



Review Article

A Systematic Review of the Cost-effectiveness of Perampanel in the Treatment of Epilepsy

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Abstract: Objective: Epilepsy is a chronic non-communicable disease that can affect all ages, genders, races, and social classes with large treatment costs that vary widely between countries and regions. Perampanel is a new generation of antiepileptic drugs (AEDs), but cost-effectiveness reports are inconsistent in several countries that have conducted pharmaco-economic evaluations. Study with the objective of systematically summarizing the evidence on the cost-effectiveness of Perampanel for the treatment of epilepsy. Methods: An exhaustive search was performed in four publication databases. Evaluation of the reporting quality of the studies using the CHEERS checklist. Results: Findings: Costs were lower in the Perampanel group than in the Lacosamide group (Perampanel 8mg/day vs. Lacosamide 400mg/day - Total cost: \$2390 (12.89%), but higher than in the antiepilepsy drugs group without perampanel (Total Direct Cost: 5475 Euro and Total Indirect Cost: -5288 Euro, Total Cost: 188 Euro) and the group with recent add-on regime such as Brivaracetam (3188 Euro in total). When compared with the Lacosamide group, the Perampanel group showed increased outcomes in all three outcomes (convulsions, LY, and QALY). Similarly, the Perampanel group showed increased outcomes in all three outcomes (convulsions, LY, and QALY) compared with groups without Perampanel. Meanwhile, QALY in the Perampanel group was lower than in the Brivaracetam group (total of 0.059 QALY). Conclusions: Perampanel as an adjunct therapy for antiepilepsy drugs may be a cost-effective treatment option in the management of epilepsy.

Keywords: Fycompa, perampanel, seizure, epilepsy, systematic review, cost-effective.

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1. Introduction

Epilepsy is a chronic non-communicable disease (NCD) that can affect all ages, genders, races, social classes, and countries around the world. Epilepsy is characterized by recurrent seizures, often occurring spontaneously and without warning [1]. According to a report by World Health Organization (WHO), currently, there are 50 million people diagnosed with epilepsy [2]. Nearly 80% of people with epilepsy live in low-income and middle-income countries [3].

Epilepsy accounts for a significant proportion of the world's total burden of disease, with over 5 million new cases per year [2]. In 2016, the DALYs index (Disability-Adjusted Life Years, which measures the loss of health determined by the total number of years of life lost due to premature death and years lived with disability) of epilepsy accounts for more than 13 million, equivalent to 0.5% of the total burden of disease throughout the world. More than any neuropathy, epilepsy causes the most burden in children and young adults, as estimated by the GBD study [4].

According to a study in the US, the annual direct cost of epilepsy is \$28 billion [5] with an average cost per patient of \$15,414 [6]. A systematic review conducted by Allers et al. stated that the total annual cost of medical care per patient ranged from €1302 in Italy to €2193 in Spain, with around €1528 per year due to loss of productivity [7]. The authors also stated that the economic burden caused by epilepsy varies widely between countries and regions, as well as depending on the duration of the disease, the severity of the disease, the ability to respond, and the type of service provider [7].

In Vietnam, epilepsy is also a common disease. Some previous studies showed that the rate of epilepsy in the community ranged from 0.2% to 0.5%, 8 and up to 1.6% in the hospitalized group [8]. Another report showed that, in Vietnam, epilepsy accounted for between 0.5% and 0.8% of the population, and the incidence rate varies from 17.3 to 136 per

100,000 population each year [9]. However nowadays, when risk factors of epilepsy such as infections, obstetric trauma, and traffic accidents are on the rise, more research is needed to update the indicators of epilepsy in Vietnam.

Dynamic current can be treated with surgical methods or medical therapy with anti-epileptic medicines [10, 11]. However, in Vietnam, the number of epilepsy patients who are successfully treated with surgical methods is very small, most of them have to take long-term antiepileptic medicines. Antiepileptic medicines are currently divided into two categories: classics and new generation medicines. Classic medicines are the ones that have been recognized and used for a long time (eg, carbamazepine, phenytoin, etc.) One of the new generation medicines of antiepileptic medicines is perampanel. Perampanel is designated for adjuvant therapy treatment of onset focal seizures, with or without secondarily generalized seizures in adults and children of 12 years and older with epilepsy. While the effects of these medicines are similar, they cause different numbers of undesirable side effects and have different cost-effectiveness. Therefore, we performed a study entitled "cost and cost-effectiveness of perampanel in the treatment of epilepsy: A systematic review" with the following objectives systematically summarizing evidence about Perampanel's cost-effectiveness for the treatment of epilepsy.

2. Subjects and Research Methodology

2.1. Study Design

This study applied the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guideline to present the process of searching, screening, and selecting the papers.

2.1.1. Eligible Criteria

The inclusion criteria and search strategy of this study were defined based on the following characteristics:

Table 1. Inclusion and exclusion criteria

Selection criteria	Exclusion criteria
1. Full economic evaluations (cost-effectiveness analysis, cost-benefit analysis, cost-utility analysis) comparing perampanel/fycompa with other treatment 2. Studies published in a prestigious, peer-reviewed international journals 3. Studies published in English 4. Studies published until July 2021	1. Abstract, paper proceedings, letter of the editor, etc. that are not original articles. 2. Studies focus on other aspects such as diagnosis, prevention, etc. rather than focusing on treatment. 3. Studies published in a non-English language

2.2. Search Methods for Identification of Studies

The Pubmed/Medline, EMBASE, and NHS Economic Evaluation Database (NHS EED) databases were used to search for studies around the world. To identify relevant studies, we combined predefined clinical search strategies (to assess the effectiveness of treatments) with a

search filter of the health information research unit of McMaster University (see: http://hiru.mcmaster.ca/hiru/HIRU_Hedges_EMBASE_Strategies.aspx), which is designed to identify health economic studies. In addition, citation tracking was performed for all included studies. The keywords used to search include three components as presented in table 2.

Table 2. Searching terms

No		
1	Population	((("Epilepsy"[MeSH Terms] OR epilepsy[TIAB] OR epileps*[TIAB] OR epilept*[TIAB]) OR ("Seizures"[Mesh Terms] OR seizure[TIAB] OR seizures[TIAB]) OR (convulsion[TIAB] OR convulsions[TIAB])))
2	Intervention	Fycompa[TIAB] OR Perampanel[TIAB])
3	Economic evaluation	(cost*[Title/Abstract] OR "costs and cost analysis"[MeSH:noexp] OR cost benefit analys*[Title/Abstract] OR cost effectiveness analys*[Title/Abstract] OR cost utility analys*[Title/Abstract] OR cost-benefit analysis[MeSH Term] OR health care costs[MeSH:noexp])
4		#1 AND #2 AND #3

Search results were downloaded from databases and imported to Endnote, a reference manager software. All titles and abstracts retrieved from the literature search were screened to determine whether the studies meet the eligibility criteria.

2.3. Data Extraction and Management

This review was performed in two stages:

Stage one: The title and summary of all search results will be reviewed. Studies that do not comply with the criteria will be excluded. Studies that match the selection criteria are stored in full text, and continue to phase two.

Phase two: Studies with appropriate titles and summaries will be read in full text and reviewed results and research methods. Full-text studies that did not meet the criteria will also be excluded from the study. The remaining relevant studies will be conducted based on the data extraction form developed. During these two phases, if there is any disagreement between the two researchers in the team, the whole research team will conduct discussions to find a final agreement.

Data were extracted using a predefined form that included the following information: study type, year of publication, year of currency and currency type, study setting (country), target

population (gender and age), analysis perspective, intervention type, health outcome measure, and type of economic evaluation.

2.4. Quality Assessment

To determine the quality of reporting of the included studies, the Consolidated Health Economic Evaluation Reporting Standards (CHEERS) statement was used [13]. This checklist has 24 items and accompanying recommendations, with some specific recommendations for single study-based and model-based economic evaluations. There are six main categories: 1) title and abstract, 2) introduction, 3) methods, 4) results, 5) discussion, and 6) other. To calculate an overall quality score for each article based on the CHEER checklist, each time a “Yes” was scored, 1 point was allocated. The total score per article was then divided by all the applicable items for that particular study [13].

2.5. Data Synthesis

The data of the studies were synthesized and described according to the criteria extracted into Microsoft Excel software and managed by Endnote software.

3. Results

Figure 1 presents the process of selecting papers as well as the number of studies included and excluded in each step. The primary literature search on three databases identified 179 papers. A total of 57 duplicates were removed and by manually screening titles and abstracts, 101 records were removed due to exclusion criteria. After screening the full-text articles, only 3 articles remained and were selected for qualitative synthesis. The basic characteristics of each study are presented in Table 3.

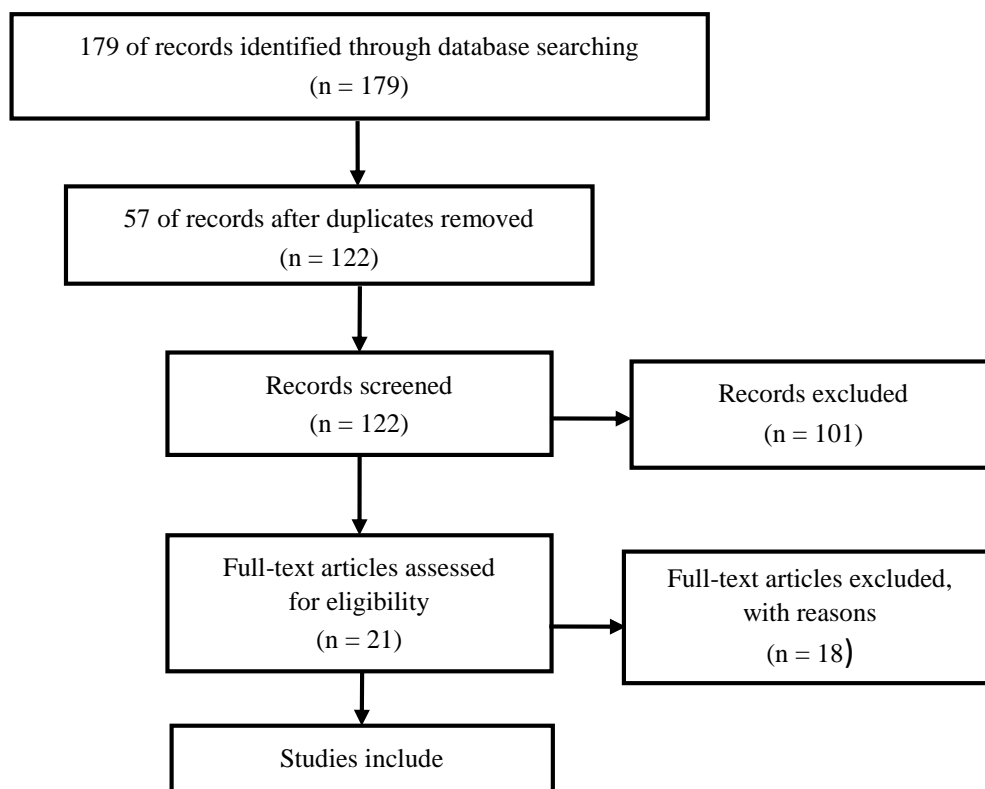


Figure 1. The selection process of papers.

Table 3. Basic characteristics of the studies

No	Author (year)	Country	Study design	Method	Perspective	Patients	Groups	Time-Frame	Model	Discount	Sensitivity analysis	Threshold of WTP
1	Donger Zhang, (2021) [14]	China	Modeling based on previous clinical trial data and literature review	Cost-effectiveness analysis	Health system	Partial-Onset Seizures	Group 1: Perampanel 4mg/day and 8mg/day Group 2: Lacosamide 400 mg/day and Lacosamide 200 mg/day	Lifetime horizon	Markov model	5% per year	One-way deterministic sensitivity analysis (DSA); Probabilistic sensitivity analysis (PSA) using Monte Carlo simulation with 10,000 iterations	10,838 - 32,515 USD/QALY
2	Gabriel Tremblay (2018) [12]	Spain	Modeling based on previous clinical trial data and literature review	Cost-effectiveness analysis	Spanish National Health Service and Societal perspectives	Primary generalized tonic-clonic seizures (PGTCS)	Group 1: Perampanel 8mg, daily dose 6.88 mg/day Group 2: None Perampanel	33-years time horizon	Markov model	3% per year	One-way sensitivity analysis, Probabilistic sensitivity analysis	30000 Euro/QALY
3	Saku Väätäinen (2020) [15]	Finland	Modeling based on previous clinical trial data and literature review	Cost-utility analysis	Health system perspective	Focal Onset Seizures	Group 1: Perampanel 4 mg, 6 mg, 8mg, 10 mg, 12 mg Group 2: Brivaracetam 100mg/day	5-year time horizon	Discrete event simulation model (DESM)	3% per year	Probabilistic sensitivity analysis	25,358 Euro and 38,036 Euro/QALY

WTP: Willingness to Pay

Table 4. Incremental cost-effectiveness ratio (ICER) of perampanel in selected studies and sensitivity analysis

Author	Incremental cost-effectiveness ratio (ICER)	WTP threshold	Sensitivity analysis
Donger Zhang et al., [14]	Perampanel 4 mg/day vs Lacosamide 200mg/day: - ICER per seizure avoid: 29.41 USD/seizure - ICER per LY: 116,275.56 USD/year - ICER per QALY: 105,193.94 USD/year	10,838 - 32,515 USD/QALY	Perampanel 8mg/day vs Lacosamide 400mg/day: 150,911 USD to 8,418 USD per QALY (extreme discount rate had the greatest impact) Perampanel 4 mg/day vs Lacosamide 200mg/day: 556,654 USD to 119,970 USD per QALY (utility value had the greatest impact) PSA results showed a large probability of being economical at various levels of willingness to pay
Gabriel Tremblay et al., [12]	Perampanel 8 mg/day - ICER per seizure avoid: 19.32 Euro/seizure - ICER per LY: 20,746 USD/year - ICER per QALY: 16,557 USD/year	30000 Euro/QALY	One-way sensitivity: ICER was influenced by rates of discounting costs and health effects PSA: At a willingness-to-pay threshold of €30,000/QALY, the probability that adjunctive perampanel was cost-effective relative to AED maintenance therapy was 89.3% from the base case perspective and over 93.4% from the societal perspective.
Saku Väättäinen et al., [15]	Brivaracetam vs perampanel: 5345 Euro/QALY	25,358 Euro and 38,036 Euro/QALY	Brivaracetam had a positive NMB and high probability of cost-effectiveness of €1190 and 71% or €1944 and 80% with the assumed willingness to pay of €25,358 or €38,036/QALY gained, respectively.

All studies are model-based health economic evaluation studies with time frames ranging from 5 years to a Lifetime horizon based on the perspective of the health system. Table 3. shows that all of the selected studies used modeling based on previous clinical trial data and a literature review approach. Each study focused on a different population. Donger Zhang et al., studied patients with partial-onset seizures, Gabriel Tremblay et al., investigated primary generalized tonic-clonic seizures (PGTCS), and Saku Väättäinen et al focused on patients with focal onset seizures [12, 14, 15].

The studies used other add-on therapeutic regimes to compare with perampanel. For instance, Donger Zhang et al compared perampanel (4mg/day and 8 mg/day) with lacosamide (Lacosamide) (400mg/day and 200 mg/day, respectively) [14]. Meanwhile, Saku

Väättäinen et al compared perampanel (4, 6, 8, 10, 12 mg/day) with Brivaracetam (100mg/day). Gabriel Tremblay et al. 54 compared AEDs with and without perampanel [15].

Table 3. shows that two studies mentioned that they used cost-effectiveness analysis, while one study mentioned cost-utility in their design. Three studies performed economic evaluation according to a health system perspective, and one study performed from a societal perspective.

Donger Zhang et al., conducted a Markov model with a lifetime horizon and a 5% discount per year. They also performed One-way deterministic sensitivity analysis (DSA) and Probabilistic sensitivity analysis (PSA) using Monte Carlo simulation with 10,000 iterations to measure the uncertainty of the result. The threshold used for the willingness-to-pay (WTP) measure was 10,838 - 32,515 USD/QALY [14].

Gabriel Tremblay et al. also used the Markov model with a 33-year time horizon and a 3% discount per year. For sensitivity analysis, they used One-way sensitivity analysis and Probabilistic sensitivity analysis. The threshold of WTP was 30000 Euro/QALY [12]. Saku Väättäinen et al. used a Discrete event simulation model (DESM) with a 5-year time horizon and a 3% discount per year. Probabilistic sensitivity analysis was used for uncertainty analysis. The threshold of 25,358 Euro and 38,036 Euro/QALY were used for the WTP measure [15].

Table 4 shows the results of the incremental cost-effectiveness ratio (ICER) of perampanel in selected studies and sensitivity analysis. In the study of Donger Zhang et al., [14] in China, the ICER of perampanel was much higher than the WTP threshold. However, it was more cost-effective than the Lacosamide regime. Meanwhile, in Gabriel Tremblay et al., [12] the ICER for perampanel was acceptable and showed cost-effectiveness when compared with the WTP threshold. In Saku Väättäinen et al., perampanel was shown to be less cost-effective than Brivaracetam with ICER 5345 Euro/QALY [15].

4. Discussion

The results of the pooled studies show that the cost of perampanel in the treatment of epilepsy fluctuates. In Donger Zhang et al. [14] the author also mentioned that the cost of Perampanel 4 mg/day was 878USD/4 month, and the cost of Perampanel 8 mg/day was 1,754USD/4 month. It was lower than its comparator (i.e. Lacosamide – Lacosamide) with 1,484 USD/4 months for Lacosamide 200 mg/day and 2,968 USD/4 months for Lacosamide 400 mg/day. Meanwhile, Gabriel Tremblay et al. [12] revealed that the yearly drug cost was 1532 Euro; the formulary price was 136.58 Euro, and the price per mg was 0.6097 Euro. Saku Väättäinen et al. [15] showed that the perampanel drug cost was 222.74 Euro/28 days.

It should be noted that AEDs had been documented as the main contributors to the cost of epilepsy. In a prospective study on direct and

indirect costs in a tertiary epilepsy center in Germany, Hamer et al. estimated the total annual costs at PPP- \$12 270 per patient. Only patients with active epilepsy (i.e. at least one seizure within the last year) who were aged >18 years were included. Direct costs were responsible for 38% of total costs, with AEDs (PPP-\$2820) being the main contributor [16]. Lan Gao et al. studied 141 epilepsy patients and 323 healthy controls in China. Authors showed that cost of anti-epileptic drugs (AEDs) (US\$394.53) followed by the cost of investigations (US\$59.34), and the cost of inpatient and outpatient care (US\$9.62) accounted for the majority of the direct medical costs. While patients' (US\$103.77) and caregivers' productivity costs (US\$103.77) constituted the major component of indirect cost. The intangible costs in terms of WTP value (US\$266.07 vs. 88.22) and utility (EQ-5D, 0.828 vs. 0.923; QWB-SA, 0.657 vs. 0.802) were both substantially higher compared to the healthy subjects [17].

Gabriel Tremblay et al., [12] showed that the cost increased significantly with perampanel compared with AED maintenance therapy alone (by 10,133 Euro). However, this cost increase was partially offset by a reduction in the cost of other healthcare resources, and it is acceptable if considering both direct and indirect costs.

When assessing the economic evaluation results, all three studies showed that perampanel was a cost-effective regime when compared with different therapies. For example, Donger Zhang et al. 56 showed that Perampanel 4 mg/day vs Lacosamide 200mg/day: ICER per seizure avoid: 29.41 USD/seizure; - ICER per LY: 116,275.56 USD/year; and ICER per QALY: 105,193.94 USD/year. The authors demonstrate that perampanel was valuable as an add-on therapy for patients with partial-onset seizures in China with a dominant advantage of cost-effectiveness compared with Lacosamide (8 vs. 400 mg/day; 4 vs. 200 mg/day), and its incremental budget impact for medical insurance payers is relatively acceptable [14]. This study had strengths in simulating the lifetime

effectiveness and cost data of patients through a Markov model, with full consideration of long-term simulation and health state classification of epileptic patients; as well as giving comprehensive consideration to the daily dose of drugs. Moreover, this study also takes into account multiple aspects of cost data to better reflect the current situation in China [14].

Gabriel Tremblay et al. suggested that the incremental cost per seizure avoided with perampanel versus AEDs alone was €19.32 for primary generalized tonic-clonic seizures [12]. The base case cost-effectiveness analysis for perampanel versus AEDs alone resulted in an ICER/QALY of €16,557 for the primary generalized tonic-clonic seizures population. It is generally accepted that the ICER threshold in Spain is in the range of 30,000 Euro to 40,000 Euro [60]. Therefore, the authors implied that the addition of perampanel to current standard maintenance treatment is therefore likely to be cost-effective in clinical practice for the treatment of PGTCs.

In terms of uncertainty analysis, the results of these studies showed robustness with one-way sensitivity analysis and probabilistic sensitivity analysis. This suggests that these results can be used and applied in formulating financial mechanisms for patients using perampanel in the treatment of epilepsy.

5. Conclusion

Perampanel as add-on therapy to AEDs is likely to be a cost-effective treatment option in the management of epilepsy.

6. Limitations of Study

This review is the first to examine economic evaluations of the use of perampanel in treating epilepsy. This study followed the PRISMA checklist and the selected studies were appraised by using the CHEER checklist. However, there are some limitations that should be noted.

Firstly, only a few studies have been done on this issue, so it is difficult to synthesize evidence showing the cost-effectiveness of perampanel. Second, the studies that were aggregated also had significant variability in study design and data sources. The heterogeneity between the studies may stress the need to define a reference case and to derive consensus on the design and parameters. Differences were not only attributable to economic parameters but also to clinical outcome measures that varied extensively. A reference case is a set of methodologic choices for a range of items relevant to conducting an economic evaluation that frames the boundaries of the study, such as model horizon, outcome measure(s), resource use, and costing [18]. Similar initiatives have been developed in the field of osteoporosis and osteoarthritis [18,19]. A previous review on economic evaluations of AEDs in partial epilepsy also concluded that several methodologic issues hampered their comparability. For example, the inclusion of productivity losses or time horizons [20]. They also emphasized that future health economic evaluations would benefit from efficacy studies that compare relevant alternatives as there is a lack of head-to-head comparisons, especially in epilepsy studies [20].

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