



Letter to the Editor

Efficacy and tolerability of perampanel as an adjunct therapy in refractory epilepsy from real-world experience



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Dear Editor

Perampanel (PER) is a new generation anti-epileptic drug (AED) by the mechanism of non-competitive antagonist of α -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptors. It has been available in the public hospital system of Hong Kong since the year of 2015. We would like to share our experience in clinical use of PER in terms of real-world efficacy and tolerability. We recruited patients using PER in two public hospitals, the Queen Mary Hospital and Tseung Kwan O Hospital, in Hong Kong from 2015 to 2018 through the computerized medical record database. Classification of epilepsy was referred to the 2017 scheme of International League Against Epilepsy (ILAE). Enzyme-inducing AEDs (EIAEDs) included carbamazepine, oxcarbazepine, phenobarbital, phenytoin and topiramate. Baseline seizure frequency was determined by that documentation in medical record just before starting PER. Resulting seizure frequency was that documented after PER reached the peak dose. Efficacy was defined by 50% responder rate, meaning subjects with at least 50% reduction in seizure frequency when comparing the baseline and resulting seizure frequencies. Seizure-freedom rate was also pursued, and it was defined as no seizure for at least 6 months. Tolerability was defined as the withdrawal rate due to treatment-emergent adverse events (TEAEs). Student *t*-Test and Chi square test were employed for statistical interpretation. Statistical significance was defined as $p < 0.05$.

Total 53 cases were collected. All subjects were Chinese with male to female ratio about 1:1. Mean age at time of starting PER was 38.77 year-old. All cases had refractory epilepsy and vast majority had focal epilepsy (93%). More than half of the cases had unknown etiology (57%). PER was used as adjunctive therapy in all cases. Median daily dose of PER was 4 mg (range 2–12 mg). Median number of concomitant anticonvulsants was 2 (range 1–5). The 3 most common concurrent AEDs were levetiracetam (LEV), valproate and clobazam. The 50% responder rate was 32.08% and seizure-freedom rate was 13.21%. The

withdrawal rate due to TEAE was 28.30%. Psychiatric adverse effects, including irritability, behavioral problems, disinhibition and psychosis, were the commonest, accounting for 13.21% of the whole group. Three of the patients with psychiatric adverse effects had concomitant LEV. However, our data did not show concomitant use of PER and LEV had significant association with the psychiatric adverse effects ($p = 1$).

Various factors were tried to be correlated with the 50% responder rate (Table 2). Subjects taking non-EIAEDs with PER did have higher response compared with those taking EIAEDs. Gender, the age and duration of epilepsy at starting PER and number of concomitant AEDs did not show statistical significance. (See Table 1.)

Our study, though limited by small sample size and constraints of retrospective design, provides an insight to the real-world experience of the PER as an adjunct therapy in refractory epilepsy. Our 50% responder rate is comparable to previous phase III trials and post-marketing studies [1–3]. The withdrawal rate due to TEAE is higher than the randomized trial but comparable to the extended phase follow-up and the post-marketing studies [4,5]. It may be due to the longer follow-up duration in the later group of studies. Psychiatric adverse effects, including irritability, behavioral problems, disinhibition and psychosis, leading to withdrawal accounted for 13.2%. This is consistent to the side-effect profile demonstrated previously. High rate of concomitant use of AEDs with potential psychiatric adverse effects may attribute to the results. Concomitant use of EIAEDs probably has detrimental effect in the efficacy of PER due to reduction in plasma concentrations [2]. The subjects of the cohort have long duration of epilepsy upon starting PER. Also, the mean number of concomitant AEDs is quite high. This may reflect our subjects had relatively severe epilepsy with refractory course.

Our study shows that PER is a choice of adjunct AED among Chinese population with reasonable efficacy and tolerability. Careful patient selection is suggested due to its psychiatric side-effect profile. Clinicians should pay attention to the concomitant AEDs use. Extra precaution on

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Table 1
Demographic and clinical characteristics of the cohort.

Cohort characteristic	Statistics
Male:female ratio	1:1
Median age at starting PER (year-old)	39 (7–69)
Mean duration of epilepsy at time of starting PER (year)	16.78 (+ / – 12.98)
Mean duration of follow-up after starting PER (week)	113.09 (+ – 88.24)
Median PER daily dose (mg)	4 (2–12)
Median number of concomitant AEDs	2 (1–5)
Epilepsy subtypes (No. of patients (%))	
Focal	49 (92.5%)
Generalized	2 (3.8%)
Unknown	2 (3.8%)
Epilepsy etiology (No. of patients (%))	
Structural	21(39.6%)
Infection	2(3.8%)
Unknown	30(56.6%)
50% responder rate	32.08%
Seizure-freedom rate	13.21%
Withdrawal rate due to adverse effects	18.52%
Reason of withdrawal (No. of patients (%))	
Dizziness	4 (7.55%)
Irritability	4 (7.55%)
Behavioral problems	1 (1.89%)
Disinhibition	1 (1.89%)
Psychosis	1 (1.89%)
Headache	1 (1.89%)
Drowsiness	1 (1.89%)
Ineffectiveness	1 (1.89%)
Concomitant AEDs (No. of patients (%))	
LEV	24 (45.28%)
VPA	20 (37.71%)
CLB	15 (28.30%)
PHT	12 (22.64%)
CBZ	11 (20.75%)
LCM	9 (16.98%)
OXC	8 (15.09%)
PB	7 (13.21%)
TPM	4 (7.55%)
PGB	3 (5.66%)
GBP	2 (3.77%)
CLN	1 (1.89%)
BRV	1 (1.89%)

AED = Anti-epileptic drug; BRV = brivaracetam; CBZ = carbamazepine; CLB = clobazam; CLN = clonazepam; GBP = gabapentin; LCM = lacosamide; LEV = levetiracetam; OXC = oxcarbazepine; PB = phenobarbital; PGB = pregabalin; PER = perampanel; PHT = phenytoin; TPM = topiramate; VPA = valproic acid.

psychiatric status monitoring should be taken if AEDs with negative psychiatric effects are used together with PER. EIAEDs may reduce the efficacy of PER in seizure control.

Declaration of Competing Interests

Chang Richard Shek-kwan has received honorarium for being a panellist at the Fycompa Exchange 2019 organised by Eisai during the 33rd International Epilepsy Congress, Bangkok, Thailand. The research

Table 2
Correlations between various factors and 50% responder status of PER.

	50% responder	Non-50% responder	p-Value
Gender			
Male	8	16	
Female	9	16	0.842
Mean age at starting PER (year-old)	44.83	42.44	0.671
Mean duration of epilepsy at starting PER (year)	15.12	17.58	0.471
Mean maximal dose (mg)	4.71	5.67	0.267
Mean number of concomitant AEDs	2.06	2.64	0.069
Concomitant EIAED(s)			
Yes	5	28	
No	12	8	0.001

AED = Anti-epileptic drug; CLB = clobazam; LEV = levetiracetam; PER = perampanel; VPA = valproic acid. EIAEDs = Enzyme-inducing AEDs which include carbamazepine, oxcarbazepine, phenobarbital, phenytoin and topiramate.

team has received donation for medical research from Eisai after submission of the manuscript.

The pharmaceutical company Eisai had no role in the current study including the study design; data collection, analysis and interpretation; writing of the paper; and in the decision to submit the paper for publication.

All other authors have nothing to disclose.

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