國立成功大學醫學院
College of Medicine,National Cheng Kung University

The practical points in elderly with epilepsy management

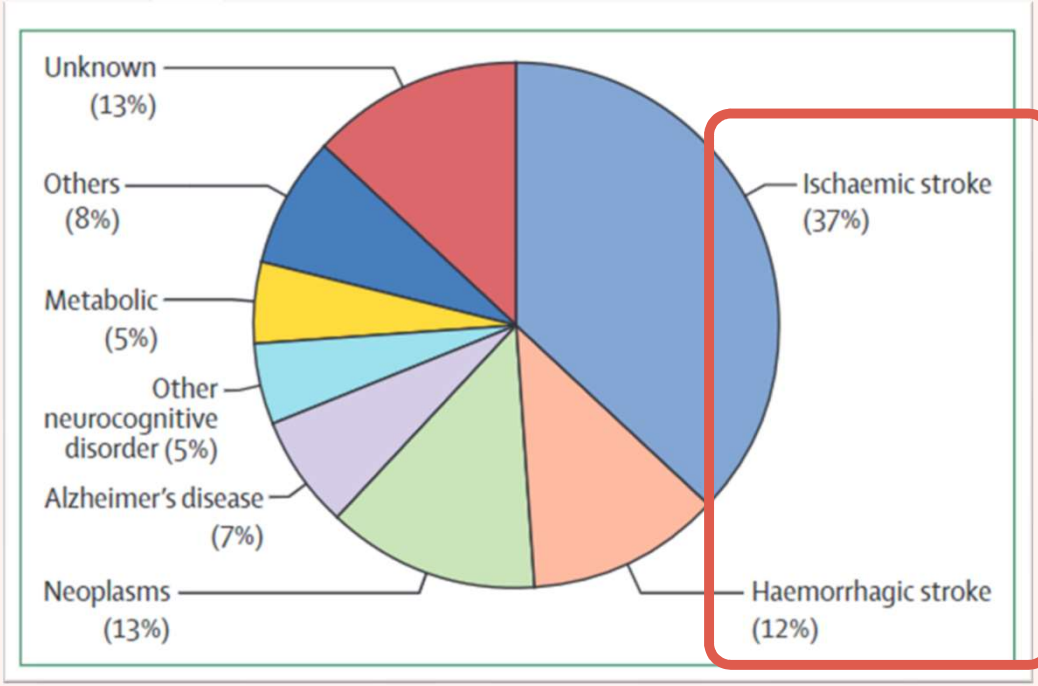
Chin-Wei Huang, MD, PhD, CSCN Diplomate (EEG), FAES

Director and Professor, Department of Neurology, College of Medicine, National Cheng Kung University, Tainan, Taiwan

President, Taiwan Epilepsy Society

Aging and the Epidemiology of Epilepsy

Causes of new-onset epilepsy in elderly



The causes of epilepsy vary across the lifespan. **In the older population the most common cause of epilepsy is stroke,** which constitutes the underlying pathology in almost half of the cases. Genetic epilepsy, relatively common in earlier life, is rare for those older than 65 years.

1.Beghi E et al.,Neuroepidemiology 2018;51:216–223:Aging and the Epidemiology of Epilepsy. 2.Arjune Sen et al., Lancet. 2020 Feb 29;395(10225):735-748:Epilepsy in older people.
3.Akamatsu et al.,Therapeutics and Clinical Risk Management 2022:18 825–832

Therapeutics and Clinical Risk Management

Dovepress

open access to scientific and medical research

Open Access Full Text Article

EXPERT OPINION

Optimal Use of Perampanel in Elderly Asian Patients with Epilepsy: Expert Opinion

Chin-Wei Huang[1], Kanokwan Boonyapisit[2], Suryani Gunadharma[3], Josephine Casanova-Gutierrez[4,5], Liri Jin[6], Dinesh Nayak[7], Naoki Akamatsu[8,9]

[1]Division of Epileptology, Department of Neurology, National Cheng Kung University Hospital, College of Medicine, National Cheng Kung University, Tainan, Taiwan; [2]Division of Neurology, Department of Medicine, Siriraj Hospital, Bangkok, Thailand; [3]Department of Neurology, Faculty of Medicine, Padjadjaran University, Hasan Sadikin Hospital, Bandung, Indonesia; [4]Department of Internal Medicine, Section of Neurology, De La Salle University Medical Center and College of Medicine, Dasmariñas, Philippines; [5]Department of Neurosciences, University of the Philippines College of Medicine–Philippine General Hospital, Manila, Philippines; [6]Department of Neurology, Peking Union Medical College Hospital, Beijing, People's Republic of China; [7]Department of Neurology, Gleneagles Global Health City, Chennai, India; [8]Department of Neurology, International University of Health and Welfare, Narita, Japan; [9]Epilepsy and Sleep Disorders Center, Fukuoka Sanno Hospital, Fukuoka, Japan

Huang CW, et al. Therapeutics and Clinical Risk Management 2022:18 825–832.

Dose optimization (the “start low and go slow” strategy)

- Titration: increase daily dose by 1 mg every 3 or 4 weeks
- Maintenance dose: 4 mg/day

Key considerations prior to initiation

Comorbidities

- Psychiatric or behavioral disorders
  - Start with 1 mg/day and uptitrate no faster than 1 mg every 4 weeks / Monitor any sudden behavior change
- Dementia
  - Consider increasing **PER** dose to 4 mg/day at an early stage if patient does not have comorbid psychiatric or behavioral disorders
- Cardiac comorbidities
  - **PER** can be safely used
- Renal impairment
  - Mild: increase dose no more frequently than once every 3 or 4 weeks / Severe: consider excluding **PER**
- Compromised hepatic clearance capability
  - Consider excluding **PER**
- Undergoing hemodialysis
  - Consider excluding **PER**

Concomitant medications

- Enzyme-inducing ASMs: consider higher **PER** dose

Huang CW, et al. Therapeutics and Clinical Risk Management 2022:18 825–832.

Managing AEs and maximizing tolerability

- If AEs occur during titration period: down titrate to previous tolerated dose and uptitrate again at smaller increments than before
- If AEs occur during maintenance period: reduce dose until AE resolves and slowly titrate to effective and tolerated maintenance dose again
- Falls: real-world analyses have not found a significantly increased risk of falls in the elderly when the “start low and go slow” strategy is employed
- Somnolence and sleep disorders: somnolence can be mitigated by taking **PER** shortly before bedtime,; **PER**’s favorable effect on sleep architecture is likely to benefit patients who suffer from sleep disorders
- Psychiatric AEs and aggression: proactively monitor for psychiatric AEs, especially aggression, and adjust **PER** dose accordingly
- Patient and caregiver education: inform on correct way and timing of taking **PER**; reassure them AEs can be effectively managed and treatment should not be stopped without consulting their physician

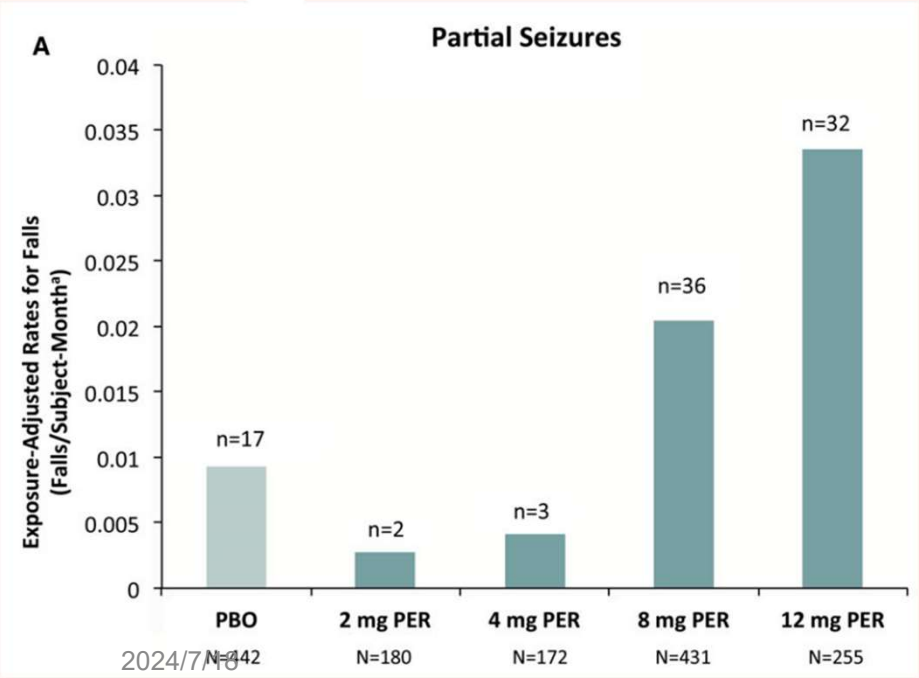
Huang CW, et al. Therapeutics and Clinical Risk Management 2022:18 825–832.

Analysis of falls in patients taking Perampanel

Analysis of falls in patients with epilepsy enrolled in the perampanel phase III randomized double-blind studies

*Ilo E. Leppik, †Haichen Yang, ‡Betsy Williams, ‡Sharon Zhou, †Randi Fain, §Anna Patten, ¶Francesco Bibbiani, and ¶Antonio Laurenza

Epilepsia, 58(1):51–59, 2017
doi: 10.1111/epi.13600



Optimal Use of Perampanel in Elderly Asian Patients with Epilepsy: Expert Opinion

Chin-Wei Huang[1], Kanokwan Boonyapisit[2], Suryani Gunadharma[3], Josephine Casanova-Gutierrez[4,5], Liri Jin[6], Dinesh Nayak[7], Naoki Akamatsu[8,9]

Box 1 Expert Recommendations on Perampanel Use in the Elderly

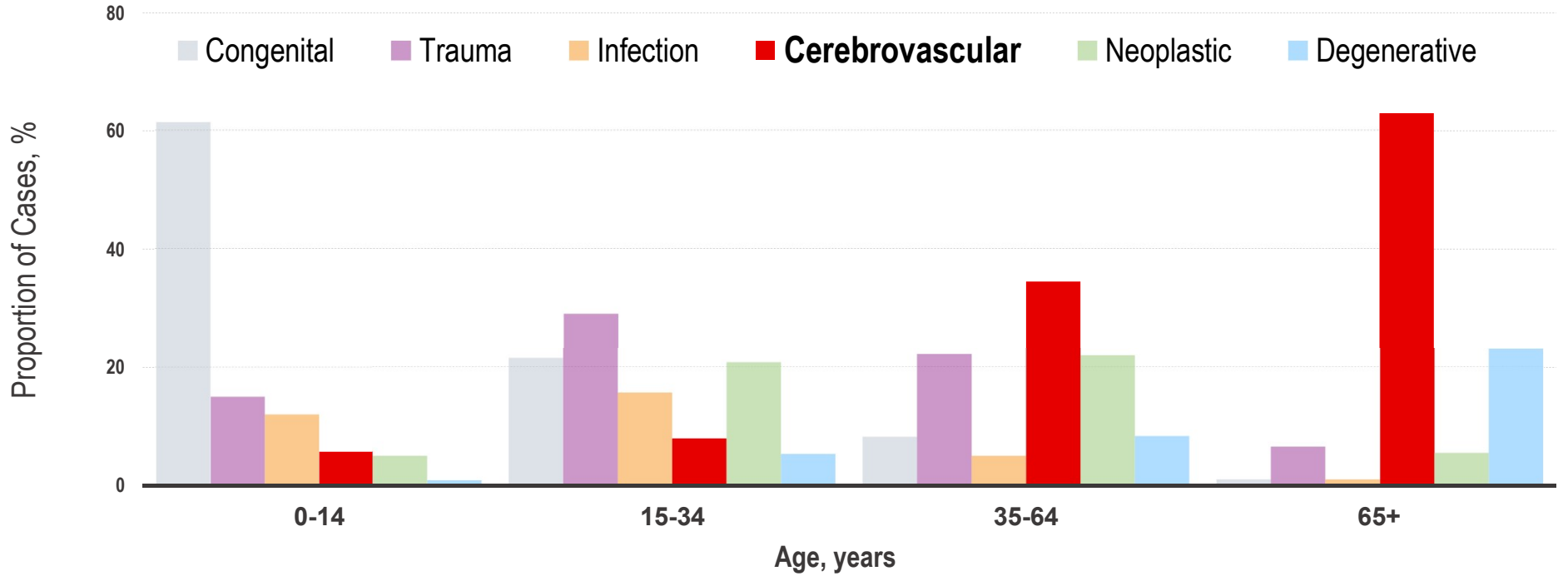
Dose optimization (the "start low and go slow" strategy)

- Starting dose: 1 or 2 mg/day
- Titration: increase daily dose by 1 mg every 3 or 4 weeks
- Maintenance dose: 4 mg/day

- **The rate for falls would increase when using 8mg < PER.**
- **The rate for falls is lower than placebo when using 4mg > PER.**
- **Expert recommendations on perampanel maintenance dose for elderly is 4mg/day.**

Cerebrovascular disease is the leading cause of epilepsy in people ≥65 years[1,2]

Proportion of cases of newly diagnosed epilepsy assigned to specific etiologic categories among those with assigned etiologies[1,a]



[a]Bar graph is a visual reorganization of the graph presented in Hauser et al, 1993, Figure 11. Because original data tables are not available, this graph should be considered an estimation.

1. Hauser WA, et al. Epilepsia. 1993;34(3):453-468. 2. Olafsson E, et al. Lancet Neurol. 2005;4(10):627-634.

In the elderly, the most common cause of epilepsy is stroke[1]

- Stroke is the most frequent cause of secondary epilepsy in the elderly
- A large population-based study has shown that in the first year after stroke, the risk of epilepsy is about 23 times higher than that in the general population
- It is hypothesized that epilepsy occurs after stroke due to the imbalance of excitatory and inhibitory transmission in the brain
- One possible mechanism of post-stroke seizures is the overactivation of glutamate receptors, which can lead to increased neuronal excitability

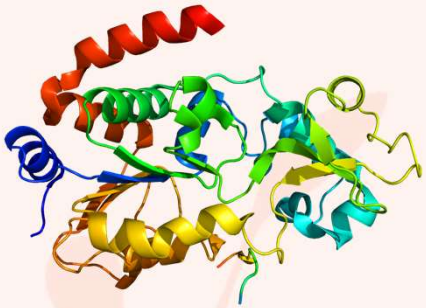
1. Chen JY et al. Acta Epileptologica 2022;4:2.

Perampanel may offer neuroprotection: Stroke models

Aside from its potential for treating seizures associated with stroke, emerging research suggests that Fycompa may have **neuroprotective effects** in stroke, which may offer a longer therapeutic window for treatment.[1,2]

In ischemic/hypoxia models of stroke, Fycompa:[1,2]

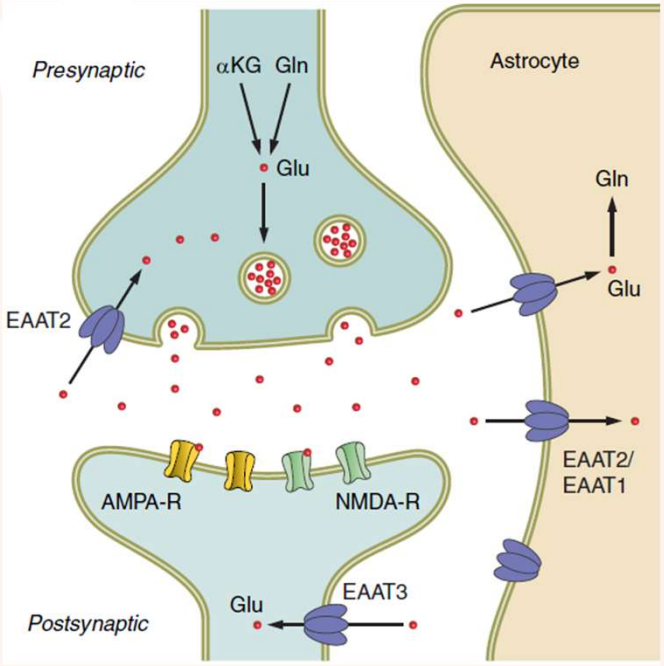
- Positively modulated blood brain barrier permeability
- Activated *Sirt3* expression – which was demonstrated to be beneficial to neurovascular and functional recovery following chronic ischemic stroke
- Abolished adenosine-induced post-hypoxia synaptic potentiation (which increases neuronal death), whereas calcium-permeable AMPA receptors did not have this effect

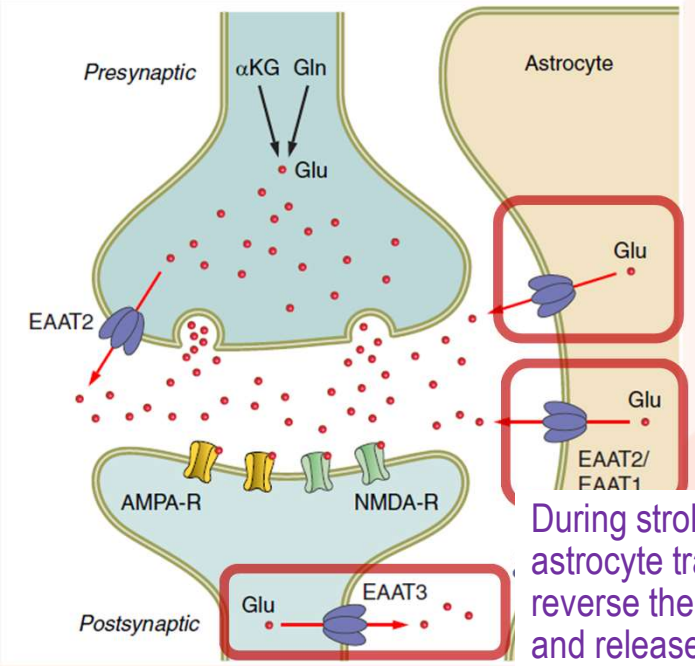


Sirt3 protein encoded by the *Sirt3* gene

1. Chen T, et al. CNS Neurosci Ther 2021;27:134–144. **2.** Qin X, et al. Mol Neurobiol 2021;58(5):1932–1951.

The role of glutamate in stroke[1]





During stroke, astrocyte transporters reverse their function and release glutamate

Under normal conditions

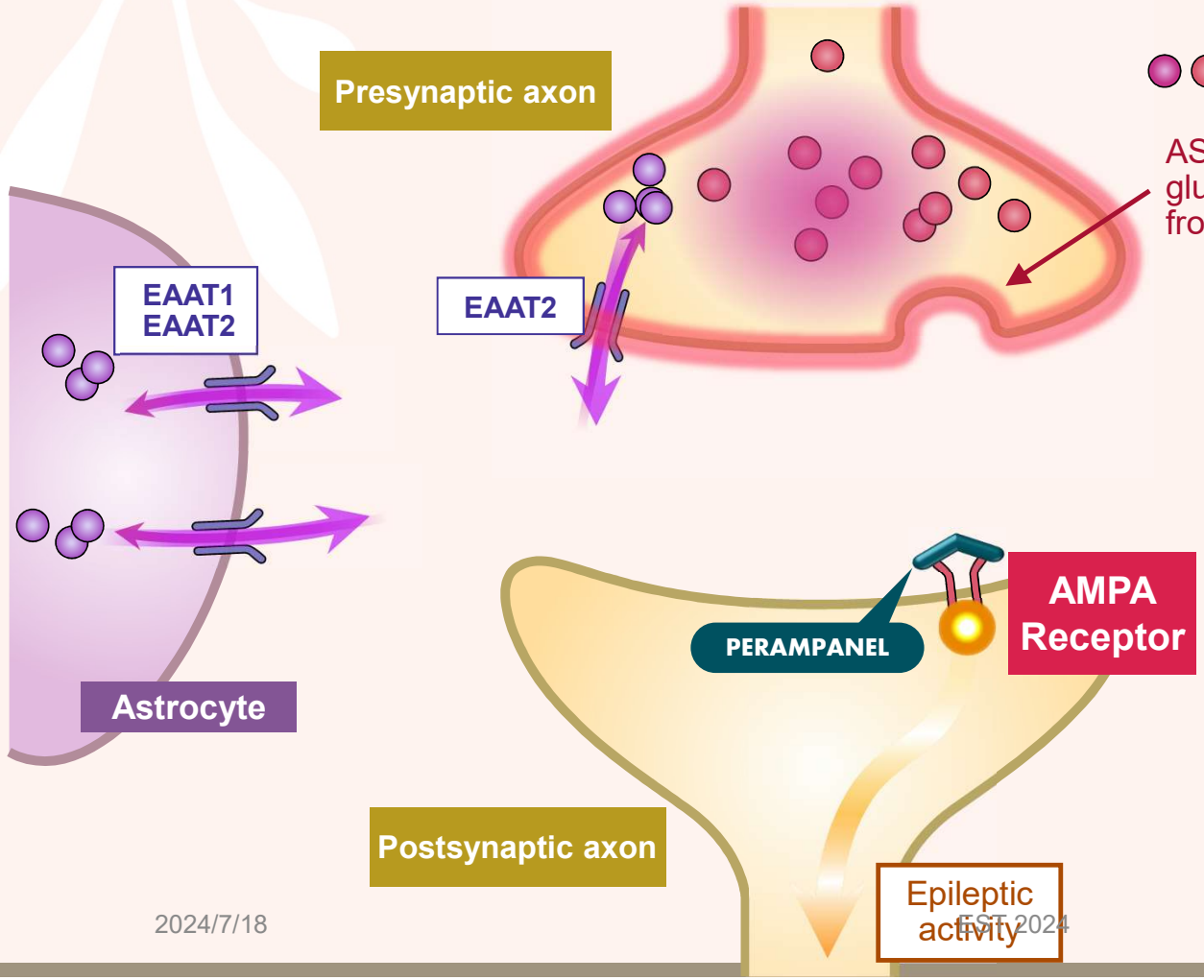
Astrocytes remove the glutamate that is released into the synapse, via glutamate transporters (EAAT1, EAAT2)

Under ischemic conditions

Disruptions to Na, K, and pH gradients can cause glutamate transporters to function in reverse, leading to elevated extracellular glutamate concentrations

1. Vandenberg RJ, Ryan RM: Physiol Rev 2013;93:1621–1657.

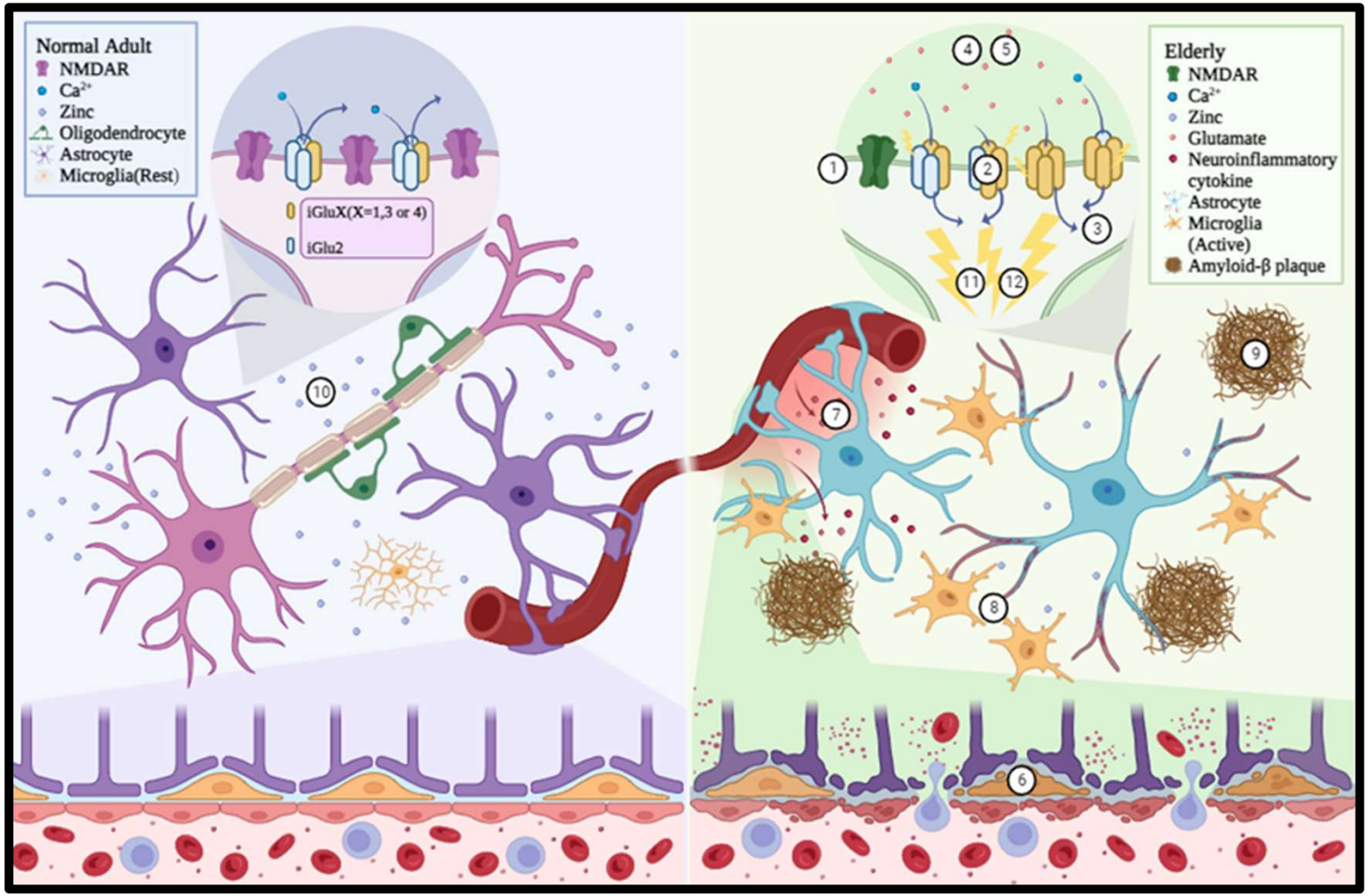
Visualizing the role of glutamate & Perampanel in stroke



PERAMPANEL blocks glutamate activity at **postsynaptic** AMPA receptors, which includes glutamate released from both the presynaptic axon and from astrocytes.

This represents a rational decision to use FYCOMPA as a first adjunctive therapy in epilepsy due to stroke

AMPAR & surrounding microenvironment in the adults and elderly



Huang et al., 2024, Archives of Geriatrics and Gerontology (accepted in revision)

The Benefits of Perampanel for Elderly Epilepsy Patients

- ✓Once-daily administration
- ✓Long half-life
- ✓Small tablet size
- ✓Rational option for post-stroke epilepsy
- ✓Less Drug-Drug interaction
- ✓Improvements in sleep parameters

Safety, efficacy and outcome-related factors of perampanel over 12 months in a real-world setting: The FYDATA study

V. Villanueva[a,*], M. Garcés[a], F.J. López-González[b], X. Rodriguez-Osorio[b], M. Toledo[c], J. Salas-Puig[c], M. González-Cuevas[c], D. Campos[d], J.M. Serratosa[e], B. González-Giráldez[e], J.A. Mauri[f], J.L. Camacho[f], A. Suller[f], M. Carreño[g], J.B. Gómez[g], J. Montoya[h], J. Rodríguez-Uranga[i], R. Saiz-Diaz[j], J. González-de la Aleja[j], A. Castillo[k], J. López-Trigo[k], J.J. Poza[l], J. Flores[m], R. Querol[n], J. Ojeda[o], P. Giner[p], A. Molins[q], P. Esteve[r], J.J. Baiges[r]

- Multicenter, retrospective, 1-year, real-world observational study of 464 patients with focal epilepsy on PER
- Mean number of prior ASMs: 7.8
- Perampanel mean dose at 12 months: 6.9 (±2.4) mg

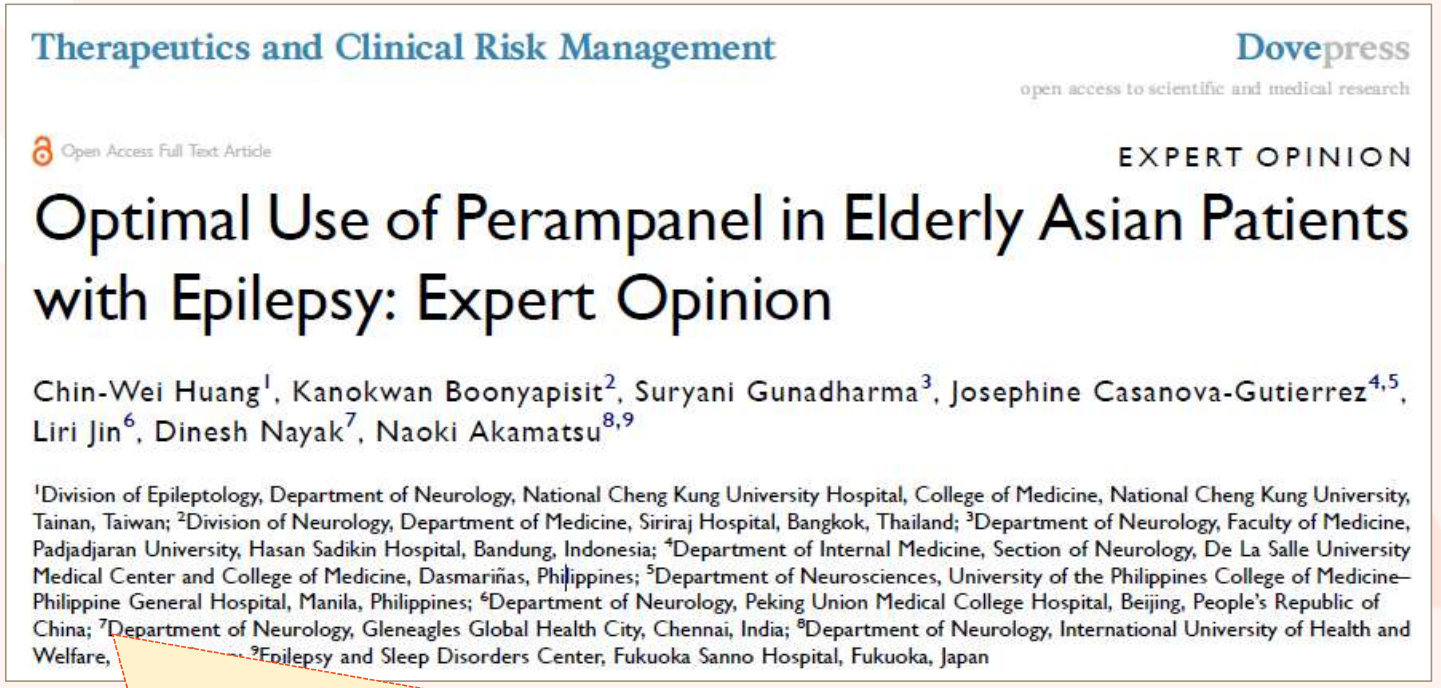
Factors associated with seizure freedom in the FYDATA study

Factor	Coefficient	Standard Error	Odds Ratio (95% CI)	p-value
Age ≥65 years	1.161	0.566	**3.194** (1.05–9.69)	p=0.040
Vascular etiology	1.232	0.582	**3.430** (1.10–10.74)	p=0.034
Lower number of prior ASMs	0.132	0.060	**1.141** (1.01–1.28)	p=0.028

Patients aged **≥65 years** with **vascular aetiology** and with **fewer prior ASMs** were more likely to achieve **seizure freedom** with Perampanel

1. Villanueva V, et al. Epilepsy Research 2016;126:201–210.

Expert Group: Perampanel "safe to use" in Asian elderly epilepsy patients with cardiac comordibidies[1]



Therapeutics and Clinical Risk Management

Dovepress

open access to scientific and medical research

Open Access Full Text Article

EXPERT OPINION

Optimal Use of Perampanel in Elderly Asian Patients with Epilepsy: Expert Opinion

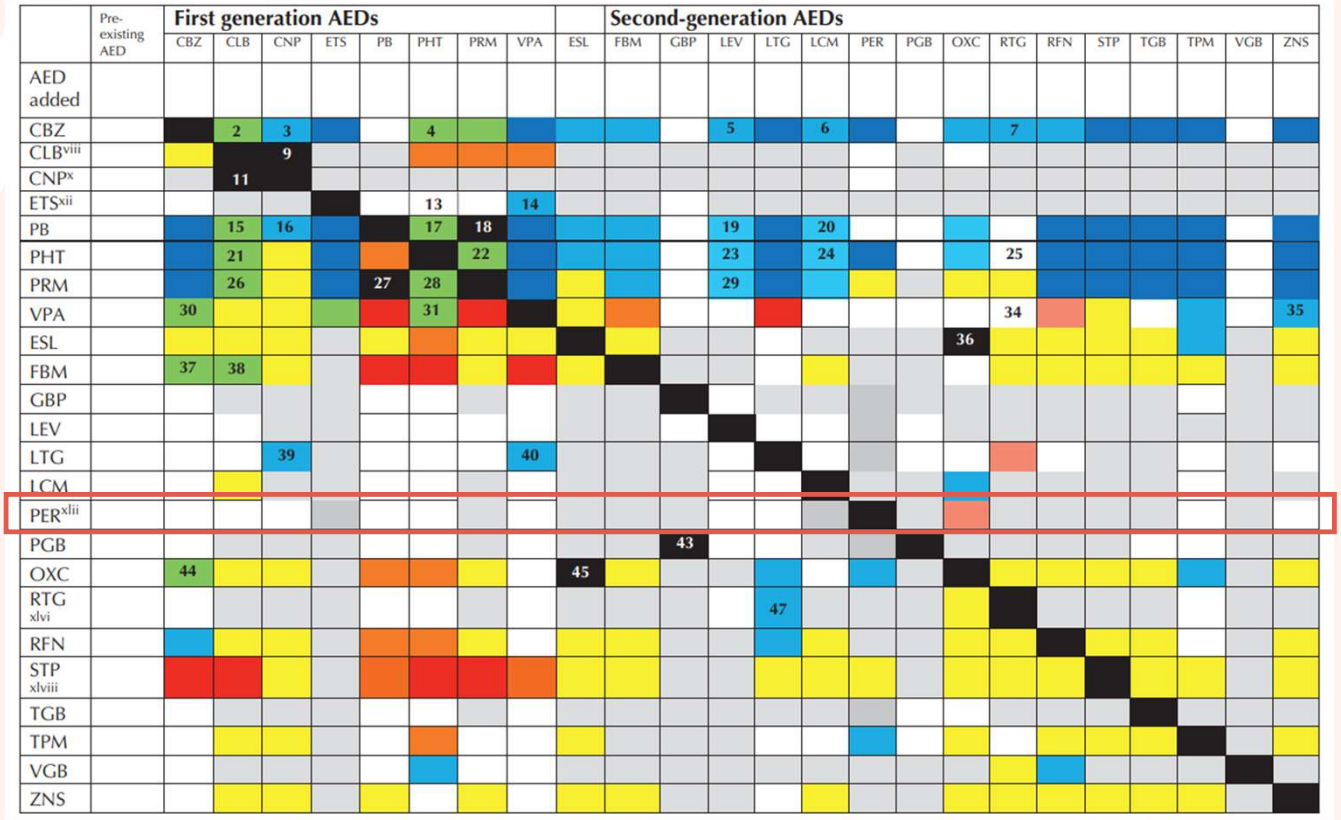
Chin-Wei Huang[1], Kanokwan Boonyapisit[2], Suryani Gunadharma[3], Josephine Casanova-Gutierrez[4,5], Liri Jin[6], Dinesh Nayak[7], Naoki Akamatsu[8,9]

[1]Division of Epileptology, Department of Neurology, National Cheng Kung University Hospital, College of Medicine, National Cheng Kung University, Tainan, Taiwan; [2]Division of Neurology, Department of Medicine, Siriraj Hospital, Bangkok, Thailand; [3]Department of Neurology, Faculty of Medicine, Padjadjaran University, Hasan Sadikin Hospital, Bandung, Indonesia; [4]Department of Internal Medicine, Section of Neurology, De La Salle University Medical Center and College of Medicine, Dasmariñas, Philippines; [5]Department of Neurosciences, University of the Philippines College of Medicine–Philippine General Hospital, Manila, Philippines; [6]Department of Neurology, Peking Union Medical College Hospital, Beijing, People's Republic of China; [7]Department of Neurology, Gleneagles Global Health City, Chennai, India; [8]Department of Neurology, International University of Health and Welfare, [9]Epilepsy and Sleep Disorders Center, Fukuoka Sanno Hospital, Fukuoka, Japan

"The expert group agreed that
Perampanel is an appropriate ASM in patients with **cardiac comorbidities**"

1. Huang CW, et al. Therapeutics & Clinical Risk Management 2022;18:825–832

Drug-drug interactions with perampanel



	Pre-existing AED	First generation AEDs								Second-generation AEDs															
		CBZ	CLB	CNP	ETS	PB	PHT	PRM	VPA	ESL	FBM	GBP	LEV	LTG	LCM	PER	PGB	OXC	RTG	RFN	STP	TGB	TPM	VGB	ZNS
AED added																									
CBZ			2	3			4						5		6				7						
CLB[viii]				9																					
CNP[x]			11																						
ETS[xii]							13		14																
PB			15	16			17	18					19		20										
PHT			21					22					23		24				25						
PRM			26			27	28						29												
VPA		30					31												34						35
ESL																		36							
FBM		37	38																						
GBP																									
LEV																									
LTG				39					40																
LCM																									
PER[xlii]																									
PGB												43													
OXC		44								45															
RTG[xlvi]														47											
RFN																									
STP[xlviii]																									
TGB																									
TPM																									
VGB																									
ZNS																									

Perampanel does not potently inhibit nor induce cytochrome P450 (CYP) isoenzymes or uridine diphosphate glucuronosyltransferases[1]

No clinically relevant interactions have been identified when perampanel is added to other drugs (including other antiepileptic drugs)[2]

- Marked increase in serum concentration
- Slight to moderate increase in serum concentraion
- No change
- No change anticipated
- Mild to moderate decrease in serum concentration
- Marked decrease in serum concentration
- Not known
- Complex or variable interaction (see note)

Zaccara C et al., Epileptic Disord. 2014 Dec;16(4):409-31,
1. Besag & Patsalos. Neuropsychiatric Disease & Treatment 2016;12:1215–1220. **2.** Schmidt & Schachter. BMJ 2014;348:g2546

2021 EHRA
(European Heart Rhythm Association)

Drug-Drug Interaction between NOACs & AEDs

	Via[426, 539-541]	Dabigatran etexilate	Apixaban	Edoxaban	Rivaroxaban
P-gp substrate		Yes	Yes	Yes	Yes
CYP3A4 substrate		No	Yes (≈25%)	No (<4%)	Yes (≈18%)
Drug					
Brivaracetam	–	No relevant interaction known/assumed			
Carbamazepine	Strong CYP3A4/P-gp induction; CYP3A4 competition	-29%[542]	-50% (SmPC)	SmPC	SmPC
Ethosuximide	CYP3A4 competition	No relevant interaction known/assumed			
Gabapentin	–	No relevant interaction known/assumed			
Lacosamide	–	No relevant interaction known/assumed			
Lamotrigine	P-gp competition	No relevant interaction known/assumed			
Levetiracetam	P-gp induction; P-gp competition				
Oxcarbazepine	CYP3A4 induction; P-gp competition				
Phenobarbital	Strong CYP3A4/possible P-gp induction		SmPC	SmPC	SmPC
Phenytoin	Strong CYP3A4/P-gp induction; P-gp competition	SmPC[543]	SmPC	SmPC	SmPC
Pregabalin	–	No relevant interaction known/assumed			
Topiramate	CYP3A4 induction; CYP3A4 competition				
Valproic acid	CYP3A4/P-gp induction/inhibition				Ref 544
Zonisamide	CYP3A4 competition; weak P-gp inhibition	No relevant interaction known/assumed (SmPC)			

J. Steffel et al., Europace (2021) 23, 1612–1676

Package Insert Information: AED effects on NOACs[1,2]

	Dabigatran	Rivaroxaban	Apixaban
Phenobarbital	→	↓	↓
Phenytoin	→	↓	↓
Carbamazepine	↓	↓	↓
Valproate	→	→	→
Gabapentin	→	→	→
Topiramate	→	→	→
Lamotrigine	→	→	→
Levetiracetam	→	→	→
Perampanel	→	→	→
Lacosamide	→	→	→

↑ Accelerates coagulation

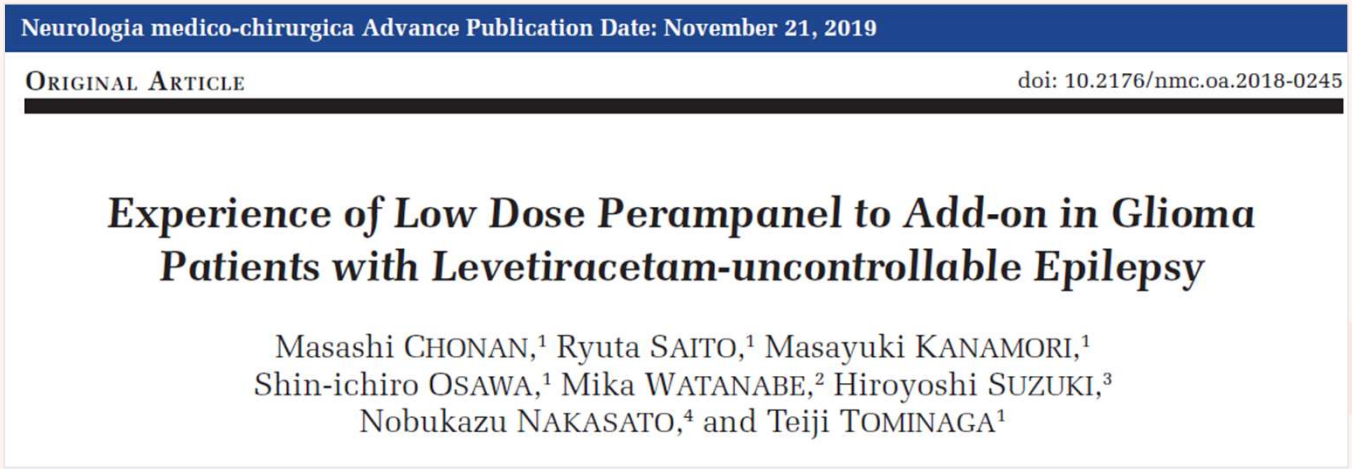
↓ Decreases coagulation efficiency

→ No description about coagulation effect on package insert

1. Hashimoto Y, Heart View Vol. 21 No. 1, 2017 (In Japanese). 2. Galgani et al. frontiers in neurology. 2018:vol. 9

Drug-drug interactions with perampanel in BTRE

- Retrospective review of 18 glioma patients with epilepsy inadequately controlled with LEV
- Median follow-up was 10.6 months
- Adjunctive perampanel was given from 2–8 mg/day



Neurologia medico-chirurgica Advance Publication Date: November 21, 2019

ORIGINAL ARTICLE doi: 10.2176/nmc.oa.2018-0245

Experience of Low Dose Perampanel to Add-on in Glioma Patients with Levetiracetam-uncontrollable Epilepsy

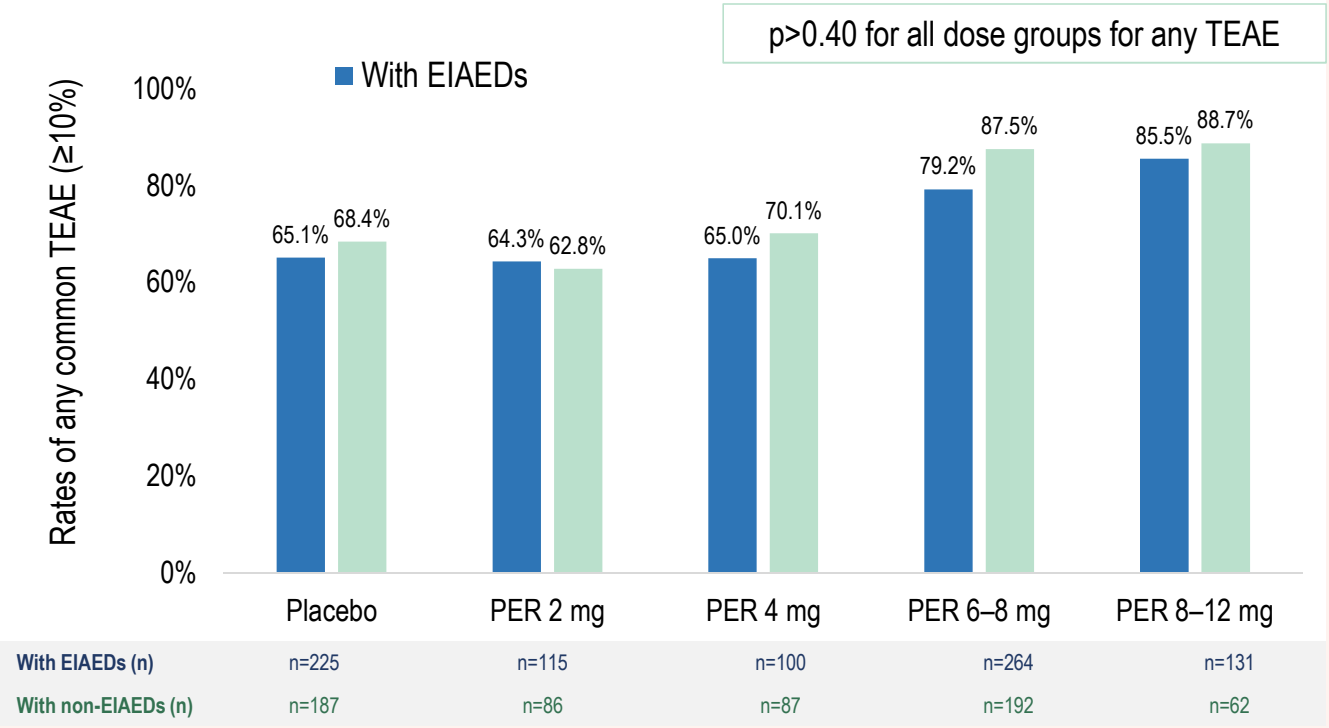
Masashi CHONAN,[1] Ryuta SAITO,[1] Masayuki KANAMORI,[1]
Shin-ichiro OSAWA,[1] Mika WATANABE,[2] Hiroyoshi SUZUKI,[3]
Nobukazu NAKASATO,[4] and Teiji TOMINAGA[1]

"Perampanel was well tolerated and did not increase the toxicity of radiation therapy and chemotherapy (ACNU, temozolomide & bevacizumab in these patients)"

Chonan M, et al. Neurol Med Chir 2020;60:37–44.

Administration of perampanel with enzyme-inducing ASMs[1]

- Pooled data from three Phase 3 studies of perampanel (study 303, 304 & 305)
- Patients with pharmacoresistant partial-onset seizures receiving 1–3 concomitant AEDs



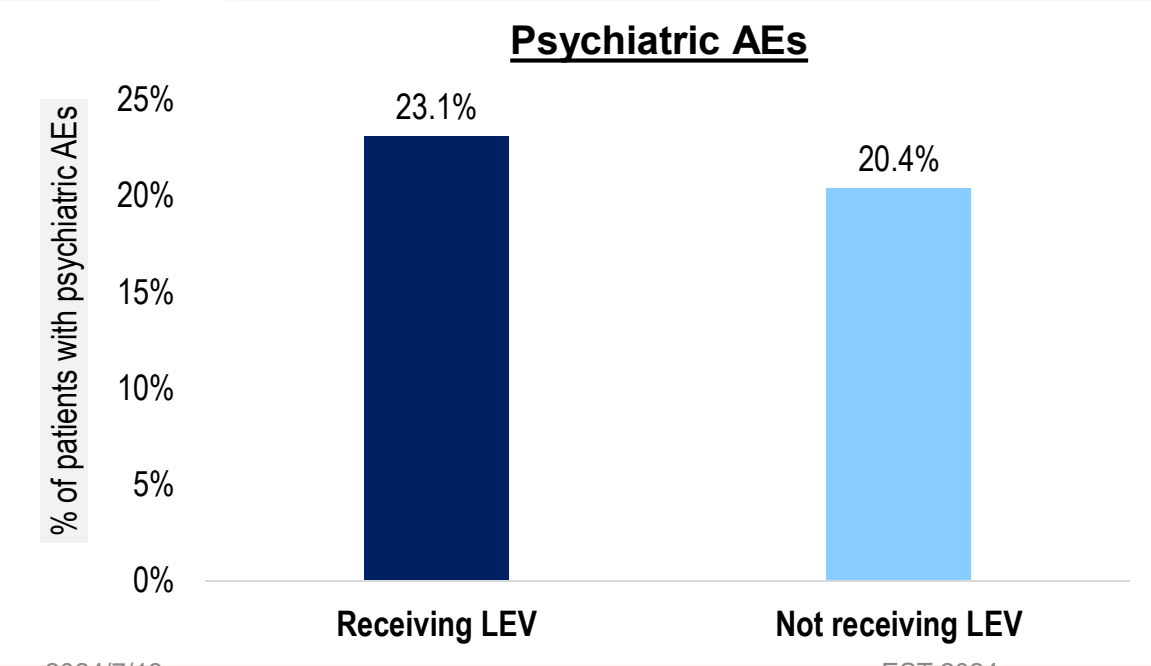
No significant differences in the incidence of any TEAE between patients on perampanel also receiving concomitant EIAEDs and non-EIAEDs

PER=perampanel; EIAED=enzyme reducing AED; TEAE=treatment-emergent adverse event

1. Gidal BE, et al. Neurology 2015;12;84(19):1972–1980.

Adjunct use of levetiracetam is not associated with psychiatric AEs

- Multicenter, retrospective, 1-year observational study of 464 patients on perampanel
- 100% of patients had focal epilepsy
- Mean number of prior AEDs: 7.8
- Perampanel mean dose at 12 months: 6.9 (±2.4) mg



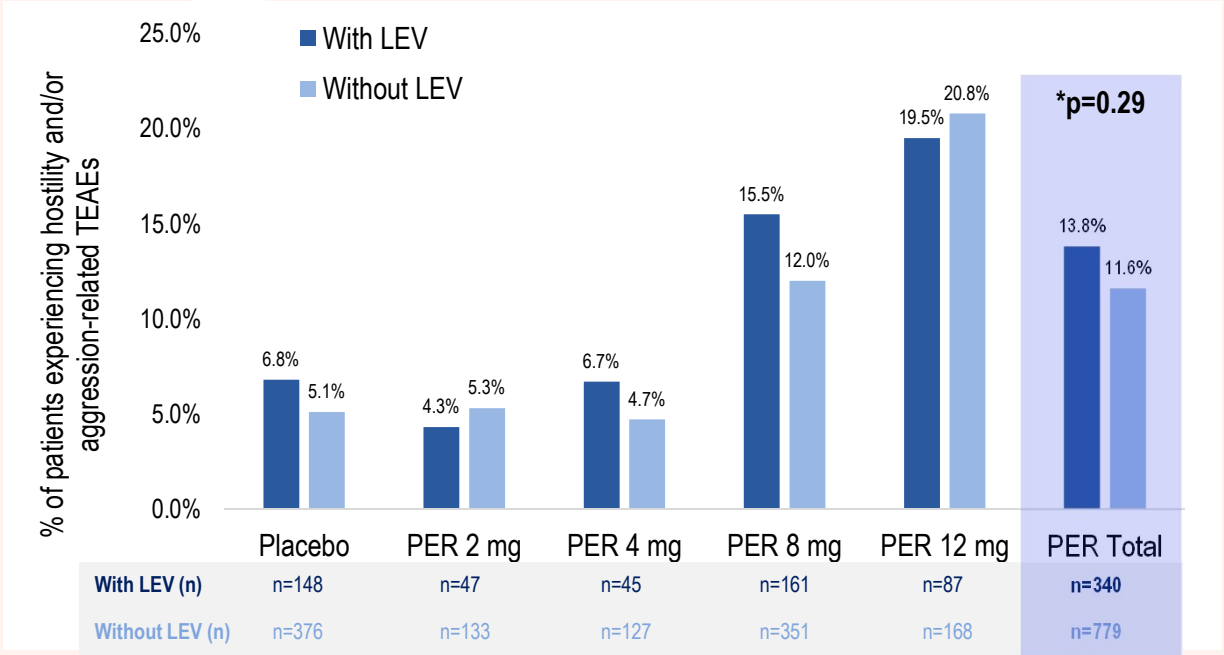
- 192 patients (41.8%) were receiving levetiracetam
- Over 12 months, concomitant use of **levetiracetam** with perampanel did not significantly impact rate of psychiatric AEs

Villanueva V, et al. Epilepsy Research 2016;126:201–210.

PER=perampanel; LEV=levetiracetam; TEAE=treatment-emergent adverse event

Adjunct use of levetiracetam is not associated with psychiatric AEs

- Pooled data from Phase III registration trials of perampanel
- Patients with partial seizures, N=1,480; patients with primary generalized tonic-clonic seizures, N=163
- Perampanel administered to patients already receiving 1–3 concomitant AEDs

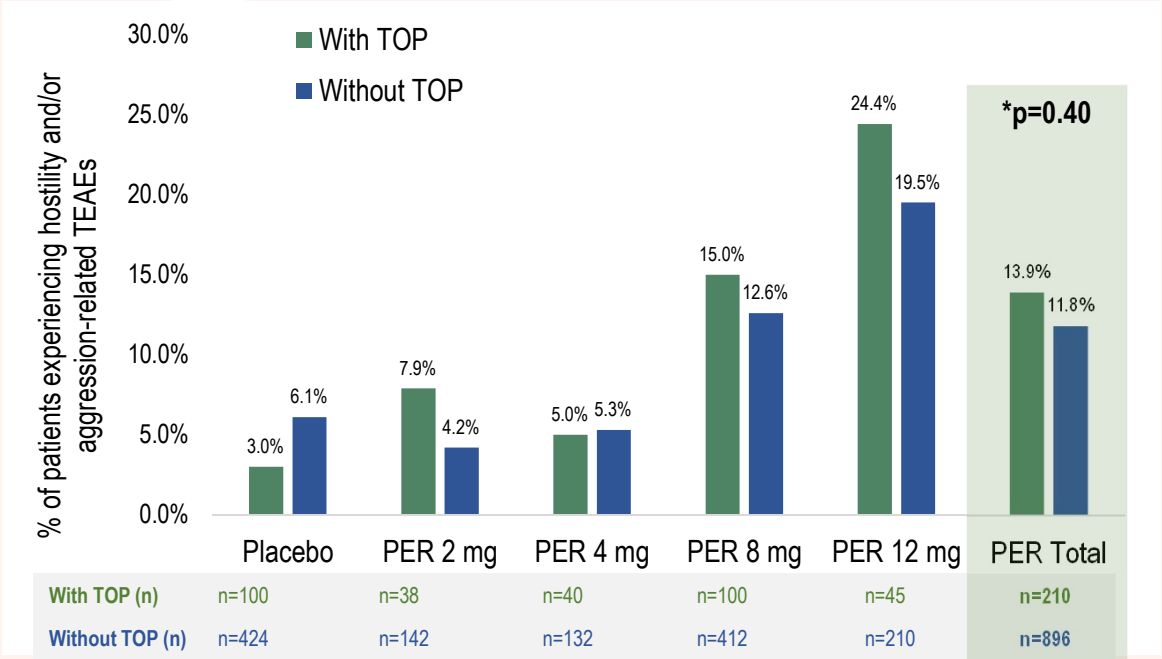


Co-administration of **levetiracetam** was <u>not associated</u> with any significant increases in hostility and aggression-related TEAEs in patients receiving perampanel

Chung S, et al. Epilepsy & Behaviour 2017;75:79–85.

Adjunct use of topiramate is not associated with psychiatric AEs

- Pooled data from Phase III registration trials of perampanel
- Patients with partial seizures, N=1,480; patients with primary generalized tonic-clonic seizures, N=163
- Perampanel administered to patients already receiving 1–3 concomitant AEDs



Co-administration of **topiramate** was <u>not associated</u> with significant increases in hostility and aggression-related TEAEs in patients receiving perampanel

Chung S, et al. Epilepsy & Behaviour 2017;75:79–85.

PER=perampanel; LEV=levetiracetam; TEAE=treatment-emergent adverse event

Elderly epilepsy patients are at higher risk of sleep disorders

Epilepsy is more common in the elderly

- In Japan, the prevalence of epilepsy is significantly higher in the elderly (>65 years) at 10.3 per 1,000 people, vs. 3.6 per 1,000 people in those aged 40–64 years (p=0.02)[1]
- Globally, epilepsy is the third-most common neurological disorder affecting older adults after stroke and dementia[2]

Insomnia is highly prevalent in the elderly

- 40–70% of older adults have chronic sleep issues,[3] and 30–48% are estimated to have insomnia symptoms[4]

Epilepsy patients are at higher risk of insomnia

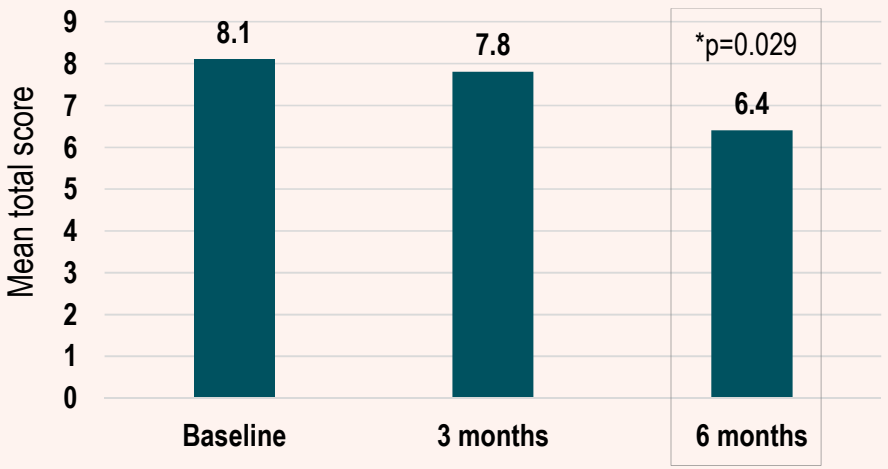
- Estimated that 24–55% of epilepsy patients experience insomnia, which is 2–3 times more common than the general population[5]

1. Tanaka A et al. Epilepsia Open 2019;4:182–86. 2. Lee SK. J Epilepsy Res 2019;9:27–35. 3. Knoema. World Data Atlas. https://knoema.com/atlas. Accessed Aug 2022. 4.Patel D, et al. J Clin Sleep Med. 2018;14:1017–1024.
5. Quigg M et al. Epilepsy Research 2016;122:91–96

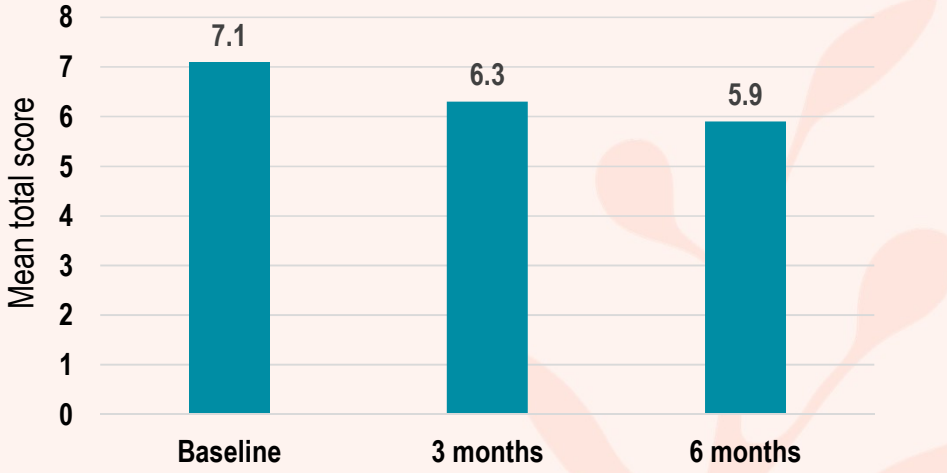
Less daytime sleepiness & better sleep quality with Perampanel

- Multicenter study that investigated the drug-resistant focal seizures who received adjunctive Perampanel sleep quality and daytime sleepiness of 72 patients aged >16 years with

Epworth Sleepiness Scale
Higher scores indicate greater daytime sleepiness



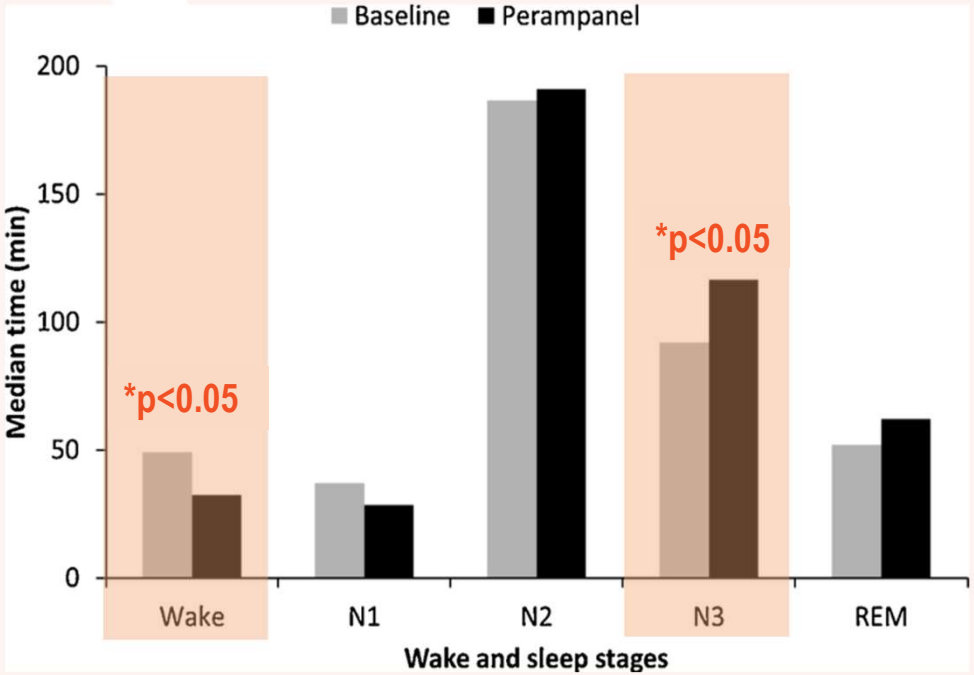
Pittsburgh Sleep Quality Index
Lower scores indicate better sleep quality



Toledo M, et al. Epilepsy and Behavior 2016;63:57–62.

Perampanel improves sleep architecture in epilepsy patients

- Study of 17 patients with refractory focal epilepsy who received adjunctive Perampanel
- At 3 months, Perampanel was associated with a ≥50% responder rate of 70.6%, with no changes to ESS or PSQI scores



Perampanel:

- Significantly **reduced** wake time
- Significantly **increased** slow wave (N3) sleep

No significant changes to N1, N2 or REM sleep were observed

ESS=Epworth Sleepiness Scale
PSQI=Pittsburgh Sleep Quality Index
REM=Rapid-eye movement

Rocamora R et al. Seizure 2020;76:137–142.

Therapeutics and Clinical Risk Management

Dovepress
open access to scientific and medical research

Open Access Full Text Article

REVIEW

Optimal Use of Perampanel in Asian Patients with Epilepsy: Expert Opinion

Yotin Chinvarun[1]
Chin-Wei Huang[2]
Ye Wu[3]
Hsiu-Fen Lee[4]
Surachai Likasitwattanakul[5]
Jing Ding[6]
Takamichi Yamamoto[7]

[1]Department of Neurology, Phramongkutklao Royal Army Hospital and Medical College, Bangkok, Thailand; [2]Department of Neurology, National Cheng Kung University Hospital College of Medicine, National Cheng Kung University, Tainan, Taiwan; [3]Department of Pediatrics, Peking University First Hospital, Beijing, People's Republic of China; [4]Division of Pediatric Neurology, Children's Medical Center, Taichung Veterans General Hospital, Taichung, Taiwan; [5]Division of Neurology, Department of Pediatrics, Faculty of Medicine, Siriraj Hospital, Mahidol University, Bangkok, Thailand; [6]Department of Neurology, Zhongshan Hospital, Fudan University, Shanghai, People's Republic of China; [7]Department of Neurosurgery, Comprehensive Epilepsy Center, Seirei Hamamatsu General Hospital, Hamamatsu, Japan

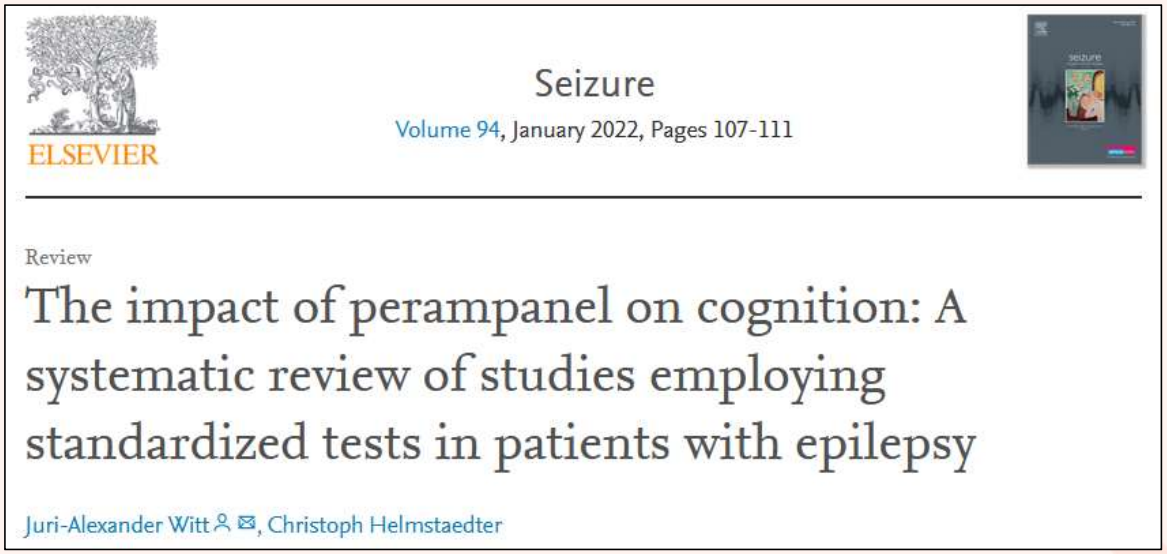
"The expert group advise that Perampanel may contribute to **improved sleep quality**, which would be highly advantageous for these patients"

Chinvarun Y, et al. Therapeutics and Clinical Risk Management 2021:17 739–746.

Perampanel is not associated with cognitive worsening

Older patients with epilepsy are at a higher risk of developing cognitive impairment

- Elderly epilepsy patients with normal results on MRI perform worse on cognitive measures when compared to older adults without epilepsy[2]



A 2022 systematic review of 9 studies totalling 241 patients reported that adjunctive Perampanel was not associated with any cognitive deteriorations[1]

1. Witt JA & Helmstaedter C. Seizure 2022;94:107–111. **2.** Miller LA, et al. Epilepsy & Behavior 2016;56:113–117.


Thanks
國立成功大學醫學院
College of Medicine, National Cheng Kung University