“New AEDs: do they solve DRE (Drug Resistant Epilepsy)?”

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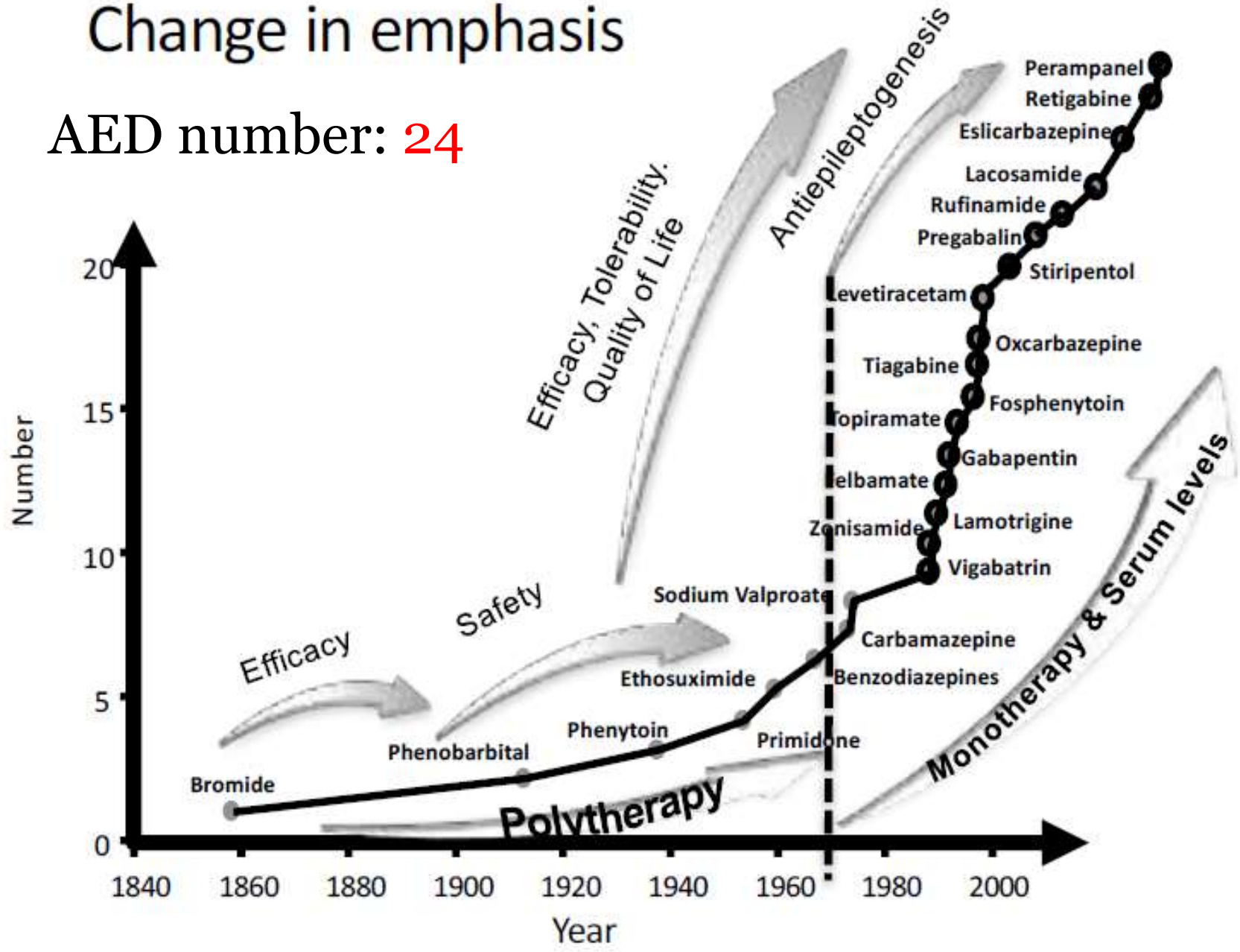
DRE: Drug Resistant Epilepsy

- 2009 ILAE task force proposal
  - Failure to achieve seizure freedom with **two** appropriately used AEDs
  - As monotherapy or combination
  - For 1 year or 3 times the longest prior seizure free interval
- **What is 2019 definition of DRE?**
  - We may need the 2nd task force for new proposal.

Change in emphasis

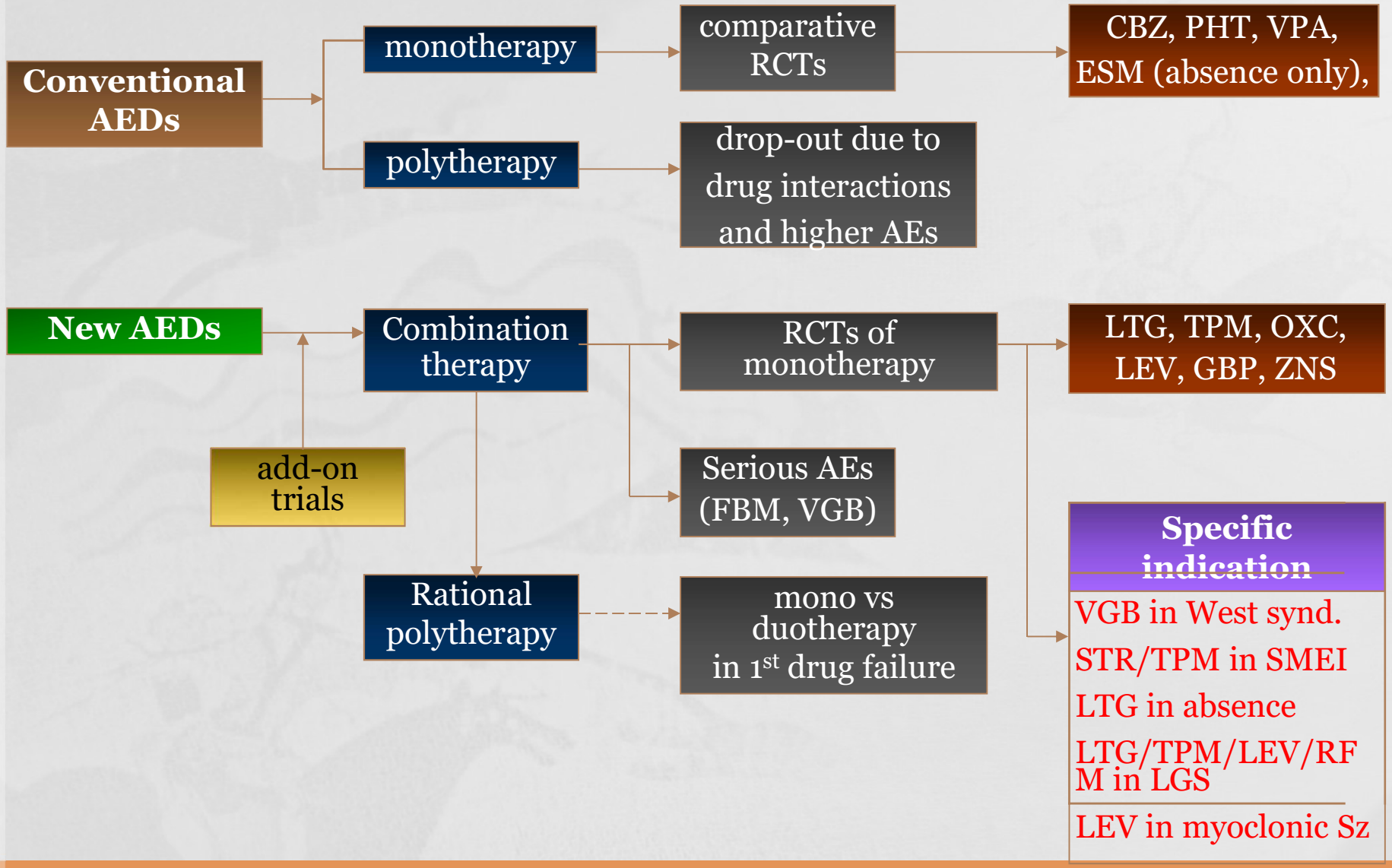
AED number: 24



Era of New AEDs

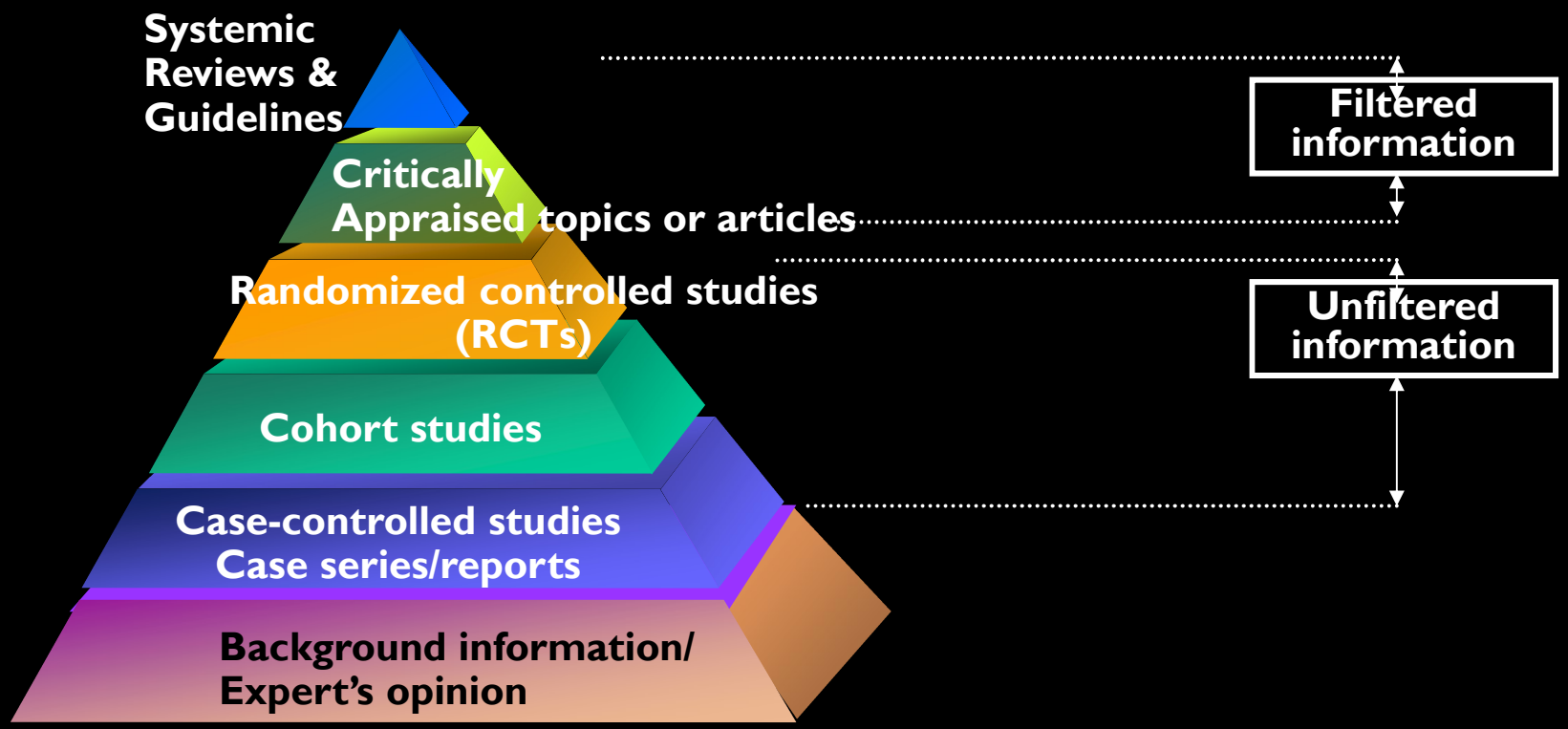
- **Era of New Drugs**
  - 17 New AEDs since 1989: > 25 AEDs in a total are available
  - **Characteristics of New AEDs**
    - Better Tolerability
    - Better Pharmacokinetic Profiles
    - Different and diverse Modes of Action
    - Efficacy is not superior but comparable to Old AEDs
  - ***Impacts on Clinical Practice***
    - Adoption of Evidence-based Medicine
    - Revival of Polytherapy
    - Paradigm Shift from **"Disease-oriented "** to ***"Patient-oriented"*** therapy

Clinical Development of AEDs: Old vs. New



Adoption of Evidence-based Medicine

- Evidence-based Medicine(EBM): Conscientious, explicit and judicious use of current best evidence in making decisions about the care of individual patient.
- Sources and hierarchy in the quality of Evidence



SPECIAL ARTICLE LEVEL OF RECOMMENDATION

Practice guideline update summary: Efficacy and tolerability of the new antiepileptic drugs I: Treatment of new-onset epilepsy

Report of the Guideline Development, Dissemination, and Implementation Subcommittee of the American Academy of Neurology and the American Epilepsy Society

Since the 2004 publications of AAN Guidelines, the US-FDA approved 6 new third generation AEDs and 2 older AEDs. This update reviews new evidence for efficacy of these AEDs in managing New-onset and treatment-resistant (TR) focal epilepsies and generalized epilepsies (GEs) in children and adults with the last literature search update in November 2015(Neurology 2018; 91:74-81, 82-90)

SPECIAL ARTICLE LEVEL OF RECOMMENDATION

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- What is the Best Combination ? -

- Combination Drug Regimens reported to have clinical synergism

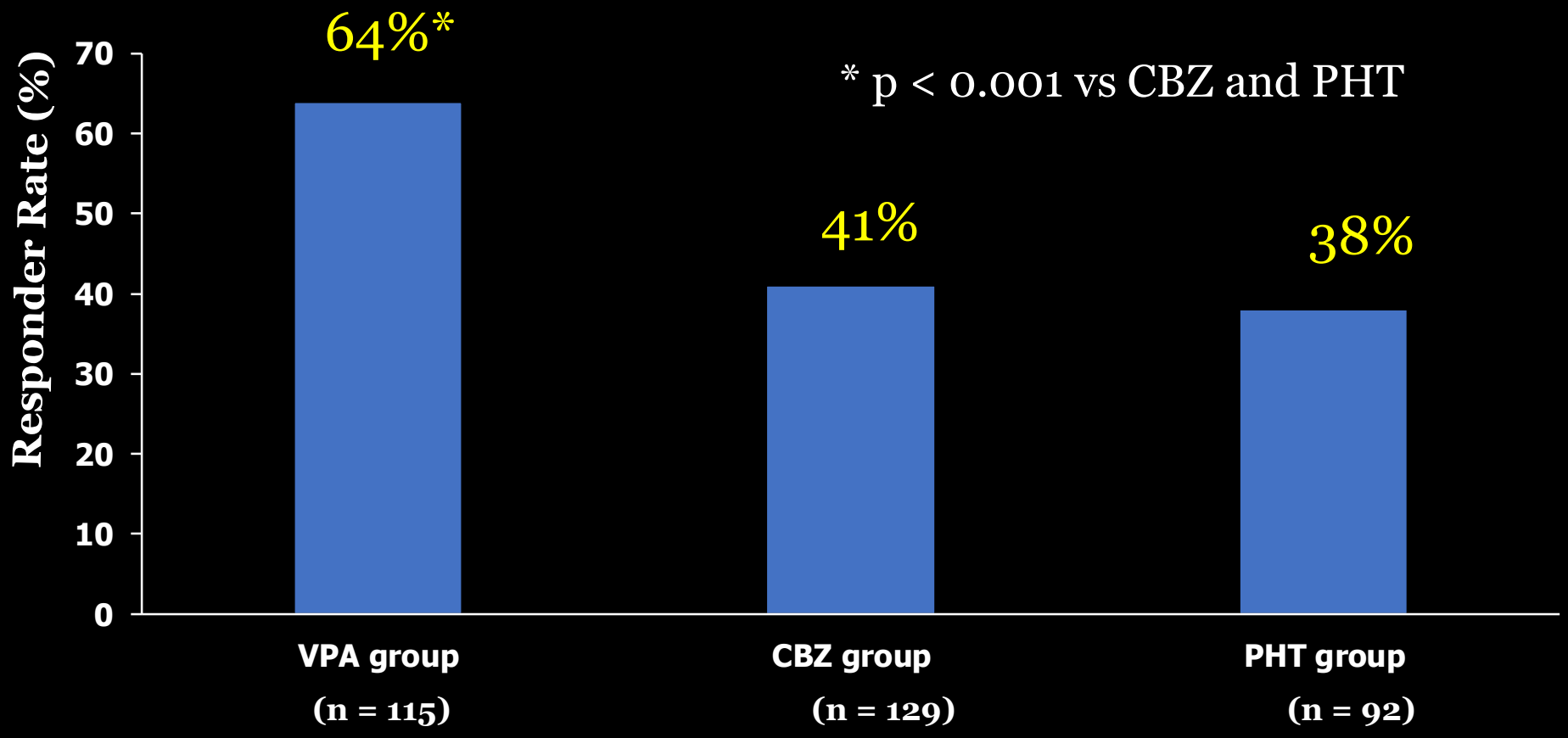
Drug combination	Level of evidence*
Valproate + Lamotrigine	+++
Valproate + Ethosuximide	++
Lamotrigine + Leviteracetam	++
Phenobarbital + Phenytoin	+
Valproate + Carbamazepine	+
Carbamazepine + Vigabatrin	+
Tiagabine + Vigabatrin	+
Topiramate + Lamotrigine	+

* +++ Controlled trials ++ Case series studies + Anedoctical

Rowan AJ et al. Arch Neruol 1983;40: 797-802, Cereghino JJ et al. Clin Pharmacol Ther 1975;18:733-741, Kwan and Brodie, Drugs 2006:66:1817-29, Brodie MJ Curr Neurol Neurosci Rep 2016;16:82, Legge AW et al. Epilepsy Res 2018:142:73-80.

What is the Best Combination Regimen ?
- LTG + VPA -

Differences in Responder Rates to Lamotrigine as a Function of Comedication



Brodie et al, Epilepsy Res.,1997; 26: 423-32

Safety and effectiveness of hormonal treatment versus hormonal treatment with vigabatrin for infantile spasms (ICISS): a randomised, multicentre, open-label trial (O'Callaghan FJK et al. Lancet Neurol 2017;16:33-42)2-14

- Multicenter trials of 102 hospitals from UK, Germany, Australia, NZ, and Switzeland
  - N= 377 infants(2-14 month- old, HT + VGB =186 vs. HT alone =191)
- Minimum doses were prednisolone 10 mg four times a day or intramuscular tetracosactide depot 0·5 mg (40 IU) on alternate days with or without vigabatrin 100 mg/kg per day
- The primary outcome: cessation of spasms between day 14 and day 42 from trial entry
- RESULTS (intention to treat analysis)
  - Spasm free: 72% in HT+VGB vs. 57% HT alone (difference 15·0%, 95% CI 5·1–24·9, p=0·002)
  - AE was not different between two groups
- **Conclusion:** Combination of HT and VGB is significantly more effective than HT alone

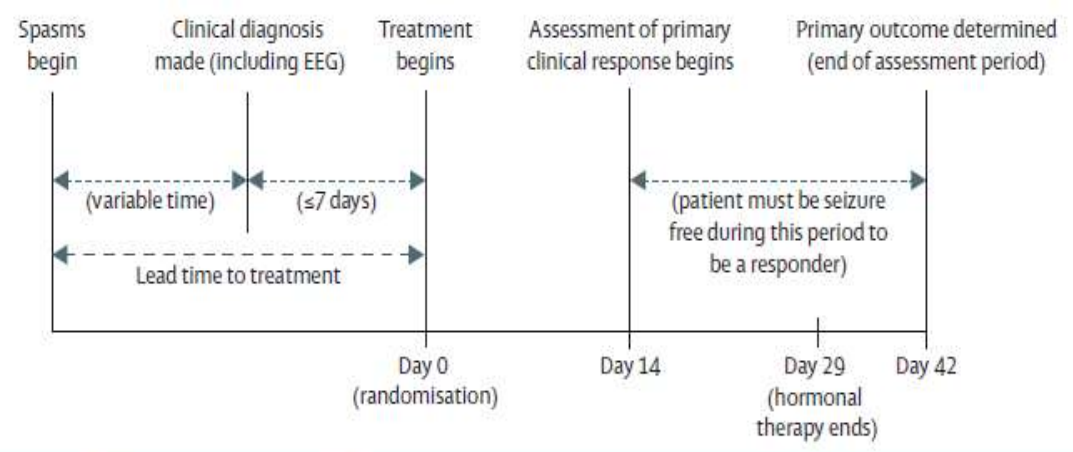
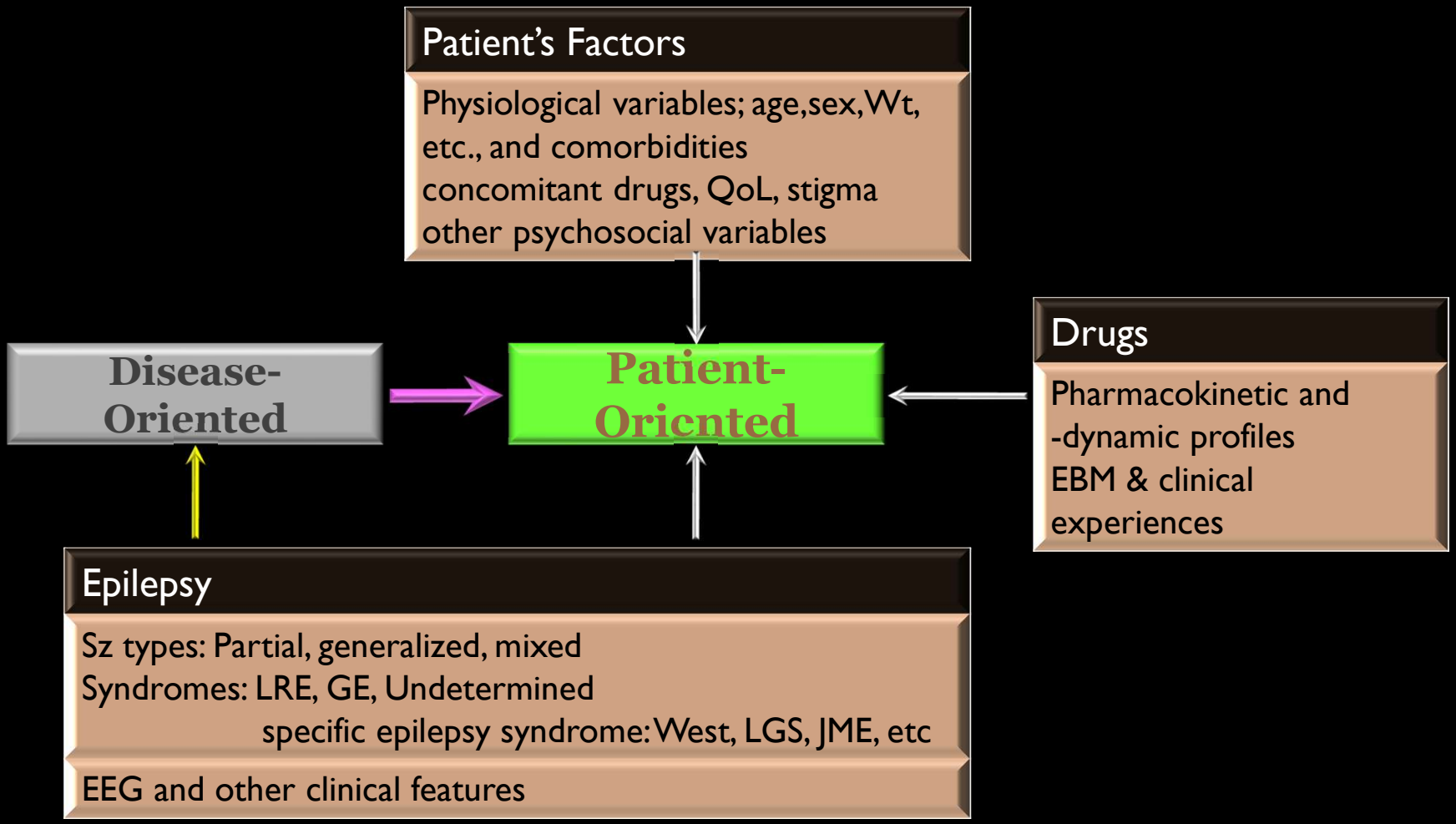


Figure 1: Trial design for assessment of primary clinical outcome

	Number of clinical responders (n/N)	Adjusted odds ratio (95% CI)	p value
Treatment modality		2·1 (1·3–3·2)	0·001
Combination	133/186		
Hormonal	108/191		
Developmental impairment		0·4 (0·3–0·6)	<0·001
High risk	114/207		
Low risk	127/170		
Hormone type		0·7 (0·4–1·1)	0·107
Prednisolone	162/265		
Tetracosactide	79/112		
Additional randomisation of type of hormonal therapy		1·2 (0·8–2·0)	0·425
Yes	92/136		
No	149/241		

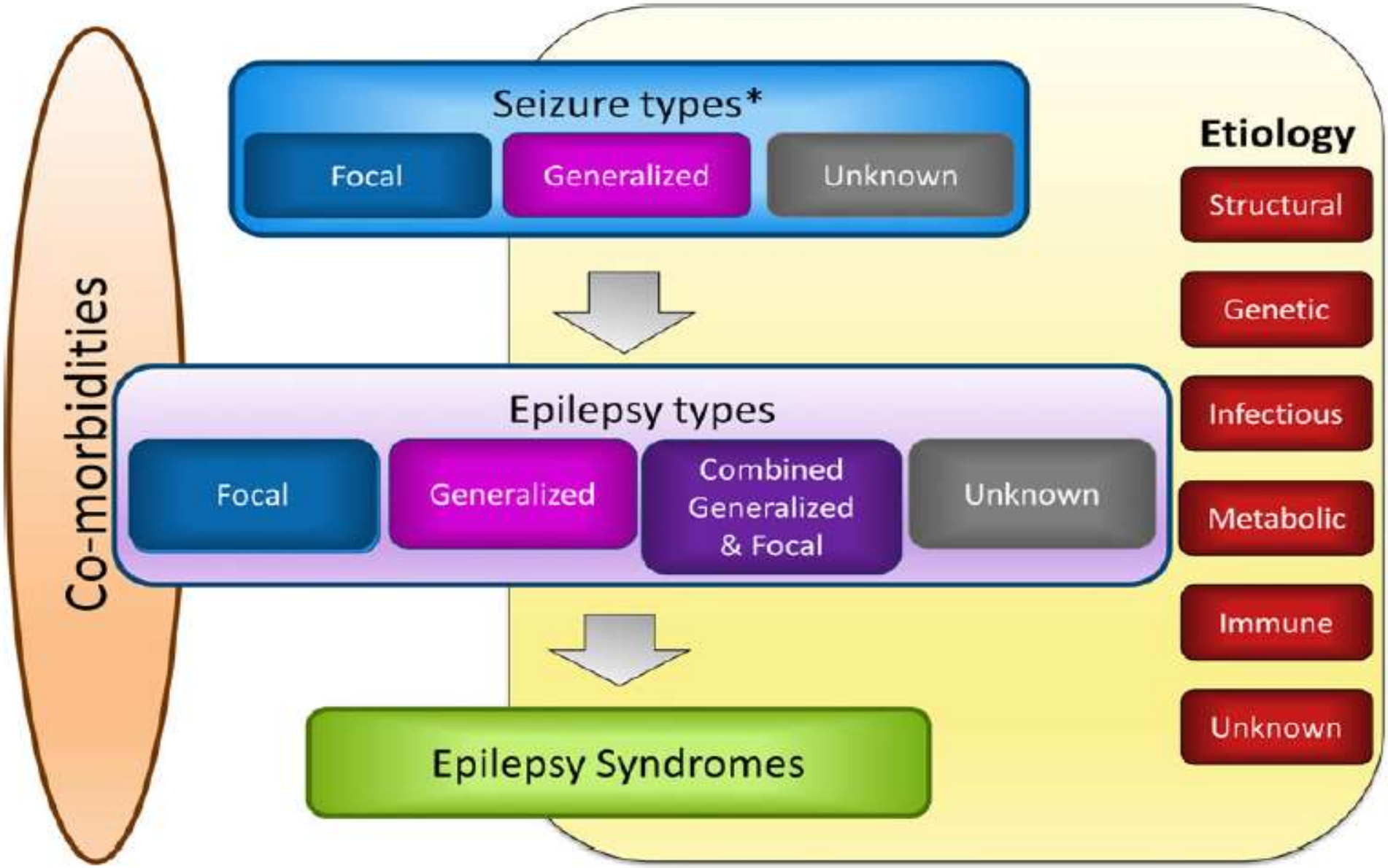
Individual Patient-oriented Pharmacotherapy



New ILAE - Classification of the Epilepsies

(Scheffer IE et al. Epilepsia, 58(4):512–521, 2017)

- A Multilevel Classification System -

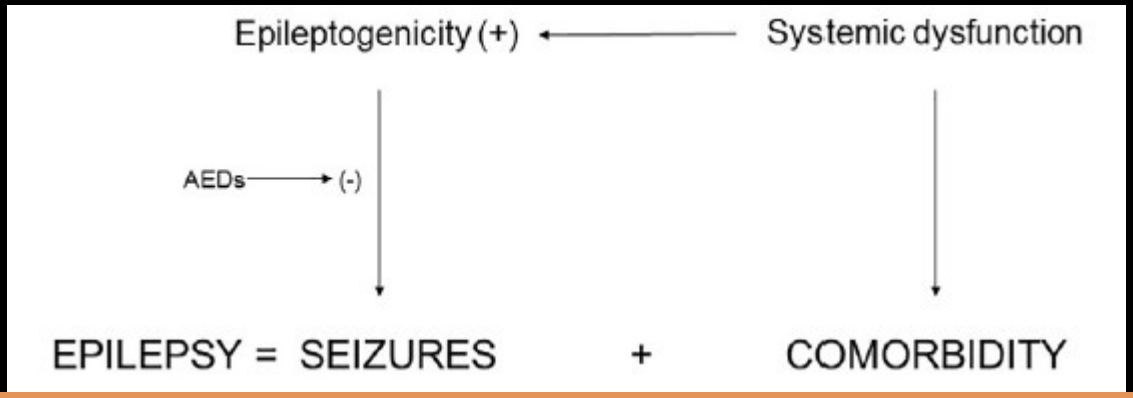


Comorbidities

- Patients with epilepsy(PWE) have two to eight times of Comorbidities than general population and > 50% of patients with epilepsy carry various types of comorbidities → Why? Due to shared systemic disorders?
  (inflammation, Oxidative stress, glycation, methylation capacity, mitochondrial efficiency : Yuen et al. Epilepsy & Behav 2018;78:57-61)

- An important factor for QOL, premature death, and choice of AEDs

- Recognition of comorbidities in 2017-ILAE Classification, including learning difficulties and psychiatric disorders, will ensure that ***epilepsy is seen as part of a broader phenotypic picture***



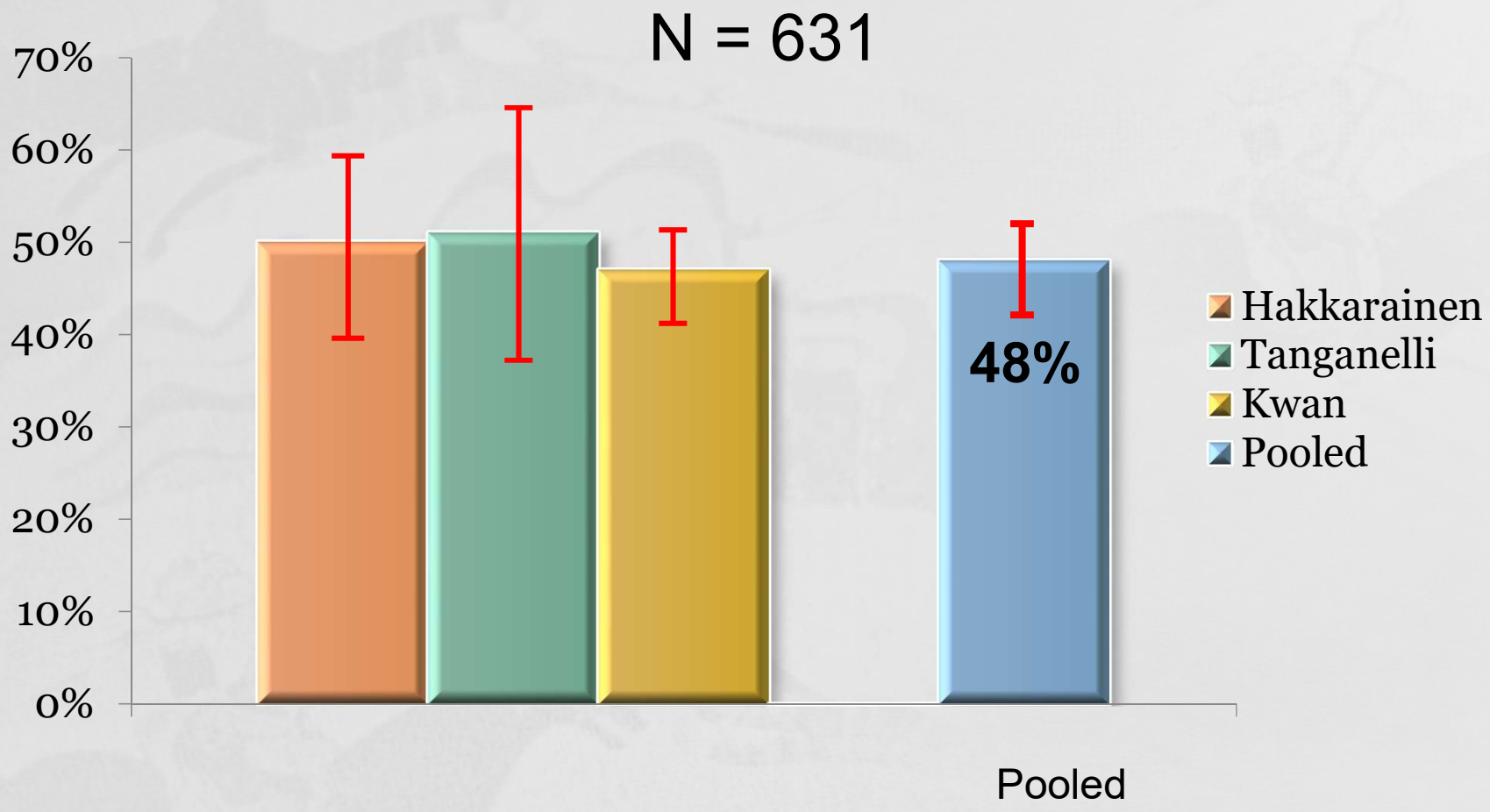
Patient-related Factors: Comorbidities for Choice of AEDs

	Choose	Avoid
Obesity ±DM :	TPM, ZNS	VPA, PGB, GBP, PER
Migraine :	TPM, VPA, ZNS, PBG, GBP	
Skin rash :	LEV, GBP, PGB, TPM, VPA, PER	LTG, OXC, CBZ, PHT, PB
Neuropathic pain:	PGB, GBP, CBZ, OXC	
± fibromyalgia		
Depression :	LTG, CBZ, OXC, VPA, PGB	LEV, PB, PRM, TPM, ZNS, PER
±behav & psych problems		
Cognitive dysfunction:	LTG, LEV, OXC	PB, TPM, ZNS
Patients under chemotherapy:	GBP, LEV, PGB, VPA	enzyme-inducing AEDs
± immunsuppressants		
± multiple drugs		
Restless legs syndrome:	GBP, PGB, CZP:	
Renal stone or glaucoma:		TPM, ZNS
Severe hematological disorders		CBZ, VPA
Hyponatremia		OXC, CBZ
hepatic disease:	New AEDs	VPA
renal disease:	Old AEDs	
Osteoporosis:	LTG	enzyme-inducing AEDs, TPM, VPA
Gait disturbance:		CBZ, PHT, PER
Tremor(parkinsonism):	TPM, PRM	VPA
Cardiac arrhythmia:		CBZ and sodium channel blockers)
Cancer:	VPA, LEV	enzyme-inducing AEDs
Once daily :	PB, PER, VPA-ER, ZNS, LEV-XR, TPM-ER	

modified from Dr. K Heo(2017)

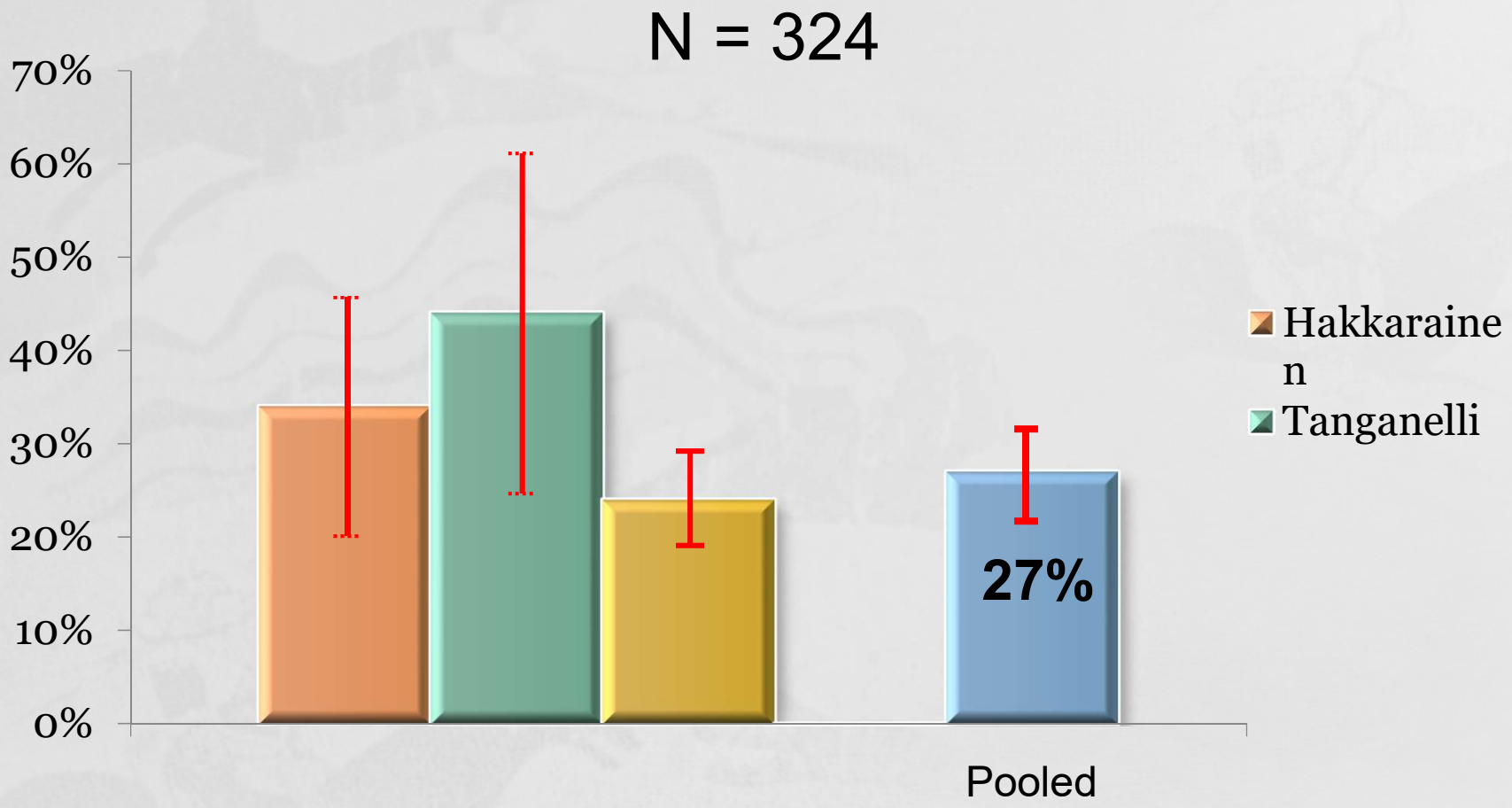
Proportion of Patients Controlled

On First Drug



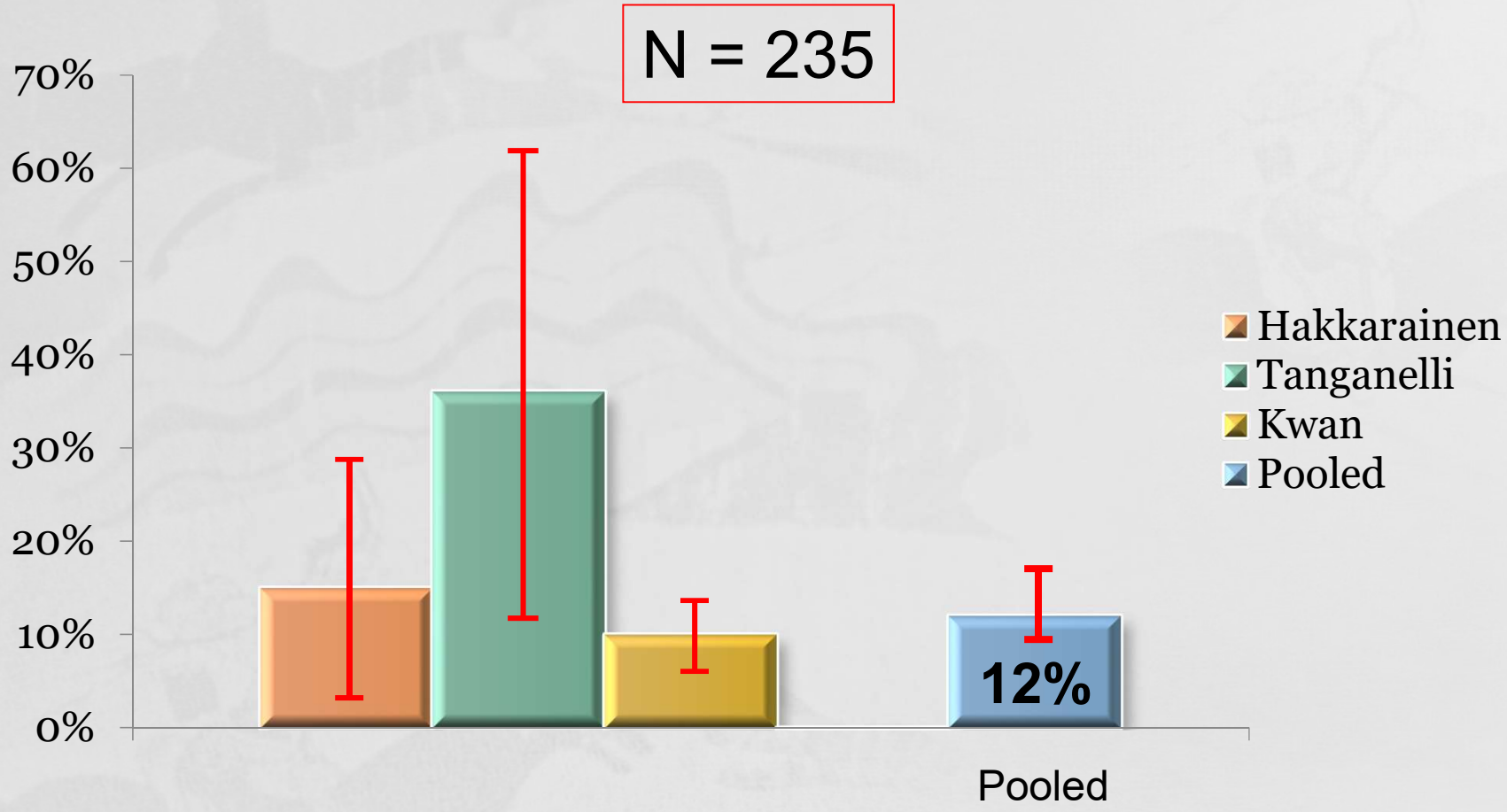
Proportion of Patients Controlled

Of Those Who Fail First Drug



Proportion of Patients Controlled

Of Those Who Fail ≥2 Drugs

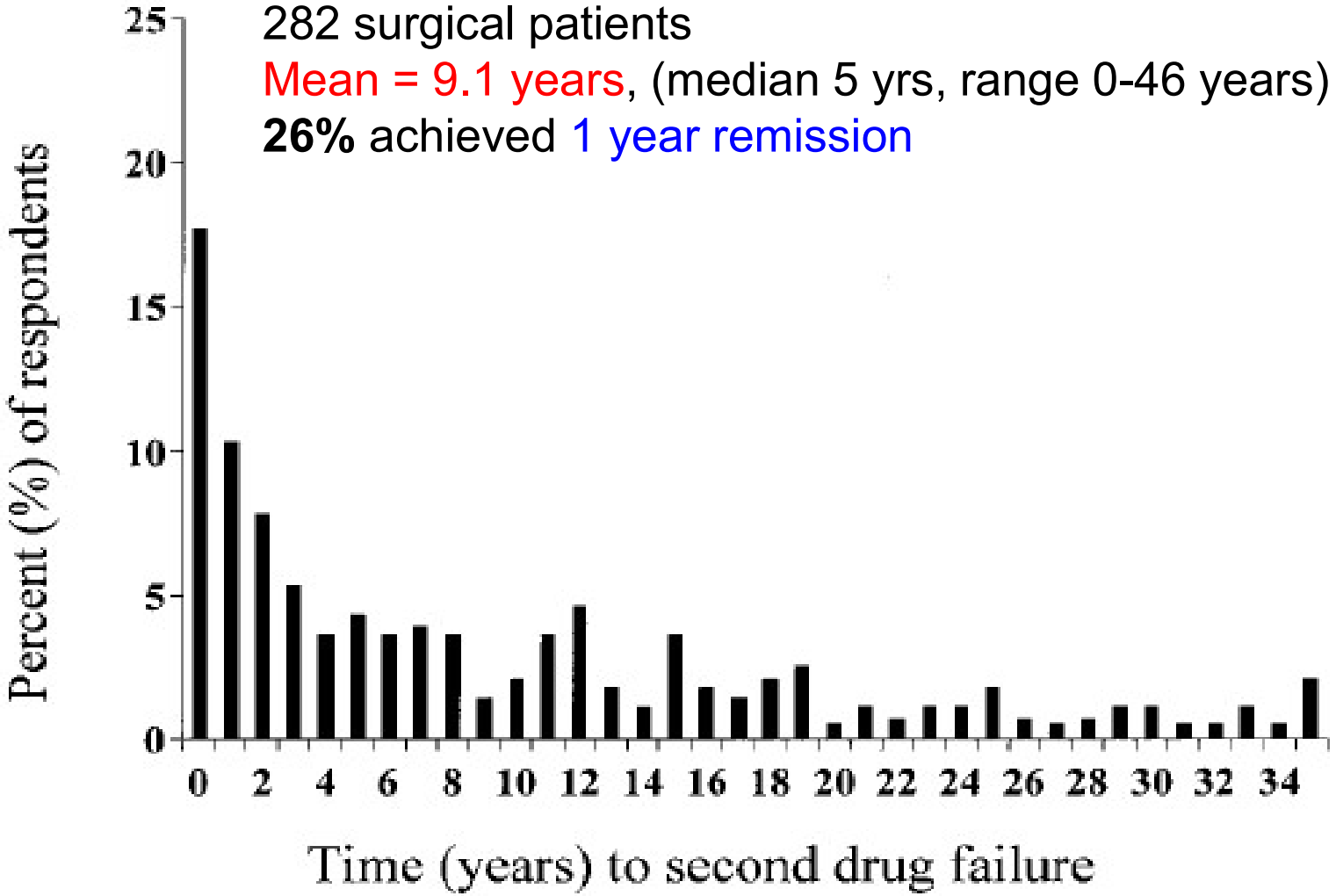


Time to Drug Intractability

282 surgical patients

Mean = 9.1 years, (median 5 yrs, range 0-46 years)

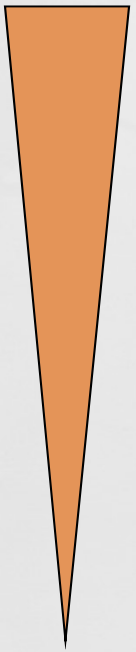
26% achieved 1 year remission



Berg, Neurology 2003

Etiology as Prognostic Factor for AED treatment

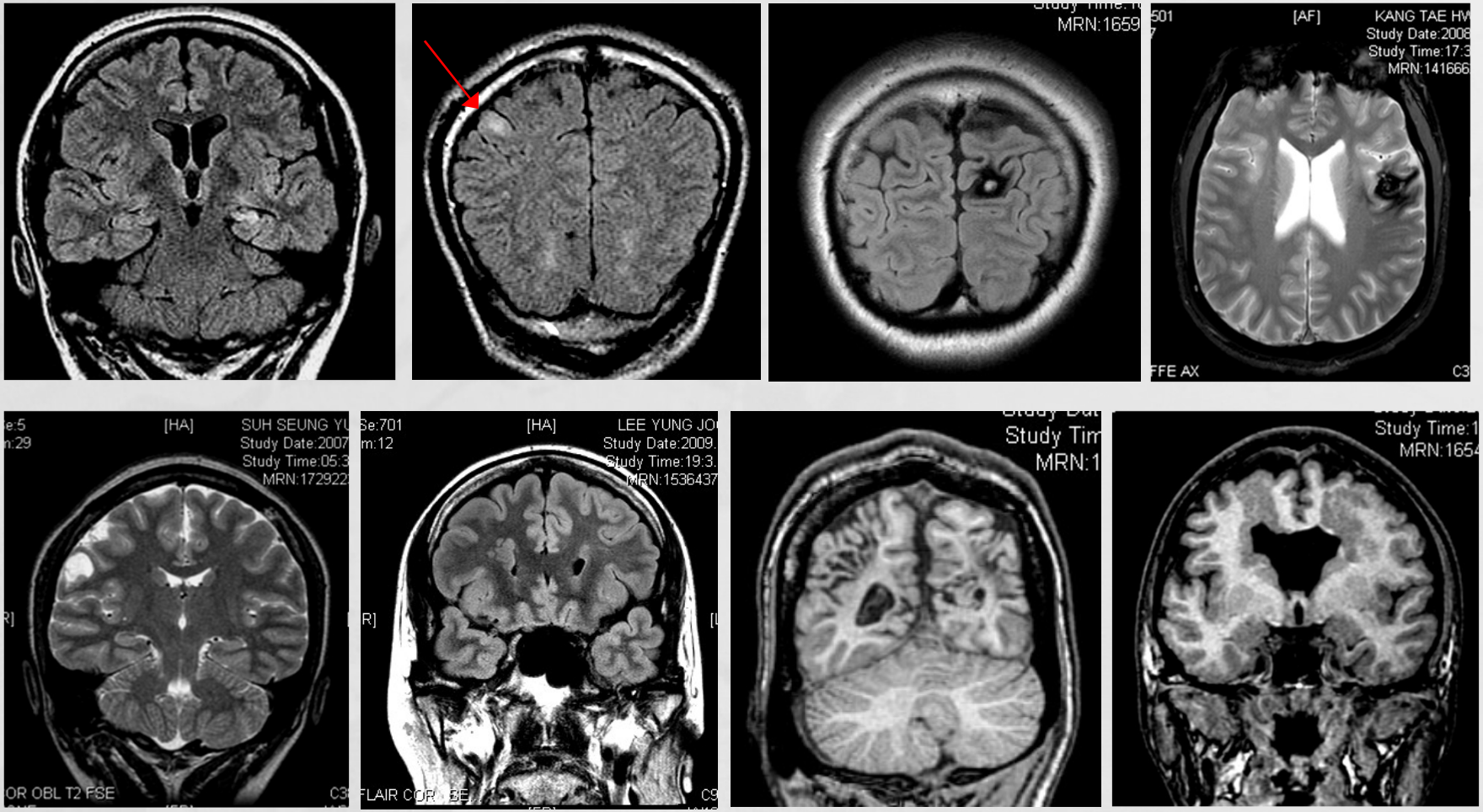
- **2,200 adults outpatients – 45% controlled (1 year seizure-free rate)**
- **Etiology:**
  - **Idiopathic generalized: 82%**
  - **Cryptogenic partial: 45%**
  - **Symptomatic partial: 35%**
  - **Extratemporal partial epilepsy: 36%**
  - **Dysgenesis: 24%**
  - **Temporal lobe epilepsy: 20%**
  - **Hippocampal sclerosis(HS): 11%**
  - **Dual pathology (HS+): 3%**



Neurology. 1998 Nov;51(5):1256-62.

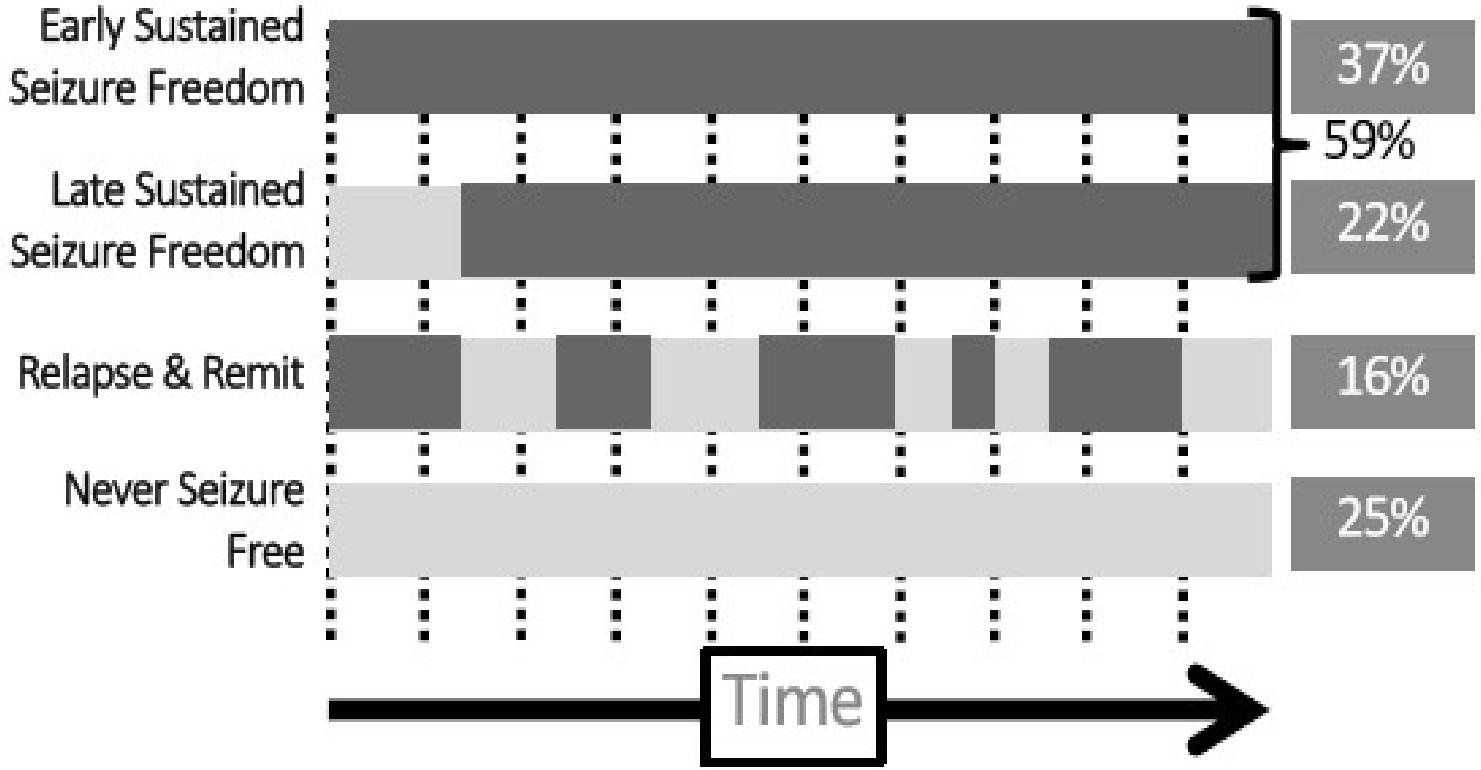
Lesions indicating high probability of DRE

Hippocampal Sclerosis, Cortical Dysplasia, Cavernous Angioma, DNT, Heterotopic Gray, Polymicrogyri, Schizencephaly



OUTCOME OVER TIME WITH AEDs

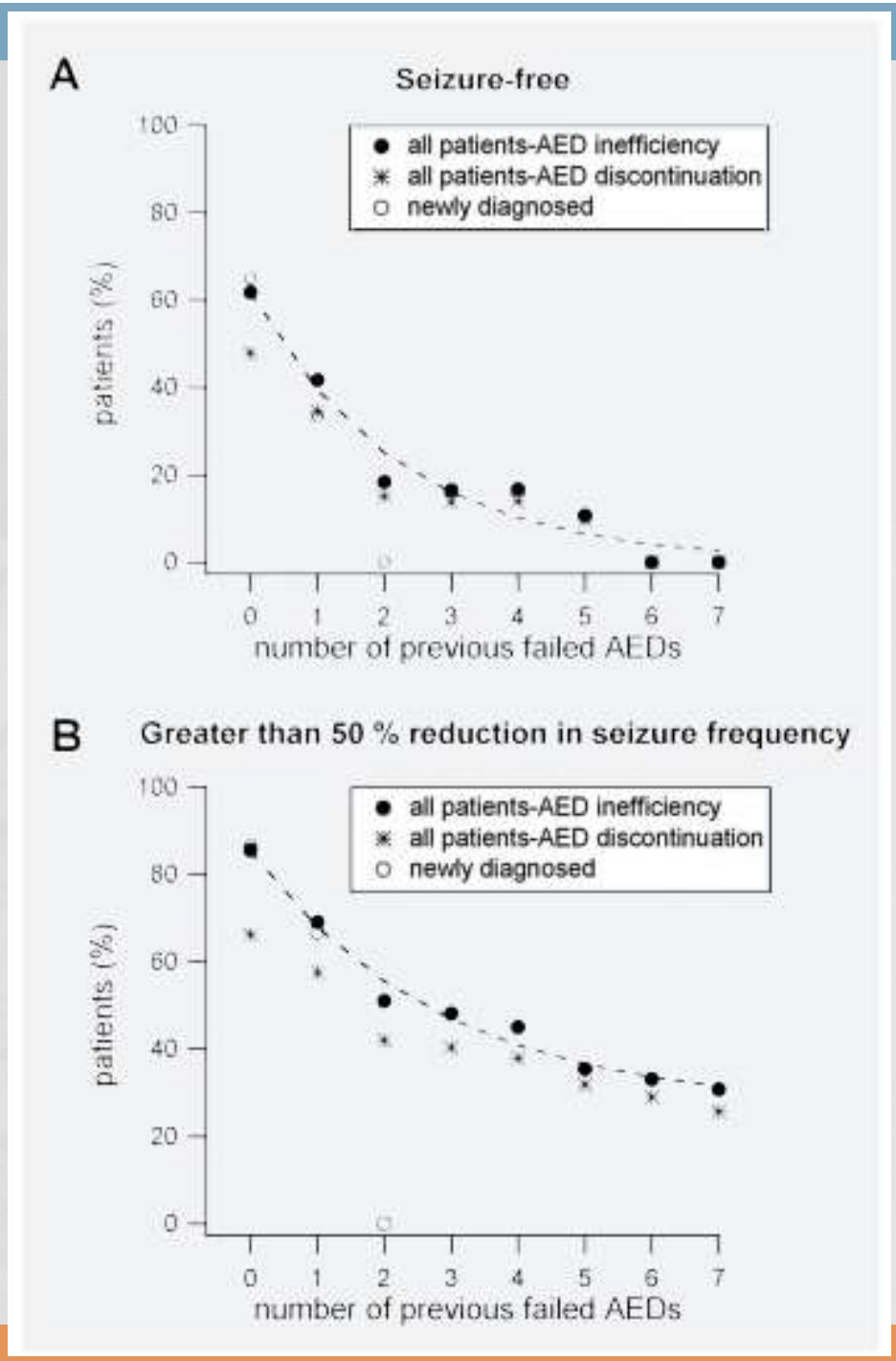
1,098 patients, median follow-up 7.5 years



Brodie et al, Neurology 2012

Evidences of polytherapy

- New AED add on therapy in patients resistant 1-3 AEDs
  - Seizure reduction rate: higher than placebo
  - Seizure free rate: higher than placebo
- Schiller and Najjar, 2008
  - Until 6th AED add-on: 16.5% seizure free rate by one AED add-on
  - 7th AED add-on: significant increase of responder rate
- Luciano and Shorvon (2007)
  - Add-on therapy of new AED: 28% one year sz free rate
- Multicenter study in Italy
  - ¾ of intractable epilepsy: polytherapy
  - 46.5%(adults), 54.2%(children): 3 or more AED
  - 7.2%: 4 or more AED



Schiller and Najjar, 2008

New definition of DRE

- At least 4 or 5 AEDs should be tried before drug resistance epilepsy is determined?
- What is enough number of monotherapy or combination therapy for DRE?
- What intensity of seizure for DRE?
  - Any seizures or seizures interfering daily life?
- It is not easy to predict patients who will be drug resistant?

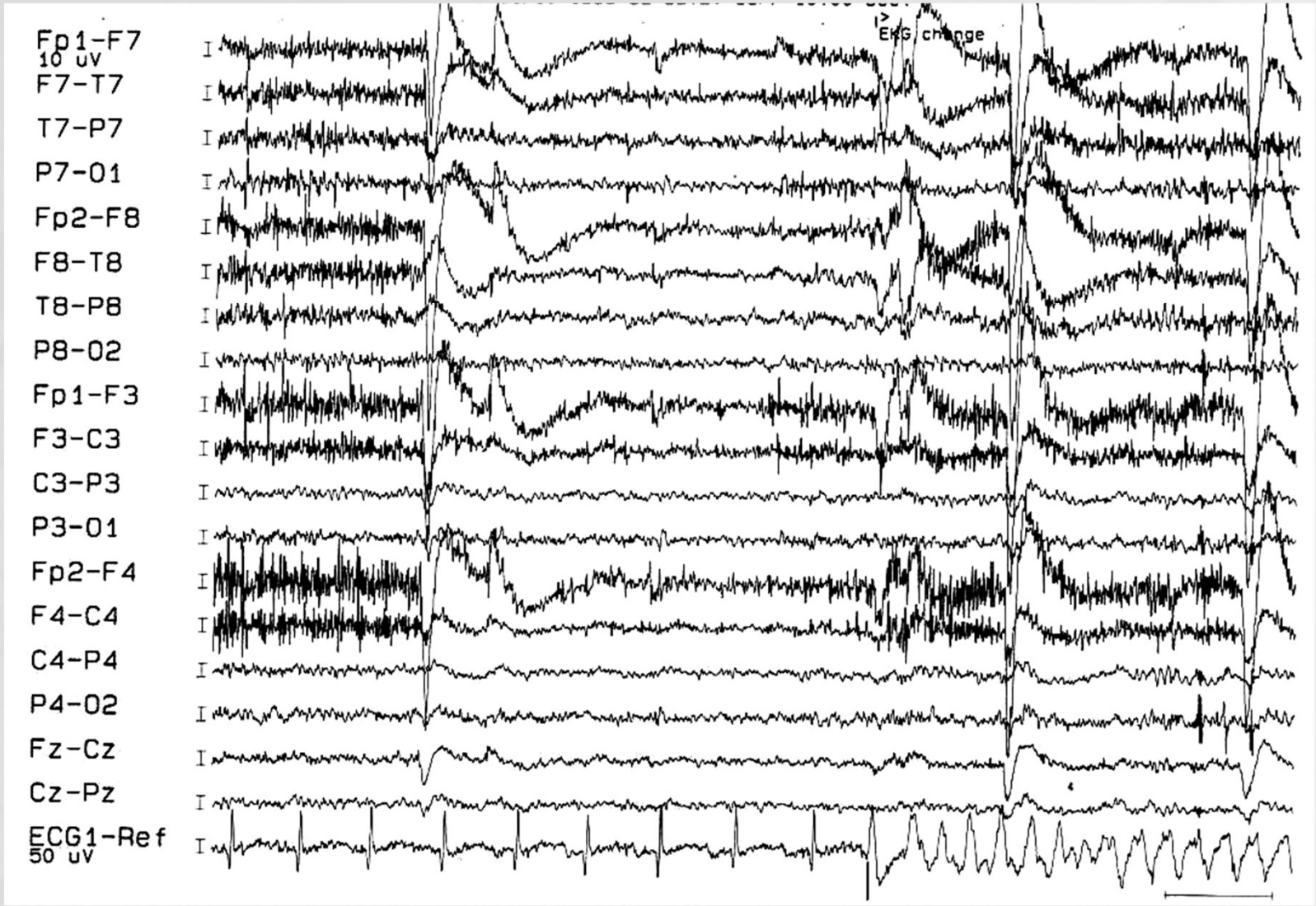
“Pseudo-intractable” seizures

- Inappropriate AED selection
- Less therapeutic serum concentration
- Non-epileptic disorders, psychogenic seizures
- 10% or more of epilepsy patients: co-existent psychogenic seizures
- Conditions resembling epilepsy in early childhood
- Mistaking complex partial seizures for absence epilepsy
- Failing to identify precipitating factors
  - AED skip, sleep deprivation, alcohol drinking, PC game, etc.
- Neurodegenerative disorders and inborn errors of metabolism
- Autoimmune encephalitis

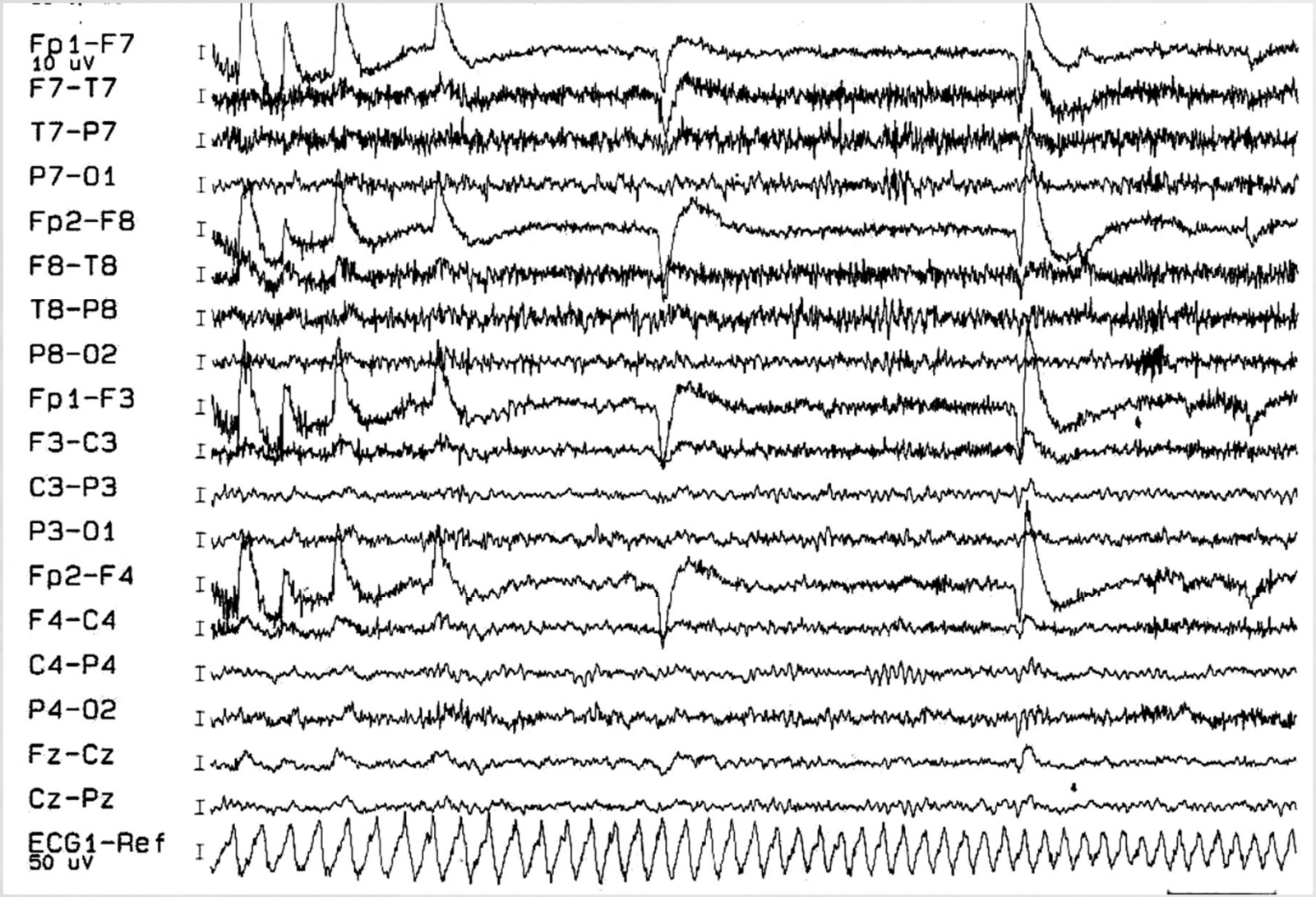
Case 1 (20/F)

- Age of seizure onset: 13 year-old
- Seizures: dizziness → upward eye deviation, falling, grunting, whole body movement, bilateral tonic clonic seizures
- Frequency: 3 - 4/year, Duration: 2-3 minutes
- AED: Tegretol-CR 400 mg, Valproate 600 mg daily
- EEG: normal (4 times)
- Brain MRI : no abnormality
- The patient was admitted to EMU to confirm her epilepsy diagnosis. She had three seizures during 3 day video-EEG monitoring period.

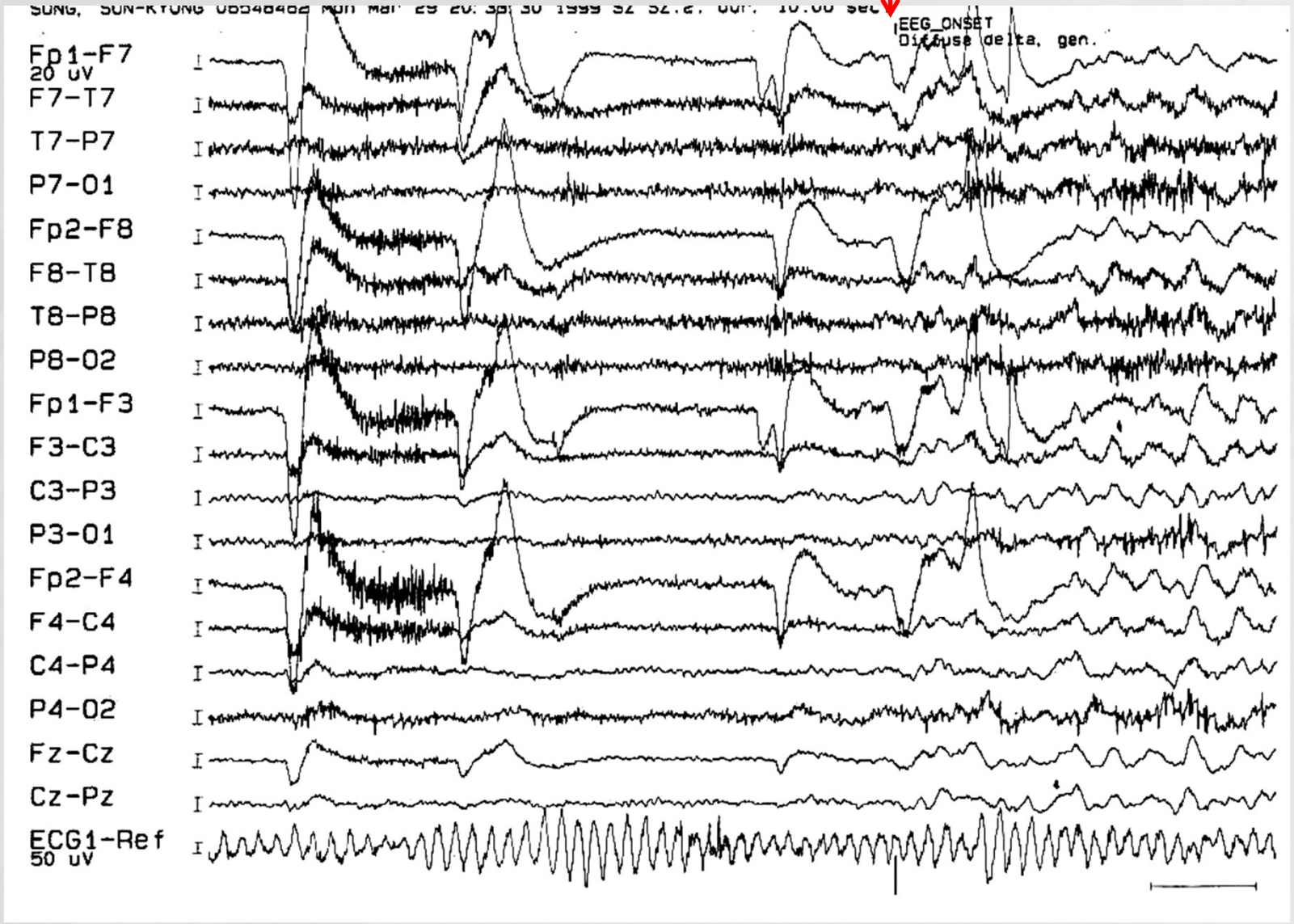
20-30 seconds prior to EEG seizure onset



15 seconds before seizure onset

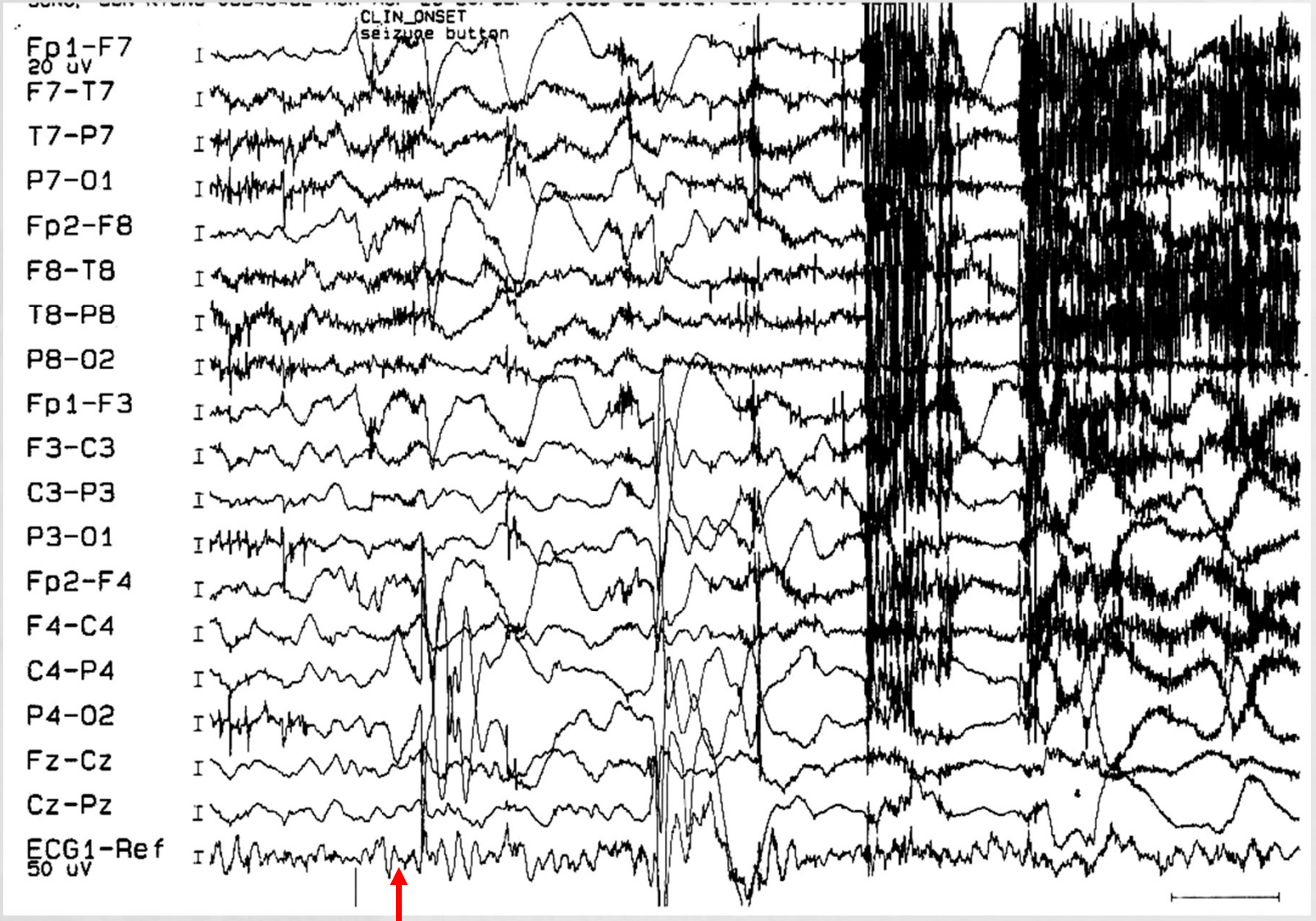


EEG seizure onset



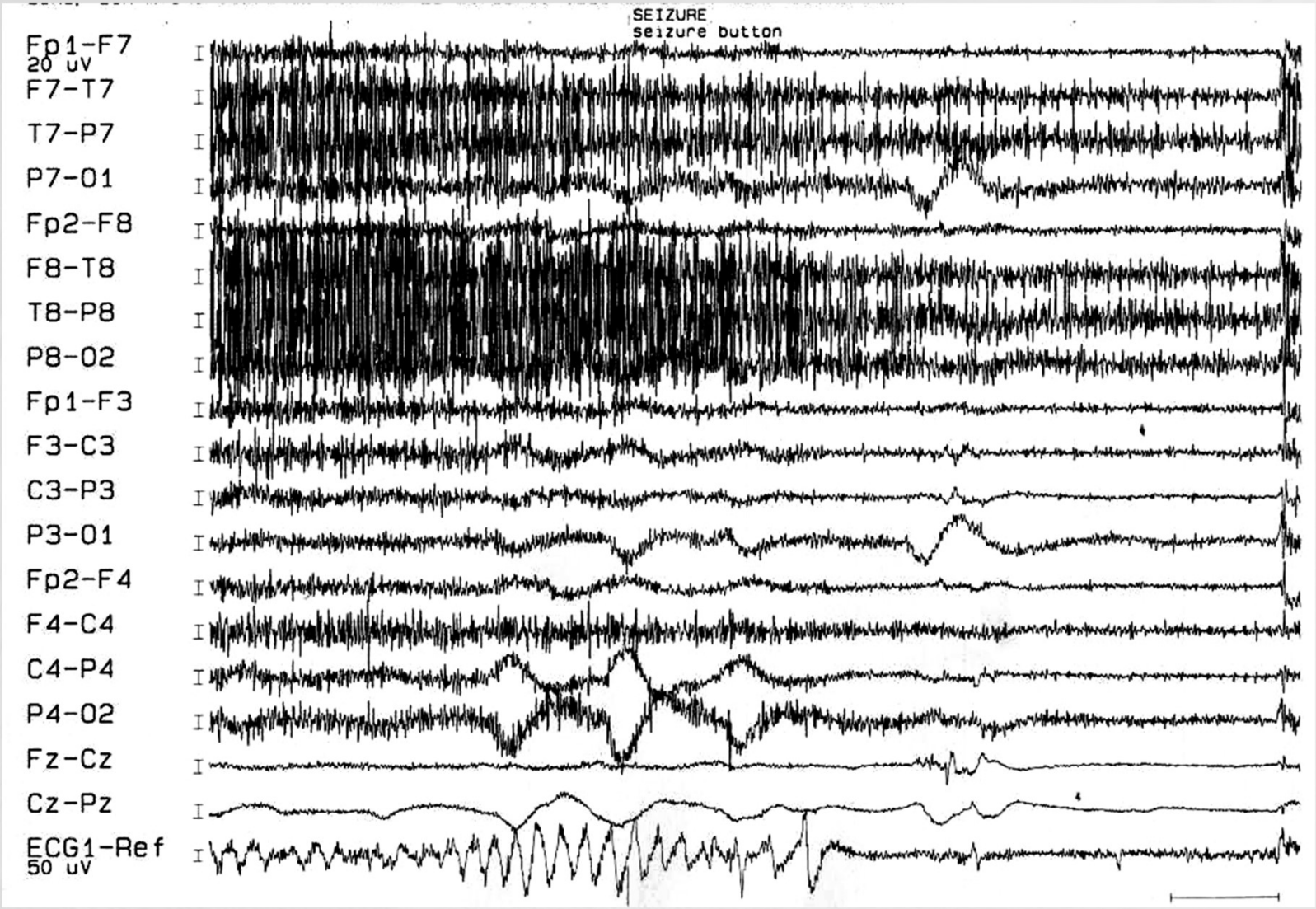
Fell down

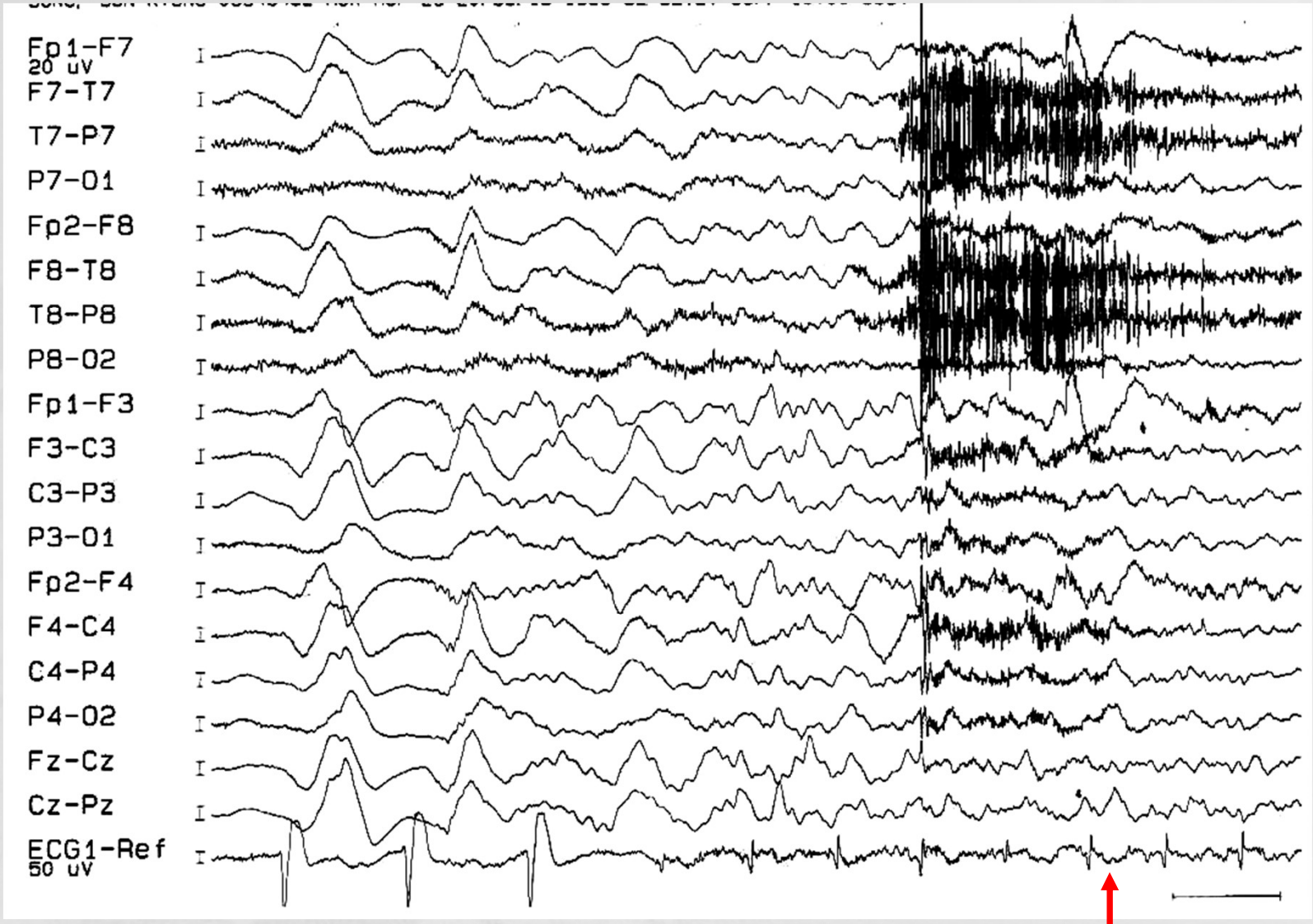
Generalized clonic seizure



Clinical seizure onset

Groaning, generalized seizure





Clinical & EEG seizure end

- Diagnosis before EMU: Epilepsy (GTC)

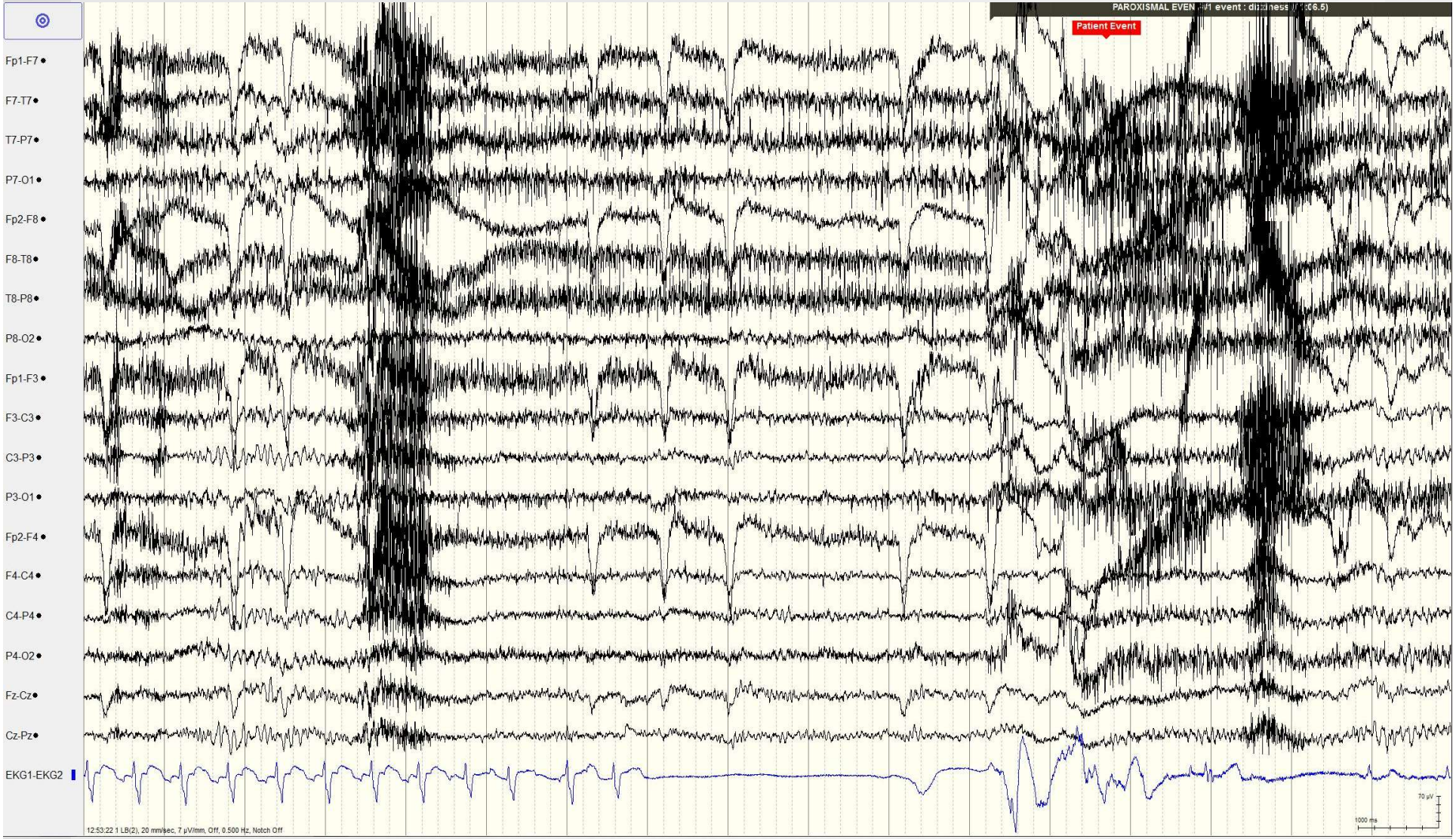
- Diagnosis after EMU → convulsive
  Cardiac syncope
  - Long-QT syndrome
  - Ventricular tachycardia

- Treatment
  - Discontinuation of antiepileptic drugs
  - Implantation of defibrillator → patient become seizure free

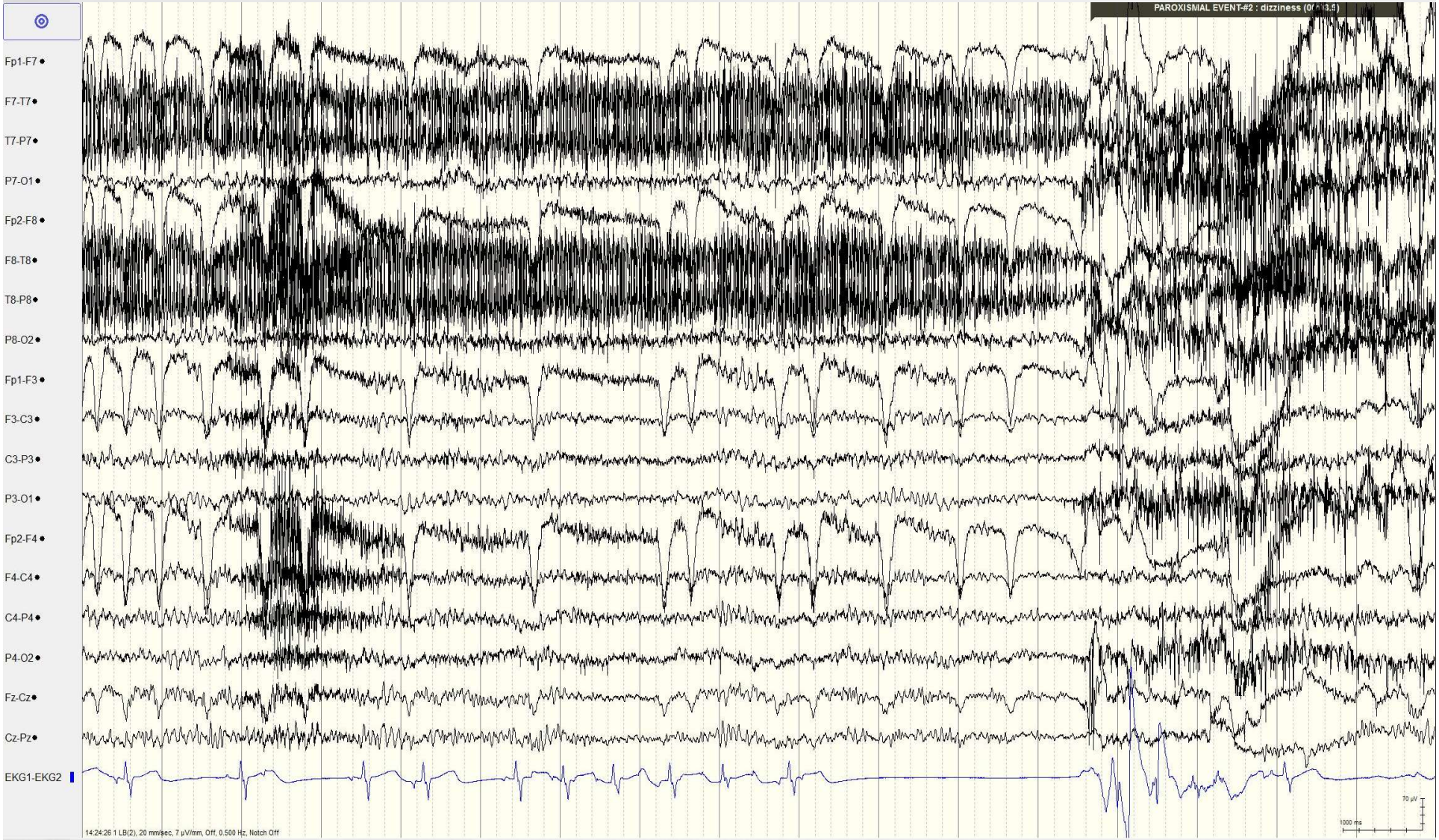
Case 2: 66/F

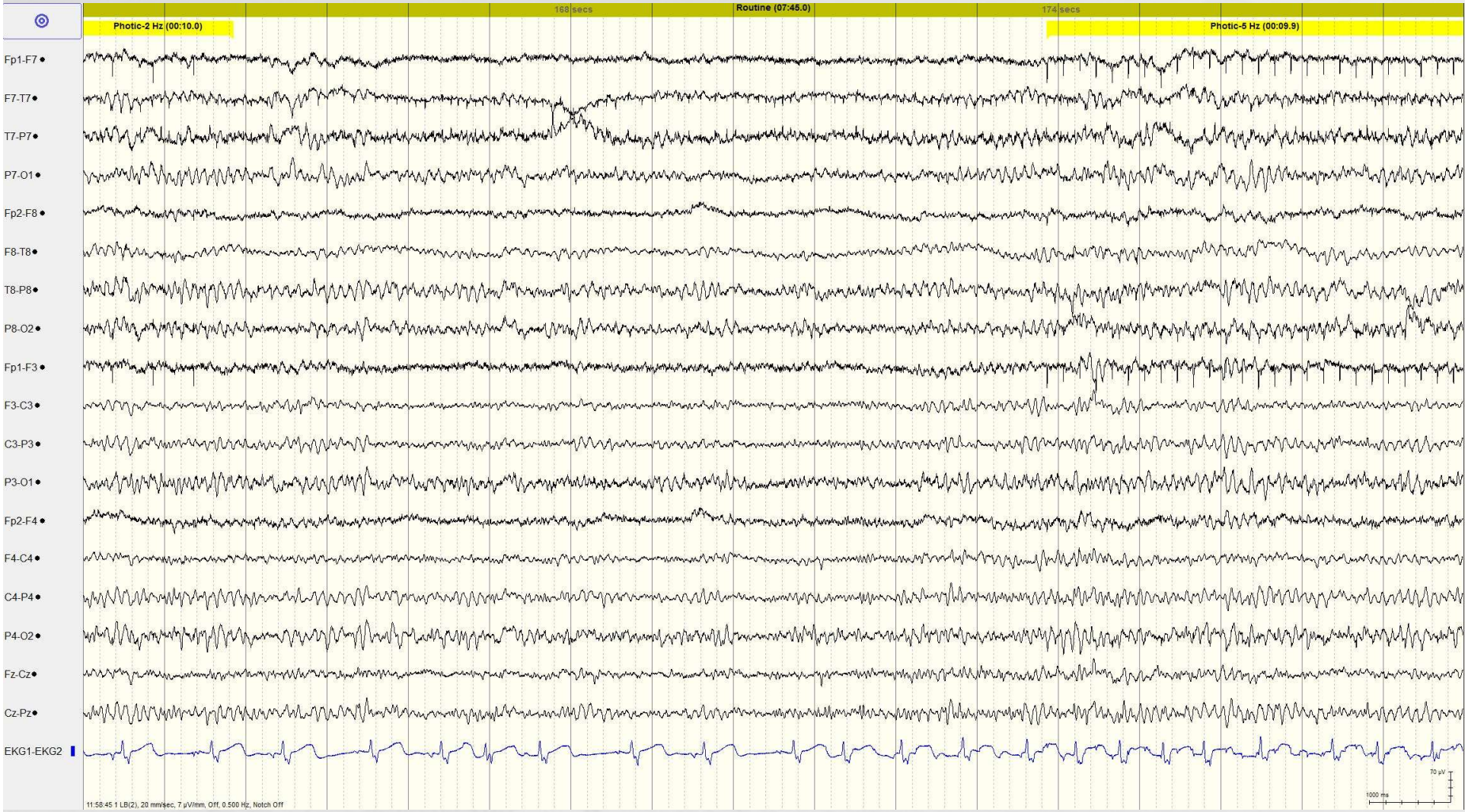
- 2005.10 : Paroxysmal atrial fibrillation was diagnosed.
- 2015 : **Paroxysmal dizziness** was started.
- 2016 : AED (CBZ 500, VPA 1200) was started due to paroxysmal dizziness and abnormality of EEG (sharp wave at left temporal lobe)
- 2019. 1: Patient had an ablation surgery for atrial fibrillation. Thereafter, paroxysmal dizziness has been worsened.
- 2019. 6 : Patient suffered greatly from dizziness episodes increased to >10 times per day (5-10 sec)
- 2019. 6. 10 : She pushed herself to EMU admission due to severe difficulty during dizziness episodes.

EEG during dizziness episode



EEG during dizziness episode

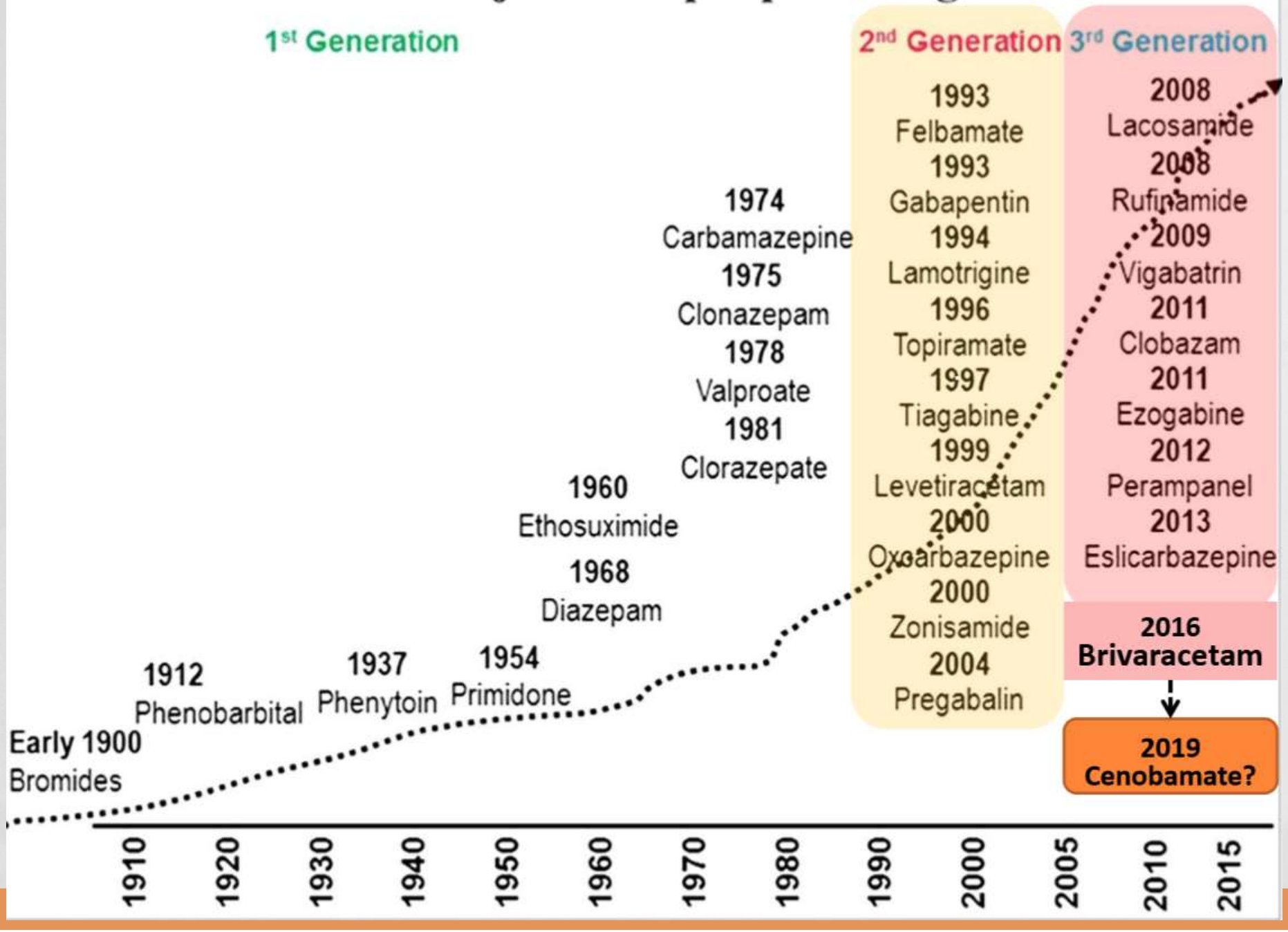



168 secs
Routine (07:45.0)
174 secs
Photic-2 Hz (00:10.0)
Photic-5 Hz (00:09.9)
Fp1-F7
F7-T7
T7-P7
P7-O1
Fp2-F8
F8-T8
T8-P8
P8-O2
Fp1-F3
F3-C3
C3-P3
P3-O1
Fp2-F4
F4-C4
C4-P4
P4-O2
Fz-Cz
Cz-Pz
EKG1-EKG2
70 µV
1000 ms
11:58:45 1 LB(2), 20 mm/sec, 7 µV/mm, Off, 0.500 Hz, Notch Off

Final diagnosis

- Sick sinus syndrome (longest pause : 7.2sec) with very frequent asystole
- 2019. 6. 13 : implantation of permanent pacemaker → dizziness disappeared.

Introduction of Major Antiepileptic Drugs in the US



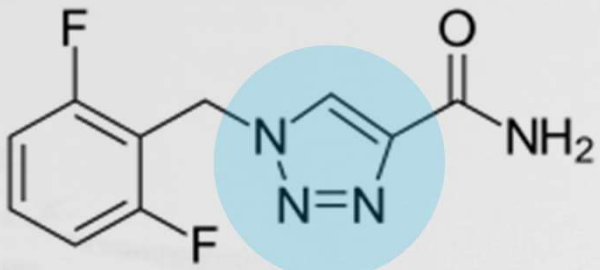
Properties of newer AEDs

Golyala, *Seizure* 2017

Drug	Trade Names	Year of appro-val	Primary MoA	Indica-tions	Absorp-tion (bio-avail-ability %)	Protein binding	Half-life(h)	Metabol-ism & routes of elimina-tion
Rufinamide	Banzel Inovelon	**2004**	Sodium-channel blockade	**LGS/ Partial**	Slow (>85%)	34%	6-10	Hepatic
Lacosamide	Vimpat	**2008**	1. Slow inactivation of sodium channel 2. Interacts with CRMP-2	**Partial**	Rapid (95-100%)	<15%	13	Hepatic
Eslicarbaze-pine acetate	Apitom Zebinix Exalief	**2009**	Sodium-channel blockade	**Partial**	Rapid (90%)	40%	**13-20**	Glucuroni-dation, Renal
Ezogabine/ Retigabine	Potiga Trobalt	**2011**	Activation of low-threshold potassium channels	**Partial**	Rapid (60%)	80%	8	Glucuroni-dation
Perampanel	Fycompa	**2012**	Non-competitive AMPA-receptor antagonist	**Partial /GTCs**	Rapid (100%)	95%	**105**	Glucuroni-dation, Feces, Urine
Brivaracetam	Briviact	**2016**	Binds to SV2A receptors	**Partial**	Rapid (100%)	<20%	7-8	Renal

1. Rufinamide (RUF)

- Triazole derivative



- **MoA**
  - Not clear
  - Limiting excessive firing of sodium-dependent action potentials

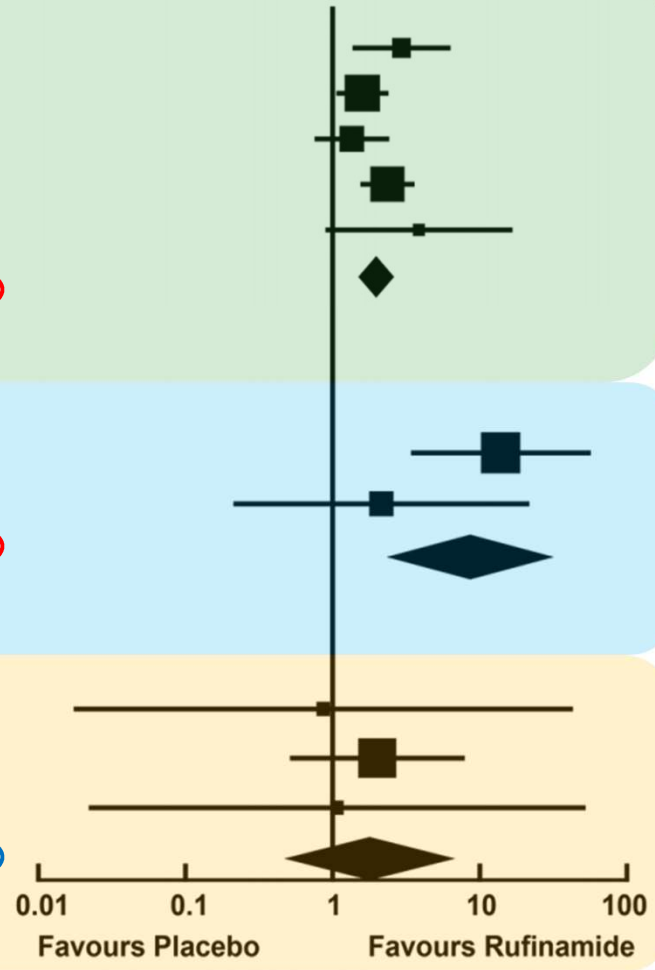
- **FDA approval**
  - **Lennox-Gastaut Syndrome** ≥4 years old
  - Add-on Tx for adults & adolescents with **focal seizures**

Rufinamide : Key studies

Study	Design & Tx regimen	Primary outcomes	Secondary outcomes
Biton 2011 **Refractory focal Sz** 12-80 yo 1-3 AEDs	**Placebo** (n=181) **3200 mg/d** (n=176) 56d baseline → 96d Tx	1. % change in focal Sz freq	1. 50% and 75% responders 2. adverse effects
Brodie 2009 **Refractory focal Sz** ≥16 yo 1-2 AEDs	**Placebo** (n=156) **3200 mg/d** (n=313) 8w baseline → 13 w Tx	1. % change in focal Sz freq	1. total focal Sz frequency 2. 50% responders 3. % change in secondary generalized Sz frequency 4. adverse effects
Elger 2010 **Refractory focal Sz** 15-65 yo 1-3 AEDs	**Placebo** (n=133) **200**(n=127)/**400**(n=125) **800**(n=129)/**1600**mg/d (n=133) 12w baseline → 12w Tx	1. mean % reduction in total focal Sz freq	1. 50% responders 2. adverse effects
Glaser 2008 **LGS** 4-30 yo 1-3 AEDs	**Placebo** (n=64) **45 mg/kg** (n=74) 28d baseline → 84d Tx	1. median % reduction in total Sz freq 2. median % reduction in tonic-atonic Sz freq 3. Sz severity rating	1. 50% responders 2. adverse effects
Ohtsuka 2014 **LGS**	**Placebo** (n=30) **45 mg/kg** (n=29)	1. % change in tonic-atonic Sz freq	1. % change in total Sz freq 2. 50% responders(T-aT Sz)

Rufinamide: Meta-analysis
Risk ratios of responders

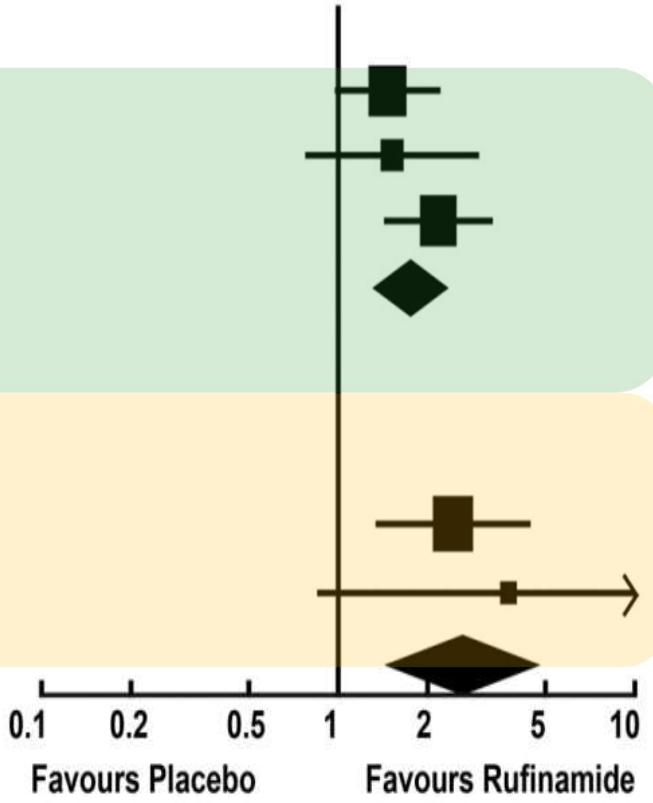
Study or Outcome	Rufinamide Events / Total	Placebo Events / Total	Weight	Risk ratio, 95% CI	p-Value
50% response					
Glaser 2008	23 / 74	7 / 64	10.13%	2.842 [1.306,6.181]	0.008
Brodie 2009	44 / 156	29 / 157	35.83%	1.527 [1.010,2.308]	0.045
Elger 2010	60 / 514	12 / 133	17.58%	1.294 [0.717, 2.333]	0.392
Biton 2011	52 / 160	25 / 175	33.68%	2.275 [1.486, 3.484]	0.000
Ohtsuka 2014	7 / 28	2 / 30	2.77%	3.750 [0.850, 16.551]	0.081
Total	**186 / 932**	**79 / 559**	**100%**	**1.852 [1.446, 2.372]**	**0.000**
Heterogeneity: Q-value = 5.966, df(Q) = 4 (*P* = 0.202), I^2 = 32.959					
Egger's regression: t = 0.901, df=3, *P* = 0.43379					
75% response					
Biton 2011	26 / 160	2 / 175	73.1%	14.219 [3.429, 58.951]	0.000
Ohtsuka 2014	2 / 28	1 / 30	26.9%	2.143 [0.205, 22.347]	0.524
Total	**28 / 160**	**3 / 205**	**100%**	**8.547 [2.534, 28.832]**	**0.001**
Heterogeneity: Q-value = 1.917, df(Q) = 1 (*P*=0.166), I^2 = 47.830					
Egger's regression: Not estimable					
Seizure free					
Glaser 2008	0 (0.5) / 74	0 (0.5) / 64	9.84%	0.865 [0.017, 42.967]	0.942
Brodie 2009	6 / 156	3 / 157	80.22%	2.053 [0.504, 8.360]	0.315
Ohtsuka 2014	0 (0.5) / 28	0 (0.5) / 30	9.94%	1.071 [0.022, 52.193]	0.972
Total	**6 (7) / 258**	**3 (4) / 251**	**100%**	**1.740 [0.511, 5.924]**	**0.376**
Heterogeneity: Q-value = 0.226, df(Q) = 2 (*P*=0.893), I^2 = 0.000					
Egger's regression: t = 6.339, df=1, *P* = 0.100 *					



Zu, *Epilepsy Res* 2016

Rufinamide: Meta-analysis
Risk ratios of 50% responder rate in partial and tonic-atonic seizures

Study or Subgroups	Rufinamide Events / Total	Placebo Events / Total	Weight	Risk ratio, 95% CI	p-Value
Partial seizures					
Brodie 2009	44 / 156	29 / 157	43.34%	1.527 [1.010,2.308]	0.045
Elger 2010	19 / 133	12 / 133	15.92%	1.583 [0.801, 3.130]	0.186
Biton 2011	52 / 160	25 / 175	40.74%	2.275 [1.486, 3.484]	0.008
Total	**115 / 449**	**66 / 465**	**100%**	**1.807 [1.376, 2.371]**	**0.000**
Heterogeneity: Q-value = 1.905, df(Q) = 2 (*P* = 0.386), I^2 = 0.000					
Egger's regression: t = 0.247, df = 1, *P* = 0.846					
Tonic-atonic seizures					
Glaser 2008	31 / 74	11 / 64	85.92%	2.437 [1.336, 4.446]	0.004
Ohtsuka 2014	7 / 30	2 / 30	14.08%	3.750 [0.850, 16.551]	0.081
Total	**38 /102**	**13 /94**	**100%**	**2.590 [1.484, 4.521]**	**0.001**
Heterogeneity: Q-value = 0.278, df(Q) = 1 (*P* = 0.598), I^2 = 0.000					
Egger's regression: Not estimable					

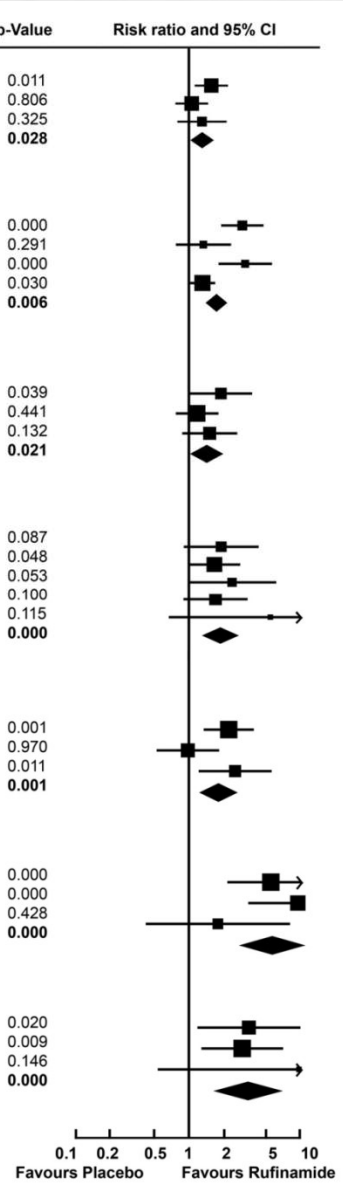


Zu, *Epilepsy Res* 2016

Rufinamide : Significant adverse effects

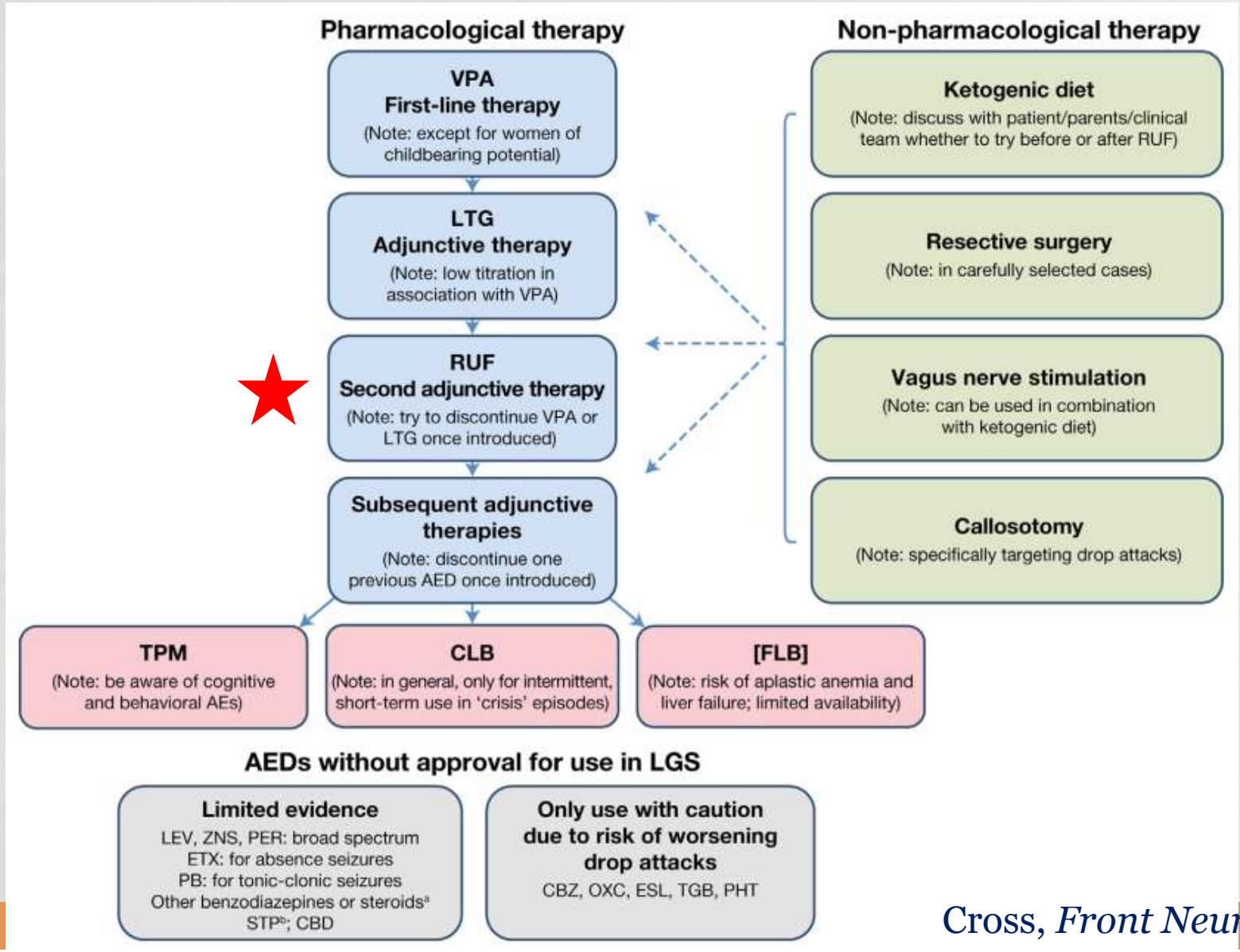
- **Headache**
- **Dizziness**
- Fatigue
- Somnolence
- Nausea
- Diplopia
- Vomiting

Study or Subgroups	Rufinamide Events / Total	Placebo Events / Total	Weight	Risk ratio and 95% CI	p-Value
Headache					
Brodie 2009	59 / 156	38 / 157	40.18%	1.563 [1.110, 2.200]	0.011
Elger 2010	129 / 514	32 / 133	41.47%	1.043 [0.745, 1.461]	0.806
Biton 2011	29 / 176	23 / 180	18.36%	1.290 [0.777, 2.139]	0.325
Total	**217 / 846**	**93 / 470**	**100%**	**1.276 [1.027, 1.585]**	**0.028**
Heterogeneity: Q-value = 2.723, df(Q) = 2 (P = 0.256), I^2 = 26.558					
Egger's regression: t = 0.065, df=1, P = 0.958					
Dizziness					
Brodie 2009	66 / 156	22 / 157	19.95%	1.748 [1.444, 2.117]	0.000
Elger 2010	68 / 154	13 / 133	11.61%	1.327 [1.027, 1.713]	0.291
Biton 2011	47 / 176	15 / 180	12.44%	3.205 [1.862, 5.515]	0.000
Ohtsuka 2014	26 / 28	21 / 30	56.01%	1.353 [0.772, 2.374]	0.030
Total	**207 / 874**	**71 / 500**	**100%**	**2.012 [1.222, 3.312]**	**0.006**
Heterogeneity: Q-value = 16.300, df(Q) = 3 (P = 0.001), I^2 = 81.595					
Egger's regression: t = 1.149, df=2, P = 0.369					
Fatigue					
Brodie 2009	25 / 156	13 / 157	24.14%	2.114 [1.039, 4.303]	0.039
Elger 2010	96 / 514	21 / 133	45.77%	1.225 [0.731, 2.052]	0.441
Biton 2011	27 / 176	18 / 180	30.09%	1.631 [0.863, 3.082]	0.132
Total	**148 / 846**	**52 / 470**	**100%**	**1.523 [1.074, 2.160]**	**0.021**
Heterogeneity: Q-value = 1.546, df(Q) = 2 (P = 0..462), I^2 = 0.000					
Egger's regression: t = 9.817, df=1, P = 0.064					
Somnolence					
Glaser 2008	18 / 74	8 / 64	18.72%	1.946 [0.908, 4.172]	0.087
Brodie 2009	32 / 156	19 / 157	39.87%	1.695 [1.005, 2.859]	0.048
Elger 2010	47 / 514	5 / 133	13.39%	2.432 [0.987, 5.995]	0.053
Biton 2011	22 / 176	13 / 180	25.51%	1.731 [0.900, 3.327]	0.100
Ohtsuka 2014	5 / 28	1 / 30	2.51%	5.357 [0.666, 43.068]	0.115
Total	**124 / 948**	**46 / 564**	**100%**	**1.889 [1.358, 2.628]**	**0.000**
Heterogeneity: Q-value = 1.502, df(Q) = 4 (P = 0..826), I^2 = 0.000					
Egger's regression: t = 7.266, df=3, P = 0.005					
Nausea					
Brodie 2009	41 / 156	18 / 157	47.47%	2.292 [1.379, 3.810]	0.001
Elger 2010	42 / 514	11 / 133	30.29%	0.988 [0.523, 1.866]	0.970
Biton 2011	23 / 176	9 / 180	22.24%	2.614 [1.244, 5.489]	0.011
Total	**106 / 846**	**38 / 470**	**100%**	**1.805 [1.008, 3.233]**	**0.001**
Heterogeneity: Q-value = 5.252 df(Q) = 2 (P = 0..072), I^2 = 61.918					
Egger's regression: t = 0.138, df=1, P = 0.912					
Diplopia					
Glaser 2008	31 / 74	5 / 64	46.95%	5.362 [2.217, 12.971]	0.000
Brodie 2009	37 / 156	4 / 157	36.09%	9.309 [3.399, 25.496]	0.000
Elger 2010	14 / 514	2 / 133	16.97%	1.811 [0.417, 7.872]	0.428
Total	**82 / 744**	**11 / 354**	**100%**	**5.443 [2.971, 9.969]**	**0.000**
Heterogeneity: Q-value = 3.245, df(Q) = 2 (P = 0.197), I^2 = 38.375					
Egger's regression: t = 1.099, df=1, P = 0.470					
Vomiting					
Glaser 2008	16 / 74	4 / 64	35.18%	3.459 [1.219, 9.820]	0.020
Brodie 2009	21 / 156	7 / 157	59.58%	3.019 [1.322, 6.898]]	0.009
Ohtsuka 2014	4 / 28	0 (0.5) / 30	5.24%	8.571 [0.474, 154.922]	0.146
Total	**41 / 258**	**11 (11.5) / 251**	**100%**	**3.336 [1.773, 6.276]**	**0.000**
Heterogeneity: Q-value = 0.469, df(Q) = 2 (P = 0.791), I^2 = 0.000					
Egger's regression: t = 17.252, df=1, P = 0.0369					



Zu, *Epilepsy Res* 2016

Treatment algorithm for a newly diagnosed LGS



Cross, *Front Neurol* 2017

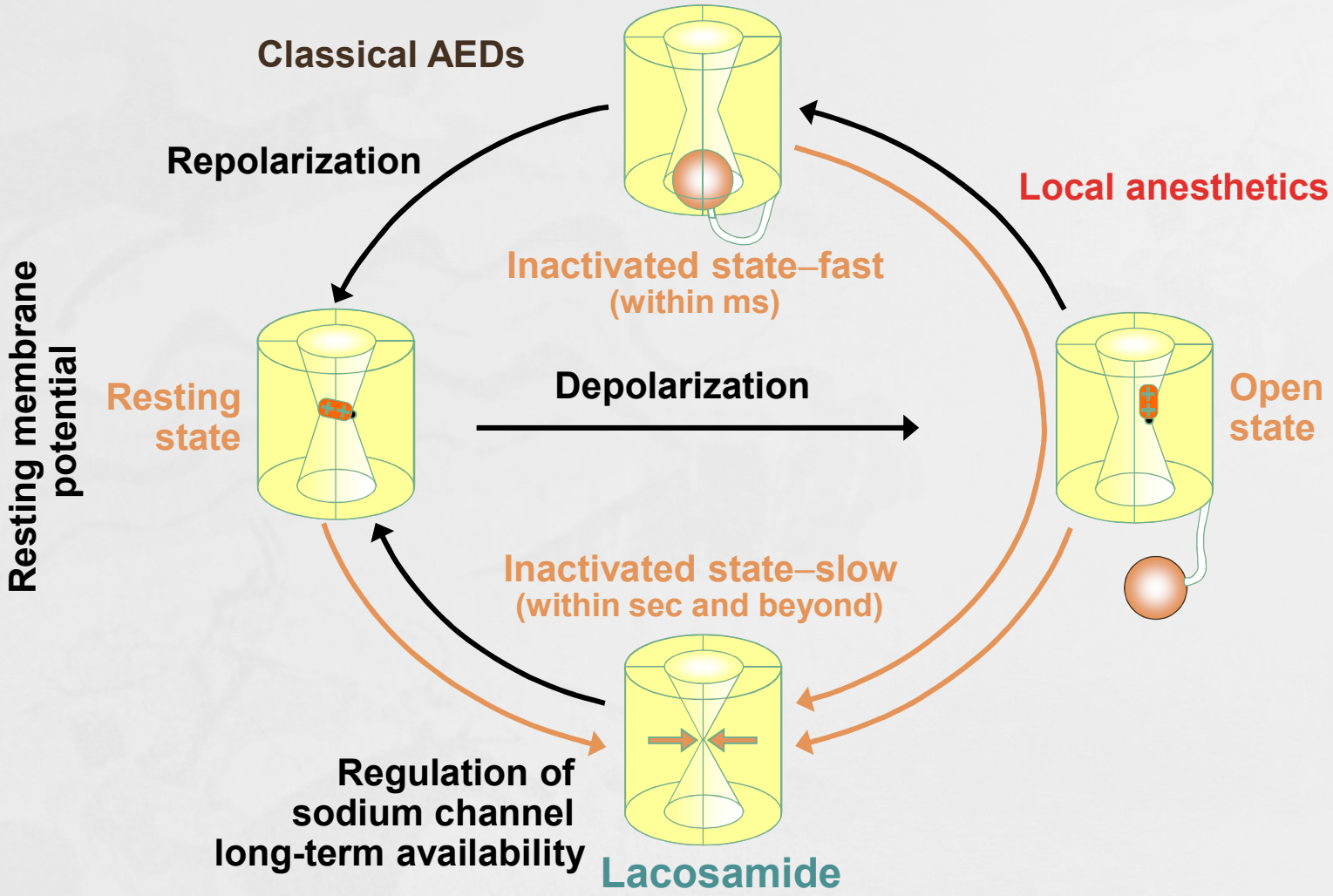
2. Lacosamide: Description

- Functionalized amino acid
- Molecular formula: $C_{13}H_{18}N_2O_3$
- Molecular weight: 250.3 g/mol

LACOSAMIDE (LCM)

- Lacosamide tablets, syrup and IV solution have been stu died as adjunctive therapy in the treatment of partial-onse t seizures in patients with epilepsy aged ≥ 16 years
- Lacosamide was approved in the EU on September 3, 20 08, and in the US on October 29, 2008

Lacosamide: Unique MOA



Beyreuther BK, et al. *CNS Drug Rev*. 2007;13:21-42.

Lacosamide: Pharmacokinetic Profile

- Linear pharmacokinetics
- Low inter- and intra-subject variability of about 20%
- T_{max}: 1-4 hrs after oral administration
- $T_{1/2}$ ~ 13 hrs (BID); steady-state achieved in 3 days
- Absolute bioavailability ~100%
- Food does not affect rate and extent of absorption
- 95% of the dose is excreted in the urine (40% as unchanged drug)
- Low protein binding (<15%)
- Low drug-drug interaction potential
- No influence of gender or race (Asian, Black, Caucasian) has been observed
- Increased plasma concentrations in elderly compared with young subjects (20%)

3 Phase IIb, III trials, and Pooled Analysis

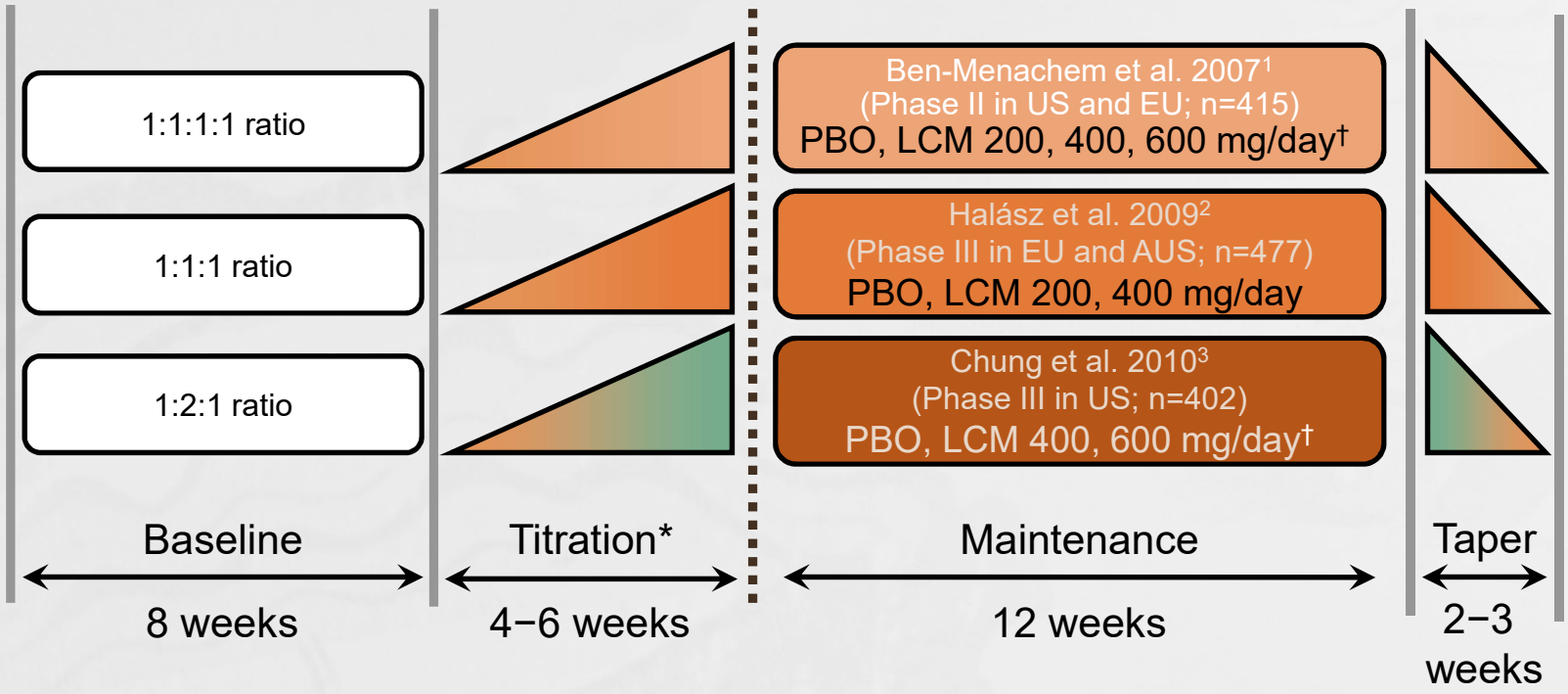
- Ben-Menachem study (SP667): Efficacy and safety of oral LCM as adjunctive therapy in adults with partial-onset seizures: *Ben-Menachem E, Biton V, Jatuzis D, Abou-Khalil B, Doty P and Rudd GD. Epilepsia 2007;48(7):1308–17*

- Chung study (SP754): Lacosamide: Efficacy and safety as oral adjunctive treatment in adults with partial-onset seizures: *Steve Chung S, Sperling M, Biton V, Krauss G, Doty P, Sullivan T. Epilepsia* 2010; 51(6):958-967

- Halasz study (SP755): Lacosamide: Efficacy and safety as oral adjunctive treatment in adults with partial-onset seizures: *Halasz P, Kälviäinen B, Mazurkiewicz-Beldzinska M, Rosenow F, Doty P, Hebert D., Sullivan T. Epilepsia 2009; 50(3): 443-453*

- Pooled Analysis: ***Chung S,*** *Ben-Menachem E., Sperling M., Rosenf eld W., Fountain B.N., Benbadis S., Hebert D., Isojävi J., Doty P. C NS Drugs. 2010: 24(12):1041-54.*

Lacosamide pivotal clinical trials



Multicentre, randomised, double-blind, placebo-controlled trials of adjunctive lacosamide in patients with partial-onset seizures taking 1 to 3 AEDs, with or without vagal nerve stimulation (VNS)

ITT population=all randomised patients receiving ≥1 dose of trial medication with ≥1 post-baseline efficacy assessment, n=1,294

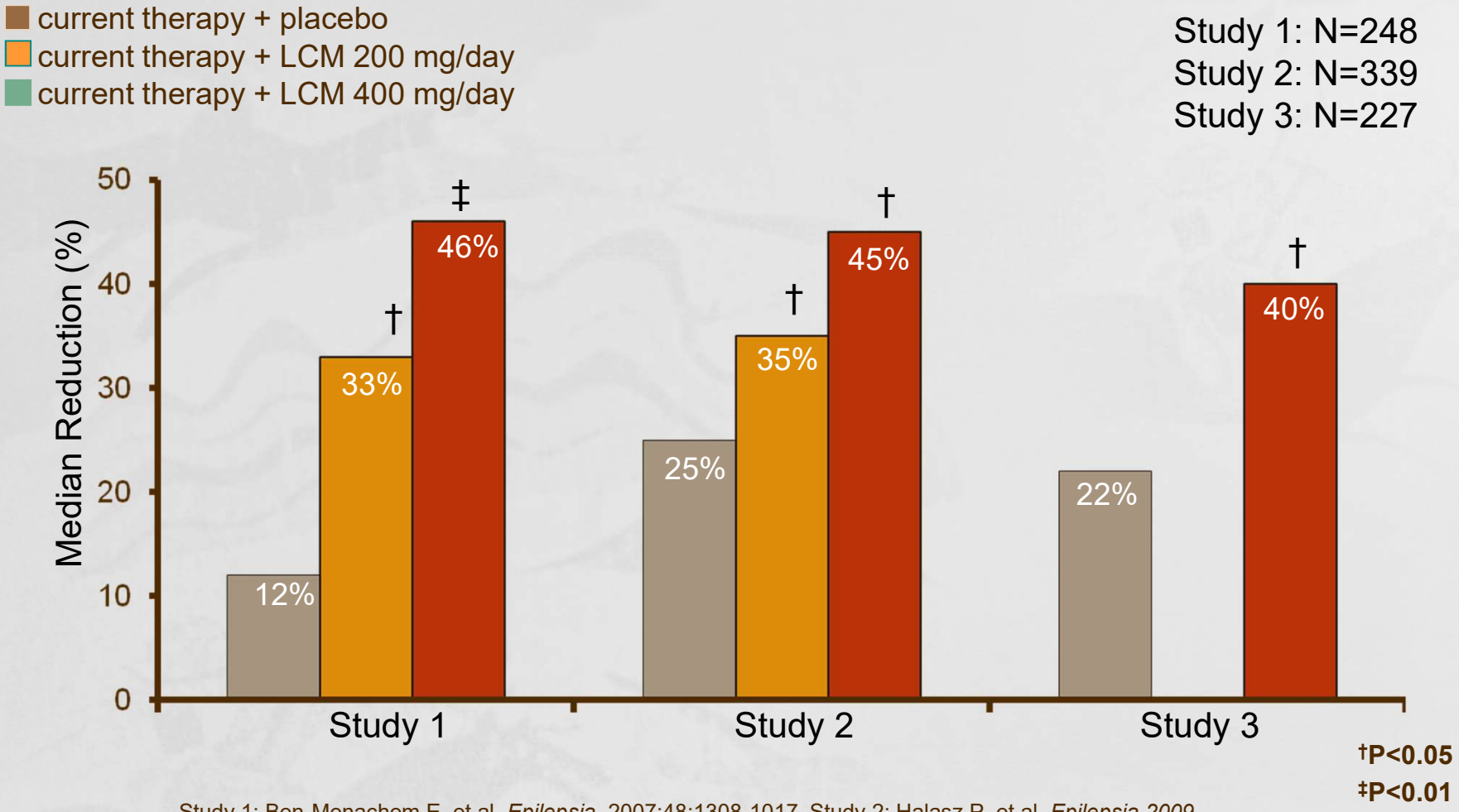
[1]Ben-Menachem et al. Epilepsia 2007;48(7):1308–1317; [2]Halász et al. Epilepsia 2009;50(3):443–453; [3]Chung et al. Epilepsia 2010;51(6):958–967

Lacosamide: Patient Characteristics

- N=1,294*[1]
- Mean age: 38.6 years[1]
- Female: 51.1%[1]
- Mean time since diagnosis: 23.7 years[1]
- Lifetime use of AEDs[1]
  - 77% tried ≥4
  - 45% tried ≥7
- Concomitant AEDs[1]
  - 1 AED: 15.5%
  - 2 AEDs: 62.4%
  - 3 AEDs: 22.0%
- Seizures at baseline
  - Simple partial: 32.1%
  - Complex partial: 84.0%
  - Partial with secondary generalizations: 41.7%
- Median baseline seizure frequency: 10 to 17 per 28 days
- Vagus nerve stimulation placement: n=216

1. Chung S, et al. Poster presented at: 62nd Annual American Epilepsy Society Meeting; December 5-9, 2008; Seattle, WA..

Lacosamide: Median Percentage Seizure Frequency Reduction from Baseline* (Per Protocol Set)



Study 1: Ben-Menachem E, et al. *Epilepsia*. 2007;48:1308-1017. Study 2: Halasz P, et al. *Epilepsia 2009* . Study 3: Chung S, et al. Epilepsia 2009

Lacosamide: Adverse Events

Most Common Adverse Events (%) Occurring in ≥10% of LCM Treated Patients and Greater than Placebo

AE	Treatment Phase	Placebo (n=364)	VIMPAT® 200 mg/day (n=270)	VIMPAT® 400 mg/day (n=471)
Dizziness	Forced-titration	7%	10%	25%
	Maintenance	2%	7%	8%
Headache	Forced-titration	6%	7%	10%
	Maintenance	5%	7%	6%
Nausea	Forced-titration	4%	6%	9%
	Maintenance	1%	2%	4%
Diplopia	Forced-titration	1%	4%	8%
	Maintenance	1%	4%	4%

Lacosamide: Cognitive Adverse Events

TEAEs Potentially Related to Cognition During the Treatment Phase

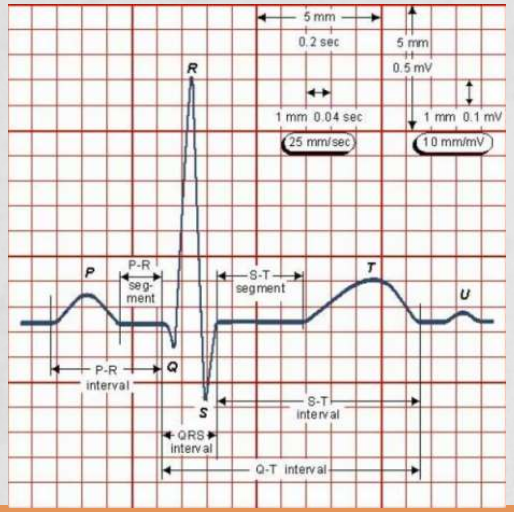
Cognitive Adverse Events	Placebo (n=364)	Lacosamide 200 mg/day (n=270)	Lacosamide 400 mg/day (n=471)
Memory impairment	1.6%	1.1%	1.5%
Cognitive disorder	0.3%	0.4%	2.1%
Confusional state	0.8%	0%	1.5%
Disturbance in attention	0.5%	0%	1.1%
Mental impairment	0%	0%	0.4%

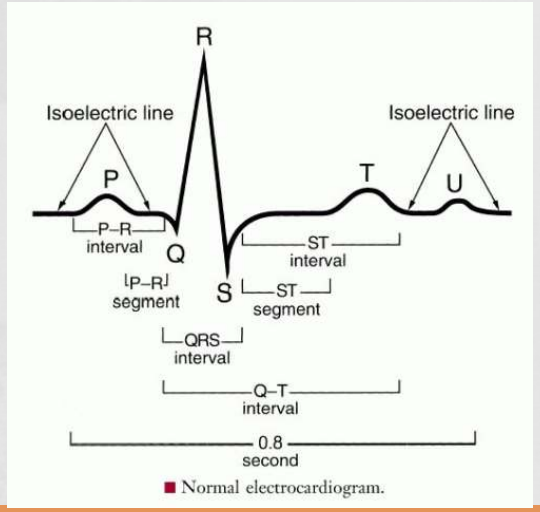
- In total, 6.1% of TEAEs were potentially related to cognition for VIMPAT®'s 200 mg/day and 400 mg/day doses vs 4.7% for placebo

Chung, et al *CNS Drugs* Jan 2011

Important Safety Information

- Caution is advised for patients with known cardiac conduction problems, who are taking drugs known to induce PR interval prolongation, or with severe cardiac disease
- Reported cases of A-fib and A-flutter in ICU patients
- In patients with known conduction problems or with severe cardiac disease, obtaining an ECG before beginning VIMPAT®, and after VIMPAT® is titrated to steady state, is recommended

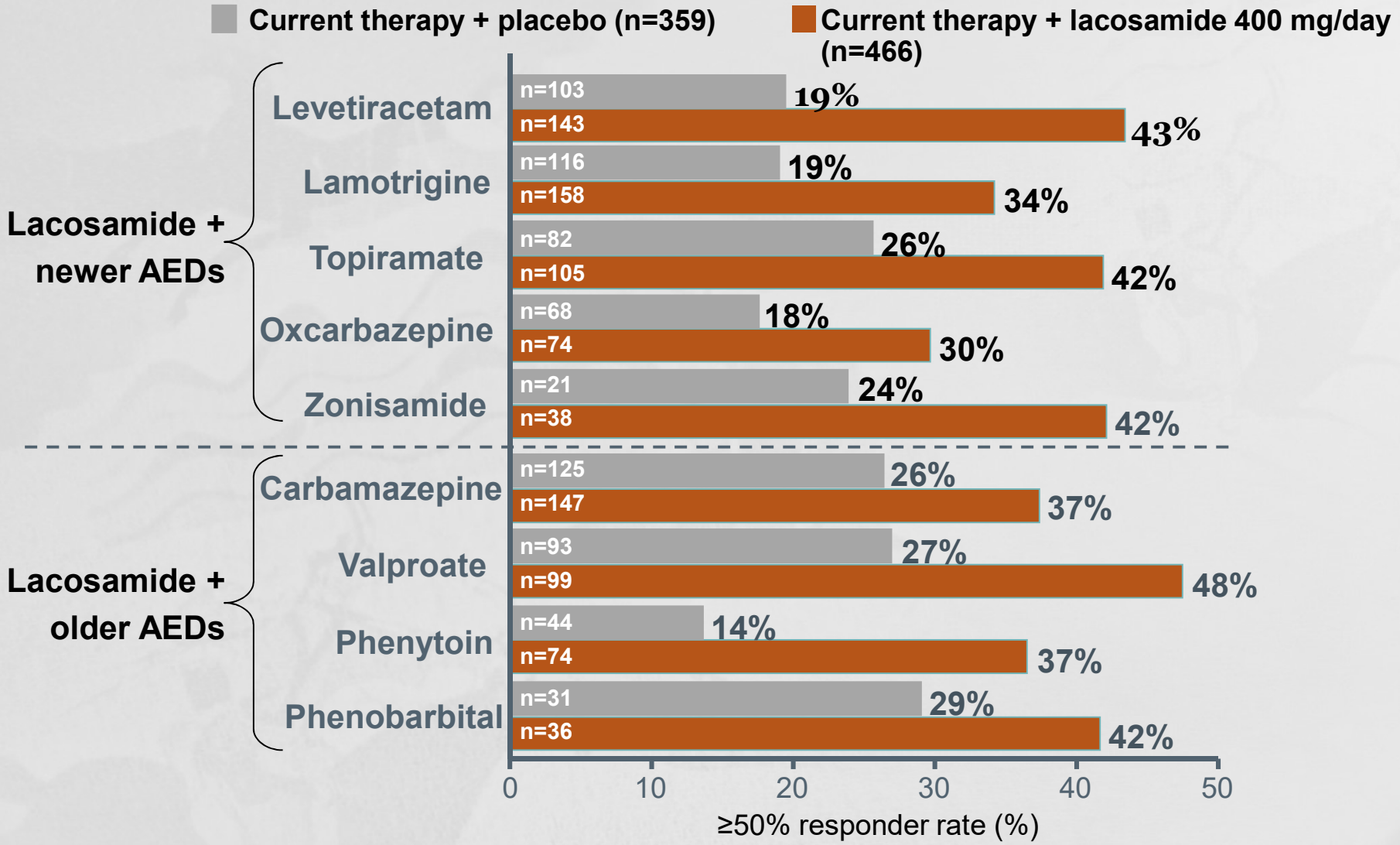




Normal electrocardiogram.

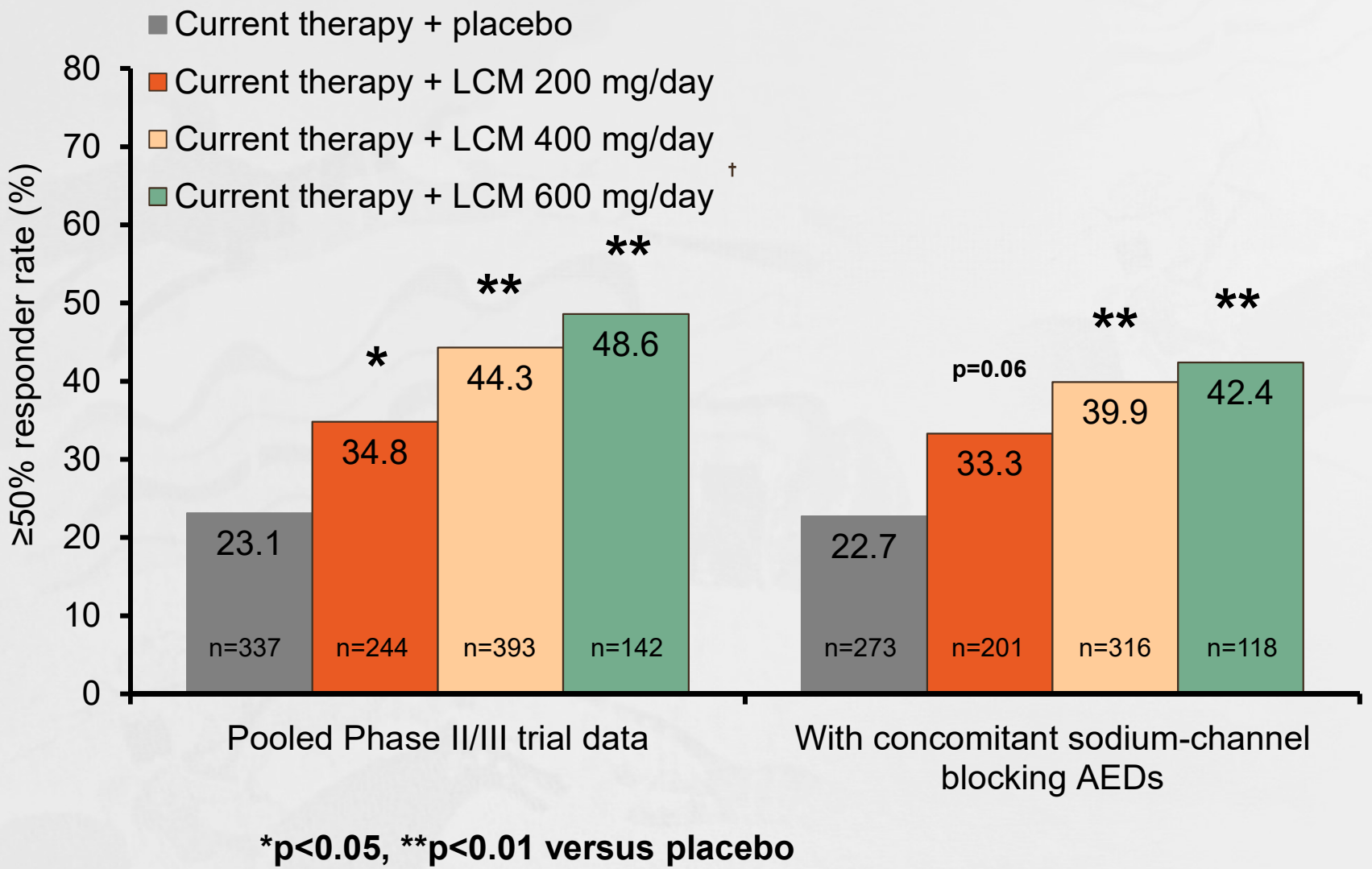
LCM: combination therapy

≥50% responder rates by concomitant AED (ITT population)



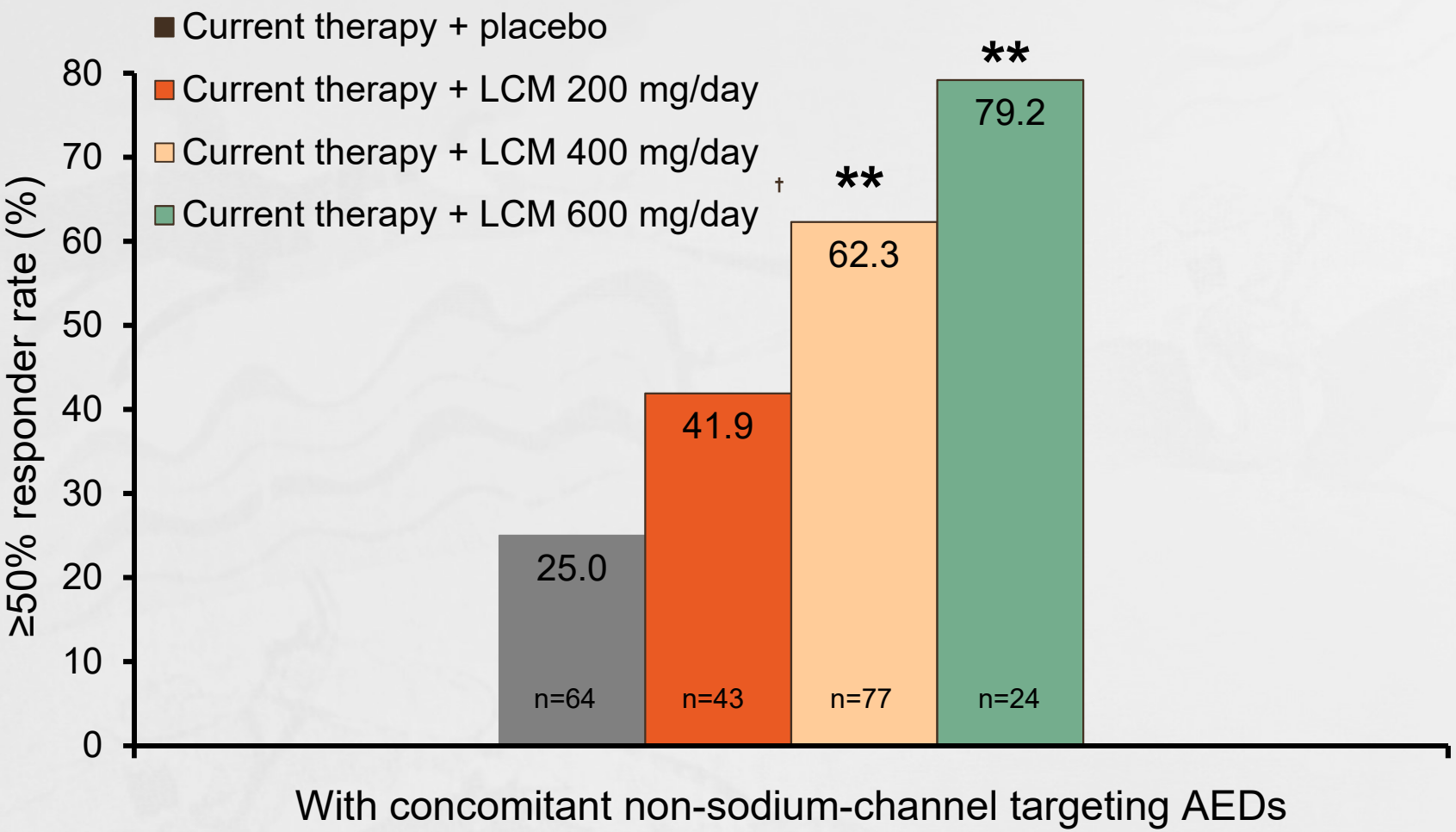
Chung et al. CNS Drugs 2010;24(12):1041–1054

≥50% responder rate in patients taking ≥1 concomitant sodium-channel blocking AEDs



***p<0.05, **p<0.01 versus placebo**

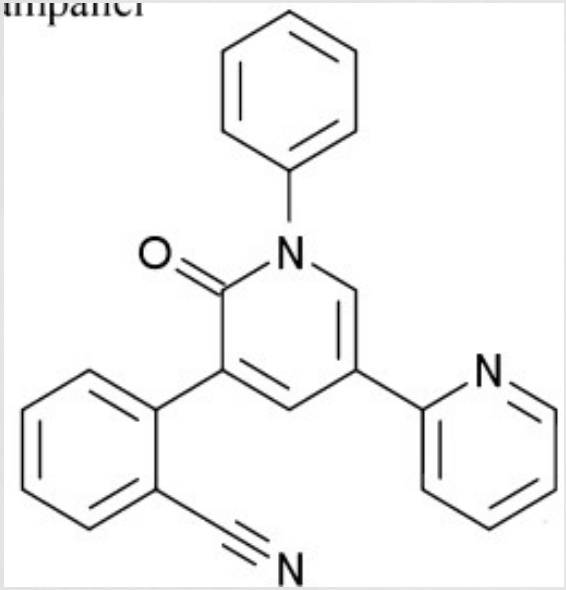
≥50% responder rate in patients taking concomitant AEDs that act on non-sodium-channel targets



**p<0.01 versus placebo

3. Perampanel (PER)

- **MoA**
  - Selectively blocks **AMPA receptor**-mediated synaptic excitation
- **FDA approval :**
  - Monotherapy & combination therapy for **Partial seizures** & **GTCs** for people older than 12 years
- **Dose**
  - Once-daily
  - P.O. at bedtime



PK profile of perampanel

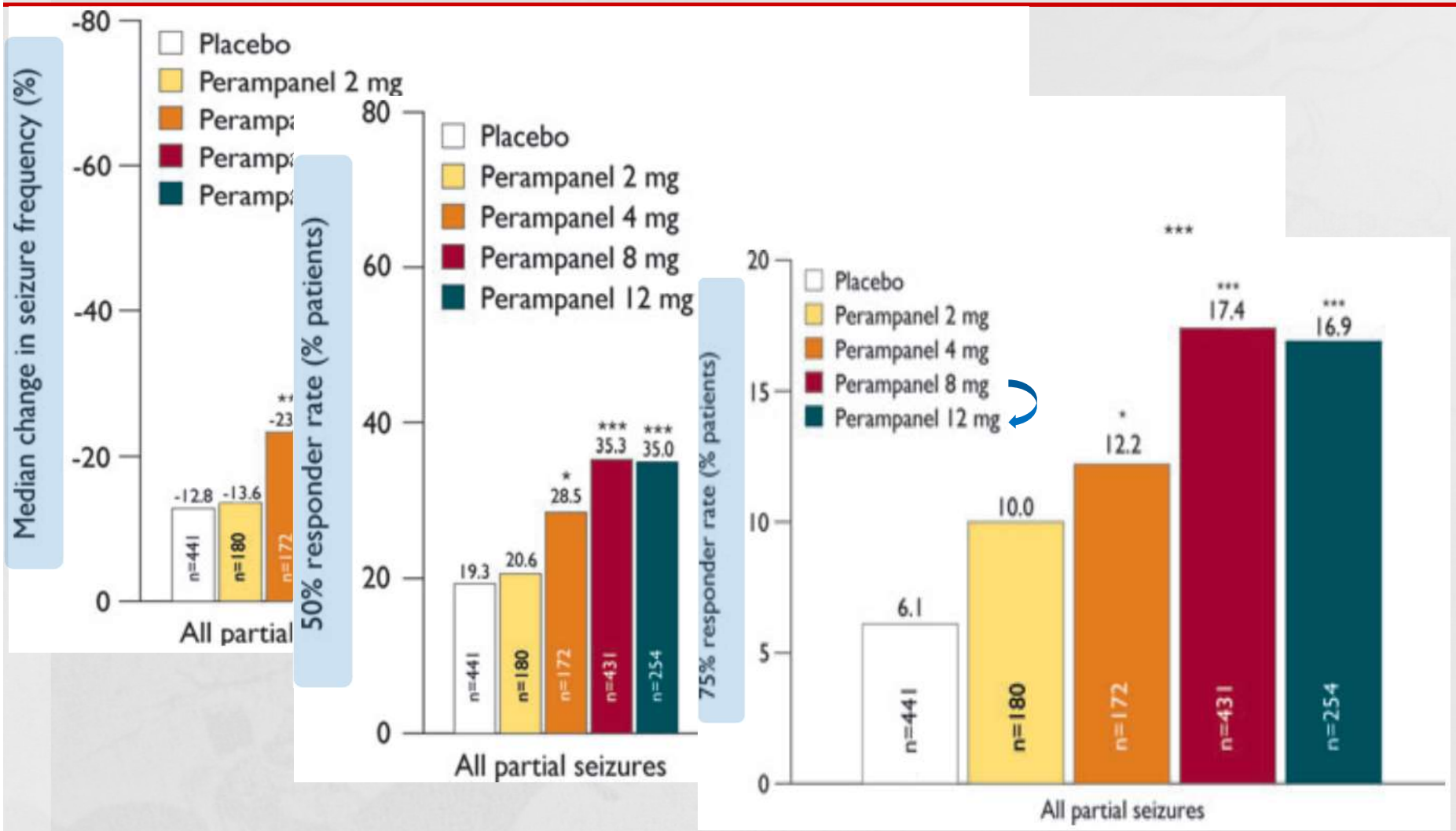
- Absorption: readily absorbed (food delays but not extent of absorption)
- Elimination half life: 105 hr (reduced to 25 hr with carbamazepine)
- Administration schedule: once daily at bedtime
- Effective dose range: 4-12mg/day
- Initiation of therapy: 2mg/day
- Gradual upward titration: 2mg every 2 weeks – 4 weeks

Perampanel : Key studies

Study	Study design & Tx regimen	Median % reduction in Sz frequency	Proportion of pts with ≥50% Sz freq reduction	Tx-related TEAEs
French 2012 **Refractory focal E** 12-80 yo 1-3 AEDs	**Placebo** (n=121) **8 mg/d** (n=133) **12 mg/d** (n=134) 6w B → 6w T → 13w M	**Placebo : 21.0%** **8 mg/d : 26.3%*** **12 mg/d : 34.5%***	**Placebo : 26.4%** **8 mg/d** : 37.6% **12 mg/d** : 36.1%	**Placebo : 47.9%** **8 mg/d** : 74.4% **12 mg/d** : 80.6% Dizziness, somnolence, HA, fall, irritability, ataxia
French 2013 **Refractory focal E** ≥16 yo 1-2 AEDs	**Placebo** (n=136) **8 mg/d** (n=129) **12 mg/d** (n=121) 6w B → 6w T → 13w M	**Placebo : 9.7%** **8 mg/d : 30.5%*** **12 mg/d : 17.6%***	**Placebo : 14.7%** **8 mg/d : 33.3%*** **12 mg/d : 33.9%***	**Placebo : 68.4%** **8 mg/d** : 86.8% **12 mg/d** : 86.0% Dizziness, somnolence, fatigue, HA
Krauss 2012 **Refractory focal E** 15-65 yo 1-3 AEDs	**Placebo** (n=185) **2 mg/d** (n=180) **4 mg/d** (n=172) **8 mg/d** (n=169) 8w B → 6w T → 12w M	**Placebo : 10.7%** **2 mg/d** : 13.6% **4 mg/d : 23.3%*** **8 mg/d : 30.8%***	**Placebo : 17.9%** **2 mg/d** : 20.6% **4 mg/d : 28.5%*** **8 mg/d : 34.9%***	**Placebo : 31.9%** **2 mg/d** : 37.2% **4 mg/d** : 44.8% **8 mg/d** : 56.8% Dizziness, somnolence, HA, fatigue, URI, nasopharyngitis, gait disturbance

Perampanel : Pooled study

Steinhoff, *Epilepsia* 2013



Perampanel : Pooled study

Steinhoff, *Epilepsia* 2013

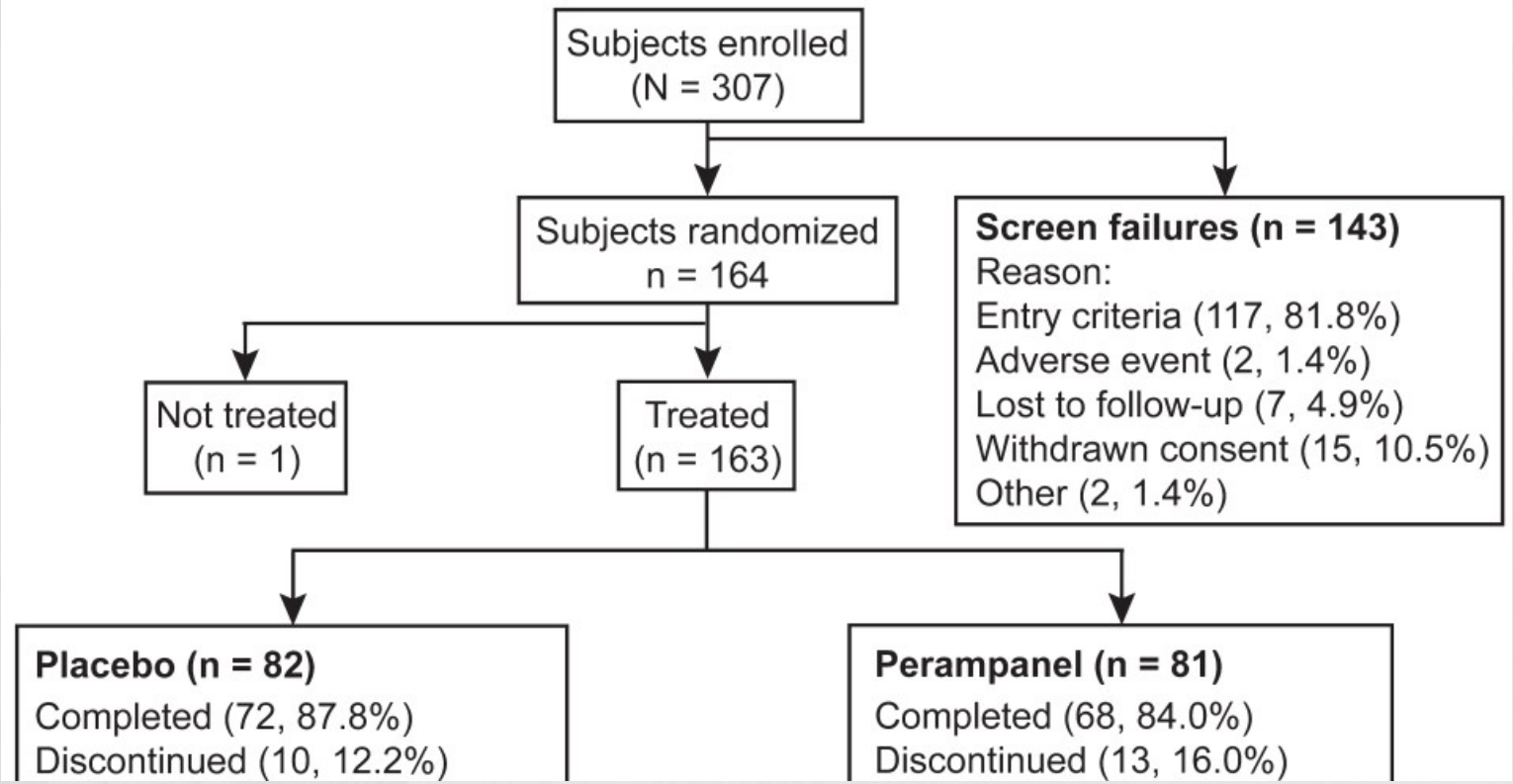
Table 4. TEAEs occurring in ≥5% of patients in any treatment group

		Perampanel			
Adverse event, n (%)	Placebo (n = 442)	2 mg (n = 180)	4 mg (n = 172)	8 mg (n = 431)	12 mg (n = 255)
Any TEAE	294 (66.5)	111 (61.7)	111 (64.5)	350 (81.2)	227 (89.0)
Dizziness	40 (9.0)	18 (10.0)	28 (16.3)	137 (31.8)	109 (42.7)
Somnolence	32 (7.2)	22 (12.2)	16 (9.3)	67 (15.5)	45 (17.6)
Headache	50 (11.3)	16 (8.9)	19 (11.0)	49 (11.4)	34 (13.3)
Fatigue	21 (4.8)	8 (4.4)	13 (7.6)	36 (8.4)	31 (12.2)
Irritability	13 (2.9)	7 (3.9)	7 (4.1)	29 (6.7)	30 (11.8)
Nausea	20 (4.5)	4 (2.2)	5 (2.9)	25 (5.8)	20 (7.8)
Fall	15 (3.4)	2 (1.1)	3 (1.7)	22 (5.1)	26 (10.2)
Nasopharyngitis	18 (4.1)	7 (3.9)	9 (5.2)	23 (5.3)	11 (4.3)
Upper respiratory tract infection	12 (2.7)	11 (6.1)	6 (3.5)	14 (3.2)	10 (3.9)
Ataxia	0 (0.0)	0 (0.0)	1 (0.6)	14 (3.2)	21 (8.2)
Balance disorder	2 (0.5)	0 (0.0)	0 (0.0)	22 (5.1)	8 (3.1)

- **Black box warning**
  - Serious psychiatric & behavioral changes
  - Homicidal or suicidal thoughts

Perampenel in primary GTCS

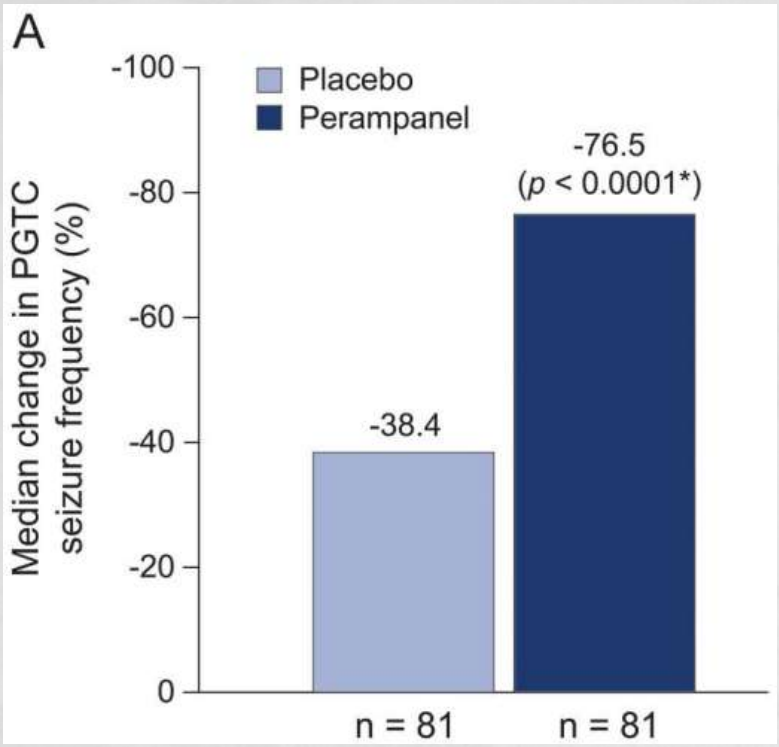
- IGE patients aged ≥ 12 y experiencing ≥ 3 primary GTCS on stable doses of 1-3 approved AEDs
- 4-week titration period (uptitrated from 2 to 8 mg/d) and 13-week maintenance period

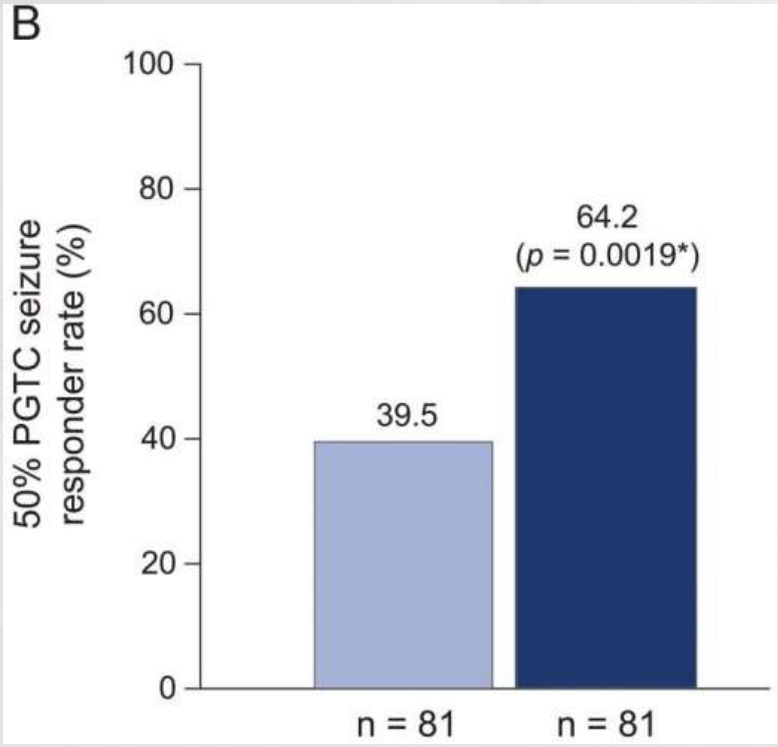


French JA, Neurology 2015

Perampenel in primary GTCS

- Primary endpoint: % change in primary GTCS frequency per 28 day
- Secondary endpoint: 50% responding rate





French JA, Neurology 2015

Effects on cognition

- 12–18 yrs, focal epilepsy on 1-3 AEDs, double-blind design of 2:1 perampanel and placebo
- 8–12 mg/day (6-week titration, 13-week maintenance)

	Placebo (n =44)	Perampanel (n = 79)	LS difference (95% CI)	*P*
Full-scale IQ score	**100.5 (12.9)**	**101.6 (14.7)**		**NS**
CDR system global cognition score	**1.6 (1.3)**	**–0.6 (1.0)**	**–2.2 (–5.2, 0.8)**	**0.145**
Power of attention	–2.7 (3.0)	–6.9 (2.3)	–4.2 (–11.0, 2.6)	0.219
Continuity of attention	**1.6 (1.2)**	**–1.7 (0.9)**	**–3.3 (–6.0, –0.7)**	**0.013**
Quality of episodic memory	**–1.2 (1.5)**	**3.0 (1.1)**	**4.2 (0.9, 7.5)**	**0.012**
Quality of working memory	2.0 (1.5)	1.1 (1.2)	–1.0 (–4.4, 2.5)	0.579
Speed of memory	**7.0 (2.7)**	**0.2 (2.1)**	**–6.6 (–12.7, –0.6)**	**0.032**
Letter of fluency	0.2 (1.1)	0.9 (0.8)	0.6 (–2.0, 3.3)	0.633
Category of fluency score	0.1 (0.5)	–0.4 (0.4)	–0.6 (–1.9, 0.7)	0.365
Groove Pegboard test	–9.2 (28.8)	0.2 (17.2)		0.143

Meador KJ, Epilepsia 2016

Effects on mood

- The effect of perampanel on aggression and depression in patients with epilepsy
  - A short-term (12 weeks) prospective study evaluating 59 patients with pharmacoresistant epilepsy

BAQ and the NDDI-E in eligible patients (n = 59).

	At the entry Mean ± SD(range)	At the 12 weeks Mean ± SD(range)	p-value
BAQ	64.8 ± 13.9 (40-103)	68.4 ± 14.9 (37-108)	0.013
Verbal aggression	14.3 ± 3.2 (8-24)	15.1 ± 3.5 (8-22)	0.045
Physical aggression	16.2 ± 5.4 (6-27)	17.6 ± 5.6 (7-34)	0.040
Anger	14.6 ± 5.0 (6-25)	15.6 ± 4.5 (8-25)	0.083
Hostility	19.7 ± 5.3 (10-33)	20.2 ± 5.2 (11-33)	0.274
NDDI-E	11.9 ± 4.0 (6-22)	13.7 ± 3.9 (6-23)	0.000

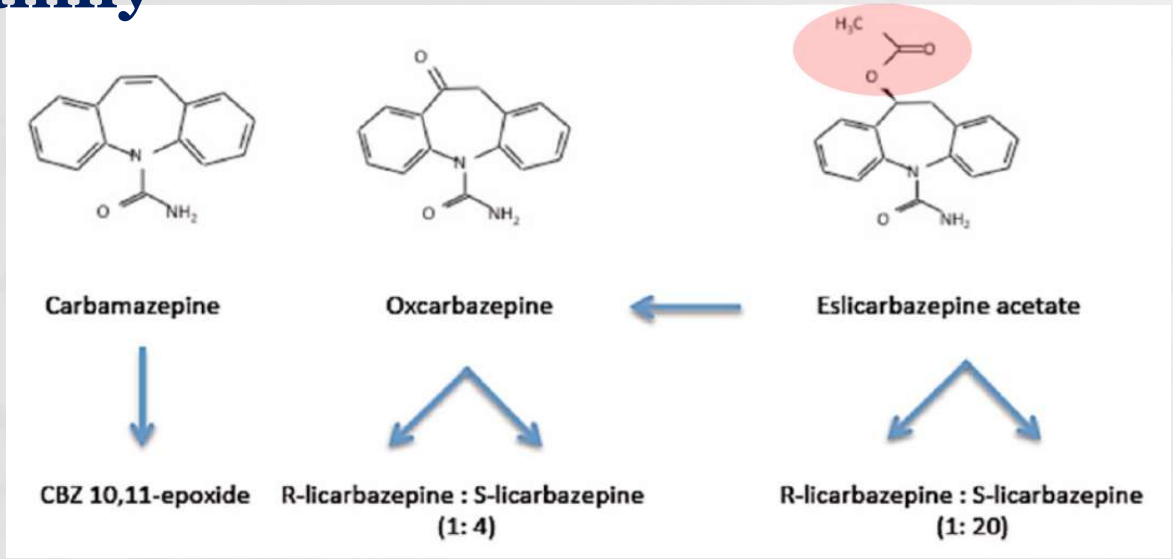
BAQ: Buss Perry Aggression Questionnaire. NDDI-E: Neurological Disorders Depression Inventory for Epilepsy.

- Perampenel significantly increases aggression and depression in patients with epilepsy

Goji H, Seizure 2019

4. Eslicarbazepine acetate (ESL)

- **Dibenzazepine family**



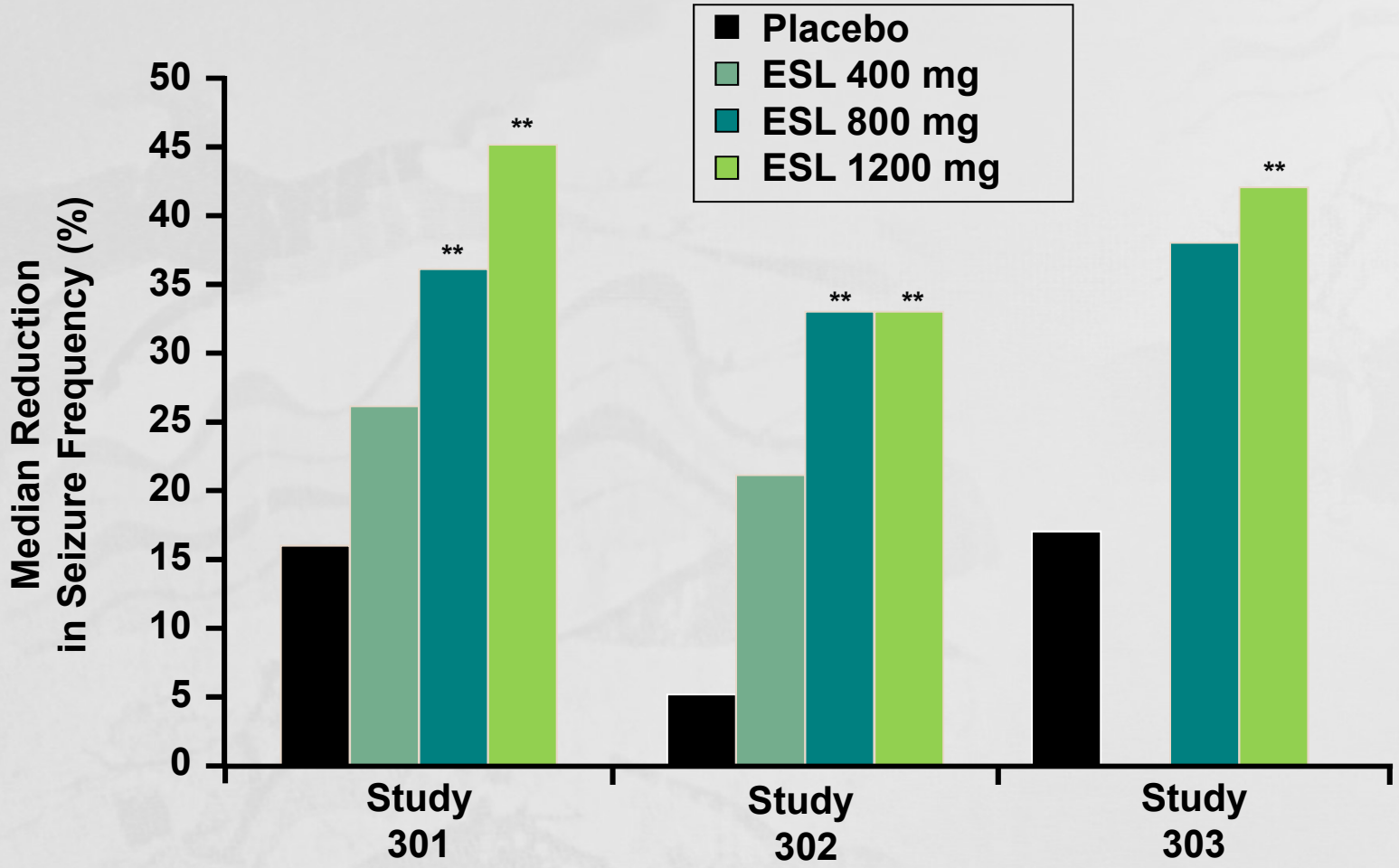
- **MoA**
  - Competitive blocker of the **voltage-gated sodium channel**
  - Reduces the **VGSC availability** by selectively enhancing **slow inactivation**, similarly to **LCM**
- **Approval** : Mono- or adjunctive Tx for partial-onset Sz
- Once-daily (400 mg → 800 mg) (→ 1200 mg)

Eslicarbazepine Acetate: PK Profile

- Linear pharmacokinetics
- T_{max}: 1-4 hrs after oral administration
- $T_{½}$ ≈20 hrs; steady-state achieved in 4-5 days
- Converts to active met of eslicarbazepine
- Food does not affect rate and extent of absorption
- Protein binding <40%
- Moderate inhibitor of 2C19
- Mild inducer of 3A4

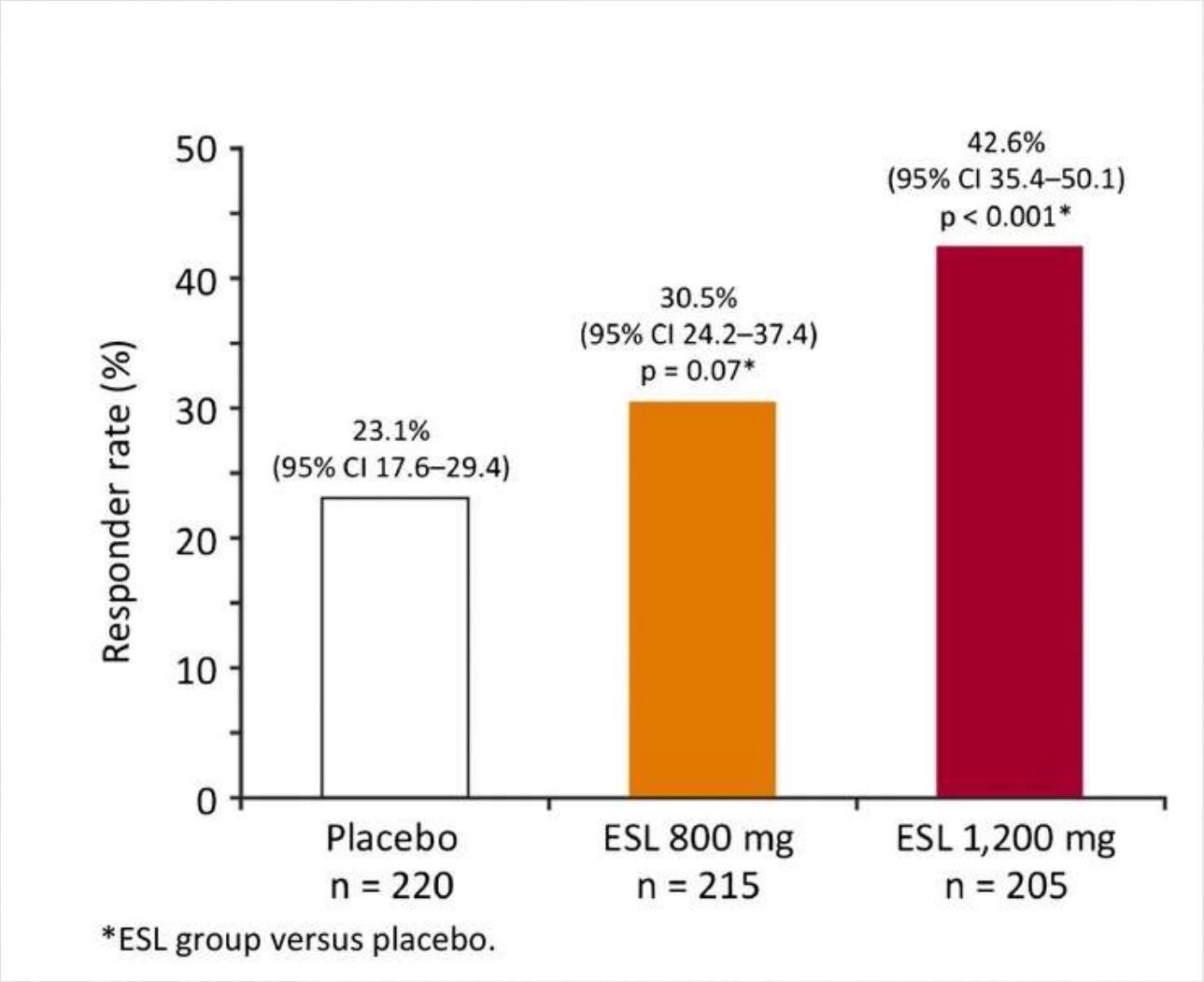
Bottom line: Better than OXC?

Eslicarbazepine Pivotal Trial Results: Percent Reduction in Seizure Frequency



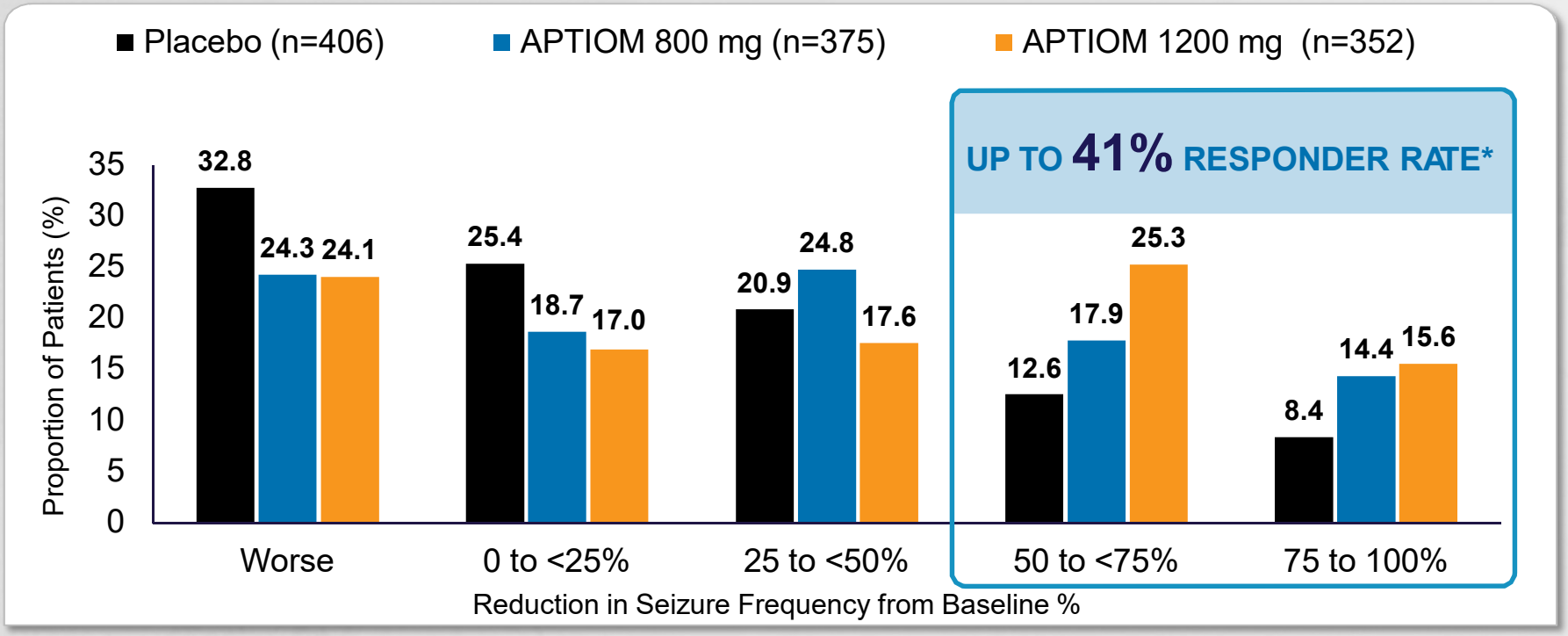
Gil-Nagel et al. Epilepsia 2013

A phase III, double-blind, randomized, placebo-controlled trial.



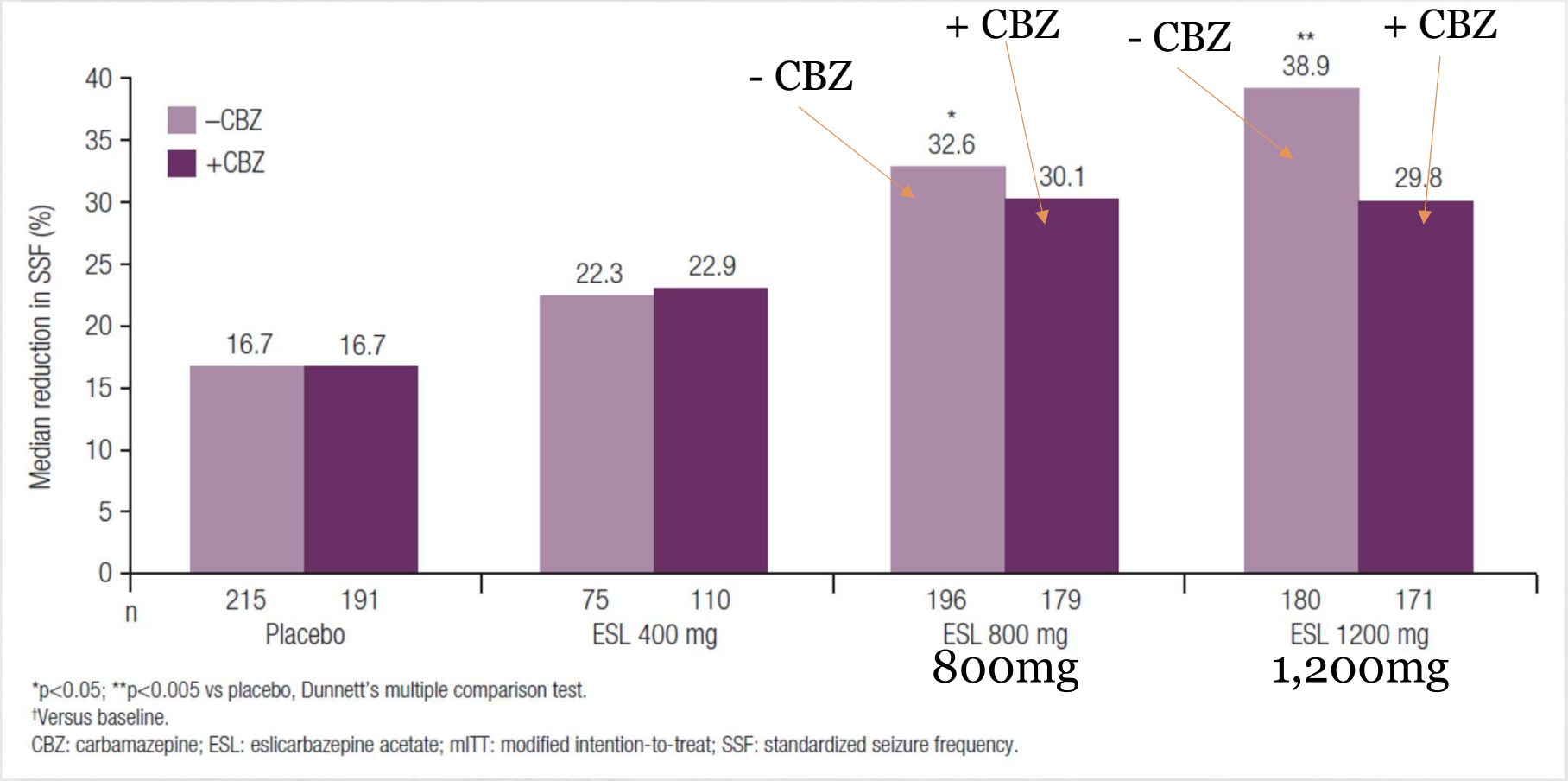
Epilepsia. 2015 Feb; 56(2): 244–253.

Pooled Data Efficacy of ESL



1.

Efficacy of ESL with concomitant CBZ

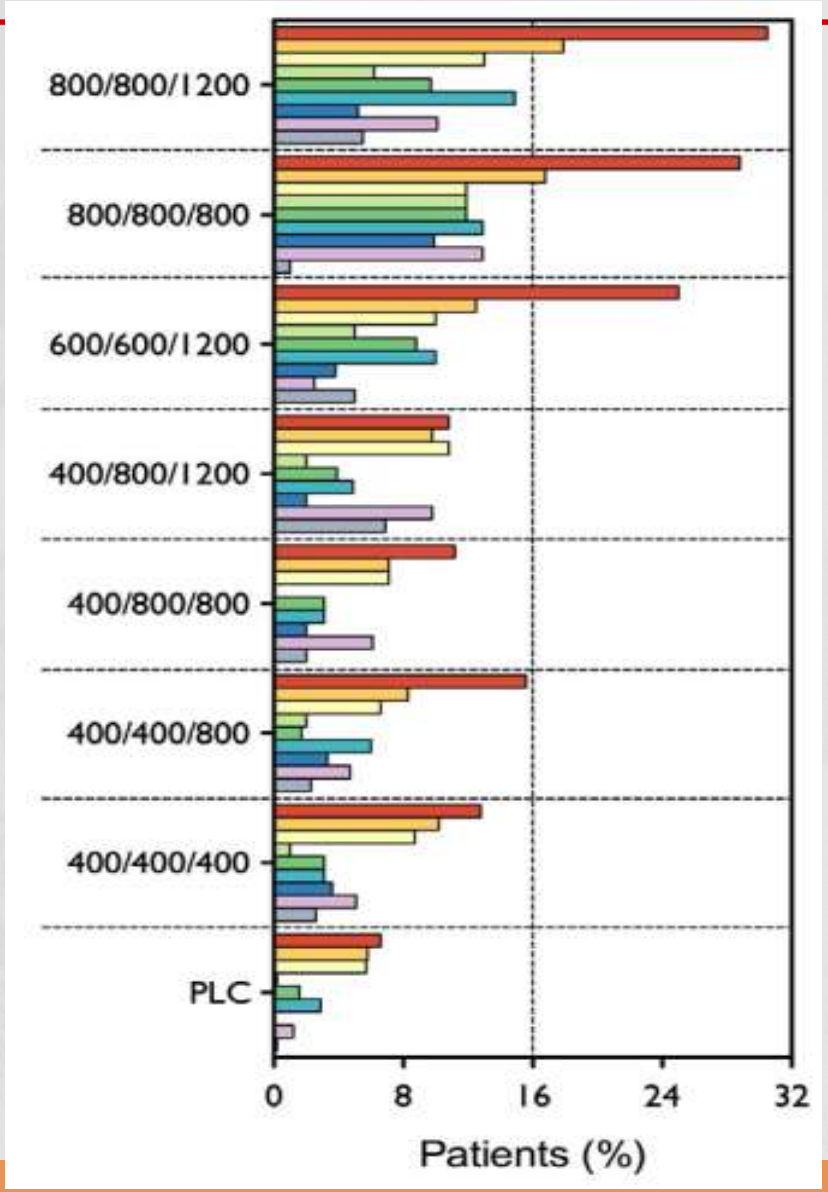


*p<0.05; **p<0.005 vs placebo, Dunnett's multiple comparison test.
†Versus baseline.
CBZ: carbamazepine; ESL: eslicarbazepine acetate; mITT: modified intention-to-treat; SSF: standardized seizure frequency.

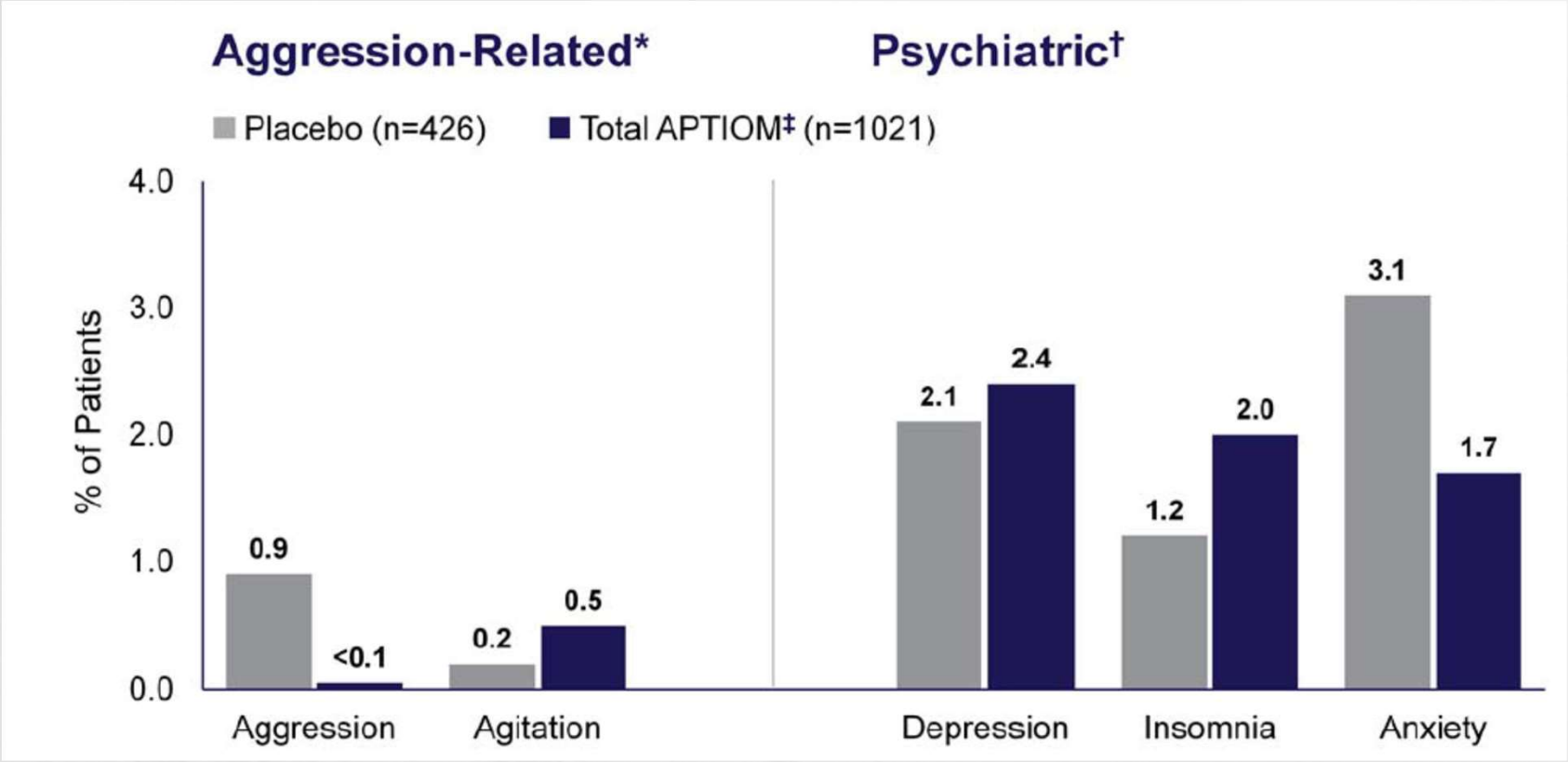
Chung S. *AAN Meeting* 2015

Eslicarbazepine acetate : Pooled study

Elger, *CNS Neurosci Ther* 2017



ESL: Behavioral and Psychiatric AEs



Dose-Dependent Increases in Cognitive Dysfunction-Related Events

% Incidences Of Dose-Dependent Cognitive Dysfunction-Related Events

Cognitive dysfunction-related events	Placebo	APTIOM 800 mg	APTIOM 1200 mg
	n=426	n=415	n=410
Memory Impairment	0.2%	1.0%	1.7%
Disturbance in attention	0.5%	0.7%	1.5%
Amnesia	0.2%	1.0%	0.7%
Confusional state	0.5%	0.5%	0.7%
Aphasia	0%	0.2%	1.2%
Speech disorder	0%	0%	0.7%
Slowness of thought	0%	0.2%	0.5%
Disorientation	0%	0.2%	0%
Psychomotor retardation	0%	0.2%	0.2%

APTIOM [prescribing information]. Sunovion Pharmaceuticals Inc., Marlborough, MA, September 2016.

Eslicarbazepine Key Points

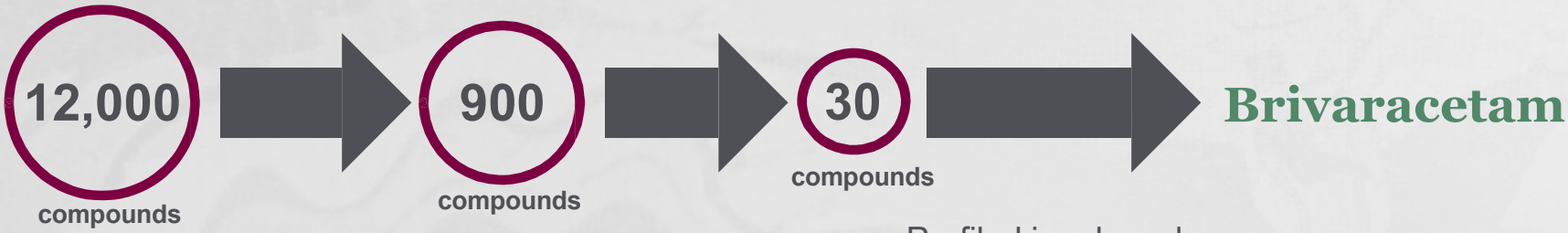
- Once-daily, immediate-release AED therapy
- Can be taken whole or crushed, with or without food
- Favorable behavioral, psychiatric, and cognitive tolerability
- Some adverse reactions occur more frequently when patient s take ESL adjunctively with carbamazepine
- FDA approval for both adjunctive and monotherapy for focal epilepsy, age 4 and above.

5. Brivaracetam: PK Profile

- Linear pharmacokinetics
- T_{max}: 1-2 hrs after oral administration
- $T_{½}$ ≈9 hrs; steady-state achieved after 2 days
- High water and fat solubility
- Food does not affect rate and extent of absorption
- Protein binding <20%
- Metabolized by CYP2C19 and 2C9
- Not an inducer of 3A4

Bottom line: Better than LEV?

Brivaracetam Is a New Molecular Entity in the Racetam Class That Targets Synaptic Vesicle Protein 2A (SV2A)



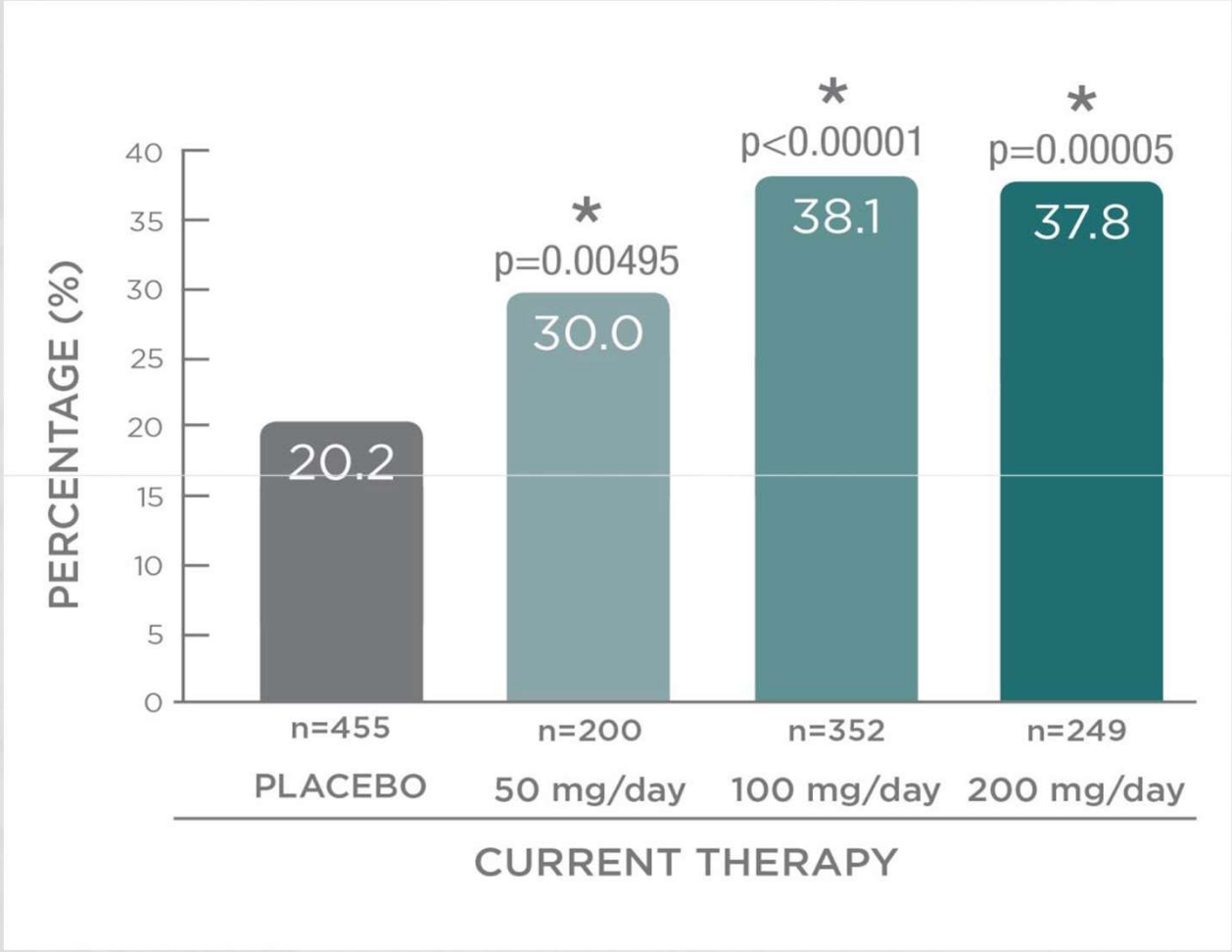
Screened for higher affinity interaction with SV2A *in vitro*[1]

Tested in an initial animal screening model of epilepsy[1]

Profiled in a broad range of animal models of seizures and epilepsy. Agents with an animal model profile similar to levetiracetam* were not pursued through Phase 3 clinical trials[1,2]

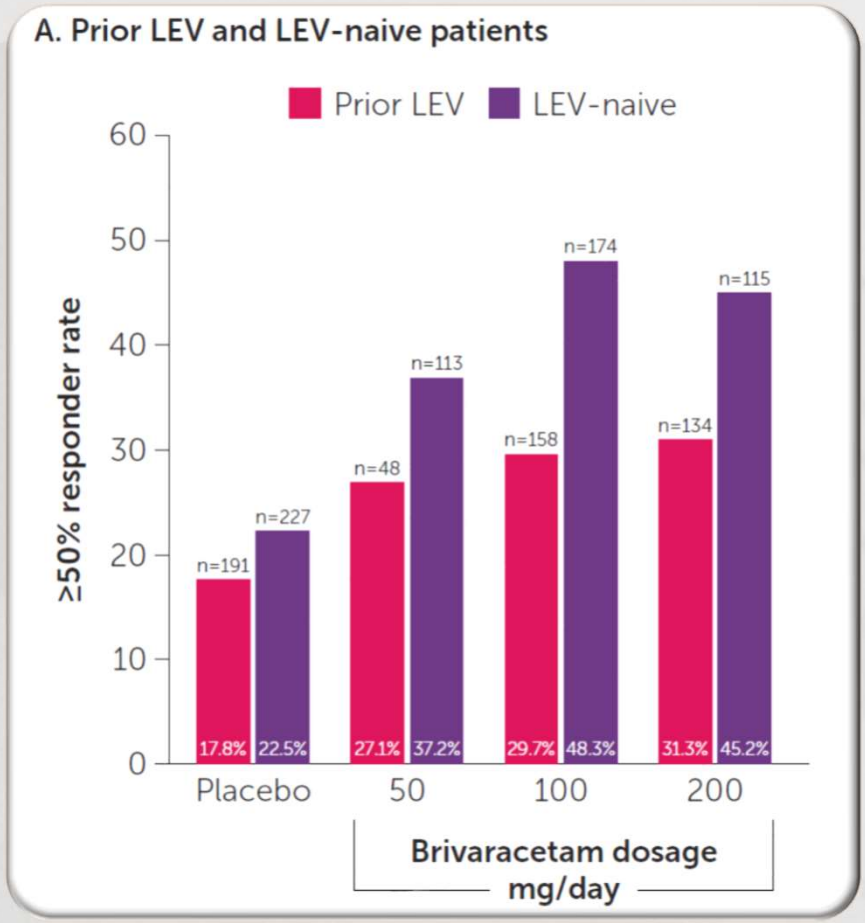
The 50% Responder Rate for Brivaracetam

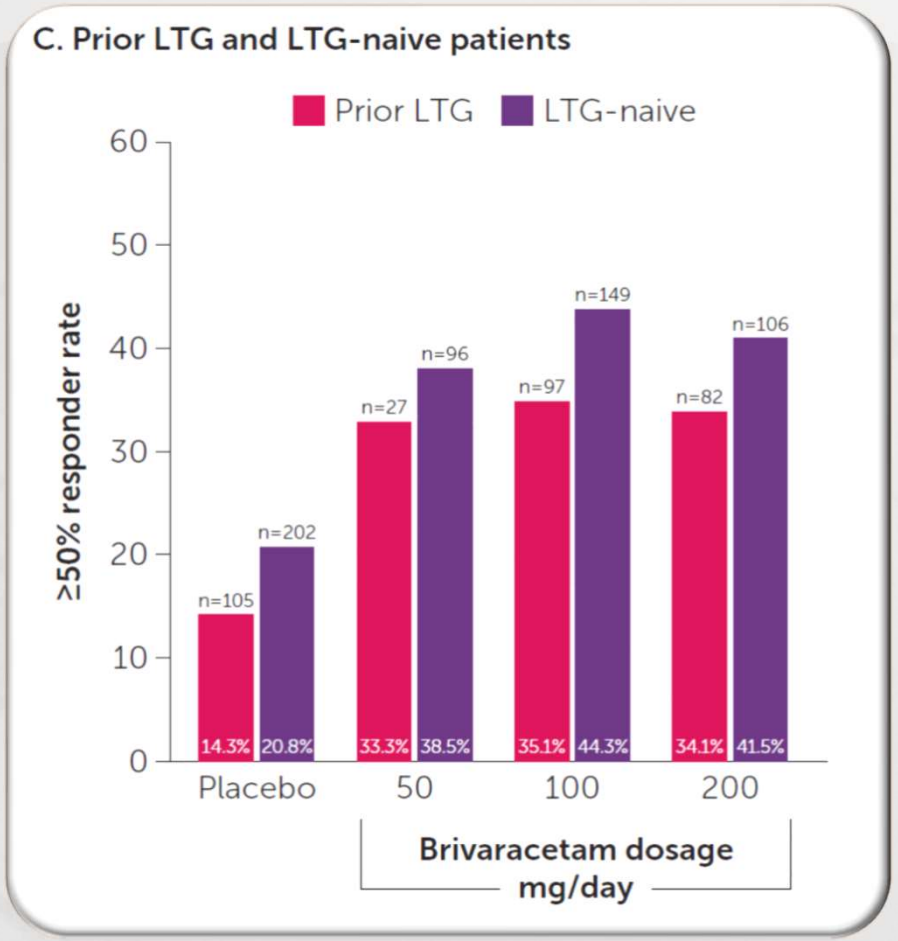
Pooled Results from Studies 1, 2, and 3



Biton et al. Epilepsia 2013

Efficacy of BRV on Previous LEV Failures





Chung et al. *AES Meeting 2016 – scientific session (Houston, TX)*
Asadi-Pooya A., Sperling M., **Chung S.S.** *Epilepsy Research* 2017, *Nov:137: 165-166.*

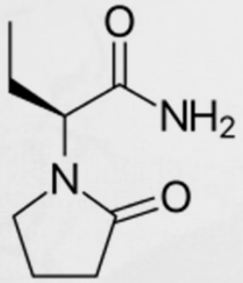
Brivaracetam: Safety and Tolerability

ADVERSE REACTIONS		BRIVARA (n=803) %	PLACEBO (n=459) %
Gastrointestinal disorders	Nausea/vomiting	5	3
	Constipation	2	0
Nervous system disorders	Somnolence and sedation	16	8
	Dizziness	12	7
	Fatigue	9	4
	Cerebellar coordination and balance disturbances*	3	1
Psychiatric disorders	Irritability	3	1

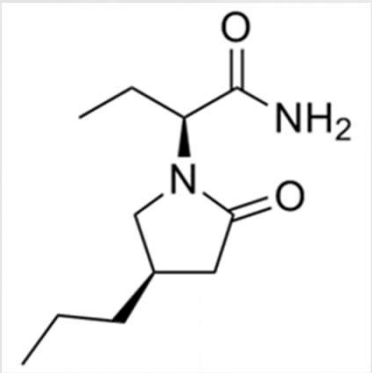
Biton et al. Epilepsia 2013

Difference Between LEV and BRV?

- BRV has much high and selective affinity for SV2A
- BRV has positive anticonvulsant effects on classic sei zure models (MES and PTZ)
- BRV is mainly metabolized via liver (CYP2C19 hydro xylation and CYP2C9 hydrolysis)
- BRV showed less irritability AEs (3% vs. 1 % placebo)
- BRV requires no titration (usual dose of 50 mg BID)
- Both has IV (10 mg/mL), but faster infusion with BR V (over 2 to 15 minutes)

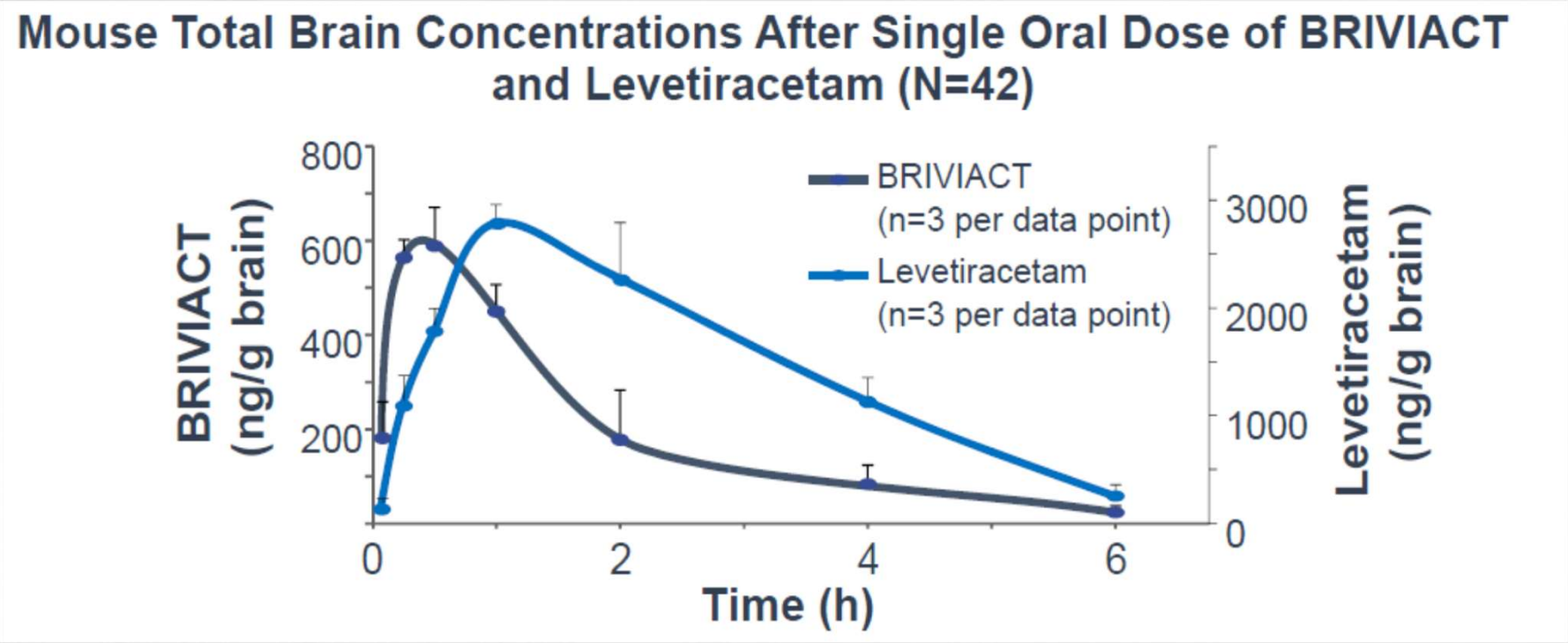


Levetiracetam



Brivaracetam

Higher lipid solubility = Faster Blood-Brain Barrier Penetration



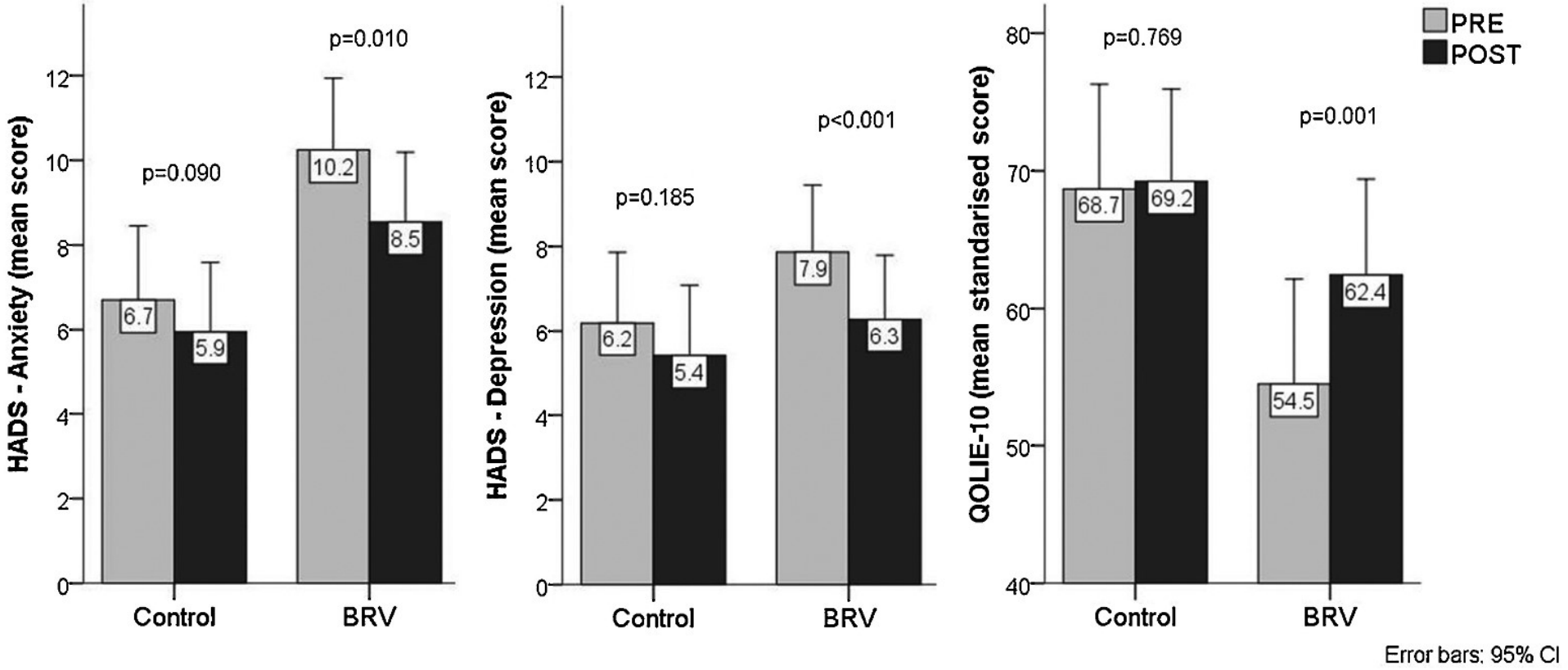
Nicolas JM, et al. *Epilepsia*. 2016;57(2):201-209.

Brivaracetam on depression and anxiety

- 37 patients with epilepsy
  - anger levels (STAXI-2), depression-anxiety (HADS) and quality of life (QOLIE-10) before adjunctive brivaracetam treatment and reassessed 3–6 months later

Seizurev Volume 69, July 2019, Pages 198-203

Depression, anxiety, QOL



Highlights

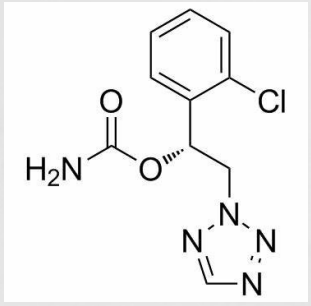
- BRV does not increase anger levels in recently diagnosed epilepsy.
- BRV effect on anger levels is conditioned by seizure reduction.
- BRV is efficacious in focal onset and idiopathic generalised epilepsies.
- LEV-related behavioural adverse events can be improved by BRV.

Brivaracetam Key Points

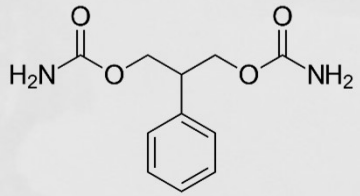
- High and selective affinity for SV2A in the brain
- IV and oral solution with 1:1 conversion ratio, rapid injection
- Favorable psychiatric (irritability) tolerability compare to LEV
- Demonstrated efficacy on patients who failed LEV previously
- Safety of converting LEV to BRV
- FDA approval for both adjunctive and monotherapy for focal e pilepsy, age 4 and above.

6. Cenobamate (YKP3089): PK Profile

- Linear pharmacokinetics
- T_{max}: 1-6 hrs after oral administration
- $T_{½}$ ≈55-60 hrs; steady-state achieved in 14 days
- No know active metabolites



Cenobamate



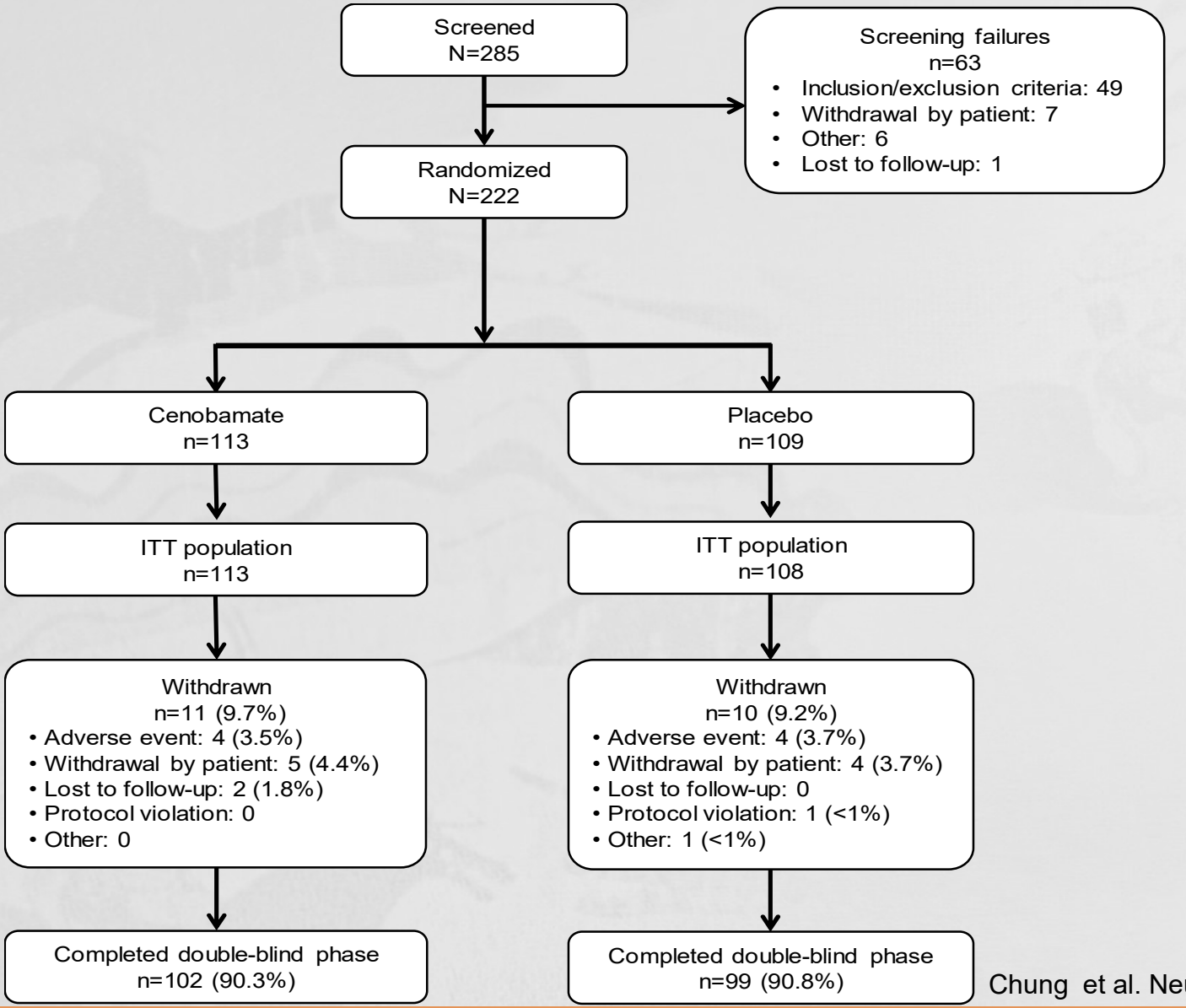
Felbamate

Bottom line: Far different from Felbamate in safety?

Cenobamate (YKP3089)

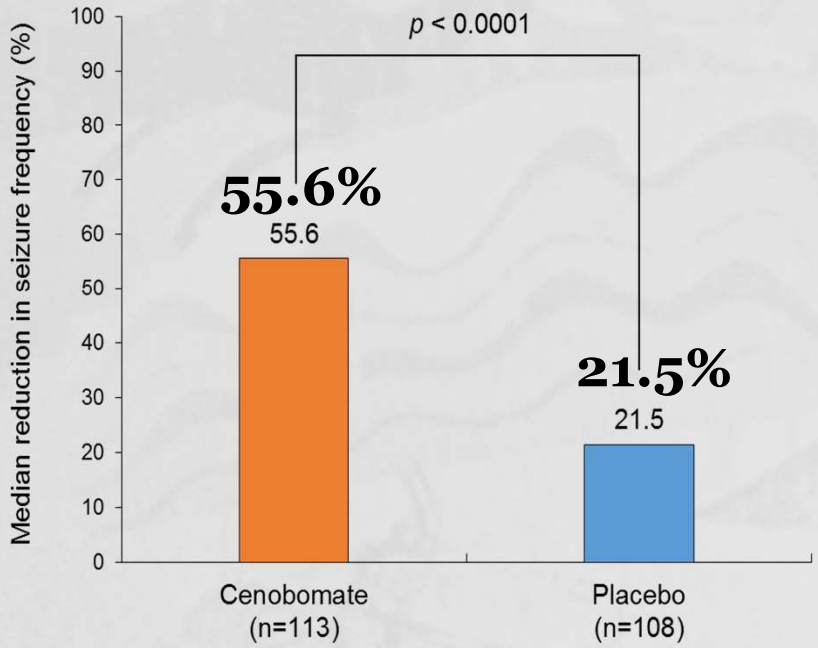
- CNB is a novel Tetrazole alkyl carbamate derivative
- Animal models suggest broad spectrum including PTZ, MES, and photosensitive epilepsy
- Once daily dosing (Phase II at 200 mg/day), starting dose at 50 mg /day with increase every 2 weeks
- Possible MOAs
  - Promotes slow inactive state of sodium channels
  - enhance $GABA_A$ without binding to $GABA_A$ subunits

Cenobamate Phase II

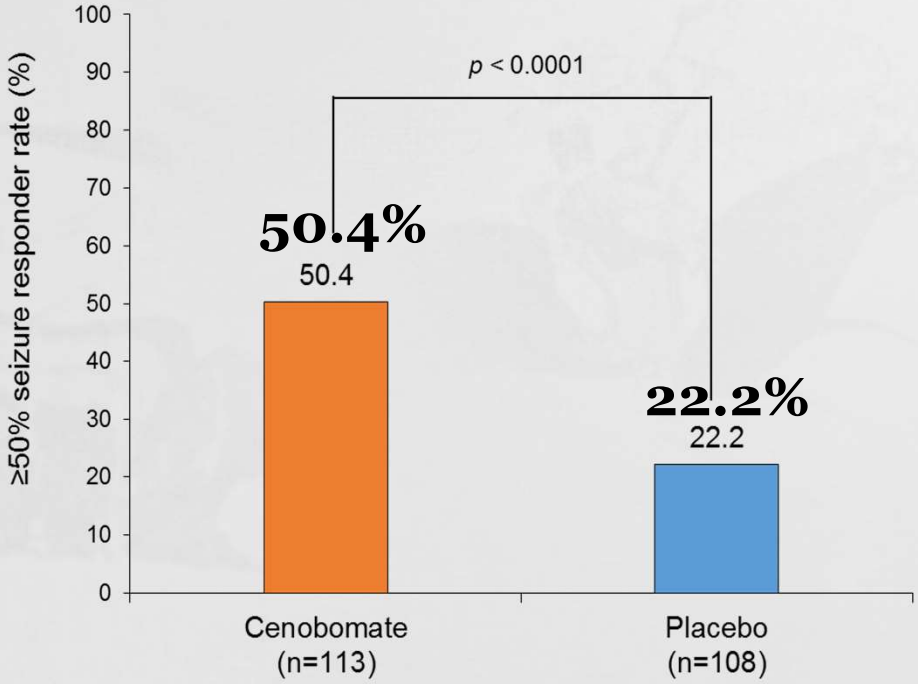


Chung et al. Neurology *in review*

Cenobamate (YKP3089): Seizure outcome



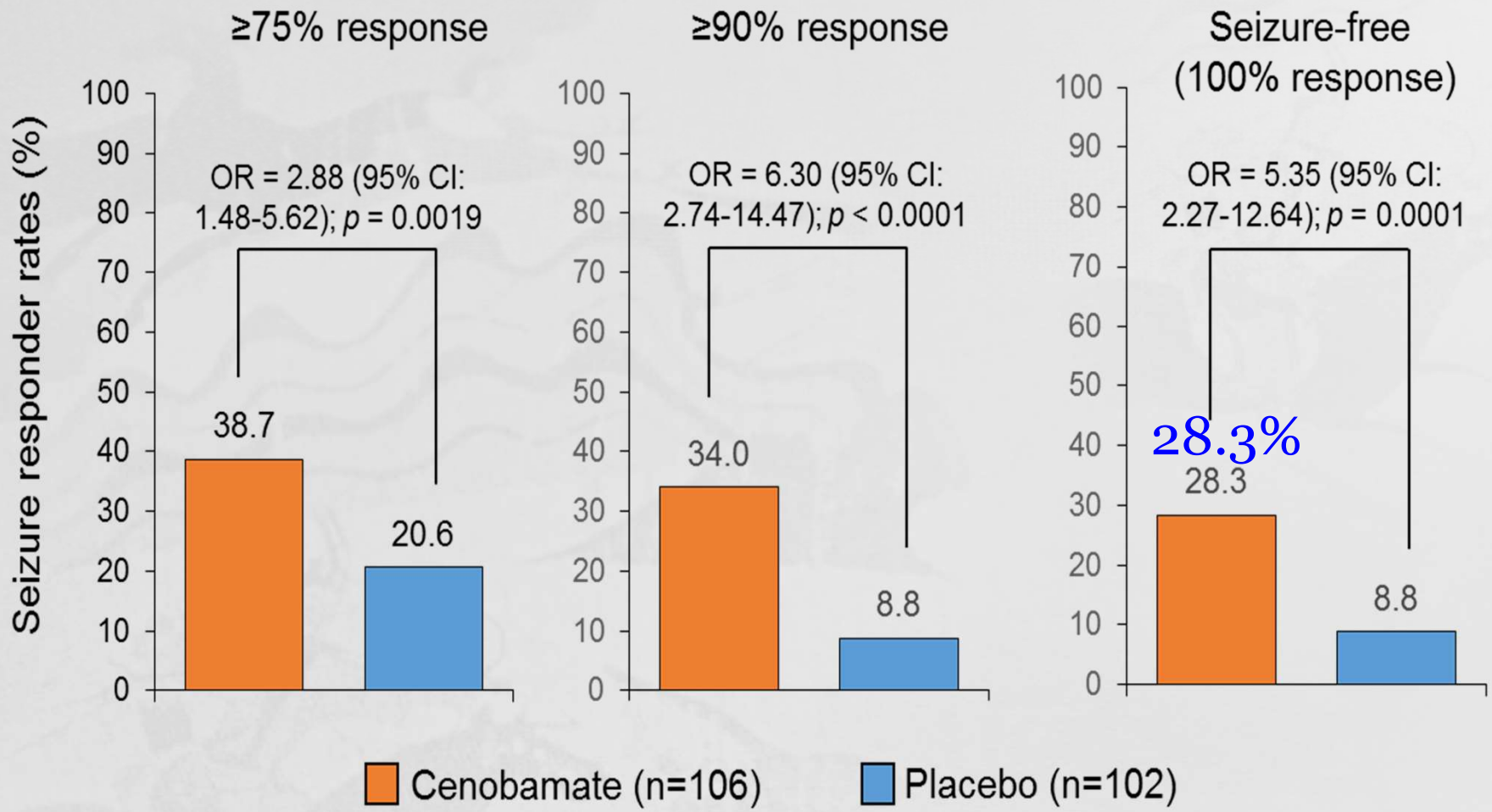
Median % Seizure Reduction



50% Responder Rate

Chung, French, Krauss et al. Neurology *in review*

Cenobamate: Superior efficacy?



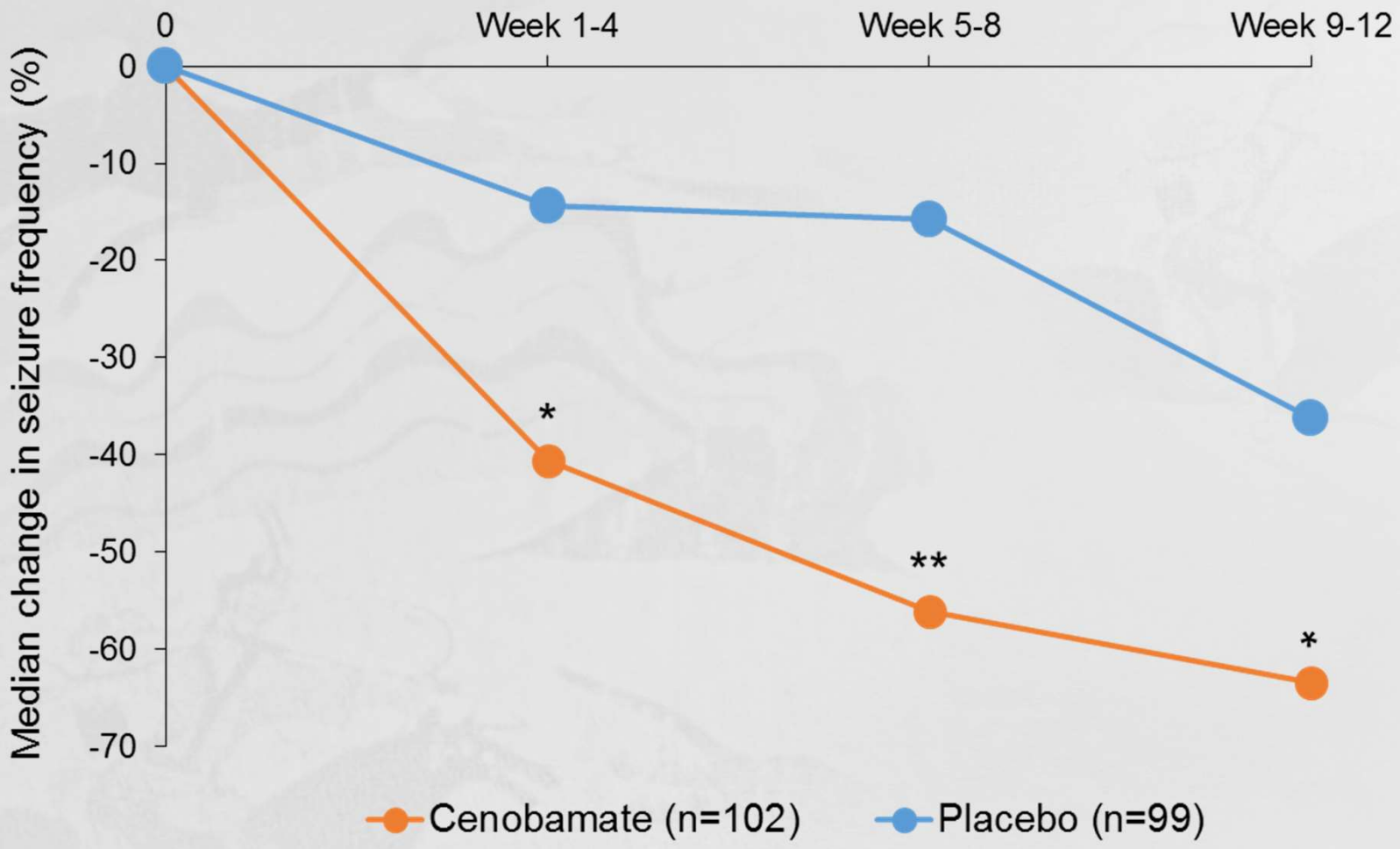
Chung, French, Krauss et al. Neurology *in review*

Cenobamate: Adverse Events

	% Patients	
	Placebo (N=109)	YKP3089 (N=113)
Any adverse event	63.3	76.1
Treatment-related adverse event	46.8	61.1
Discontinuations due to AEs	3.7	3.5
Treatment-emergent adverse event		
Somnolence	11.9	22.1
Dizziness	16.5	21.2
Nausea	4.6	11.5
Fatigue	6.4	10.6
Headache	11.0	10.6
Nystagmus	0	9.7
Balance disorder	0.9	8.0
Upper respiratory tract infection	4.6	7.1
Urinary tract infection	1.8	7.1
Tremor	1.8	6.2
Constipation	0	5.3
Diarrhea	0	5.3
Vomiting	1.8	5.3
Nasopharyngitis	0.9	5.3

Chung et al. AES 2014

CNB: Slow Titration but Early Efficacy



CNB Key Points

- Once daily dose with early efficacy from phase II study
- Favorable psychiatric and behavioral tolerability
- Quite different safety profile compare to FBM
- Demonstrated broad spectrum potential from preclinical studies
- Limited data but higher seizure freedom rate than other new AEDs
- FDA approval pending (for focal epilepsy), may available early next year or late this year in US.

Adjunctive everolimus therapy for treatment-resistant focal-onset seizures associated with tuberous sclerosis (EXIST-3): a phase 3, randomised, double-blind placebo-controlled study

French JA et al, Lancet. 2016; 388:2153-2163

- Patients of 2-65 years-old with TSC and DRE(≥16 in 8-week baseline) under 1-3 AEDs
- Randomize into : PLC(n=119)
  Low-exposure group (everolimus concentration 3-7 ng/ml; n=117)
  High-exposure group (9-15ng/ml; n=130)
- Titration phase of 6 weeks f/b 12 week of maintenance phase
- RESULTS
  - Response rate: 15.1% vs. 28.2%(p=0.0077) vs. 40.0%(P<0.0001) in PLC, Low- and High-exp groups, respectively
  - Median % reduction in Sz Freq: 14.9% vs. 29.3%(p=0.0028) vs. 39.6%(p<0.0001), respectively
  - Seizure free rate: 0.8% vs. 5.1% vs. 3.8%, respectively
  - TEAEs: 77% vs. 92% vs. 95% respectively with most common AE reported in everolimus group(>15%)
    being stomatitis, diarrhea, nasopharyngitis, pyrexia, and URI
  - AE led to treatment withdrawal : 2(2%) vs. 6(5%) vs. 4(3%), respectively
- Conclusion: *Adjunctive everolimus treatment significantly reduced seizure frequency with a tolerable safety profile in patients with TSC and drug-resistant seizures*

- *Everolimus targeting the underlying molecular pathology of TSC represent a new treatment option for patients with TSC and drug-resistant seizures (and probably in other patient with DREs due to dysregulated mTOR signaling pathway: upstream pathway genes: STRADα, DEPDC5, P13K or FCD related to **mTOR gene** mutation)*

Summary

- New AEDs are better tolerable and have less adverse events.
- New AEDs are able to reduce seizure frequency significantly in patients with DRE.
- New AEDs may make them seizure free in a small portion of patients with DRE.
- The right choice and better combination of AEDs are important.
- Comorbidity should be considered on drug choice.
- But DRE is still about 20-30% despite to increased number of new AEDs.
- Surgery and neurostimulation should be considered when patients are intractable to 5 or more AEDs.