.2-1.7)
	Prevalent clinic referral cases		2689	7 [2]	2.0 (1.8-2.3)
Tyrol, Austria [l]	Cohort of attendees of epilepsy referral clinic	3	3334	≤29	2.2 (2.0-2.4)
Tyrol, Austria [m]	Cohort of attendees of epilepsy referral clinic (extended follow-up and expansion of above)	3	4295	≤39	1.7 (1.6-1.9)

From parts of Thurman 2017[26] Table 1

*The study quality was evaluated by Thurman 2017 and given 1-4 with 1 being the best quality. This evaluation was based on Sensitivity of Epilepsy Case and of Mortality Case Ascertainment, Accuracy of Diagnoses of Epilepsy and of Cause of Death, and Representativeness of the Study Population. See more details in Appendix 3.

**The standardised mortality ratio (SMR) is the mortality rate of the observed cohort compared to the mortality rate in the standard population accounting for age- and gender-specific mortality. An SMR greater than 1 indicates higher mortality than the standard population.

1) Number of persons with epilepsy followed

2) Median or mean follow-up period

a) Lhatoo 2001[44]; b) Lindsten 2000[46]; c) Hauser 1980[38]; d) Benn 2008[33]; e) Cockerell 1997[35]; f) Neligan 2011[50]; g) Morgan 2002[49]; h) Olafsson 1998[52]; i) Rakitin 2011[53]; j) Nilsson 1997[51]; k) Mohanraj 2006[48]; l) Trinka 2013[56]; m) Granbichler 2015[36]

CI = confidence interval; MN = Minnesota; SMR = standardised mortality ratio; UK = United Kingdom; USA = United States of America

FAQ 4: Will it affect my quality of life?

The clinical evidence for the decision matrix is presented in Tables 24-25.

Overall there is no significant or consistent difference between the AEDs, and the evidence is questionable. There are missing data on eslicarbazepine acetate (ESL), lacosamide (LCM) and zonisamide (ZNS).

A recent systematic review finds no reported evidence for clinically important change in quality of life (Maguire 2016).[17] And recent network meta-analysis (Campos 2016)[8] did not evaluate the impact of AEDs on quality of life (QoL) due to the difference of methodologies used by the sparse number of studies.

But QoL seems to be significantly linked to the frequency of seizures (frequency versus aspects of QoL: primary study Guekht 2007[37] mentioned in Rosenow 2012;[21] 12 month seizure freedom and treatment failure versus QoL: HTA by Marson 2007[18]) and adverse events. And the higher the incidence of adverse reactions the lower the QoL (primary study by Alexandre 2011[32] mentioned in NMA by Campos 2016[8]).

Table 25 presents parts of the NEWQOL battery (Newly Diagnosed Epilepsy Quality of Life) from baseline and up to two years, presenting data from the SANAD trial. For arm A (LTG, TPM, OXC comparison), original numbers are presented. For the B arm (the LTG, TPM and VPA comparison), only data containing imputed values was available. As this includes imputed values across AEDs, it is particularly problematic comparing AEDs on the basis of these results.

For both arms A and B, none of the found QoL score differences were significant. There were no important differences or trends for scores on the AEP, the EQ-5D or for Gloobal Quality of Life (GQoL). There were non-significant reductions in risk of anxiety for TPM compared with LTG or OXC, and of depression for LTG compared with the other AEDs. However, differences were identified between baseline QoL and clinical outcomes of responders compared to non-responders which could imply that patients with the poorest QoL outcomes had a lower return rate on the two year questionnaire (Marson 2007[18]).

Table 26 presents evidence for LEV compared to LTG for 26 weeks and assessing Quality of Life in Epilepsy 10 questionnaire (QOLIE-10).

Table 25: Quality of life scores over two years on AED

	Lamotrigine (LTG)	Topiramate (TPM)	Oxcarbazepine (OXC)		Lamotrigine (LTG)	Topiramate (TPM)	Valproic Acid (VPA)
No. of patients	177 (92)*	172 (90)*	92		118	113	125
	Arm A, original values*				Arm B, imputation using best and worst case data**		
	Difference in mean for coefficients from a multiple regression representing the difference between treatments, with 95% CIs						
GQoL (a single-item measure)							
LTG	-	0.83 (0.56, 1.23)	1.02 (0.64, 1.64)	LTG	-	0.98 (0.62, 1.54)	1.02 (0.66, 1.59)
TPM	1.20 (0.81, 1.77)	-	1.22 (0.76, 1.97)	TPM	1.02 (0.65, 1.61)	-	1.05 (0.67, 1.64)
OXC	-1.02 (-0.64, -1.64)	-1.22 (-0.76, -1.97)	-	VPA	0.98 (0.63, 1.52)	0.96 (0.61, 1.50)	-
Anxiety* **							
LTG	-	0.75 (-0.07, 1.56)	-0.23 (-1.21, 0.76)	LTG	-	0.61 (-0.91, 2.12)	0.80 (-0.74, 2.34)
TPM	-0.75 (-1.56, 0.07)	-	-0.97 (-1.96, 0.01)	TPM	-0.61 (-2.12, 0.91)	-	0.19 (-1.36, 1.74)
OXC	0.23 (1.21, -0.76)	0.97 (1.96, -0.01)	-	VPA	-0.80 (-2.34, 0.74)	-0.19 (-1.74, 1.36)	-
Depression* **							
LTG	-	-0.44 (-1.13, 0.25)	-0.63 (-1.47, 0.20)	LTG	-	-0.39 (-1.55, 0.77)	-0.23 (-1.43, 0.98)
TPM	0.44 (-0.25, 1.12)	-	-0.20 (-1.04, 0.64)	TPM	0.39 (-0.77, 1.55)	-	0.10 (-1.18, 1.39)
OXC	0.63 (1.47, -0.20)	0.20 (1.04, -0.64)	-	VPA	0.23 (-0.98, 1.43)	-0.10 (-1.39, 1.18)	-
Adverse Events Profile (AEP) (19-item scale; score of 0–57)							
LTG	-	1.07 (-0.85, 2.99)	0.91 (-1.44, 3.26)	LTG	-	0.77 (-2.73, 4.26)	-0.02 (-3.66, 3.62)
TPM	-1.07 (-2.99, 0.85)	-	-0.15 (-2.48, 2.19)	TPM	-0.77 (-4.26, 2.73)	-	-0.77 (-4.28, 2.75)
OXC	-0.91 (1.44, -3.26)	0.15 (2.48, -2.19)	-	VPA	0.02 (-3.62, 3.66)	0.77 (-2.75, 4.28)	-
EQ-5D							
LTG	-	-0.01 (-0.06, 0.04)	0.03 (-0.03, 0.08)	-	-	-	-
TPM	0.01 (-0.04, 0.06)	-	0.04 (-0.02, 0.10)	-	-	-	-
OXC	-0.03 (0.03, -0.08)	-0.04 (0.02, -0.10)	-	-	-	-	-

From Marson 2007[18], Tables 21, 22, 23, 25, 84, 85, 86, 87, 89 (LTG, TPM, OXC) and Jacoby 2015[13], Tables 1, 4 (LTG, TPM, VPA)
Please note that there was a skewed response to the questionnaires which underlie the results presented:
1) females were more likely to respond to the questionnaires than males; 2) median age for responders was higher than for non-responders; 3) 2 years non-responders had worse QoL at baseline than 2-years responders; 4) 2 years non-responders were less likely to have achieved a 12-month seizure freedom of seizures prior to the 2-year follow up; 5) 2 years non-responders were more likely to have been withdrawn from the drug to which they were allocated at randomisation
*Number of randomised patients returning a baseline and 2-year questionnaire; original numbers with no imputation; numbers in parenthesis are the numbers for the OXC comparisons (as OXC was added after start of trial)

	Lamotrigine (LTG)	Topiramate (TPM)	Oxcarbazepine (OXC)		Lamotrigine (LTG)	Topiramate (TPM)	Valproic Acid (VPA)
No. of patients	177 (92)*	172 (90)*	92		118	113	125
	Arm A, original values*				Arm B, imputation using best and worst case data**		
	Difference in mean for coefficients from a multiple regression representing the difference between treatments, with 95% CIs						

**Number of randomised patients returning between 1 and 4 questionnaires (baseline, 3-month, 1 year, 2 years); Imputation: a sensitivity analysis for the longitudinal models fitted, using a best case and worst case data set generated by identifying the best and worst QoL values recorded in each questionnaire across all treatments. These questionnaire-specific best and worse values were then used to impute values for individuals failing to return that particular questionnaire.
***Hospital Anxiety and Depression Scale (HADS) (14-item scale; 7 items = anxiety; 7 items = depression; score of 0–21 for each domain)
AED = anti epilepsy drug; AEP = Adverse Events Profile; EQ-5D = European Quality of Life-5 Dimensions; GQoL = Global Quality of Life; LTG = lamotrigine; OXC = oxcarbazepine; TPM = topiramate; VPA = valproic acid

Table 26: Quality of life over 26 weeks LEV compared to LTG

AED	Number of patients*	Timepoint	Mean QoL (SD)
Levetiracetam (LEV)	148	Start of treatment	2.5 (0.9)
		26 weeks	2.2 (0.9)
Lamotrigine (LTG)	155	Start of treatment	2.5 (0.9)
		26 weeks	2.2 (0.9)

Rosenow 2012[21]
Changes in QoL between the two AEDs were not significantly different (p=0.69)
*Patients aged 12 years or over with newly diagnosed focal or generalised epilepsy
AED = Anti epileptic drug; LEV = Levetiracetam; LTG = Lamotrigine; QoL = quality of life; SD = standard deviation

FAQ 5: Which side effects/complications might be related to treatment?

Below are listed the tables of side effects (Table 27) and adverse events (Tables 28-38). There is no clear distinction in the evidence found for epilepsy between adverse events and side effects as can be evidenced by comparing the table of side effects (table 27) with the table of most commonly reported adverse events for some of the anti-epileptic-drugs (AEDs) (table 38).

Not all patients receiving a particular AED will experience the listed possible side-effects/adverse events. Moreover, most of the side effects/adverse events could be experienced more or less severely.

Please note that if the patient is a girl or woman of child bearing potential, risk of congenital malformation should be taken into account, as reported under FAQ 1.

For adverse events we have evidence covering the various AEDs from two sources: Lattanzi 2018[12] covering ESL, LCM and LEV (Tables 28-29), and Nevitt 2017[19] covering LTG, LEV, OXC, TPM, VPA and ZNS. For the Nevitt results, withdrawal due to adverse events was not directly reported, but can be somewhat inferred from a combination of Tables 30-33: time to withdrawal of treatment for focal and generalised seizures, and Tables 34-36: reasons for withdrawal from allocated treatment. Presented is also Tables 37 and 38: number of participants and rate of occurrence of most commonly reported adverse events, respectively.

The quality of the evidence on adverse events is varying and results are not clear cut. Lattanzi 2018[16] mentions that their "pre-planned analysis of occurrence of adverse events was not performed due to variability in methods and details of reporting".

Most of the individual types of adverse events can occur for all AEDs but due to the differing reporting method and poor reporting quality of available evidence, comparisons between AEDs can only be hinted at. An overall view of number of patients reporting AE seems to hint that 3/4 of patients on LEV or TPM report AEs, roughly 1/2 of patients on VPA and LTG report AEs, while OXC and ZNS are somewhere in between (Table 37). However, this does not take into account if they are minor AEs or debilitating AEs.

A more reliable method may be to concentrate on time to withdrawal. Here it is shown that for focal seizures LEV is preferable to TPM, while LTG is preferable to OXC, TPM, VPA, and ZNS (Table 30). For generalised seizures LTG and VPA seem to be preferable to TPM (Table 32).

The rest of the AED comparisons are not showing a clear advantage towards any one AED.

Table 27: Potential side effects

Potential side effects
Eslicarbazepine acetate (ESL)
Common (1-10 per 100) or very common (more than 1 in 10) Dizziness; drowsiness; fatigue; gastro-intestinal disturbances; headache; impaired coordination; rash; tremor; visual disturbances **Frequency not known** PR-interval prolongation; suicidal ideation
BNF[6], classification based on BNF[54]
Lacosamide (LCM)
Common (1-10 per 100) or very common (more than 1 in 10) Abnormal gait; blurred vision; cognitive disorder; constipation; depression; dizziness; drowsiness; fatigue; flatulence; headache; impaired coordination; nausea; nystagmus; pruritus; tremor; vomiting **Frequency not known** Aggression; agitation; agranulocytosis; atrial fibrillation; atrial flutter; AV block; bradycardia; confusion; dry mouth; dysarthria; dyspepsia; euphoria; hypoesthesia; irritability; muscle spasm; PR-interval prolongation; psychosis; rash; suicidal ideation; tinnitus
BNF[6], classification based on BNF[54]
Lamotrigine (LTG)
Common (1-10 per 100) or very common (more than 1 in 10) Blurred vision; aggression; agitation; arthralgia; ataxia; back pain; diarrhoea; diplopia; dizziness; drowsiness; dry mouth; headache; insomnia; nausea; nystagmus; rash; tremor; vomiting **Frequency not known** Aseptic meningitis; suicidal ideation
BNF[6], classification based on BNF[54]
Levetiracetam (LEV)
Common (1-10 per 100) or very common (more than 1 in 10) Abdominal pain; aggression; anorexia; anxiety; ataxia; convulsion; cough; depression; diarrhoea; dizziness; drowsiness; dyspepsia; headache; insomnia; irritability; malaise; nasopharyngitis; nausea; rash; tremor; vertigo; vomiting **Frequency not known** Completed suicide; pancytopenia
BNF[6], classification based on BNF[54]
Oxcarbazepine (OXC)
Common (1-10 per 100) or very common (more than 1 in 10)

Potential side effects
Abdominal pain; acne; agitation; alopecia; amnesia; asthenia; ataxia; confusion; constipation; depression; diarrhoea; diplopia; dizziness; drowsiness; headache; hyponatraemia; impaired concentration; nausea; nystagmus; rash; tremor; visual disorders; vomiting **Frequency not known** Aplastic anaemia; bone marrow depression; hypertension; hypothyroidism; neutropenia; osteoporotic bone disorders; pancytopenia; suicidal ideation
BNF[6], classification based on BNF[54]
Topiramate (TPM)
Common (1-10 per 100) or very common (more than 1 in 10) Abdominal pain; aggression; agitation; alopecia; anaemia; anxiety; appetite changes; arthralgia; cognitive impairment; confusion; constipation; depression; diarrhoea; dizziness; drowsiness; dry mouth; dyspepsia; dyspnoea; epistaxis; gastritis; impaired attention; impaired coordination; irritability; malaise; mood changes; movement disorders; muscle spasm; muscular weakness; myalgia; nausea; nephrolithiasis; nystagmus; paraesthesia; pruritus; rash; seizures; sleep disturbance; speech disorder; taste disturbance; tinnitus; tremor; urinary disorders; visual disturbances; vomiting **Frequency not known** Encephalopathy; hyperammonaemia; maculopathy; toxic epidermal necrolysis
BNF[6], classification based on BNF[54]
Valproic Acid (VPA)
Common (1-10 per 100) or very common (more than 1 in 10) Aggression; anaemia; confusion; convulsion; deafness; diarrhoea; extrapyramidal disorders; gastric irritation; haemorrhage; headache; hyponatraemia; memory impairment; menstrual disturbance; nausea; nystagmus; somnolence; stupor; thrombocytopenia; transient hair loss (regrowth may be curly); tremor; weight gain **Frequency not known** Hypersensitivity reactions; suicidal ideation
BNF[6], classification based on BNF[54]
Zonisamide (ZNS)
Common (1-10 per 100) or very common (more than 1 in 10) Abdominal pain; agitation; alopecia; anorexia; ataxia; confusion; constipation; depression; diarrhoea; diplopia; dizziness; drowsiness; ecchymosis; fatigue; impaired attention; impaired memory; insomnia; irritability; nausea; nystagmus; paraesthesia; peripheral oedema; pruritus; psychosis; pyrexia; rash (consider withdrawal); speech disorder; tremor; weight loss
BNF[6], classification based on BNF[54]
BNF = British National Formulary; ESL = Eslicarbazepine acetate; LCM = Lacosamide; LEV = Levetiracetam; LTG = lamotrigine; OXC = oxcarbazepine; TPM = topiramate; UK = United Kingdom; VPA = valproic acid; ZNS = zonisamide

Table 28: Treatment emergent adverse events, in individuals with focal-onset seizures with or without secondarily generalisation

	Eslicarbazepine acetate (ESL)	**Lacosamide (LCM)**	**Levetiracetam (LEV)**	**Zonisamide (ZNS)**	**Carbamazepine CR (CBZ-CR)**
No. of patients with TEAEs/all patients	302/401 (75.3%)	328/444 (73.9%)	227/285 (79.6%)	170/281 (60%)	320/412 (77.7%) (vs ESL) 332/442 (75.1%) (vs LCM) 235/291 (80.8%) (vs LEV) 185/300 (62%) (vs ZNS)
	OR (95% CrI)				
ESL	-	0.9 (0.56, 1.38)	0.92 (0.52, 1.5)	0.89 (0.54, 1.39)	0.84 (0.59, 1.15)
LCM	1.11 (0.72, 1.79)	-	1.04 (0.61, 1.67)	1.01 (0.63, 1.56)	0.95 (0.7, 1.28)
LEV	1.09 (0.67, 1.92)	0.96 (0.6, 1.64)	-	0.94 (0.57, 1.66)	0.95 (0.62, 1.4)
ZNS	1.12 (0.72, 1.85)	0.99 (0.64, 1.59)	1.06 (0.61, 1.75)	-	0.97 (0.69, 1.33)

From Lattanzi 2018[16] Table 4 and 2. All included studies were deemed to be of low risk of bias (selection, performance, detection, attrition, reporting, funding)
OR < 1 indicates an advantage to the AED in the row over the column. None of the results were significantly different between AEDs
CBZ-CR = controlled-release carbamazepine; CrI = credible interval, ESL = eslicarbazepine acetate; LCM = lacosamide, LEV = levetiracetam; No. = number; OR = odds ratio; TEAEs = treatment emergent adverse events; ZNS = zonisamide

Table 29: Withdrawal due to treatment emergent adverse events, in individuals with focal-onset seizures with or without secondarily generalisation

	Eslicarbazepine acetate (ESL)	**Lacosamide (LCM)**	**Levetiracetam (LEV)**	**Zonisamide (ZNS)**	**Carbamazepine CR (CBZ-CR)**
No. of withdrawals due to TEAEs/patients	54/401 (13.5%)	47/444 (11%)	41/285 (14.4%)	31/281 (11%)	74/412 (18.0%) (vs ESL) 69/442 (16%) (vs LCM) 56/291 (19.2%) (vs LEV) 35/300 (12%) (vs ZNS)
	OR (95% CrI)				
ESL	-	1.17 (0.65, 1.94)	1.07 (0.57, 1.81)	0.81 (0.41, 1.44)	0.73 (0.49, 1.05)
LCM	0.85 (0.52, 1.54)	-	0.95 (0.51, 1.66)	0.72 (0.35, 1.32)	**0.65 (0.43, 0.95)**
LEV	0.93 (0.55, 1.75)	1.05 (0.6, 1.96)	-	0.7 (0.38, 1.47)	0.72 (0.45, 1.09)
ZNS	1.23 (0.69, 2.44)	1.39 (0.76, 2.86)	1.42 (0.68, 2.61)	-	0.97 (0.56, 1.57)

From Lattanzi 2018[16] Table 4 and 2. All included studies were deemed to be of low risk of bias (selection, performance, detection, attrition, reporting, funding)
OR < 1 indicates an advantage to the AED in the row over the column. None of the results were significantly different between AEDs, except in comparison between LCM and CBZ-CR, results favouring LCM (marked in bold)
CBZ-CR = controlled-release carbamazepine; CrI = credible interval, ESL = eslicarbazepine acetate; LCM = lacosamide, LEV = levetiracetam; No. = number; OR = odds ratio; TEAEs = treatment emergent adverse events; ZNS = zonisamide

Table 30: Time to withdrawal of treatment for individuals with focal seizures

	Lamotrigine (LTG)	Levetiracetam (LEV)	Oxcarbazepine (OXC)	Topiramate (TPM)	Valproic Acid (VPA)	Zonisamide (ZNS)
	HR (95% CI) Direct evidence %					
LTG	-	0.91 (0.74, 1.12) 23.7	**0.68 (0.52, 0.9)** 4.4	**0.63 (0.51, 0.78)** 20.9	**0.72 (0.58, 0.9)** 5.1	**0.69 (0.49, 0.97)** 0
LEV	1.1 (0.89, 1.35) 23.7	-	0.75 (0.55, 1.03) 0	**0.69 (0.54, 0.89)** 0	0.79 (0.61, 1.03) 17.2	0.76 (0.53, 1.08) 0
OXC	**1.46 (1.11, 1.92)** 4.4	1.33 (0.97, 1.82) 0	-	0.92 (0.69, 1.22) 4.9	1.05 (0.76, 1.44) 0	1.01 (0.67, 1.52) 0
TPM	**1.59 (1.29, 1.95)** 20.9	**1.45 (1.12, 1.85)** 0	1.09 (0.82, 1.44) 4.9	-	1.14 (0.88, 1.48) 33.7	1.1 (0.76, 1.56) 0
VPA	**1.39 (1.11, 1.72)** 5.1	1.27 (0.97, 1.64) 17.2	0.95 (0.69, 1.32) 0	0.88 (0.68, 1.14) 33.7	-	0.96 (0.67, 1.37) 0
ZNS	**1.45 (1.03, 2.04)** 0	1.32 (0.93, 1.88) 0	0.99 (0.66, 1.49) 0	0.91 (0.64, 1.31) 0	1.04 (0.73, 1.5) 0	-

From Nevitt 2017[19] figure 8.
HR < 1 indicates an advantage to the AED in the row over the column; results highlighted in bold are statistically significant
CI = confidence interval, LEV = Levetiracetam; LTG = lamotrigine; OXC = oxcarbazepine; TPM = topiramate; VPA = valproic acid; ZNS = zonisamide

Table 31: Time to withdrawal of treatment for individuals with focal seizures, extra information

Intervention	Comparison	No of participants (studies) with direct evidence	Relative effect HR (95% CI) fixed-effect analyses		Proportion of direct evidence	Quality of the evidence (GRADE)*
			Direct evidence Heterogeneity: I^2	Direct + indirect evidence NMA		
Lamotrigine (LTG)	Carbamazepine	2268 (9 studies)	**0.76 (0.61 to 0.95)** I^2 = 39.3%	**0.75 (0.65 to 0.86)**	28.9%	High
Levetiracetam (LEV)	Carbamazepine	1567 (3 studies)	**0.70 (0.52 to 0.94)** I^2 = 0%	**0.82 (0.69 to 0.97)**	37.9%	High
Oxcarbazepine (OXC)	Carbamazepine	562 (2 studies)	4.62 (0.95 to 22.4) I^2 = 0%	1.09 (0.84 to 1.42)	5.7%	High
Topiramate (TPM)	Carbamazepine	937 (2 studies)	1.04 (0.52 to 2.07) I^2 = 0%	1.18 (0.98 to 1.43)	7.4%	High
Valproic Acid (VPA)	Carbamazepine	814 (5 studies)	0.94 (0.73 to 1.19) I^2 = 0%	1.04 (0.86 to 1.25)	40.1%	High
Zonisamide (ZNS)	Carbamazepine	583 (1 study)	1.08 (0.81 to 1.44) I^2 = NA	1.08 (0.79 to 1.48)	100%	High

From Nevitt 2017[19] abstract Table (+ figure 8 + Table 8)

HR = hazard ratio; HR < 1 indicates an advantage to the intervention rather than the comparison; results highlighted in bold are statistically significant; HRs and 95% CIs are calculated from fixed-effect analyses (pairwise and network meta-analysis); where substantial heterogeneity was present (I2 > 50%), random-effects meta-analysis was also conducted

NA - heterogeneity is not applicable as only one study contributed direct evidence

*Several trials contributing direct evidence or contributing to the network meta-analysis were at high risk of bias for at least one domain; sensitivity analyses were performed in the case of particular sources of bias or inconsistencies within individual participant data provided. Results of sensitivity analyses showed similar numerical results and no changes to conclusions, therefore any risks of bias within the trials included in these analyses have not influenced the overall results (no downgrade of quality of evidence). No indication of inconsistency between direct evidence and network meta-analysis results (no downgrade of quality of evidence).

CI = confidence interval; GRADE = Grading of Recommendations, Assessment, Development and Evaluation; LEV = Levetiracetam; LTG = lamotrigine; NMA = network meta-analysis; OXC = oxcarbazepine; TPM = topiramate; VPA = valproic acid; ZNS = zonisamide

Table 32: Time to withdrawal of treatment for individuals with generalised tonic clonic seizures

	Lamotrigine (LTG)	Levetiracetam (LEV)	Oxcarbazepine (OXC)	Topiramate (TPM)	Valproic Acid (VPA)
	HR (95% CI) Direct evidence %				
LTG	-	0.85 (0.46, 1.59) 0	0.63 (0.13, 3.03) 7.6	**0.51 (0.32, 0.8)** 7.3	0.9 (0.6, 1.35) 14.8
LEV	1.17 (0.63, 2.19) 0	-	0.74 (0.14, 3.86) 0	0.6 (0.33, 1.09) 0	1.05 (0.58, 1.9) 18.6
OXC	1.58 (0.33, 7.67) 7.6	1.35 (0.26, 7.14) 0	-	0.81 (0.17, 3.85) 9	1.42 (0.29, 6.92) 0
TPM	**1.96 (1.25, 3.08)** 7.3	1.67 (0.92, 3.03) 0	1.24 (0.26, 5.94) 9	-	**1.76 (1.22, 2.53)** 22.4
VPA	1.11 (0.74, 1.67) 14.8	0.95 (0.53, 1.72) 18.6	0.7 (0.14, 3.45) 0	**0.57 (0.4, 0.82)** 22.4	-

From Nevitt 2017[19] figure 9
HR < 1 indicates an advantage to the AED in the row over the column; results highlighted in bold are statistically significant
CI = confidence interval, LEV = Levetiracetam; LTG = lamotrigine; OXC = oxcarbazepine; TPM = topiramate; VPA = valproic acid

Table 33: Time to withdrawal of treatment for individuals with generalised tonic clonic seizures, extra information

Intervention	Comparison	No of participants (studies) with direct evidence	Relative effect HR (95% CI) fixed-effect analyses		Proportion of direct evidence	Quality of the evidence (GRADE)
			Direct evidence Heterogeneity: I^2	Direct + indirect evidence NMA		
Lamotrigine (LTG)	Carbamazepine	302 (7 studies)	1.23 (0.72 to 2.10) I^2 = 0%	**0.63 (0.45 to 0.89)**	39.2%	Not reported*
Levetiracetam (LEV)	Carbamazepine	251 (2 studies)	1.22 (0.74 to 2.02) I^2 = 0%	0.74 (0.44 to 1.23)	57%	Not reported*
Oxcarbazepine (OXC)	Carbamazepine	9 (1 studies)	0.39 (0.03 to 4.35) I^2 = NA	1.00 (0.21 to 4.81)	3.9%	Not reported*
Topiramate (TPM)	Carbamazepine	101 (2 studies)	1.10 (0.51 to 2.36) I^2 = 0%	1.24 (0.90 to 1.71)	23.2%	Not reported*
Valproic Acid (VPA)	Carbamazepine	405 (4 studies)	1.26 (0.73 to 2.20) I^2 = 6.6%	**0.70 (0.54 to 0.92)**	27.3%	Not reported*
Zonisamide (ZNS)	No information					

From Nevitt 2017[19] Table 9 (+ figure 9)

HR = hazard ratio; HR < 1 indicates an advantage to the intervention rather than the comparison; results highlighted in bold are statistically significant; HRs and 95% CIs are calculated from fixed-effect analyses (pairwise and network meta-analysis); where substantial heterogeneity was present (I2 > 50%), random-effects meta-analysis was also conducted

NA - heterogeneity is not applicable as only one study contributed direct evidence

*Not reported, but likely to be high, since for the outcomes in Nevitt where GRADE was reported were all high risk ("Time to 12-month seizure freedom for individuals with focal seizures" and "Time to withdrawal of treatment for individuals with focal seizures"), and since the studies contributing to those also contributed to the outcomes in this table.

CI = confidence interval; GRADE = Grading of Recommendations, Assessment, Development and Evaluation; LEV = Levetiracetam; LTG = lamotrigine; NMA = network meta-analysis; OXC = oxcarbazepine; TPM = topiramate; VPA = valproic acid; ZNS = zonisamide

Table 34: Reasons for withdrawal from allocated treatment – overview of events and censored

Reason	Lamotrigine (LTG)	Levetiracetam (LEV)	Oxcarbazepine (OXC)	Topiramate (TPM)	Valproic Acid (VPA)	Zonisamide (ZNS)
Events	570 (29%)	344 (27%)	137 (29%)	545 (47%)	478 (28%)	96 (34%)
Censored	1396 (71%)	909 (73%)	333 (70%)	599 (52%)	1176 (70%)	186 (66%)
Events + Censored	1978 (100%)	1253 (100%)	478 (100%)	1158 (100%)	1680 (100%)	282 (100%)
Missing	12	0	8	14	26	0
Grand total	1990	1253	486	1172	1706	282

From Nevitt 2017[19] Table 7
LEV = Levetiracetam; LTG = lamotrigine; OXC = oxcarbazepine; TPM = topiramate; VPA = valproic acid; ZNS = zonisamide

Table 35: Reasons for withdrawal from allocated treatment – events details

Reason	Lamotrigine (LTG)	Levetiracetam (LEV)	Oxcarbazepine (OXC)	Topiramate (TPM)	Valproic Acid (VPA)	Zonisamide (ZNS)
Adverse events	235 (41%)	134 (39%)	56 (41%)	259 (48%)	132 (28%)	31 (32%)
Inadequate response	144 (26%)	89 (26%)	36 (26%)	148 (27%)	140 (29%)	23 (24%)
Both adverse events and inadequate response	32 (6%)	0 (0%)	11 (8%)	46 (8%)	107 (22%)	0 (0%)
Protocol violation/non compliance	68 (12%)	21 (6%)	27 (20%)	0 (0%)	11 (2%)	3 (3%)
Withdrew consent	65 (11%)	68 (20%)	2 (1%)	55 (10%)	64 (13%)	35 (36%)
Other*	26 (5%)	32 (9%)	5 (4%)	37 (7%)	24 (5%)	4 (4%)
Total events	570	344	137	545	478	96

From Nevitt 2017[19] Table 7
*Other treatment-related reasons included: physician's decision, drug-related death, pregnancy or perceived seizure freedom, or non specific (drug-related) reason
LEV = Levetiracetam; LTG = lamotrigine; OXC = oxcarbazepine; TPM = topiramate; VPA = valproic acid; ZNS = zonisamide

Table 36: Reasons for withdrawal from allocated treatment – censored details

Reason	Lamotrigine (LTG)	Levetiracetam (LEV)	Oxcarbazepine (OXC)	Topiramate (TPM)	Valproic Acid (VPA)	Zonisamide (ZNS)
Illness or death	20 (1%)	0 (0%)	1 (0%)	10 (2%)	7 (1%)	0 (0%)
Remission of seizures	40 (3%)	0 (0%)	12 (4%)	44 (7%)	75 (6%)	0 (0%)
Lost to follow-up	33 (3%)	41 (5%)	24 (7%)	18 (3%)	63 (5%)	0 (0%)
Other*	31 (2%)	0 (0%)	5 (2%)	26 (4%)	82 (7%)	25 (13%)
Completed study	1272 (91%)	868 (95%)	291 (87%)	501 (84%)	949 (81%)	161 (87%)
Total censored	1396	909	333	599	1176	186

From Nevitt 2017[19] Table 7
*Other non treatment-related reasons included: epilepsy diagnosis changed, participants developed other medical disorders including neurological and psychiatric disorders or non specific (non drug-related) reason
LEV = Levetiracetam; LTG = lamotrigine; OXC = oxcarbazepine; TPM = topiramate; VPA = valproic acid; ZNS = zonisamide

Table 37: Adverse events - number of participants and adverse events

Number of…	Lamotrigine (LTG)	Levetiracetam (LEV)	Oxcarbazepine (OXC)	Topiramate (TPM)	Valproic Acid (VPA)	Zonisamide (ZNS)
Participants randomised	3064	1898	979	1209	2303	282
Participants reporting adverse events (%)	1608 (52%)	1441 (76%)	623 (64%)	920 (76%)	1294 (56%)	182 (65%)
Adverse events reported (event per afflicted)	6296 (3.9)	4258 (3)	1000 (1.6)	6316 (6.9)	3599 (2.8)	606 (3.3)

From Nevitt 2017[19] Table 16
LEV = Levetiracetam; LTG = lamotrigine; OXC = oxcarbazepine; TPM = topiramate; VPA = valproic acid; ZNS = zonisamide

Table 38 contains the most commonly reported adverse events by patients taking one of the below AEDs. Please note that not all studies contributing data to the table have reported all AEs or might have reported AEs in slightly different manners, so comparing fine numbers will most likely not make sense. But a general idea of the incidence can be had by comparing event counts and number of patients on the specific AED.

Table 38: Adverse events - rate of occurrence of most commonly reported adverse events

Adverse event type	Lamotrigine (LTG)	Levetiracetam (LEV)	Oxcarbazepine (OXC)	Topiramate (TPM)	Valproic Acid (VPA)	Zonisamide (ZNS)
Number of participants randomised*	**3064**	**1898**	**979**	**1209**	**2303**	**282**
Accidental injury	110	58	5	95	28	8
Anorexia or weight loss	116	62	6	394	24	25
Anxiety/depression	171	163	32	309	59	16
Aphasia	26	11	4	106	11	2
Asthenia	41	37	1	31	26	10
Ataxia	55	32	17	61	32	8
Cognitive (memory, concentration, confusion etc.)	204	73	44	439	100	19
Dental problems	62	70	5	61	28	7
Dizziness/faintness	348	394	140	269	171	23
Drowsiness/fatigue	539	477	233	628	422	33
Fever or viral infection	172	338	24	84	68	37
Gastrointestinal disturbances	394	284	33	236	246	42
Hair loss	22	16	15	39	130	3
Headache or migraine	556	596	137	315	264	47
Impotence	17	11	0	27	13	3
Increased/worsened seizures	164	140	6	58	31	6
Infection	90	63	4	56	19	5
Laboratory results abnormal	117	90	8	47	103	32
Menstrual problems	31	39	1	22	28	4
Mood or behavioural change	163	121	25	415	128	15
Nausea/vomiting	233	142	53	132	167	20
Pain	250	251	6	154	65	25
Paraesthesia or tingling	33	28	2	708	22	7
Problems sleeping/nightmares	197	101	16	147	46	14
Rash or skin disorder	420	125	73	163	46	31
Renal/urinary disorder	78	93	2	92	27	21
Respiratory disorder	124	131	4	190	53	17
Tremor or twitch	219	51	19	56	258	2

Adverse event type	Lamotrigine (LTG)	Levetiracetam (LEV)	Oxcarbazepine (OXC)	Topiramate (TPM)	Valproic Acid (VPA)	Zonisamide (ZNS)
Number of participants randomised*	**3064**	**1898**	**979**	**1209**	**2303**	**282**
Visual disturbance/nystagmus	96	33	33	86	53	8
Weight gain	167	70	22	71	347	1
From Nevitt 2017[19] Table 17, *from Table 16 LEV = Levetiracetam; LTG = lamotrigine; OXC = oxcarbazepine; TPM = topiramate; VPA = valproic acid; ZNS = zonisamide						

FAQ 6: How will it impact my daily life?

Some of the side effects/adverse events which in a severe form may affect e.g. ability to drive or handle heavy machinery are: dizziness; drowsiness; somnolence; fatigue; blurred vision; cognitive disorder; impaired coordination.

The impact on daily life will thus depend on which side-effects/adverse events the person with epilepsy encounters and how his or her individual life will be impacted by the ability not to drive a car versus depression or gastrointestinal disturbances.

Please note that not all patients receiving a particular AED will experience the listed possible side-effects/adverse events in FAQ 5. Moreover, most of the side effects/adverse events could be experienced more or less severely.

Help with official guidelines as to the impact of epilepsy on fitness to drive can be found on www.bast.de[28] . On this site the German evaluation guidelines for driving ability is available (https://www.bast.de/BASt_2017/DE/Verkehrssicherheit/Fachthemen/BLL/Begutachtungsleitlinien.pdf?__blob=publicationFile&v=17). Section 3.9.6 on page 48-52 handles epilepsy and epileptic seizures. A copy of the tabular overview on the Evaluation guideline page 51 is available in appendix 4.

3.3 ASSESSMENT OF THE CLINICAL REVIEW EVIDENCE

Table 39: Overview of clinical evidence reviews populating the evidence table

Study ID	Participants	Interventions	Outcomes	Setting Country	Study Design	Follow-up duration
Campos 2016[8]	All ages	Monotherapy with	Number of patients	Not reported	NMA of RCTs	Unrestricted

Study ID	Participants	Interventions	Outcomes	Setting Country	Study Design	Follow-up duration
		antiepileptic drugs at optimal doses. Maintenance treatment period of at least 15 days. Studies comparing different pharmaceutical formulations or doses were excluded.	becoming seizure free at the end of the maintenance treatment period; number of withdrawals because of inefficacy; withdrawals because of adverse reactions.			
DeGiorgio 2018[9]	SUDEP cases in studies of people with epilepsy	Not reported	Comparative risk of SUDEP	Not reported	Evidence review (specifics not reported)	Not reported
Hampel 2017[12]	Not reported	Not reported	Not reported	Not reported	Evidence review (specifics not reported)	Not reported
Jacoby 2015[13]	≥ 16 years with a history of two or more clinically definite unprovoked seizures in the previous year and without any substantial learning disability (as judged by the randomising clinician from the history and examination)	Carbamazepine versus lamotrigine, gabapentin, oxcarbazepine and topiramate, and valproate versus lamotrigine and topiramate.	QoL assessment, using a battery of previously validated generic and epilepsy-specific measures taken from the NEWQOL (Newly Diagnosed Epilepsy Quality of Life) Battery. In addition, a revised 12-item version of the "impact of epilepsy scale", a single item measure of global QoL, and single items relating to education, employment, driving, and marital status	UK	Report on data from SANAD trial	Up to 4 years
Kwan 2004[14]	Not reported	Not reported	Remission	Not reported	Evidence review (specifics not reported)	Not reported
Lamberink	Seizure free	Not applicable (Epidemiological	Primary: Occurrence and	Unrestricted	Systematic	Unrestricted

Study ID	Participants	Interventions	Outcomes	Setting Country	Study Design	Follow-up duration
2017[15]	patients who started antiepileptic drug withdrawal	review)	timing of seizure recurrence at 2 and 5 years after initiation of antiepileptic drug withdrawal. Secondary: Long-term seizure outcome, with favourable outcome defined as complete seizure freedom in the last year of follow-up, suggesting either no recurrence or recurrence with subsequent regain of seizure control		review and meta analysis of published evidence (with individual patient data)	
Lattanzi 2018[16]	≥ 16 years. Any gender, ethnicity. Diagnosed with epilepsy with focal-onset seizures (simple focal, complex focal or secondary generalised tonic-clonic seizures). Excluded ≥ 60 years of age.	Monotherapy comparing gabapentin, eslicarbazepine acetate, felbamate, lacosamide, lamotrigine, levetiracetam, oxcarbazepine, perampanel, pregabalin, retigabine, tiagabine, topiramate, vigabatrin or zonisamide versus controlled-release carbamazepine.	Proportion of patients achieving at least 26-weeks seizure freedom during the maintenance period and the proportion of seizure-free patients for at least 52 consecutive weeks. Also the proportion of patients who experienced any treatment emergent adverse events (TEAE) and withdrawals due to TEAEs.	Unrestricted	NMA of RCTs	Unrestricted
Maguire 2016[17]	Any age Diagnosis of epilepsy (any type) Receiving an intervention for	Early versus delayed presurgical evaluation for lesional epilepsy Educational programmes Seizure-monitoring devices	Primary outcomes: Number of deaths from SUDEP Secondary outcomes: Number of other deaths (unrelated to SUDEP)	Unrestricted	Cochrane SR of RCTs, quasi-RCTs and cluster-RCTs; prospective non-	Unrestricted

Study ID	Participants	Interventions	Outcomes	Setting Country	Study Design	Follow-up duration
	prevention of SUDEP.	Safety pillows Nocturnal supervision SSRIs Opiate antagonists Adenosine antagonists	Change in mean depression and anxiety scores (as defined within the study) Clinically important change in quality of life: any change in quality of life score (average and endpoint) according to validated quality of life scales Number of hospital attendances for seizures		randomised cohort controlled and un-controlled studies; case control studies.	
Marson 2007[18]	Patients with an adequately documented history of two or more clinically definite unprovoked epileptic seizures within the last year for whom treatment with a single antiepileptic drug represented the best therapeutic option.	Arm A was carbamazepine (CBZ) versus gabapentin (GBP) versus lamotrigine (LTG) versus oxcarbazepine (OXC) versus topiramate (TPM). Arm B valproate (VPA) versus LTG versus TPM	Time to treatment failure (withdrawal of the randomised drug for reasons of unacceptable adverse events or inadequate seizure control or a combination of the two) and time to achieve a 12-month remission of seizures. Time from randomisation to first seizure, 24-month remission of seizures, incidence of clinically important adverse events, quality of life (QoL) outcomes and health economic outcomes.	UK	Report on data from SANAD trial	Up to 2 years
Nevitt 2017[19]	Children or adults with partial onset seizures (simple	10 anti epileptic drugs currently licensed and commonly used as	Primary outcome: Time to withdrawal of allocated treatment	Unrestricted	SR and NMA (where applicable) of	Unrestricted

Study ID	Participants	Interventions	Outcomes	Setting Country	Study Design	Follow-up duration
	partial, complex partial, or secondarily generalised tonic-clonic seizures) or generalised onset tonic-clonic seizures (with or without other generalised seizure types).	monotherapy in our network of treatments: Carbamazepine, Phenytoin, sodium valproate, phenobarbitone, oxcarbazepine, lamotrigine, gabapentin, topiramate, levetiracetam, zonisamide Included trials had to make at least one pairwise comparison between at least two of the 10 AEDs included in the network.	(retention time). Secondary outcomes: • Time to achieve 12-month seizure-free period (remission) after randomisation • Time to achieve six-month seizure-free period (remission) after randomisation • Time to first seizure post randomisation • Occurrence of adverse events (reported narratively)		RCTs using either: • an adequate method of allocation concealment (e.g. sealed, opaque envelopes); • a quasi method of randomisation (e.g. allocation by date of birth). Trials may be double-blind, single-blind or unblinded.	
Rosenow 2012[21]	Age ≥ 12 years. Body weight ≥ 30 kg (patients 12-15 years of age) and ≥ 40 kg (patients over 16 years of age), respectively. Newly diagnosed with focal, generalised or unclassified epilepsy receiving one antiepileptic	lamotrigine (LTG) and levetiracetam (LEV)	Primary outcome: Seizure freedom in the first 6 weeks after randomisation. Secondary outcomes: Seizure freedom during the last 16 weeks of the trial and during the complete treatment period calculated as the rate of seizure-free patients between week 11 and the end of the treatment, and	Not directly reported, probably Germany	Report on data from LaLiMo trial	26 weeks

Study ID	Participants	Interventions	Outcomes	Setting Country	Study Design	Follow-up duration
	drug at enrolment.*		randomisation and the end of treatment, respectively. Seizure-free time was calculated from randomisation to the first seizure documented during the treatment period of 26 weeks. Retention time was calculated as the interval from randomisation to the regular end of treatment (26 weeks) or the premature end of treatment.			
Ryvlin 2011[22]	Adult patients with uncontrolled partial or primary generalised tonic-clonic seizures	Treatment with adjunctive AEDs vs monotherapy	Comparative risk of SUDEP	Unrestricted	Review of RCTs	Unrestricted
Strozzi 2015[24]	People with epilepsy in remission	Withdrawal of any antiepileptic drug and randomising people to differing durations of AED treatment while seizure-free	Primary outcome: risk ratio of seizure relapse as a consequence of early AED discontinuation in contrast to late withdrawal	Unrestricted	SR and MA of RCTs	Unrestricted
Thurman 2017[26]	All ages	Not applicable (Epidemiological review)	Mortality (incidence rate, standardised mortality ratio and any other comparative risk ratios)	Focused on high income countries. Population or community based.	SR of Clinical cohorts or case control studies. Excluded case reports	Unrestricted
Tomson 2015[27]	Girls and women	Valproate, Carbamazepine,	Frequencies of major	Not reported	Review of	Not reported

Study ID	Participants	Interventions	Outcomes	Setting Country	Study Design	Follow-up duration
	(with epilepsy) of childbearing potential	Lamotrigine, Phenobarbital, Phenytoin, Levetiracetam, Oxcarbazepine, Topiramate	congenital malformations.		available evidence	

* Excluded were: Patients with non epileptic seizures or acute symptomatic seizures whose cause can be corrected. Patients who suffer from absence seizures or simple partial seizures without motor signs (aura) only. Patients who had a chronic focal epilepsy or an epileptic state in their medical history Patients with progressive neurological, degenerative or malignant diseases which are clinically relevant from the investigator's point of view (e.g. cardiovascular or endocrine diseases). Patients who have been treated with levetiracetam or lamotrigine before. Patients with known manifest renal insufficiency (creatinine clearance < 50 mL/min, and 80ml/min for patients under the age of 18 years). Patients with known hypersensitivity to levetiracetam, lamotrigine or another component of the trial drugs. Patients who are attended by a legal guardian. Patients suffering from a psychiatric disease or affective disorders (within the past 6 months), which had to be treated with electric convulsive therapy, tranquilising agents, monoamine oxidase inhibitors or CNS active sympathomimetic drugs (e.g. methylphenidate). Patients who were suffering from alcohol or drug addiction within the past 12 months. Pregnant or breast feeding women. Patients who participated in another clinical trial within the past 30 days.
Epilepsy was defined by either two or more unprovoked seizures or one first seizure with high risk for recurrence, such as lesion on cerebral imaging, a focal neurological deficit, based on ictal symptomatology, or a pathological EEG.
NMA = network meta-analysis; SUDEP = sudden unexpected death in epilepsy

4. DISCUSSION

4.1 STRENGTHS, LIMITATIONS AND UNCERTAINTIES

This report builds on the most up to date information available in secondary publications.

The relevant German guideline was identified; however, it is an expert consensus-based guideline (S1 guideline). This report mainly uses results from two network meta analyses from 2017 and 2018 to answer the questions about seizure control (FAQ 2: will my symptoms get better?) and adverse events (FAQ 5: side effects and complications).

The report also uses other evidence reviews (not all of which are systematic) and a range of patient and clinician tailored authoritative web resources to answer FAQ 1: what does it involve? FAQ 3: will it affect my life expectancy? and FAQ 4: will it affect my quality of life?

Whereas there is good evidence for some of the anti epileptic drugs, the evidence on others is sparse. The probable explanation for this is that a number of the AEDs were only recently authorised for monotherapy treatment and thus were not included in trials as monotherapy.

The evidence on SUDEP and on adverse events is however sparse and mostly of low quality. The impression on SUDEP is that it is not dependent on the AED, but on other factors e.g. the type of epilepsy and frequency of seizures. With regards to adverse events, the available evidence use reporting methods too poorly or too divergent for a precise summary.

None of the available evidence gives assumed absolute risk differences, perhaps because the differences between the AEDs for the most is not statistically different, and when it is (for adverse events) the reporting standard or comparability of the underlying evidence is not perfect.

5. REFERENCES

[1] Elger CE, Berkenfeld R, (geteilte Erstautorenschaft) et al. S1-Leitlinie Erster epileptischer Anfall und Epilepsien im Erwachsenenalter. 2017. In: *Deutsche Gesellschaft für Neurologie, Hrsg. Leitlinien für Diagnostik und Therapie in der Neurologie. Online: www.dgn.org/leitlinien (abgerufen am 11.09.2018)*, 2017.

[2] Proposal for revised classification of epilepsies and epileptic syndromes. Commission on Classification and Terminology of the International League Against Epilepsy. *Epilepsia* 1989;30(4):389-99.

[3] Berg AT, Berkovic SF, Brodie MJ, Buchhalter J, Cross JH, van Emde Boas W, et al. Revised terminology and concepts for organization of seizures and epilepsies: report of the ILAE Commission on Classification and Terminology, 2005-2009. *Epilepsia* 2010;51(4):676-85.

[4] Scheffer IE, Berkovic S, Capovilla G, Connolly MB, French J, Guilhoto L, et al. ILAE classification of the epilepsies: position paper of the ILAE Commission for Classification and Terminology. *Epilepsia* 2017;58(4):512-21.

[5] Canadian Agency for Drugs and Technologies in Health. *PRESS - Peer Review of Electronic Search Strategies: 2015 guideline explanation and elaboration (PRESS E&E) [Internet]*. Ottawa: CADTH, 2016 [accessed 26.2.18] Available from: https://www.cadth.ca/press-2015-guideline-explanation-and-elaboration

[6] Joint Formulary Committee. British National Formulary [online]. London: BMJ Group and Pharmaceutical Press <http://www.new.medicinescomplete.com/> (accessed on [11 Sep 2018]).

[7] Joint Formulary Committee. British National Formulary: Epilepsy [online]. London: BMJ Group and Pharmaceutical Press <https://bnf.nice.org.uk/treatment-summary/epilepsy.html> (accessed on [14 Sep 2018]).

[8] Campos MS, Ayres LR, Morelo MR, Marques FA, Pereira LR. Efficacy and tolerability of antiepileptic drugs in patients with focal epilepsy: systematic review and network meta-analyses. *Pharmacotherapy* 2016;36(12):1255-1271.

[9] DeGiorgio CM, Curtis A, Hertling D, Moseley BD. Sudden unexpected death in epilepsy: Risk factors, biomarkers, and prevention. *Acta Neurol Scand* 2018.

[10] Deutsche Gesellschaft für Epileptologie e.V. Empfehlung Generika, Februar 2013 [Internet]. Berlin, Germany: Deutsche Gesellschaft für Epileptologie e.V., 2013 [accessed 14.9.18]. Available from: http://www.izepilepsie.de/cweb2/cgi-bin-noauth/cache/VAL_BLOB/5018/5018/1348/Empfehlung%20Generika%202013.pdf

[11] UMC Utrecht. Epilepsy prediction tools [Internet]. UMC Utrecht, 2017 [accessed 7.1.19]. Available from: http://epilepsypredictiontools.info/

[12] Hampel KG, Rocamora Zuniga R, Quesada CM. [Unravelling the mysteries of sudden unexpected death in epilepsy]. *Neurologia* 2017;Epub ahead of print.

[13] Jacoby A, Sudell M, Tudur Smith C, Crossley J, Marson AG, Baker GA, et al. Quality-of-life outcomes of initiating treatment with standard and newer antiepileptic drugs in adults with new-onset epilepsy: findings from the SANAD trial. *Epilepsia* 2015;56(3):460-72.

[14] Kwan P, Sander JW. The natural history of epilepsy: an epidemiological view. *J Neurol Neurosurg Psychiatry* 2004;75(10):1376-81.

[15] Lamberink HJ, Otte WM, Geerts AT, Pavlovic M, Ramos-Lizana J, Marson AG, et al. Individualised prediction model of seizure recurrence and long-term outcomes after withdrawal of antiepileptic drugs in seizure-free patients: a systematic review and individual participant data meta-analysis. *Lancet Neurol* 2017;16(7):523-31.

[16] Lattanzi S, Zaccara G, Giovannelli F, Grillo E, Nardone R, Silvestrini M, et al. Antiepileptic mono-therapy in newly diagnosed focal epilepsy. A network meta-analysis. *Acta Neurol Scand* 2018;Epub ahead of print.

[17] Maguire MJ, Jackson CF, Marson AG, Nevitt SJ. Treatments for the prevention of Sudden Unexpected Death in Epilepsy (SUDEP). *Cochrane Database of Systematic Reviews 2016, Issue 7. Art. No.: CD011792. DOI: 10.1002/14651858.CD011792.pub2*, 2016.

[18] Marson AG, Appleton R, Baker GA, Chadwick DW, Doughty J, Eaton B, et al. A randomised controlled trial examining the longer-term outcomes of standard versus new antiepileptic drugs. The SANAD trial. *Health Technol Assess* 2007;11(37):iii-iv, ix-x, 1-134.

[19] Nevitt SJ, Sudell M, Weston J, Tudur SC, Marson AG. Antiepileptic drug monotherapy for epilepsy a network meta-analysis of individual participant data. *Cochrane Database Syst Rev* 2017, Issue 6. Art. No.: CD011412. DOI: 10.1002/14651858.CD011412.pub2

[20] Patient.info [Internet]. Patient Platform Limited, [accessed 11.9.18]. Available from: https://patient.info/medicine

[21] Rosenow F, Schade-Brittinger C, Burchardi N, Bauer S, Klein KM, Weber Y, et al. The LaLiMo Trial: lamotrigine compared with levetiracetam in the initial 26 weeks of monotherapy for focal and generalised epilepsy--an open-label, prospective, randomised controlled multicenter study. *J Neurol Neurosurg Psychiatry* 2012;83(11):1093-8.

[22] Ryvlin P, Cucherat M, Rheims S. Risk of sudden unexpected death in epilepsy in patients given adjunctive antiepileptic treatment for refractory seizures: a meta-analysis of placebo-controlled randomised trials. *Lancet Neurol* 2011;10(11):961-8.

[23] Scottish Intercollegiate Guidelines Network. *Diagnosis and management of epilepsy in adults [SIGN CPG 143]*. Edinburgh: SIGN, 2015 [accessed 5.4.18] Available from: http://www.sign.ac.uk/sign-143-diagnosis-and-management-of-epilepsy-in-adults.html

[24] Strozzi I, Nolan SJ, Sperling MR, Wingerchuk DM, Sirven J. Early versus late antiepileptic drug withdrawal for people with epilepsy in remission. *Cochrane Database Syst Rev* 2015, Issue 2. Art. No.: CD001902. DOI: 10.1002/14651858.CD001902.pub2

[25] SUDEP Action. SUDEP Action [Internet]. SUDEP Action, [accessed 11.9.18]. Available from: http://sudep.org

[26] Thurman DJ, Logroscino G, Beghi E, Hauser WA, Hesdorffer DC, Newton CR, et al. The burden of premature mortality of epilepsy in high-income countries: a systematic review from the Mortality Task Force of the International League Against Epilepsy. *Epilepsia* 2017;58(1):17-26.

[27] Tomson T, Marson A, Boon P, Canevini MP, Covanis A, Gaily E, et al. Valproate in the treatment of epilepsy in girls and women of childbearing potential. *Epilepsia* 2015;56(7):1006-19.

[28] Bundesanstalt für Straßenwesen. Begutachtungsleitlinien zur Kraftfahreignung [Internet]. Bergisch Gladbach, Germany: Bundesanstalt für Straßenwesen, 2018 [accessed 11.9.18]. Available from: https://www.bast.de/BASt_2017/DE/Verkehrssicherheit/Fachthemen/BLL/BLL-Download.html?nn=1817128

[29] European Medicines Agency. European Medicines Agency [Internet]. London: European Medicines Agency, [accessed 14.9.18]. Available from: http://www.ema.europa.eu/

[30] Institute for Quality and Efficiency in Health Care (IQWiG). InformedHealth.org [Internet]. Cologne, Germany: Institute for Quality and Efficiency in Health Care (IQWiG), [accessed 11.9.18]. Available from: https://www.informedhealth.org/

[31] Pharma*Wiki* [Internet]. [accessed 11.9.18]. Available from: https://www.pharmawiki.ch/wiki/

[32] Alexandre V, Jr., Monteiro EA, Freitas-Lima P, Pinto KD, Velasco TR, Terra VC, et al. Addressing overtreatment in patients with refractory epilepsy at a tertiary referral centre in Brazil. *Epileptic Disorders* 2011;13(1):56-60.

[33] Benn EKT, Hauser WA, Shih T, Leary L, Bagiella E, Dayan P, et al. Estimating the incidence of first unprovoked seizure and newly diagnosed epilepsy in the low-income urban community of Northern Manhattan, New York City. *Epilepsia* 2008;49(8):1431-9.

[34] Campbell E, Kennedy F, Russell A, Smithson WH, Parsons L, Morrison PJ, et al. Malformation risks of antiepileptic drug monotherapies in pregnancy: updated results from the UK and Ireland Epilepsy and Pregnancy Registers. *J Neurol Neurosurg Psychiatry* 2014;85(9):1029-34.

[35] Cockerell OC, Johnson AL, Sander JW, Shorvon SD. Prognosis of epilepsy: a review and further analysis of the first nine years of the British National General Practice Study of Epilepsy, a prospective population-based study. *Epilepsia* 1997;38(1):31-46.

[36] Granbichler CA, Oberaigner W, Kuchukhidze G, Bauer G, Ndayisaba JP, Seppi K, et al. Cause-specific mortality in adult epilepsy patients from Tyrol, Austria: hospital-based study. *J Neurol* 2015;262(1):126-33.

[37] Guekht AB, Mitrokhina TV, Lebedeva AV, Dzugaeva FK, Milchakova LE, Lokshina OB, et al. Factors influencing on quality of life in people with epilepsy. *Seizure* 2007;16(2):128-33.

[38] Hauser WA, Annegers JF, Elveback LR. Mortality in patients with epilepsy. *Epilepsia* 1980;21(4):399-412.

[39] Hernandez-Diaz S, Smith CR, Shen A, Mittendorf R, Hauser WA, Yerby M, et al. Comparative safety of antiepileptic drugs during pregnancy. *Neurology* 2012;78(21):1692-9.

[40] Hesdorffer DC, Tomson T, Benn E, Sander JW, Nilsson L, Langan Y, et al. Combined analysis of risk factors for SUDEP. *Epilepsia* 2011;52(6):1150-9.

[41] Hesdorffer DC, Tomson T, Benn E, Sander JW, Nilsson L, Langan Y, et al. Do antiepileptic drugs or generalized tonic-clonic seizure frequency increase SUDEP risk? A combined analysis. *Epilepsia* 2012;53(2):249-52.

[42] Hunt S, Russell A, Smithson WH, Parsons L, Robertson I, Waddell R, et al. Topiramate in pregnancy: preliminary experience from the UK Epilepsy and Pregnancy Register. *Neurology* 2008;71(4):272-6.

[43] Lamberts RJ, Thijs RD, Laffan A, Langan Y, Sander JW. Sudden unexpected death in epilepsy: people with nocturnal seizures may be at highest risk. *Epilepsia* 2012;53(2):253-7.

[44] Lhatoo SD, Johnson AL, Goodridge DM, MacDonald BK, Sander JW, Shorvon SD. Mortality in epilepsy in the first 11 to 14 years after diagnosis: multivariate analysis of a long-term, prospective, population-based cohort. *Ann Neurol* 2001;49(3):336-44.

[45] Liebenthal JA, Wu S, Rose S, Ebersole JS, Tao JX. Association of prone position with sudden unexpected death in epilepsy. *Neurology* 2015;84(13):703-9.

[46] Lindsten H, Nyström L, Forsgren L. Mortality risk in an adult cohort with a newly diagnosed unprovoked epileptic seizure: a population-based study. *Epilepsia* 2000;41(11):1469-73.

[47] Mawhinney E, Craig J, Morrow J, Russell A, Smithson WH, Parsons L, et al. Levetiracetam in pregnancy: results from the UK and Ireland epilepsy and pregnancy registers. *Neurology* 2013;80(4):400-5.

[48] Mohanraj R, Norrie J, Stephen LJ, Kelly K, Hitiris N, Brodie MJ. Mortality in adults with newly diagnosed and chronic epilepsy: a retrospective comparative study. *Lancet Neurol* 2006;5(6):481-7.

[49] Morgan CL, Kerr MP. Epilepsy and mortality: a record linkage study in a U.K. population. *Epilepsia* 2002;43(10):1251-5.

[50] Neligan A, Bell GS, Johnson AL, Goodridge DM, Shorvon SD, Sander JW. The long-term risk of premature mortality in people with epilepsy. *Brain* 2011;134(Pt 2):388-95.

[51] Nilsson L, Tomson T, Farahmand BY, Diwan V, Persson PG. Cause-specific mortality in epilepsy: a cohort study of more than 9,000 patients once hospitalized for epilepsy. *Epilepsia* 1997;38(10):1062-8.

[52] Olafsson E, Hauser WA, Gudmundsson G. Long-term survival of people with unprovoked seizures: a population-based study. *Epilepsia* 1998;39(1):89-92.

[53] Rakitin A, Liik M, Oun A, Haldre S. Mortality risk in adults with newly diagnosed and chronic epilepsy: a population-based study. *Eur J Neurol* 2011;18(3):465-70.

[54] Tomson T, Battino D, Bonizzoni E, Craig J, Lindhout D, Sabers A, et al. Dose-dependent risk of malformations with antiepileptic drugs: an analysis of data from the EURAP epilepsy and pregnancy registry. *Lancet Neurol* 2011;10(7):609-17.

[55] Tomson T, Battino D. Teratogenic effects of antiepileptic drugs. *Lancet Neurol* 2012;11(9):803-13.

[56] Trinka E, Bauer G, Oberaigner W, Ndayisaba JP, Seppi K, Granbichler CA. Cause-specific mortality among patients with epilepsy: results from a 30-year cohort study. *Epilepsia* 2013;54(3):495-501.

[57] Veiby G, Daltveit AK, Engelsen BA, Gilhus NE. Fetal growth restriction and birth defects with newer and older antiepileptic drugs during pregnancy. *J Neurol* 2014;261(3):579-88.

[58] Fisher RS, Cross JH, D'Souza C, French JA, Haut SR, Higurashi N, et al. Instruction manual for the ILAE 2017 operational classification of seizure types. *Epilepsia* 2017;58(4):531-42.

APPENDIX 1: SEARCH STRATEGIES

Table 40: Systematic reviews and guideline search results

Results

Database	Dates	Results
CDSR	2012 - Iss 2, Feb 2018	216
DARE	2012 - Iss 2, Apr 2015	82
HTA	2012 - Iss 4, Oct 2016	27
KSR Evidence	01/01/2012 - 26/02/2018	20
NICE Evidence	2016 - 2018	425
GIN	all years	38
Total		**808**
Total after de-duplication		**738**

Search strategies

Cochrane Database of Systematic Reviews (CDSR) (Wiley): Issue 2 of 12, February 2018
Database of Abstracts of Reviews of Effects (DARE) (Wiley): Issue 2 of 4, April 2015
Health Technology Assessment Database (HTA) (Wiley): Issue 4 of 4, October 2016
Searched: 26.2.18

#1 MeSH descriptor: [Epilepsy] explode all trees 2396
#2 MeSH descriptor: [Seizures] explode all trees 683
#3 (epileps* or epileptic* or seizure* or convuls*):ti,ab,kw 8711
#4 (comitial disease or falling sickness or myoclonic or tonic-clonic):ti,ab,kw 590
#5 #1 or #2 or #3 or #4 Publication Year from 2012 to 2018 3444

CDSR = 216
DARE = 82
HTA = 27

KSR Evidence: 2015-2018/02/26
www.ksrevidence.com
Searched: 26.2.18

Searched across any field

Epileps
OR
Seizure
OR
epileptic
OR
convulsion
OR
clonic

2015-2018 = 425 results

International Guideline Library (GIN) (Internet): up to 2018/02/26
Searched 26.2.18
http://www.g-i-n.net

Search terms	Results (Published guidelines only)
Epilepsy	33
Seizure	3
epileptic	2
convulsion	0
clonic	0
Total retrieved	**38**
Total (without duplicates)	**31**

NICE Evidence Search: limited to guidance and SRs only (Internet): 2018/02/26
Searched 26.02.18
https://www.evidence.nhs.uk/

Search terms	Results (Guidance and SRs only)
Epilepsy	8
Seizure	7
epileptic	1
convulsion	4
clonic	0
Total retrieved	**20**
Total (without duplicates)	**15**

Table 41: Health-related quality of life search results

Results

Database	Dates	Results
Embase	1974-2018/week 35	205
MEDLINE	1946-2018/Aug week 3	57
PreMEDLINE	August 28, 2018	21
PubMed	up to 29 August 2018	22
CENTRAL	Issue 7 of 12, July 2018	57
Total		**362**
Total after de-duplication		**255**

Search strategies

Cochrane Central Register of Controlled Trials (CENTRAL): Issue 7 of 12, July 2018
Searched: 29.8.18

#1 MeSH descriptor: [Epilepsy] explode all trees 2139
#2 MeSH descriptor: [Seizures] explode all trees 871
#3 (epileps* or epileptic* or seizure* or convuls*):ti,ab,kw 9379
#4 (comitial NEXT disease or falling NEXT sickness or myoclonic or tonic-clonic):ti,ab,kw 637
#5 #1 or #2 or #3 or #4 9455
#6 (lacosamide or "ADD 243037" or erlosamide or harkoseride or vimpat):ti,ab,kw 206
#7 (levetiracetam or elepsia or keppra or kopodex or levesam or levipil or levroxa or matever or spritam):ti,ab,kw 615
#8 ((valproic NEXT acid) or (Acide NEXT valproique) or (Acido NEXT valproico) or (Acidum NEXT valproicum) or Depakene or Depakin* or dipropylacetate or (Dipropylacetic NEXT acid) or Ergenyl or Kyselina or Mylproin or (Myproic NEXT acid) or (Propylvaleric NEXT acid) or Stavzor or Valproate or Vupral):ti,ab,kw 2135
#9 (eslicarbazepine or aptiom or bia2093 or erelib or exalief or exelief or pazzul or stedesa or zebinix):ti,ab,kw 194
#10 (zonisamid* or exceglan or excegram or excegran or excemid or zonegran):ti,ab,kw 229
#11 #6 or #7 or #8 or #9 or #10 3092
#12 #5 and #11 with Publication year from 2012 to 2018, in Trials 614
#13 MeSH descriptor: [Quality of Life] explode all trees 20225
#14 ("quality of life"):ti,ab,kw 67280
#15 (sf36 or "sf 36" or sf-36 or "short form 36" or "shortform 36" or "sf thirtysix" or "sf thirty six" or "shortform thirtysix" or "shortform thirty six" or "short form thirty six" or "short form thirtysix" or "short form thirty six"):ti,ab,kw 7962
#16 (sf6 or "sf 6" or sf-6 or "short form 6" or "shortform 6" or "sf six" or sfsix or "shortform six" or "short form six"):ti,ab,kw 146
#17 (sf12 or "sf 12" or sf-12 or "short form 12" or "shortform 12" or "sf twelve" or sftwelve or "shortform twelve" or "short form twelve"):ti,ab,kw 1525
#18 (sf6D or "sf 6D" or sf-6D or "short form 6D" or "shortform 6D" or "sf six D" or sfsixD or "shortform six D" or "short form six D"):ti,ab,kw 219
#19 (sf20 or "sf 20" or sf-20 or "short form 20" or "shortform 20" or "sf twenty" or sftwenty or "shortform twenty" or "short form twenty"):ti,ab,kw 67
#20 (sf8 or "sf 8" or sf-8 or "short form 8" or "shortform 8" or "sf eight" or sfeight or "shortform eight" or "short form eight"):ti,ab,kw 106
#21 ("health related quality of life"):ti,ab,kw 10364
#22 ("Quality adjusted life" or "Quality-adjusted-life"):ti,ab,kw 3150
#23 (euroqol or "euro qol" or eq5d or "eq 5d"):ti,ab,kw 4022
#24 (hql or hrql or hqol or hrqol or "hr qol" or hye or hyes):ti,ab,kw 4248
#25 ("health year equivalent" or hui or hui1 or hui2 or hui3 or hui4 or hui-4 or hui-1 or hui-2 or hui-3):ti,ab,kw 157
#26 ("Disability adjusted life" or "Disability-adjusted life" or "health adjusted life" or "health-adjusted life" or "years of healthy life" or "healthy years equivalent" or "years of potential life lost" or "years of health life lost"):ti,ab,kw 127

#27 ("quality time" or qwb or "quality of well being" or "quality of wellbeing" or "index of wellbeing" or "index of well being"):ti,ab,kw 137
#28 (QALY* or DALY$* or HALY* or YHL or HYES or YPLL or YHLL or qald* or qale* or qtime* or AQoL*):ti,ab,kw 2314
#29 (timetradeoff or "time tradeoff" or "time trade-off" or "time trade off" or TTO or "standard gamble" or "willingness to pay"):ti,ab,kw 1096
#30 (HSUV* or "health state value" or "health state preference" or HSPV*):ti,ab,kw 16
#31 #13 or #14 or #15 or #16 or #17 or #18 or #19 or #20 or #21 or #22 or #23 or #24 or #25 or #26 or #27 or #28 or #29 or #30 73418
#32 #12 and #31 57

Embase (Ovid): 1974-2018/week 35
Searched: 30.8.18
1 exp *"seizure, epilepsy and convulsion"/ (179625)
2 (epileps$ or epileptic$ or seizure$ or convuls$).ti,ab. (256180)
3 (comitial disease or falling sickness or myoclonic or tonic-clonic).ti,ab. (16876)
4 or/1-3 (288817)
5 eslicarbazepine acetate/ (695)
6 (eslicarbazepine acetate or aptiom or bia2093 or "bia 2 093" or bia 2093 or "bia2 093" or erelib or exalief or exelief or pazzul or stedesa or zebinix or 236395-14-5).ti,ab,rn. (725)
7 lacosamide/ (798)
8 (lacosamide or "ADD 243037" or erlosamide or harkoseride or spm 927 or spm927 or vimpat or 175481-36-4).ti,ab,rn. (2898)
9 Levetiracetam/ (3725)
10 (levetiracetam or elepsia or keppra or kopodex or levesam 500 or levipil or levroxa or matever or spritam or "ucb l 059" or ucb l059 or 102767-28-2).ti,ab,rn. (16082)
11 valproic acid/ (58805)
12 (valproic acid or 2-Propylpentanoic acid or 2-Propylvaleric acid or 4-Heptanecarboxylic acid or Acide valproique or Acido valproico or Acidum valproicum or Depakene or Depakin$ or dipropylacetate or Dipropylacetic acid or Ergenyl or Kyselina 2-propylvalerova or Mylproin or Myproic acid or Propylvaleric acid or Stavzor or Valproate or Vupral or 99-66-1).ti,ab,rn. (60445)
13 zonisamide/ (5943)
14 (zonisamid$ or ad 810 or ad810 or ci 912 or ci912 or exceglan or excegram or excegran or excemid or zonegran or 68291-97-4).ti,ab,rn. (6170)
15 or/5-14 (72237)
16 exp *Quality of Life/ (92175)
17 quality of life.ti,kw. (115544)
18 ((instrument or instruments) adj3 quality of life).ab. (4088)
19 or/16-18 [terms taken from CADTH filter] (132069)
20 *quality adjusted life year/ or *quality of life index/ (1679)
21 Short Form 12/ or Short Form 20/ or Short Form 36/ or Short Form 8/ (27713)
22 "International Classification of Functioning, Disability and Health"/ or "ferrans and powers quality of life index"/ or "gastrointestinal quality of life index"/ (2814)
23 (sf36 or sf 36 or sf-36 or short form 36 or shortform 36 or sf thirtysix or sf thirty six or shortform thirtysix or shortform thirty six or short form thirty six or short form thirtysix or short form thirty six).ti,ab,ot. (35946)

24 (sf6 or sf 6 or sf-6 or short form 6 or shortform 6 or sf six or sfsix or shortform six or short form six).ti,ab,ot. (2002)
25 (sf12 or sf 12 or sf-12 or short form 12 or shortform 12 or sf twelve or sftwelve or shortform twelve or short form twelve).ti,ab,ot. (7771)
26 (sf6D or sf 6D or sf-6D or short form 6D or shortform 6D or sf six D or sfsixD or shortform six D or short form six D).ti,ab,ot. (1270)
27 (sf20 or sf 20 or sf-20 or short form 20 or shortform 20 or sf twenty or sftwenty or shortform twenty or short form twenty).ti,ab,ot. (407)
28 (sf8 or sf 8 or sf-8 or short form 8 or shortform 8 or sf eight or sfeight or shortform eight or short form eight).ti,ab,ot. (772)
29 "health related quality of life".ti,ab,ot. (51176)
30 (Quality adjusted life or Quality-adjusted-life).ti,ab,ot. (15676)
31 "assessment of quality of life".ti,ab,ot. (2535)
32 (euroqol or euro qol or eq5d or eq 5d).ti,ab,ot. (15564)
33 (hql or hrql or hqol or h qol or hrqol or hr qol).ti,ab,ot. (27375)
34 (hye or hyes).ti,ab,ot. (118)
35 health$ year$ equivalent$.ti,ab,ot. (40)
36 (hui or hui1 or hui2 or hui3 or hui4 or hui-4 or hui-1 or hui-2 or hui-3).ti,ab,ot. (2696)
37 (quality time or qwb or "quality of well being" or "quality of wellbeing" or "index of wellbeing" or index of well being).ti,ab,ot,hw. (1057)
38 (Disability adjusted life or Disability-adjusted life or health adjusted life or health-adjusted life or "years of healthy life" or healthy years equivalent or "years of potential life lost" or "years of health life lost").ti,ab,ot. (3788)
39 (QALY$ or DALY$ or HALY$ or YHL or HYES or YPLL or YHLL or qald$ or qale$ or qtime$ or AQoL$).ti,ab,ot. (20060)
40 (timetradeoff or time tradeoff or time trade-off or time trade off or TTO or Standard gamble$ or "willingness to pay").ti,ab,ot. (9406)
41 15d.ti,ab,ot. (2278)
42 (HSUV$ or health state$ value$ or health state$ preference$ or HSPV$).ti,ab,ot. (508)
43 (utilit$ adj3 ("quality of life" or valu$ or scor$ or measur$ or health or life or estimat$ or elicit$ or disease$)).ti,ab,ot. (16326)
44 (utilities or disutili$).ti,ab,ot. (10027)
45 (PedsQL or Epilepsy Module).ti,ab. (1942)
46 (CHEQOL or Health Related Quality of Life in Children with Epilepsy).ti,ab. (62)
47 (KAS or Katz Adjustment Scale$).ti,ab. (954)
48 (GEOS or Glasgow Epilepsy Outcome Scale$).ti,ab. (194)
49 (ESI-55 or Epilepsy Surgery Inventor$).ti,ab. (41)
50 (QOLIE-10 or QOLIE-89 or QOLIE-31 or Quality of Life in Epilepsy Inventor$).ti,ab. (840)
51 (NEWQOL or Quality of Life in Newly Diagnosed Epilepsy measure$).ti,ab. (9)
52 (QOLCE or Quality of Life in Childhood Epilepsy Questionnaire$).ti,ab. (90)
53 (RLIES or Revised Liverpool Impact of Epilepsy Scale$).ti,ab. (1)
54 (QOLIE-AD-48 or Quality of Life in Epilepsy Inventory Adolescents).ti,ab. (38)
55 (LSSS or Liverpool Seizure Severity Scale$).ti,ab. (154)
56 or/20-55 [NICE DSU: HRQoL] (153148)
57 animal/ or animal experiment/ (3598137)

58 (rat or rats or mouse or mice or murine or rodent or rodents or hamster or hamsters or pig or pigs or porcine or rabbit or rabbits or animal or animals or dogs or dog or cats or cow or bovine or sheep or ovine or monkey or monkeys).ti,ab,ot,hw. (6227397)
59 or/57-58 (6227397)
60 exp human/ or human experiment/ (18679778)
61 59 not (59 and 60) (4809898)
62 (letter or editorial or note).pt. (2318165)
63 4 and 15 and (19 or 56) (435)
64 63 not (61 or 62) (431)
65 limit 64 to yr="2012 -Current" (205)

QoL terms based on:
Strings attached: CADTH database search filters [Internet]. Ottawa: CADTH; 2016. [cited 2018 08 29]. Available from: /resources/finding-evidence
And
HRQoL free-text terms based on: Figure 4: Common free-text terms for electronic database searching for HSUVs in Papaioannou D, Brazier JE, Paisley S. NICE DSU Technical Support Document 9: the identification, review and synthesis of health state utility values from the literature (Internet), 2011 (accessed: 18.8.11) Available from: http://www.nicedsu.org.uk

MEDLINE: 1946-2018/August week 3
Searched: 29.8.18
1 exp Epilepsy/ (103843)
2 exp Seizures/ (58490)
3 (epileps$ or epileptic$ or seizure$ or convuls$).ti,ab. (168940)
4 (comitial disease or falling sickness or myoclonic or tonic-clonic).ti,ab. (9823)
5 or/1-4 (201014)
6 (lacosamide or "ADD 243037" or erlosamide or harkoseride or spm 927 or spm927 or vimpat or 175481-36-4).ti,ab,rn. (584)
7 (levetiracetam or elepsia or keppra or kopodex or levesam 500 or levipil or levroxa or matever or spritam or "ucb l 059" or ucb l059 or 102767-28-2).ti,ab,rn. (2595)
8 Valproic Acid/ (11796)
9 (valproic acid or 2-Propylpentanoic acid or 2-Propylvaleric acid or 4-Heptanecarboxylic acid or Acide valproique or Acido valproico or Acidum valproicum or Depakene or Depakin$ or dipropylacetate or Dipropylacetic acid or Ergenyl or Kyselina 2-propylvalerova or Mylproin or Myproic acid or Propylvaleric acid or Stavzor or Valproate or Vupral or 99-66-1).ti,ab,rn. (16682)
10 (eslicarbazepine acetate or aptiom or bia2093 or "bia 2 093" or bia 2093 or "bia2 093" or erelib or exalief or exelief or pazzul or stedesa or zebinix or 236395-14-5).ti,ab,rn. (177)
11 (zonisamid$ or ad 810 or ad810 or ci 912 or ci912 or exceglan or excegram or excegran or excemid or zonegran or 68291-97-4).ti,ab,rn. (1213)
12 or/6-11 (19893)
13 Quality of Life/ (165484)
14 quality of life.ti,kf. (57643)
15 ((instrument or instruments) adj3 quality of life).ab. (2751)
16 or/13-15 [terms taken from CADTH filter] (168632)
17 quality-adjusted life years/ or quality of life/ (173942)

18 (sf36 or sf 36 or sf-36 or short form 36 or shortform 36 or sf thirtysix or sf thirty six or shortform thirtysix or shortform thirty six or short form thirty six or short form thirtysix or short form thirty six).ti,ab,ot. (20004)
19 (sf6 or sf 6 or sf-6 or short form 6 or shortform 6 or sf six or sfsix or shortform six or short form six).ti,ab,ot. (1207)
20 (sf12 or sf 12 or sf-12 or short form 12 or shortform 12 or sf twelve or sftwelve or shortform twelve or short form twelve).ti,ab,ot. (4124)
21 (sf6D or sf 6D or sf-6D or short form 6D or shortform 6D or sf six D or sfsixD or shortform six D or short form six D).ti,ab,ot. (631)
22 (sf20 or sf 20 or sf-20 or short form 20 or shortform 20 or sf twenty or sftwenty or shortform twenty or short form twenty).ti,ab,ot. (361)
23 (sf8 or sf 8 or sf-8 or short form 8 or shortform 8 or sf eight or sfeight or shortform eight or short form eight).ti,ab,ot. (381)
24 "health related quality of life".ti,ab,ot. (30710)
25 (Quality adjusted life or Quality-adjusted-life).ti,ab,ot. (9011)
26 "assessment of quality of life".ti,ab,ot. (1420)
27 (euroqol or euro qol or eq5d or eq 5d).ti,ab,ot. (6870)
28 (hql or hrql or hqol or h qol or hrqol or hr qol).ti,ab,ot. (14640)
29 (hye or hyes).ti,ab,ot. (57)
30 health$ year$ equivalent$.ti,ab,ot. (38)
31 (hui or hui1 or hui2 or hui3 or hui4 or hui-4 or hui-1 or hui-2 or hui-3).ti,ab,ot. (1125)
32 (quality time or qwb or quality of well being or "quality of wellbeing" or "index of wellbeing" or "index of well being").ti,ab,ot,hw. (707)
33 (Disability adjusted life or Disability-adjusted life or health adjusted life or health-adjusted life or "years of healthy life" or healthy years equivalent or "years of potential life lost" or "years of health life lost").ti,ab,ot. (2676)
34 (QALY$ or DALY$ or HALY$ or YHL or HYES or YPLL or YHLL or qald$ or qale$ or qtime$ or AQoL$).ti,ab,ot. (10123)
35 (timetradeoff or time tradeoff or time trade-off or time trade off or TTO or Standard gamble$ or "willingness to pay").ti,ab,ot. (5321)
36 15d.ti,ab,ot. (1439)
37 (HSUV$ or health state$ value$ or health state$ preference$ or HSPV$).ti,ab,ot. (319)
38 (utilit$ adj3 ("quality of life" or valu$ or scor$ or measur$ or health or life or estimat$ or elicit$ or disease$)).ti,ab,ot. (8887)
39 (utilities or disutili$).ti,ab,ot. (5318)
40 (PedsQL or Epilepsy Module).ti,ab. (895)
41 (CHEQOL or Health Related Quality of Life in Children with Epilepsy).ti,ab. (31)
42 (KAS or Katz Adjustment Scale$).ti,ab. (613)
43 (GEOS or Glasgow Epilepsy Outcome Scale$).ti,ab. (86)
44 (ESI-55 or Epilepsy Surgery Inventor$).ti,ab. (27)
45 (QOLIE-10 or QOLIE-89 or QOLIE-31 or Quality of Life in Epilepsy Inventor$).ti,ab. (340)
46 (NEWQOL or Quality of Life in Newly Diagnosed Epilepsy measure$).ti,ab. (9)
47 (QOLCE or Quality of Life in Childhood Epilepsy Questionnaire$).ti,ab. (46)
48 (RLIES or Revised Liverpool Impact of Epilepsy Scale$).ti,ab. (1)
49 (QOLIE-AD-48 or Quality of Life in Epilepsy Inventory Adolescents).ti,ab. (19)
50 (LSSS or Liverpool Seizure Severity Scale$).ti,ab. (89)
51 or/17-50 [NICE DSU: HRQoL] (206781)

52 animals/ not (animals/ and humans/) (4456014)
53 (letter or editorial or historical article).pt. (1685587)
54 5 and 12 and (16 or 51) (148)
55 54 not (52 or 53) (145)
56 limit 55 to yr="2012 -Current" (57)

QoL terms based on:
Strings attached: CADTH database search filters [Internet]. Ottawa: CADTH; 2016. [cited 2018 08 29]. Available from: /resources/finding-evidence
And
HRQoL free-text terms based on: Figure 4: Common free-text terms for electronic database searching for HSUVs in Papaioannou D, Brazier JE, Paisley S. NICE DSU Technical Support Document 9: the identification, review and synthesis of health state utility values from the literature (Internet), 2011 (accessed: 18.8.11) Available from: http://www.nicedsu.org.uk

MEDLINE Epub Ahead of Print (Ovid): August 28, 2018; MEDLINE In-Process & Other Non-Indexed Citations (Ovid): August 28, 2018; MEDLINE Daily Update (Ovid): August 28, 2018 Searched: 29.8.18
1 exp Epilepsy/ (111)
2 exp Seizures/ (62)
3 (epileps$ or epileptic$ or seizure$ or convuls$).ti,ab. (19508)
4 (comitial disease or falling sickness or myoclonic or tonic-clonic).ti,ab. (1103)
5 or/1-4 (19606)
6 (lacosamide or "ADD 243037" or erlosamide or harkoseride or spm 927 or spm927 or vimpat or 175481-36-4).ti,ab,rn. (164)
7 (levetiracetam or elepsia or keppra or kopodex or levesam 500 or levipil or levroxa or matever or spritam or "ucb l 059" or ucb l059 or 102767-28-2).ti,ab,rn. (581)
8 Valproic Acid/ (14)
9 (valproic acid or 2-Propylpentanoic acid or 2-Propylvaleric acid or 4-Heptanecarboxylic acid or Acide valproique or Acido valproico or Acidum valproicum or Depakene or Depakin$ or dipropylacetate or Dipropylacetic acid or Ergenyl or Kyselina 2-propylvalerova or Mylproin or Myproic acid or Propylvaleric acid or Stavzor or Valproate or Vupral or 99-66-1).ti,ab,rn. (1644)
10 (eslicarbazepine acetate or aptiom or bia2093 or "bia 2 093" or bia 2093 or "bia2 093" or erelib or exalief or exelief or pazzul or stedesa or zebinix or 236395-14-5).ti,ab,rn. (50)
11 (zonisamid$ or ad 810 or ad810 or ci 912 or ci912 or exceglan or excegram or excegran or excemid or zonegran or 68291-97-4).ti,ab,rn. (163)
12 or/6-11 (2287)
13 Quality of Life/ (376)
14 quality of life.ti,kf. (12591)
15 ((instrument or instruments) adj3 quality of life).ab. (291)
16 or/13-15 [terms taken from CADTH filter] (12913)
17 quality-adjusted life years/ or quality of life/ (397)
18 (sf36 or sf 36 or sf-36 or short form 36 or shortform 36 or sf thirtysix or sf thirty six or shortform thirtysix or shortform thirty six or short form thirty six or short form thirtysix or short form thirty six).ti,ab,ot. (2781)

19 (sf6 or sf 6 or sf-6 or short form 6 or shortform 6 or sf six or sfsix or shortform six or short form six).ti,ab,ot. (682)
20 (sf12 or sf 12 or sf-12 or short form 12 or shortform 12 or sf twelve or sftwelve or shortform twelve or short form twelve).ti,ab,ot. (721)
21 (sf6D or sf 6D or sf-6D or short form 6D or shortform 6D or sf six D or sfsixD or shortform six D or short form six D).ti,ab,ot. (82)
22 (sf20 or sf 20 or sf-20 or short form 20 or shortform 20 or sf twenty or sftwenty or shortform twenty or short form twenty).ti,ab,ot. (22)
23 (sf8 or sf 8 or sf-8 or short form 8 or shortform 8 or sf eight or sfeight or shortform eight or short form eight).ti,ab,ot. (92)
24 "health related quality of life".ti,ab,ot. (5550)
25 (Quality adjusted life or Quality-adjusted-life).ti,ab,ot. (1605)
26 "assessment of quality of life".ti,ab,ot. (211)
27 (euroqol or euro qol or eq5d or eq 5d).ti,ab,ot. (1674)
28 (hql or hrql or hqol or h qol or hrqol or hr qol).ti,ab,ot. (2561)
29 (hye or hyes).ti,ab,ot. (4)
30 health$ year$ equivalent$.ti,ab,ot. (2)
31 (hui or hui1 or hui2 or hui3 or hui4 or hui-4 or hui-1 or hui-2 or hui-3).ti,ab,ot. (178)
32 (quality time or qwb or quality of well being or "quality of wellbeing" or "index of wellbeing" or "index of well being").ti,ab,ot,hw. (94)
33 (Disability adjusted life or Disability-adjusted life or health adjusted life or health-adjusted life or "years of healthy life" or healthy years equivalent or "years of potential life lost" or "years of health life lost").ti,ab,ot. (529)
34 (QALY$ or DALY$ or HALY$ or YHL or HYES or YPLL or YHLL or qald$ or qale$ or qtime$ or AQoL$).ti,ab,ot. (1928)
35 (timetradeoff or time tradeoff or time trade-off or time trade off or TTO or Standard gamble$ or "willingness to pay").ti,ab,ot. (1062)
36 15d.ti,ab,ot. (158)
37 (HSUV$ or health state$ value$ or health state$ preference$ or HSPV$).ti,ab,ot. (45)
38 (utilit$ adj3 ("quality of life" or valu$ or scor$ or measur$ or health or life or estimat$ or elicit$ or disease$)).ti,ab,ot. (1584)
39 (utilities or disutili$).ti,ab,ot. (1049)
40 (PedsQL or Epilepsy Module).ti,ab. (164)
41 (CHEQOL or Health Related Quality of Life in Children with Epilepsy).ti,ab. (5)
42 (KAS or Katz Adjustment Scale$).ti,ab. (114)
43 (GEOS or Glasgow Epilepsy Outcome Scale$).ti,ab. (49)
44 (ESI-55 or Epilepsy Surgery Inventor$).ti,ab. (1)
45 (QOLIE-10 or QOLIE-89 or QOLIE-31 or Quality of Life in Epilepsy Inventor$).ti,ab. (67)
46 (NEWQOL or Quality of Life in Newly Diagnosed Epilepsy measure$).ti,ab. (1)
47 (QOLCE or Quality of Life in Childhood Epilepsy Questionnaire$).ti,ab. (7)
48 (RLIES or Revised Liverpool Impact of Epilepsy Scale$).ti,ab. (0)
49 (QOLIE-AD-48 or Quality of Life in Epilepsy Inventory Adolescents).ti,ab. (2)
50 (LSSS or Liverpool Seizure Severity Scale$).ti,ab. (16)
51 or/17-50 [NICE DSU: HRQoL] (15316)
52 5 and 12 and (16 or 51) (21)

QoL terms based on:
Strings attached: CADTH database search filters [Internet]. Ottawa: CADTH; 2016. [cited 2018 08 29]. Available from: /resources/finding-evidence
And
HRQoL free-text terms based on: Figure 4: Common free-text terms for electronic database searching for HSUVs in Papaioannou D, Brazier JE, Paisley S. NICE DSU Technical Support Document 9: the identification, review and synthesis of health state utility values from the literature (Internet), 2011 (accessed: 18.8.11) Available from: http://www.nicedsu.org.uk

PubMed (NLM): up to 29 August 2018
Searched: 29.8.18
#6 Search (#4 and #5) 22
#5 Search (pubstatusaheadofprint OR publisher[sb] OR pubmednotmedline[sb]) 2956778
#4 Search (#1 and #2 and #3) 177
#3 Search "quality of life"[tiab] or "quality-adjusted life year"[tiab] or "quality-adjusted life years"[tiab] or "quality adjusted life year"[tiab] or "quality adjusted life years"[tiab] or qol[tiab] or hrqol[tiab] or qaly[tiab] 236914
#2 Search lacosamide[tiab] or levetiracetam[tiab] or "valproic acid"[tiab] or eslicarbazepine[tiab] or zonisamide[tiab] 12108
#1 Search epilepsy[tiab] or epileptic[tiab] or seizure[tiab] or seizures[tiab] 171284

APPENDIX 2: EPILEPSY DEFINITIONS

Table 42: Classifications of epilepsy

ILAE 1989[2]	Berg 2010[3] (ILAE)	Scheffer 2017[4] (ILAE)
Idiopathic	Genetic	Genetic
Symptomatic	Structural/ metabolic	Structural
		Infectious
		Metabolic
		Immunologic
Kryptogenic	Unknown reason	Unknown
From Elger 2017[1], Table 1		

Table 43: Classifications of epileptic seizures

ILAE 1989[2]	Berg 2010[3] (ILAE)	Fisher 2017[58] (ILAE)
GENERALISED SEIZURES **Tonic–clonic (Grand)** **Absences** **Myoclonic** **Clonic** **Tonic** **Atonic (astatic)**	**GENERALISED SEIZURES** **Tonic–clonic (in any combination)** **Absence** • Typical • Atypical • Absence with special features - Myoclonic absence - Eyelid myoclonia **Myoclonic** • Myoclonic • Myoclonic atonic • Myoclonic tonic **Clonic** **Tonic** **Atonic**	**GENERALISED ONSET** **Motor** • Tonic–clonic • Clonic • Tonic • Myoclonic • Myoclonic-tonic-clonic • Myoclonic-atonic • Atonic • Epileptic spasms **Nonmotor (absence)** • Typical • Atypical • Myoclonic • Eyelid myoclonia
LOCALISATION-RELATED (focal, partial seizures) **Single-focal (single-partial)** • Focal motor • Aura • Automatismen **Complex-focal (complex-partial), psychomotor**	**FOCAL SEIZURES** Depending on the impairment during the seizure: • Without impairment of consciousness or awareness • With observable motor or autonomic components (roughly corresponds to the concept of ‘‘simple partial	**FOCAL ONSET** With preserved or limited consciousness **Motor onset** • Automatisms • Atonic • Clonic • Epileptic spasms • Hyperkinetic

ILAE 1989[2]	Berg 2010[3] (ILAE)	Fisher 2017[58] (ILAE)
Secondary-generalised	seizure) • Involving subjective sensory or psychic phenomena only (corresponds to the concept of an aura) • With impairment of consciousness or awareness (roughly corresponds to the concept of complex partial seizure. Dyscognitive) • Evolving to a bilateral, convulsiveb seizure (involving tonic, clonic, or tonic and clonic components) (replaces ‘‘secondarily generalised seizure”)	• Myoclonic • Tonic **Nonmotor onset** • Autonomic • Behaviour arrest • Cognitive • Emotional • Sensory **Focal to bilateral tonic-clonic**
NOT CLASSIFIABLE	**UNKNOWN ONSET** **Epileptic spasms**	**UNKNOWN ONSET** **Motor** • Tonic-clonic • Epileptic spasms **Nonmotor** • Behaviour arrest
	UNCLASSIFIED*	**UNCLASSIFIED****

From Elger 2017[1], Table 2, Berg 2010 and Fisher 2017
*Seizure that cannot be clearly diagnosed into one of the preceding catego-ries should be considered unclassified until further information allows their accurate diagnosis. This is not considered a classification category.
**Due to inadequate information or inability to place in other categories
ILAE = International League Against Epilepsy

APPENDIX 3: CRITERIA FOR ASSESSING STRENGTH OF EVIDENCE IN TABLE 24

Criteria for Assessing Strength of Evidence used by Thurman 2017[26] (supporting Table 1b), reported in table 24 in this evidence report.

Sensitivity of Epilepsy Case Ascertainment

1 = Screening methods appear likely to ascertain nearly all (≥ 85%) cases in population
2 = Screening methods appear likely to ascertain most (70 - 84%) cases in population
3 = Screening methods appear likely to ascertain majority (50 - 69%) of cases in population
4 = Screening methods appear unlikely to ascertain majority of cases in population OR information published is insufficient to assess
N/A = Not applicable: not a population-based study or sensitivity of methods of epilepsy case ascertainment not relevant to quality of study.

Sensitivity of Mortality Case Ascertainment

1 = Fatalities appear likely to be recorded in nearly all (≥ 85%) cases in study population
2 = Fatalities appear likely to be recorded in most (70 - 84%) cases in study population
3 = Fatalities appear likely to be recorded in majority (50 - 69%) of cases in study population
4 = Fatalities appear unlikely to be recorded in majority of cases in study population OR information published is insufficient to assess

Accuracy of Diagnoses of Epilepsy

1 = Cases are diagnosed (or confirmed) by specialist clinician (i.e., with neurologic training), AND ILAE case definition applied
2 = Cases are often diagnosed by non-specialist clinician, OR minor deviation from ILAE case definition
3 = All or substantial proportion of cases diagnosed based on self-report or non-clinical sources with specified criteria judged to have fair positive predictive value
4 = All or substantial proportion of cases diagnosed with poorly defined criteria from non-clinical sources; positive predictive value judged to be poor OR information published is insufficient to assess

Accuracy of Diagnoses of Cause of Death

1 = Determined mainly from either autopsy, medical examiner/coroner investigation, or other clinical investigation (e.g., review of medical records, structured interview of survivors or “verbal autopsy”)
2 = Determined largely or wholly from death certificate data, when such data are judged to have good positive predictive value for the specific causes of interest
3 = Determined largely or wholly from death certificate data, when such data are judged to have only fair positive predictive value for the specific causes of interest
4 = Other sources of data deemed to have poor positive predictive value for the causes of interest OR information published is insufficient to assess

Representativeness of the study population

1 = Cohort studies of incident epilepsy whose enrolled cases appear highly representative of the population of interest
2 = Studies of prevalent epilepsy whose enrolled cases appear highly representative of the population of interest
3 = Studies of epilepsy whose enrolled cases appear somewhat representative of the population of interest
4 = Studies of epilepsy whose enrolled cases appear poorly representative of the population of interest or where representativeness cannot be assessed

APPENDIX 4: TABLE OVERVIEW OF FITNESS TO DRIVE

Table 44: Tabular overview of German evaluation guidelines for driving ability (translation next page)

Störung	**Gruppe 1** (Führer von Fahrzeugen der Klassen A, A1, A2, B, BE, AM, L, T)	**Gruppe 2** (Führer von Fahrzeugen der Klassen C, C1, CE, C1E, D, D1, DE, D1E und die Fahrerlaubnis zur Fahrgastbeförderung (FzF))
Erstmaliger, unprovozierter Anfall ohne Anhalt für eine beginnende Epilepsie	Keine Kraftfahreignung für 6 Monate	Keine Kraftfahreignung für 2 Jahre
Erstmaliger, provozierter Anfall mit vermeidbarem Auslöser	Keine Kraftfahreignung für minimal 3 Monate	Keine Kraftfahreignung für minimal 6 Monate
Epilepsie	In der Regel keine Kraftfahreignung; Ausnahme: • Mindestens 1-jährige Anfallsfreiheit (auch mit medikamentöser Therapie) • Keine eignungsausschließenden Nebenwirkungen der Therapie	In der Regel keine Kraftfahreignung; Ausnahme: • Mindestens 5-jährige Anfallsfreiheit ohne medikamentöse Therapie
Persistierende Anfälle ohne zwangsläufige Einschränkung der Kraftfahreignung	• Ausschließlich an den Schlaf gebundene Anfälle nach mindestens 3-jähriger Beobachtungszeit • Ausschließlich einfache fokale Anfälle ohne Bewusstseinsstörung und ohne motorische, sensorische oder kognitive Behinderung nach mindestens 1-jähriger Beobachtungszeit	Keine Kraftfahreignung
Anfallsrezidiv bei bestehender Fahreignung nach langjähriger Anfallsfreiheit	Kraftfahreignung nach 6 Monaten wieder gegeben (falls keine Hinweise auf erhöhtes Wiederholungsrisiko). Bei Vermeidbaren Provokationsfaktoren 3 Monate Fahrpause	Keine Kraftfahreignung
Beendigung einer antiepileptischen Therapie	Keine Kraftfahreignung für die Dauer der Reduzierung des letzten Medikamentes sowie die ersten 3 Monate ohne Medikation (Ausnahmen in gut begründeten Fällen möglich)	Keine Kraftfahreignung
From www.bast.de[28], German evaluation guidelines for driving ability page 51 and page 6, available from https://www.bast.de/BASt_2017/DE/Verkehrssicherheit/Fachthemen/BLL/BLL-Download.html?nn=1817128		

Disorder	Group 1 (Driver of vehicles category A, A1, A2, B, BE, AM, L, T)	Group 2 (Driver of vehicles category C, C1, CE, C1E, D, D1, DE, D1E and the driver's license for passenger transport (FzF))
First time, unprovoked seizure without indication of an incipient epilepsy	No fitness to drive for 6 months	No fitness to drive for 2 years
First time, provoked seizure with avoidable trigger	No fitness to drive for 3 months minimum	No fitness to drive for 6 months minimum
Epilepsy	As a rule, no fitness to drive; Exception: • At least 1 year of seizure freedom (also with drug therapy) • No therapy side effects which would exclude fitness to drive	As a rule, no fitness to drive; Exception: • At least 5-years seizure freedom without medical treatment therapy
Persistent seizures without inevitable restriction in the fitness to drive	• Exclusively sleep-related seizures after a minimum of 3 years of observation • Exclusively simple partial seizures without disturbance of consciousness and without motor, sensory or cognitive impairment after a minimum of 1 year of observation	No fitness to drive
Seizure recurrence with existing fitness to drive after many years of seizure freedom	Fitness to drive is given again after 6 months if no indications of increased risk of recurrence. If avoidable trigger: 3 months break	No fitness to drive
Termination of antiepileptic therapy	No fitness to drive for the duration of the reduction of the last drug and the first 3 months without medication (exceptions are possible in well-founded cases)	No fitness to drive
From www.bast.de[28], German evaluation guidelines for driving ability page 51 and page 6, available from https://www.bast.de/BASt_2017/DE/Verkehrssicherheit/Fachthemen/BLL/BLL-Download.html?nn=1817128		