



Cost-effectiveness of perampanel as an adjunctive treatment for uncontrolled focal seizures in pediatric patients: a Chinese perspective

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Contributions: (I) Conception and design: Both authors; (II) Administrative support: H Dai; (III) Provision of study materials or patients: Y Hu; (IV) Collection and assembly of data: Y Hu; (V) Data analysis and interpretation: Y Hu; (VI) Manuscript writing: Both authors; (VII) Final approval of manuscript: Both authors.

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Background: The incidence of epilepsy is 41–187 per 100,000 person-year in children. The health care costs for children with uncontrolled epilepsy is a huge burden. Perampanel (PER) was effective, safety and well-tolerated as add-on therapy in pediatric patients aged 4 to <12 years with uncontrolled focal seizures. However, there is still limited evidence on cost-effectiveness of PER in pediatric patients. We aimed to evaluate the cost-effectiveness of PER as an add-on therapy for pediatric patients with uncontrolled focal seizures.

Methods: A Markov model was established to conduct an analysis from the perspective of the Chinese health system and society. The incremental cost-effectiveness ratio (ICER) of patients using PER and conventional therapy versus patients using conventional therapy alone were estimated and compared. The transition probability of the response level, health state utility values, and costs were derived from clinical trials and the literature. Costs, including medical, drug, transportation and indirect costs, were calculated. We performed 1-way sensitivity analyses and probabilistic sensitivity analyses. A subgroup analysis of different ages was also conducted.

Results: The base-case analysis indicated that compared to maintaining conventional therapy, adding PER as an adjuvant drug therapy had an increased cost of \$3,449.85 over 5 years, with an incremental quality-adjusted life years (QALY) value of 0.40, resulting in an ICER of \$8,582.58 per additional QALY. The health state utility value had the greatest effect on the ICER. The probabilistic sensitivity analyses showed that the probability of PER being cost-effective was 76.72% at a willingness-to-pay of \$11,293/QALY. The ICER of the subgroup ranged from \$7,167.95/QALY to \$19,710.96/QALY.

Conclusions: Our study demonstrated that PER is a cost-effective add-on therapy for pediatric patients.

Keywords: Perampanel (PER); cost-effectiveness; pediatric patients; focal seizure

Submitted Jan 17, 2022. Accepted for publication Mar 21, 2022.

doi: 10.21037/atm-22-994

View this article at: <https://dx.doi.org/10.21037/atm-22-994>

Introduction

Epilepsy is a common chronic disease that affects 65–70 million people worldwide, and accounts for 0.5% of the global disease burden (1,2). It has an incidence of 41–187 per 100,000 person-years in children, and most

children have their first seizure at the age of 1–10 years (3). The severity of epilepsy varies from individual to individual, and is related to different epilepsy types (i.e., focal epilepsy, generalized epilepsy, and combined focal and generalized epilepsy (4). Antiepileptic drugs (AEDs) are the most

commonly used and preferred treatment for epilepsy. Most patients with epilepsy are seizure free after the first AED treatment, but nearly 1/3 of epilepsy patients continue to have uncontrolled seizures (5). Approximately 14% of patients need to switch to or add 2nd- or 3rd-line AEDs to control their seizures (6-8). It has been reported that 10% of children with newly diagnosed epilepsy will develop refractory epilepsy (9).

The health care costs for children with epilepsy is a huge burden for families and countries. The annual cost of epilepsy in children between 2003 and 2014 was approximately \$5.8 billion in United States (US) (10). The severity of epilepsy is an important factor affecting healthcare costs (11). For example, the average annual cost of children with uncontrolled epilepsy (\$30,343) is significantly higher than that of patients with stable epilepsy (\$18,206) (12).

Since 2012, 4 randomized, multicenter, clinical trials have proven that compared to conventional therapy, perampanel (PER) is effective, safe, and well-tolerated in the treatment of focal epilepsy as an adjunctive drug in different populations (13-17), which indicates that PER can be used as adjuvant therapy for adults (18). In 2021, PER was approved as adjuvant therapy for pediatric patients aged 4–12 years in the US (18). This indication was also approved in China in July 2021, which can be attributed to a multicenter study conducted in pediatric patients (aged 4 to <12 years) (19). This study found that PER was also effective, safe, and well-tolerated in pediatric patients. Lin *et al.* also reported that the 50% response rate of PER in the adjuvant treatment for children with uncontrolled seizures was 34.7% at 12 months, and that PER appeared to be effective in a real-world study (20).

Cost-effectiveness analysis, one of the methods of pharmacoeconomics, aims to evaluate the cost per gained effectiveness of two or more therapies. The results will help clinicians obtain the best effect with the lowest consumption, and promote clinical rational drug use. Evidence of the cost-effectiveness of PER is limited. A cost-effectiveness study conducted with generalized epilepsy patients in Spain showed that the incremental cost-effectiveness ratio (ICER) of €16,557/quality-adjusted life year (QALY) of PER as adjuvant therapy was superior to that of conventional treatment regimens (21). Zhang *et al.* compared the cost-effectiveness of PER at 4 mg/day or 8 mg/day to lacosamide (LCM) at 200 mg/day or 400 mg/day in patients with focal epilepsy in China, and found that PER

is more cost-effective than LCM (22). Both studies were conducted in adults. As PER had been proved effective and covered by medical insurance in China, its cost-effectiveness as adjuvant therapy for focal epilepsy is still unclear, especially in pediatric patients aged 4 to <12 years old. The cost-effectiveness of PER will help clinicians and families choose AEDs more suitably in terms of pharmacoeconomics and expound the value of PER for pediatric patients.

Our study aimed to evaluate the cost-effectiveness of PER as an adjuvant drug in pediatric patients aged 4 to <12 years with uncontrolled focal seizures from the perspective of the Chinese health system and society. We present the following article in accordance with the CHEERS reporting checklist (available at <https://atm.amegroups.com/article/view/10.21037/atm-22-994/rc>).

Methods

Model

Since epilepsy is a chronic disease, a Markov model was adopted to evaluate the cost-effectiveness of PER + AEDs to that of AEDs in patients with uncontrolled focal epilepsy in China from the perspective of the Chinese health system and society. AEDs refer to the maintenance of conventional treatment. The model converts between the following 4 health states (defined by seizure frequency): (I) ≥ 53 times per year; (II) 13–52 times per year; (III) 1–12 times per year; (IV) seizure free. The conversion between the 4 health states is as follows: <50% response, 50–74% response, 75–99% response, and seizure free. The <50% response includes an increase in seizure frequency and a decrease in seizure frequency of no more than 50%. The cycle period of the model is 6 months, which is consistent with the core phase of the clinical trial. Due to the limited efficacy data, we only compared the 5-year cost-effectiveness of the treatments between the 2 groups. The schematic structure of the Markov model is shown in *Figure 1*. We also performed a subgroup analysis of different age groups (i.e., 4 to <7 years old and 7 to <12 years old).

Outcomes

The primary outcome was the ICER, which was defined as an increase in the cost for the additional QALY gained. The following formula was used to calculate the ICER: $(C_{\text{PER} + \text{AEDs}} - C_{\text{AEDs}}) / (E_{\text{PER} + \text{AEDs}} - E_{\text{AEDs}})$, where C

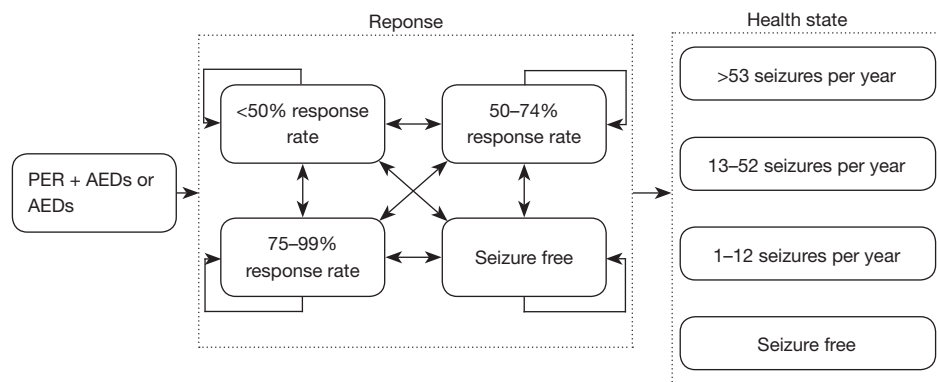


Figure 1 The schematic structure of the Markov model. AEDs refer to the maintenance of conventional therapy. PER, perampanel; AED, antiepileptic drug.

Table 1 Baseline characteristics of patients from the clinical trials

Baseline characteristics	AEDs	PER + AEDs
Total number of patients	100	149
Mean age (SD), years	11.2 (3.2)	8.1 (2.1)
Sex, n (%)		
Female	55 (55.0)	77 (51.7)
Male	45 (45.0)	72 (48.3)
Mean (SD) time since diagnosis, years	5.4 (3.7)	5.7 (2.7)
Number of concomitant AEDs, n (%)		
0	1 (1.0)	0 (0.0)
1	39 (39.0)	27 (18.1)
2	60 (60.0)	83 (55.7)
3	0 (0.0)	39 (26.2)
Seizure type ^a , n (%)		
Simple FS without motor signs	34 (34.0)	19 (12.8)
Simple FS with motor signs	10 (10.0)	46 (30.9)
Complex FS	58 (58.0)	116 (77.9)
Complex FS with FBTCS	33 (33.0)	82 (55.0)

^a, patients may have had more than 1 seizure type. AEDs refer to the maintenance of conventional therapy. AED, antiepileptic drug; PER, perampanel; SD, standard deviation; FS, focal seizures; FBTCS, focal to bilateral tonic-clonic seizures.

represents the cost, and E represents the effectiveness.

Data resources

The study was conducted in accordance with the

Declaration of Helsinki (as revised in 2013).

The transition probability of the PER + AEDs treatment among the states comes from Study 311(19), a clinical trial on the efficacy and tolerability of PER in pediatric patients aged 4 to <12 years with focal seizures. The study ran for up to 52 weeks. Thus, we extracted the transition probabilities from this study for use in the 1st and 2nd cycles of the model. As Study 311 was not a placebo-controlled study, the transition probability of the AEDs group was derived from a phase-III, randomized, study comparing the effectiveness and safety of zonisamide to placebo in pediatric patients with focal seizures (23). In the literature, the initial state distribution probability for >53 seizures per year is 87.76%, and that for 13–52 seizures per year is 12.24% (24). We assumed that the initial state distribution probability was the same in the 2 groups. *Table 1* shows the baseline characteristic of the 2 groups.

From the 3rd cycle, the transition probability between the states was derived from a 5-year long-term follow-up study (25). The 5-year transition probability of the study was converted into a 6-month transition rate using the following formula: $P_{6 \text{ months}} = 1 - \exp[(1/10) \times \ln(1 - P_{5 \text{ years}})]$ (26). *Table 2* shows the details.

The health state utility values, which were derived from the extension phase of Study 311, are from the same population (27). A total of 176 EQ-5D-Y-3L observations from 60 patients were assigned to calculate the health state utility value.

From the perspective of society and the health system, the total cost was the sum of the drug, medical, transportation, and indirect costs. The medical cost comprised the laboratory and instrument tests, outpatient visits, hospitalization, and emergency costs, which were

Table 2 Transition probability among different states

Transition probability	1st cycle		2nd cycle	
	PER + AEDs	AEDs	PER + AEDs	AEDs
<50% response rate	0.508	0.690	0.380	0.333
50–74% response rate	0.189	0.190	0.212	0.181
75–99% response rate	0.161	0.030	0.215	0.375
Seizure free rate	0.142	0.090	0.193	0.111

AEDs refer to the maintenance of conventional therapy. AED, antiepileptic drug; PER, perampanel.

calculated by multiplying the frequency by the unit price. The frequency of each cost came from a study on the economic burden of epilepsy in China (28). To reflect the current economic level, we discounted the unit price reported in the study by 5%. The drug cost included the conventional treatment and PER costs. The cost of PER was obtained by multiplying the average daily dose (7.0 mg/day) in Study 311 by the unit price. The unit price of PER was derived from the China Drug Bidding Database. As PER was covered by medical insurance, the unit price of PER was the price at patients' own expense after medical insurance. The cost of the AEDs group was derived from a real-world study reporting the annual cost of childhood epilepsy in mainland China (29).

The indirect cost, which was calculated based on per capita disposable income, refers to any loss of income as a result of taking care of a child or going to the hospital for clinical appointments. As reported, the loss of income decreased with the decreasing seizure frequency, such that the loss of income for a patient with a health state of >53 seizures per year was 40%, that for a patient with a health state of 13–52 seizures per year was 36.8%, that for a patient with a health state of 1–12 seizures per year was 26.6%, and that for a patient who was seizure free was 18.7% (30).

The Chinese 2020 per capita disposable income was \$5,048 (31). The discount rate was 5% according to Chinese guidelines for pharmaco-economic evaluations. All Chinese yuan were converted into US dollars, 1 US. dollar =6.3587 yuan. The medical costs are detailed in *Table 3*.

Statistical analysis and sensitivity analysis

One to three times Chinese gross domestic product (GDP) per capita is set as the threshold for judging the value of the ICER. Chinese GDP per capita in 2020 was \$11,293.

One-way sensitivity analyses and probabilistic sensitivity analyses were performed to assess the uncertainty impact on the results of our study. We performed 1-way sensitivity analyses to analyze whether the drug cost, medical cost, transportation cost, indirect cost, health state utility values, and the discount rate affected the results. The cost and health state utility values varied in the 95% confidence intervals reported in the literature or fluctuated by 20% (27). The discount rate ranged from 0–8% (see *Table 4* for further details).

In total, 10,000 Monte Carlo simulations were performed to conduct the probabilistic sensitivity analysis. The standard deviation of the cost and health state utility values came from the article mentioned above, and the parameter distribution is set out in *Table 4*, which refers to the International Society for Pharmacoeconomics and Outcomes Research and Society for Medical Decision Making (ISPOR-SMDM) Modeling Good Research Practice Task Force (32). Cost including direct and indirect cost follows a gamma distribution as the cost is positive and the range is wide. Health states utility values follow beta distribution.

Results

Base-case analysis

Compared to maintaining conventional therapy, adding PER as adjuvant therapy increased the cost by \$3,449.85 over 5 years, with an incremental QALY of 0.40, resulting in an ICER of \$8,582.58 per additional QALY (see *Table 5*).

Sensitivity analysis

Figure 2 shows the results of the univariable sensitivity analysis. The ICER of the PER + AEDs group compared to the AEDs group ranged from \$151,222/QALY to \$6,876/QALY, and the utility value of the seizure-free state had the greatest effect on the ICER. Factors such as a utility value of 1–12 seizures per year, the cost of PER, a utility value of ≥53 seizures per year, the drug cost of the AEDs group, and the indirect cost of 1–12 seizures per year also affected the ICER, while the other factors had little effect on the ICER.

The probabilistic sensitivity analyses represent the probability of cost-effectiveness between the PER + AEDs and AEDs groups at various levels of willingness-to-pay. The willingness-to-pay varied from 1 to 3 times the Chinese GDP per capita (\$11,293–33,879) in 2020. The

Table 3 Medical direct cost by health state per 6 months

Components	Unit cost (\$)	≥53 seizures per year	13–52 seizures per year	1–12 seizures per year	Seizure free
Outpatient visits (n)	149.77	2.80	2.06	1.06	0.74
Emergency-room visits (n)	119.18	0.20	0.20	0.20	0.10
Hospitalization (n)	130.69	0.30	0.10	0.10	0.00
Total costs (\$)	–	482.40	345.43	195.66	122.75

Table 4 Input in the CE model

	Base case	Range	Distribution	References
Drug cost per 6 months (\$)				
AEDs + PER ^a	808.17	±10%	Gamma	Study 311 (NCT02849626)
AEDs	356.58	±10%	Gamma	(29)
Medical cost per 6 months (\$)				
≥53 seizures per year	482.40	±20%	Gamma	(22,28)
13–52 seizures per year	345.43	±20%	Gamma	(22,28)
1–12 seizures per year	195.66	±20%	Gamma	(22,28)
Seizure free	122.75	±20%	Gamma	(22,28)
Transportation per 6 months (\$)				
≥53 seizures per year	148.37	±20%	Gamma	(28)
13–52 seizures per year	79.05	±20%	Gamma	(28)
1–12 seizures per year	55.52	±20%	Gamma	(28)
Seizure free	23.84	±20%	Gamma	(28)
Indirect cost (\$)				
≥53 seizures per year	1009.72	±20%	Gamma	(30)
13–52 seizures per year	928.94	±20%	Gamma	(30)
1–12 seizures per year	671.46	±20%	Gamma	(30)
Seizure free	472.04	±20%	Gamma	(30)
Health utilities				
≥53 seizures per year	0.284	0.014–0.582	Beta	(27)
13–52 seizures per year	0.596	0.338–0.855	Beta	(27)
1–12 seizures per year	0.620	0.506–0.734	Beta	(27)
Seizure free	0.914	0.587–1.240	Beta	(27)

^a, we adopted the price of PER after medical insurance; thus, a small range (10%) of the drug cost was used in the one-way sensitivity analysis. AEDs refer to the maintenance of conventional therapy. CE, cost-effectiveness; AED, antiepileptic drug; PER, perampanel.

Table 5 Base-case analysis results

Groups	Effect	Increased effect	Cost (\$)	Increased cost (\$)	ICER (\$/QALY)	C/E
AEDs	5.77	–	11,699.09	–	–	2,025.51
AEDs + PER	6.17	0.40	15,148.94	3,449.85	8,582.58	2,452.14

AEDs refer to the maintenance of conventional therapy. ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life years; C/E, C represents cost, E represents effect; PER, perampanel; AED, antiepileptic drug.

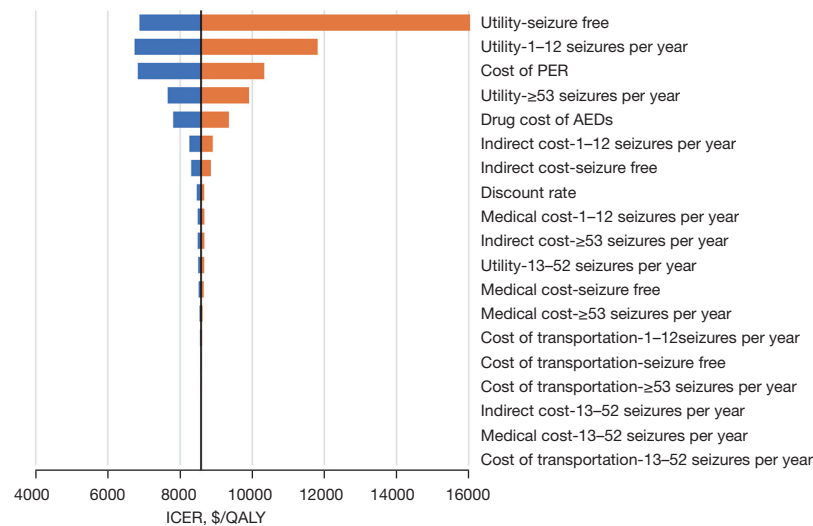


Figure 2 Tornado diagram of the univariable sensitivity analysis. The diagram shows the association of variables with the ICER of PER + AEDs vs. AEDs in pediatric patients with focal seizures. The vertical black line represents the base-case results of \$8,582 per QALY. AEDs refer to the maintenance of conventional therapy. PER, perampanel; AED, antiepileptic drug; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life years.

results showed that the PER + AEDs treatment had a large probability of being cost-effective compared to the AEDs alone treatment (see *Figure 3*). For example, the probability of the PER + AEDs treatment being cost-effective was 76.72% and 89.43% at a willingness-to-pay of \$11,293/QALY and \$33,879/QALY. *Figure 3* shows the scatter plot after 10,000 Monte Carlo simulations.

Subgroup analysis

The ICER of the PER + AEDs treatment compared to the AEDs treatment was \$19,710.96 per QALY in pediatric patients aged 4 to <7 years with focal seizures, and \$7,167.95 per QALY in patients aged 7 to <12 years (see *Table 6*). The 1-way analyses showed that the utility value of being seizure free was a key factor affecting the ICER in both groups (see *Figure 4*). The probabilistic sensitivity analyses revealed a large probability of PER being cost-effective in both groups

(see *Figure 5*); however, the patients aged 7 to <12 years had a higher probability in terms of willingness-to-pay than patients aged 4 to <7 years.

Discussion

Our research showed the cost-effectiveness of PER as an adjuvant drug for the treatment of focal epilepsy in children after its inclusion in medical insurance in China. Currently, there are few articles on the cost-effectiveness of PER in pediatric patients. However, research in patients aged >12 years old showed that PER as adjunctive therapy is more cost-effective than conventional regimens. A cost-effectiveness study conducted in Spain showed that PER as an add-on therapy to conventional regimens decreased the health burden, but increased the drug cost (21). With the ICER of €16,557/QALY in generalized tonic-clonic seizures, PER had an 89.3% probability of being cost-

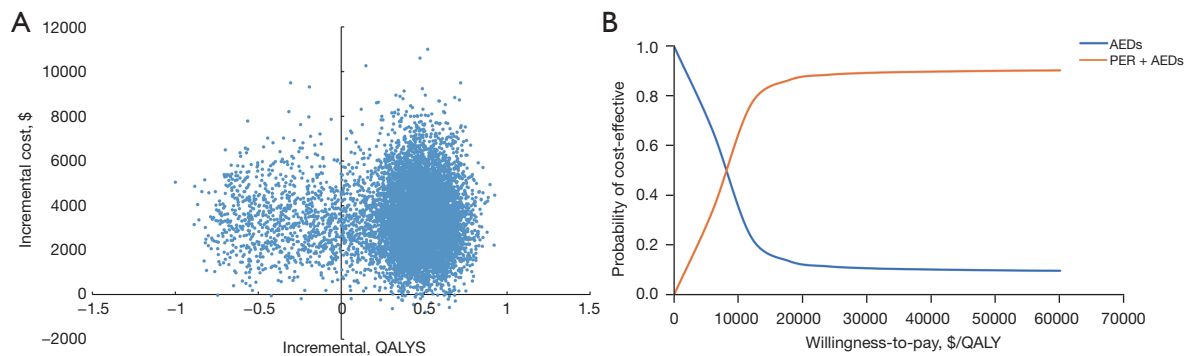


Figure 3 Probability sensitivity analysis in whole cohort. (A) Scatterplot of the cost-effectiveness plane. (B) The cost-effectiveness acceptability curve. Results of the probabilistic sensitivity analysis based on 10000 Monte Carlo simulations, which involved sampling cost and probabilities variables of the model from distributions imposed on variables to explore the uncertainty of cost-effectiveness between PER + AEDs and AEDs at different willingness-to-pay thresholds. AEDs refer to the maintenance of conventional therapy. PER, perampanel; AED, antiepileptic drug; QALY, quality-adjusted life years.

Table 6 Cost-effectiveness analysis of subgroups

Subgroups	Effect	Increased effect	Cost (\$)	Increased cost (\$)	ICER (\$/QALY)	C/E
Pediatric patients aged 4 to <7 years						
AEDs	5.77	–	11,699.09	–	–	2,025.51
AEDs + PER	5.96	0.19	15,446.98	3,747.89	19,710.96	2,589.16
Pediatric patients aged 7 to <12 years						
AEDs	5.78	–	11,699.09	–	–	2,025.51
AEDs + PER	6.24	0.46	15,446.98	3,354.11	7,167.95	2,410.90

AEDs refer to the maintenance of conventional therapy. ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life years; C/E, C represents cost, E represents effect; PER, perampanel; AED, antiepileptic drug.

effective at a willingness-to-pay of €30,000/QALY. Another study, from the perspective of China, conducted an analysis of patients with focal seizures, and showed that PER had a great advantage over LCM because of its increased efficacy and decreased cost (22). Both studies were conducted in adults. Our study, from the perspective of the Chinese health system and society, showed that the ICER of PER as an add-on therapy to the conventional regimen was \$8,582.58/QALY. Its probability of being cost-effective was 89.43% at a willingness-to-pay of \$33,879/QALY. Different from the studies mentioned above, our study was for pediatric patients with focal epilepsy. The cost-effectiveness of PER as add-on therapy in pediatric patients was the same as that of adults in terms of the current literature.

We also performed an analysis of different age groups to investigate whether age is a sensitive factor affecting our

results. In Study 311, the median percentage change in seizure frequency per 28 days was not significantly different between the group aged 4 to <7 years (58.92%) and the group aged 7 to <12 years (70.33%) (19). However, the 100% response rate of pediatric patients aged 4 to <7 years (15.0%) was slightly lower than that of patients aged 7 to <12 years (20.8%), as was the 50% response rate at week 52 in Study 311. Thus, our results showed the ICER of the younger group was higher than that of the older group (\$19,710.96/QALY *vs.* \$7,167.95/QALY). Additionally, the probability of PER being cost-effective in the younger group was lower than that of the older group at a willingness-to-pay of \$33,879/QALY (81.54% *vs.* 90.37%).

In our study, we used real-world data from China to ensure our results reflected reality. As we know, pharmacoeconomics evaluations are related to the economic level

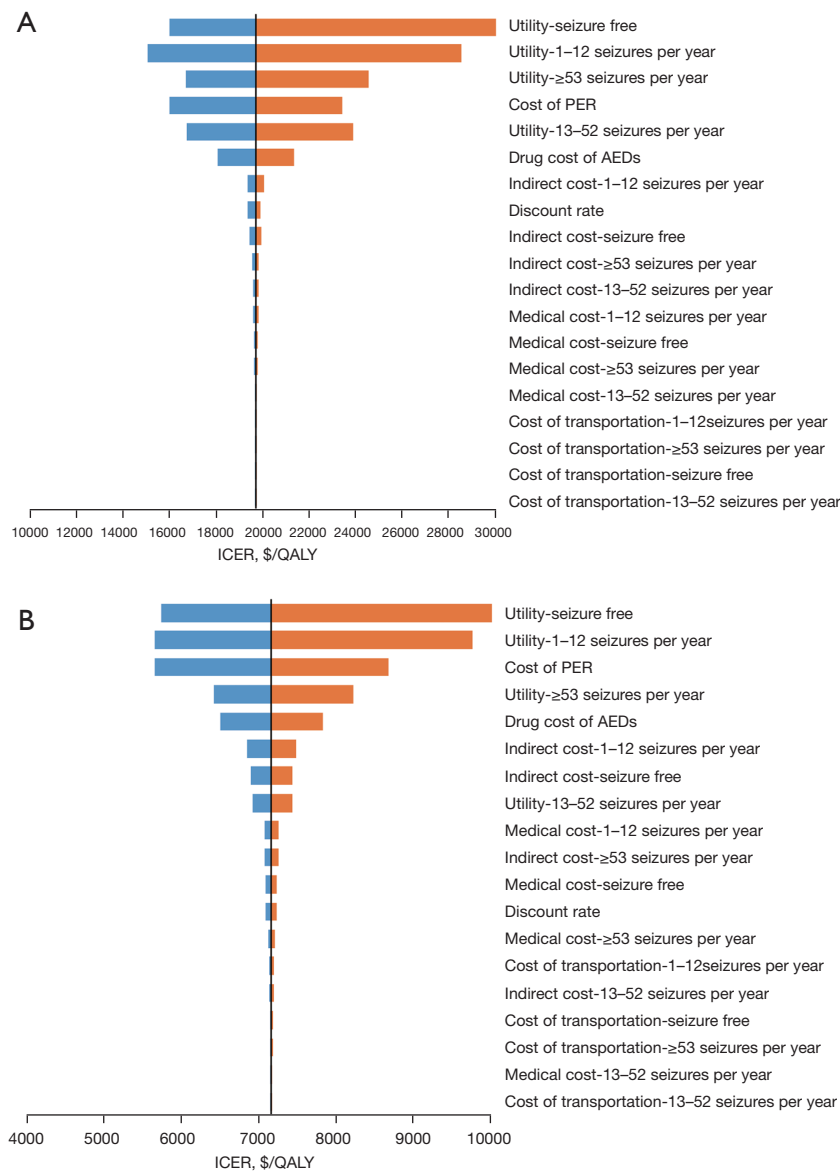


Figure 4 Tornado diagram of univariable sensitivity analysis in the subgroups. (A) The diagram shows the association of variables with the ICER of PER + AEDs vs. AEDs in subgroup of pediatric patients aged 4 to <7 years with focal seizures. The vertical black line represents the base-case results of \$19,710.96 per QALY. (B) The diagram shows the association of variables with the ICER of PER + AEDs vs. AEDs in subgroup of pediatric patients aged 7 to <12 years with focal seizures. The vertical black line represents the base-case results of \$7167.95 per QALY. AEDs refer to the maintenance of conventional therapy. PER, perampanel; AED, antiepileptic drug; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life years.

and policy of each country. Costs vary from country to country (11,28,33-35), and from children to adults (36), and the proportions of cost components also differ. A study on the cost of medical care for epilepsy conducted in the US showed that the annual hospitalization cost for epilepsy was \$22305, which was several times that of the other

expenses (37). More and more studies have shown that the cost of AED is becoming a major component of direct medical costs (38-40). The indirect cost of epilepsy is also an uncertain factor affecting the cost of epilepsy. Average indirect costs, which cover a large range, account for 12-85% of the total annual costs (38). Thus, we searched

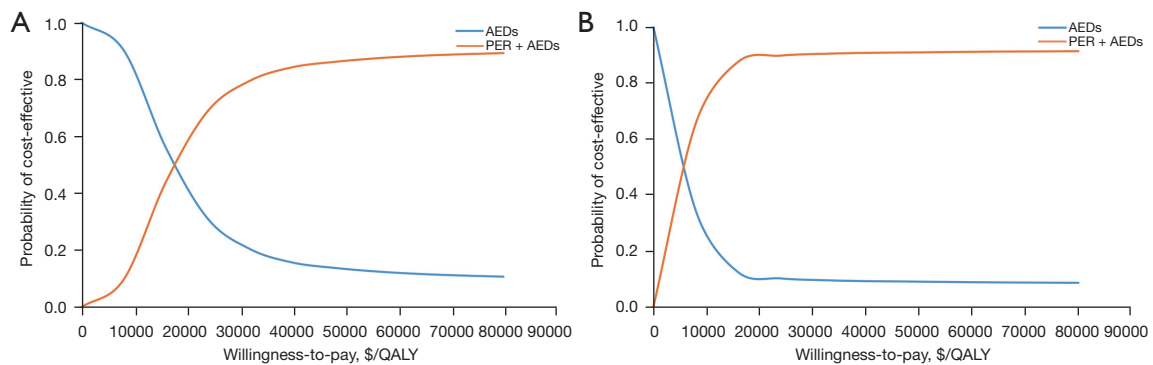


Figure 5 Probability sensitivity analysis of the subgroups. (A) Subgroup of pediatric patients aged 4 to <7 years. (B) Subgroup of pediatric patients aged 7 to <12 years. Results of the probabilistic sensitivity analysis based on 10,000 Monte Carlo simulations, which involved sampling cost and probabilities variables of the model from distributions imposed on variables to explore the uncertainty of cost-effectiveness between PER + AEDs and AEDs in subgroup at different willingness-to-pay thresholds. AEDs refer to the maintenance of conventional therapy. PER, perampanel; AED, antiepileptic drug; QALY, quality-adjusted life years.

for recently published data to enter the model. However, only 1 study detailed the cost of children with epilepsy in China (29). More studies should be conducted to address the lack of data. We also included the indirect cost in our study, as while children cannot work, a child with active seizures requires the care of a guardian, which results in productivity losses.

Our study had some limitations. First, the efficacy data were not from China. In Study 311, 43.6% of the patients were Japanese and 3.4% were other Asians (19), which may have caused a bias in our results. Additionally, the transition probabilities of the 3rd cycle and next cycles were from a long-term follow-up study in The Netherlands (25). Second, we assumed that the costs of different age groups were the same in the subgroup analysis. Due to the lack of a rate of initial distribution, we referred to the literature to get the rate of initial distribution from a Chinese Markov model (22). Third, our model covered a 5-year horizon period rather than a lifetime, and thus we did not add mortality as a factor to the model. Other therapies, such as epilepsy surgery and a ketogenic diet, may be used to treat uncontrolled seizures if the efficacy of the drugs is poor. Forth, the cost we estimated from an up-to-bottom approach was based on literature, so it only represents the majority of pediatric patients in China. The results should be used with caution. Finally, as we set the transition probability as a time independent variable, we did not consider it as an influencing factor.

Conclusions

This cost-effectiveness analysis for pediatric patients aged 4 to <12 years with focal seizures revealed that PER as an add-on therapy to conventional regimens is likely to be cost-effective from a Chinese perspective.

Acknowledgments

Funding: None.

Footnote

Reporting Checklist: The authors have completed the CHEERS reporting checklist. Available at <https://atm.amegroups.com/article/view/10.21037/atm-22-994/rc>

Data Sharing Statement: Available at <https://atm.amegroups.com/article/view/10.21037/atm-22-994/dss>

Conflicts of Interest: Both authors have completed the ICMJE uniform disclosure form (available at <https://atm.amegroups.com/article/view/10.21037/atm-22-994/coif>). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are

appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013).

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Cite this article as: Hu Y, Dai H. Cost-effectiveness of perampanel as an adjunctive treatment for uncontrolled focal seizures in pediatric patients: a Chinese perspective. *Ann Transl Med* 2022;10(6):364. doi: 10.21037/atm-22-994