South African National Essential Medicine List
Adult Hospital Level Medication Review Process
Component: Neurology

MEDICINE REVIEW:

1. Executive Summary

Date: 22 January 2019
Medicine (INN): Levetiracetam, oral
Medicine (ATC): N03AX14
Indication (ICD10 code): First onset seizures partial(G40.2) or generalized tonic-clonic seizures (G40.3)
Patient population: Adults
Prevalence of condition: Systematic review and meta-analysis[i] of prevalence and incidence studies reported global estimate of active focal seizures of 2.99 per 1000 (95% CI 1.39 to 6.42); for all epilepsy types 6.38 per 1000 (95% CI 5.57 to 7.30) and for generalized seizures 4.33 (95% CI 2.55 to 8.32).
Level of Care: Secondary level of care
Prescriber Level: Medical officers
Current standard of Care: Carbamazepine, lamotrigine or phenytoin, oral
Efficacy estimates: (Not possible to calculate NNT)

- *Primary outcome:* Time to withdrawal of allocated treatment (retention time)

Network analysis
Partial: CBZ vs LEV **HR 0.82 (0.69-0.97)** Direct evidence 37.9%
LTG vs LEV HR 1.10 (0.89-1.35) Direct evidence 23.7%
PHT vs LEV HR 0.73 **(0.56-0.95)** No direct evidence.
Generalized: CBZ vs LEV HR 0.74 (0.44-1.23) Direct evidence 57%
LTG vs LEV HR 1.17 (0.63-2.19) No direct evidence
PHT vs LEV HR 0.80 (0.42-1.55) No direct evidence [ii]:

- *Secondary* outcome: Time to 12-month seizure free remission.

Network analysis
Partial: CBZ vs LEV **HR 1.35 (1.09-1.69)** Direct evidence 14.2%
LTG vs LEV HR 1.16 (0.93-1.46) Direct evidence 26.6%
PHT vs LEV HR 1.32 (0.96-1.75) No direct evidence
Generalized: CBZ vs LEV HR 1.33 (0.81-2.22) Direct evidence 16.6%
LTG vs LEV HR 1.05 (0.40-2.78) No direct evidence
PHT vs LEV HR 1.56 (0.87-2.78) No direct evidence[ii]
Motivator/reviewer name(s): Dr S Rossouw, Ms TD Leong, Prof A Moodley
PTC affiliation: Dr R Rossouw: East London Hospital Complex PTC
Dr A Black: Helen Joseph Hospital PTC

2. Name of author(s)/motivator(s)

Primary reviewers: Dr S Rossouw, Ms TD Leong, Prof A Moodley
Secondary reviewers: Prof AG Parrish, Dr A Black, Dr L Robertson

3. Author affiliation and conflict of interest details

Dr S Rossouw:

- *Affiliation:* East London Hospital Complex Pharmacy Therapeutics Committee, Adult Hospital Level Committee member.

- *Conflict of interests:* Angels Initiative (funded by Boehringer and Ingelheim): Member of National Steering Committee, honorarium for conference and workshop attendance; Sanofi-Aventis: Honorarium for conference attendance and workshops, and training.

Ms TD Leong:

- *Affiliation:* National Department of Health, Essential Drugs Programme, Secretariat to the Adult Hospital Level Committee.
- *Conflict of interests:* none declared.

Prof A Moodley:

- *Affiliation:* Tertiary & Quaternary Committee; University of the Free State.
- *Conflicts of interests:* none declared.

Prof AG Parrish:

- *Affiliation:* National Essential Medicines List Committee;
- *Conflict of interests:* none declared.

Dr A Black:

- *Affiliation:* National Department of Health, Essential Drugs Programme, Adult Hospital Level Committee. Helen Joseph Hospital Pharmacy Therapeutics Committee
- *Conflict of interests:* none declared.

Dr L Robertson:

- *Affiliation:* Adult Hospital Level Committee; University of the Witwatersrand. *Conflict of interests:* none declared.

4. Introduction/ Background

Epilepsy is a common neurological condition with a worldwide prevalence of around 1%. A large proportion of those with epilepsy (60% to 70%) will achieve a long-term remission from seizures with most achieving remission shortly after starting antiepileptic drug treatment. The aim is to achieve this remission rate on a single antiepileptic drug (monotherapy).

Currently, the Adult Hospital Level STGs and EML, 2015 [iii] recommends either carbamazepine, lamotrigine or phenytoin as first line options for partial or generalised seizures.

The aim of this evidence review is to determine the safety and efficacy of levetiracetam monotherapy for new onset seizures (partial or generalized clonic-tonic) versus current first line agents.

5. Purpose/Objective i.e. PICO question

-P: Adult patients with first onset seizures (partial or focal)
-I: Levetiracetam, oral monotherapy
-C: Carbamazepine, lamotrigine or phenytoin, oral monotherapy
-O: Primary outcome: Time to treatment withdrawal.
Secondary outcome: time to 12-month seizure free remission.

PICO question: In adult patients with new onset seizures is levetiracetam comparable to standard of care (carbamazepine, lamotrigine or phenytoin) in terms of efficacy and safety?

6. Methods:

Two reviewers reviewed the databases for data selection, extraction and analysis. Any disagreement was resolved by consensus.

A: Search I:

a. **Data sources:** Cochrane Library
b. **Search terms:** Levetiracetam AND partial seizures AND first onset seizures
   1 Systematic review (SR) – included (*Nevitt et al, 2018)*
   8 Clinical trials – 8 excluded (not relevant to the PICO question)

B: Search II:

a. **Data sources:** PUBMED
b. **Search strategy A:** ((("etiracetam"[Supplementary Concept] OR "etiracetam"[All Fields] OR "levetiracetam"[All Fields]) AND ("seizures"[MeSH Terms] OR "seizures"[All Fields] OR ("partial"[All Fields] AND "seizures"[All Fields]) OR "partial seizures"[All Fields])) AND ("adult"[MeSH Terms] OR "adult"[All Fields] OR "adults"[All Fields])) AND ("randomized controlled trial"[Publication Type] OR "randomized controlled trials as topic"[MeSH Terms] OR "randomised controlled trials"[All Fields] OR "randomized controlled trials"[All Fields]) AND ("humans"[MeSH Terms] AND "adult"[MeSH Terms])
   88 studies retrieved; 86 excluded; 1 SR (*Nevitt et al, 2018)* and 1 RCT (Pohlmann-Eden *et al, 2016)* retrieved – see evidence synthesis table below

c. **Search strategy B:** ((("levetiracetam"[Supplementary Concept] OR "levetiracetam"[All Fields] OR "levetiracetam"[All Fields]) AND ("seizures"[MeSH Terms] OR "seizures"[All Fields] OR ("generalised"[All Fields] AND "seizures"[All Fields]) OR "generalised seizures"[All Fields])) AND ("adult"[MeSH Terms] OR "adult"[All Fields] OR "adults"[All Fields])) AND ("randomized controlled trial"[Publication Type] OR "randomized controlled trials as topic"[MeSH Terms] OR "randomised controlled trials"[All Fields] OR "randomized controlled trials"[All Fields]) AND ("humans"[MeSH Terms] AND "adult"[MeSH Terms])

88 studies retrieved; 87 excluded; 1 SR (*Nevitt et al, 2018)* included – see evidence synthesis table below.

d. Search strategy C: ((("etiracetam"[Supplementary Concept] OR "etiracetam"[All Fields] OR "levetiracetam"[All Fields]) AND ("seizures"[MeSH Terms] OR "seizures"[All Fields] OR ("partial"[All Fields] AND "seizures"[All Fields]) OR "partial seizures"[All Fields])) AND ("adult"[MeSH Terms] OR "adult"[All Fields] OR "adults"[All Fields])) AND ("randomized controlled trial"[Publication Type] OR "randomized controlled trials as topic"[MeSH Terms] OR "randomised controlled trials"[All Fields] OR "randomized controlled trials"[All Fields]) AND ("humans"[MeSH Terms] AND "adult"[MeSH Terms])
88 studies retrieved; 87 excluded; 1 SR *(Nevitt et al, 2018)* included – see evidence synthesis table below.

C: Search III:

a. Data sources: Tripsdatabase (open access)

b. Search strategy: partial seizures, first onset seizure, levetiracetam, carbamazepine, lamotrigine, adults – restricted to SRs and clinical trials

- 1 SR retrieved and excluded *(Wilby et al, 2005).*

D: Search IV:

a. Data sources: Google scholar
Search strategy: *'phenytoin for partial seizures'*
1 Systematic review and meta-analysis retrieved and excluded *(Nevitt et al, 2016)*

Reference lists of retrieved trials were also reviewed to search for additional reports of relevant trials, none retrieved.

E: Excluded studies: See Appendix I for detailed information.

b. Evidence synthesis

Author, date	*Type of study*	n	Population	Comparators	Primary outcome	Effect sizes	Comments
Nevitt et al, 2017 ii	Individual participant data (IPD) review (pairwise meta-analysis using direct evidence) & network meta-analysis (using direct and indirect evidence (vs placebo))	36 RCTs, n=12,391	Children and adults with partial onset seizures or generalised onset tonic-clonic seizures (with or without other generalised seizure types).	Carbamazepine, phenytoin, sodium valproate, phenobarbitone, oxcarbazepine, lamotrigine, gabapentin, topiramate, levetiracetam, zonisamide as monotherapy	*Primary outcome:* Time to withdrawal of allocated treatment (retention time) for partial seizures. This is a combined outcome reflecting both efficacy & tolerability, as treatment may be withdrawn due to continued seizures, adverse effects or a combination of both. This is an outcome to which the participant makes a contribution, & is the primary effectiveness outcome measure recommended by the Commission on Antiepileptic Drugs of the International League Against Epilepsy. *[Secondary outcomes:* time to achieve 12-month remission; time to achieve six-month remission; time to first seizure	***Primary outcome:*** Time to withdrawal of allocated treatment. (Network meta-analysis (direct & indirect evidence) <u>*Partial:*</u> CBZ vs LEV **HR 0.82 (0.69 to 0.97)** Direct evidence 37.9% LTG vs LEV HR 1.10 (0.89 to 1.35) Direct evidence 23.7% PHT vs LEV HR 0.73 **(0.56 to 0.95)** No direct evidence. <u>*Generalized:*</u> CBZ vs LEV HR 0.74 (0.44 to 1.23) Direct evidence 57% LTG vs LEV HR 1.17 (0.63 to 2.19) No direct evidence PHT vs LEV HR 0.80 (0.42 to 1.55) No direct evidence ***Secondary outcome****:* Time to 12-month seizure free remission. <u>*Partial:*</u> CBZ vs LEV **HR 1.35 (1.09 to 1.69)** Direct evidence 14.2% LTG vs LEV HR 1.16 (0.93 to 1.46) Direct evidence 26.6% PHT vs LEV HR 1.32 (0.96 to 1.75) No direct evidence <u>*Generalized:*</u> CBZ vs LEV HR 1.33 (0.81 to 2.22) Direct evidence 16.6% LTG vs LEV HR 1.05 (0.40 to 2.78) No direct evidence PHT vs LEV HR 1.56 (0.87 to 2.78) No direct evidence Generally, direct evidence & network meta-analysis estimates (direct & indirect evidence) were numerically similar & consistent with confidence intervals of effect sizes overlapping.	Review was well conducted with an 'a priori' design and research questions were well defined – patient population included both adults and children; primary outcome is an outcome to which the participant makes a contribution, & is the primary effectiveness outcome measure recommended by the Commission on Antiepileptic Drugs of the International League Against Epilepsy. Search strategy was comprehensive and selection bias minimised as all language studies included in the analyses. Grey literature was included and Individual RCTS eligible for inclusion were reported. Review methodology, including quality assessment of included RCTs, was rigorous using two independent reviewers with disagreements resolved through discussion or consulting a third reviewer; minimising the potential for error and/or bias and results were adequately reported. Two methodologies were used for the analysis i) pairwise meta-analysis (direct evidence) and network meta-analysis (using direct and indirect evidence). It was noted that the effect sizes of these two analyses were generally similar with confidence effect sizes overlapping. Evidence for Partial seizures was of high quality while for generalized seizures quality was moderate Heterogeneity assessed appropriately and conflicts of interests were declared. It is noted that a consortium of pharmaceutical companies funded the National Audit of Seizure Management in Hospitals (NASH) through grants paid to the University of Liverpool.

					post-randomisation, & occurrence of adverse events].	Most commonly reported AEs for all medicines were drowsiness/fatigue, headache or migraine, gastrointestinal disturbances, dizziness/ faintness & rash or skin disorders.	This review was supported by the National Institute for Health Research, via Cochrane Infrastructure funding to the Cochrane Epilepsy.
Pohlmann-Eden et al, 2016[iv]	Subgroup analysis of unblinded 52 week superiority RCT (KOMET study)	n=308	Patients, aged ≥ 60 yrs at trial entry with newly diagnosed epilepsy	<u>VPE-ER stratum:</u> LEV (n = 48) vs VPA-ER (n = 53) <u>CBZ-CR stratum</u>. LEV (n = 104) vs CBZ-CR (n = 103) **NB:** Focal seizure analysis was only done for the CBZ-CR stratum	*Primary outcome:* time to withdrawal from study medication *Secondary outcomes:* time to first seizure calculated from randomization; and treatment withdrawal and seizure freedom rates at 6 and 12 months.	***VPE-ER stratum:*** • Treatment withdrawal rate (%) of all seizures at 12/12's (95% CI): o VPA ER vs LEV: 23.1 (13.8 to 37.0) vs 10.4 (4.5 to 23.2); NNT 8 (7.25 to 11) ***CBZ-CR stratum:*** • Treatment withdrawal rate (%) of all seizures at 12/12's (95% CI): o CBZ CR (n=134) vs LEV (n=104): 46.6 (37.6 to 56.7) vs 25.0 (17.8 to 34.5); NNT 5 (4.5 to 5.06) • Treatment withdrawal rate (%) of focal seizures only at 12/12's (95% CI): o CBZ CR (n=94) vs LEV (n=93): 45.8 (36.4 to 56.4) vs 24.7 (17.2 to 34.8); NNT 5 (1 to 5.2) ***Tolerability:*** Discontinuation rate for CBZ-CR > LEV or VPA-ER. But, initial target dose of CBZ-CR (600 mg/day) may have been too high & too rapidly titrated. Differences in withdrawal rates due to AEs between KOMET overall and this elderly subgroup: CBZ-CR: 18.8% vs 35.0%; LEV: 8.3 % vs. 11.3%; VPA-ER (4.7 % vs. 10.2 %) – suggesting that overall time to treatment withdrawal may be due to differences in tolerability.	Clearly defined study question, investigating of time to treatment withdrawal of AEDS for new onset epilepsy in the elderly – though this is a subgroup analysis of KOMET RCT. KOMET study was unblinded, randomised superiority study. ITT analysis and baseline demographics similar in the LEV and other AED groups. Primary focus of the post-hoc analysis was interaction of LEV with age, and therefore statistical analysis was only done for this interaction. Study sponsored by pharmaceutical industry, which was also involved in design & conduct of the study; collection, management & analysis of the data; &preparation and review of the manuscript. Risk of bias includes selection, information and publication bias.

Abbreviations: CBZ-carbamazepine; CR-controlled release; ER-extended release; GAB-gabapentin; LEV-levetiracetam; LTG-lamotrigine; PHB-phenobarbitone; PHT-phenytoin; TOP-topiramate; VPA-valproic acid

Evidence quality:

High quality evidence systematic review (Nevitt et al, 2017) supports NICE Guideline [v] recommendations that carbamazepine and lamotrigine are suitable first-line treatments for individuals with partial onset seizures; and that levetiracetam may be a suitable alternative. In the Network analysis carbamazepine was found to be equivalent to phenytoin, however phenytoin was not as effective as lamotrigine or levetiracetam in achieving the primary end point for partial seizures.

High quality evidence RCT review (Nevitt et al, 2017) of the head-to-head comparison between LEV and CBZ (Brodie et al, 2007[vii] being the largest of the 4 RCTs included in the SR), reported similar seizure freedom rates at 6 months with a favourable withdrawal rate for those on LEV (14.4 VS 19.2%). Similar efficacy rates were seen in head-to-head comparison between LEV and LTG (Motamedi[viii] et al, 2013) with less side effects experienced in the LTG group.

The review supports the use of sodium valproate as the first-line treatment for individuals with generalised tonic-clonic seizures (with or without other generalised seizure types) and also demonstrates that lamotrigine, carbamazepine, phenytoin and levetiracetam would be suitable alternatives. The STG's have attempted to avoid different medications based on sex and does not include sodium valproate as a first line treatment agent due to teratogenicity and equal efficacy of other available agents. (AGREE II assessment of NICE Guidelines attached as appendix II).

While levetiracetam showed greater efficacy than carbamazepine and phenytoin for the primary outcome in persons with partial seizures this was not seen in the persons with generalized seizures.

The study by Pohlmann-Eden et al, 2016, was a sub group analysis of a larger trial and looked at persons >60 years of age. While there was a high rate of withdrawal in the carbamazepine CR group due to inability to tolerate the medication it has been suggested they may be partly due to rapid up titration and a high initial dose of carbamazepine CR. The numbers are also small and there is concern about potential bias. This paper should not influence decision-making, but does alert one to a potential sub-group of patients that may need special consideration when selecting anti-epileptic medications.

Zhu et al, 2015[vi] used observational data confined to partial seizures in Chinese patients, nearly a quarter of discontinuation of medications occurred early in treatment and despite carbamazepine having a high incidence of adverse reactions it was the medication that patients were most likely to remain on.

EVIDENCE TO DECISION FRAMEWORK

	JUDGEMENT	SUPPORTING EVIDENCE & ADDITIONAL CONSIDERATIONS
QUALITY OF EVIDENCE	**What is the overall confidence in the evidence of effectiveness?** Confident [X] Not confident [ ] Uncertain [ ]	Meta-analysis by Nevitt et al, 2017.
BENEFITS & HARMS	**Do the desirable effects outweigh the undesirable effects?** Benefits outweigh harms [X] Harms outweigh benefits [ ] Benefits = harms or Uncertain [ ]	
THERAPEUTIC INTERCHANGE	Therapeutic alternatives available: Yes [X] No [ ] List the members of the group. • Lamotrigine • Carbamazepine • Levetiracetam • Phenytoin List specific exclusion from the group: n/a	*Rationale for therapeutic alternatives included:* Evidence of comparable efficacy of carbamazepine vs lamotrigine vs levetiracetam. *References:* Nevitt SJ, Sudell M, Weston J, Tudur Smith C, Marson AG. Antiepileptic drug monotherapy for epilepsy: a network meta-analysis of individual participant data. Cochrane Database Syst Rev. 2017 Dec 15;12:CD011412. https://www.ncbi.nlm.nih.gov/pubmed/29243813 *Rationale for exclusion from the group:* n/a *References:* n/a
VALUES & PREFERENCES / ACCEPTABILITY	**Is there important uncertainty or variability about how much people value the options?** Minor [ ] Major [ ] Uncertain [X] **Is the option acceptable to key stakeholders?** Yes [X] No [ ] Uncertain [ ]	
RESOURCE USE	**How large are the resource requirements?** More intensive [ ] Less intensive [ ] Uncertain [X]	Price of medicines/ month (28 days): based on WHO DDD **Medicine** / **Cost (ZAR)** Levetiracetam, oral, 1500 mg daily — 150 Carbamazepine, oral, 600 mg 12 hrly — 51.662** Lamotrigine, oral 300 mg daily — 48.175* Lamotrigine, oral 400 mg daily — 96.35* Phenytoin, oral 300 mg daily — 50.819*** Valproate 1.5g daily — 106.44**** * Contract circular HP09-2016SD ** Contract circular HP09-2016SD: Weighted average price 200 mg tab R0.308. ***Contract circular HP09-2016SD: Weighted average price 100 mg cap R0.605 **** Contract circular HP09-2016SD: Weighted average price 500 mg tab R0.95 **Refer to the levetiracetam CEA and BIA report** **Additional resources:** n/a

EQUITY	**Would there be an impact on health inequity?** Yes ☐ No ☒ Uncertain ☐	
FEASIBILITY	**Is the implementation of this recommendation feasible?** Yes ☒ No ☐ Uncertain ☐	

Type of recommendation	We recommend against the option and for the alternative	We suggest not to use the option or to use the alternative	We suggest using either the option or the alternative	We suggest using the option	We recommend the option
	☐	☐	☒	☐	☐

Recommendation:

Based on this evidence review, the Adult Hospital Level Committee reccomends that levetiracetam be considered as an alternative to lamotrigine, carbamazpine or phenytoin for partial or focal seizures in adult epileptics. Adverse effects associated with specific AEDs and affordability would further inform recommendations.

Rationale:

- Avaliable evidence suggests that levetiracetam is as efficacious as lamotrigine and better than carbamazepine or phenytoin for time to withdrawal of allocated treatment in partial seizures.
- For generalized seizures levetiracetam was equally efficacious when compared to carbamazepine, lamotrigine and phenytoin.
- An economic evaluation taking cognicance of the relative prevelance of partial and generalised seizures in our population is required to further inform decision-making.
- Better tolerability of levetiracetam when compared to both carbamazepine and lamotrigine.

Level of Evidence: I Metaanalysis

Review indicator:

Evidence of efficacy	Evidence of harm	Price reduction
☐	☐	☒

VEN status:

Vital	Essential	Necessary
☐	☒	☐

NEMLC MEETING OF 11 JULY 2019:

NEMLC Recommendations:

- Levitaracetam not be considered for inclusion to the Adult Hospital Level EML for newly diagnose epilepsy, as this medicine considered to be not-cost effective and unaffordable.
- The final reports be published on the NDoH website and the respective companies be advised of the estimated willingness to pay (93% reduction of model medicine price: 250 mg tablets, 30 = R 2.149; 500 mg tablets, 20 = R4.298, 750 mg tablets, 30 = R 6.447).

Monitoring and evaluation considerations: n/a

Research priorities

Cost-effectiveness analyses and relative budget impact analysis of AEDs effective as monotherapy for the management of partial and generalized seizures in new onset adult epileptics.

APPENDIX I: Excluded studies

Fanella et al, Clin Neuropharmacol. 2017 Nov/Dec;40(6):239-242.	Not applicable to the research question (Epitram is the comparator)
Swallow et al, CNS Drugs. 2017 Oct;31(10):899-910	Not applicable to the research question (Brivaracetam is the comparator)
Schoenberg et al, Epilepsia. 2017 Sep;58(9):1566-1574	Not applicable to the research question (Indication is cognition, mood and balance)
Khan et al. J Ayub Med Coll Abbottabad. 2016 Jul-Sep;28(3):455-460.	Indication: Early post traumatic seizures.
Gujar et al, Seizure. 2017 Jul;49:8-12.	Indication: Status epilepticus
Kim et al, Epilepsia. 2017 Apr;58(4):e70-e74.	Comparator: Oxcarbazepine
Liu et a, Cochrane Database Syst Rev. 2016 Nov 2;11:CD011922.	Epilepsy in Alzheimer's disease
Nevitt et al, Cochrane Database Syst Rev. 2017 Jun 29;6:CD011412.	Update available
Ben-Menachem et al, Neurology. 2016 Jul 19;87(3):314-23.	Brivaracetam for partial-onset seizures.
Schoemaker et al, J Clin Pharmacol. 2016 Dec;56(12):1591-1602.	Brivaracetam pharmacokinetic study.
Majid et al, Br J Clin Pharmacol. 2016 Aug;82(2):422-30.	Not applicable to the research question
Chung et al, Epilepsy Res. 2016 Feb;120:7-12.	Levetiracetam extended release long-term safety study
Navarro et al, Lancet Neurol. 2016 Jan;15(1):47-55.	Levetiracetam plus clonazepam for status epilepticus
Klain et al, Epilepsia. 2015 Dec;56(12):1890-8	Adjunctive brivaracetam for refractory partial-onset seizures.
Misra et al, Int J Neurosci. 2016 Nov;126(11):1013-9.	Indication: Status epilepticus
Biton et al, Epilepsy Behav. 2015 Nov;52(Pt A):119-27.	Locsamide as adjunctive therapy for partial-onset seizures.
Thompson et al, Cochrane Database Syst Rev. 2015 Aug 10;(8):CD009900.	Indication: Epilepsy following traumatic head injury
Toublanc et al, Clin Drug Investig. 2015 Aug;35(8):495-503.	Pharmacokinetic study of oral vs IV levetiracetam
Mundlamari et al, Epilepsy Res. 2015 Aug;114:52-8.	Indication: generalised convulsive status epilepticus
Chakravarthi et al, J Clin Neurosci. 2015 Jun;22(6):959-63.	Indication: Status epilepticus
Inoue et al, Psychiatry Clin Neurosci. 2015 Oct;69(10):640-8.	Levetiracetam as adjunctive therapy for partial-onset seizures.
Werhahn et al, Epilepsia. 2015 Mar;56(3):450-9.	RCT cited in Cochrane review– Nevitt et al, 2017
Iuchi et al, J Neurol Neurosurg Psychiatry. 2015 Oct;86(10):1158-62.	Indication: Seizure prophylaxis after craniotomy
Zaccara et al, Epilepsia. 2014 Jul;55(7):1048-57.	Comparator is Pregabalin.
Milburn-McNulty et al, Cochrane Database Syst Rev. 2014 Mar 9;(3):CD010062.	Sulthiame monotherapy.
Rossetti et al, Neuro Oncol. 2014 Apr;16(4):584-8.	Levetiracetam and pregabalin for antiepileptic monotherapy – primary brain tumors.
Ryvlin et al, Epilepsia. 2014 Jan;55(1):47-56.	Adjunctive brivaracetam in uncontrolled focal epilepsy.
Fang et al, J Clin Neurosci. 2014 Jan;21(1):55-62.	Levetracetam as adjunctive therapy in epilepsy.
Bleck et al, Epilepsia. 2013 Sep;54 Suppl 6:89-92.	Indication: Status epilepticus trial
Connor et al, J Clin Epidemiol. 2013 Aug;66(8 Suppl):S130-7.	Indication: Status epilepticus
Novy et al, Epilepsy Res. 2013 Sep;106(1-2):250-6.	Lacosamide retention in medically refractory epilepsy.
Inaba et al, J Trauma Acute Care Surg. 2013 Mar;74(3):766-71; discussion 771-3.	Indication: Early posttraumatic seizure prophylaxis
Craig et al, Pharmacoeconomics. 2013 Feb;31(2):101-10.	Retigabine as adjunctive therapy for partial-onset seizures.

Consoli et al, Cerebrovasc Dis. 2012;34(4):282-9.	Indication: Late post stroke seizures
Mbizvo et al, Cochrane Database Syst Rev. 2012 Sep 12;(9):CD001901.	Levetiracetam add on for drug –resistant focal epilepsy
Trinka et al, J Neurol Neurosurg Psychiatry. 2013 Oct;84(10):1138-47.	RCT cited in Cochrane review– Nevitt et al, 2017
Fuller et al, Epilepsia. 2013 Jan;54(1):45-57.	Levetiracetam vs phenytoin IV – prophylaxis post craniotomy.
Zafar et al, BMC Neurol. 2012 May 29;12:30.	Seizure prophylaxis after brain injury.
Rosenow et al, J Neurol Neurosurg Psychiatry. 2012 Nov;83(11):1093-8.	RCT cited in Cochrane review– Nevitt et al, 2017
Chung et al, Epilepsy Res. 2012 Aug;101(1-2):92-102.	Levetiracetam extended release
Steinbaugh et al, Epilepsy Behav. 2012 Mar;23(3):280-4.	Comparator: fosphenytoin
Navarro et al, Epilepsia. 2011 Oct;52 Suppl 8:48-9.	Indication: Status epilepticus
Misra et al, J Neurol. 2012 Apr;259(4):645-8	Indication: Status epilepticus
Kerrigan et al, Cochrane Database Syst Rev. 2011 Aug 10;(8):CD008586.	Seizures in adults with brain tumours
Uthman et al, Curr Med Res Opin. 2011 Jul;27(7):1285-93.	Pregabalin add on to levetiracetam for refractory partial-onset seizures
Lo et al, Can J Neurol Sci. 2011 May;38(3):475-86.	Levetiracetam as adjunctive therapy for refractory epilepsy
van Tuijl JH et al, Seizure. 2011 May;20(4):285-91.	Post-stroke prevention of seizures
Stockis et al, Clin Ther. 2010 Sep;32(10):1813-21.	Bioavailability study
Houtkamp M. Curr Opin Crit Care. 2011 Apr;17(2):94-100.	Refractory staus epilepticus
Kwan et al, Epilepsy Behav. 2010 May;18(1-2):100-5.	Levetiracetam as adjunctive therapy for uncontrolled partial epilepsy
Cumbo et al, Epilepsy Behav. 2010 Apr;17(4):461-6.	Epileptic seizures with Alzheimer's disease
Szaflarski et al, Neurocrit Care. 2010 Apr;12(2):165-72.	Seizure prophylaxis after neurological surgery
Levisohn et al, Epilepsia. 2009 Nov;50(11):2377-89.	Neurocognitive effects of adjunctive levetiracetam in children with partial onsey seizures
Richy et al, Epilepsy Behav. 2009 Oct;16(2):240-5.	Extended- vs immediate release formulation comparison of levetiracetam
Rosenfeld et al, Epilepsy Res. 2009 Jul;85(1):72-80	Adjunctive levetiracetam for idiopathic generalised epilepsy syndromes
Peltola et al, Epilepsia. 2009 Mar;50(3):406-14.	Adjunctive extended release levetiracetam for partial-onset seizures
Xiao et al, Eur Neurol. 2009;61(4):233-9.	Levetiracetam adjunctive therapy for refractory partial onset seizures
Lim et al, J Neurooncol. 2009 Jul;93(3):349-54.	Seizure control post craniotomy
Labiner et al, Epilepsia. 2009 Mar;50(3):434-42.	Adjunctive levetiracetam and anger, hostility and total mood effects in partial epilepsy
Wu et al, Epilepsia. 2009 Mar;50(3):398-405.	Adjunctive levetiracetam therapy
Noachtar et al, Neurology. 2008 Feb 19;70(8):607-16.	Idiopathic generalised epilepsy with myoclonic seizures
Zhou et al, Epilepsy Behav. 2008 Feb;12(2):305-10.	Adjunctive levetiracetam for refractory partial epilepsy
Marson et al, Health Technol Assess. 2007 Oct;11(37):iii-iv, ix-x, 1-134.	SANAD trial – Lamotrigine and carbamazepine reviewed for partial onset seizures – levetiracetam then newly licensed in UK
Berkovic et al, Neurology. 2007 Oct 30;69(18):1751-60.	Indication: idiopathic generalised epilepsy
Brodie et al, Neurology. Neurology. 2007 Feb 6;68(6):402–8	RCT cited in Cochrane review– Nevitt et al, 2017
Tilz et al, Eur J Neurol. 2006 Dec;13(12):1352-8.	Pharmacology/pharmacodynamic study of levetiracteam
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