South African National Essential Medicines List
Adult Hospital Medication Review Process
Cost-effectiveness and budget impact analyses
Levetiracetam for the treatment of Epilepsy in the South African Public Sector

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Conflict of Interest: None declared.

1. INTRODUCTION

Medication: Levetiracetam 1500mg 12 hourly.

Background:

Epilepsy is a chronic neurological condition responsible for considerable morbidity and mortality globally (1). It has a global prevalence between 0.4% and 1.0% and in South Africa of 1% or approximately 560,000 people (2)(3). Patients with uncontrolled epilepsy experience significant disability according to the Global Burden of Disease study, with total burden of epilepsy distributed between early mortality and morbidity, signifying the importance of quality of life with regards to the treatment of epilepsy (4)(5). Epilepsy can also have substantial individual and societal economic impacts, with economic costs ranging from direct and indirect costs of treatment and loss of productivity due to illness (5). A relationship has also been found between epilepsy prevalence and social deprivation (1).

At least 25% of epilepsy patients continue to have seizures despite optimal treatment with one or more antiepileptic drugs (AEDs) due to lack of efficacy of available drugs or treatment limitations due to side effects (6). AEDs can be divided into first- and second-generation drugs. Phenytoin, valproate and carbamazepine are first-generation, while lamotrigine and levetiracetam are second-generation AEDs. Second-generation AEDs have been found to generally have better tolerability, improved safety profiles and fewer drug interactions compared to first-generation AEDs (6). Levetiracetam is under consideration for inclusion on the South African Essential Medicines List.

No cost-effectiveness studies on the first-line treatment of epilepsy have been conducted in the South African context or in similar contexts using the combination of drugs under analysis. Current first-line epilepsy treatment in South Africa is lamotrigine, phenytoin or carbamazepine (7) (8). There is need to determine the cost-effectiveness of the available options of AEDs in South Africa to ensure the efficient use of limited resources for health. Interventions implemented in the healthcare sector must be effective, both clinically and economically to ensure access, availability and acceptability of the

interventions to patients (9). Although there is limited evidence of a greater effectiveness of levetiracetam relative to other treatment options in the treatment of newly diagnosed epilepsy, the reported absence of serious side effects, its ease of use, linear pharmacokinetics and reduced interactions with other drugs is motivation for this analysis (10). Some AEDs such as lamotrigine may cause hypersensitivity reactions in susceptible patients which can be serious for example in the case of Steven-Johnson Syndrome (11). An estimated incidence of hypersensitive reactions from AEDs ranges from 1 per 1000 to 1 per 10 000 users (11). Reports have shown carbamazepine, phenytoin and lamotrigine to be connected to hypersensitivity reactions (11).

2. INDICATIONS

Drug	Doses	Indications	Adverse Effects
Lamotrigine	3000 mg daily	Monotherapy or add-on therapy for focal epilepsy with or without secondary generalized tonic-clonic seizures and in primary generalized tonic-clonic seizures; adjunctive therapy for children, and for Lennox-Gastaut syndrome. Also registered for bipolar affective disorder.	Maculopapular rash manifesting within 4 weeks of initiating treatment, which occasionally progresses to severe generalized hypersensitivity reactions such as Steven-Johnson syndrome.
Carbamazepine	600 mg 12 hrly	First-line management of generalized and focal seizures but not effective in the treatment of absence seizures or atonic seizures.	Sedation, ataxia, gastrointestinal effects. Side effects may subside spontaneously after 7-14 days' treatment, or with dose reductions.
Valproate	2000 mg daily	All forms of epilepsy. Also used as prophylaxis for migraines and for control of the acute manic phase of bipolar disorder.	Gastrointestinal effects, dose-related CNS effects such as fatigue and sedation, ataxia and dysarthria. Teratogenic in pregnancy, classified as a category D drug.
Phenytoin	300 mg daily	All forms of epilepsy except absence and myoclonic seizures. Also used in status epilepticus.	Related to plasma levels. Nausea, vomiting, tremor, ataxia, nystagmus and speech disturbances. Category D drug in pregnancy due to increased risk of fetal abnormalities.
Levetiracetam	1500 mg 12 hrly	Mono- or add-on therapy for focal seizures in patients from 16 years of age. Add-on therapy for primary generalized tonic-clonic seizures from 16 years of age. Add-on therapy for myoclonic seizures in adults and adolescents from 12 years of age.	Somnolence, fatigue, dizziness. Limited serious side effects.

Table 1: Indications of medicines under analysis (12).

3. METHODS

The study conducted was a model-based economic evaluation in the form of a cost-effectiveness analysis (CEA) and a budget impact analysis (BIA). The CEA was conducted over a five-year time horizon and the BIA represents annual spending. The study was from the providers' perspective, specifically in the South African public sector. Levetiracetam as first-line treatment in patients with newly

diagnosed epilepsy was compared to lamotrigine, carbamazepine, phenytoin and valproate. A decision-tree was used for the CEA representing the first six months of treatment and a Markov Model to extend the analysis to a five-year period. Methodology for the study was based on the International Decision Support Initiative (IDSI) reference case and previous CEA and BIA conducted to contribute to EDP processes (13). Effectiveness parameters were extracted from the Adult ERC Levetiracetam medicine review 2019 (Adult ERC Lev MR) and the remaining model parameters were obtained from literature. Costs related to epilepsy treatment were obtained from appropriate costing studies on epilepsy treatment and adapted to the South African context.

An analysis of the decision-tree was conducted for the first six months of treatment based on the costs and effects collected for that period. Based on this data collected, the interventions were listed from least expensive to most expensive to determine if there were any strategies that incur higher costs but provide lower effects (i.e. dominated strategies). These strategies were excluded from the analysis. Incremental Cost-Effectiveness Ratios (ICERs) were calculated for the appropriate strategies, using the previous less costly treatment strategy for comparison. Results were presented in tabular form and on a cost-effectiveness plane. For analysis of the Markov Model the same process was carried out. The resulting ICERs were also expressed in both tabular form and on a cost-effectiveness plane.

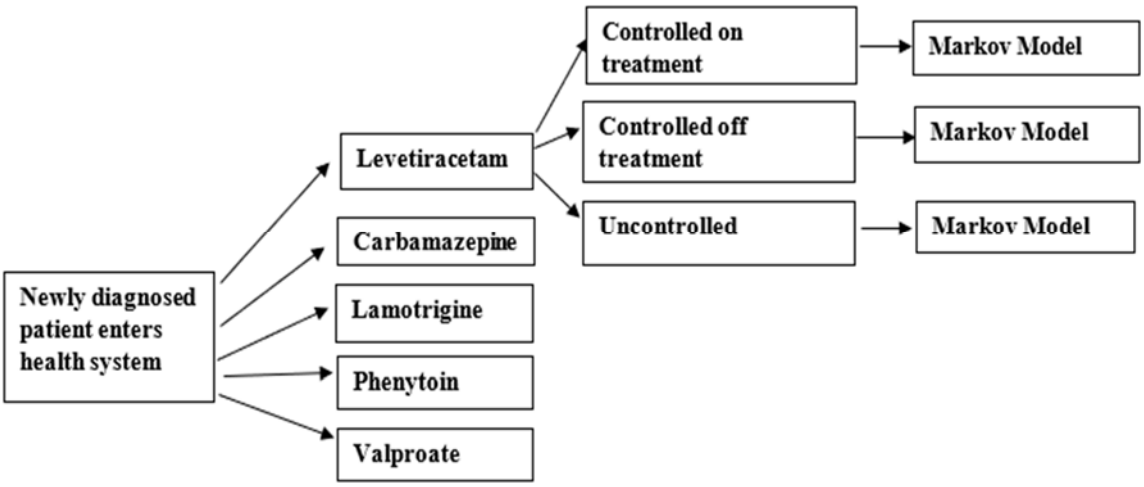

Figure 1: Structure of Decision-Tree Model.

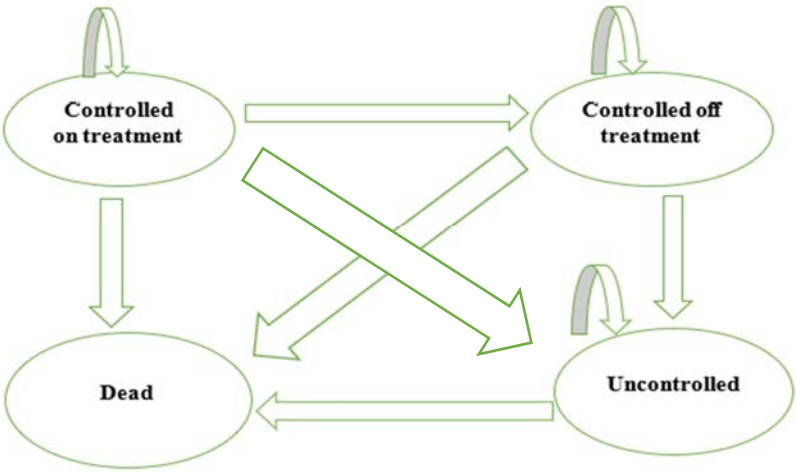

Figure 2: Structure of Markov Model.

A budget impact analysis was conducted for each of the five strategies from the providers' perspective over a one-year period. The analysis followed the Principles of Good Practice for ISPOR (International Society for Pharmacoeconomics and Outcomes Research) (14). Results were presented in a table as the costs of adopting each of the treatment options.

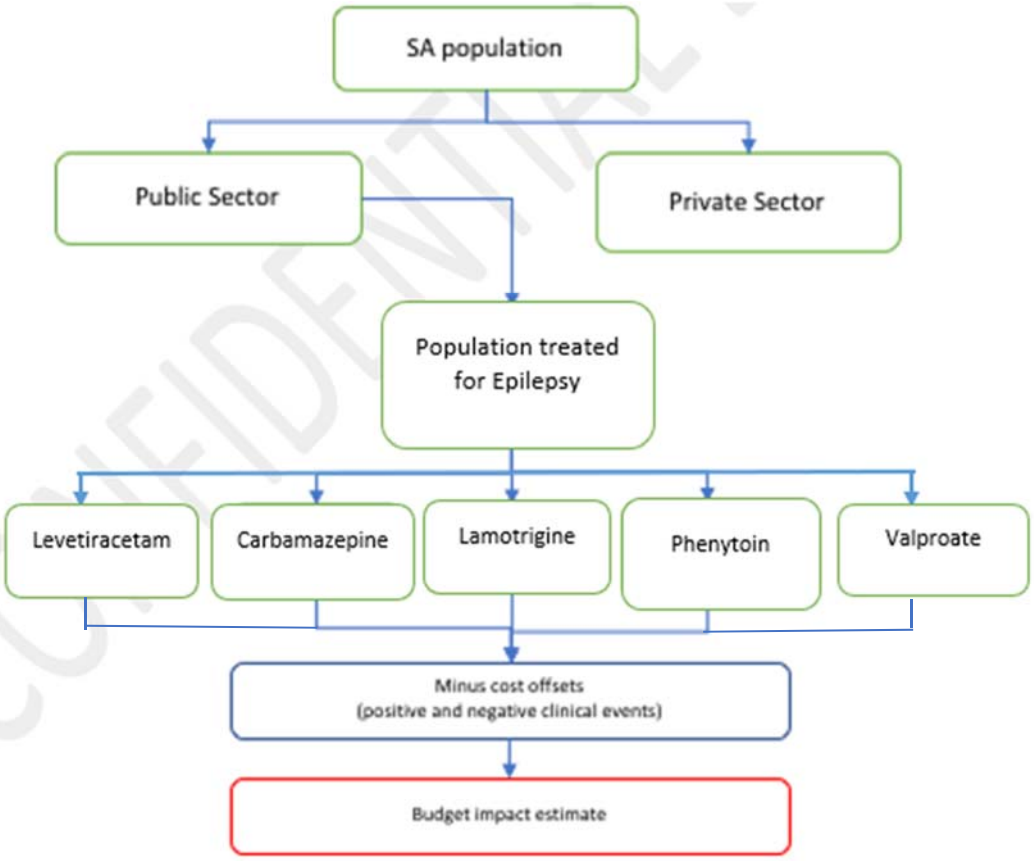

Figure 3: Framework to estimate budget impact of introducing levetiracetam to the South African public health system in Treatment of Epilepsy.

Sensitivity analyses were conducted to address uncertainty. One-way sensitivity analyses for both the CEA and the BIA were performed to cater for possible long-term changes in the context of the South African public sector. The results for the CEA sensitivity analysis were presented in the form of a tornado diagram.

Study details

Setting	-South African public health sector
Patient Population	-Adults with newly diagnosed epilepsy in need of first-line treatment in the South African public sector.
Participants	-Non-applicable as secondary data will be used.
Economic Evaluation	-Economic evaluation which consisted of a cost-effectiveness analysis and a budget impact analysis. -A time horizon of 6 months which was extended to a 5-year period was used for the CEA. -Levetiracetam was the intervention under analysis and phenytoin, carbamazepine, lamotrigine and valproate were the comparators -Costs were expressed as South African Rands, 2018 value.

	-Effects were expressed as QALYs for both the 5-year and 6-month CEAs. -Results were expressed as ICERs.

Table 2: Summary of study details.

4. CLINICAL INPUTS

Clinical inputs were calculated based on the findings from the Adult ERC Lev MR and those not included in the review were collected from literature.

Probability Table

Description	Value	Source
Probability of death when uncontrolled	0,01085	3.1*Population death-rate Wagner (2015) reported that risk of mortality for people whose epilepsy is uncontrolled is 3.1 greater than in the general population. (4)
Probability of going from 'controlled on treatment' to 'controlled off treatment'	0,0425	Wagner (2015) (4)
Probability of remaining uncontrolled	0,98915	Calculated through probability panel (probabilities leaving each health state must add up to 1)
Probability of remaining 'controlled off treatment'	0,98915	Calculated from Wagner (2015)
Probability of staying 'controlled on treatment' for LEV	0,43884	Adult ERC Lev MR and Seizure free proportions from LEV trial (27).[1]
Probability of going from 'controlled on treatment' to 'uncontrolled' on LEV	0,51516	Adult ERC Lev MR and Seizure free proportions from LEV trial (27)[2]
Probability of staying 'controlled on treatment' for LTG	0,5019	Adult ERC Lev MR and Seizure free proportions from LEV trial (27)[1]
Probability of going from 'controlled on treatment' to 'uncontrolled' on LTG	0,4521	Adult ERC Lev MR and Seizure free proportions from LEV trial (27)[2]
Probability of staying 'controlled on treatment' for VPA	0,34344	Adult ERC Lev MR and Seizure free proportions from LEV trial (27)[1]
Probability of going from 'controlled on treatment' to 'uncontrolled' on VPA	0,61056	Adult ERC Lev MR and Seizure free proportions from LEV trial (27)[2]
Probability of staying 'controlled on treatment' for PHT	0,34344	Adult ERC Lev MR and Seizure free proportions from LEV trial (27)[1]

Probability of going from 'controlled on treatment' to 'uncontrolled' on PHT	0,61056	Adult ERC Lev MR and Seizure free proportions from LEV trial (27)[2]
Probability of staying 'controlled on treatment' for CBZ	0,34344	Adult ERC Lev MR and Seizure free proportions from LEV trial (27)[1]
Probability of going from 'controlled on treatment' to 'uncontrolled' on CBZ	0,61056	Adult ERC Lev MR and Seizure free proportions from LEV trial (27)[2]
Probability of death when controlled on treatment/controlled off treatment (underlying mortality)	0,0035	Average age specific death rate for the median age-group in South Africa (25 years-30 years) WHO (2018) (28)

Table 3:Key Clinical Inputs.

[1] Average of hazard ratio used for the calculation is obtained from proportions of partial and generalized seizures from the Adult ERC Lev MR. Average of HR is then multiplied by the "seizure freedom" proportion obtained from the clinical trial data to get values for each comparative drug under analysis. Primary outcome from review was used for analysis.
[2] The residual probability from the probability table.

Utilities

The long-term outcomes associated with each treatment regimen are calculated by applying an annual estimate of the health-related quality of life associated with each health state in the model. The annual utilities accrued to an epileptic patient are detailed in the table below, with death incurring no utility.

Health State	HRQoL Value	Source
Controlled on treatment	0,94	Wilby et al (2003) (17)
Controlled off treatment	0,94	Wilby et al (2003) (17)
Uncontrolled (Second Line)	0,84	Wilby et al (2003) (17)
Dead	0	

Table 4: Markov States utility values

Model Assumptions

- The cost per emergency room visit is 1.5 times the cost per PDE and the cost per inpatient day is equal to the cost per PDE
- In the treatment of status epilepticus, seizures are under control after 2 doses of lorazepam and one dose of phenytoin (based on the Standard Treatment Guidelines)

- Most of the side-effects associated with AED treatment disappear when treatment is stopped, requiring no further treatment, except for Steven-Johnson Syndrome
- The seizure freedom rate provided in the levetiracetam clinical trial was obtained from the start of the trial
- **The proportion of HIV positive patients is evenly distributed among the various Markov states, therefore has no impact on the resulting ICER values**
- Patients cannot move "back" to controlled from uncontrolled as the uncontrolled state is intended to be a broad classification representing costs and health of those that have failed first-line therapy

5. COST INPUTS

The main costs included in both the decision tree and the Markov model were associated with the drug procurement costs of the AEDs and the hospital costs associated with the treatment of seizures and related events. The central costing parameters were obtained from the Master Procurement Catalogue (Jan 2019), the Health Systems Trust Report, District Health Barometer (2017/2018) and the fondaparinux analysis conducted for the committee. The utilization rates for the hospital services were obtained from the CEA study conducted by Wilby et al 2005 and were categorized based on whether the patient was controlled or uncontrolled (1).

Though levetiracetam is not currently on the EML, the Department of Health currently has the drug on tender, therefore a set tender price was available for the analysis.

DESCRIPTION	ANNUAL VALUE	VALUE FOR SIX MONTHS	SOURCE
Estimated cost for inpatient visits when controlled	R156,97	R78,48	Health Systems Trust and Wilby et al 2005 study[3]
Estimated cost for inpatient visits when uncontrolled	R3 991,47	R1 995,74	Health Systems Trust and Wilby et al 2005 study[3]
Estimated cost for outpatient visits when controlled	R243,00	R121,50	Health Systems Trust and Wilby et al 2005 study[3]
Estimated cost for outpatient visits when uncontrolled	R567,00	R283,50	Health Systems Trust and Wilby et al 2005 study[3]
Estimated cost emergency room visits when controlled	R87,66	R43,83	Health Systems Trust and Wilby et al 2005 study[3]

[3] The monetary values from the Health Systems Trust Report are multiplied by the utilization rates for patients who are controlled and those who are uncontrolled from the Wilby et al 2005 study (1).
https://www.hst.org.za/publications/District%20Health%20Barometers/DHB+2017-18+Web+8+Apr+2019.pdf

Estimated cost emergency room visits when uncontrolled	R1 008,06	R504,03	Health Systems Trust and Wilby et al 2005 study[3]
Estimated cost for an AED visits	R384,00	R192,00	Administration Pharmacy Cost multiplied by number of monthly visits
Estimated total cost for lamotrigine titration	R232,02	R232,02	Pharmaceutical costs based on STG recommendations
Estimated total cost for carbamazepine titration	R116,01	R116,01	Pharmaceutical costs based on STG recommendations
Estimated total cost for valproate titration	R77,34	R77,34	Pharmaceutical costs based on STG recommendations

Table 5: Cost Inputs for the models.

DESCRIPTION	EXPECTED VALUE	PROBABILITY OF USE PER PATIENT	AVERAGE VALUE PER PATIENT
Inpatient days when controlled	1	0,01	0,01
Inpatient days when uncontrolled	1	0,16	0,16
Average length of stay controlled			5,6
Average length of stay uncontrolled			8,9
Outpatient visits when controlled	3	0,18	0,54
Outpatient visits when uncontrolled	3	0,42	1,26
Emergency room visits controlled	1	0,02	0,02
Emergency room visits uncontrolled	1	0,23	0,23
Visits for medication collection			12
Hospital visits for lamotrigine titration			6
Hospital visits for carbamazepine titration			3
Hospital visits for valproate titration			2

Table 6: Utilisation Rates (1).

Drug	Percentage Risk (%)	Reference
Levetiracetam	0,00	
Carbamazepine	0,05	Bae et al. (2013) (18)
Lamotrigine	0,04	Bloom et al. (2017) (19)
Phenytoin	0,07	Rodriguez-Martin et al (2018) (20)
Valproate	0,00	

Table 7: Risk of getting Steven-Johnson Syndrome

Treatment of each case of Steven-Johnson Syndrome was estimated to cost R65 855,00 to the health system (21).

Drug	Daily Dosage (mg)	Tablet Strength (mg)	Number of Tablets per day	Cost per tablet	Number of monthly tablets (28 days)	Cost per month	Cost per patient for first six months	Cost per patient (first year)	Source
Levetiracetam	3000	750	4	R3,07	112	R343,84	R2 063,04	R4 126,08	Master Procurement Catalogue 15 Jan 2019[4]
Carbamazepine	1200	200	6	R0,31	168	R51,74	R305,97	R616,43	Contract circular HP09-2016SD (as used in Adult ERC Lev MR)
Lamotrigine	300	100	3	R0,94	84	R78,96	R340,48	R814,24	Master Procurement Catalogue 15 Jan 2019
Phenytoin	300	100	3	R0,61	84	R50,82	R304,92	R609,84	Contract circular HP09-2016SD (as used in Adult ERC Lev MR)
Valproate	1500	500	3	R0,95	84	R79,80	R469,84	R948,64	Contract circular HP09-2016SD (as used in Adult ERC Lev MR)

Table 8: Pharmaceutical Costs associated with each treatment regimen.

6. RESULTS

a. COST-EFFECTIVENESS ANALYSIS

The use of levetiracetam along with the use of phenytoin, valproate and carbamazepine in the treatment of newly diagnosed epilepsy was found to be dominated by treatment using lamotrigine. Treatment with lamotrigine over a five-year period was found to be the least costly treatment option and had the highest number of QALYs gained. The estimated cost of treating one case of epilepsy was R1 252 higher using levetiracetam compared to using lamotrigine. Levetiracetam had 0,02 QALYs lower than those of lamotrigine. Phenytoin, carbamazepine and valproate were found to have the same effect size of 3,97 QALYs.

Drug	**Expected Cost** (Rands)	**Expected Effect** (QALYs)	ICER
Lamotrigine	R63 567	4,01	
Levetiracetam	R64 819	3,99	Dominated[5]
Phenytoin	R66 028	3,97	Dominated
Valproate	R66 588	3,97	Dominated
Carbamazepine	R66 983	3,97	Dominated

Table 9: Summary of the cost-effectiveness results for the treatment of epilepsy using levetiracetam.

[4] Master Procurement Catalogue was used where there were better tablet strengths to suite the daily dose compared to those used in the Adult ERC Lev MR.

[5] Dominated strategy is one which costs more but has a lower health effect.

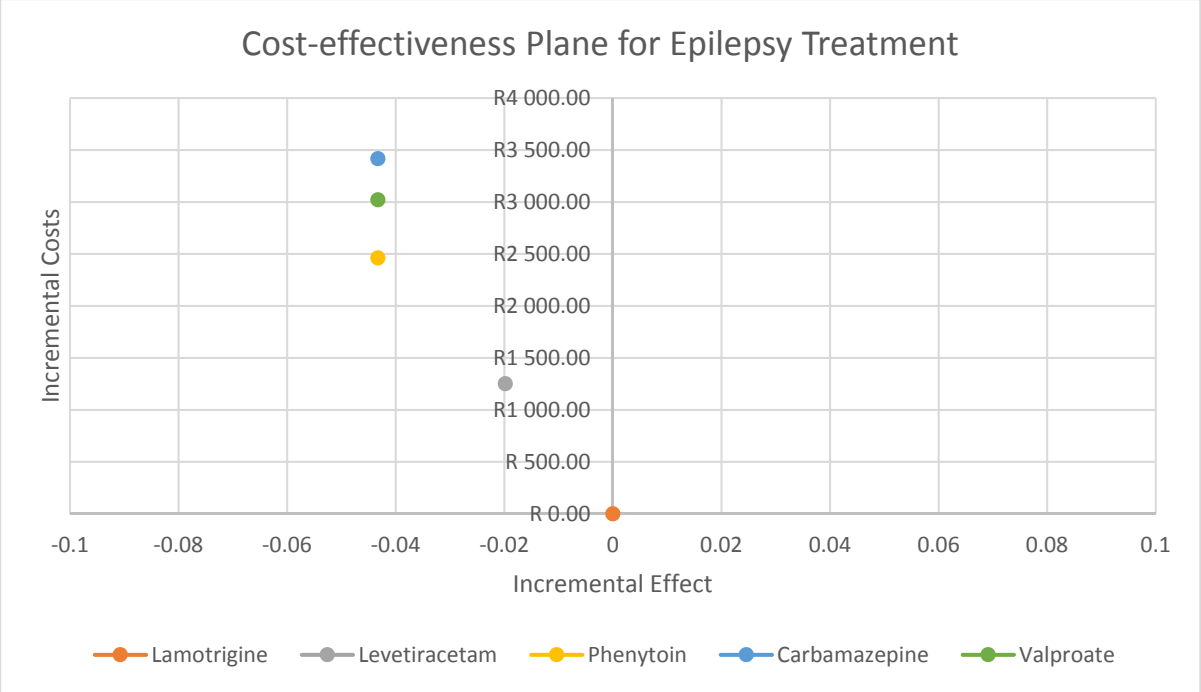

Figure 4: Cost-effectiveness plane for the treatment of epilepsy with levetiracetam.

Sensitivity Analysis

Sensitivity analyses were conducted on parameters considered to have a large impact on the ICER values obtained in the decision-tree model. Levetiracetam was compared to lamotrigine, which was found to be the dominating strategy in the main analysis.

A limitation of one-way sensitivity analysis is that the parameters rarely move independently of each other. This was the problem faced with the inclusion of transition probabilities in the sensitivity analysis, therefore it was only limited to costs and quality of life values. More complex sensitivity analysis, (e.g. probabilistic sensitivity analysis) is beyond the scope of this assessment. However, this basic sensitivity analysis provides a general overview for key drivers of uncertainty.

Parameter	Lower Value	Baseline	Upper Value
QoL when "uncontrolled"	0,50	0,84	0,95
QoL when "controlled on treatment"	0,70	0,94	1,0
LEV-input for "controlled on treatment"	R1 249,43	R2 498,85	R3 748,28
LEV unit cost	R1,54	R3,07	R4,61

Table 10: Values used for the decision-tree sensitivity analyses.

	ICER at lower parameter value	ICER at higher parameter value
QoL when "uncontrolled"	-R87 829	R3 855 875

QoL when "controlled on treatment"	R276 044	-R241 518
LEV- cost input for "controlled on treatment"	-R207 845	-R700 983
LEV unit cost	-R166 514	-R454 415

Table 11: ICERs obtained from sensitivity analyses.

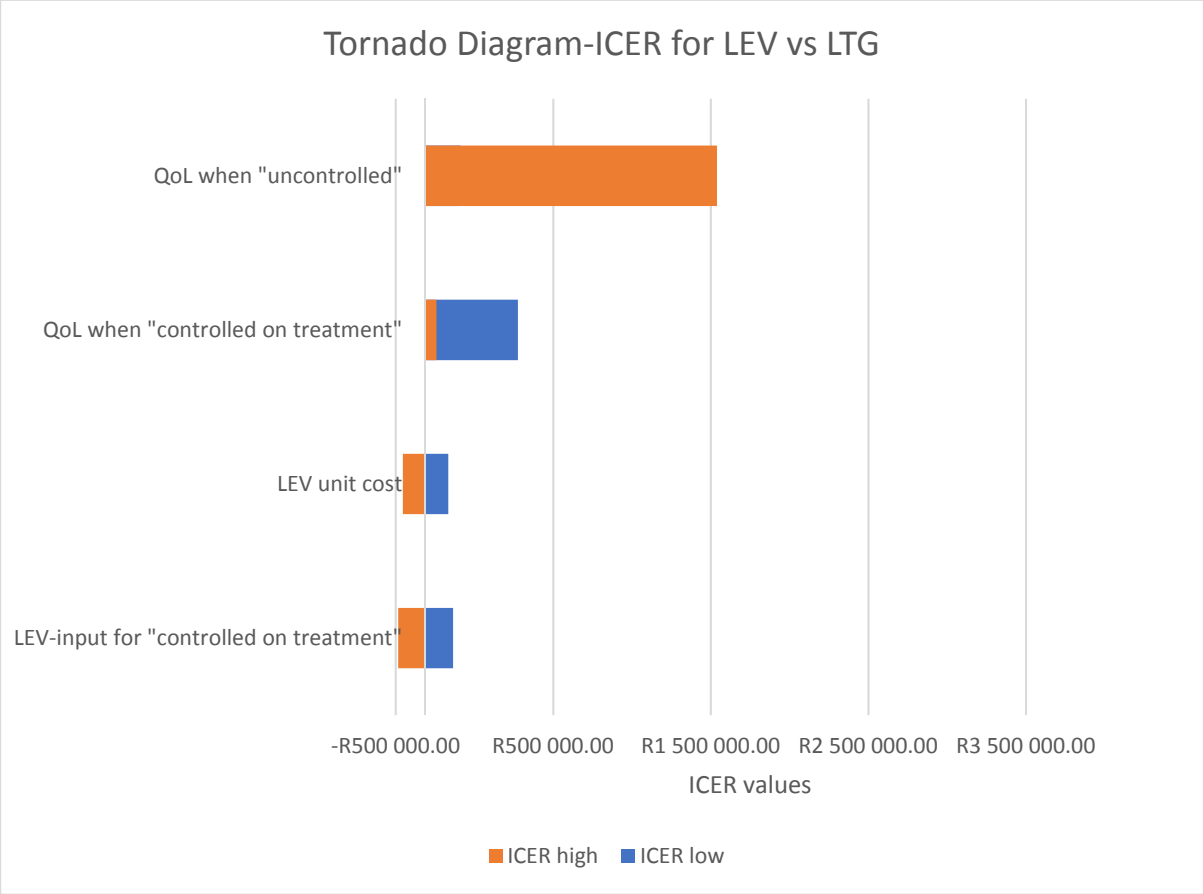

Figure 5: Tornado Plot for Sensitivity Analyses.

Both the levetiracetam-related costs used in the sensitivity analysis showed that lower cost values were associated with less negative ICER values (i.e. levetiracetam became comparatively more cost-effective as the levetiracetam-related costs became lower). There were no trends observed regarding the impact of the quality of life measures on the ICER values obtained.

b. BUDGET IMPACT ANALYSIS

The pharmaceutical costs of treating newly diagnosed epilepsy with levetiracetam were found to be higher in comparison to those of comparators. For a 100% treatment coverage, the cost of treatment with lamotrigine, the other second-generation AED under analysis was about R28,4 million cheaper compared to treatment with levetiracetam over a one-year period. Treatment with phenytoin was found to be the cheapest option, costing about R30,1 million less than treatment with levetiracetam. The trends observed under 100% treatment coverage were also observed at 80%, 50% and 10% treatment coverage.

Drug	8568 patients[6] 100% coverage	6854 patients 80% coverage	4284 patients 50% coverage	857 patients 10% coverage
Levetiracetam	R35 352 047	R28 281 637	R17 676 023	R3 535 205
Carbamazepine	R5 281 576	R4 225 261	R2 640 788	R528 158
Lamotrigine	R6 976 368	R5 581 094	R3 488 184	R697 637
Phenytoin	R5 225 079	R4 180 063	R2 612 539	R522 508
Valproate	R8 127 900	R6 502 320	R4 063 950	R812 790

Table 12: BIA for pharmaceutical costs.

Levetiracetam would still be the most expensive treatment option even with a 50% price reduction.

Drug	50% price	100% price	150% price
Levetiracetam	R17 676 023	R35 352 047	R53 028 070
Carbamazepine	R5 281 576	R5 281 576	R5 281 576
Lamotrigine	R6 976 368	R6 976 368	R6 976 368
Phenytoin	R5 225 079	R5 225 079	R5 225 079
Valproate	R8 127 900	R8 127 900	R8 127 900

Table 13: BIA sensitivity analysis for the cost of levetiracetam.

A reduction in the differences in cost between treatment with levetiracetam and the comparator drugs was observed on inclusion of other health systems costs associated with the treatment of epilepsy, such as the cost of treating Steven-Johnson Syndrome and non-pharmaceutical costs associated with seizure treatment (e.g. inpatient days, emergency room stays, outpatient days and AED collection visits). Levetiracetam was still found to be the costliest treatment option and lamotrigine was now found to be the least costly treatment option.

Drug	8568 patients 100% coverage	6854 patients 80% coverage	4284 patients 50% coverage	857 patients 10% coverage
Levetiracetam	R66 271 794	R53 017 435	R33 135 897	R6 627 179
Carbamazepine	R42 097 810	R33 678 248	R21 048 905	R4 209 781
Lamotrigine	R37 296 164	R29 836 931	R18 648 082	R3 729 616
Phenytoin	R41 160 616	R32 928 493	R20 580 308	R4 116 062
Valproate	R39 051 277	R31 241 021	R19 525 638	R3 905 128

Table 14: BIA for health systems costs from the providers' perspective.

7. INTERNATIONAL RECOMMENDATIONS

NICE (National Institute for Health and Clinical Excellence).

[6] The number of patients that constitute a 100% treatment coverage was calculated as follows; 84% (proportion of South Africans serviced in the public sector) * 0,02% (estimated incidence of epilepsy in South Africa) * 58 620 346 (estimated total population of South Africa in 2019).

The recommended first-line treatment in children, young people and adults with newly diagnosed epilepsy with focal seizures is either carbamazepine or lamotrigine (22). Levetiracetam was not cost-effective at the June 2011 unit costs which were used to inform the treatment guidelines (22). The recommended first-line treatment in children, young people and adults with newly diagnosed epilepsy with generalized tonic-clonic seizures is valproate, with lamotrigine as an option for patients who cannot be given valproate (22). Levetiracetam is only offered as adjunctive therapy to patients with generalized tonic-clonic seizures (22).

CADTH (Canadian Agency for Drugs and Technologies in Health).
The Canadian guidelines for the treatment of newly diagnosed epilepsy state that pharmacological monotherapy should be initiated but do not specify the appropriate agencies to use for each diagnosis (23). The agency conducted a study on the safety and cost-effectiveness of levetiracetam in the treatment of epileptic patients which was non-conclusive with regards to the cost-effectiveness of levetiracetam (23).

SIGN (Scottish Intercollegiate Guidelines Network).
For the treatment of focal epilepsy in the Scottish public health sector, lamotrigine is recommended and is the preferred drug relative to carbamazepine (24). The guidelines acknowledge the presence of clinical trial evidence that levetiracetam can also be used as monotherapy for the treatment of focal epilepsy (24). In the treatment of genetic generalized epilepsy lamotrigine and sodium valproate are recommended (24). Levetiracetam is recommended as first-line treatment in some instances, for example in women of reproductive age (24).

8. DISCUSSION

Key limitations of this analysis include the absence of context specific effect measures and context specific utilization rates. This leads to the assumption that utilization rates in a LMIC like South Africa are the same as those observed in high income countries from which data on utilization rates was obtained.

The effect sizes of all the treatments under analysis were similar, with a difference of 0,04 QALYs between the most effective and the least effective treatment option. This led to costs being the main driver of the resulting ICER values. Although levetiracetam, together with phenytoin had the lowest values for non-pharmaceutical costs associated with the treatment of epilepsy, the high pharmaceutical costs of the drug led to its dominance by lamotrigine. Approximately a 93% price reduction is required for levetiracetam to be more cost-effective than lamotrigine.

The cost of treating Steven-Johnson Syndrome was also included in the analysis, with a single case costing R65 855, but due to the low prevalence of the condition, this cost had a lower impact on the ICER values compared to pharmaceutical costs. Levetiracetam and valproate did not incur the costs associated with the treatment of this side effect.

For the sensitivity analysis, ICER values were obtained for levetiracetam relative to lamotrigine. The quality of life measures included in the sensitivity analysis showed no trends with regards to the resulting ICERs. Changes in the quality of life values for both the “uncontrolled” and “controlled on treatment” groups impacted both levetiracetam and lamotrigine, though to different extents. The lower quality of life value for the “controlled on treatment” group resulted in a positive ICER value for levetiracetam due to the negative incremental effect observed due to the comparatively lower proportion of patients in the “controlled on treatment” group for the levetiracetam treatment strategy. The upper quality of life value for the “uncontrolled” group also resulted in a positive ICER

for levetiracetam due to the negative incremental effect observed due to the comparatively higher proportion of patients in the "uncontrolled" group for levetiracetam. No trend was observed due to the changes in the ICER sign associated with varying the HRQoL values and the varying impact of those values for both treatment options under analysis.

The model results agree with the study by Wilby et al 2005, which was conducted to inform the NICE treatment guidelines, which found that levetiracetam was not cost-effective. Lamotrigine is recommended for the treatment of both partial and generalized tonic-clonic seizures by both NICE and SIGN. It is the only drug recommended for the treatment of both indications, with carbamazepine also being recommended for the treatment of partial seizures and valproate for the treatment of generalized tonic-clonic seizures.

In conclusion, levetiracetam was found to not be a cost-effective treatment option for both generalized tonic-clonic seizures and partial seizures in the South African public health sector context, even when accounting for the titration period associated with some of the comparators and the drug prevalence of Steven Johnson Syndrome in some of the comparators.

9. REFERENCES

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