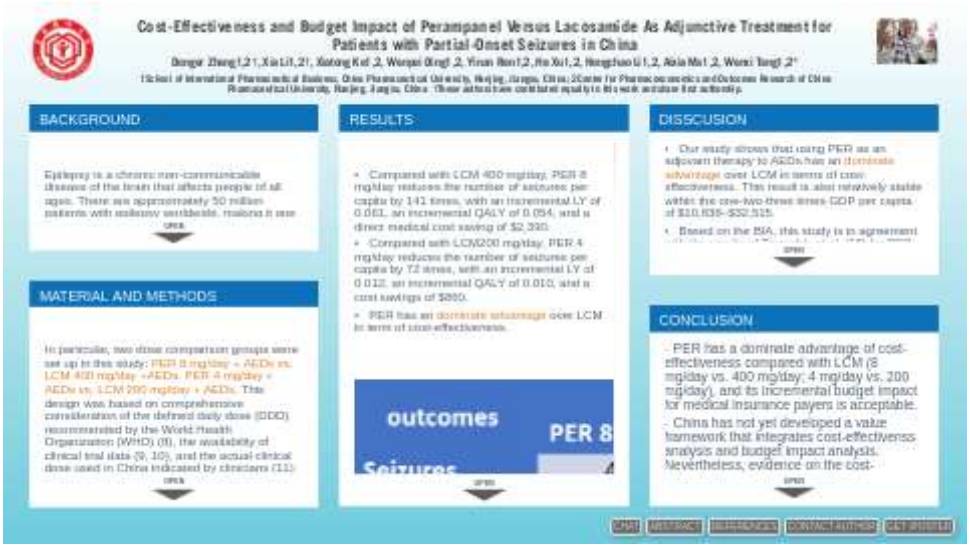
Cost-Effectiveness and Budget Impact of Perampanel Versus Lacosamide As Adjunctive Treatment for Patients with Partial-Onset Seizures in China



Donger Zhang1,2†, Xia Li1,2†, Xiatong Ke1,2, Wenpei Ding1,2, Yinan Ren1,2, He Xu1,2, Hongchao Li1,2, Aixia Ma1,2, Wenxi Tang1,2*

1School of International Pharmaceutical Business, China Pharmaceutical University, Nanjing, Jiangsu, China; 2Center for Pharmacoeconomics and Outcomes Research of China Pharmaceutical University, Nanjing, Jiangsu, China †These authors have contributed equally to this work and share first authorship.

PRESENTED AT:

BACKGROUND

• Epilepsy Population

Epilepsy is a chronic non-communicable disease of the brain that affects people of all ages. There are approximately 50 million patients with epilepsy worldwide, making it one of the most common neurological diseases in the world (1). China has approximately six million patients with active epilepsy every year, and 60% of them suffer from partial-onset seizures (2, 3) with a mortality risk of 2–3 times that of the general population(4).

• Burden of epilepsy

Epilepsy accounts for 5% of the global economic burden of mental illnesses (5). Long-term administration of anti-epileptic drugs (AEDs) and other costs of diagnosis and treatment impose a heavy economic burden to families. Moreover, The stigma of epilepsy brings about a serious psychological burden to patients and their families, which discourages the patients from seeking treatment and reduces their quality of life (1).

• Third-generation AED：perampanel

Epilepsy is a treatable disease, with AEDs being the most important treatment approach. Third-generation antiepileptic drugs perampanel (PER) and lacosamide (LCM), showing advantages in terms of efficacy, safety, and tolerability over first- and second-generation AEDs, are recommended for the treatment of refractory focal epilepsy in adults (6). PER has been included in Chinese National Reimbursement Drug List in 2020, one year after its approval(LCM was approved in 2018 and listed in 2019).

• Objectives

According to the Institute for Clinical and Economic Review (ICER) Value Framework 2.0, the economic efficiency and affordability of a drug should be simultaneously included in its value evidence (7). The economic efficiency of LCM compared with conventional therapy was proven in 2010. However, the economic efficiency of PER therapy for partial-onset seizures in China remains unknown. Therefore, this study aim to evaluate the value of PER as an add-on regimen for the treatment of partial-onset seizures to provide evidence on both cost-effectiveness and affordability from Chinese health system perspective.

MATERIAL AND METHODS

• Interventions

In particular, two dose comparison groups were set up in this study: PER 8 mg/day + AEDs vs. LCM 400 mg/day +AEDs, PER 4 mg/day + AEDs vs. LCM 200 mg/day + AEDs. This design was based on comprehensive consideration of the defined daily dose (DDD) recommended by the World Health Organization (WHO) (8), the availability of clinical trial data (9, 10), and the actual clinical dose used in China indicated by clinicians (11).

• Outcomes

Health outcomes includes number of epileptic seizures, life years (LYs), quality-adjusted life years (QALYs). Only direct medical costs were considered in this study, including drug costs and medical costs (covering outpatient, emergency, and inpatient treatment costs).

• Markov model

A Markov model was constructed to evaluate PER + AEDs vs. LCM + AEDs. The seizure frequency was dependent on the response rate after medication (the scale of the decrease in baseline number of seizures). The cycle period was set to 4 months (consistent with the medication regimen). A lifetime horizon was adopted. Health outcomes and costs were discounted at an annual discount rate of 5%. The seizure-free population was considered to have the same mortality risk as the general population.

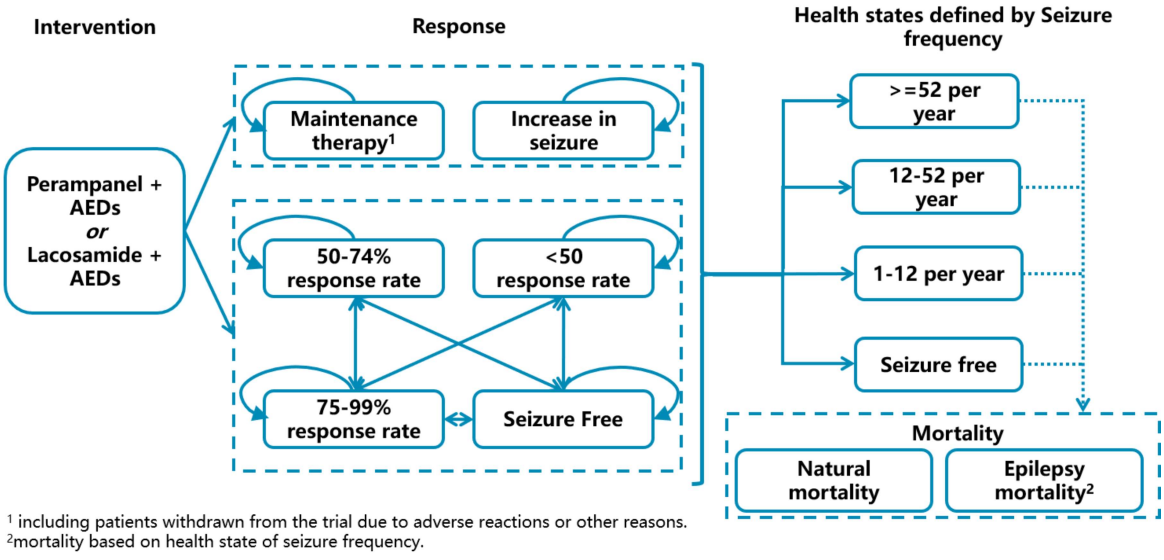


Figure 1 Markov Model Structure

• Data sources

For the first cycle in the model, response rates were derived from clinical trials 335 (trial registration number: NCT01618695) and EP0008 (trial registration number: NCT01710657). We used indirect comparison method to acquire the risk ratio values of PER and LCM response rates with conventional therapy as the bridge.

Table 1 Response distribution in the first cycle

	Maintenance therapy	Increase in seizure	<50% Response	50-74% Response	75-99% Response	Seizure free
PER 8mg/day	9.43%	26.42%	20.75%	22.64%	13.21%	7.55%
LCM 400mg/day	16.3%	28.2%	0.9%	33.6%	17.6%	3.3%
PER 4mg/day	6.52%	28.26%	41.3%	4.35%	13.04%	6.52%
LCM 200mg/day	8.6%	22.2%	20.4%	26.4%	18.5%	3.8%

From the second cycle, transition probabilities were obtained from 5-year follow-up data. 5-year transition probabilities were converted to 4-month cycle period according to the equation: P4month = 1 – exp ((1/15) * (ln(1–P5year).

Table 2 Response transition probabilities

From/to	Maintenance therapy	Increase in seizure	<50% Response	50-74% Response	75-99% Response	Seizure free
PER 8mg/day vs. LCM 400mg/day						
Maintenance	100.0%	0.0%	0.0%	0.0%	0.0%	0.0%
Increase in seizure	100.0%	0.0%	0.0%	0.0%	0.0%	0.0%
< 50% Response	0.0%	0.0%	97.7%	1.1%	0.6%	0.6%
50-74% Response	0.0%	0.0%	3.2%	96.0%	0.0%	0.8%
75%-99% Response	0.0%	0.0%	3.2%	0.0%	96.0%	0.8%
Seizure free	0.0%	0.0%	0.3%	1.7%	0.9%	97.1%
PER 4mg/day vs. LCM 200mg/day						
Maintenance	100.0%	0.0%	0.0%	0.0%	0.0%	0.0%
Increase in seizure	100.0%	0.0%	0.0%	0.0%	0.0%	0.0%
< 50% Response	0.0%	0.0%	97.7%	1.0%	0.7%	0.6%
50-74% Response	0.0%	0.0%	3.2%	96.0%	0.0%	0.8%
75%-99% Response	0.0%	0.0%	3.2%	0.0%	96.0%	0.8%
Seizure free	0.0%	0.0%	0.3%	1.5%	1.0%	97.2%

Natural mortalities were obtained from the life table in China published by the WHO (13). Base value, DSA range and data sources of epilepsy Mortalities, drug costs, medical costs and Health state utilities are shown in table 3.

Table 3 Inputs in Markov model

	Base case	DSA Range	Distribution	Source
Relative risks of mortality				
≥53 seizures/year	10.16	2.94-35.18	-	(14)
13-52 seizures/year	8.64	2.88-25.93	-	(14)
≤12 seizures/year	7.21	2.52-20.6	-	(14)
Drug costs per 4 months ($)				
PER 4mg/day	878	±10%	Gamma	MENET[a], 335 clinical trial
AEDs - PER4mg/day group	692	-20%-0%	Gamma	
PER 8mg/day	1754	±10%	Gamma	MENET[a], 335 clinical trial
AEDs - PER 8mg/day group	827	-20%-0%	Gamma	
LCM 200mg/day	1484	-20%-0%	Gamma	MENET[a], (10)
AEDs - LCM 200mg/day group	695	-20%-0%	Gamma	
LCM 400mg/day	2968	-20%-0%	Gamma	MENET[a], (10)
AEDs - LCM 400mg/day group	549	-20%-0%	Gamma	
Medical costs per 4 months ($)				
≥53 seizures/year	571	±20%	Gamma	health care documents[b], KOL
13-52 seizures/year	441	±20%	Gamma	health care documents[b], KOL
≤12 seizures/year	273	±20%	Gamma	health care documents[b], KOL
Seizure free	180	±20%	Gamma	health care documents[b], KOL
Health Utilities per 4 months				
≥53 seizures/year	0.619	±0.15	Beta	
13-52 seizures/year	0.628	±0.12	Beta	(15)
≤12 seizures/year	0.673	±0.14	Beta	(15)
Seizure free	0.711	±0.14	Beta	(15)

a. China Drug Bidding Database (shuju.menet.com.cn)
b. The health care documents from the 9 provinces medical security bureaus

- **sensitivity analysis**

We performed deterministic sensitivity analysis (DSA) using the 95% confidence interval reported in the literature as the variation range. The variation range of other parameters that lacked documented reports was assumed based on KOL (Key Opinion Leader) opinions.

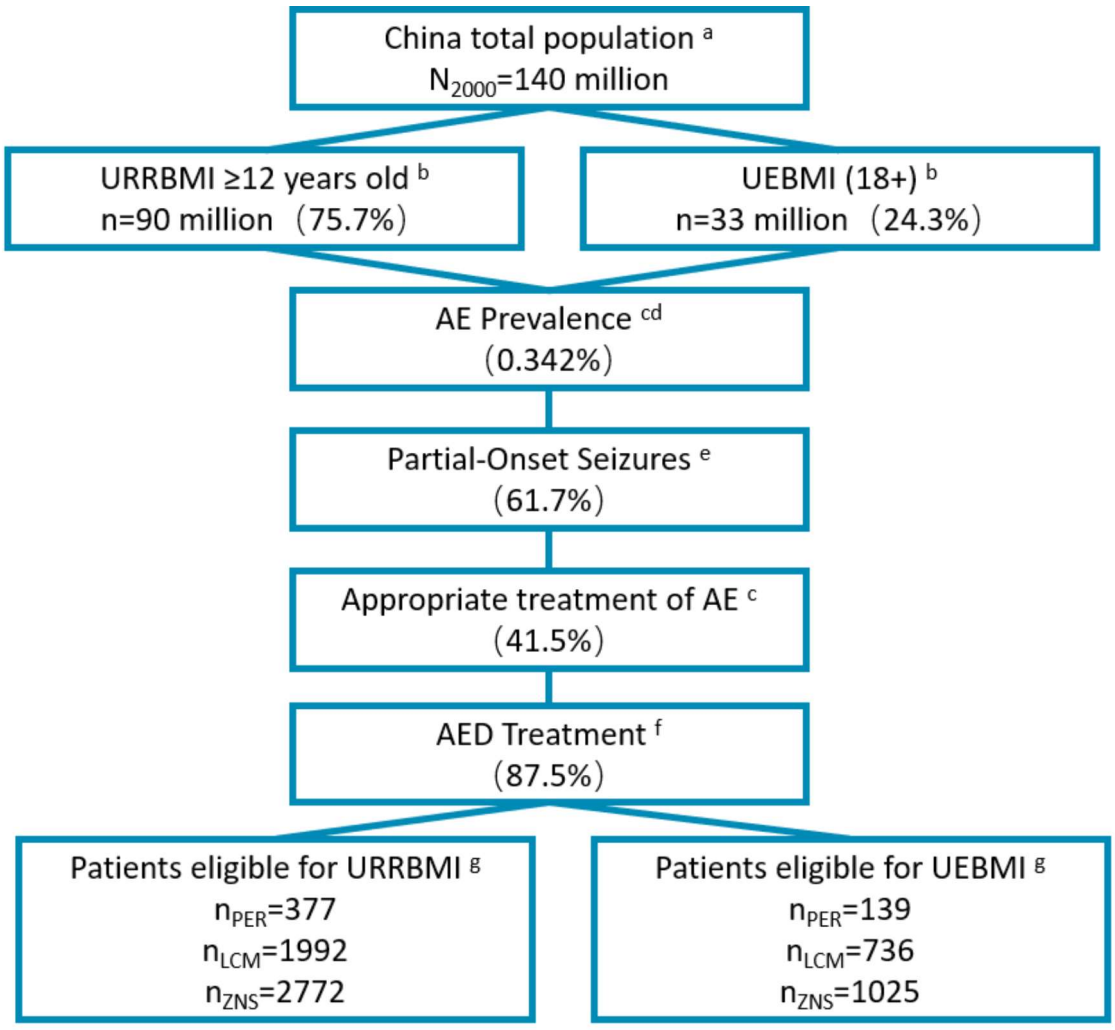
Probabilistic sensitivity analysis (PSA) was performed using Monte Carlo simulation with 10,000 iterations. The parameter characteristics of cost and utility value are listed in Table 4. In addition we assumed that LY conforms to a normal distribution, with its mean and standard deviation derived from the model.

- **Budget Impact**

We analyzed the impact of covering PER on the medical insurance budget in 2021–2023. Considering the substitution of other similar drugs by PER, we added zonisamide (ZNS) as a reference drug in addition to LCM. The market share of the three drugs in 2020–2023 was obtained by Eisai Co., Ltd. (table 4). Cost data were derived from the CEA results. For the two groups of daily doses, we obtained the use ratio of clinical patients for different daily doses of PER and LCM by consulting KOL for weighting in the cost calculation.

Table 4 Market share (Before and after the inclusion of PER in the NRDL)

Drugs	Before, %				After, %		
	2020	2021	2022	2023	2021	2022	2023
PER	0.060	0.140	0.240	0.340	0.350	0.700	1.250
LCM	0.320	0.660	1.150	1.610	0.620	1.090	1.420
ZNS	0.480	0.410	0.340	0.290	0.390	0.310	0.240
Total	0.860	1.210	1.730	2.240	1.360	2.100	2.910



a. Data from the National Bureau of Statistics of China (data.stats.gov.cn).
b. Basic medical insurance participation data from reports of medical insurance bureau (nhsa.gov.cn), and proportion of people over 12 years old from 2010 Census Report (data.stats.gov.cn).
c. Prevalence of active epilepsy and rate of standardized treatment from Ding et al. (16).
d. Annual growth rate of the prevalence during 2021–2023 from Song et al. (17)
e. Proportion of patients with partial seizures from Yu et al. (2).
f. Standardized treatment rate of drugs from investigation results of 18 clinical experts.
g. Market shares of three drugs provided by Eisai Co., Ltd. (Table 4).

Figure 2 Patient disposition in BI model (2020)

RESULTS

Base Case Analysis

- Compared with LCM 400 mg/day, PER 8 mg/day reduces the number of seizures per capita by 141 times, with an incremental LY of 0.061, an incremental QALY of 0.054, and a direct medical cost saving of $2,390.

- Compared with LCM200 mg/day, PER 4 mg/day reduces the number of seizures per capita by 72 times, with an incremental LY of 0.012, an incremental QALY of 0.010, and a cost savings of $860.

- PER has an dominate advantage over LCM in term of cost-effectiveness.

Table 5 Base case analysis results

outcomes	Absolute		Incremental		Absolute		Incremental	
	PER 8mg/day	LCM 400mg/day		%	PER 4mg/day	LCM 200mg/day		%
Seizures	467	608	-141	-23.2	717	789	-72	-9.1
LYs	4.940	4.879	0.061	1.3	5.17	5.158	0.012	0.2
QALYs	3.137	3.083	**0.054**	1.8	3.278	3.268	**0.010**	0.3
Drug costs	9144	11462	-2318	-20.2	7304	8229	-925	-11.2
Medical costs	7001	7073	-72	-1.0	7400	7335	65	0.9
Total costs	16145	18535	**-2390**	-12.9	14704	15564	**-860**	-5.5

Sensitivity Analysis

- The DSA results show that the ICER of PER 8 mg/day vs. LCM 400 mg/day group ranges from $150,911 to $8,418/QALY, with the extreme discount rate having the greatest impact on ICER. The ICER of PER 4 mg/day vs. LCM 200 mg/day group ranges from $556,653 to $119,970/QALY, with the utility value having the greatest impact on ICER.

- The PSA results show that the two dose groups of PER have a large probability of being economical at various levels of willingness-to-pay. The one-to-three times GDP per capita was $10,838–$32,515 in China in 2019.

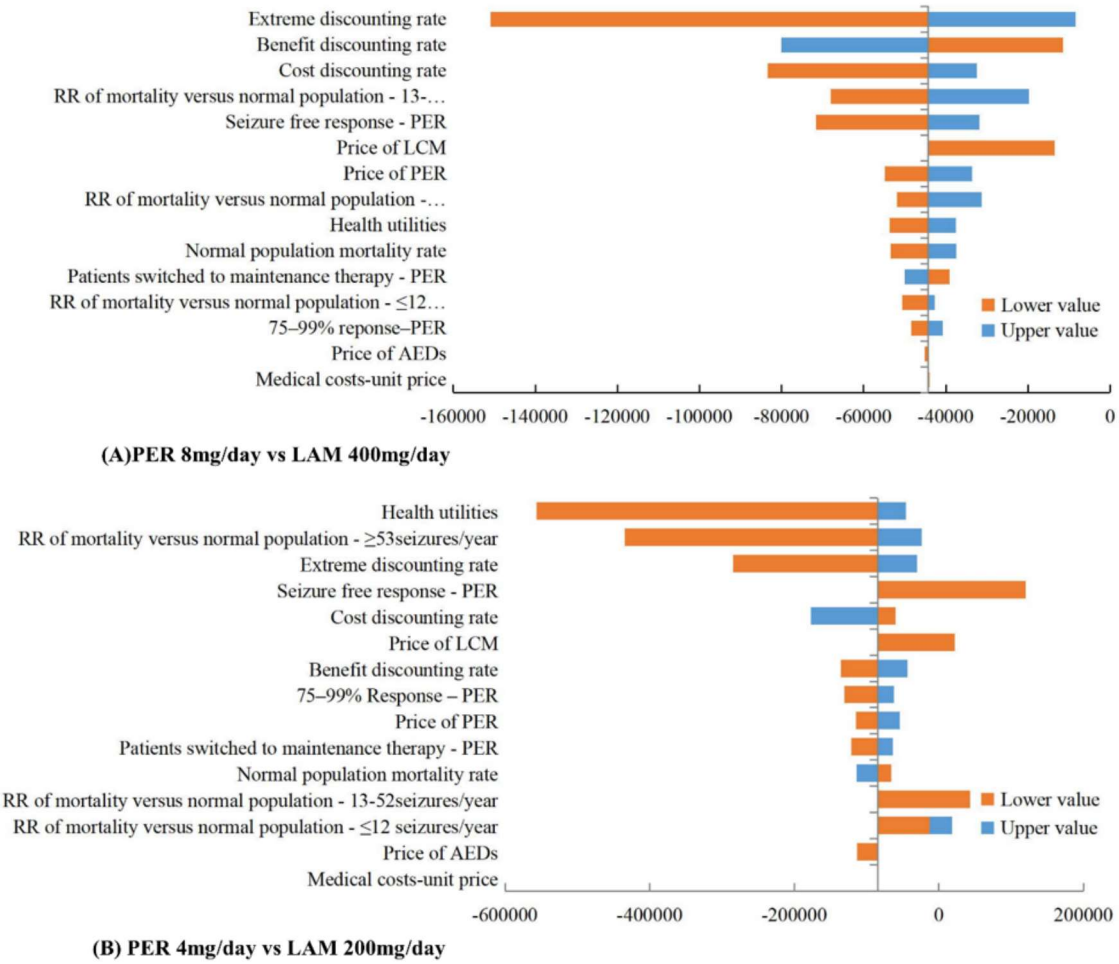


Figure 3 Tornado diagram of deterministic sensitivity analysis

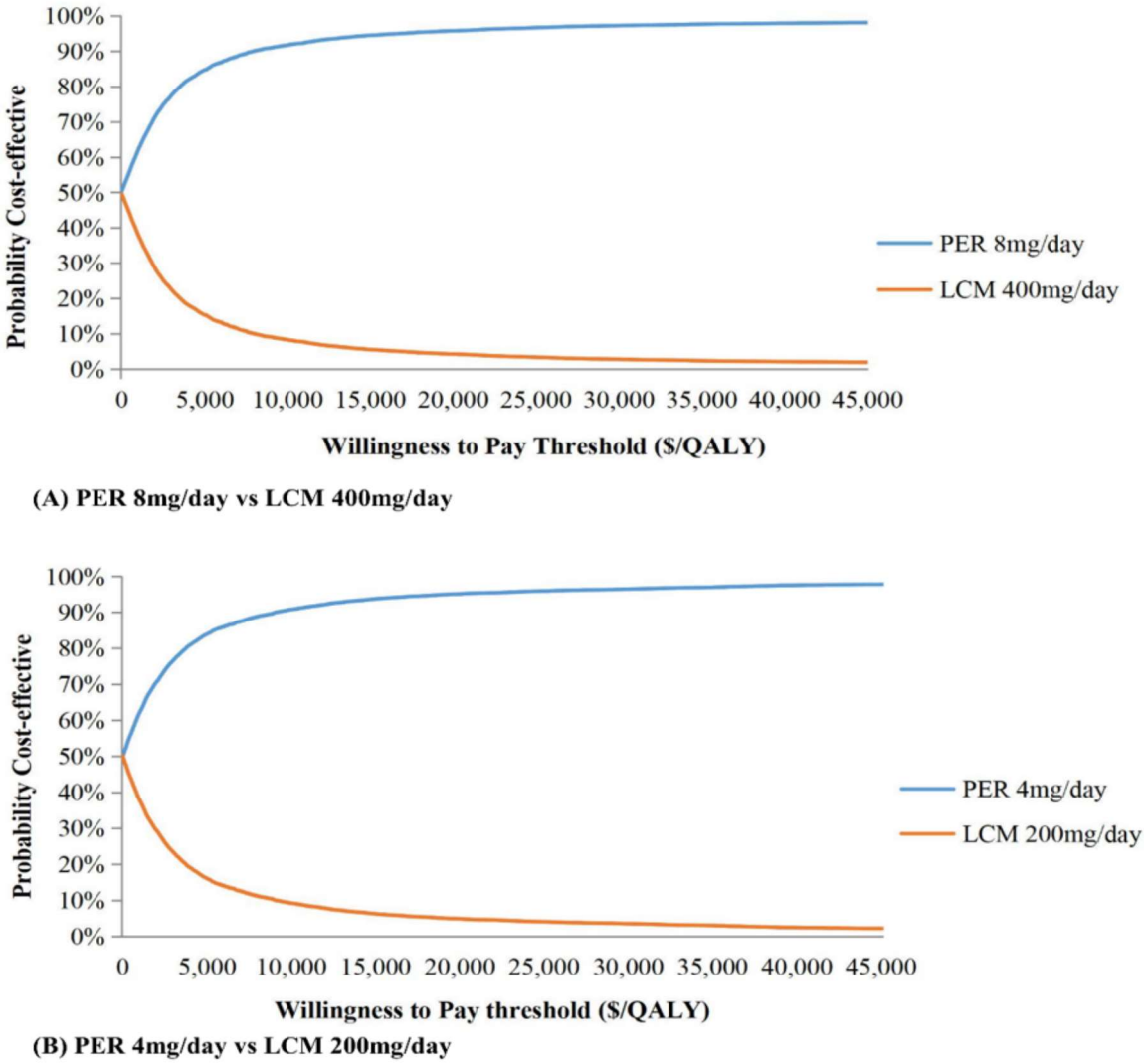


Figure 4 Cost-effectiveness acceptability curve

Budget Impact Analysis

- Before and after the inclusion of PER, the absolute budget impact over 2021–2023 will be $17.30, $27.78, and $39.08 million and $18.58, $30.61, and $43.65 million, respectively.

- The incremental budget impact (including drug and medical service costs) over the 3 years will be $1.28, $2.83, and $4.56 million, respectively, accounting for 0.00037%, 0.00082%, and 0.00132% of the total expenditure of national medical insurance in that year.

Table 6 Results of Budget Impact Analysis

Costs (million USD)	Before the inclusion of PER in the NRDL					After the inclusion of PER in the NRDL			
	2020	2021	2022	2023	3-Year total	2021	2022	2023	3-Year total
Durg	5.60	9.33	15.16	21.25	51.34	10.72	18.18	26.23	60.73
Direct medical	5.01	7.96	12.62	17.83	43.43	7.86	12.43	17.41	42.71
Total	10.61	17.30	27.78	39.08	94.77	18.58	30.61	43.65	103.45

- Among them, drug costs will increase by $1.39, $3.02, and $4.99 million, whereas medical service costs will be reduced by $0.10, $0.19, and $0.42 million.

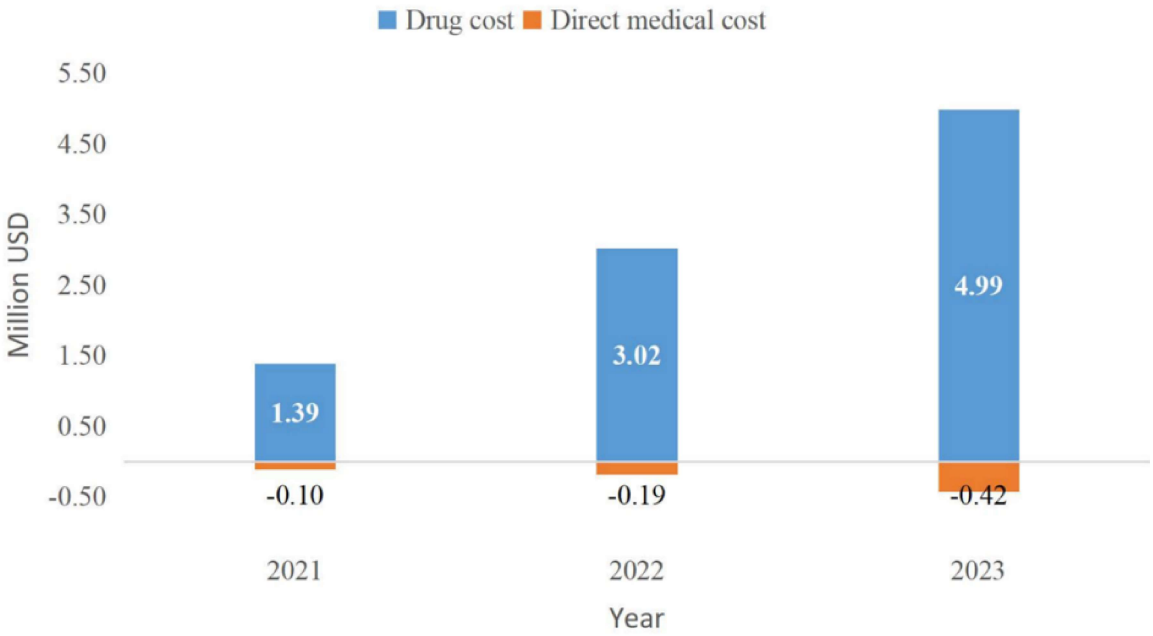


Figure 5 Incremental budget impact of the inclusion of PER (2021-2023)

DISSCUSION

- Our study shows that using PER as an adjuvant therapy to AEDs has an dominate advantage over LCM in terms of cost-effectiveness. This result is also relatively stable within the one-two-three times GDP per capita of $10,838–$32,515.

- Based on the BIA, this study is in agreement with the results of Tremebly et al. (18) for PER; that is, PER as an add-on brings about an increase budget year by year while also resulting in a medical service cost savings. This result is mainly attributed to the improvement of health state after the use of PER, which in turn reduces the direct medical costs.

Innovations

- First study to assess the value of PER with respect to cost effectiveness and medical insurance affordability

- Modeling lifetime effectiveness and cost of epilepsy patients with full consideration of long-term simulation and health state classification of epileptic patients.

- Using indirect comparison between PER and LCM as no head- to-head clinical trials is available.

- Including two pairs of daily dose comparisons comprehensively considering WHO recommendation, KOL opinions and clinical trials.

Limitations

- Data availability is the biggest problem in this study. For example, no data are available on the utility ,mortality risk of epilepsy and transition probabilities in the Chinese population, which may introduce potential bias.

- Compliance and adverse reaction are not considered in the model.

CONCLUSION

- PER has a dominate advantage of cost-effectiveness compared with LCM (8 mg/day vs. 400 mg/day; 4 mg/day vs. 200 mg/day), and its incremental budget impact for medical insurance payers is acceptable.
- China has not yet developed a value framework that integrates cost-effectivenss analysis and budget impact analysis. Nevertheless, evidence on the cost-effectiveness and affordability of drugs has received increasing attention in this country. The present study also provides a reference for stakeholders to judge the value of PER.

ABSTRACT

OBJECTIVES: Perampanel (PER) has been included in Chinese National Reimbursement Drug List in 2020, one year after its approval. This study aims at evaluating cost-effectiveness and budget impact of PER+ antiepileptic drugs (AEDs) versus lacosamide (LCM)+AEDs (one year ahead of PER in drug approval and listing, respectively) for patients with partial-onset seizures in China.

METHODS: The study perspective is Chinese health system. A Markov model with four states (yearly seizure frequency of ≥53, 13-52, 1-12 and seizure free) was developed. Efficacy data were derived from trials (NCT01618695, NCT01710657). Utilities and mortality were derived from literature. Quality-adjusted life year (QALY) was estimated for health outcomes. Life-time direct costs were included. All outcomes were discounted using 5% discounting rate. Deterministic and probabilistic sensitivity analysis were performed. This study also estimated budget impact to Chinses payers for the first three years (2021-2023) after listing.

RESULTS: In the base case analysis, PER (8mg/d)+AEDs per patient was associated with a gain of 0.054 QALYs and $2390 cost saving compared to LCM (400mg/d)+AEDs. PER (4mg/d)+AEDs per patient was associated with a gain of 0.010 QALYs and $860 cost saving compared to LCM (200mg/d)+AEDs. Utilities and extreme discounting rate were the most sensitive parameters. The base-case results were robust after 10,000 iterations. For budget impact, the incremental expenditure of PER listing would be 1.28, 2.83 and 4.56 million USD from 2021 to 2023, respectively, but covering more eligible epileptic patients in the same time (1918, 4287 and 8983, respectively). Market share, prevalence and proportion of PER clinical dose used by patients were the most sensitive parameters.

CONCLUSIONS: This study indicates that PER as adjunctive treatment brings value to patients with partial-onset seizures in China. The cost-effectiveness of PER is dominant to its peer and the incremental budget is within affordability of Chinese payers.

REFERENCES

1.World Health Organization. Epilepsy: a public health imperative. (2019) https://www.ilae.org/about-ilae/policy-and-advocacy/international-public-policy-activities/global-epilepsy-report-2019 [Accessed Apil 9, 2020].

2.Yu P, Zhou D, Liao W, Wang X, Wang Y, Wang T, et al. An investigation of the characteristics of outpatients with epilepsy and antiepileptic drug utilization in a multicenter cross-sectional study in China. Epilepsy Behav (2017) 69:126-32. doi: 10.1016/j.yebeh.2016.09.021. PubMed PMID: 28242476.

3.Wang WZ, Wu JZ, Wang DS, Dai XY, Yang B, Wang TP, et al. The prevalence and treatment gap in epilepsy in China: an ILAE/IBE/WHO study. Neurology (2003) 60(9):1544-5. doi: 10.1212/01.wnl.0000059867.35547.de. PubMed PMID: 12743252.

4.Thurman DJ, Logroscino G, Beghi E, Hauser WA, Hesdorffer DC, Newton CR, et al. The burden of premature mortality of epilepsy in high-income countries: A systematic review from the Mortality Task Force of the International League Against Epilepsy. Epilepsia (2017) 58(1):17-26. doi: 10.1111/epi.13604. PubMed PMID: 27888514.

5.Global, regional, and national burden of neurological disorders during 1990-2015: a systematic analysis for the Global Burden of Disease Study 2015. Lancet Neurol (2017) 16(11):877-97. doi: 10.1016/S1474-4422(17)30299-5. PubMed PMID: 28931491.

6.Kanner AM, Ashman E, Gloss D, Harden C, Bourgeois B, Bautista JF, et al. Practice guideline update summary: Efficacy and tolerability of the new antiepileptic drugs II: Treatment-resistant epilepsy: Report of the Guideline Development, Dissemination, and Implementation Subcommittee of the American Academy of Neurology and the American Epilepsy Society. Neurology (2018) 58(Suppl. 8).

7.Pearson SD. The ICER Value Framework: Integrating Cost Effectiveness and Affordability in the Assessment of Health Care Value. Value Health (2018) 21(3):258-65. doi: 10.1016/j.jval.2017.12.017. PubMed PMID: 29566831.

8.World Health Organization. ATC/DDD Index (2020). http://www.whocc.no/atc_ddd_index/ [Accessed April 15, 2020]

9.Nishida T, Lee SK, Inoue Y, Saeki K, Ishikawa K, Kaneko S. Adjunctive perampanel in partial-onset seizures: Asia-Pacific, randomized phase III study. Acta Neurol Scand (2018) 137(4):392-9. doi: 10.1111/ane.12883. PubMed PMID: 29250772.

10.Hong Z, Liao W, Meng H, Du X, Toru O, Hiroshi S, et al. Efficacy and Safety of Lacosamide as Adjunctive Therapy in Chinese Patients with Partial-onset Seizures: Subgroup and Post Hoc Analyses of A Randomized Double-blind Trial and Open-label Extension. Chinese Journal of Clinical Neurosciences (2019) 27(04):361-78.

11.China Association Against EpilepsyChinese medical association. Chinese guidelines on the diagnosis and treatment forof epilepsy.BeiJing: People's Medical Publishing House (2015).

12.Neligan A, Bell GS, Elsayed M, Sander JW, Shorvon SD. Treatment changes in a cohort of people with apparently drug-resistant epilepsy: An extended follow-up. Journal of Neurology Neurosurgery & Psychiatry (2012) 83(8):810-3.

13.World Health Organization. Life tables by country China (2015). WHO. https://apps.who.int/gho/data/view.main.60340?lang=enLife tables by country. [Accessed April 15, 2020]

14.Nilsson L, Farahmand BY, Persson PG, Thiblin I, Tomson T. Risk factors for sudden unexpected death in epilepsy: a case-control study. Lancet (1999) 353(9156):888-93.

15.Tsong, Wan, Gupta, Shaloo, Kwan, Patrick, et al. Understanding the burden of idiopathic generalized epilepsy in the United States, Europe, and Brazil: An analysis from the National Health and Wellness Survey. Epilepsy & behavior: E&B (2016).

16.Ding X, Zheng Y, Guo Y, Shen C, Wang S, Chen F, et al. Active epilepsy prevalence, the treatment gap, and treatment gap risk profile in eastern China: A population-based study. Epilepsy Behav (2018) 78:20-4. doi: 10.1016/j.yebeh.2017.10.020. PubMed PMID: 29161630.

17.Song P, Liu Y, Yu X, Wu J, Poon AN, Demaio A, et al. Prevalence of epilepsy in China between 1990 and 2015: A systematic review and meta-analysis. J Glob Health (2017) 7(2):20706. doi: 10.7189/jogh.07-020706. PubMed PMID: 29302325.

18.Tremblay G, Barghout V, Patel V, Tsong W, Wang Z. Budget impact of perampanel as adjunctive treatment of uncontrolled partial-onset and primary generalized tonic-clonic seizures in the United States. Epilepsy Behav (2017) 68:196-202. doi: 10.1016/j.yebeh.2016.12.029. PubMed PMID: 28236697.