National Essential Medicine List
Paediatric Hospital Level Medication Review Process
Component: Central Nervous System

MEDICINE MOTIVATION:

1. Executive Summary

Date: September 2019
Medicine (INN): Levetiracetam (LEV)
Medicine (ATC): N03AX14
Indication (ICD10 code): *G40.9*
Patient population: Childhood Epilepsy: Generalised and Focal
Prevalence of condition: 144 per 100,000 person years in infancy, 58 per 100,000 from 1-10 years[1]
Level of Care: Hospital level
Prescriber Level: Medical officer or specialist
Current standard of Care:

Seizure type	First line	Second line
Generalised	Sodium valproate Or Phenobarbital (<6 months old)	Lamotrigine
Focal	Carbamazepine	Lamotrigine Topiramate

Efficacy estimates: (Not possible to calculate NNT)

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

Network meta-analysis:
Partial
CBZ vs LEV HR 0.82 (0.69-0.97)
LTG vs LEV HR 1.10 (0.89-1.35)
Topiramate vs LEV: no data
Generalised:
CBZ vs LEV HR 0.74 (0.44-1.23)
LTG vs LEV HR 1.17 (0.63-2.19)
LEV vs VAL HR 1.41 (0.83-2.44)

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

Network meta-analysis:
Partial
CBZ vs LEV HR 1.35 (1.09-1.69)
LTG vs LEV HR 1.16 (0.93-1.46)
Topiramate vs LEV: no data
Generalised
CBZ vs LEV HR 1.33 (0.81-2.22)
LTG vs LEV HR 1.05 (0.40-2.78) (No direct evidence)
VAL vs LEV No data
Motivator/reviewer name(s): Members of Paediatric Hospital Level Expert Review Committee

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

Dr T Dennis, Ms K MacQuilkan, Dr J Riddin, and Paediatric Expert Review Committee.

3. Author affiliation and conflict of interest details

Dr T Dennis

- Affiliation: Paediatric Hospital Level Committee member

- Conflict of interest: None to declare

Ms K MacQuilkan

- Affiliation: Paediatric Hospital Level Committee member
- Conflict of interest: None to declare

Dr J Riddin

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- Conflict of interest: None To declare

4. Introduction/ Background

Epilepsy is a common chronic neurological disorder. Multiple antiepileptic drugs (AED) are available for its management, though notably only 60 to 70% enter remission once initiated on treatment. The ideal of treatment is to achieve seizure freedom with minimal adverse effects. Multiple new AED are available and it is increasingly important to ensure that appropriate drug choices are made with consideration for age, gender, type of epilepsy as well as co-morbidities. At present the Paediatric Hospital Level STGs and EML, 2017 recommends VAL or phenobarbitone (first line) and lamotrigine (second line) for generalised seizures, and CBZ (first line) and lamotrigine or topiramate (second line) for focal seizures.

Concern regarding the use of sodium valproate (VAL) in women of childbearing age is growing, though its teratogenicity has long since been established. At present, the BNF for Children[2] and NICE guidelines[3] caution against the use of VAL in adolescent and pre-adolescent girls who are likely to remain on treatment into their childbearing years. In some countries its use has been banned in women of childbearing age (Macfarlane 2018).

Levetiracetam is increasingly being used as first line therapy for various seizure types[4,5]. Its efficacy has been shown in various age groups[6,7] and generally has a favourable adverse effect profile.[8]

Recommendations in international practice is that LEV is at least a viable alternative to first line therapy, or for use as adjunctive therapy in the paediatric population with generalised seizures or focal seizures. The lack of evidence available is frequently commented on in published papers on the topic. Head to head trials comparing first line therapies to the newer therapies in the paediatric population are scarce. Despite this, in many countries LEV is the most commonly prescribed AED in the paediatric population. Its efficacy (established in placebo-controlled trials),[9] favourable side effect profile and safety in pregnancy are among the reasons for this.

This review was prompted by the reconsideration of the recommendation to use of VAL in adolescent and preadolescent girls who are likely to remain on AED into their childbearing years as well as the trend towards using LEV in epileptic patients of all ages. The aim is to determine the safety and efficacy of levetiracetam monotherapy for new onset seizures (focal or generalised) versus currently recommended agents (first and second line).

Note: In accordance with the International League Against Epilepsy reviewed guidelines on the classification of epilepsies 2017, partial seizures have been reclassified as focal seizures.[10]

5. Purpose/Objective i.e. PICO question [comparison to current standard of care for a specific

-P: *Paediatric patients with newly diagnosed or untreated generalised epilepsy or focal epilepsy*
-I: *Levetiracetam*
-C: *Sodium valproate/Carbamazepine/Lamotrigine*
-*O**: Time to withdrawal of AED/retention on treatment, seizure freedom at 12 months*

6. Methods:

a. Data sources *Pubmed, Cochrane Library*

Search strategy 1: Pubmed

("network meta-analysis"[MeSH Terms] OR ("network"[All Fields] AND "meta-analysis"[All Fields]) OR "network meta-analysis"[All Fields] OR ("network"[All Fields] AND "meta"[All Fields] AND "analysis"[All Fields]) OR "network meta

analysis"[All Fields]) AND ("anticonvulsants"[Pharmacological Action] OR "anticonvulsants"[MeSH Terms] OR "anticonvulsants"[All Fields] OR ("antiepileptic"[All Fields] AND "drug"[All Fields]) OR "antiepileptic drug"[All Fields])

Results yielded: 62 results, including Nevitt, et al 2017, Campos 2018, Campos 2016

((("pediatrics"[MeSH Terms] OR "pediatrics"[All Fields] OR "paediatric"[All Fields]) AND "epilepsy"[MeSH Major Topic]) AND (("levetiracetam"[MeSH Terms] OR "levetiracetam"[All Fields]) AND monotherapy[All Fields])) AND (first[All Fields] AND ("age of onset"[MeSH Terms] OR ("age"[All Fields] AND "onset"[All Fields]) OR "age of onset"[All Fields] OR "onset"[All Fields]) AND ("seizures"[MeSH Terms] OR "seizures"[All Fields]))

2 trials: 2 excluded (not relevant to PICO question)

((((("pediatrics"[MeSH Terms] OR "pediatrics"[All Fields] OR "paediatric"[All Fields]) AND "epilepsy"[MeSH Major Topic]) AND ("levetiracetam"[MeSH Terms] OR "levetiracetam"[All Fields])) AND ("lamotrigine"[MeSH Terms] OR "lamotrigine"[All Fields])) AND monotherapy[All Fields]

9 trials: 9 excluded (not relevant to PICO question)

((first[All Fields] AND ("age of onset"[MeSH Terms] OR ("age"[All Fields] AND "onset"[All Fields]) OR "age of onset"[All Fields] OR "onset"[All Fields]) AND ("seizures"[MeSH Terms] OR "seizures"[All Fields])) AND ("Childhood"[Journal] OR "childhood"[All Fields])) AND ("levetiracetam"[MeSH Terms] OR "levetiracetam"[All Fields])

7 trials: 7 excluded (not relevant to PICO question)

Search strategy 2: Cochrane library

Search terms: Levetiracetam AND partial seizures AND first onset seizures
1 Systematic review – included (Nevitt et al, 2018)
13 clinical trials – excluded (not relevant to PICO question)

Search terms: Levetiracetam AND generalised epilepsy AND first onset seizures
2 Systematic review – 1 included (Nevitt et al, 2018), 1 excluded (not relevant to PICO question)
16 clinical trials – excluded (not relevant to PICO question)

Ongoing studies:
A study of Standard and New Antiepileptic Drugs – SANAD-II
http://www.who.int/trialsearch/trial2.aspx? Trialid=euctr2012-001884-64-gb, 2012 | added to CENTRAL: 31 March 2019 | 2019 Issue 3
EUCTR2012-001884-64-GB
Frith et al 2015 https://doi.org/10.1016/j.jns.2015.08.492

b. Excluded studies: see addendum A

c. Evidence synthesis

A significant limitation to this review is that paediatric specific data is not available for drugs in question. As such network meta-analysis data for all age groups forms the bulk of the evidence. Specifically, head to head trials comparing LEV and lamotrigine (LTG), LEV and VAL and LEV and carbamazepine (CBZ) for childhood epilepsy have not been published.

Network meta-analysis: Summary

Author, date	*Type of study*	n	Population	Comparators	Primary outcome	Effect sizes	Comments
Nevitt, et al 2017[12]	*Individual participant data (IPD) review (pairwise meta-analysis using direct evidence) and network meta-analysis (using direct and indirect evidence (vs placebo))*	36 RCTs, n =12,391	Children and adults with partial onset epilepsy or generalised onset tonic-clonic seizures (with or without 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 and 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, and is the primary effectiveness outcome measure recommended by the Commission of Antiepileptic Drugs of the ILAE. [Secondary outcomes: time to achieve 12 month remission; time to achieve six-month remission; time to first seizure post-randomisation, and occurrence of adverse events]	Primary outcome: <u>Partial:</u> CBZ vs LEV HR 0.82 (0.69 to 0.97) Direct evidence 37.9% I^2 = 0% LTG vs LEV HR 1.10 (0.89 to 1.35) Direct evidence 23.7% I^2 = NA <u>Generalised:</u> CBZ vs LEV HR 0.74 (0.44 to 1.23) Direct evidence 57% I^2 = 0% LTG vs LEV HR 1.17 (0.63 to 2.19) No direct evidence I^2 = NA	Well conducted review Comprehensive search strategy Rigorous review of methodology Two methodologies used for analysis Heterogeneity was appropriately assessed, conflict of interest declared
Campos 2016[13]	*Systematic review and network meta-analyses combining direct and indirect evidence.*	65 RCTs included n=16,025 28 RCTs reported efficacy outcomes n=7761 58 RCTs reported tolerability outcomes n=15,417	Patients with focal epilepsy (adults and children included)	Phenobarbitone, zonisamide, phenytoin, lamotrigine, sulthiame, levetiracetam, gabapentin, clobazam, valproate, vigabatrin, oxcarbazepine	Seizure free at the end of the maintenance period and withdrawal of AED due to therapeutic inefficacy Tolerability analysis – withdrawals due to AE	Seizure free (OR): CBZ vs LTG -0.03 (-0.36 to 0.35), p=0.22 CBZ vs LEV 0.4 (-0.3 to 0.7), p=0.49 LTG vs LEV 0.44 (-0.28 to 0.61), p=0.45 Withdrawal due to therapeutic inefficacy (OR): CBZ vs LEV OR 1.49 (0.74 to 3.31) CBZ vs LTG 0.97 (0.70 to 1.42) LTG vs LEV -0.05 (-0.79 to 0.04), p=0.14	Minimum maintenance period for assessment of primary out 15 days (to ensure plasma concentrations had reached steady state). Only RCT included, some open label, various age groups represented including elderly Methodologic analysis of quality: 22.7% low risk of bias 47% unclear risk of bias 30.3% high risk of bias

						Tolerability outcomes: CBZ vs LTG 0.42 (0.25 to 0.67) CBZ vs LEV 0.88 (0.45 to 1.88) LTG vs LEV 2.15 (1.06 to 4.7)	Included studies listed by location, not author, unable to correlate whether the same studies were included in Nevitt et al, 2017
Campos 2018[13]	*Systematic review and network meta-analyses*	7 RCTs n=1,809	Patients with generalised epileptic seizures, all ages	Valproate, carbamazepine, lamotrigine, levetiracetam, phenobarbital, phenytoin, topiramate	Seizure free and withdrawal due to therapeutic inefficacy	Seizure free (OR): LTG vs LEV 1.09 (0.38 to 3.24) LEV vs VAL 1.31 (0.58 to 3.13) LTG vs VAL 1.40 (0.80 to 2.82) Withdrawal due to therapeutic inefficacy: LTG vs VAL 0.36 (0.03 to 5.19) LEV vs VAL 1.38 (0.09 to 2.62)	Selection of RCTs done by 2 reviewers independently, disputes resolved by consensus Quality analysis: 43.8% unclear risk of bias, 37.5% high risk of bias, 18.8% low risk of bias Median follow up time: 48 weeks

While prescribing LEV in the paediatric population as first line therapy for generalised and focal seizures is common practice in multiple centres globally, evidence to prove its superiority to VAL, CBZ and LTG is not available. Estimates of efficacy in the network meta-analysis point towards equal efficacy with some benefits regarding tolerability.

7. Alternative agents:

Lamotrigine (generalised and focal seizures): currently second line treatment for absence seizures though evidence for VAL and ethosuximide have better efficacy.

Topiramate (Focal seizures)

8. Cost consideration

See cost analysis document

In the cost analysis there are two notable factors:

1. A relatively high price of LTG dispersible tablets compared to LEV liquid formulation
2. Lower price of LTG tablets vs LEV tablets

Presuming that the children initiated on LEV syrup remain on treatment into school years, they would transition to tablets at some point in their treatment. Meltzer, et al 2006 suggests that children aged 6 to 11 years can be taught to swallow tablets if needed. It is further noted that children with severe neurodevelopmental delay may remain on liquid formulation medication indefinitely. More than 50% of children with epilepsy go into remission and no longer require AED[11], thus may not require a switch to tablets.

EVIDENCE TO DECISION FRAMEWORK

	JUDGEMENT	SUPPORTING EVIDENCE & ADDITIONAL CONSIDERATIONS
QUALITY OF EVIDENCE	**What is the overall confidence in the evidence of effectiveness?** Confident [ ] Not confident [ ] Uncertain [X]	Recommendations of equivalence based on mainly adult data. Lack of head-to-head studies.
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 [ ]	Lamotrigine Topiramate
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]	Cost of medicines/ month: **Medicine** / **Cost/annum** Lamotrigine dispersible tablets (5kg child) — R2485.17 (contract) Levetiracetam syrup (5kg child) — R1154.95 (SEP) Lamotrigine tablets (20kg child) — R357.10 (contract) Levetiracetam tablets (20kg child) — R7438.62 (SEP) **Additional resources:** Although the levetiracetam syrup is more affordable than dispersible lamotrigine tablets; standard lamotrigine tablets are the most affordable option. Thus if rational medicine is not observed there may be a potential for abuse of the liquid formulation.

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

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
	☐	☐	**X**	☐	☐

Recommendation

It is recommended that levetiracetam solution be included on the Essential Medicines List for children who are unable to swallow and require a liquid formulation.

Rationale:

Levetiracetam solution is more cost effective than dispersible lamotrigine tablets in this age group.

Level of Evidence:

Review indicator:

Evidence of efficacy	Evidence of harm	Price reduction
X		X

VEN status:

Vital	Essential	Necessary
X		

Monitoring and evaluation considerations

Research priorities

References:

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7. Arzimangolou A, Lösch C, Garate P and Bentz J. Safety of levetiracetam among infants younger than 12 months – Results from a European multicentre observational study. Eur J Paediatr Neurol. 2016; May 20(3):368-375.
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11. Camfield PR, Camfield CS. What happens to children with epilepsy when they become adults? Some facts and opinions. Pediatr Neurol. 2014 Jul;51(1):17–23.
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13. Campos MS de A, Ayres LR, Morelo MRS, Marques FA, Pereira LRL. Efficacy and Tolerability of Antiepileptic Drugs in Patients with Focal Epilepsy: Systematic Review and Network Meta-analyses. Pharmacotherapy. 2016 Dec;36(12):1255–71
14. Campos MS de A, Ayres LR, Morelo MRS, Carizio FAM, Pereira LRL. Comparative efficacy of antiepileptic drugs for patients with generalized epileptic seizures: systematic review and network meta-analyses. Int J Clin Pharm. 2018 Jun;40(3):589–98.

Addendum A: **Levetiracetam excluded studies**

Burns, et al 2018	Outcomes not relevant to PICO question, not RCT
Faught, et al 2018	Database analysis, not relevant to PICO question
Aneja, Sharma 2013	Not RCT
Cho, et al 2015	Not RCT
Takeuchi, et al 2016	Not relevant to PICO question
Coppola 2004	Not RCT
Glauser 2004	Not relevant to PICO question, not RCT
Borusiak, et al 2013	Not relevant to PICO question, not RCT
Yang, et al 2012	Study not in English, not relevant to PICO question
Wilmhurst, et al 2015	Not RCT, not relevant to PICO question
Coppola 2013	Not relevant to PICO question
Tan, et al 2014	Not relevant to PICO question
Hughes 2009	Not RCT, not relevant to PICO question
Verrotti, et al 2013	Not relevant to PICO question
Mangano, et al 2013	Not relevant to PICO question
DiMauro, Hirano 2003	Not relevant to PICO question
Snoeck, Stockis 2007	Adjunctive therapy, not relevant to PICO question
Stefan, et al 2006	Not relevant to PICO question
Chung, et al 2016	Not RCT
Harden 2001	Not RCT
Beran, et al 2005	Not RCT
French, Arrigo 2005	Not relevant to PICO question
Steinhoff, et al 2016	Not relevant to PICO question
Tsai, et al 2006	Not relevant to PICO question
EUCTR2007-002929-78-BE	Not relevant to PICO question
Krauss, et al 2011	Not relevant to PICO question
Arnold, et al 2018	Not relevant to PICO question
ACTRN12609000600246	Not relevant to PICO question
NCT00221988	Not relevant to PICO question
Hu, et al 2018	Pilot study, not relevant to PICO question
Frith, et al 2015	Relevant trial, ongoing
Sasso, et al 2004	Not relevant to PICO question
Grinspan 2018	Not RCT, observational study for use of LEV instead of phenobarb in infants
Wild, et al 2014	Not relevant to PICO question
Krauss, et al 2011	Not relevant to PICO question
Nickels 2019	Not RCT
Ferro, et al 2016	Not relevant to PICO question
Perry 2019	Not relevant to PICO question
Veroniki, et al 2017	Not relevant to PICO question
Khera, et al 2016	Not relevant to PICO question
Zaccara, et al 2017	Not relevant to PICO question

Zhuo, et al 2017	Refractory epilepsy - not relevant to PICO question
Hu, et al 2018	Not relevant to PICO question
Westby, et al 2017	Not relevant to PICO question
Iftikhar et al 2017	Not relevant to PICO question
Zhao, et al 2016	Not relevant to PICO question
Jackson, et al 2015	Not relevant to PICO question
Wiffen, et al 2017	Not relevant to PICO question
He, et al 2017	Not relevant to PICO question
Rosati, et al 2018	??
Rudroju, et al 2014	Not relevant to PICO question
Mayo-Wilson, et al 2014	Not relevant to PICO question
Nüesch, et al 2013	Not relevant to PICO question
Qin, et al 2018	Not relevant to PICO question
Khan, et al 2017	Not relevant to PICO question
Zhao, et al 2017	?
Griebelar, et al 2014	Not relevant to PICO question
Shamliyan, et al 2013	Not relevant to PICO question
Lee and Song, 2016	Not relevant to PICO question
Lattanzi, et al 2019	Adult population – not relevant to PICO question
Haas, et al 2012	Not relevant to PICO question
Song, et al 2018	Not relevant to PICO question
Glue and Herbison 2015	Not relevant to PICO question
Tangamornsuksan, et al 2013	Not relevant to PICO question
Sridharan and Sivaramakrishnan 2018	Not relevant to PICO question
Arya, et al 2015	Not relevant to PICO question
Zheng, et al 2015	Not relevant to PICO question
Zaccara, et al 2014	Drug-resistant epilepsy – not relevant to PICO question
Brigo, et al 2018	Not relevant to PICO question
Bodalia, et al 2013	Refractory epilepsy – not relevant to PICO question
Alencar, et al 2018	Not relevant to PICO question
Tricco, et al 2014	Study protocol
Sarkis, et al 2018	Not relevant to PICO question
Tangamornsuksan, et al 2018	Not relevant to PICO question
Khan, et al 2013	Refractory partial seizures – not relevant to PICO question
Derry, et al 2016	Not relevant to PICO question
Wertli, et al 2014	Not relevant to PICO question
Brigo, et al 2019	Not relevant to PICO question
Zaccara, et al 2013	Not relevant to PICO question
Busse, et al 2018	Not relevant to PICO question
Tenforde, et al 2018	Not relevant to PICO question
Fu, et al 2018	Not relevant to PICO question
Zaccara, et al 2013	Refractory epilepsy – not relevant to PICO question
Cooper, et al 2017	Not relevant to PICO question

Epstein, et al 2015	Not relevant to PICO question
Duke, et al 2017	Not relevant to PICO question
Rogers and Taylor 2017	Not relevant to PICO question
Khan, et al 2019	Not relevant to PICO question
McCormack, et al 2018	Not relevant to PICO question
Craig, et al 2013	Not relevant to PICO question
Martyn-St James, et al 2012	Not relevant to PICO question
Geitona, et al 2019	Not relevant to PICO question
Costantine and Weiner, 2009	Not relevant to PICO question
Choy, et al 2011	Not relevant to PICO question
Steinberg 2018	Not relevant to PICO question
Wolff, et al 2011	Not relevant to PICO question
Peng, et al 2007	Not relevant to PICO question
Donoghue 2018	Not relevant to PICO question
Schmitz, et al 2006	Not relevant to PICO question, not published in English
Marson, et al 1996	Not relevant to PICO question