HEALTH TECHNOLOGY ASSESSMENT FOR LEVETIRACETAM IN THE TREATMENT OF NEWLY DIAGNOSED EPILEPSY IN THE SOUTH AFRICAN PUBLIC HEALTH SECTOR.

BY ESTHER Z CHANAKIRA (CHNEST004)

SUBMITTED TO THE SCHOOL OF PUBLIC HEALTH AND FAMILY MEDICINE, UNIVERSITY OF CAPE TOWN IN PARTIAL FULFILMENT OF THE REQUIREMENTS FOR THE DEGREE: MASTER OF PUBLIC HEALTH (MPH)

UNIVERSITY OF CAPE TOWN

SEPTEMBER 2019

SUPERVISOR: VIMBAYI MAFUNDA

CO-SUPERVISOR: TOMMY WILKINSON

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ABSTRACT

Epilepsy, a chronic neurological disorder has an estimated prevalence of between 0.4% and 1.0% globally, and 1% in South Africa. Epilepsy has multiple underlying causes including head injuries, vascular insults, hippocampal sclerosis, cortical dysgenesis, drug or alcohol abuse and infectious diseases, such as neurocysticercosis and HIV/AIDS. Causes in South Africa are likely to be infectious due to the high HIV and tuberculosis prevalence. The condition has substantial individual and societal economic impacts, with economic costs ranging from the direct and indirect costs of treatment and loss of productivity due to illness. Primary treatment of epilepsy in the South African public sector is through pharmacotherapy, with monotherapy being preferred to polytherapy. 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 in this analysis which are levetiracetam, lamotrigine, carbamazepine, phenytoin and valproate. The current first-line epilepsy treatment in South Africa is lamotrigine, phenytoin or carbamazepine. Levetiracetam is under consideration for use as a first-line treatment due to the reported minimal serious side effects, its ease of use, linear pharmacokinetics and reduced interaction with other drugs.

The study was model-based and conducted from the providers' perspective, specifically in the South African public health sector. It compared levetiracetam, lamotrigine, carbamazepine, phenytoin and valproate as first-line treatment in focal seizures (International Classification of Diseases (ICD)-10 code: G40.2) and generalized tonic-clonic seizures (ICD-10 code: G40.3). The population considered for the analysis was patients with newly diagnosed epilepsy expected to utilize services in the public health sector. The analysis consisted of a cost-effectiveness analysis and a budget impact analysis. The budget impact analysis was conducted for the first year of treatment for each of the treatment strategies, while the cost-effectiveness analysis was conducted for a five-year period. Both a decision-tree representing the first six months of treatment and a Markov model representing the rest of the treatment period were used for the cost-effectiveness analysis. The methodology for the cost-effectiveness analysis was based on the International Decision Support Initiative (IDSI) reference case. Costs were expressed as South African Rands, 2018 value and effects were expressed as Quality Adjusted Life Years (QALYs). Results were expressed as Incremental Cost-Effectiveness Ratios (ICERs) and sensitivity analyses were performed to cater for uncertainty.

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 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.

Sensitivity analyses were conducted using some levetiracetam-related costs and quality of life values. Both the levetiracetam-related costs used in the sensitivity analyses 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 and the probability of remaining controlled on levetiracetam on the ICER values obtained.

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 R19 million cheaper compared to treatment with levetiracetam over a one-year period. Treatment with carbamazepine was found to be the cheapest option, costing about R20 million less than treatment with levetiracetam. On inclusion of other health systems costs associated with seizure and side-effect treatment levetiracetam was still found to be the costliest treatment option while lamotrigine became the least costly option.

The effect sizes of all the treatments under analysis were similar, with a difference of 0,04 QALYs being observed between the most effective and the least effective treatment option. This led to costs being the main driver of the resulting ICER values. Approximately a 93% price reduction is required for levetiracetam to be more cost-effective than lamotrigine. The model results for the cost-effectiveness analysis agree with the findings from the study conducted to inform the National Institute for Health and Clinical Excellence (NICE) treatment guidelines in the United Kingdom, which found that levetiracetam was not cost-effective. Lamotrigine is recommended for the treatment of both partial and generalized tonic-clonic seizures by the Health Technology Assessment Agencies in the United Kingdom and Scotland. It is the only drug recommended for the treatment of both indications, with carbamazepine

being recommended for the treatment of partial seizures and valproate for the treatment of generalized tonic-clonic seizures.

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 and the drug prevalence of Steven Johnson Syndrome associated with some of the comparators. Lamotrigine is therefore recommended for use as the first-line treatment of epilepsy in the South African public health sector.

ACKNOWLEDGEMENTS

Vimbayi Mafunda and Thomas Wilkinson are acknowledged for their assistance, supervision and guidance in the development of this project. Members of the Health Economics Unit at the University of Cape Town for their technical support in the carrying out of this project. I would also like to acknowledge the contributions by the National Essential Medicines List Committee in the development of the research protocol for this study and technical support throughout the development of this project.

My deep and sincere gratitude to my family for the financial and emotional support provided throughout this period. Thank you for always believing in me and allowing me to follow my dreams. I would also like to thank my friends for all the encouragement and providing distractions when needed.

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Part A: Research protocol

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ABBREVIATIONS

- AED – Antiepileptic Drugs
- CBZ – Carbamazepine
- CEA – Cost-Effectiveness Analysis
- CLB- Clobazam
- GBP – Gabapentin
- HR – Hazard Ratio
- HRQoL – Health-related Quality of Life
- ICER – Incremental Cost-Effectiveness Ratio
- LEV – Levetiracetam
- LMICs - Low and Middle-Income Countries
- LTG – Lamotrigine
- OXC – Oxcarbazepine
- PB- Phenobarbitone
- PHT – Phenytoin
- QALY – Quality Adjusted Life-Year
- QoL – Quality of Life
- TPM – Topiramate
- VPA – Valproate
- YLD – Years of Life lived with Disability.

PART A: RESEARCH PROTOCOL

A cost-effectiveness analysis and budget impact of levetiracetam compared to other available epilepsy pharmacotherapy treatments in the South African public health sector.

Aim

To establish the cost-effectiveness and budget impact of levetiracetam compared to lamotrigine/carbamazepine/phenytoin/valproate as first line treatment for newly diagnosed epilepsy patients in the South African public health sector.

Research question

What is the cost-effectiveness and budget impact of levetiracetam compared to standard care (lamotrigine/carbamazepine/phenytoin/valproate) as first line treatment for epilepsy in the South African public health sector?

The population considered for the cost-effectiveness analysis will be patients with newly diagnosed epilepsy in need of first-line treatment in the South African public sector (1). Although there are multiple algorithms for the treatment of epilepsy in multi-morbid patients and the possibility of moving to second-line treatment in cases where there is treatment failure, this analysis will solely focus on the use of the above stated drugs in first-line treatment regardless of co-morbidities. The study will focus on the treatment of focal seizures (International Classification of Diseases (ICD)-10 code: G40.2) and generalized tonic-clonic seizures (ICD-10 code: G40.3). Results will be presented as costs and effects. Cost will be expressed as South African Rands, 2018 value and will be calculated from the perspective of the South African government. Outcomes will be expressed as Quality Adjusted Life Years (QALYs). Each of the five treatment options will be considered as mutually exclusive, different, independent strategies for the analysis and will be compared to each other. A budget impact analysis will be carried out to inform considerations of affordability from a public-sector provider's perspective for all patients who are eligible for treatment.

Literature review

Background on economic evaluations

Economic evaluations are essential in the health sector decision-making process in order to maximize the benefits obtained from the available resources to society, minimizing opportunity costs (2). This is especially important in the context of low and middle-income countries (LMICs) where opportunity costs of public health programs can be high relative to other needed services in competing sectors (2). The spiralling increase in healthcare costs and the continued development of medical technology has contributed to the need for economic evaluations in health-related decision-making. An economic evaluation is defined as the comparative analysis of two or more alternative courses of action in terms of both their costs and effects (3). Full economic evaluations include; cost-utility analysis (CUA), cost-effectiveness analysis (CEA) and cost-benefit analysis (CBA) (3). A CEA will be performed for this study and it is defined as an analysis whereby costs are related to a single, common effect that may differ in magnitude between the alternative interventions (3). CEAs measure both allocative and technical efficiency in the allocation of resources (4). The methodology for the CEA section of this study will be based on the International Decision Support Initiative (IDSI) reference case (5) which provides a technical guide for economic evaluations. The reference case consists of eleven principles which are transparency, comparators, evidence, study perspective, measure of health outcomes, costs, time horizon and discount rate, heterogeneity, uncertainty, constraints and equity considerations (5).

Principle	**Description**
Transparency	-Requires declaration of all interests by analysts, acknowledgement of limitations to the study and a full and accurate description of the decision problem to be reported (5).
Comparators	-Current practice in the context of the decision problem must be used as comparators in the analysis. -Where possible the best supportive, non-interventional care must be included as a comparator (5).
Evidence	-A transparent, systematic approach in obtaining evidence must be used (5). -Estimates of the clinical effects should be informed through a systematic review of the literature (5)

Study Perspective	-Must be determined prior to the economic evaluation to ensure that data collected is appropriate. -Three possible perspectives for an analysis are; providers' perspective, patients' perspective and the societal perspective. -Societal perspective should be used in an economic evaluation where possible. -Requires analysis to reflect direct costs and health outcomes for the chosen perspective (5).
Measure of Health Outcomes	-A CEA allows for the measurement of both morbidity and mortality, giving a broader measure of the health outcomes (4). -QALYs and Disability Adjusted Life Years (DALYs) are commonly used as multi-dimensional outcomes (4). -Disease specific measures, for example seizure control in epilepsy, can also be used as outcome measures (4). - The IDSI reference case requires a detailed, transparent description of the method used in calculating the chosen outcome measures for the analysis (5).
Measure of Costs	-Involves the identification, quantification and valuation of all resources used in the implementation of a given health intervention (6). -Costs are measured in monetary terms and are determined by the study perspective (4). -The IDSI reference case requires the analysis to include costs that where not incurred in the study settings for trial-based studies but which are likely to be incurred if the intervention is to be rolled out (5). -Analysis should also include estimates of changes in costs due to economies or diseconomies of scale (5).
Time Horizon and Discount Rate	- Time horizon is the duration over which the health outcomes and costs for the study will be calculated (7). -In principle, it should be the period over which the costs and/or effects of the treatment options under analysis are expected to differ and often a patients' lifetime is used to fully capture these differences (3). - The same time horizon must be used for both costs and effects (7). - Discounting is the adjustment of the value of costs and effects incurred in future (over a year after the initiation of the intervention) in order to demonstrate time preference (8).

	-The IDSI reference case requires the use of a 3% annual discount rate for both costs and effects, with additional analyses exploring different rates, including an annual discount rate reflecting the rate for government borrowing (5).
Heterogeneity	-Refers to heterogeneity of the population under analysis. -Should be considered in population subgroups whereby the characteristics of the different populations may influence the absolute health effect, or the costs associated with the intervention (5). -The IDSI reference case requires subgroup analysis to be determined by the evidence base and whether the differences between the populations have an important influence on costs and effects (5).
Constraints	-The IDSI reference case requires that financial constraints be explored through a budget impact analysis. -The budget impact analysis should estimate the implications of implementing the intervention using approximations of disease prevalence and numbers in need of the intervention (5). -Budget impact analysis should also reflect the decision problem and the constituency in which the intervention will be used (5).
Uncertainty	-Can be due to the generalization of results from research settings to other settings, extrapolation of data, sampling of data or choice of analytic method (9). -Sensitivity analysis is used in economic evaluations to cater for uncertainty. -Three types of sensitivity analyses can be used; simple sensitivity analysis, probabilistic sensitivity analysis and threshold analysis. -The IDSI reference case requires that economic evaluations explore all possible sources of uncertainty where feasible (5).
Equity Considerations	-The IDSI reference case requires the use of an appropriate mechanism for the assessment of equity implications regarding an intervention based on the decision problem (5). -There is need for consideration of equity implications at all stages of the evaluation (5).

Table 1: Summary of the IDSI reference case principles.

The decision rule for economic evaluations, specifically CEAs is based on the ICER values obtained. If the ICER of an intervention is equal to or less than a given threshold that represents

"willingness-to-pay", the intervention is considered "cost-effective" and therefore worth implementing (4). The ICERs obtained from an analysis can be plotted on a cost-effectiveness plane as shown in figure 1.

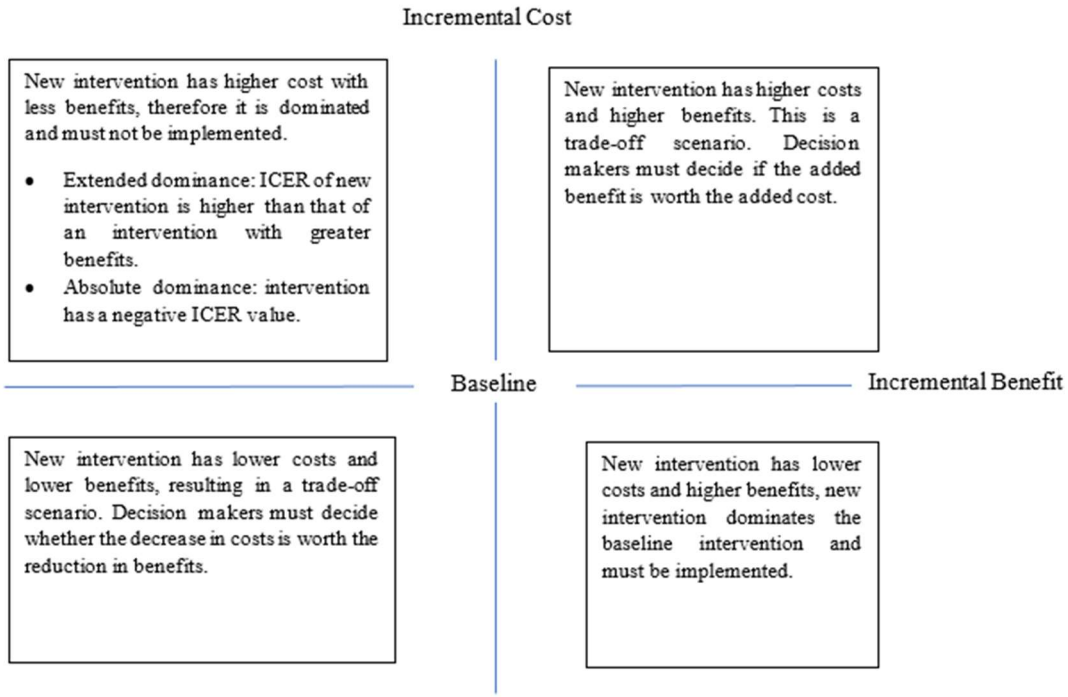

Figure 1: The cost-effectiveness plane and decision-making.

Background on Epilepsy

Epilepsy is a chronic neurological condition associated with considerable morbidity and mortality globally (10). Epilepsy is characterized by recurrent unprovoked seizures, which are brief episodes of involuntary movements and is associated with excess morbidity and mortality, which have been found to be higher in LMICs compared to high income countries (11)(12). Causes of epilepsy-related mortality range from direct causes such as sudden unexpected death in epilepsy (SUDEP) and status epilepticus, and indirect causes such as suicides and complications of antiepileptic drugs (13). Seizures are classified based on their origin in the brain (14). Focal seizures originate in a network localized in one brain hemisphere and may or may not lead to the loss of consciousness (14). Focal seizures can spread to the rest of the brain, resulting in a generalized seizure (secondary generalization) (10). Generalized seizures rapidly engage networks from both sides of the brain and range from brief absence attacks to major convulsions (10). Seizures can also have an unknown origin (14). Epilepsy has multiple

underlying causes including head injuries, vascular insults, hippocampal sclerosis, cortical dysgenesis, drug or alcohol abuse and infectious diseases, such as neurocysticercosis and HIV/AIDS (15)(10). Common causes of epilepsy in South Africa are likely to be infectious (15).

Epilepsy, a chronic neurological disorder has an estimated prevalence of between 0.4% and 1.0% globally, and 1% in South Africa (12)(16). The prevalence of epilepsy is two to three times higher in LMICs compared to high income countries (11). Prevalence is also higher in rural areas within the LMICs compared to urban areas (11). The 2013 global burden of disease study identified uncontrolled epilepsy as one of the diseases associated with a high disability weight (17). Half of the burden attributed to epilepsy is estimated to be due to morbidity, while the other half is due to mortality, signifying the importance of quality of life with regards to the treatment of epilepsy (11). Studies conducted in LMICs suggest that mortality rates are 6 to 9 times higher among people with epilepsy compared to the general population and an increased age-standardized mortality rate of 2 to 3 times that of the general population has also been observed (11). A significant proportion of the burden caused by epilepsy in developing countries can be averted through scaling up the routine availability of cost-effective treatment (18). Epilepsy also has social implications for individuals living with the disease which contributes to a lower quality of life (11). This includes high levels of stigma especially in the African context whereby it is believed that epilepsy is a result of a curse and is a contagious condition in some social circles (11). Epilepsy is also an economic problem, with economic costs ranging from direct and indirect costs of treatment and loss of productivity due to illness (11). A relationship between epilepsy prevalence and social deprivation has also been found (10).

Epilepsy is mostly treated using anti-epileptic drugs (AEDs). The epilepsy treatment gap is defined as the difference between the number of people with active epilepsy and the number of people whose seizures are adequately suppressed, expressed as a percentage (11). The treatment gap has been found to be higher in LMICs compared to high income countries, and in rural areas compared to urban areas (11). In LMICs the treatment gap is about 75% due to multiple factors (12). These factors include lack of skilled health care professionals and the unavailability of AEDs in the health system, the inability of patients to access health facilities, high treatment costs and misconceptions of the causes of epilepsy and fear of stigmatization (11). At least 25% of epilepsy patients continue to have seizures despite optimal treatment with one or more AEDs due to lack of efficacy of available drugs or treatment limitations due to

side effects (14). AEDs can be classified 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 (14). Levetiracetam is under consideration for inclusion on the South African Essential Medicines List due to its favourable side-effect profile and minimal drug interactions. This is especially important considering the high HIV prevalence in South Africa.

Comparison of anti-epileptic agents

Drug	Dose	Mechanism of Action	Indications	Adverse Effects
Lamotrigine	Initially 25mg daily for 2 weeks, then 50mg daily for 2 weeks, thereafter increase by up to 50-100 mg every 1-2 weeks according to response. Usual maintenance dose is 100-200 mg/day up to 500mg/day as required.	Inhibition of the release of the excitatory neurotransmitter glutamate. Sodium channel blockade.	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	Initially 100-200 mg twice daily, with increments of 100-200 mg/day at weekly intervals according to seizure control and adverse effects	Sodium channel blockade.	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	Initially 600mg/day in divided doses, increase by 200mg/day at 3-day intervals until control is achieved. Maximum 2.5g/day	Unknown	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	Initially 150-300 mg daily, after 5-20 days small increments may be made if required. Maintenance range: 5-7mg/kg/day.	Unknown	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 foetal abnormalities.
Levetiracetam	Initially 250 mg twice daily, increasing to initial therapeutic dose of 500mg twice daily. Adjust according to need with 500 mg twice daily every 2-4 weeks. Maximum dose 3g/day	Unknown	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. Infrequent reports of serious side effects such as Steven-Johnson syndrome.

Table 2: Treatment options for newly diagnosed epilepsy under the South African Standard Treatment Guidelines (19).

Comparative clinical effectiveness of levetiracetam

The Komet study (2013) found that time to withdrawal from treatment was not significantly different between levetiracetam and the standard AEDs valproate and carbamazepine for newly diagnosed epilepsy (20). A study by Brodie et al. (2007) found that levetiracetam and controlled-release carbamazepine produced equivalent seizure freedom rates in newly diagnosed epilepsy patients at optimal dosing in a setting mimicking clinical practice (21). No conclusive evidence on the superiority of levetiracetam in the treatment of newly diagnosed epilepsy was found (22).

Comparative costs of AEDs

The acquisition costs of second-generation AEDs as a therapeutic class are higher than those of first-generation AEDs, but their use in clinical practice is justified due to an observed higher rate of seizure control compared to first-generation AEDs (23).

Cost-effectiveness analyses for the treatment of epilepsy using AEDs

Various studies have been conducted to determine the cost-effectiveness of some of the drugs under analysis, below is a summary of some the studies which have been identified. A study conducted in the WHO developing subregions comparing first generation AEDs found that phenytoin and phenobarbitone were the most cost-effective treatment options compared to carbamazepine and valproate (18). A study comparing treatment strategies for first- and second-line treatment for newly diagnosed epilepsy found the use of carbamazepine followed by valproate as second-line treatment to be the most cost-effective option (1). Most of the studies identified were carried out in Europe, limiting their applicability in the South African setting due to differences in economic status, quality of life and availability of resources. Both trial-based and model-based studies were identified and the study perspective for the studies was either the providers' perspective or societal perspective.

Author	Study Setting and population	Perspective	Intervention and comparators	Trial or Model-based EE	Time Horizon and Discount Rate	Cost measures	Effectiveness measures	ICER Calculation	ICER values where applicable and main study findings.
Chisholm (2005) (18)	-WHO developing subregions -Patients with idiopathic epilepsy and epilepsy syndromes.	Providers' Perspective	-PB -PHT -CBZ -VPA	Model-Based using a Markov model with three possible states; healthy and susceptible to epilepsy, diseased and dead.	-10-year time horizon -3% discount rate	International Dollars (I$)	DALYs lost	ICERs for all treatment options were calculated relative to the "Do Nothing Approach".	-ICER range for PHT and PB: I$ 800 – I$ 2,000 per DALY averted. -Average ICER range for CBZ and VPA: I$ 1,100–3,000 per DALY averted. -PHT and PB were found to be the most cost-effective options.
Knoester et al. (2007) (1)	-Data on treatment effects was obtained from literature. - Studies included had a study population of patients ≥12 years with newly diagnosed epilepsy. -Cost data was collected in Netherlands.	Societal Perspective	-CBZ followed by LTG as second line treatment -CBZ followed by VPA as second line treatment -LTG followed by CBZ as second line treatment -LTG followed by VPA as second line treatment -VPA followed by CBZ as second line treatment -VPA followed by LTG as second line treatment	Model-based using a decision tree with three outcome groups; complete success, partial success and failure.	-1-year time horizon -N/A	Euros (€)	-Complete success (defined as a patient being seizure free) -Partial Success (defined as a reduction in seizure rate by at least 50%) -Failure (defined as inadequate seizure control or the occurrence of unacceptable side effects).	ICERs were calculated relative to the previous less costly option. CBZ followed by VPA as second line treatment was used as the reference treatment since it was the least costly.	-The ICER of CBZ followed by LTG relative to the CBZ followed by VPA strategy was €6,079 per additional complete success patient. -The ICER of LTG followed by VPA relative to CBZ followed by VPA was €40,422 per additional complete success patient. -CBZ followed by VPA as second line treatment was found to be the most cost-effective strategy. -Use of LTG as second-line treatment was found to likely be the most cost-effective option in a case were willingness to pay was more than €6000 for an additional complete success patient. -The rest of the strategies where dominated.
Ranjana et al. (2017) (23)	Patients in India with newly diagnosed epilepsy 18 years and older	Societal perspective	-PHT -VPA -CBZ -LEV -OXC -TPM **For each of the first-line treatment options CLB was used as**	Model-based analysis using a decision-tree model with two outcomes; complete success and failure of treatment.	-1-year time horizon -N/A	United States Dollars (US$)	-Complete success -Failure of seizure control	ICER was calculated relative to the previous less costly option. CBZ followed by the addition of CLB was used as the reference treatment since it was the least costly.	-The ICER for TPM with CLB as add on therapy was US$ 764,98 per additional patient with complete success. -The LEV with CLB as add on therapy was the costliest treatment strategy. -The strategies containing PHT, VPA and OXC as first-line treatment were dominated. -TPM with CLB as add on therapy was found to be a cost-effective strategy.

			add on therapy in the case of treatment failure in the first six months of treatment.						-The study concluded that the use of TPM alone, followed by CLB as add on therapy was more cost-effective compared to CBZ alone followed by CLB as add-on therapy, -The WHO threshold was used to determine cost-effectiveness.
Marson et al. (2007) (24) Arm A	-Patients ≥5 years in the United Kingdom who are candidates for epilepsy monotherapy	Providers' Perspective	-CBZ -GBP -LTG -OXC -TPM	Trial-based study	-2-year time horizon -3.5% for costs	Pounds (£)	-QALYs gained -seizures avoided	ICER was calculated relative to the previous less costly option and not based on a baseline. CBZ was considered as the standard treatment.	-Economic analysis supported the use of LTG over CBZ in terms of both cost per seizure avoided and cost per QALY gained. -Results did not support the use of GBP or TPM over the standard treatment of CBZ. -Uncertainty with regards to the comparison of CBZ and OXC.
Marson et al. (2007) (24) Arm B	-Patients ≥5 years in the United Kingdom who are candidates for epilepsy monotherapy	Providers' Perspective	-VPA -LTG -TPM	Trial-based study	-2-year time horizon -3.5% for costs	Pounds (£)	-QALYs gained -seizures avoided	ICER was calculated relative to the previous less costly option and not based on a baseline. VPA was considered as the standard treatment.	-Economic analysis based on cost per seizure avoided supported that VPA should remain the first-choice drug for idiopathic generalized or unclassified epilepsy. -The cost per QALY analysis suggests that there is a high probability that TPM is a cost-effective alternative to VPA

Table 3: Cost-effectiveness analyses on the first-line treatment of epilepsy.

Recommendations by HTA agencies

Institution	Recommendations
National Institute for Health and Clinical Excellence (NICE) (2012)	-First-line treatment in patients with newly diagnosed epilepsy with focal seizures is either carbamazepine or lamotrigine (25). - First-line treatment in patients with newly diagnosed epilepsy with generalized tonic-clonic seizures is valproate, with lamotrigine as an option for patients who cannot be given valproate (25). - Levetiracetam was not cost-effective at the June 2011 unit costs which were used to inform the treatment guidelines and is only offered as adjunctive therapy to patients with generalized tonic-clonic seizures (25).
Canadian Agency for Drugs and Technologies in Health (CADTH) (2011)	-Pharmacological monotherapy is recommended for the treatment of newly diagnosed epilepsy with no drug specifications for each diagnosis (26). - Conducted a study on the safety and cost-effectiveness of levetiracetam in the treatment of epileptic patients which was non-conclusive regarding the cost-effectiveness of levetiracetam (26).
Scottish Intercollegiate Guidelines Network (SIGN) (2018)	-Lamotrigine is preferred to carbamazepine for the treatment of focal epilepsy (27). -Guidelines acknowledge the presence of clinical trial evidence that levetiracetam can also be used as monotherapy for the treatment of focal epilepsy (27). - Lamotrigine and sodium valproate are recommended for the treatment of genetic generalized epilepsy (27). - Levetiracetam is recommended as first-line treatment in some instances, for example in women of reproductive age (27).

Table 4: Summary of recommendations by HTA agencies.

No cost-effectiveness studies on the first-line treatment of epilepsy have been conducted in the South African context or in a similar context using the combination of drugs under analysis. Current first-line epilepsy treatment in South Africa is lamotrigine, phenytoin or carbamazepine (28). There is need to determine the cost-effectiveness of all the available options for AEDs in South Africa due to the vast healthcare needs related to the quadruple burden of disease, scarcity of resources and the demand for efficient use of finances. Interventions implemented into the healthcare sector must be effective, both clinically and economically to ensure access, availability and acceptability of the interventions to patients (23). Some countries are estimated to spend as much as 1% of their total national health care expenditure on epilepsy care and treatment (11). This demonstrates the high healthcare expenditure associated with epilepsy treatment, solidifying the need for evidence-based decision making to maximize the efficient use of resources. Although there is not enough

evidence of a greater effectiveness of levetiracetam in the treatment of newly diagnosed epilepsy, the infrequency of serious side effects, its ease of use, linear pharmacokinetics and lack of interactions with other drugs justifies the need for this analysis (22). 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 (29). An estimated incidence of hypersensitive reactions from AEDs ranges from 1 per 1000 to 1 per 10 000 users (29). Reports have shown carbamazepine, phenytoin, phenobarbitone, and lamotrigine to be connected to hypersensitivity reactions (29).

Methodology

Study design

A cost-effectiveness analysis evaluating first-line treatment strategies in adult patients (18 years and over) with newly diagnosed epilepsy will be conducted along with a budget impact analysis for each possible treatment strategy. A providers' perspective, specifically in the public sector will be adopted for the economic evaluation. A cost-effectiveness analysis will be conducted for the first six months of treatment and will be extended to a five-year period. A decision tree will be used for the analysis over the first six months of treatment and a Markov model will be employed to extend the analysis to a five-year period. Microsoft excel will be used to create both the decision tree and the Markov model.

Decision Tree

A decision tree will be used for the five available treatment strategies with the following outcomes; "controlled on treatment", "controlled off treatment" and "uncontrolled". A controlled patient will be defined as one who is seizure-free from onset of treatment to the end of the six-month period. The decision tree will represent costs and effects for the first six months of treatment.

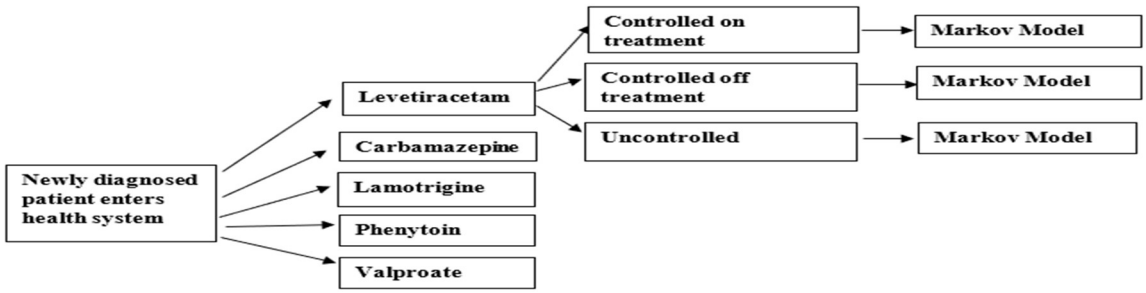

Figure 2: Structure of the decision tree model.

Markov Model

The Markov Model will be used to calculate costs and outcomes for the five-year period. Each Markov state will have a health outcome and cost associated with it (30). Transition probabilities will be used to describe all possible movements between the Markov states and transitions will occur after each Markov cycle (30).

Five iterations of the model will be evaluated based on the following treatment strategies; levetiracetam, lamotrigine, carbamazepine, phenytoin and valproate. The iterations will each have four Markov states; controlled on treatment, controlled off treatment, uncontrolled and dead. The uncontrolled state will represent the costs and health of all patients who have failed first-line treatment. The structure of the model is based on literature and will be validated through clinical expert opinion. Each state will have a health-related quality of life measure (HRQoL), which will be estimated from literature. Transition probabilities will be based on values obtained from the literature. The time horizon used will be five years and a cycle length of 6 months will be used to capture transitions between Markov states (23). Utilization rates of epilepsy-related services will be obtained from studies conducted in the South African context, and if none are found, values will be obtained from similar settings. A 3% annual discount rate on both the costs and the outcomes will be used in accordance with the requirements for the IDSI reference case (5).

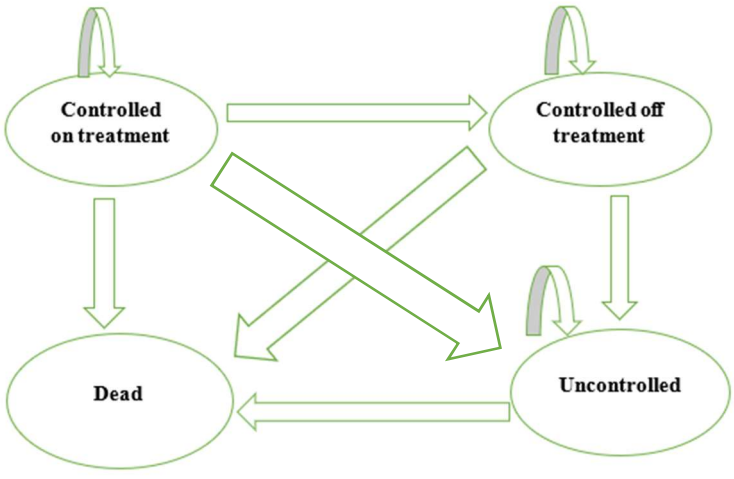

Figure 3: Structure of the Markov model for analysis

Decision model inputs

Collection of data on effects

Effectiveness parameters will be extracted from an unpublished systematic review conducted for the South African National Essential Medicines List Committee (NEMLC) (31). The remaining model parameters will be based on literature data. These include; service cost parameters, pharmaceutical costs, utility values and parameters to determine transition probabilities for the Markov model. The search will not be limited by date. A snowballing approach will be used to identify studies through checking the citations of relevant studies.

Collection of data on costs

Costs will be collected from available literature and secondary sources from a providers' perspective. Costing items willing include; pharmaceutical costs, hospitalization costs and costs associated with the treatment of side-effects. Costs will be obtained from appropriate costing studies on epilepsy treatment and then adapted to the South African context using the following sources and where necessary expert opinion on clinical practice (32);

- Uniform Patient Fee Schedule April 2018 for inpatient costs
- Health Systems Trust Report, District Health Barometer (2017/2018)
- National Health Laboratory Service State Price List for diagnostic costs
- Single Exit Price and National contract circulars for the drug unit prices.

Costs will be expressed as South African Rands (ZAR) in 2018 values.

Review of epilepsy economic evaluations

An iterative snowball search will be conducted to identify economic evaluations on the pharmacological treatment of epilepsy. Both trial-based and model-based evaluations will be included. The following inclusion criteria will be used

- Studies in English looking at an adult population diagnosed with epilepsy;
- Cost-effectiveness and cost-minimization studies on epilepsy treatment with one of the drugs of interest as either a comparator or an intervention;
- Outcomes of interest must include the level of seizure control.

The following exclusion criteria will be used:

- Studies considering seizures that are not identified as having a partial or generalized origin.

A literature table will be used to record information obtained from the studies.

Quality assessment strategy

The Consensus on Health Economics Checklist Extended (CHEC-extended) will be used to determine the quality of economic evaluations included in the review (33).

Data extraction

The following will be extracted onto a data extraction sheet from the eligible studies:

- Study identifiers, which will be authors' names, study title, publication date, journal name, volume, issue, page numbers in publication and place of publication;
- Setting or location of the economic evaluation;
- Information on target population, including gender and age;
- Comparators used in the study, time horizon of study, study perspective, discounting rate for both costs and effects if discounting is applied and type of modelling used if applicable;
- Inflation rates (if applicable), reference year of study, data sources for both costs and effects;
- Details on outcomes;
- Details on cost-effectiveness results and sensitivity analyses.

Cost-effectiveness analysis

An analysis of the decision-tree will be conducted for the first six months of treatment. Costs and effects in the first six months of treatment will be obtained. The values obtained will be fed into the Markov model.

The analysis of the Markov model will result in transition probabilities of a theoretical patient ending up in one of four Markov states; death, controlled on treatment, controlled off treatment and uncontrolled. Treatment outcomes will be extrapolated to effects over a five-year period in the form of QALYs. Based on the transition probabilities, the expected costs of the five treatment options over the five-year period will be determined. Based on this data collected, the interventions will be listed from least expensive to most expensive to determine if there are

any dominated strategies. ICERs will be calculated for the non-dominated strategies, using the previous less costly treatment strategy for comparison. The following formula will be used to calculate the ICER:

$$\text{ICER} = \frac{(mean\ treatment\ cost\ per\ patient)_{strategy\ X} - (\ mean\ treatment\ cost\ per\ patient)_{\ strategy\ (x-1)}}{(Effect\ gained)_{strategy\ X} - (Effect\ gained)_{strategy\ (x-1)}}$$

Results will be presented in tabular form and on a cost-effectiveness plane.

Budget impact analysis

A budget impact analysis will be conducted for each of the five strategies from the providers' perspective for the first year of treatment. The analysis will follow the Principles of Good Practice for ISPOR (International Society for Pharmacoeconomics and Outcomes Research) (34) and will be conducted using Microsoft excel. The five strategies will be treated as mutually exclusive in the analysis. The target population for which the budget impact analysis will be conducted is adult patients with newly diagnosed epilepsy who have access to the South African public health sector. Population size will be determined through data obtained from literature on the prevalence, incidence, utilization rates and death rates related to epilepsy in South Africa where possible. If data specific to South Africa is not found, data from international sources or similar populations will be used. Unit costs will represent the annual healthcare costs of providing treatment for each patient for each strategy and will be calculated based on the direct costs of disease-related treatments and the direct costs of resources required for putting the intervention into effect (35). These resources will include medication, equipment and labour costs (35). Utilization rates will be multiplied by the target population. This value will be multiplied by the unit cost of providing each intervention to get the annual total expenditure for each strategy. Results will be presented in a table as the total costs of adopting each of the five treatment strategies. The computing framework and input data will be validated through expert consultation in the development phase and the verification of costs.

Sensitivity analysis

Sensitivity analyses will be conducted to address uncertainty. One-way sensitivity analyses for both the cost-effectiveness analysis and the budget impact analysis will be performed to cater for possible long-term changes in context in the South African public sector. The results will be presented in the form of tornado diagrams.

Benefit of study to the health system

The results and recommendations from the study can be used in the decision-making process for determining the drugs to be included on the Essential Medicines List (EML) and Standard Treatment Guidelines for first line treatment of epilepsy in South Africa. Following a determination for listing on the EML, Provincial Departments of Health will consider whether and how levetiracetam should be used for the treatment of epilepsy. This study is likely to have a significant impact in the way in which the approximately 6 000 patients with newly diagnosed epilepsy in South Africa are treated in the public health system. The study will also add to the body of knowledge on the cost-effectiveness of the various available epilepsy pharmacotherapy, which is especially important in the context of the developing world where there is scarce research on this and a shortage of resources to conduct the required research.

Conflict of interest

No conflict of interest.

Study limitations

- The translation of the level of seizure control into a HRQoL value.
- A systematic review of the literature on economic evaluations for epilepsy is preferred but will not be conducted due to resource limitation.
- Some of the model parameters used will not be specific to the South African context.
- Assumptions will be used in the modelling process which may not be representative of the heterogenous patterns seen in clinical practice.
- There are no effectiveness studies directly comparing all the drugs under analysis, therefore data will be obtained through indirect comparison from multiple studies.
- Analysis will not consider the impact of co-morbidities on the treatment of epilepsy.

Research outputs/Dissemination of results

- Policy Briefs
- Engagement with policy makers through NEMLC
- Peer reviewed journal article

Ethical considerations

There are no ethical considerations with regards to consent and privacy as the data used for the study will not contain any information which can result in the identification of participants, nor is the study proposing to involve any patient-level primary data collection. The study will adhere to the required international ethical standards, which will be confirmed through ethical approval by the relevant institutions.

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APPENDIX

I) Comparative clinical effectiveness of levetiracetam

Author	Study Setting, Size and Population	Study Design	Study Length	Comparators	Treatment Outcome	Results Obtained
Trinka E et al for the KOMET Study Group 2013 (20)	• Patients ≥16 years of age with ≥2 unprovoked seizures in the previous 2 years and ≥1 in the previous 6 months • Patients were excluded if they had been treated with LEV, VPA or CBZ for any indication or treated for epilepsy with any other AED in the last 6 months • Number of participants: 1688	Unblinded, randomized, superiority trial with a two-parallel-group design	52 weeks	• Extended-release VPA • Controlled-release CBZ	• Time to treatment withdrawal • Time to first seizure.	• Time to treatment withdrawal was not significantly different between LEV and standard AEDs. HR (95% CI) 0.90 (0.74 to 1.08). • Time to first seizure was significantly longer for patients on standard AEDs compared to patients on LEV. HR (95% CI) 1.20 (1.03 to 1.39). • LEV monotherapy was not superior to standard AEDs for the global outcome, namely time to treatment withdrawal, in patients with newly diagnosed focal or generalized seizures
Brodie, M J. et al 2007 (21)	• Adults with ≥2 partial or generalized tonic–clonic seizures in the previous year • Exclusion criteria - pseudoseizures, seizures occurring only in clusters, and clinical or electroencephalographic findings suggestive of idiopathic generalized seizures. • Number of participants: 576	Multicenter, double-blind, non-inferiority, parallel-group trial with a per protocol analysis	56 weeks	• Controlled-release CBZ	• Patients seizure free at last evaluated dose • Withdrawal rates	• LEV (73.0%) and controlled-release CBZ (72.8%) produced equivalent seizure freedom rates in newly diagnosed epilepsy patients at optimal dosing in a setting mimicking clinical practice • Withdrawal rates were higher for CBZ (19.2%) compared to LEV (14.4%)

Table 1: Clinical effectiveness or efficacy of levetiracetam in the treatment of newly diagnosed epilepsy.

II) Results for cost-effectiveness analysis

Strategy	Cost	Effectiveness	ICER
1			
2			
3			
4			
5			

Table 2: Results for cost-effectiveness analysis for the five treatment strategies.

III) Cost-effectiveness plot

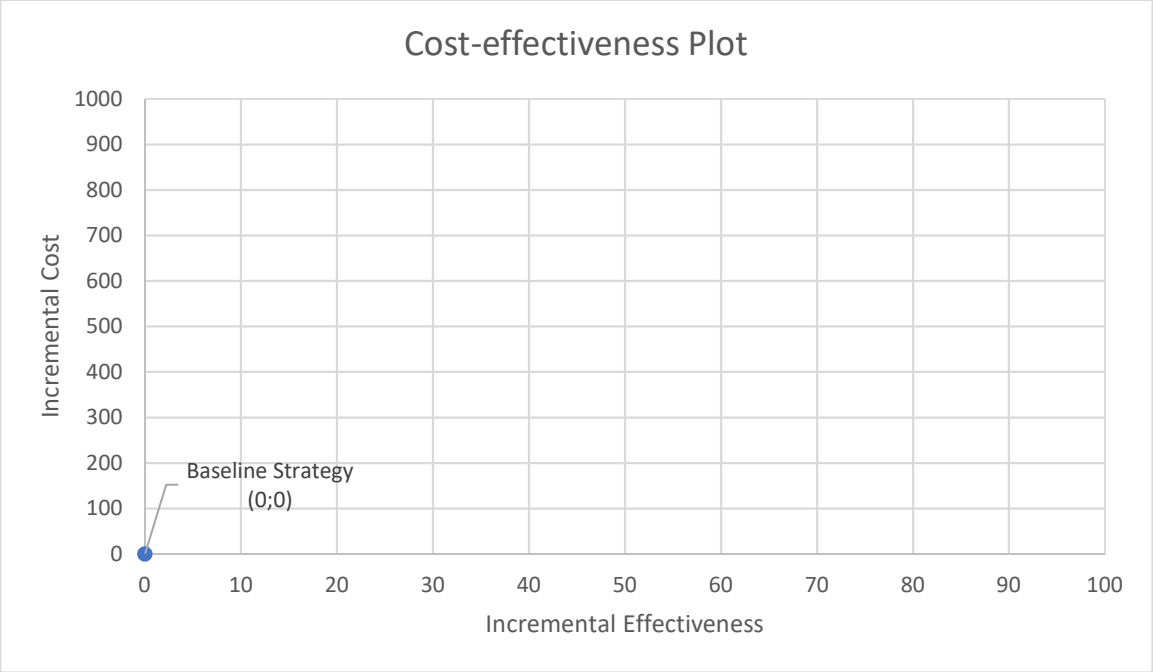

Figure 1: A cost-effectiveness plot showing incremental costs and incremental benefits.

IV) Results for budget impact analysis

	Coverage (%)	**100%**	**80%**	**50%**	**10%**
	Coverage (# of Patients)				
Drug name	Levetiracetam				
	Carbamazepine				
	Lamotrigine				
	Phenytoin				
	Valproate				

Table 3: Budget impact for epilepsy first-line treatment.

PART B: STRUCTURED LITERATURE REVIEW

Objectives of literature review

- To obtain information on the use of economic evaluations in the health sector and the associated limitations.
- To obtain information on the disease process of epilepsy, its economic and social impact and the available treatment options for the disease.
- To obtain information on the overall status of epilepsy in South Africa.
- To obtain information on the current epilepsy treatment practices in South Africa and the drug selection process for the Essential Medicines List.
- To obtain information on economic evaluations that have been conducted on the use of monotherapy in the treatment of epilepsy.
- To identify gaps in the literature and areas where further research is required.

Use of economic evaluations in the health sector

Economic evaluations aim to provide information on the efficiency of interventions, with efficiency being defined as the maximization of health benefits and the minimization of opportunity costs (1). This is especially important in the context of low- and middle-income countries (LMICs) where opportunity costs of public health programs can be high relative to other services needed in competing sectors (2). The spiraling increase in healthcare costs and the continued development of medical technology has contributed to the need for economic evaluations in health-related decision-making. An economic evaluation is defined as the comparative analysis of alternative courses of action in terms of costs and consequences (3). In the health sector, economic evaluations are used for the following purposes; to maximise benefits obtained from health care spending, to overcome regional variations in access, to develop clinical practice guidelines, to contain costs and manage demand and to provide bargaining power with suppliers of health care products (4). There are several types of economic evaluations which include; cost-minimization analysis (CMA), cost-effectiveness analysis (CEA), cost-utility analysis (CUA) and cost-benefit analysis (CBA) (1).

Type of Economic Evaluation	Measurement/Valuation of Costs	Measurement/Valuation of Effects	Advantages of study
Cost-minimization Analysis	Monetary Units	Equal effects, therefore effects are not included in the analysis.	Does not require the measurement of effects.
Cost-effectiveness Analysis	Monetary Units	Effects are measured in natural units. A single outcome of interest common to the interventions under analysis is identified. The outcomes for the interventions under analysis must be quantitatively different.	Measurement of outcomes is not likely to be biased as data on natural units is often readily available.
Cost-utility Analysis	Monetary Units	Effects are in the form of a utility measure, usually "quality-adjusted life-years" (QALYs) or "disability adjusted life-years" (DALYs). Single or multiple effects can be measured, they do not necessarily have to be common to all the alternatives under analysis.	Can be used to ensure allocative efficiency. Comparison can be made across different diseases.
Cost-Benefit Analysis	Monetary Units	Effects are measured in monetary terms. Single or multiple effects can be measured, and the effects do not necessarily have to be common to all the alternatives under analysis.	Easier comparison of costs and effects since both are measured in monetary terms.

Table 1: A comparison of the types of economic evaluations (5)(3) .

A CEA will be conducted for this study, and methodology will be based on the International Decision Support Initiative (IDSI) reference case which provides a technical guide for

economic evaluations (6). The reference case consists of eleven principles which are transparency, comparators, evidence, study perspective, measure of health outcomes, costs, time horizon and discount rate, heterogeneity, uncertainty, constraints and equity considerations (6).

Transparency

Requires the declaration of all interests by analysts, acknowledgement of limitations to the study and the full and accurate description of the decision problem to be reported (6).

Comparators

The reference case requires current practice in the context of the decision problem to be used as a comparator in the analysis, and where possible the best supportive, noninterventional care to be included in the analysis as a comparator (6).

Evidence

A transparent, systematic approach in obtaining evidence must be used in carrying out economic evaluations (6). The estimates of the clinical effects should be informed through a systematic review of the literature (6).

Study Perspective

The study perspective must be determined prior to the economic evaluation to ensure that data collected is appropriate. The three possible perspectives for an analysis are; providers' perspective, patients' perspective and the societal perspective. A societal perspective which is the broadest perspective should be used in an economic evaluation where possible.

Measure of Health Outcomes

The use of a CEA in an economic evaluation allows for the measurement of both morbidity and mortality, giving a broader measure of health outcomes (5). QALYs and DALYs are commonly used as multi-dimensional outcomes in economic evaluations and are considered measures of health (5). QALYs measure an individuals' life-expectancy adjusted by a health-related quality of life (HRQoL) factor, with one year of perfect health being valued as one QALY (5). DALYs measure the years of life lost added to years lived with a disability (YLD). Disease specific outcomes, for example seizure control in epilepsy, can also be used when conducting a CEA (5). The IDSI reference case requires a full, transparent description of the method used in the calculation of the chosen outcome measures for the analysis (6).

Measure of Costs

Costing involves the identification, quantification and valuation of all resources used in the implementation of a given health intervention (7). The costs of all interventions included in the analysis are measured in monetary terms and are dependent on the study perspective (5). A study from a providers' perspective should measure and value the direct medical costs associated with the provision of the intervention. A study from the patients' perspective should include both direct and indirect costs incurred in the provision and use of the intervention. Direct costs include both medical and non-medical costs, while indirect costs include loses due to reduced productivity (5). Intangible costs such as the value of pain and suffering can also be included (5). A societal perspective is inclusive of both the provider and patient costs and considers the economic impact of the condition on society. An ingredients approach or a step-down approach can be used to collect the costs associated with an intervention (5). The ingredients approach is a detailed approach to costing which involves the detailed measurement of all the resources used in the provision of the intervention (5). The step-down method is a more aggregative method of costing which involves estimating the cost of an event using the cost of shared resources that are not directly linked to patient use (5). The costing method used is dependent on the research question. The IDSI reference case requires the analysis to include costs that where not incurred in the study settings for trial-based studies but which will likely be incurred if the intervention is to be rolled out (6). The analysis should also include estimates of changes in costs due to economies or diseconomies of scale (6).

Time Horizon and Discount Rate

Time horizon is the duration over which the health outcomes and costs for the study will be calculated (8). In principle, it should be the period over which the costs and/or effects of the treatment options under analysis are expected to differ and often a patients' lifetime is used to fully capture these differences (9). The same time horizon must be used for both costs and effects (8). Discounting is the adjustment of the value of costs and effects incurred in future (over a year after the initiation of the intervention) in order to demonstrate time preference (10). The IDSI reference case requires the use of a 3% annual discount rate for both costs and effects, with additional analyses exploring different rates, including an annual discount rate that reflects the rate of government borrowing (6).

Heterogeneity

It refers to the heterogeneity of the population under analysis. Heterogeneity should be considered in population subgroups whereby the characteristics of the different populations may influence the absolute health effect, or the costs associated with the intervention (6). The IDSI reference case requires subgroup analysis to be determined by the evidence base and whether the differences between the populations have an important influence on costs and effects (6).

Constraints

The IDSI reference case requires that financial constraints be explored through a budget impact analysis. The budget impact analysis should estimate the implications of implementing the intervention using approximations of disease prevalence and numbers in need of the intervention (6). The budget impact analysis should also reflect the decision problem and the constituency in which the intervention will be used (6).

Uncertainty

Uncertainty can be due to the generalization of results from research settings to other settings, extrapolation of data, sampling of data or choice of analytic method (11). Sensitivity analysis is used in economic evaluations to cater for uncertainty. Three types of sensitivity analyses can be used; simple sensitivity analysis, threshold analysis and probabilistic sensitivity analysis. For simple sensitivity analysis one or more variables are varied across a plausible range to assess the impact of the variables on costs, effects and the resulting Incremental Cost-Effectiveness Ratios (ICERs) (11). Threshold analysis requires the identification of the values of variables at which the decision to implement the intervention might change based on either the maximum budget or the ICER threshold (11). For probabilistic sensitivity analysis uncertainty intervals are captured around all possible variables using a Monte Carlo simulation which involves running the model multiple times using randomly sampled values of the model inputs (12). The IDSI reference case requires the economic evaluation to explore all possible sources of uncertainty where feasible (6).

Equity considerations

Equity in health care is based on the principle that the availability of health care services should be independent of an individuals' ability to pay (5). There are two dimensions to equity which are horizontal and vertical equity. Horizontal equity stipulates that individuals with equal health

care needs should have equal access to health care, while vertical equity stipulates that individuals with different health care needs should be treated differently (5). The IDSI reference case requires the use of an appropriate mechanism for the assessment of equity implications regarding an intervention based on the decision problem (6). It also requires the consideration of equity implications at all stages of the evaluation (6).

The decision rule for economic evaluations, specifically CEAs is based on the ICER values obtained. If the ICER of an intervention is equal to or less than a given threshold that represents "willingness-to-pay", the intervention is considered "cost-effective" and therefore worth implementing (5). The ICERs obtained from an analysis can be plotted on a cost-effectiveness plane as shown in figure 1.

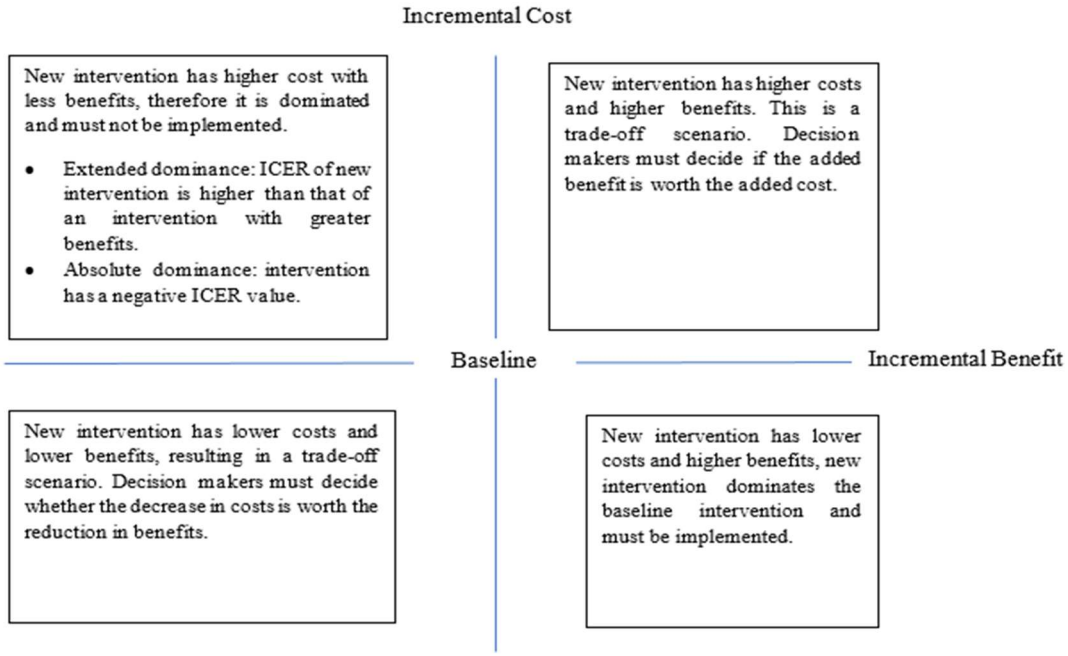

Figure 1: The cost-effectiveness plane and decision-making.

Economic modelling

Decision analytical models are used to compare the expected costs and effects of a decision option through the synthesis of information from multiple sources and the application of mathematical techniques, usually with computer software (13).

Decision trees

Decision trees are the simplest decision analytical model for economic evaluations. The first point of a decision tree is the decision node which represents the decision question (13). The branches from the decision node represent the available intervention options. The pathways that follow each intervention option represent a series of logically ordered alternative events (13). Each set of options emanates from a chance node and the alternatives at each chance node must be mutually exclusive with their probabilities of occurrence adding up to one (13). The end points of each pathway are represented by terminal nodes to which the values for the costs and effects are assigned (13). Decision trees lack explicit time variables; therefore cannot be appropriately used in economic evaluations with time dependent elements (13).

Markov models

In a Markov model patients are assumed to reside in one of a finite number of health states at any point in time and can transition between those health states over several cycles (13). The probability of remaining in a health state/Markov state or moving to another state is dependent on transition probabilities (13). For each cycle the sum of the transition probabilities out of each health state must equal 1 (13). The model must have termination conditions, for example a specific number of cycles, a proportion of the population passing through or accumulating in a health state or the entire population reaching a health state which cannot be exited (absorbing state) (13). An assumption is made that the transition probabilities only depend on the current health state and are independent of historical experience (13). Each health state will have cost and health utility values associated with it. Markov models usually simulate the transition of a hypothetical cohort through the model over time, allowing for the estimation of the expected costs and effects (13). The estimated costs and effects are calculated through the summing up of costs and effects across health states that are weighted by the proportion of the cohort expected to be in each state. The values obtained for each cycle are then summed up to determine the total costs and effects for the model (13).

Limitations of economic evaluations

There is a level of diversity in the methodological requirements for conducting economic evaluations in different settings, making it challenging to compare resulting studies for decision-making and to transfer study results to other settings (14). Decision makers are sceptical about the validity of results obtained from economic evaluations due to the

vulnerability of the studies to bias due to poor availability of quality data, especially in the context of LMICs (14). The IDSI reference case for economic evaluations aids with harmonizing the methodology of economic evaluations and encourages transparency in the conduct of analyses, improving decision-makers confidence in results obtained. Social expectations that health related decisions must be made based on the best interests of the patient also limit the use of economic evaluations (6)(14). These expectations may lead to conflict when deciding on the implementation of an intervention that is not cost-effective or considered to be value for money but can save a life (14).

Due to the use of both QALYs and DALYs as effect measures in CEAs, decision makers are required to compare results from different studies using DALYs and QALYs, with no formula on how to convert one to the other, or information on how the two are comparable. This limits the use of economic evaluations, specifically CEAs in the policy space.

Selection process for medicines for use in the South African public health sector

The National Drug Policy (NDP) for South Africa which was published in 1996 resulted in the establishment of the Essential Drug Program (EDP) which in turn resulted in the formation of a Ministerial appointed National Essential Medicines List Committee (NEMLC) (15). The main objective of the NDP was to improve equitable access to medicines through addressing a range of components including the selection of medicines (16). One of the economic objectives of the NDP is to promote the cost-effective and rational use of medicines and this can be achieved through the use of economic evaluations in the medicine selection process (16). The committee has a multi-professional membership and is responsible for the development of the Standard Treatment Guidelines (STG) and the associated Essential Medicines List (EML) for the primary health care (PHC) and secondary hospital levels of the public sector (15). For the tertiary/quaternary level the EML is a list of recommendations and non-recommendations of treatments for specific conditions which is found on the National Department of Health (NDoH) website (15). Essential medicines are defined as medicines that satisfy the priority health care needs of the population (17). South Africa's first STG/EML was published for PHC in 1996, and 12 editions of PHC, paediatric and adult hospital level STG/EMLs have been published since (15). The process for reviewing chapters of the STG/EML starts with a notice for the request for comments which results in the circulation of the chapter to the appropriate stakeholders (15). The medicines for consideration are selected through the Evidence Based Medicine (EBM) process which looks at the quality, safety, efficacy and cost-effectiveness of the medicine under consideration (15). The technical expert review committee, which is a

support structure for NEMLC reviews the medicines under consideration based on reviewer guidelines and interpret the results obtained from the EBM process and tables recommendations to NEMLC (15). NEMLC then takes the recommendations by the technical expert review committee under consideration and makes the decision regarding the proposed amendments (15). This is then circulated again to stakeholders for comments. The Minister of Health must endorse the decision by NEMLC before the amendment of the STG/EMLs (15). The selection process is dynamic and consists of multi-disciplinary and multi-stakeholder contributions in decision-making (15).

The provincial Pharmacy and Therapeutics Committees (PTCs) form part of the support structures for NEMLC (15). The PTCs have a degree of autonomy as their provincial Member of the Executive Council (MEC) or Head of Department allows the selection of medicines for provincial use that are funded from the provincial budget (16). Decision making regarding the selection of medicines therefore may differ by province, resulting in inequitable access to medicines (16).

Background information on epilepsy

Disease process

Epilepsy is a chronic neurological condition responsible for considerable morbidity and mortality globally (18). Epilepsy is characterized by recurrent unprovoked seizures, which are brief episodes of involuntary movements and is associated with excess morbidity and mortality, which have been shown to be higher in LMICs compared to high income countries (19)(20). Causes of epilepsy-related mortality range from direct causes such as sudden unexpected death in epilepsy (SUDEP) and status epilepticus, and indirect causes such as suicides and complications of antiepileptic drugs (21). Seizures are classified based on their origin in the brain (22). Focal seizures originate in a network localized in one brain hemisphere and may or may not lead to the loss of consciousness (22). Focal seizures can spread to the rest of the brain, resulting in a generalized seizure (secondary generalization) (18). Generalized seizures rapidly engage networks from both sides of the brain and range from brief absence attacks to major convulsions (18). Seizures can also have an unknown origin (22). Epilepsy has multiple underlying causes including head injuries, vascular insults, hippocampal sclerosis, cortical dysgenesis, drug or alcohol abuse and infectious diseases, such as neurocysticercosis and HIV/AIDS (23)(18). Diagnosis of epilepsy is usually through a diagnostic clinical interview and a neurological examination; difficult cases may require an electroencephalogram or

neuroimaging. A diagnostic clinical interview requires a detailed description of the event experienced by the patient prior to, during and after the seizure attack. This also involves interviewing any witnesses of the seizures. This assists with the classification of the seizure type which is essential in determining the appropriate treatment.

HRQoL

Quality of Life is defined as "an individuals' perception of their position in life in the context of the culture and value system in which they live and in relation to their goals, expectations, standards and concerns" (24). HRQoL represents the gap between the reality of an individuals' perception of their health and their expectation (24). Frequency and severity of seizures, presence of psychiatric disorders, polytherapy, side-effects from AEDs and the presence of a comorbidity have been found to be strongly related to a reduced HRQoL (24) (25). Epilepsy significantly impacts an individuals' cognitive and psychological wellbeing, resulting in a decreased health-related quality of life (HRQoL) (25). The frequency and severity of seizures can lead to cognitive dysfunction, which can be reduced or reversed through effective seizure control (25). A study conducted found that the HRQoL, especially social function and seizure worry improved in newly diagnosed epilepsy patients after successful treatment with AEDs for a period of 12 months (25). In this study, the seizure free group demonstrated a 6.7 mean point increase on the Quality of Life in Epilepsy-31 test, while the non-seizure free group demonstrated a 0.3 mean point decrease (25). The incidence of psychiatric disorders in people with epilepsy is also significantly higher than in the general population, with up to 50% to 60% of patients with chronic epilepsy having at least one mood disorder such as depression or anxiety (26). Patients on monotherapy have been found to have a better quality of life due to less medicine-related side effects (27). Clinical counselling, patient education together with community support groups can also assist in addressing some of the psychosocial issues that negatively impact the quality of life of epileptic patients (28).

Epilepsy treatment

Epilepsy has multiple treatment options which include neurostimulation, pharmacotherapy, surgery and the ketogenic diet.

<u>Neurostimulation</u>

Excitability-reducing neurostimulation is used as alternative therapy for refractory epilepsy when pharmacotherapy and surgery have failed or are not indicated (29).

The ketogenic diet

The ketogenic diet is a low-carbohydrate, adequate protein and high-fat diet (30). It has been established as an effective nonpharmacological treatment option for the management of refractory epilepsy (30). Multiple theories have been put forward to explain the efficacy of the ketogenic diet, with one of them being that ketone bodies have similar anticonvulsant activity to that of antiepileptic drugs (30). The brain is an avid user of glucose as a source of energy, but in a carbohydrate restricted diet, the brain no longer uses only glucose for energy, but also starts to oxidise ketone bodies obtained from the fat component of the diet (30). Efficacy of the ketogenic diet is dependent on multiple factors such as the type of seizures, aetiology of the seizures, age of the patient (use is preferred in children between the ages of 2 and 10), compliance with diet and length of follow-up (30). Side effects of the ketogenic diet include; hypoglycaemia, dehydration, poor appetite, nausea, vomiting and constipation (30).

Surgery

Epilepsy surgery is the best treatment for focal refractory epilepsy, especially when it is associated with a focal lesion (31). On average, about 10 percent of epileptics could be considered good candidates for surgery, but fewer than 4% of potential candidates receive surgical treatment due to the invasive and irreversible nature of surgery (31). Although the presurgical evaluation required for epilepsy surgery and the actual surgery cost a lot of money, studies have shown that the benefits achieved in terms of clinical improvements and reduced requirements for medication and medical services in the long-run outweighed the surgical costs, making the intervention cost-effective (31).

Pharmacotherapy

Pharmacotherapy with AEDs is the most common treatment for people with epilepsy. Treatment is long-term , lasting several years and often a lifetime (32). Seizure type, patients' age, gender and comorbidities are some of the factors that should be considered when deciding on the appropriate drug for treatment (32). AEDs can be divided into first- and second-generation drugs. First generation drugs are AEDs that where licensed prior to the 1990s and include phenytoin, valproate and carbamazepine (22). Second-generation AEDs are those approved and registered during and after the 1990s, these include lamotrigine and levetiracetam (22). Second-generation AEDs have been found to generally have better tolerability, improved safety profiles and fewer drug interactions in comparison to first-generation AEDs (22). At least 25% of epilepsy patients continue to have seizures despite optimal treatment with one or

more AEDs due to lack of efficacy of available drugs or treatment limitations due to side effects (22). Monotherapy is advised in the treatment of epilepsy due to drug interactions between some of the AEDs in some instances, for example carbamazepine and lamotrigine, complicating the use of adjunctive therapy (33). Polytherapy should preferably only be used when monotherapy with several alternative drugs has been found to be ineffective (33).

Comparison of anti-epileptic agents

Drug	Dose	Mechanism of Action	Indications	Adverse Effects
Lamotrigine	Initially 25mg daily for 2 weeks, then 50mg daily for 2 weeks, thereafter increase by up to 50-100 mg every 1-2 weeks according to response. Usual maintenance dose is 100-200 mg/day up to 500mg/day as required.	Inhibition of the release of the excitatory neurotransmitter glutamate. Sodium channel blockade.	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 develops within 4 weeks of initiating treatment, which occasionally progresses to severe generalized hypersensitivity reactions such as Steven-Johnson syndrome.
Carbamazepine	Initially 100-200 mg twice daily, with increments of 100-200 mg/day at weekly intervals according to seizure control and adverse effects	Sodium channel blockade.	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	Initially 600mg/day in divided doses, increase by 200mg/day at 3-day intervals until control is achieved. Maximum 2.5g/day	Unknown	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	Initially 150-300 mg daily, after 5-20 days small increments may be made if required. Maintenance range: 5-7mg/kg/day.	Unknown	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	Initially 250 mg twice daily, increasing to initial therapeutic dose of 500mg twice daily. Adjust according to need with 500 mg twice daily every 2-4 weeks. Maximum dose 3g/day	Unknown	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. Infrequent occurrence of serious side effects such as Steven-Johnson syndrome.

Table 2: Treatment options for newly diagnosed epilepsy under the South African Standard Treatment Guidelines (34).

Phenytoin has a narrow therapeutic range therefore has a high potential for toxicity especially in chronic use (35). A change in formulation of phenytoin can also result in toxicity due to the complex pharmacokinetics of the drug, necessitating the maintenance of the same brand in treatment which is challenging in the public health sector (35). Phenytoin, lamotrigine and carbamazepine are associated with Steven-Johnsons syndrome which is potentially life-threatening (35). This is especially a concern in the context of South Africa due to the high prevalence of HIV which increases the risk of getting Steven-Johnson syndrome. Phenytoin and carbamazepine increase the metabolism of hormonal contraceptives, potentially rendering them ineffective (35). This is especially a problem if pregnancy occurs during long-term use of phenytoin as prophylaxis for seizure control as it has teratogenic effects and is associated with low folic acid levels (35). The use of sodium valproate during pregnancy is also associated with congenital malformations (35). Levetiracetam has a favorable pharmacokinetic profile and has no serious side-effects.

Clinical effectiveness and/or efficacy of levetiracetam as first-line treatment in newly diagnosed epilepsy

Author	Study Setting, Size and Population	Study Design	Study Length	Comparators	Treatment Outcome	Results Obtained
Trinka E et al for the KOMET Study Group 2013 (36)	• Patients ≥16 years of age with ≥2 unprovoked seizures in the previous 2 years and ≥1 in the previous 6 months • Patients were excluded if they had been treated with LEV, VPA or CBZ for any indication or treated for epilepsy with any other AED in the last 6 months • Number of participants: 1688	Unblinded, randomized, superiority trial with a two-parallel-group design	52 weeks	• Extended-release VPA • Controlled-release CBZ	• Time to treatment withdrawal • Time to first seizure.	• Time to treatment withdrawal was not significantly different between LEV and standard AEDs. HR (95% CI) 0.90 (0.74 to 1.08). • Time to first seizure was significantly longer for patients on standard AEDs compared to patients on LEV. HR (95% CI) 1.20 (1.03 to 1.39). • LEV monotherapy was not superior to standard AEDs for the global outcome, namely time to treatment withdrawal, in patients with newly diagnosed focal or generalized seizures
Brodie, M J. et al 2007 (37)	• Adults with ≥2 partial or generalized tonic–clonic seizures in the previous year • Exclusion criteria - pseudoseizures, seizures occurring only in clusters, and clinical or electroencephalographic findings suggestive of idiopathic generalized seizures. • Number of participants: 576	Multicenter, double-blind, non-inferiority, parallel-group trial with a per protocol analysis	56 weeks	• Controlled-release CBZ	• Patients seizure free at last evaluated dose • Withdrawal rates	• LEV (73.0%) and controlled-release CBZ (72.8%) produced equivalent seizure freedom rates in newly diagnosed epilepsy patients at optimal dosing in a setting mimicking clinical practice • Withdrawal rates were higher for CBZ (19.2%) compared to LEV (14.4%)

Table 3:Clinical effectiveness or efficacy of levetiracetam in the treatment of newly diagnosed epilepsy.

Comparative costs of AEDs

The acquisition costs of second-generation AEDs as a group are higher than those of first-generation AEDs, but their use in clinical practice is justified because they are more effective in controlling seizures (38).

Economic impact of epilepsy

Epilepsy is associated with multiple challenges for the epileptic individual which includes medical, psychological, social and economic problems (39). Economic problems are associated with both the direct and indirect costs for the treatment of epilepsy. Indirect costs include loss of income due to the reduced productivity associated with morbidity (39). Epileptics have a limited potential in the labour market, with unemployment and underemployment occurring more frequently in epileptics compared to the rest of the population (39). Uncontrolled epileptics also require a lot of care and attention, which may require relatives to devote productive hours to the care of the epileptic, reducing productivity (39). This in turn affects national productivity and, in some instances, returns on investment with regards to the labour market. The estimated percentage of the global burden of disease associated with epilepsy in developing countries is about 90%, while only 20% of all epilepsy related health expenditure is spent in developing countries (39).

Epilepsy in South Africa

The burden of epilepsy in South Africa is largely unknown, but is estimated to be about 1% (40). Two studies conducted in the South African context in the 1960s reported a prevalence of 2.2/1000 and 3.7/1000 (41)(42) . A study conducted on the prevalence of epilepsy in children between the ages of 2 and 9 in rural South Africa found a lifetime prevalence of 7.3/1000 and an active prevalence of 6.7/1000 (43). For the study, active prevalence was defined as the proportion of participants who had experienced an epileptic seizure in the preceding 2 years or had recently been on or was currently on AEDs (43). ‘Lifetime’ prevalence was defined as the proportion of participants with a history of epilepsy (43). Trauma and infectious diseases such as HIV/AIDS and neurocysticercosis are common causes of epilepsy in South Africa (23). Epilepsy usually manifests in HIV positive patients in the advanced stages of the disease and can be a direct result of an HIV infection of the central nervous system, or a result of an opportunistic infection (23). The cultural beliefs and attitudes of both the epileptic and society affects how the disease is treated (23). In the South African context, there are often fears of,

and stigma associated with epilepsy, with widely held beliefs that it is caused by supernatural forces and is contagious (23). This belief in the supernatural origins of epilepsy has fuelled the important role of traditional healers in the management of epilepsy in the rural African setting (44). Given this belief, there is a high likelihood that epileptics combine Western medicine with traditional treatments, which may negatively impact treatment outcomes. This brings rise to a need to accompany pharmacological treatment with patient education. In South Africa epilepsy is mainly treated through pharmacotherapy. The treatment gap for epilepsy in LMICs is estimated to be 75% due to a poor resource base (20). This includes poor infrastructure, insufficient availability of cost-effective drugs and scarcity of trained medical staff (44) On initiating pharmacotherapy, the aim is to use a single anticonvulsant for seizure control (45). The guidelines stipulate that if initial treatment fails, a second medicine must be tried (45). If both drugs fail, and alcohol and poor adherence have been excluded, then combination therapy may be required (45). In the South African public health sector carbamazepine, lamotrigine and phenytoin are the recommended first-line treatments for both partial seizures and generalized tonic-clonic seizures (45). Valproate is used as second-line treatment for patients who do not stabilize on the above stated medicines or who cannot tolerate them (45). Lamotrigine and valproate are the recommended treatments for HIV positive epileptics due to the potential drug interactions with antiretroviral drugs of phenytoin and carbamazepine (45). Levetiracetam is under consideration for inclusion on the South African Essential Medicines List due to its favorable side-effect profile and minimal drug interactions. This is especially important considering the high HIV and hypertension prevalence in South Africa.

Review of economic evaluations for pharmacotherapy in epilepsy

Literature search

Population	Adult patients with newly diagnosed epilepsy
Intervention	Levetiracetam OR Lamotrigine OR Valproate OR Carbamazepine OR Phenytoin OR Anticonvulsants
Comparator	Levetiracetam OR Lamotrigine OR Valproate OR Carbamazepine OR Phenytoin OR Anticonvulsants
Outcome	Economic: • cost per utility measure (QALY, DALY) • cost per seizure-free patient

	• cost per treatment success.

Study inclusion criteria

1. Studies published in English considering human participants.
2. Cost-effectiveness and cost-minimization studies on epilepsy treatment with one or more of the drugs of interest as either a comparator or an intervention as monotherapy.

Study exclusion criteria

1. Studies considering seizures that are not identified as having a partial or generalized origin.
2. Studies solely targeting children and adolescents.
3. Studies including one or more of the drugs under analysis as adjunctive therapy.

Cost-minimization Studies on epilepsy pharmacotherapy

The following table is a summary of the cost-minimization studies

Author & Title	Study Setting and population	Trial or Model-based EE	Perspective	Drugs (daily regimen dose (mg))	Year of Costing	Time Horizon and Discount Rate	Cost collected	Study Findings
Heaney DC et al. (1998) An Economic Appraisal of Carbamazepine, Lamotrigine, Phenytoin and Valproate as Initial Treatment in Adults with Newly Diagnosed Epilepsy (46).	-United Kingdom -Patients > 12 years with newly diagnosed generalized or partial epilepsy.	Model-based study.	Providers' Perspective (NHS)	-CBZ - 600 -LTG - 150 -PHT - 300 -VPA - 1000	1996	Time horizon – 2 years	-Hospital and general practitioner consultations -Side effects cost -Emergency Room attendance -Laboratory tests -Drug withdrawal -Direct drug costs	- The cost of treatment for the two-year period was found to be €795-829 for CBZ, €1,525-2,076 for LTG, €736-768 for PHT, and €868-884 for VPA. -Sensitivity analysis provided similar relative estimates. -Use of LTG for newly diagnosed epilepsy is significantly more expensive compared to the other available choices.
Shakespeare A, Simeon G (1998) Economic analysis of epilepsy treatment: a cost minimization analysis comparing carbamazepine and lamotrigine in the UK (47).	-United Kingdom -Patients > 12 years with newly diagnosed partial and/or generalized tonic-clonic seizures.	Model-based study.	Providers' Perspective (NHS)	-CBZ - 600 -LTG - 150	1994	Time Horizon – 12 months Discount Rate- N/A	-Direct drug costs -Costs associated with adverse effects **N.B**: An assumption was made that the cost of routine care will be the same for both drugs since there was no difference in efficacy.	-Treatment with carbamazepine costs about one-third (£179) of the cost of treatment with LTG (£522) even after considering costs associated with the management of side effects and therapeutic switching.
Heaney DC et al. (2000) Cost Minimization Analysis of Antiepileptic Drugs in Newly Diagnosed Epilepsy in 12 European Countries (48).	-12 countries in Western and Central Europe -Adult patients with newly diagnosed epilepsy	Model-based study.	Societal Perspective (but only considering direct costs)	-CBZ - 600 -LTG - 150 -PHT - 300 -VPA - 1000	-	Time Horizon – 12 months Discount Rate – N/A	-Direct drug costs -Consultation fees -Laboratory tests -Hospital costs	-Direct costs associated with the use of CBZ, PHT and VPA were similar in all countries for all three drugs. -Direct costs associated with the use of LTG were two to four times those of using CBZ, PHT and VPA in each of the countries.

Table 4: A summary of identified cost-minimization studies.

The study conducted by Heaney et al. (1998) investigated the use of carbamazepine, lamotrigine, valproate and phenytoin in the treatment of newly diagnosed epilepsy (46). The study found that the cost of using lamotrigine for treatment was higher than that of the other drugs under analysis. The drug costs of lamotrigine and the costs incurred during the titration period were driving factors in the overall cost of treatment. This study was very robust with extensive sensitivity analysis, with the costing model being applied to all available randomised control trial data (46). The findings from the various combinations of assumptions and modes of analysis were consistent, confirming validity of the study (46). The findings were supported by the cost-minimization study conducted by Heaney et al. (2000) in 12 European countries which found that the direct costs associated with the use of lamotrigine were two to four times the direct costs of using carbamazepine, phenytoin and valproate in each of the countries (48). A cost-minimization study by Shakespeare et al. (1998) in the United Kingdom found that treatment with carbamazepine for newly diagnosed epilepsy cost about one-third (£179) of the cost of treatment with lamotrigine (£522) even after considering costs associated with the management of side effects, supporting the findings by Heaney et al. (2000) in the 12 European countries (47). All the studies identified support the assertation that second-generation AEDs have a higher associated cost of treatment compared to first-generation AEDs.

The treatment model for the study by Shakespeare et al. (1998) also considered second-line treatment in case of treatment failure in the first year of treatment. This inclusion was accounted for in the sensitivity analysis. The study focused on costs incurred in the treatment of side effects and not those incurred in routine care, as an assumption was made that the resources used would be the same due to an assumed equal efficacy. This assumption may have affected the accuracy of the model as routine care for the initiation of carbamazepine therapy is different from that of initiating lamotrigine therapy since the initiation of lamotrigine requires a titration period.

All the studies clearly identified the study setting, treatments under analysis, costs identified, time horizon and were applicable the study perspective was clearly stated. The studies assumed equal efficacy of the AEDs under analysis. All the studies where model-based with the structures of the treatment pathways devised from expert opinion based on clinical practice. The results obtained from the included cost-minimization studies show that first-generation AEDs in epilepsy treatment are less costly compared to second-generation AEDs. Within the first-generation AEDs the treatment costs incurred from the providers' perspective appear to be similar. All the studies found were conducted in the context of the United Kingdom or

Western and Central Europe, considerably affecting transferability of the results to the setting of a LMIC such as South Africa.

Cost-effectiveness analysis for the monotherapy of epilepsy

The studies identified below are cost-effectiveness analysis containing AEDs used as monotherapy in the treatment of epilepsy.

Author	Study Setting and population	Perspective	Intervention and comparators	Trial or Model-based EE	Time Horizon and Discount Rate	Cost measures	Effectiveness measures	ICER Calculation	ICER values where applicable and main study findings.
Chisholm (2005) Cost-effectiveness of first-line antiepileptic drug treatments in the developing world: A population-level analysis (49).	-WHO developing subregions -Patients with idiopathic epilepsy and epilepsy syndromes.	Providers' Perspective	-PB -PHT -CBZ -VPA	Model-Based using a state-transition population model with three possible states; healthy and susceptible to epilepsy, diseased and dead.	-10 years -3% for both costs and effects	International Dollars (I$)	DALYs lost	ICERs for all treatment options were calculated relative to a "Do Nothing Approach".	-ICER range for PHT and PB: I$ 800 – I$ 2,000 per DALY averted. -Average ICER range for CBZ and VPA: I$ 1,100–3,000 per DALY averted. -PHT and PB were found to be the most cost-effective options.
Knoester et al. (2007) A cost-effectiveness decision model for antiepileptic drug treatment in newly diagnosed epilepsy patients (50).	-Data on treatment effects was obtained from literature. - Studies included had a study population of patients ≥12 years with newly diagnosed epilepsy. -Cost data was collected in Netherlands.	Societal Perspective	-CBZ followed by LTG as second line treatment -CBZ followed by VPA as second line treatment -LTG followed by CBZ as second line treatment -LTG followed by VPA as second line treatment -VPA followed by CBZ as second line treatment -VPA followed by LTG as second line treatment	Model-based using a decision tree with three outcome groups; complete success, partial success and failure.	-1 year -N/A	Euros (€)	-Complete success (defined as a patient being seizure free) -Partial Success (defined as a reduction in seizure rate by at least 50%) -Failure (defined as inadequate seizure control or the occurrence of unacceptable side effects).	ICERs were calculated relative to the previous less costly option. CBZ followed by valproate as second line treatment was used as the reference treatment since it was the least costly.	-The ICER of CBZ followed by LTG relative to the CBZ followed by VPA strategy was €6,079 per additional complete success patient. -The ICER of LTG followed by VPA relative to CBZ followed by VPA was €40,422 per additional complete success patient. -CBZ followed by VPA as second line treatment was found to be the most cost-effective strategy. -Use of LTG as second-line treatment was found to likely be the most cost-effective option in a case were willingness to pay was more than €6,000 for an additional complete success patient. -The rest of the strategies where dominated.
Ranjana et al. (2017) Cost-effectiveness analysis (CEA) of Antiepileptic Drug	Patients in India with newly diagnosed	Societal perspective	-PHT -VPA -CBZ -LEV	Model-based analysis using a decision-tree model with two outcomes;	-1 year -N/A	United States Dollars (US$)	-Complete success -Failure of seizure control	ICER was calculated relative to the previous less costly option. CBZ followed by the addition	-The ICER for TPM with CLB as add on therapy was US$ 764.98 per additional patient with complete success.

(AED) Treatment in Newly Diagnosed Patients with Epilepsy : Findings From a Tertiary Care Hospital in India (38).	epilepsy 18 years and older		-OXC -TPM **For each of the first-line treatment options CLB was used as add on therapy in the case of treatment failure in the first six months of treatment.**	complete success and failure of treatment.				of clobazam was used as the reference treatment since it was the least costly.	-The LEV with CLB as add on therapy was the costliest treatment strategy. -The strategies containing PHT, VPA and OXC as first-line treatment were dominated. -TPM with clobazam as add on therapy was found to be a cost-effective strategy. -The study concluded that the use of TPM alone, followed by CLB as add on therapy was more cost-effective compared to CBZ alone followed by CLB as add-on therapy, -The WHO threshold was used to determine cost-effectiveness.
Marson et al (2007) Longer-term outcomes of standard versus new antiepileptic drugs (51). Arm A	-Patients ≥5 years in the United Kingdom who are candidates for epilepsy monotherapy	Providers' Perspective	-CBZ -GBP -LTG -OXC -TPM	Trial-based study	-2 years -3.5% for costs	Pounds (£)	-QALYs gained -seizures avoided	ICER was calculated relative to the previous less costly option and not based on a baseline. CBZ was considered as the standard treatment.	-Economic analysis supported the use of LTG over CBZ in terms of both cost per seizure avoided and cost per QALY gained. -Results did not support the use of GBP or TPM over the standard treatment of CBZ. -Uncertainty with regards to the comparison of CBZ and OXC.
Marson et al. (2007) Longer-term outcomes of standard versus new antiepileptic drugs (51). Arm B	-Patients ≥5 years in the United Kingdom who are candidates for epilepsy monotherapy	Providers' Perspective	-VPA -LTG -TPM	Trial-based study	-2 years -3.5% for costs	Pounds (£)	QALYs gained -seizures avoided	ICER was calculated relative to the previous less costly option and not based on a baseline. VPA was considered as the standard treatment.	-Economic analysis based on cost per seizure avoided supported that VPA should remain the first-choice drug for idiopathic generalized or unclassified epilepsy. -The cost per QALY analysis suggests that there is a high probability that TPM is a cost-effective alternative to VPA
Beghi et al. (2008) Economic analysis of newer antiepileptic drugs (52).	-Patients in the United Kingdom with newly diagnosed epilepsy	Providers' Perspective	-LTG -OXC -CBZ -VPA -PHT -TPM **N.B for generalized seizures valproate was only compared to lamotrigine.**	Model-based study with a probabilistic model	-15 years	Pounds (£)	QALYs gained	ICER was calculated relative to the previous less costly option and not based on a baseline.	-For partial seizures valproate was found to be the most cost-effective treatment option with an ICER of £ 11,731 -LTG was dominated by VPA for the treatment of generalized seizures.
	-Patients in the United Kingdom legible for	Providers' Perspective	-CBZ -VPA -LTG	Model-based study with a probabilistic model	-15 years	Pounds (£)	QALYs gained	ICER was calculated relative to the previous	-Both VPA and LTG were dominated in the analysis for the treatment of partial seizures.

	monotherapy with refractory epilepsy							less costly option and not based on a baseline.	
Remak et al. (2003) A Markov model of treatment of newly diagnosed epilepsy in the UK: An initial assessment of cost-effectiveness of topiramate (53).	-Patients with newly diagnosed partial epilepsy in the United Kingdom	Providers' Perspective (NHS)	-TPM -CBZ -LTG **N.B: All possible combinations of the 3 drugs as first- and second-line treatment were included in the analysis.**	Model-based study using a Markov model with four Markov states; seizure free, not seizure free, switch to new treatment and dead.	-15 years	Pounds (£)	QALYs gained	ICER values were calculated for each strategy relative to all the other strategies under analysis.	-The combinations of TPM and CBZ as first- and second-line treatment were both considered as the most cost-effective treatment options. Both scenarios had similar costs and QALYs gained.
	-Patients with newly diagnosed generalized epilepsy in the United Kingdom	Providers' Perspective (NHS)	-TPM -VPA -LTG **N.B: All possible combinations of the 3 drugs as first- and second-line treatment were included in the analysis.**	Model-based study using a Markov model with four Markov states; seizure free, not seizure free, switch to new treatment and dead.	-15 years -6% for costs -1.5% for effects	Pounds (£)	QALYs gained	ICER values were calculated for each strategy relative to all the other strategies under analysis.	-Topiramate followed by lamotrigine as second-line treatment was found to be the most cost-effective treatment option for the treatment of generalized epilepsy.
Hawkins et al. (2005) Assessing the Cost-Effectiveness of New Pharmaceuticals in Epilepsy in Adults: The Results of a Probabilistic Decision Model (54).	-Patients in the United Kingdom with newly diagnosed partial seizures	Providers' Perspective (NHS)	-CBZ -VPA -LTG -OXC -TPM	Model-based study using a state transition model with the following states; newly diagnosed patients starting on monotherapy, patients switch to another monotherapy when there is non-response, combination therapy on failure to respond to second-line treatment and maintenance therapy in all treatment failure. Death can	-15 years -6% for costs -1.5% for effects	Pounds (£)	QALYs gained	-ICER was calculated relative to the previous less costly option and not based on a baseline.	-QALY values obtained for the various treatment options were very similar with a difference of 0.038 units, demonstrating equal efficacy among the drugs. -The LTG and OXC strategies were found to be dominated by the CBZ, VPA and TPM strategies. -VPA was found to be the most cost-effective treatment option with an ICER of £11,731 per additional QALY.

				occur at any stage in the model.					
	-Patients in the United Kingdom with newly diagnosed generalized epilepsy.	Providers' Perspective (NHS)	-VPA -LTG	Model-based study using a state transition model with the following states; newly diagnosed patients starting on monotherapy, patients switch to another monotherapy when there is non-response, combination therapy on failure to respond to second-line treatment and maintenance therapy in all treatment failure. Death can occur at any stage in the model.	-15 years -6% for costs -1.5% for effects	Pounds (£)	QALYs gained	-ICER was calculated relative to the previous less costly option and not based on a baseline.	-VPA dominates LTG.
Wilby et al. (2003) A rapid and systematic review of the clinical effectiveness, tolerability and cost effectiveness of newer drugs for epilepsy in adults (33).	-Patients in the United Kingdom legible for monotherapy treatment for epilepsy.	Providers' Perspective (NHS)	-VPA -CBZ -LTG -OXC -TPM	Model-based study	-1 year -N/A	Pounds (£)	QALYs gained	-ICER was calculated relative to the previous less costly option and not based on a baseline.	-CBZ, LTG and OXC were dominated. -VPA was the most cost-effective treatment option. -TPM is cost-effective at a high ICER threshold of more than £60,000.
	-Patients in the United Kingdom with refractory epilepsy and are legible for monotherapy	Providers' Perspective (NHS)	-CBA -VPA -LTG	Model-based study	-1 year -N/A	Pounds (£)	QALYs gained	-ICER was calculated relative to the previous less costly option and not based on a baseline.	-CBZ was the most cost-effective option, with the rest of the treatment strategies dominated.

Table 5: A summary on the cost-effectiveness studies identified.

The study by Chisholm (2005) conducted for the WHO in its developing subregions and the study conducted by Ranjana et al. (2017) in India were the only CEAs conducted analysing the use of monotherapy in the treatment of epilepsy in developing countries found during this review. The study by Chisholm (2005) compared the cost-effectiveness of first-generation AEDs in the treatment of idiopathic epilepsy and other epilepsy syndromes (49). It compared the use of phenobarbitone, phenytoin, carbamazepine and valproate (49). The analysis considered both treatment response and patient adherence at different population-level intervention coverages in an attempt to better capture treatment effectiveness (49). Phenytoin and phenobarbitone were found to be the most cost-effective treatment options and the scaling up of treatment coverage from 50% to 80% was found to be favourable in the African context (49). A drawback of the study was that all types of epilepsy were treated as one syndrome, therefore there was no consideration for the drug of choice for each seizure type. The study also did not include the costs associated with the treatment of side-effects associated with each treatment option, which may have inevitably affected the analysis as the impact of side-effects on quality of life was considered through the use of disability weights.

The study by Ranjana et al (2017) looked at patients with newly diagnosed epilepsy and compared the use of phenytoin, valproate, carbamazepine, levetiracetam, oxcarbazepine and topiramate as first-line agents followed by the addition of clobazam as an adjunctive in case of treatment failure in the first six months of treatment (38). The results showed that levetiracetam as first-line treatment was the costliest treatment option and topiramate, a second-generation AED, as first-line treatment was the most cost-effective treatment option (38). The cost-effectiveness of topiramate as first-line treatment for newly diagnosed epilepsy was also supported by studies by Remak et al. (2003) and Marson et al (2007) (51)(53). The study by Wilby et al. (2003) concluded that the use of topiramate may be cost-effective in a context with a high willingness to pay threshold (33). Studies by Ranjana et al (2017) and Knoester et al (2007) were conducted from a societal perspective providing a more holistic picture of the economic burden exerted by epilepsy and the impact of each treatment option on society. These studies also used disease specific outcomes reducing the level of uncertainty by avoiding the conversion of disease specific outcomes to universal outcomes. Although this can be an advantage for the analysis, it limits the comparability of the obtained results to the other studies identified in this analysis and in the health system.

Prior to running an integrated cost-effectiveness model, Wilby et al. (2003) conducted a systematic review of economic evaluations for monotherapy in the treatment of epilepsy and

identified four studies with similar findings that even when the most optimistic treatment scenario for the newer AEDs was compared to the worst-case scenario for the older drugs, monotherapy with the older drugs was considerably less costly, and therefore concluded that second-generation AEDs should not be used as first-line therapy for newly diagnosed epilepsy patients (33). None of these studies identified included levetiracetam as a comparator. Beghi et al (2008) also conducted a systematic review before conducting an integrated analysis which reached the same conclusions as those reached by the systematic review by Wilby et al. (2003). The only exception was the finding by Beghi et al (2008) that the use of topiramate over a fifteen-year time horizon dominated all first- and second-generation AEDs under analysis.

Overall the studies that contained both first- and second-generation AEDs in the analysis did not provide conclusive evidence as to whether first-generation AEDs as a therapeutic class are more cost-effective compared to second-generation AEDs. Topiramate was found to be cost-effective in scenarios where there was a high willingness to pay threshold. The findings from the SANAD study by Marson et al. (Arm A) (2007) supported the use of lamotrigine as first-line treatment over the use of carbamazepine (51). The study conducted in the United Kingdom by Wilby et al (2003) found valproate to be the most cost-effective monotherapy for epilepsy and carbamazepine to be the most cost-effective option for refractory epilepsy (33). The study by Hawkins et al. (2005) also included an analysis of the use of the drugs under analysis as adjunctive therapy in refractory epilepsy for partial seizures and found oxcarbazepine to dominate the other treatment options (54).

The comparison of the various studies identified in this review was challenging due to the differences in study design, study populations and the cost items included in the various analyses.

Overall the results from the identified studies do not answer the question currently posed in the South African public health sector of whether levetiracetam is more cost-effective than the current available treatment options. Transferability of the results obtained in the various contexts of these studies to the South Africa context is difficult due to the absence of a willingness to pay threshold in the South African public health sector. There is need for the development of a willingness to pay threshold through the continued use of cost-effectiveness analysis in health-related decision making.

In future studies researchers should consider specifically recruiting patients based on their seizure type since efficacy of some AEDs varies depending on seizure type. Researchers should

also consider the inclusion of sub-group analysis for the cost-effectiveness of AEDs in populations such as pregnant women, lactating women, the elderly and HIV-positive patients especially in the context of South Africa. There is need for prospective trial-based studies to capture accurate information on both the costs and effects associated with the various treatment options. The continued use of conflicting literature from past studies in the development of epilepsy related cost-effectiveness models results in the continued recycling of the high levels of uncertainty associated with the studies.

Recommendations by HTA agencies

NICE (National Institute for Health and Clinical Excellence)

The recommended first-line treatment in patients with newly diagnosed epilepsy with focal seizures is either carbamazepine or lamotrigine (55). Levetiracetam was not cost-effective at the June 2011 unit costs which were used to inform the treatment guidelines (55). The recommended first-line treatment in patients with newly diagnosed epilepsy with generalized tonic-clonic seizures is valproate, with lamotrigine as an option for patients who cannot be given valproate (55). Levetiracetam is only offered as adjunctive therapy to patients with generalized tonic-clonic seizures (55).

CADTH (Canadian Agency for Drugs and Technologies in Health)

The Canadian guidelines for the treatment of newly diagnosed epilepsy, published in 2011, state that pharmacological monotherapy should be initiated but do not specify the appropriate agencies to use for each diagnosis (56). 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 (56).

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 (57). The guidelines published in 2018 acknowledge the presence of clinical trial evidence that levetiracetam can also be used as monotherapy for the treatment of focal epilepsy (57). In the treatment of genetic generalized epilepsy lamotrigine and sodium valproate are recommended (57). Levetiracetam is recommended as first-line treatment in some instances, for example in women of reproductive age (57).

No cost-effectiveness studies on the first-line treatment of epilepsy have been conducted in the South African context or in a similar context using the combination of drugs under analysis. Current first-line epilepsy treatment in South Africa is lamotrigine, phenytoin or carbamazepine (45). There is need to determine the cost-effectiveness of all the available options for AEDs in South Africa due to the vast healthcare needs related to the quadruple burden of disease, scarcity of resources and the demand for efficient use of finances. Interventions implemented into the healthcare sector must be effective, both clinically and economically to ensure access, availability and acceptability of the interventions to patients (38). Some countries are estimated to spend as much as 1% of their total national health care expenditure on epilepsy care and treatment (19). This demonstrates the high healthcare expenditure associated with epilepsy treatment, solidifying the need for evidence-based decision making to maximize the efficient use of resources. 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 (58). An estimated incidence of hypersensitive reactions from AEDs ranges from 1 per 1000 to 1 per 10 000 users (58). Reports have shown carbamazepine, phenytoin, phenobarbitone, and lamotrigine to be connected to hypersensitivity reactions (58). Phenytoin has a narrow therapeutic range therefore a high potential for toxicity especially in chronic use (35). A change in formulation of phenytoin can result in toxicity due to its complex pharmacokinetics, leading to the need to maintain the use of the same brand which is challenging in the public health sector (35). Phenytoin and carbamazepine increase the metabolism of hormonal contraceptives, potentially rendering them ineffective (35). This is especially a problem if pregnancy occurs during the use of phenytoin as it has teratogenic effects and is associated with low folic acid levels (35). Use of sodium valproate during pregnancy is also associated with congenital malformations (35). Levetiracetam has a favorable pharmacokinetic profile and has no serious side-effects. Although there is not enough evidence of a greater effectiveness of levetiracetam in the treatment of newly diagnosed epilepsy, the limited presence of serious side effects, its ease of use, linear pharmacokinetics and lack of interactions with other drugs justifies the need for this analysis (59).

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PART C: JOURNAL ARTICLE

HEALTH TECHNOLOGY ASSESSMENT FOR LEVETIRACETAM IN THE TREATMENT OF NEWLY DIAGNOSED EPILEPSY IN THE SOUTH AFRICAN PUBLIC SECTOR.

ESTHER ZVIKOMBORERO CHANAKIRA

HEALTH ECONOMICS UNIT: SCHOOL OF PUBLIC HEALTH,

FACULTY OF HEALTH SCIENCES,

UNIVERSITY OF CAPE TOWN,

OBSERVATORY,

CAPE TOWN,

WESTERN CAPE.

CHNEST004@myuct.ac.za

ABSTRACT

Introduction: Epilepsy, a chronic neurological disorder has an estimated prevalence of 1% in the South African population and an estimated incidence of 0,2%. Epilepsy has multiple underlying causes including head injuries, vascular insults, hippocampal sclerosis, cortical dysgenesis, drug or alcohol abuse and infectious diseases, such as neurocysticercosis and HIV/AIDS. Causes in South Africa are likely to be infectious due to the high HIV and tuberculosis prevalence. The condition has substantial individual and societal economic impacts, with economic costs ranging from the direct and indirect costs of treatment and loss of productivity due to illness. Primary treatment of epilepsy in the South African public sector is through pharmacotherapy, with treatment using a single anti-epileptic agent being preferred to polytherapy. 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 in this analysis which are levetiracetam, lamotrigine, carbamazepine, phenytoin and valproate. The current first-line epilepsy treatment in South Africa is lamotrigine, phenytoin or carbamazepine. Levetiracetam is under consideration for use as a first-line treatment due to the reported absence of serious side effects, its ease of use, linear pharmacokinetics and reduced interactions with other drugs.

Methods: The study was model-based and conducted from the providers' perspective, specifically in the South African public health sector. It compared levetiracetam, lamotrigine, carbamazepine, phenytoin and valproate as first-line treatment in focal seizures (International Classification of Diseases (ICD)-10 code: G40.2) and generalized tonic-clonic seizures (ICD-10 code: G40.3). The population considered for the analysis was adult patients with newly diagnosed epilepsy expected to utilize services in the public health sector. The analysis consisted of a cost-effectiveness analysis and a budget impact analysis. The budget impact analysis was conducted for the first year of treatment for each of the treatment strategies, while the cost-effectiveness analysis was conducted for a five-year period. Both a decision-tree representing the first six months of treatment and a Markov model representing the rest of the treatment period were used for the cost-effectiveness analysis. The methodology for the cost-effectiveness analysis was based on the International Decision Support Initiative (IDSI) reference case. Costs were expressed as South African Rands, 2018 value and effects were expressed as Quality Adjusted Life Years (QALYs). Results were expressed as Incremental Cost-Effectiveness Ratios (ICERs) and sensitivity analyses were performed to cater for uncertainty.

Results: 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 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.

Sensitivity analyses were conducted using some levetiracetam-related costs and quality of life values. 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 and the controlled on levetiracetam treatment variable on the ICER values obtained.

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 anti-epileptic drug (AED) under analysis was about R19 million cheaper compared to treatment with levetiracetam over a one-year period. Treatment with carbamazepine was found to be the cheapest option, costing about R20 million less than treatment with levetiracetam. On inclusion of other health systems costs associated with seizure and side-effect treatment levetiracetam was still found to be the costliest treatment option while lamotrigine became the least costly option.

Discussion: The effect sizes of all the treatments under analysis were similar, with a difference of 0,04 QALYs being observed 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 had the second lowest value for the 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 model results for the cost-effectiveness analysis agree with the findings from the study conducted to inform the National Institute for Health and Clinical Excellence (NICE) treatment guidelines in the United Kingdom, which found that levetiracetam was not cost-effective. Lamotrigine is recommended for the treatment of both partial and generalized tonic-clonic seizures by the Health Technology Assessment Agencies

in the United Kingdom and Scotland. It is the only drug recommended for the treatment of both indications, with carbamazepine being recommended for the treatment of partial seizures and valproate for the treatment of generalized tonic-clonic seizures.

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 and the drug prevalence of Steven Johnson Syndrome associated with some of the comparators.

Key Words: epilepsy; health technology assessment; budget impact analysis; cost-effectiveness analysis; antiepileptic drugs; levetiracetam; quality adjusted life years; newly diagnosed epilepsy.

INTRODUCTION

Epilepsy is estimated to have a global prevalence of between 0,4% and 1,0% (1). The prevalence of epilepsy in South Africa is largely unknown, but is estimated to be about 1% (2). The condition comprises of different seizure types and syndromes, leading to complexities in determining incidence, prevalence and prognosis of the disease (3)(4). Seizures are classified based on their origin in the brain (5). Focal seizures originate in a network localized in one brain hemisphere and may or may not lead to the loss of consciousness (5). Focal seizures can spread to the rest of the brain, resulting in a generalized seizure (secondary generalization) (3). Generalized seizures rapidly engage networks from both sides of the brain and range from brief absence attacks to major convulsions (3). Seizures can also have an unknown origin (5). This neurological disorder is associated with an increased mortality rate in uncontrolled patients when compared to the general population, with a crude mortality ratio of 3.1 (6). Increased mortality in epileptics can be attributed to direct causes such as sudden unexpected death in epilepsy (SUDEP) and status epilepticus, and indirect causes such as suicides and complications due to antiepileptic drugs (AEDs) (4). Epilepsy has multiple underlying causes including head injuries, vascular insults, hippocampal sclerosis, cortical dysgenesis, drug or alcohol abuse and infectious diseases such as neurocysticercosis and HIV/AIDS (7)(3). Causes in South Africa are likely to be infectious due to the high HIV and tuberculosis prevalence (7). Epilepsy also negatively impacts the patients' quality of life. This is due to the diseases' significant impact on an individuals' cognitive and psychological wellbeing (8). Frequency and severity of seizures, presence of psychiatric disorders, polytherapy, side-effects from AEDs and the presence of a comorbidity have been found to contribute to a reduced quality of life (9)(8). A study conducted in Korea published in 2015 found that health-related quality of life (HRQoL), especially regarding social function and seizure worry improved in newly diagnosed epilepsy patients after successful treatment with AEDs for a period of 12 months (8). The incidence of psychiatric disorders in people with epilepsy is also significantly higher than in the general population, with between 50% and 60% of patients with chronic epilepsy having at least one mood disorder such as depression or anxiety (10). Epilepsy also has social implications for individuals living with the condition. This is especially true in the African context were there are high levels of stigma associated with the disease due to the belief that the disease is contagious and a result of a curse (11).

Epilepsy has multiple treatments including pharmacotherapy, surgery, neurostimulation and the ketogenic diet. Epilepsy surgery is the best treatment for focal refractory epilepsy,

especially when it is associated with a focal lesion (12). When surgery and pharmacotherapy have failed or are not indicated, excitability-reducing neurostimulation is used as alternative therapy for refractory epilepsy (13). The ketogenic diet has been established as an effective non-pharmacological treatment option for the management of refractory epilepsy, especially in children between the ages of two and ten (14). Treatment of epilepsy is primarily through pharmacotherapy with AEDs which can be classified as first- and second-generation drugs. First generation drugs are AEDs that where licensed prior to the 1990s and include phenytoin, valproate and carbamazepine (5). Second-generation AEDs are those approved and registered during and after the 1990s and these include lamotrigine and levetiracetam (5). Second-generation AEDs have been found to have improved safety profiles, better tolerability and fewer drug interactions compared to first-generation AEDs (5). Acquisition costs of second-generation AEDs as a therapeutic class are higher than those of first generation AEDs, but their use in practice is justified because they are more effective in seizure control (15). Monotherapy is advised for the treatment of epilepsy to minimize drug interactions and because monotherapy has been found to be associated with a better quality of life compared to polytherapy due to less side effects (16)(17). The current first-line epilepsy treatment in South Africa is lamotrigine, phenytoin or carbamazepine (18). Polytherapy should preferably only be used when monotherapy with several alternative drugs has been found to be ineffective (16).

At least 25% of epilepsy patients continue to have seizures despite optimal treatment with one or more AEDs due to lack of efficacy of available drugs or treatment limitations due to side effects (5). Some AEDs such as phenytoin, carbamazepine, lamotrigine and levetiracetam may cause hypersensitivity reactions in patients who are susceptible, for example those with a weakened immune system due to HIV (19). Hypersensitive reactions include Steven Johnson Syndrome, a rare but serious disorder of the skin associated with painful red blisters and can lead to death (20). Phenytoin has a narrow therapeutic range, resulting in an increased likelihood of toxicity in chronic use (21). Phenytoin and carbamazepine increase the metabolism of hormonal contraceptives, potentially rendering them ineffective (21). This is especially a problem if pregnancy occurs during the use of phenytoin as it has a teratogenic effect and is associated with low folic acid levels (21). Use of valproate during pregnancy is also associated with congenital malformations (21). Lamotrigine, together with carbamazepine and valproate are titrated to optimal dose on treatment initiation, in order to minimize adverse events and improve tolerability, leading to an increase in the associated treatment costs due to increased hospital visits (22). Titration of AEDs can also potentially lead to lower adherence

due to an increased patient load with regards to hospital visits (22). The titration process is also associated with higher health care resource use given the increased number of hospital visits, which is not ideal in the resource constrained setting of the South African public health sector (22). Suboptimal AED dosing during the titration period may also result in breakthrough seizures, further exacerbating costs.

Epilepsy also presents an economic problem both at a micro- and macro- level, with some countries being estimated to spend as much as 1% of their total national healthcare expenditure on epilepsy treatment (11). At a personal level epileptics have limited potential in the labour market, with unemployment and underemployment occurring more frequently in epileptics compared to the rest of the population (23). Uncontrolled epileptics also require a lot of care and attention, which may require relatives to devote productive hours to the care of the epileptic, reducing productivity (23). The estimated percentage of the global burden of disease associated with epilepsy-related morbidity and mortality found in developing countries is about 90%, while only 20% of all epilepsy related health expenditure is spent in developing countries (23). This, together with other factors such as poor infrastructure and scarcity of trained medical staff, has resulted in an estimated treatment gap for epilepsy in low- and middle-income countries (LMICs) of 75% (24). To ensure the efficient use of limited resources for epilepsy, especially in developing countries, there is need for economic evaluations to ensure that cost-effective treatments are funded. An economic evaluation is defined as the comparative analysis of alternative courses of action in terms of costs and consequences (25). In the health sector, economic evaluations are utilized for the following purposes; to maximise benefits obtained from health care spending, to overcome regional variations in access, to develop clinical practice guidelines, to contain costs and manage demand and to provide bargaining power with suppliers of health care products (26). Most economic evaluations conducted on the treatment of epilepsy were conducted in European settings, limiting their applicability in the South African context, due to differences in socio-economic conditions and availability of health care resources. A study conducted within the World Health Organization (WHO) developing subregions comparing first generation AEDs found that phenytoin together with phenobarbitone were the most cost-effective treatment options compared to carbamazepine and valproate (27). Another study was conducted in India, evaluating the cost-effectiveness of first- and second-line treatment strategies for newly diagnosed epilepsy. The study found the use of carbamazepine followed by valproate as second-line treatment to be the most cost-effective strategy (28).

This study was conducted to determine whether levetiracetam is cost-effective compared to carbamazepine, lamotrigine, phenytoin and valproate as first-line treatment for newly diagnosed epilepsy in the South African public sector. The study focused on the treatment of focal seizures (ICD-10 code: G40.2) and generalized tonic-clonic seizures (ICD-10 code: G40.3) (18). No cost-effectiveness studies on the first-line treatment of epilepsy have been conducted in South Africa or any other LMIC context using the combination of drugs under analysis.

METHODS

The study population was epileptic adult South Africans expected to be serviced by the public health sector. The study protocol was reviewed by the Human Research Ethics Committee at the University of Cape Town (HREC REF: 362/2019). A cost-effectiveness analysis (CEA) was conducted to evaluate first-line treatment strategies in patients with newly diagnosed epilepsy over a five-year period and a budget impact analysis was conducted for each possible treatment strategy for the first year of treatment. The cost-effectiveness analysis was conducted in the form of a decision-tree for the first six months of treatment and this was extended through a Markov model to a five-year period. Methodology for the cost-effectiveness analysis was based on the International Decision Support Initiative (IDSI) reference case (29), while the budget impact analysis followed the Principles of Good Practice for ISPOR (International Society for Pharmacoeconomics and Outcomes Research) (30). Microsoft excel was used for modelling for both the CEA and the BIA. A providers' perspective, specifically in the public sector was adopted for the economic evaluation.

Data collection

Secondary data was used for the analysis. Data was collected from literature to inform the input parameters for the models, which were in the form of costs and effects.

Effectiveness parameters were primarily extracted from the Adult Expert Review Committee (ERC) levetiracetam medicine review 2019 (Adult ERC Lev MR) (31), any remaining parameters were obtained from literature through an iterative snowball search. Both trial-based and model-based studies published in English were used to inform effectiveness measures. Effects were presented as QALYs, which measure an individuals' life-expectancy adjusted by a health-related quality of life measure, with one year of perfect health being valued as one QALY (32).

Pharmaceutical costs were primarily collected from the Master Procurement Catalogue 2018 of the South African Department of Health. Costs of patient services were mainly obtained from the Health Systems Trust Report, District Health Barometer (2017/2018)(33). Costs that could not be obtained from the above stated sources were collected from international literature and adapted to the South African context and expressed as South African Rands (ZAR), 2018 values. This was done by applying the average currency conversion rates in the year of study to the derived costs, followed by the inflation/deflation of the values obtained to 2018 values. Utilization rates were adopted from the Wilby et al (2005) study conducted in the United Kingdom and were based on the seizure freedom status of the patient (3). Only the direct medical costs associated with the provision of care related to epilepsy were used in the analysis based on the study perspective.

Decision tree model

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. Possible treatment outcomes for each drug were expressed as "controlled on treatment", "controlled off treatment" and "uncontrolled". Each treatment outcome had an associated HRQoL measure and cost value based on the probability of occurrence of the outcome. The effect measure for each treatment outcome was calculated as the product of the probability of occurrence and the value of the associated HRQoL measure. Costs for each outcome were also obtained by multiplying the probability of occurrence and the estimated cost of treatment. A controlled patient was defined as seizure free from treatment onset for the duration of the cycle and an uncontrolled patient was defined as one who has not achieved seizure freedom. The values obtained for both the cost and effect measures for each treatment strategy and possible treatment outcome were transferred to the Markov model.

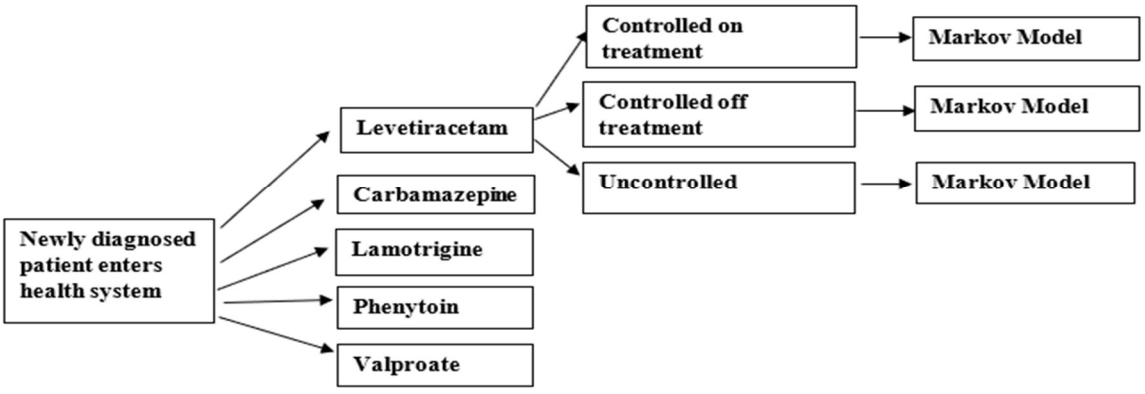

Figure 1: Decision-tree model for the first 6 months of treatment.

Markov model

A Markov Model was used to calculate costs and effects over a five-year period. Each Markov state was associated with a health outcome and a cost value. Five iterations of the model were evaluated based on the following treatment strategies; levetiracetam, lamotrigine, carbamazepine, phenytoin and valproate. The iterations each had four Markov states; controlled on treatment, controlled off treatment, uncontrolled and dead. The structure of the model was based on literature and validated through expert opinion. Each state had an associated HRQoL measure which was obtained from literature (3). Transition probabilities were used to describe all possible movements between the Markov states after each cycle and were calculated based on literature findings. A time horizon of five years and a cycle length of six months were used to capture movement between the Markov states. A 3% discount rate on both costs and effects was used for each subsequent year after the first year of treatment as stipulated by the IDSI reference case (29). Based on the outcome values, the interventions were listed from least expensive to most expensive to determine if there were any strategies that incur higher costs but provided 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. Incremental Cost-Effectiveness Ratios were calculated using the following formula;

$$\text{ICER} = \frac{(mean\ treatment\ cost\ per\ patient)_{strategy\ X} - (mean\ treatment\ cost\ per\ patient)_{strategy\ (x-1)}}{(Effect\ gained)_{strategy\ X} - (Effect\ gained)_{strategy\ (x-1)}}$$

The resulting ICERs were expressed in both tabular form and on a cost-effectiveness plane.

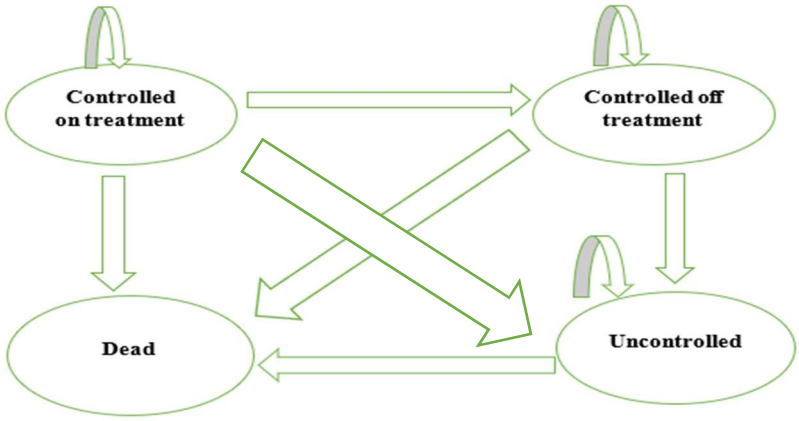

Figure 2: *Structure of the Markov model.*

Budget impact analysis

A budget impact analysis was conducted for each of the five strategies from the providers' perspective over a one-year period. The target population was adult patients with newly diagnosed epilepsy who are serviced by the public sector. This population was estimated by multiplying the estimated adult population size obtained from Statistics South Africa by the estimated incidence rate of epilepsy in South Africa and the estimated percentage of the population that is serviced by the public sector (34)(6). Utilization rates were incorporated in the calculation of both pharmaceutical costs and costs to the health system. The five treatment strategies were treated as mutually exclusive in the analysis. Results were presented in tabular form as the total pharmaceutical, non-pharmaceutical and health systems costs for adopting each of the five treatment strategies.

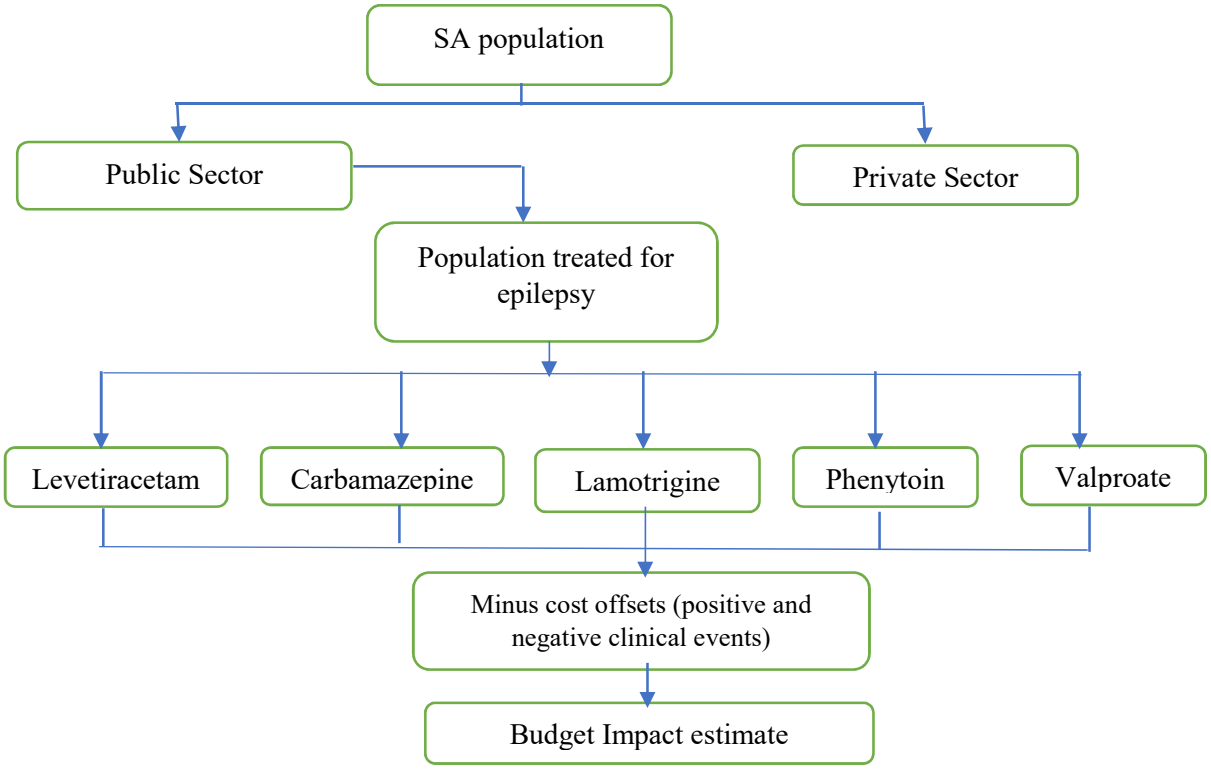

Figure 3: Framework to estimate budget impact of introducing levetiracetam to the South African public health system for the treatment of epilepsy.

Model inputs

Clinical inputs

Probability table

Transition probabilities for death, remission and relapse were obtained from literature. The transition probabilities for a patient remaining controlled were calculated through the multiplication of hazard ratios of the comparator treatment strategies relative to levetiracetam obtained from the Adult ERC LEV MR and the "seizure freedom" proportion obtained from the levetiracetam trial. The rest of the transition probabilities were obtained using probability tables given the condition that the transition probabilities associated with each Markov state must add up to a value of 1.

Description	Value	Source
Probability of death when uncontrolled	0,01085	3.1*Population death-rate Wagner (2015) reported that the risk of mortality for people whose epilepsy is uncontrolled is 3.1 times greater than in the general population. (6)

Probability of going from 'controlled on treatment' to 'controlled off treatment'	0,0425	Wagner (2015) (6)
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	Wagner (2015) (6)
Probability of staying 'controlled on treatment' for LEV	0,43884	Adult ERC Lev MR and Seizure free proportions from LEV trial (35).
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)
Probability of staying 'controlled on treatment' for LTG	0,5019	Adult ERC Lev MR and Seizure free proportions from LEV trial (27)
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)
Probability of staying 'controlled on treatment' for VPA	0,34344	Adult ERC Lev MR and Seizure free proportions from LEV trial (27)
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)
Probability of staying 'controlled on treatment' for PHT	0,34344	Adult ERC Lev MR and Seizure free proportions from LEV trial (27)
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)
Probability of staying 'controlled on treatment' for CBZ	0,34344	Adult ERC Lev MR and Seizure free proportions from LEV trial (27)
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)
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) (36)

Table 1: Key clinical inputs.

Utilities

The long-term outcomes associated with each treatment regimen were calculated by applying an annual estimate of the health-related quality of life value associated with each health state

in the model. The annual utilities which 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) (16)
Controlled off treatment	0,94	Wilby et al (2003) (16)
Uncontrolled (Second Line)	0,84	Wilby et al (2003) (16)
Dead	0	

Table 2: Utility values for each Markov state.

Cost inputs

The main costs included in both the budget impact analysis and the cost effectiveness analysis were associated with the drug procurement costs of the AEDs, drug titration for some treatment options and the hospital costs associated with the treatment of seizures and related events. Costs associated with the diagnosis of epilepsy were not included in the analysis as they would be common to all patients regardless of the resulting treatment choice. Costs were categorized based on whether the patient was controlled or uncontrolled due to the varying utilization rates (3). Per patient costs were calculated by multiplying unit costs by utilization rates.

Utilization rates were obtained from the study by Wilby et al (2005) (3). The average per patient values were calculated by multiplying the expected value for utilization by the probability of use of the services for each patient which was based on seizure freedom status. The number of hospital visits associated with each titration period was based on STG recommendations.

DESCRIPTION	PROBABILITY	VALUE
Inpatient days when controlled	0,01	0,01
Inpatient days when uncontrolled	0,16	0,16
Average length of stay controlled	1,00	5,6
Average length of stay uncontrolled	1,00	8,9
Outpatient visits when controlled	0,18	0,54
Outpatient visits when uncontrolled	0,42	1,26
Emergency room visits controlled	0,02	0,02
Emergency room visits uncontrolled	0,23	0,23
Visits for medication collection	1,00	12
Hospital visits for lamotrigine titration	1,00	6
Hospital visits for carbamazepine titration	1,00	3
Hospital visits for valproate titration	1,00	2

Table 3: Utilization rates for services (3).

DESCRIPTION	COST PER VISIT[a]	ANNUAL UTILIZATION RATE[b]	ANNUAL VALUE[c] (a*b)	VALUE FOR SIX MONTHS (c/2)	SOURCE
Estimated cost for inpatient visits when controlled	R2 803,00	0,056	R156,97	R78,48	Health Systems Trust (33) and Wilby et al (2005) (3)
Estimated cost for inpatient visits when uncontrolled	R2 803,00	1,424	R3 991,47	R1 995,74	Health Systems Trust (33) and Wilby et al (2005) (3)
Estimated cost for outpatient visits when controlled	R450,00	0,54	R243,00	R121,50	Health Systems Trust (33) and Wilby et al (2005) (3)
Estimated cost for outpatient visits when uncontrolled	R450,00	1,26	R567,00	R283,50	Health Systems Trust (33) and Wilby et al (2005) (3)
Estimated cost emergency room visits when controlled	R4 382,88	0,02	R87,66	R43,83	Health Systems Trust (33) and Wilby et al (2005) (3)
Estimated cost emergency room visits when uncontrolled	R4 382,88	0,23	R1 008,06	R504,03	Health Systems Trust (33) and Wilby et al (2005) (3)
Estimated cost for AED visits	R32,00	12	R384,00	R192,00	Administration Pharmacy Cost multiplied by number of monthly visits
Estimated total cost for lamotrigine titration	R38,67	6	R232,02	R232,02	Pharmaceutical costs based on Standard Treatment Guidelines (STG) recommendations
Estimated total cost for carbamazepine titration	R38,67	3	R116,01	R116,01	Pharmaceutical costs based on STG recommendations
Estimated total cost for valproate titration	R38,67	2	R77,34	R77,34	Pharmaceutical costs based on STG recommendations

Table 4: Cost Inputs for the models.

The percentage risk for Steven-Johnson Syndrome was obtained from literature. Treatment of each case of Steven-Johnson Syndrome was estimated to cost R65 855,00 to the health system based on a study conducted in Thailand (20). This value was obtained by applying the 2013 US$ to ZAR exchange rate on the value obtained from the study followed by inflating the value to its South African 2018-rand value (37). The estimated annual cost per patient was calculated by multiplying the percentage risk by the estimated cost of treating each case.

Drug	Percentage Risk (%)	Estimated Annual Cost per Patient	Source
Levetiracetam	0,01	R6,59	UCB Pharma Limited (2019) (35) Frey et al (2017) (38)
Carbamazepine	0,02	R13,17	Frey et al (2017)

			(38)
Lamotrigine	0,05	R29,63	Frey et al (2017) (38)
Phenytoin	0,05	R29,63	Frey et al (2017) (38)
Valproate	0,00	R0,00	

Table 5: Per patient cost of treating Steven-Johnson Syndrome.

Pharmaceutical costs were calculated based on the 2018 tender prices for each drug as informed by the Master Procurement Catalogue (39). The values for "cost per patient for first six months of treatment" incorporated titration schedules as informed by the Standard Treatment Guidelines (STGs) were appropriate. Daily doses were obtained from the Adult ERC Lev MR.

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 1 June 2018
Carbamazepine	1200	200	6	R0,31	168	R51,74	R305,97	R616,43	Master Procurement Catalogue 1 June 2018
Lamotrigine	300	100	3	R0,90	84	R75,60	R330,40	R784,00	Master Procurement Catalogue 1 June 2018
Phenytoin	300	100	3	R0,86	84	R72,24	R433,44	R866,88	Master Procurement Catalogue 1 June 2018
Valproate	1500	500	3	R0,79	84	R66,36	R402,64	R800,80	Master Procurement Catalogue 1 June 2018

Table 6: Pharmaceutical costs associated with each treatment regimen.

Drug	Length of Titration Period (days)	Cost over Titration Period	Reference
Carbamazepine	28	R32,55	STG (18)
Lamotrigine	84	R102,34	STG (18)
Valproate	28	R66,36	STG (18)

Table 7: Pharmaceutical costs over titration period.

The cumulative costs for each Markov health state where calculated as shown in the table below.

Markov State	Cost Calculation
Controlled on treatment	(Pharmaceutical costs + Non-pharmaceutical costs + Cost of treating Steven-Johnson Syndrome) * Probability of patient being in the "controlled on treatment" state
Controlled off treatment	(Non-pharmaceutical costs) * Probability of patient being in the "controlled off treatment" state
Uncontrolled	(A flat fee of R5 000 was added to the non-pharmaceutical costs associated with the uncontrolled state) * Probability of patient being in the "uncontrolled" state
Dead	(Patients in the dead state incurred no costs) * Probability of patient being dead

Table 8: Calculations for costs associated with the Markov model.

Model assumptions for both the CEA and BIA

- The cost per emergency room visit is 1.5 times the cost per "Patient Day Equivalence" (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)
- 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

Sensitivity analysis

Sensitivity analyses were conducted to address uncertainty for the cost-effectiveness analysis using the outputs of the decision-tree. Sensitivity analysis was 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, limiting the number of parameters that could be included in the analysis. The cost values for carbamazepine, lamotrigine, phenytoin and valproate were not included as they were considered fixed based on tender prices. More complex sensitivity analysis, (e.g. probabilistic sensitivity analysis) was beyond the scope of this study. The results obtained were presented in the form of a tornado diagram.

RESULTS

Cost-effectiveness analysis

The expected cost of treatment for a single case of epilepsy over a five-year period was found to range from R63 567 with lamotrigine to R66 970 with carbamazepine. The expected effect size was between 4,01 QALYs and 3,97 QALYs. 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. A dominated strategy is defined as one which costs comparatively more but has a lower health effect (40). 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
Phenytoin	R66 023	3,97	Dominated
Valproate	R66 550	3,97	Dominated
Carbamazepine	R66 970	3,97	Dominated

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

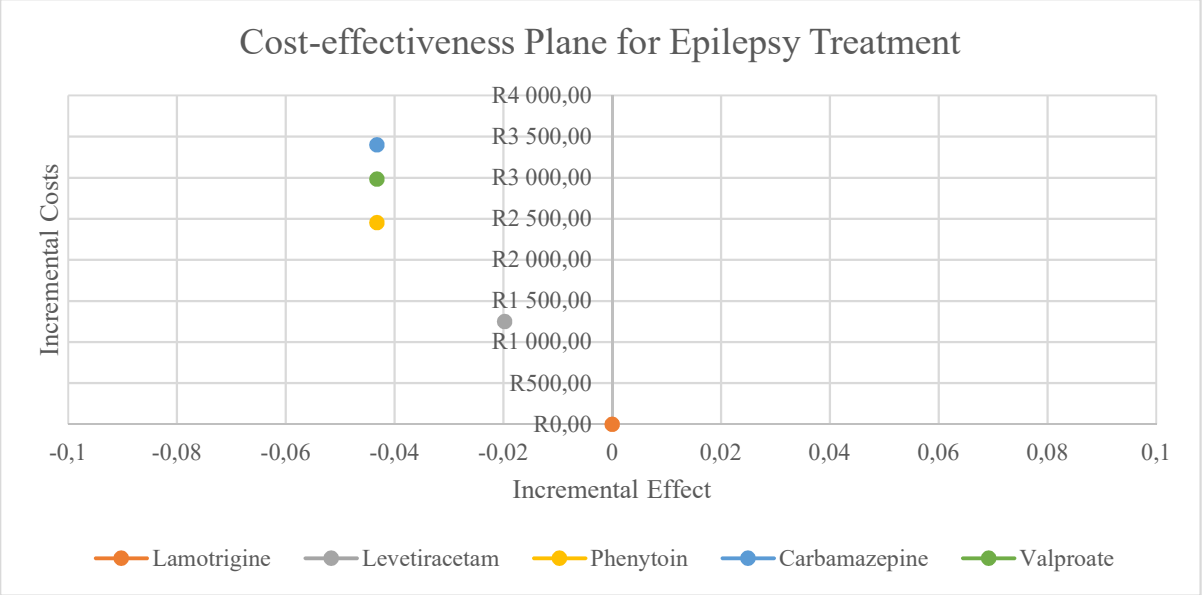

Figure 4: Cost-effectiveness plane for the first-line treatment of epilepsy with levetiracetam.

Sensitivity analysis

Both the levetiracetam-related costs used in the sensitivity analyses 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 and the probability of remaining controlled on levetiracetam.

Parameter	Lower Value	Baseline	Upper Value
HRQoL when "uncontrolled"	0,50	0,84	0,95
HRQoL 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
Controlled on treatment (LEV)	0,33884	0,43884	0,53884

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

	ICER at lower parameter value	ICER at higher parameter value
HRQoL when "uncontrolled"	-R116 856	R5 130 201
HRQoL when "controlled on treatment"	R213 303	-R186 624
LEV- cost input for "controlled on treatment"	-R130 816	-R466 406
LEV unit cost	-R161 711	-R456 208
Controlled on treatment (LEV)	-R187 062	R232 642

Table 11: ICERs obtained from sensitivity analyses.

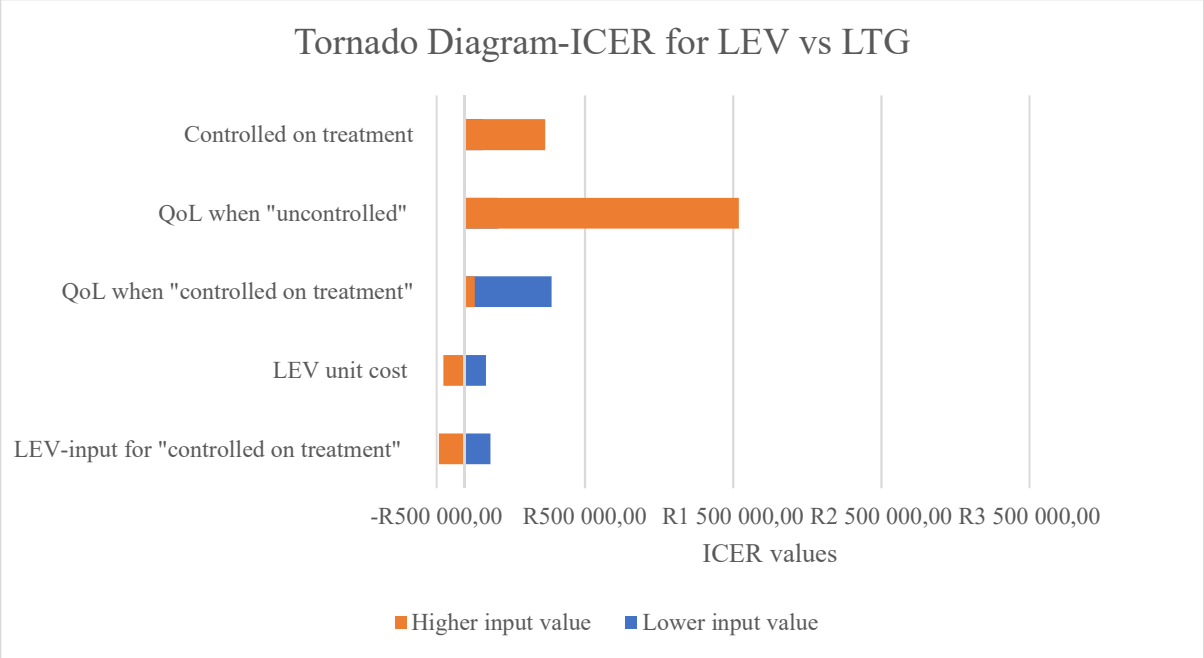

Figure 5: Tornado plot for sensitivity analyses.

Budget impact analysis

The population of interest, which was the number of adult patients with newly diagnosed epilepsy serviced by the South African public health sector was calculated by multiplying the estimated incidence rate by the estimated adult population of South Africa and the estimated proportion of South African serviced by the public health sector.

Parameter	Value	Source
Total adult population	38 923 910	Stats SA (2018) (33)
Estimated incidence rate	0,0174%	Wagner (2015) (6)
Estimated proportion of South Africans serviced by the public sector	84,00%	Health Systems Trust (33)
Estimated population of interest	5 689	

Table 12: Calculation for the estimated population of interest.

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 R19 million cheaper compared to treatment with levetiracetam over a one-year period. Treatment with carbamazepine was found to be the cheapest option, costing about R20 million less than

treatment with levetiracetam. The trends observed under 100% treatment coverage were also observed at 80%, 50% and 10% treatment coverage.

	Coverage (%)	**100%**	**80%**	**50%**	**10%**
	Coverage (no of patients)	5 689	4 551	2 845	569
Drug name	Levetiracetam	R23 473 759	R18 779 007	R11 736 879	R2 347 376
	Carbamazepine	R3 423 336	R2 738 669	R1 711 668	R342 334
	Lamotrigine	R4 453 101	R3 562 481	R2 226 550	R445 310
	Phenytoin	R4 931 783	R3 945 427	R2 465 892	R493 178
	Valproate	R4 530 359	R3 624 287	R2 265 180	R453 036

Table 13: Budget Impact Analysis for pharmaceutical costs in first line treatment of epilepsy.

Levetiracetam would still be the most expensive treatment option even with a 50% price reduction while maintaining the prices of the other drugs.

	Price (%)	**50%**	**100%**	**150%**
Drug name	Levetiracetam	R11 736 880	R23 473 759	R35 210 638
	Carbamazepine	R3 506 966	R3 506 966	R3 506 966
	Lamotrigine	R4 632 308	R4 632 308	R4 632 308
	Phenytoin	R3 469 452	R3 469 452	R3 469 452
	Valproate	R5 396 926	R5 396 926	R5 396 926

Table14: Budget Impact Analysis sensitivity analysis for the cost of levetiracetam in the first-line treatment of epilepsy.

Lamotrigine incurred the least non-pharmaceutical costs associated with epilepsy treatment, followed by levetiracetam, with a difference of R546 886. Carbamazepine incurred the highest costs, followed by valproate. The trends observed at a 100% coverage were also observed at 80%, 50% and 10% coverage.

	Coverage (%)	**100%**	**80%**	**50%**	**10%**
	Coverage (no of patients)	5 689	4 551	2 845	569
Drug Name	Levetiracetam	R20 518 480	R16 414 784	R10 259 240	R2 051 848
	Carbamazepine	R24 244 183	R19 395 346	R12 122 091	R2 424 418
	Lamotrigine	R19 971 594	R15 977 275	R9 985 797	R1 997 159
	Phenytoin	R23 584 188	R18 867 350	R11 792 094	R2 358 419
	Valproate	R24 024 184	R19 219 348	R12 012 092	R2 402 418

Table 15: Non-pharmaceutical costs associated with the treatment of epilepsy.

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 costing about R44 million to the health system and lamotrigine was found to be the least costly treatment option costing about R25 million to the health system. Non-pharmaceutical costs were found to be the cost drivers in the analysis for all the treatment options, except for treatment with levetiracetam. Pharmaceutical costs accounted for 53,3% of the levetiracetam treatment costs.

	Coverage (%)	**100%**	**80%**	**50%**	**10%**
	Coverage (no of patients)	5 689	4 551	2 845	569
Drug Name	Levetiracetam	R44 041 937	R35 233 549	R22 020 968	R4 404 194
	Carbamazepine	R27 757 093	R22 205 674	R13 878 546	R2 775 709
	Lamotrigine	R24 604 055	R19 683 244	R12 302 028	R2 460 406
	Phenytoin	R28 699 209	R22 959 367	R14 349 605	R2 869 921
	Valproate	R25 063 481	R20 050 785	R12 531 741	R2 506 348

Table 16: Budget Impact Analysis for health systems costs from the providers' perspective in first-line treatment of epilepsy.

DISCUSSION

This study was the first cost-effectiveness analysis of anti-epileptic drugs in the South African context and will likely impact the Standard Treatment Guidelines for the first-line treatment of epilepsy in South Africa positively impacting the lives of adult epileptics. The study also contained a Budget Impact Analysis, providing policy makers with budgetary estimates for the implementation of the various treatment options.

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 the 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. First generation AEDs had the same effect value and higher associated costs in the five years of treatment represented by the cost-effectiveness analysis. Costs were found to be the main driver of the

resulting ICER values. 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. Valproate did not incur the costs associated with the treatment of this side effect. Although lamotrigine incurred the cost of treating Steven-Johnson Syndrome, the drug still had the lowest health systems costs. This is due to the higher effectiveness of the drug, which leads to lower costs incurred on treatment of seizures.

Cost-minimization studies conducted in Europe by Heaney et al (2000) found that the direct costs of using lamotrigine in the treatment of newly diagnosed epilepsy were higher than those of using carbamazepine, valproate and phenytoin (41). These finding are not consistent with the findings from the budget impact analysis of this study, which found that the use of lamotrigine incurred the least health systems cost compared to the first-generation AEDs. This highlights the differences in context and pricing, further indicating that the use of studies conducted in developed countries over a different time-period to inform decisions in developing countries may not be appropriate.

An assumption was made in this analysis that the "uncontrolled" state is a broad classification representing the costs and health of patients who have failed first-line treatment. All patients in this state where considered to incur the same cost related to treatment which may not be an accurate depiction of clinical practice, as various options of treatment are available as second-line treatment and beyond. Analysis of costs and health effects associated with treatment post first-line treatment was beyond the scope of this study.

The effect measures for the study were determined by the probabilities of seizure control and the HRQoL measures. The HRQoL values were obtained from a study conducted in the United Kingdom, introducing uncertainty into the analysis due to differences in context which may impact some domains related to quality of life. The impact of this on the study findings was investigated through sensitivity analysis. 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 trends were observed due to changes in the ICER sign associated with varying the HRQoL values and the varying impact of the HRQoL values on both the treatment options under analysis. An increase in the probability of remaining controlled on treatment whilst on levetiracetam was associated with an increase in effect size and a decrease in costs. Although this was observed, there was no trend regarding the ICER values as the change in probability affected both the costs and effects associated with levetiracetam treatment disproportionately.

The model results for the cost-effectiveness analysis 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 (42). The study conducted by the Scottish Intercollegiate Guidelines Network (SIGN) was non-conclusive with regards to the cost-effectiveness of levetiracetam. Lamotrigine is recommended for the treatment of both partial and generalized tonic-clonic seizures by both NICE and SIGN (43)(42). 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.

The absence of a South African specific ICER threshold prevents conclusion in absolute terms on the cost-effectiveness of any of the treatment options. The threshold represents willingness to pay and is ideally the ICER value of the last funded intervention in the health sector.

The budget impact analysis was conducted based on the estimated incidence of epilepsy in South Africa and the estimated utilization rate for public sector services of 84%. The budget impact analysis was conducted at two levels. The first level only considered pharmaceutical costs and levetiracetam was found to be the costliest treatment option, while carbamazepine was found to be the least costly treatment option. The pharmaceutical costs used for this study were solely obtained from tender prices unique to the South African public sector, limiting the generalizability of the results obtained in this study to other contexts. Even when the price of levetiracetam is lowered to 50%, treatment with levetiracetam is still more costly than the other available options. On inclusion of other health systems costs associated with the treatment of seizures and the management of side effects, lamotrigine was found to be the least costly

treatment option. This demonstrates its higher effect size which is associated with a lower cost of treatment for seizures. Levetiracetam was still found to be the most expensive treatment option on inclusion of other health systems costs in the budget impact analysis, costing the health system almost double the amount it would cost for treatment with lamotrigine. Given the higher effect size of lamotrigine and the high demand for resources in the South African health sector due to the quadruple burden of diseases, the use of lamotrigine as first line treatment for epilepsy would be most appropriate.

The introduction of cost-effective epilepsy treatment must be accompanied by patient education in the South African context to maximise health outcomes through improved patient adherence. There is also need to address the combined use of Western medicines with traditional treatments, mostly in rural areas, which may negatively impact treatment outcomes (24). Community education must also be introduced in order to tackle the stigma associated with epilepsy so as to improve utilization rates of epilepsy treatment and seizure prophylaxis (7). Further studies to differentiate the cost-effectiveness of levetiracetam in comparison to lamotrigine in rural areas versus in urban areas given the differences in access to health care services which may impact the titration of lamotrigine may also be necessary. There is also need for further studies examining the characteristics of the health care system that contribute to the epilepsy treatment gap. To improve the accuracy of future cost-effectiveness analysis, there is need to invest in epidemiological studies to inform context specific burden of disease and service utilization rates.

CONCLUSION

Based on the findings of the study and recommendations from international organizations, lamotrigine would be the most cost-effective first line treatment of newly diagnosed epilepsy, even when accounting for the titration period associated with this drug and the associated risk of Steven-Johnson Syndrome as a side-effect. It is effective in the treatment of both partial seizures and generalized tonic-clonic seizures. For levetiracetam to be more cost-effective than lamotrigine, a price decrease of 93% is required, which is unlikely given that the South African Department of Health already has the drug on tender. There is need for further research on the cost-effectiveness of levetiracetam in the treatment of specific sub-groups in the epileptic population such as pregnant women, lactating women, the elderly, those who are HIV positive and patients with other co-morbidities.

LIMITATIONS OF THE STUDY

- The translation of "time to seizure-freedom" which was the primary outcome measure for the Adult ERC Lev MR into transition probabilities for the cost-effectiveness analysis.
- Data on effectiveness was obtained from multiple studies, therefore there was indirect comparison of the drugs under analysis.
- A systematic review of the literature on economic evaluations for epilepsy to determine model input parameters is preferred but was not conducted due to resource limitations.
- Some of the model parameters used were not specific to the South African context.
- Assumptions were made in the modelling process which may not be representative of the heterogenous patterns seen in clinical practice.
- Analysis did not consider the impact of co-morbidities on the choice of treatment for epilepsy.

COMPETING INTERESTS

The author(s) declare that they have no competing interests.

ACKNOWLEDGEMENT

Vimbayi Mafunda and Thomas Wilkinson are acknowledged for their assistance, supervision and guidance in the development of this project. Members of the Health Economics Unit at the University of Cape Town for their technical support in the carrying out of this project. I would also like to acknowledge the contributions by the National Essential Medicines List Committee in the development of the research protocol for this study and technical support throughout the development of this project.

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PART D: APPENDICES TO THE DISSERTATION

UNIVERSITY OF CAPE TOWN
Faculty of Health Sciences
Human Research Ethics Committee

Room E53-46 Old Main Building
Groote Schuur Hospital
Observatory 7925
Telephone [021] 406 6492
Email: sumayah.arieff@uct.ac.za
Website: www.health.uct.ac.za/fhs/research/humanethics/forms

18 June 2019

HREC REF: 362/2019

Ms V Mafunda
Health Economics Unit
School of Public Health & Family Medicine
FHS

Dear Ms Mafunda

PROJECT TITLE: A COST-EFFECTIVENESS ANALYSIS AND BUDGET IMPACT OF LEVETIRACETAM COMPARED TO OTHER AVAILABLE PHARMACOTHERAPY TREATMENTS FOR NEWLY DIAGNOSED EPILEPSY IN THE SOUTH AFRICAN PUBLIC SECTOR (MPH CANDIDATE - MS E CHANAKIRA)

Thank you for submitting your study to the Faculty of Health Sciences Human Research Ethics Committee (HREC) for review.

It is a pleasure to inform you that the HREC has **formally approved** the above-mentioned study.

Approval is granted for one year until the 30 June 2020.

Please submit a progress form, using the standardised Annual Report Form if the study continues beyond the approval period. Please submit a Standard Closure form if the study is completed within the approval period.
(Forms can be found on our website: www.health.uct.ac.za/fhs/research/humanethics/forms)

Please quote the HREC REF in all your correspondence.

We acknowledge that the student: Miss Esther Chanakira will also be involved in this study.

Please note that the ongoing ethical conduct of the study remains the responsibility of the principal investigator.

Please note that for all studies approved by the HREC, the principal investigator must obtain appropriate institutional approval, where necessary, before the research may occur.

Yours sincerely

Signature Removed

PROFESSOR M BLOCKMAN
CHAIRPERSON, FHS HUMAN RESEARCH ETHICS COMMITTEE

Federal Wide Assurance Number: FWA00001632

Institutional Review Board (IRB) number: IRB00001938
NHREC-registration number: REC-210208-007

This serves to confirm that the University of Cape Town Human Research Ethics Committee complies to the Ethics Standards for Clinical Research with a new drug in patients, based on the Medical Research Council (MRC-SA), Food and Drug Administration (FDA-USA), International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use: Good Clinical Practice (ICH GCP), South African Good Clinical Practice Guidelines (DoH 2006), based on the Association of the British Pharmaceutical Industry Guidelines (ABPI), and Declaration of Helsinki (2013) guidelines. The Human Research Ethics Committee granting this approval is in compliance with the ICH Harmonised Tripartite Guidelines E6: Note for Guidance on Good Clinical Practice (CPMP/ICH/135/95) and FDA Code Federal Regulation Part 50, 56 and 312.

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List the names and initials of all authors if there are 3 or fewer; otherwise list the first 3 and add 'et al.' (The exception is the Journal of Medical Genetics, which lists all authors). Use one space only between words up to the year and then no spaces. The journal title should be in italic and abbreviated according to the style of Medline. If the journal is not listed in Medline then it should be written out in full.

Check journal abbreviations using PubMed
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Example references

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- Book: 15 Howland J. Preventing Automobile Injury: New Findings From Evaluative Research. Dover, MA: Auburn House Publishing Company 1988:163–96.
- Chapter in a book: 14 Nagin D. General deterrence: a review of the empirical evidence. In: Blumstein A, Cohen J, Nagin D, eds. Deterrence and Incapacitation: Estimating the Effects of Criminal Sanctions on Crime Rates. Washington, DC: National Academy of Sciences 1978:95–139.
- Abstract/supplement: 16 Roxburgh J, Cooke RA, Deverall P, et al. Haemodynamic function of the carbomedics bileaflet prosthesis [abstract]. *Br Heart J* 1995;73(Suppl 2):P37.
- Electronic citations: Websites are referenced with their URL and access date, and as much other information as is available. Access date is important as websites can be updated and URLs change. The "date accessed" can be later than the acceptance date of the paper, and it can be just the month accessed.
- Electronic journal articles: Morse SS. Factors in the emergency of infectious diseases. *Emerg Infect Dis* 1995 Jan-Mar;1(1). www.cdc.gov/ncidod/EID/vol1no1/morse.htm (accessed 5 Jun 1996).
- Electronic letters: Bloggs J. Title of letter. *Journal name* Online [eLetter] Date of publication. url eg: Krishnamoorthy KM, Dash PK. Novel approach to transseptal

puncture. *Heart* Online [eLetter] 18 September 2001. http://heart.bmj.com/cgi/eletters/86/5/e11#EL1

- Legal material: Toxic substances Contro Act: Hearing on S776 Before the Subcommittee of the Environment of the Senate Comm. on Commerce, 94th Congress 1st September (1975).
- Law references: The two main series of law reports, Weekly Law Reports (WLR) and All England Law Reports (All ER) have three volumes a year e.g. Robertson v Post Office [1974] 1 WLR 1176

There are good historical precedents for the use of square and round brackets. Since 1891, round ones have referred to the date of the report, square ones to the date of publication of the report. Apart from not italicising the name of the case, we use the lawyers' style; be careful with punctuation, e.g. Caparo Industries plc v Dickman and others [1990] 1 All ER 568-608.

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PART E: POLICY BRIEF

EXECUTIVE SUMMARY

Epilepsy is a condition associated with the occurrence of seizures and it is estimated that 1% of South Africans have this condition. The condition is primarily managed through seizure prevention using medicines called anti-epileptics. The anti-epileptic drugs (AEDs) currently used in South Africa after an initial epilepsy diagnosis are carbamazepine, lamotrigine and phenytoin. Valproate is sometimes used in practice for patients with a new epilepsy diagnosis. Levetiracetam is under consideration as a replacement for the above stated medicines in the treatment of partial and generalized seizures because of its reported ease of use for both patients and health care professionals. It has also been reported that levetiracetam has less serious side effects compared to the other available medicines. This study was carried out to determine if levetiracetam is more cost-effective in comparison to the medicines currently used in practice over five years to ensure the efficient allocation of resources in the health sector. This was done by conducting a cost-effectiveness analysis. A cost-effective treatment is one which provides relatively good value for money. The study was carried out by comparing the costs and health effects of the medicines under analysis. Health effects were measured as Quality Adjusted Life-Years (QALYs), which represent both the number of years lived by the patient and their quality of life over those years. Costs were presented as the South African Rand, 2018 value. The study was conducted from the perspective of the South African public health sector. Lamotrigine was found to be the most cost-effective treatment option over a five-year period. It had the lowest cost of treatment and the highest health effects. 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 had the lowest number of QALYs gained at 3,97 QALYs each. The study also evaluated the cost

of treatment for each of the medicines under analysis over the first year of treatment through a budget impact analysis. Levetiracetam was found to incur the highest cost of treatment both when only considering the cost of purchasing the medicine for treatment and when considering the total cost of treatment to the health care system. Treatment with levetiracetam was found to cost about R44 million to the health system and treatment with lamotrigine was found to be the least costly option costing about R25 million to the health system. Levetiracetam was not found to be cost-effective as the initial treatment for epilepsy in the South African public health sector. For levetiracetam to be cost-effective, a price reduction of 93% is required. Following the findings of this study, lamotrigine is recommended as the first-line treatment for epilepsy associated with generalized tonic-clonic seizures and partial seizures.

INTRODUCTION

Epilepsy is a chronic condition of the nervous system that affects approximately 560,000 people in South Africa (1). The condition results in seizures which may or may not lead to loss of consciousness (2). It is associated with considerable disability in patients who are uncontrolled and can lead to premature death (3)(4). Underlying causes of epilepsy include head injuries, drug and alcohol abuse and infectious diseases such as HIV/AIDS and tuberculosis (5)(2). Causes in South Africa are likely to be infectious due to the high HIV and tuberculosis prevalence (5). Epilepsy also has a negative impact on the quality of life of patients living with the disease as it affects their psychological wellbeing (6). Frequency and severity of seizures, depression usually associated with uncontrolled epilepsy and side-effects due to AEDs all contribute to a reduced quality of life (7)(6). Individuals with epilepsy are significantly more likely to have a mood disorder compared to the general population, with between 50% and 60% of patients with chronic epilepsy having at least one mood disorder (8).

Adequate seizure control can result in an improved quality of life especially due to improved social function (6). Epilepsy is also associated with high levels of stigma in the African context, especially in rural areas due to a belief that the disease is contagious and a result of a curse (4). The disease has significant negative economic effects at both individual and societal level. At individual level, costs range from those directly associated with treatment such as the cost of medicines for the prevention and treatment of seizures to the loss of income due to the lower productivity associated with illness (4). At national level some countries spend as much as 1% of their total health care expenditure on epilepsy treatment, signifying the economic burden of the disease (4). The estimated percentage of the global burden of disease associated with epilepsy in developing countries is about 90%, while only 20% of all epilepsy related health expenditure is spent in developing countries (9). This, together with other factors such as poor infrastructure and scarcity of trained medical staff, has resulted in an estimated 75% of epileptics in developing countries not receiving treatment (10). To ensure that the money spent on epilepsy treatment in developing countries is used efficiently, there is need to conduct economic evaluations to ensure that cost-effective treatments are funded. This is especially important in the context of South Africa were the public health sector is strained due to the quadruple burden of disease (11). An economic evaluation is defined as the comparative analysis of alternative courses of action in terms of costs and effects (12).

Epilepsy has multiple treatments which include; the use of medicines, surgery, neurostimulation and the ketogenic diet. Surgery and neurostimulation are usually used when the individual is not responsive to medicines used in preventing seizures (13)(14). The ketogenic diet, which is a low-carbohydrate, adequate protein and high-fat diet has been established as an effective option for managing refractory epilepsy in children between the ages of two and ten (15). In South Africa, epilepsy is managed primarily through the prevention of

seizures using AEDs. Use of a single AED compared to multiple AEDs is advised to limit side effects associated with treatment (16). 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 (17). Second-generation AEDs have been found to be safer for patients compared to first-generation AEDs, although they cost more (17). Some AEDs such as phenytoin, carbamazepine, levetiracetam and lamotrigine may cause intense allergic reactions in patients who are susceptible, for example those with a weakened immune system due to HIV (18). Hypersensitive reactions includes Steven Johnson Syndrome which is a rare but serious disorder of the skin associated with painful red blisters and can lead to death (19). Phenytoin and carbamazepine increase the rate at which hormonal contraceptives are cleared from the body, potentially rendering them ineffective (20). This is especially a problem if pregnancy occurs during the use of phenytoin as it can lead to foetal malformation (20). Use of valproate during pregnancy is also associated with malformations during foetal development (20). Lamotrigine, together with carbamazepine and valproate require a gradual increase in dose until the optimum dose is reached on treatment initiation in order to minimize the occurrence of side-effects (21). This process results in an increased cost of treatment due to the increased number of hospital visits (21). The blood levels lower than the effective threshold during the dose adjustment period may also lead to breakthrough seizures, further increasing treatment costs (21).

The current first-line treatment of epilepsy on diagnosis in South Africa is lamotrigine, phenytoin or carbamazepine (22)(23). Valproate is occasionally used in practice. Levetiracetam is under consideration for inclusion on the South African Essential Medicines List due to its better side-effect profile and associated ease of use compared to the other

treatment options (24). It is crucial to determine the cost-effectiveness of these available AED options in South Africa to ensure the efficient use of the limited resources for health.

RESEARCH OBJECTIVE

The study assessed the cost-effectiveness of levetiracetam compared to the other available treatment options in the South African public health sector which are lamotrigine, carbamazepine, phenytoin and valproate over a five-year period. This was achieved using a cost-effectiveness analysis. The study also assessed the cost of treatment using each of the five AEDs under analysis for the first year of treatment. This was achieved through a budget impact analysis. Use of the AEDs was considered to be mutually exclusive in this study.

What is a cost-effectiveness analysis?

- A cost-effectiveness analysis compares the costs and effects associated with different treatment interventions over a set period through the generation of incremental cost-effectiveness ratios (ICERs).
- ICERs are ratios of incremental costs and incremental effects of the available treatment options. Before ICERs can be calculated, the treatment options must be listed from least costly to most costly. Interventions that cost more but have lower effect sizes are "dominated" and are excluded from the analysis. ICERs are calculated for the appropriate strategy using the previous less costly treatment strategy for comparison.
- Interventions with low ICER values are usually preferred compared to those with higher ICER values because of their lower additional cost per additional unit of effect.
- A country threshold in the form of the cost of the last fully funded health care intervention is usually used to represent the health systems' 'willingness to pay'.

What is a budget impact analysis?

- A budget impact analysis is an estimate of the cost of introducing an intervention in the health system.
- The costs directly associated with the resources needed for the introduction of the intervention to the health care sector are added up.
- These costs can include the cost of medicines, the cost of services provided along with the intervention and the costs of treating side effects that can occur due to the treatment option.
- The analysis considers the proportion of the population that will have access to the resources and their expected rate of use of the resources.

METHODS

Both the budget impact analysis and the cost-effectiveness analysis were conducted from a providers' perspective in the provision of care to newly diagnosed adult epilepsy patients in the public sector. This means that only costs directly incurred by the South African public health sector in introducing and offering each intervention were collected for the analysis. The study utilized secondary data and the estimated input costs and effects of the treatment options were obtained from literature. No primary data was collected or used. Where possible, input values specific to South Africa were used. The outputs for the study were estimated using models based on the Standard Treatment Guidelines and literature findings. The budget impact analysis was conducted over the first year of treatment and the cost-effectiveness analysis over

the first five years of treatment. Costs were presented as the South African Rand; 2018 value and effects were expressed as QALYs. Costs used in the analysis include the pharmaceutical costs associated with treatment, costs associated with the treatment of expected seizures over the treatment period and the treatment cost of Steven Johnson Syndrome. Steven Johnson Syndrome is a hyperallergic reaction that may occur in patients taking lamotrigine, carbamazepine and phenytoin. QALYs measure the years of life lived by the patient adjusted by a quality of life measure. A perfectly healthy patient over a one-year period has a QALY value of 1 and the QALY value for death is O. Quality of life measures were based on the patients' seizure freedom status. Patients experiencing seizures were considered to have a lower quality of life measure compared to patients without seizures. The effect size for each treatment option was based on the probability of a patient becoming seizure-free on that treatment. Treatments that had a higher probability of leading to a seizure-freedom state in patients had a higher effect size. The costs and cost-effectiveness of treatment with levetiracetam for patients with newly diagnosed epilepsy were compared to treatment with lamotrigine, carbamazepine, phenytoin and valproate. Sensitivity analyses on costs associated with treatment using levetiracetam and some quality of life measures were also conducted for the first 6 months of treatment to address uncertainty with regards to the cost-effectiveness analysis. The costs used for the sensitivity analysis were the unit cost of levetiracetam and the total treatment cost for a patient on levetiracetam over six months. The quality of life measures used were those of patients who are "controlled on treatment" and patients who are "uncontrolled".

FINDINGS

Cost-effectiveness analysis

- Seizure-free patients incurred lower costs compared to patients who had seizures due to their lower utilization of health care resources.
- Treatment with lamotrigine incurred the lowest cost and had the highest number of QALYs gained compared to levetiracetam, carbamazepine, phenytoin and valproate. Lamotrigine was therefore the most cost-effective treatment option.
- The cost of treating a single case of epilepsy over five years ranged from R63 567 using lamotrigine to R66 970 using carbamazepine.
- Effect size ranged between 4,01 QALYs for lamotrigine and 3,907 QALYs for valproate, carbamazepine and phenytoin. Lamotrigine therefore had the highest effect size.
- Levetiracetam treatment resulted in a gain of 3,99 QALYs.
- The other treatment options were dominated by lamotrigine, therefore ICERs were not calculated. A dominated strategy is one which costs more but has a lower effect size (25).
- The findings of the sensitivity analysis showed that lowering both the cost of purchase for levetiracetam and the total cost associated with treatment using levetiracetam resulted in levetiracetam becoming comparatively more cost-effective compared to lamotrigine.
- For levetiracetam to become more cost-effectiveness than lamotrigine, a price reduction of 93% is required.

- Quality of life measures were also varied as part of sensitivity analysis, but no trends regarding the relationship between the quality of life measures and the comparative cost-effectiveness of levetiracetam were observed.
- The probability of remaining controlled on levetiracetam was also varied and no trend on the resulting ICER values was observed.

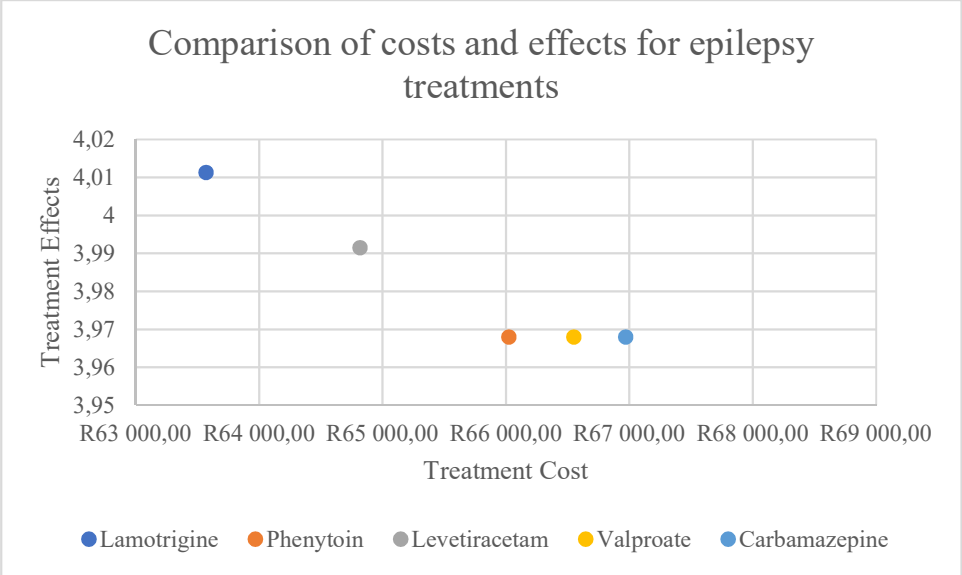

Figure 1: Comparison of costs and effects of the treatment options.

Budget impact analysis

- The cost of purchasing levetiracetam was found to be higher than that of purchasing the other comparators, costing R23,5 million.
- Treatment with carbamazepine was the cheapest option, costing about R20 million less than treatment with levetiracetam.
- Levetiracetam would still be the most expensive treatment option even with a 50% price reduction while maintaining the prices of the other drugs.
- The cost of purchasing levetiracetam accounted for 53,3% of the total cost of treating an epilepsy patient with levetiracetam.

- Levetiracetam was still the costliest treatment option on inclusion of other health systems costs such as the cost of treating Steven-Johnson Syndrome and non-pharmaceutical costs associated with seizure treatment, costing about R44 million to the health system and lamotrigine was found to be the least costly treatment option costing about R25 million to the health system.
- Treatment with lamotrigine incurred the least non-pharmaceutical costs associated with epilepsy treatment, followed by levetiracetam, with a difference of R546 886. Carbamazepine incurred the highest costs, followed by valproate.
- A reduction in the differences in cost between treatment with levetiracetam and the comparator drugs was observed on inclusion of the other health systems costs.

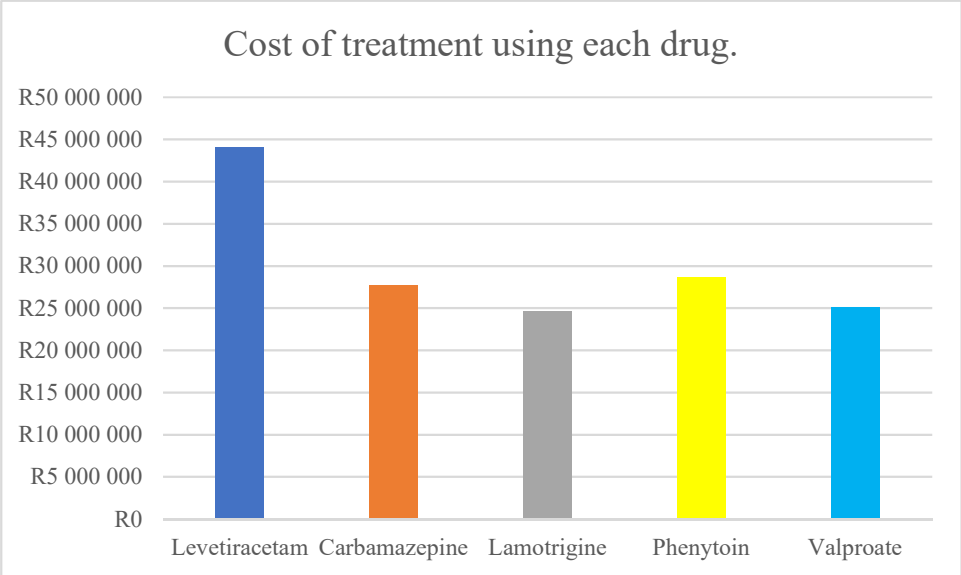

Figure 2: Comparison of the total cost to the health system of treatment using the drugs under analysis.

CONCLUSION

Lamotrigine was found to be the most cost-effective and appropriate treatment option for epilepsy related to both partial and generalized seizures. Levetiracetam was found to not be

cost-effective in the treatment of newly diagnosed epilepsy in the South African public health sector. These findings agree with those from the study conducted for the National Institute for Health and Clinical Excellence (NICE) in the United Kingdom which concluded that use of levetiracetam as first line treatment for epilepsy was not cost-effective. For levetiracetam to be more cost-effective than lamotrigine, a price reduction of 93% is required, which is not likely to occur in the South African context as levetiracetam is already obtained by the government on tender. The use of lamotrigine as first line epilepsy treatment is recommended by both NICE and the Scottish Intercollegiate Guidelines Network (SIGN).

Other considerations in maximising treatment outcomes after the introduction of cost-effective treatment include patient adherence and proper use of medication. This is especially important in the South African context, specifically in rural areas, where Western medicines are often mixed with traditional medicines (10). Treatment outcomes and treatment seeking behaviour is also inevitably affected by societal views on the disease (5).

This study did not include sub-group analysis, for example; the cost-effectiveness of levetiracetam in treating pregnant women, the elderly or patients who are HIV positive. Further research on these sub-groups is necessary to ensure appropriate treatment for all epileptics. Challenges faced in the conducting of this study include access to South African specific data on the epidemiology of epilepsy. To improve the accuracy of future studies, there is need to improve information databases.

POLICY RECOMMENDATIONS

- Strengthen health information and surveillance systems to better capture data on epilepsy.

- Using lamotrigine as the primary first line treatment for epilepsy.
- Provision of training to healthcare professionals on epilepsy diagnosis along with the proper use and titration of lamotrigine.
- Provision of patient education alongside treatment to ensure treatment adherence and maximize treatment outcomes.
- Introduction of an educational program on epilepsy in rural areas through community health workers to reduce the stigma associated with epilepsy and encourage epileptics to seek treatment.
- Provision of education to the families of epileptics on how to deal with seizures and minimize the chances of a seizure related death.

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