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Treatment of DRE
Medications & Other Options



Drug Resistant Epilepsy (DRE)

Definition of drug resistant epilepsy: Consensus proposal by the ad hoc Task Force of the ILAE Commission on Therapeutic Strategies

*[1]Patrick Kwan, †Alexis Arzimanoglou, ‡Anne T. Berg, §Martin J. Brodie, ¶W. Allen Hauser, #[2]Gary Mathern, **Solomon L. Moshé, ††Emilio Perucca, ‡‡Samuel Wiebe, and §§[2]Jacqueline French

Kwan P et al.; Epilepsia 2010

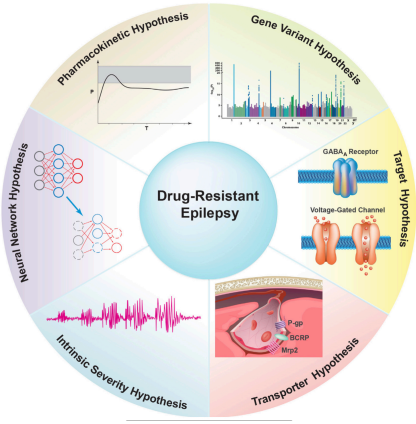
Goals

- Aid nonspecialists in recognizing patients with drug resistant epilepsy for prompt referral to specialist centers for evaluation
- Facilitate comparison and meaningful synthesis of results across studies

Drug resistant epilepsy may be defined as **failure of adequate trials of two tolerated and appropriately chosen and used AED schedules** (whether as monotherapies or in combination) to achieve sustained seizure freedom

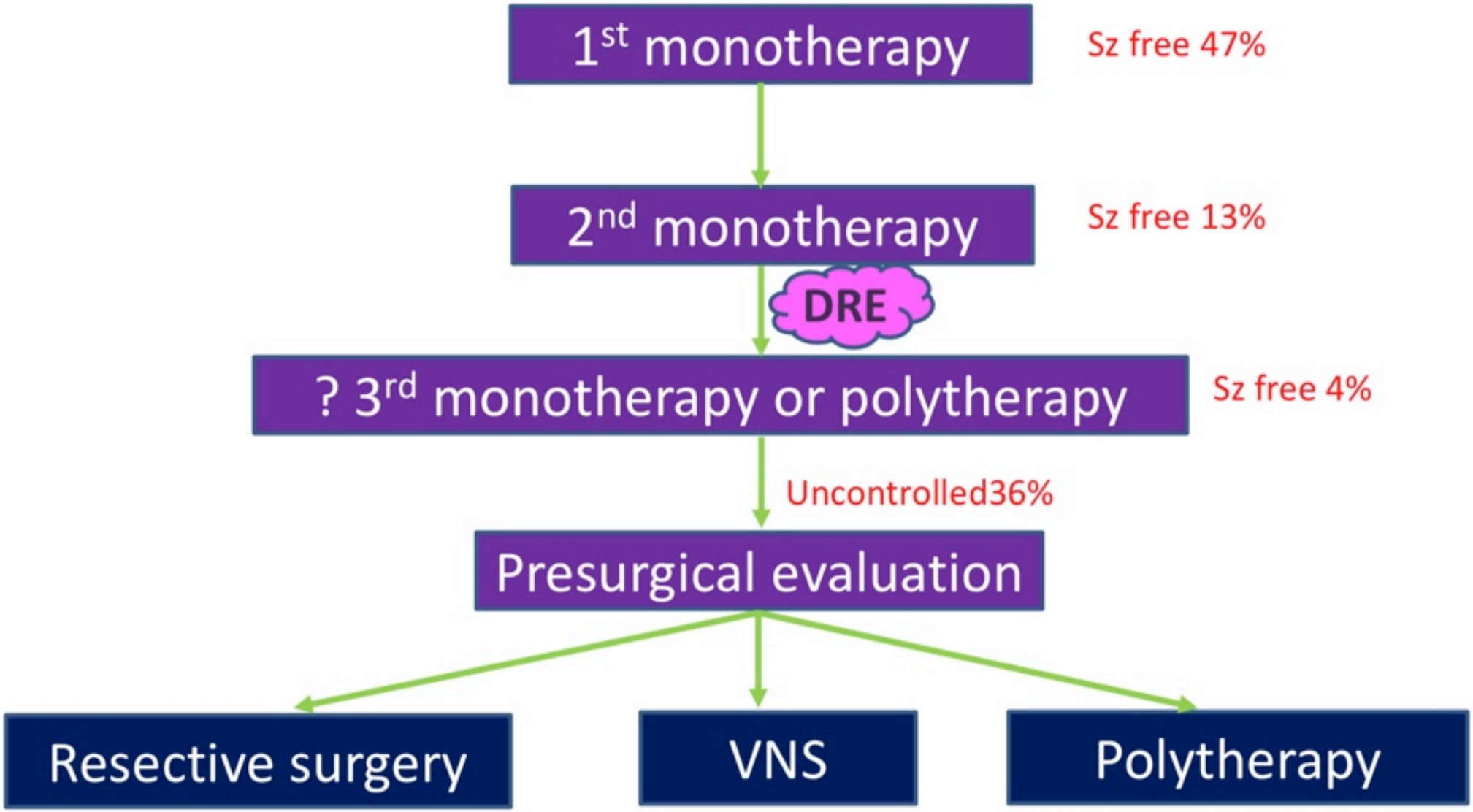
The consensus to adopt the failure of two (rather than greater numbers) AED schedules in the definition represents a testable hypothesis and aims to avoid unnecessary delay in evaluation, and **may be revised as more high quality data become available**

DRE: common cause



- Focal (structural) epilepsy
  - Focal cortical dysplasia / hemispheric epilepsy
  - Hippocampal sclerosis
  - Dual pathologies
- LGS
- Dravet syndrome
- West syndrome
- Epileptic encephalopathy (EIEE, EME) eg. NKH
- Others: Ring chromosome 20, Angelman syndrome, Febrile Infection-Related Epilepsy Syndrome (FIRES), Miller-Dieker syndrome (lissencephaly)

Drug Resistant Epilepsy (DRE)



Kwan P, et al. Epilepsia 2010

Treatment of DRE

Medications

Other treatment options

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DRE: Medications



DRE: predictors of AED resistance

- Initial response to AED
- Underlying cause
  - Structural cause > genetic (idiopathic epilepsy syndrome)
  - Non-acquired cause (stroke, tumor, vascular malformation)
- High frequency of pre-AED seizure (> 10 seizures)
- Seizure clustering
- ? Early age of onset, status epilepticus?
- These factors are useful in only some, Not all, patient

French. Refractory epilepsy: clinical overview. Epilepsia. 2007
Tang et al. Drug-resistant epilepsy. Frontiers in Neurology. 2017

AED Options ?

- Polytherapy
- Newer AEDs → better efficacy ?
- How many AEDs trial before thinking of other options ?

Polytherapy

Multicenter study in Italy

- 3⁄4 of intractable epilepsy → polytherapy
- 46.5% (adults), 54.2% (children) → 3 or more AEDs
- 7.2% → 4 or more AEDs

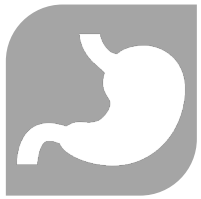
Canevini et al. Epilepsia 2010;51:797-804

✓ Consider efficacy/benefit vs side effects

Considerations of AED Use for Epilepsy



SEIZURE TYPE / EPILEPTIC SYNDROME



PHARMACOKINETIC PROFILES



MECHANISM



DRUG INTERACTION



SIDE EFFECT



CO-MORBIDITY

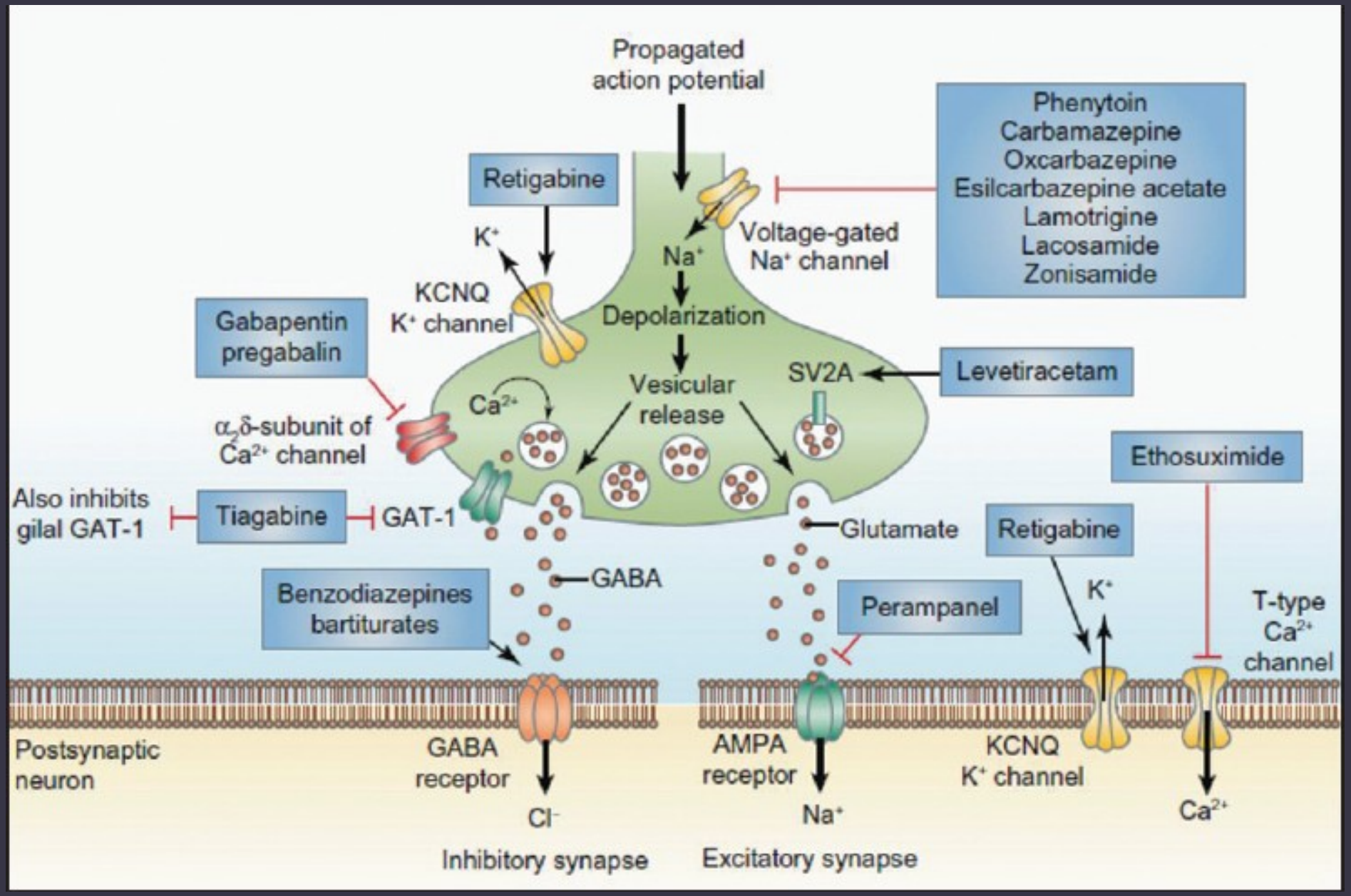


FAMILIARITY



COST

AED Mechanism



Singh. Muller J Med Sci Res 2014

Mechanism	Drugs
Sodium channel	PHT, CBZ, OXC, ESLI, LCM
Sodium channel “plus”	LTG, ZNS, RUF
GABA	PB, Benzodiazepine, VGB
SV2A	LEV
Pre-synaptic calcium channel	GBP, PGB
AMPA receptor	PER
Multiple actions	VPA, TPM

Adapted from Brodie MJ, et al. Epilepsy & Behaviour 2011;21:331-341.

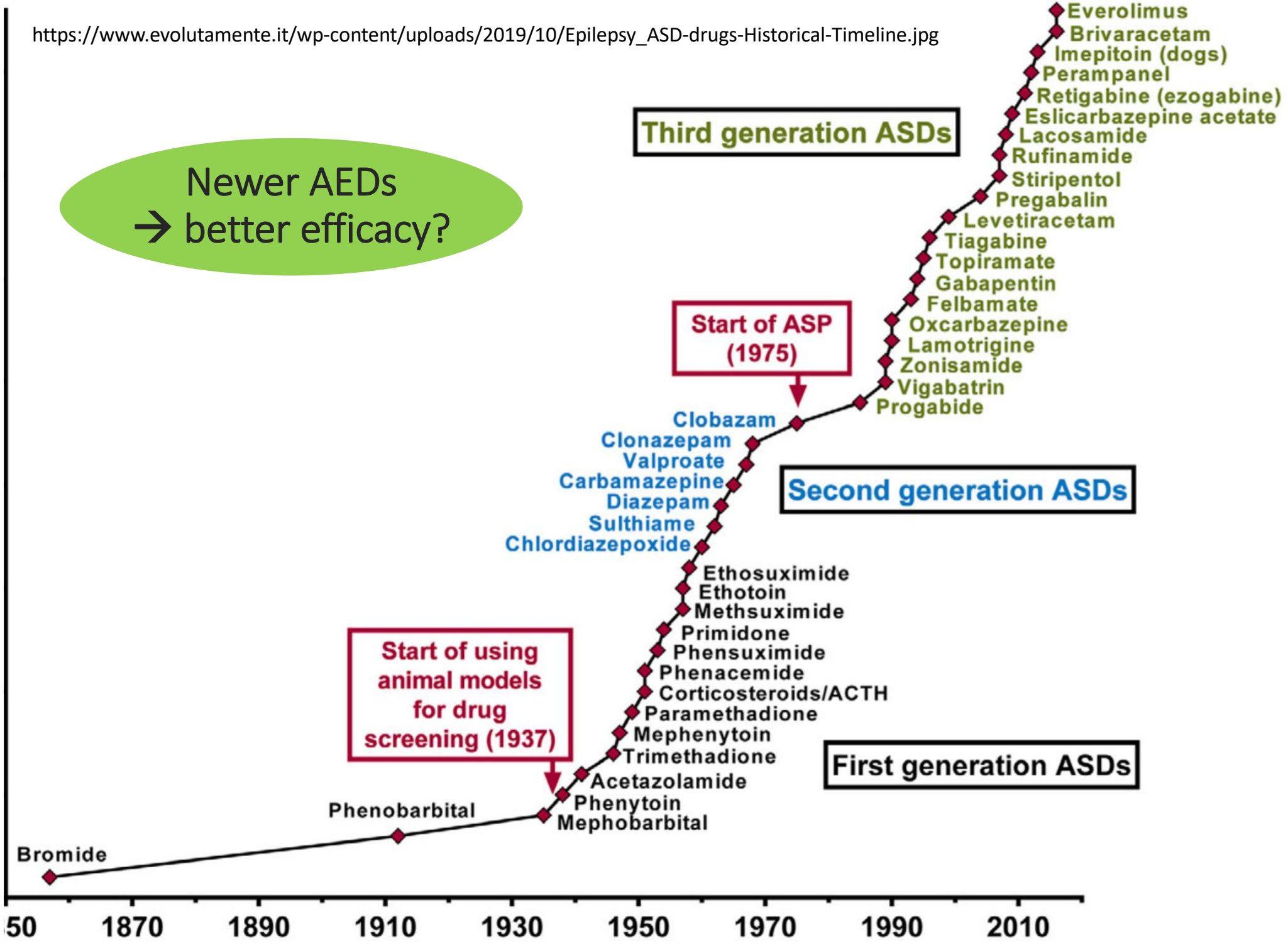
Good AED combination: Synergistic effect

Drug combination	Level of evidence
Valproate and lamotrigine[25-29]	+++
Valproate and ethosuximide[30]	++
Lamotrigine and topiramate[31]	+
Lacosamide and levetiracetam[32,33]	++
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Combinations containing enzyme-inducing drugs were excluded.
+++, from controlled trials; ++, from case series or observational studies; +, case reports.

Park KM et al. Journal of Epilepsy Research 2019

https://www.evolutamente.it/wp-content/uploads/2019/10/Epilepsy_ASD-drugs-Historical-Timeline.jpg



New AEDs: Add on medication

Add-on therapy of new AED

- 28% had 1-year sz free rate
- 21% had 50% sz reduction

Luciano and Shorvon. Ann Neurol 2007;62:375-81

Rufinamide

FDA approval

- Lennox-Gastaut syndrome ≥ 4 years

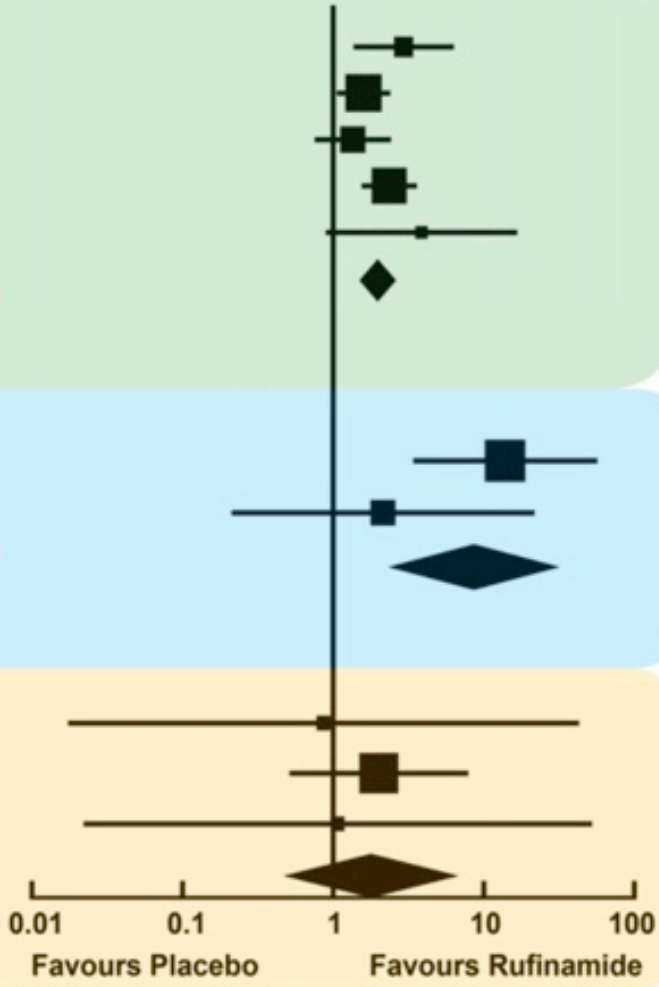
- Add-on for adults & adolescents with focal seizures

❖ Sodium channel blocker

Rufinamide: Meta-analysis
Risk ratios of responders

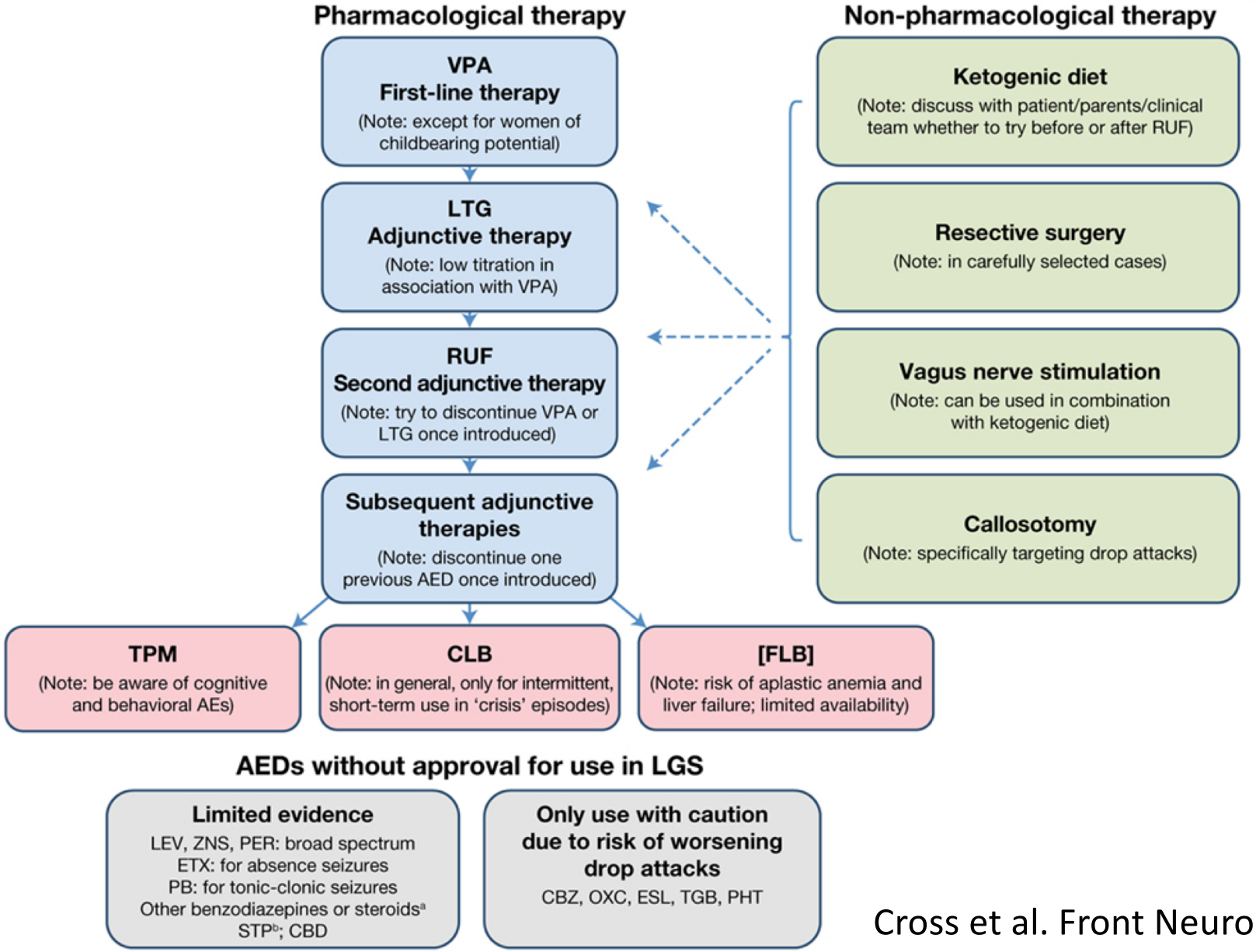
Study or Outcome	Rufinamide Events / Total	Placebo Events / Total	Weight	Risk ratio, 95% CI	p-Value
50% response					
Glaser 2008	23 / 74	7 / 64	10.13%	2.842 [1.306,6.181]	0.008
Brodie 2009	44 / 156	29 / 157	35.83%	1.527 [1.010,2.308]	0.045
Elger 2010	60 / 514	12 / 133	17.58%	1.294 [0.717, 2.333]	0.392
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 *					

Risk ratio and 95% CI



Zu, Epilepsy Res 2016

LGS Algorithm



Cross et al. Front Neurol 2017

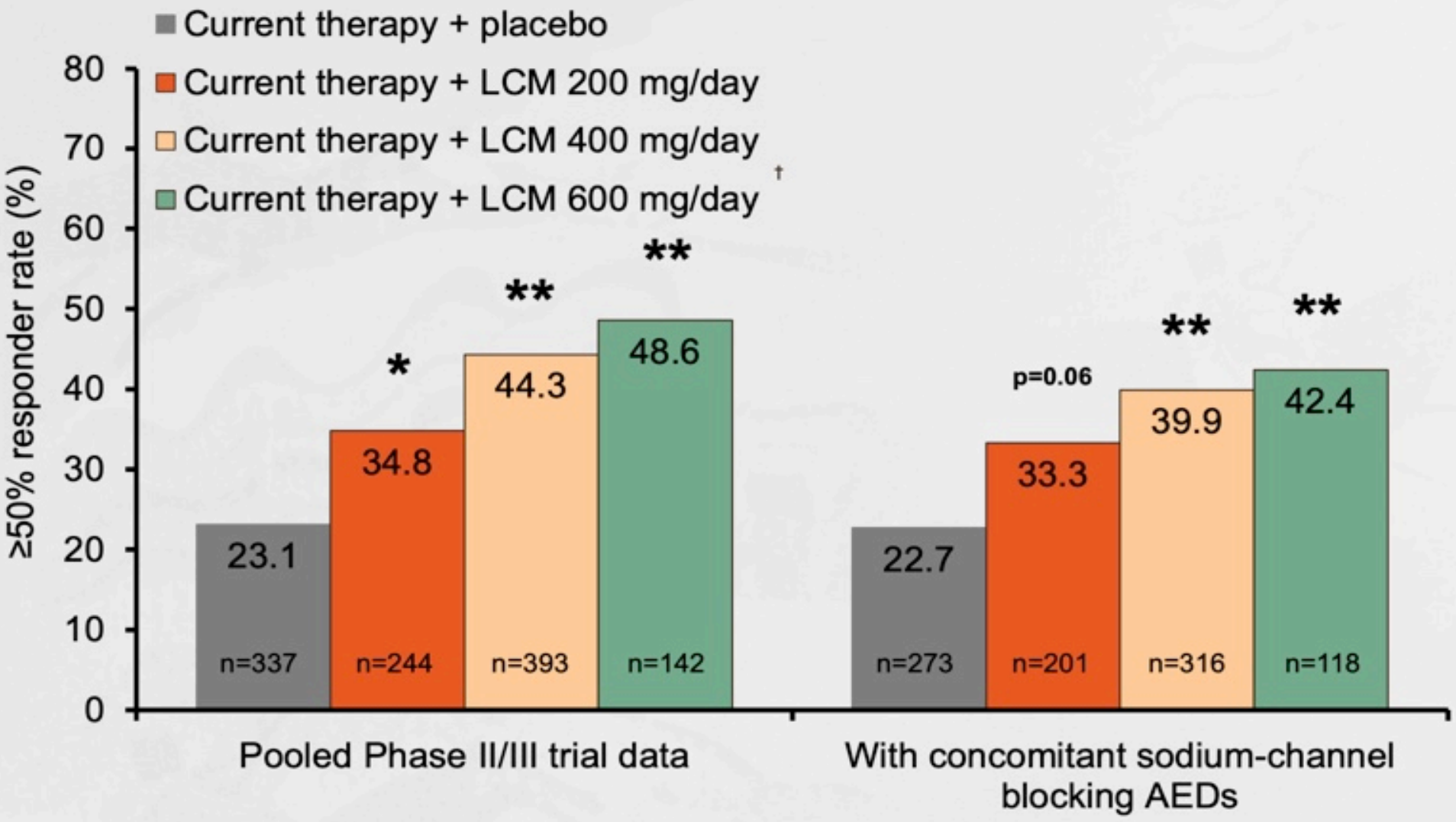
Lacosamide (LCM)

- Enhances the slow inactivated state of voltage-gated sodium channels

US FDA indication

- Oral treatment of **partial-onset seizures** in patients > 4 years
- IV short-term replacement when oral administration is not feasible in adult > 17 years

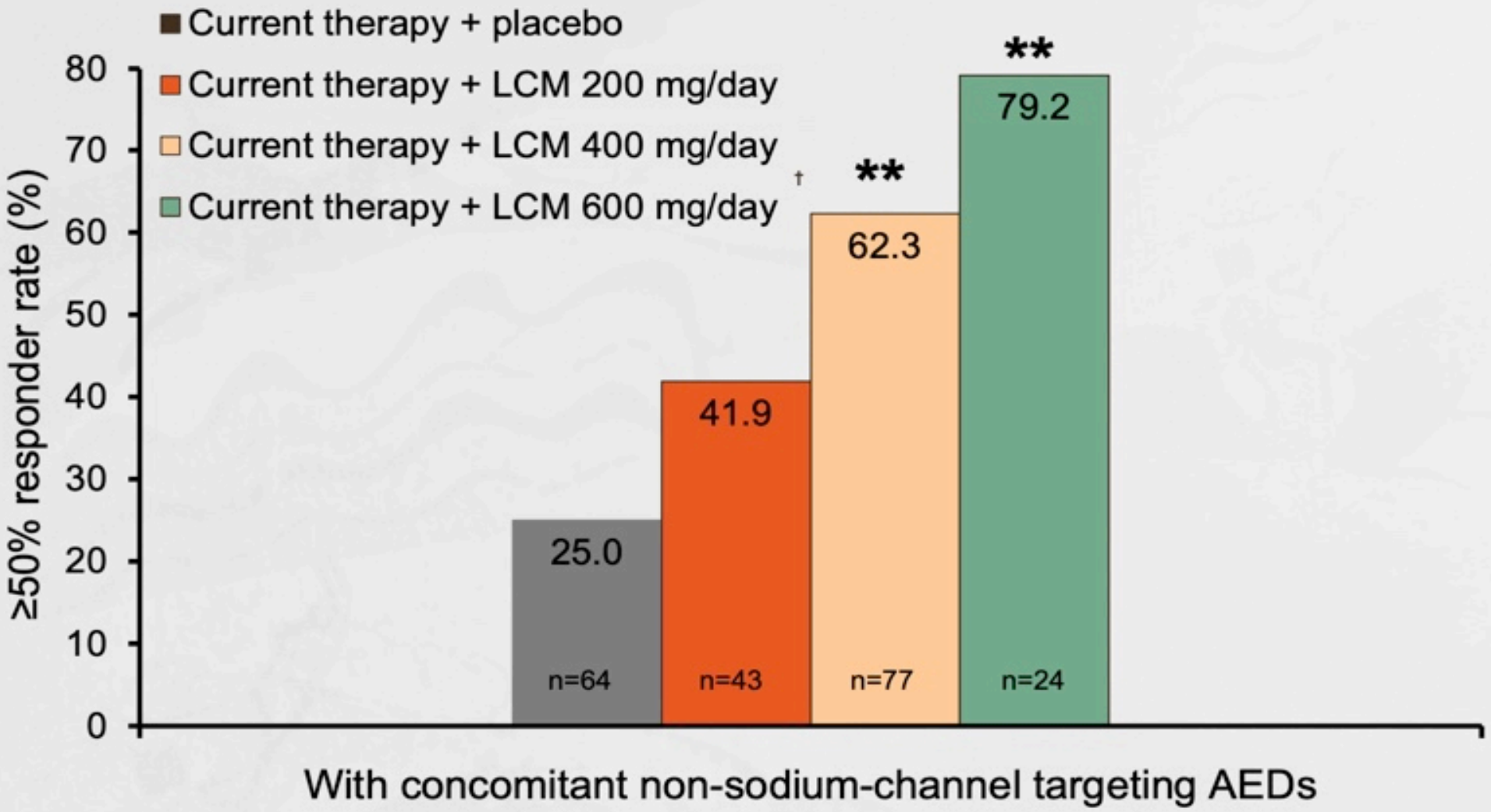
≥50% responder rate in patients taking ≥1 concomitant sodium-channel blocking AEDs



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

Sake et al. CNS Drugs 2010;24(12):1055–1068;
UCB Data on file Ref Type: Poster Isojarvi et al. ECE 2010

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



**p<0.01 versus placebo

Sake et al. CNS Drugs 2010;24(12):1055–1068

LCM

Warning

- Arrhythmia: PR prolongation
- esp. if dose > 10 mg/kg/day

Perampanel (PER)

- Selectively blocks AMPA receptor
- Monotherapy & combination therapy for Partial & GTC seizures for people older than 12 years
- Recently, US & Japan FDA has approved PER usage in patients with epilepsy 4 years or older
- Dose 2-8 mg/day once daily at bedtime
- Gradual titrate 2 mg every 2-4 weeks

PER

Black box warning

- Serious psychiatric & behavioral changes
- Homicidal or suicidal thoughts

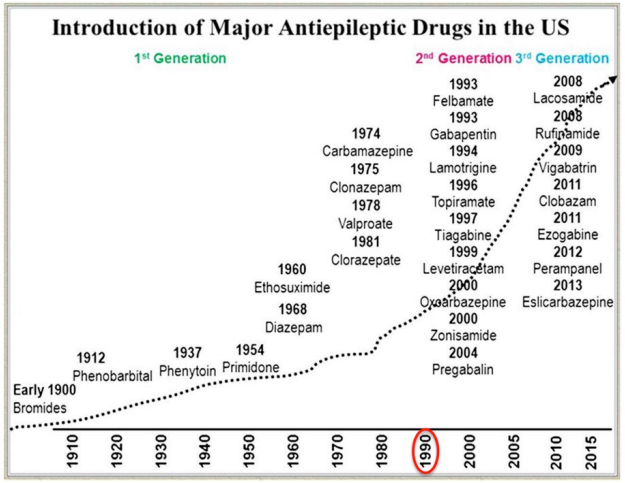
❖ Higher doses of 8 mg and 12 mg daily provide greater therapeutic benefits but with increased adverse events

New AEDs

- Better tolerable and have less adverse events
- Reduce seizure frequency significantly in DRE
- Seizure free: only few
- Right combination of AEDs are important
- But DRE is still about 20-30% despite to increased number of new AEDs

How many AEDs trial before thinking of other options ?

- Expert opinion: 4 – 5 AEDs should be tried
- Rational polytherapy



Drug combination	Level of evidence
Valproate and lamotrigine[25-29]	+++
Valproate and ethosuximide[30]	++
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Lacosamide and levetiracetam[32,33]	++
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Combinations containing enzyme-inducing drugs were excluded. +++, from controlled trials; ++, from case series or observational studies; +, case reports.

Prof. Seung Bong Hong, EST Annual Meeting 2019

Park KM et al. Journal of Epilepsy Research 2019

Treatment of DRE

Medications

Other treatment options

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DRE: Other Options

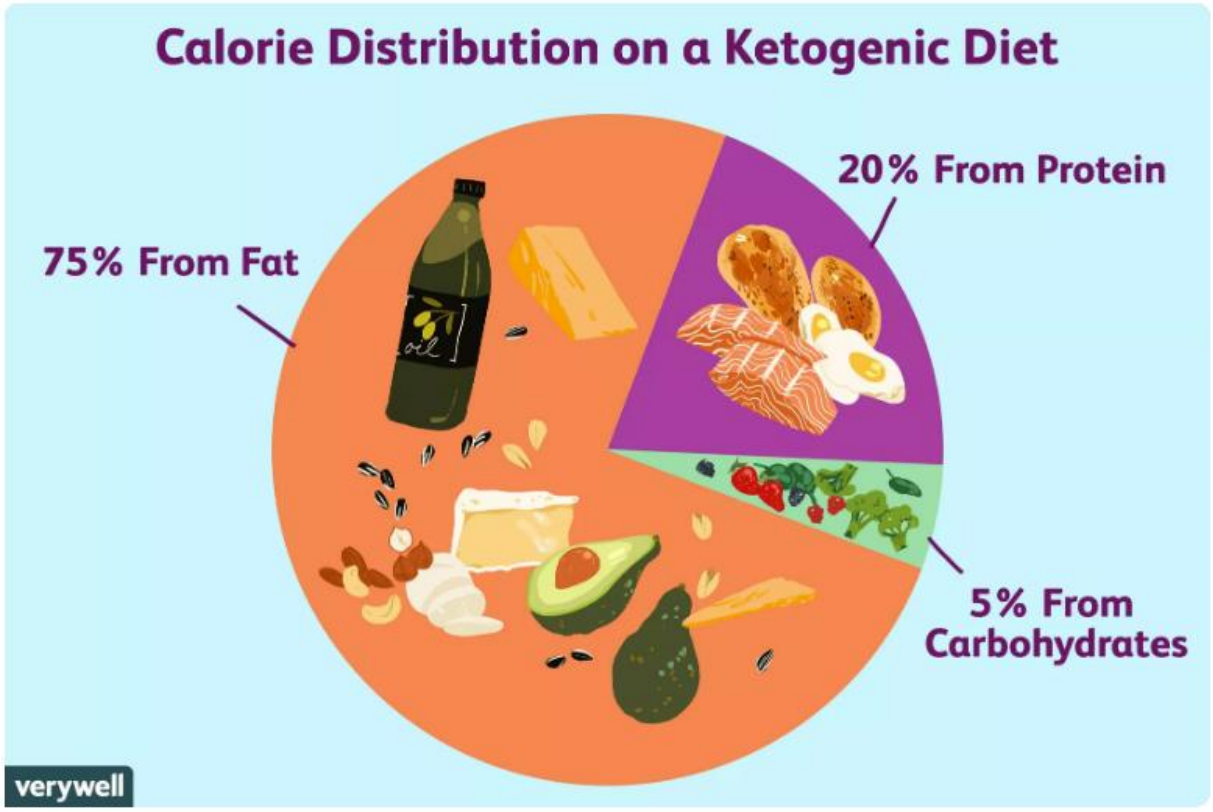


DRE: other options

- Ketogenic diet (KD)
- Cannabidiol (CBD)
- Surgery
  - Resective
  - Non-resective - Corpus callosotomy (CC)
    - Multiple subpial transections (MST)
    - Vagus nerve stimulation (VNS)

Ketogenic diet

- To mimic the effect of starvation
- First report of use in 1921
- High-fat, adequate protein, low-carbohydrate diet



KD: possible mechanism

- Direct anticonvulsant effect
- Enhance GABA production
- Mitochondrial change: anti-oxidative, anti-inflammation
- Glycolytic restriction / increase in non-glucose source

KD: indication

- Probable
  - GLUT-1 def. (glucose transporter 1 def.)
  - PHD (Pyruvate dehydrogenase deficiency)

  - Doose syndrome: Myoclonic-astatic epilepsy
  - Tuberous Sclerosis Complex, Rett syndrome
  - Dravet syndrome
  - Epileptic spasms
  - FIRES (febrile infection-related epilepsy syndrome)
  - SSPE
  - Landau-Kleffner syndrome
  - Lafora body disease
  - Selected mitochondrial disorders
  - Glycogenosis type V

Kossoff et al. Epilepsia, 2008

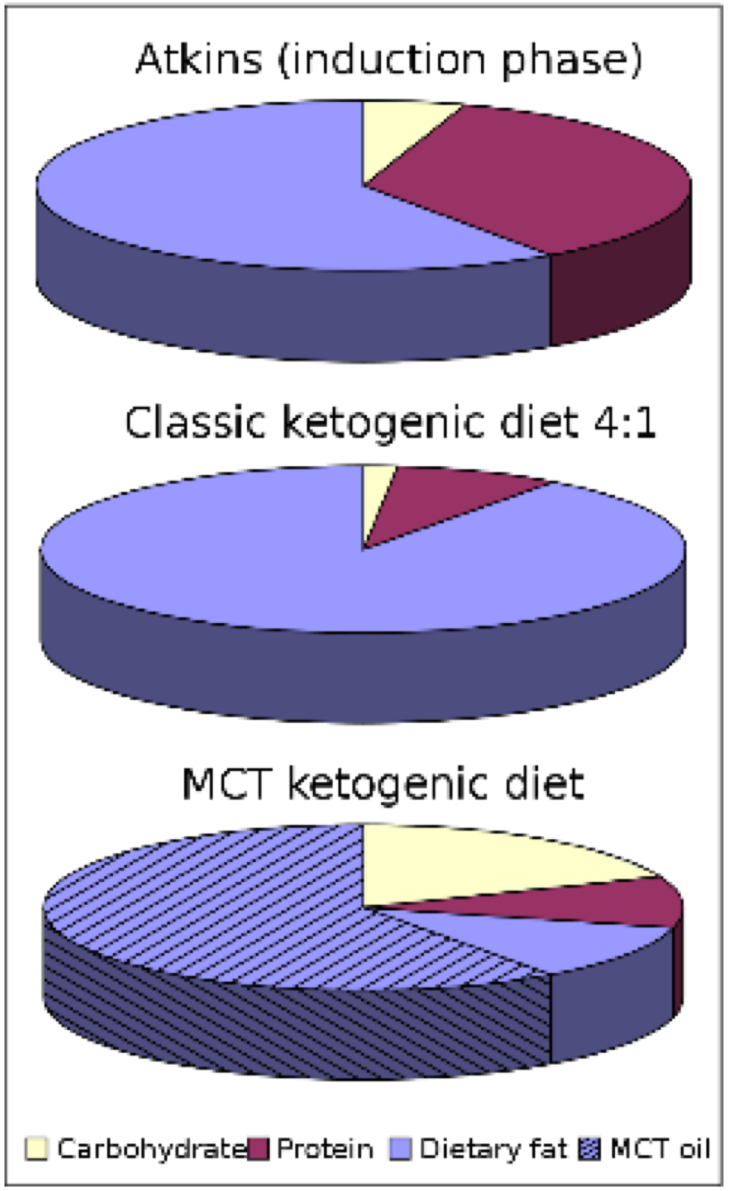
Contraindications to use of KD

- Absolute
  - Carnitine def. or CPT I or II def., Carnitine tranlocase deficiency
  - B-oxidation defects (MCAD, LCAD, SCAD)
  - Pyruvate carboxylase deficiency
  - Porphyria
- Relative
  - Inability to maintain adequate nutrition, caregiver noncompliance, surgical candidate
  - High cholesterol, bone disease

Kossoff et al. Epilepsia, 2008

Dietary therapies for epilepsy

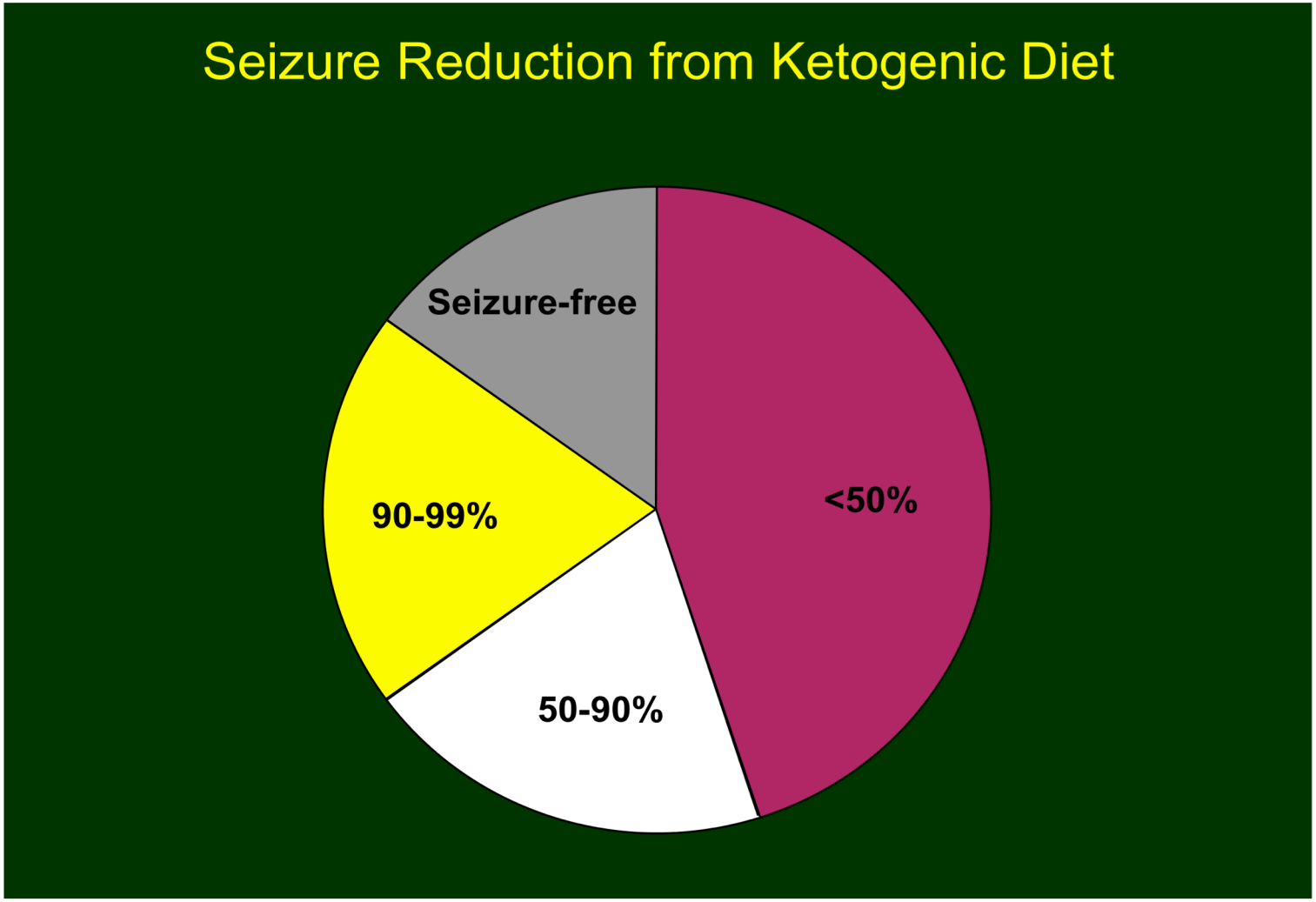
- **Classic ketogenic diet**
- MCT ketogenic diet
- Modified Atkins diet
- Low glycemic index diet



KD: Short-term benefit

- KD works quickly when effective, typically within the first 1–2 weeks
- Median time at which parents reported significant seizure reduction was after 5 days (range, 1–65 days)
- If the KD has not led to seizure reduction after 3-4 months, it can probably be discontinued
- If response, continue at least 2 years

KD: Effectiveness at 3-6 mo F/U



KD: efficacy

- Retrospective study, 59 children
- 26 classical KD, 20 MCT and 13 combination LCT/MCT
- Follow up at 3, 6, 9, 12 months

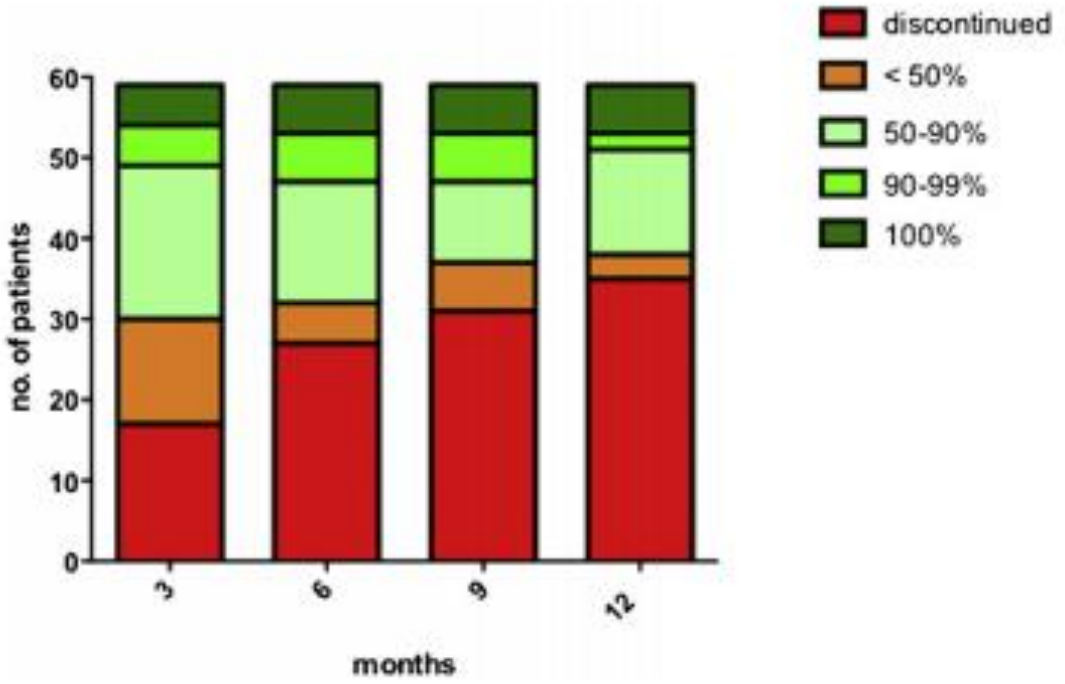


Fig. 1 – Seizure reduction distribution at 3,6,9 and 12 months after diet initiation.

Vehmeijer, et al. Eur J Ped Neurol 2015

KD: Complications

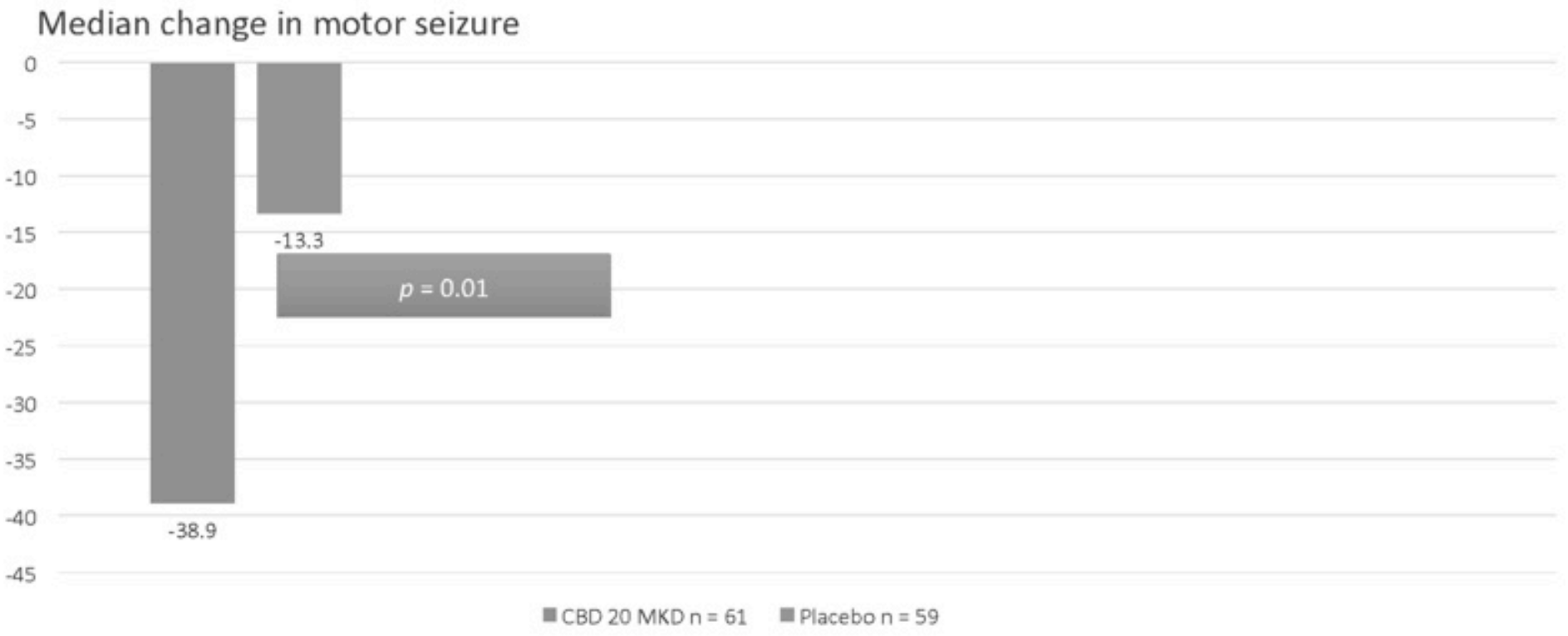
- Acute:
  - Acidosis
  - Dehydration
- Chronic
  - Elevated cholesterol/triglycerides
  - Constipation/diarrhea
  - Kidney stones
  - Poor linear growth
  - Nutritional deficiency

Cannabidiol (CBD)

- US FDA and EMA approval for
- Adjunctive therapy in children > 2 years with
  - ✓ Dravet syndrome
  - ✓ LGS

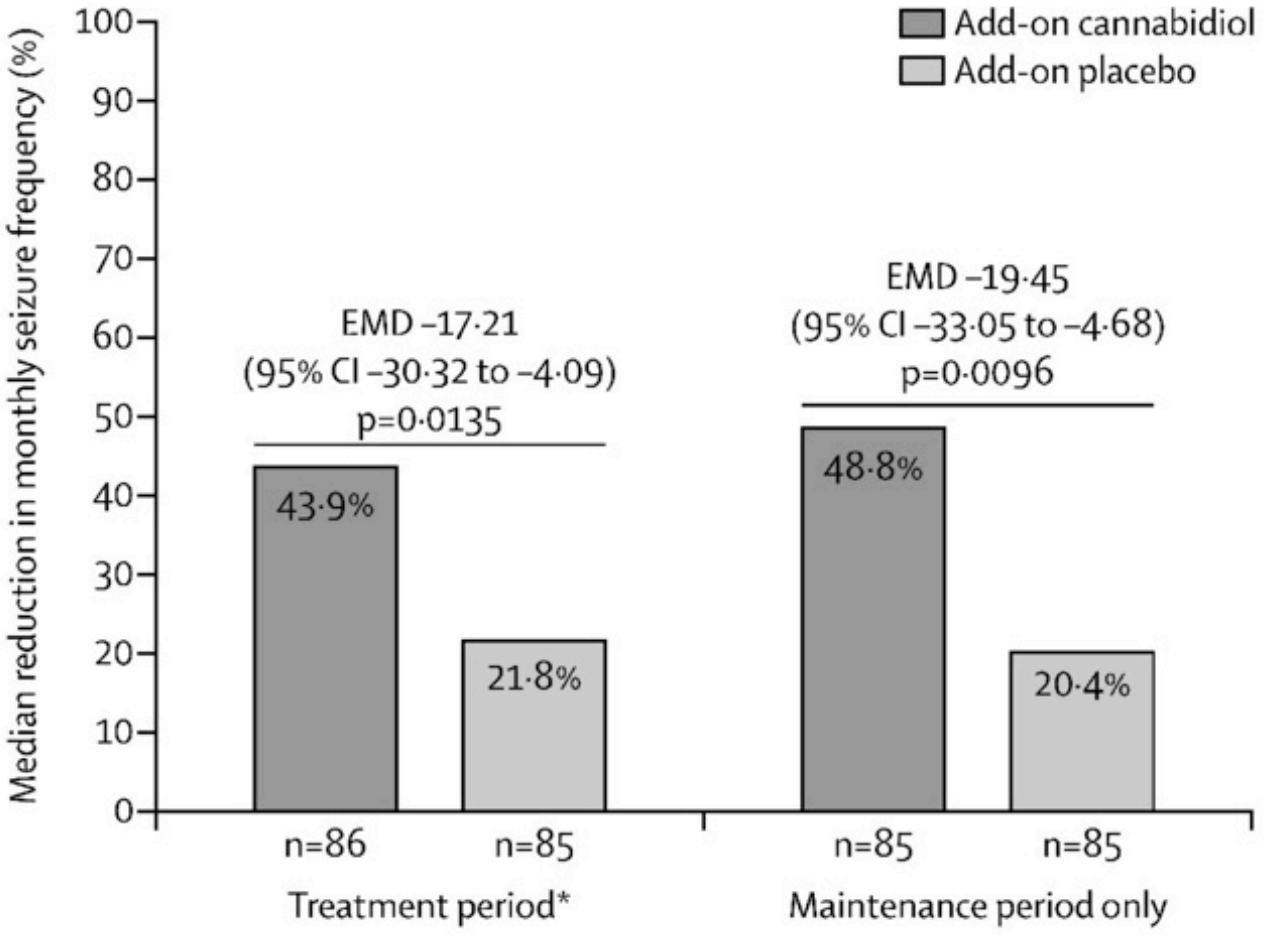
- Adjunctive therapy in DRE

CBD in Dravet syndrome



Devinski O, et al. N Engl J Med. 2017; 376: 2011-20

CBD in LGS



Thiele EA, et al. Lancet 2018; 391: 1085-96

CBD in DRE

- Motor seizure frequency (median) decreased from 30/ mo. to 15.8 at 12 weeks
  - Median change -36.5%
  - Seizure free in 5 (4%)
- Seizure types
  - Total: -34.6%
    - Focal : -55%
    - Atonic : -54.3%
    - Tonic : -36.5%
    - Tonic-clonic : -16%

Devinski O, et al. Lancet Neurol 2016; 15: 270-8

CBD with AEDs

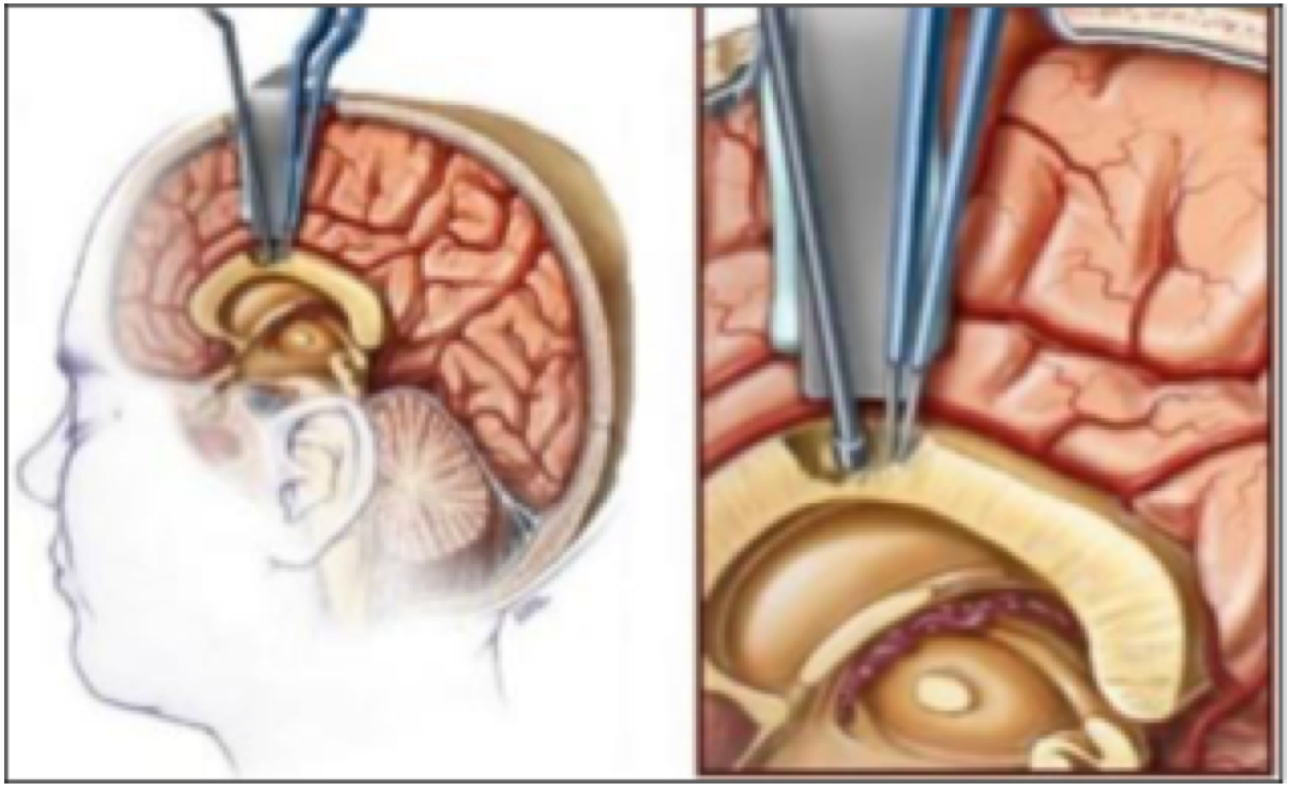
Drug interaction

- Decrease CBD level with
  - Carbamazepine
  - Phenytoin
  - Rifampin
- CBD increase level of
  - N-desmethyl-clobazam (active metabolite of clobazam)
  - Topiramate
  - Rufinamide
  - Zonisamide
  - Eslicarbazepine

Perruca E. J of Epilepsy Research. 2017;

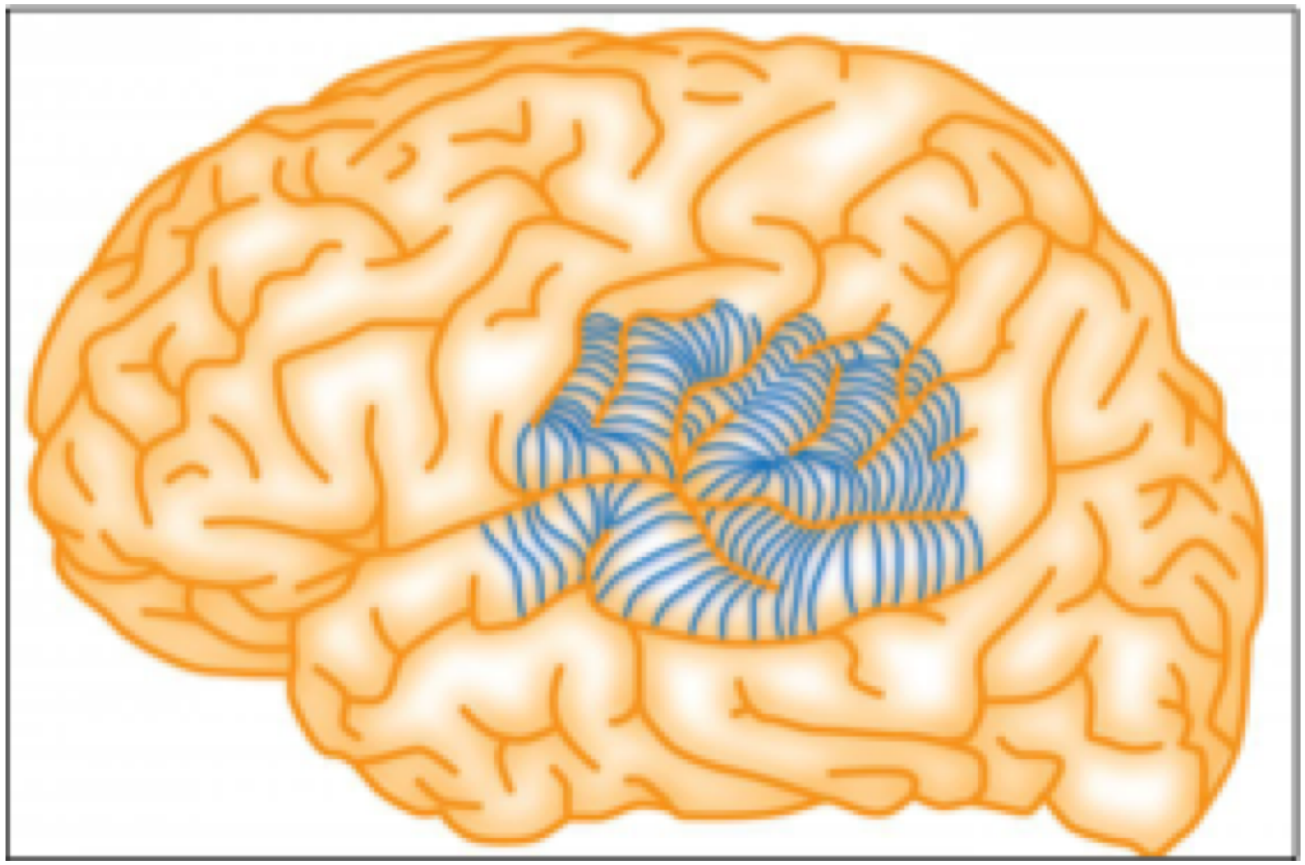
Corpus callosotomy (CC)

- LGS
- Decrease drop attack
- Still having other seizure type eg. GT



Multiple subpial transections (MST)

- Palliative surgery for DRE
- Eloquent cortex



Vagus nerve stimulation (VNS)

Devices

✓ VNS: FDA approved for epilepsy in 1997

- RNS (responsive neurostimulation): FDA approved for partial onset epilepsy in 2013
- DBS: for epilepsy in 2018

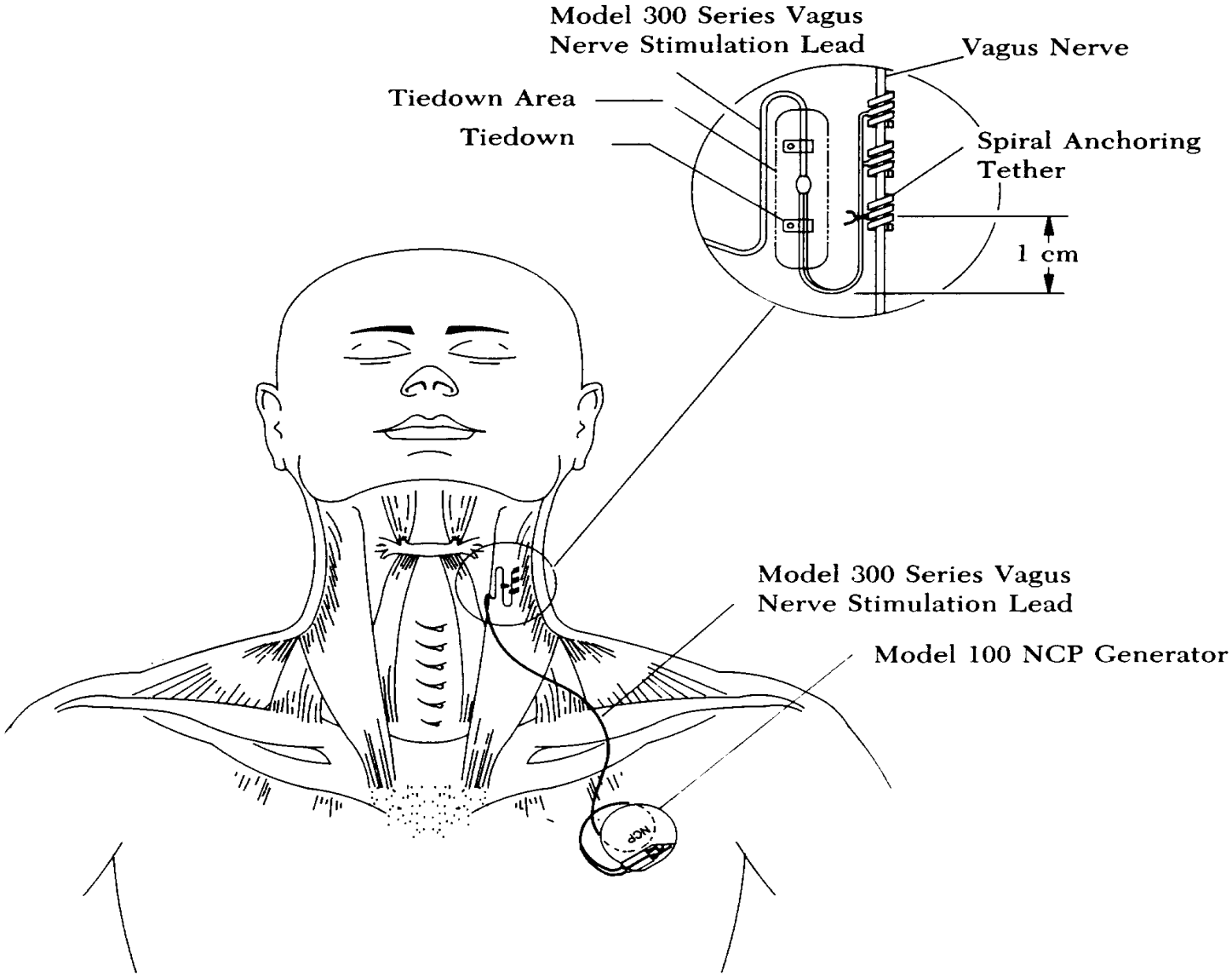
Vagus nerve stimulation (VNS)

Indications:

- ✓ Focal epilepsy (DRE), aged > 4 years, not amenable to surgical resection (or when the patient refuses a recommendation for epilepsy surgery)

- ✓ Lennox-Gastaut syndrome esp. for drop attack, tonic seizure

VNS: Implantation



VNS: Outcome

- Overall, 30 to 40% have had at least a 50% reduction in seizure frequency in long-term study (> 5 years F/U)
- Seizure freedom has been reported in only 5% of patients
- Magnet use: sometimes stop ongoing sz
- Also improve quality of life, mood, attention, and learning



VNS: Side effect

- Transient hoarseness and voice modulation associated with stimulation (55% after 12 weeks)
- Headache (22%)
- Cough, dysphagia, neck pain, shortness of breath (15-20%)

- Infection (5-7%)
- Vocal cord paralysis: rare (1%)

Summary

Medications

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FACULTY OF MEDICINE SIRIRAJ HOSPITAL

Thank You

