Management of Drug-resistant epilepsy (DRE)

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Epilepsy Care

Seizure

Epilepsy diagnosis

Medication trials

Imaging for pathology

Medical intractability

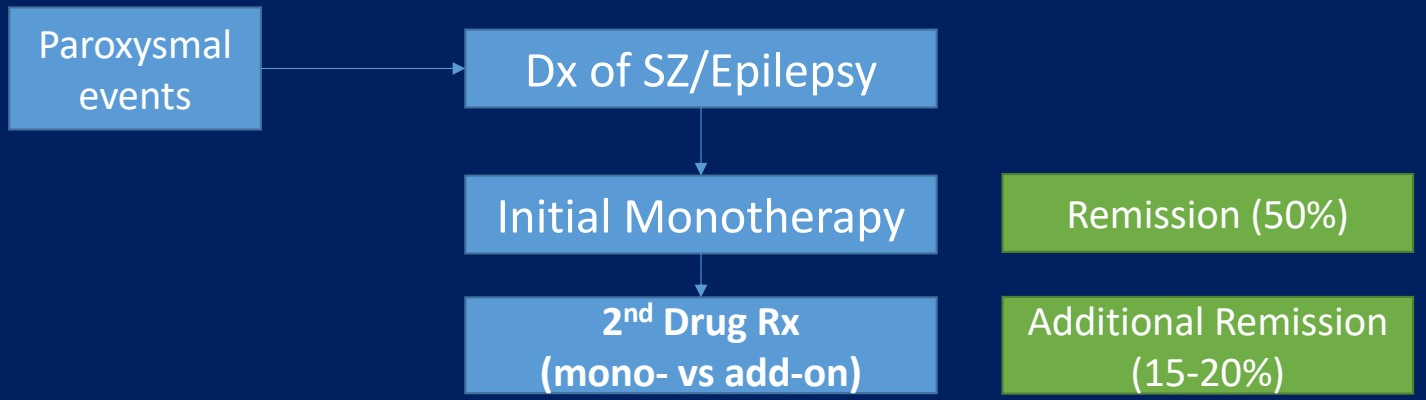
Surgical Consideration

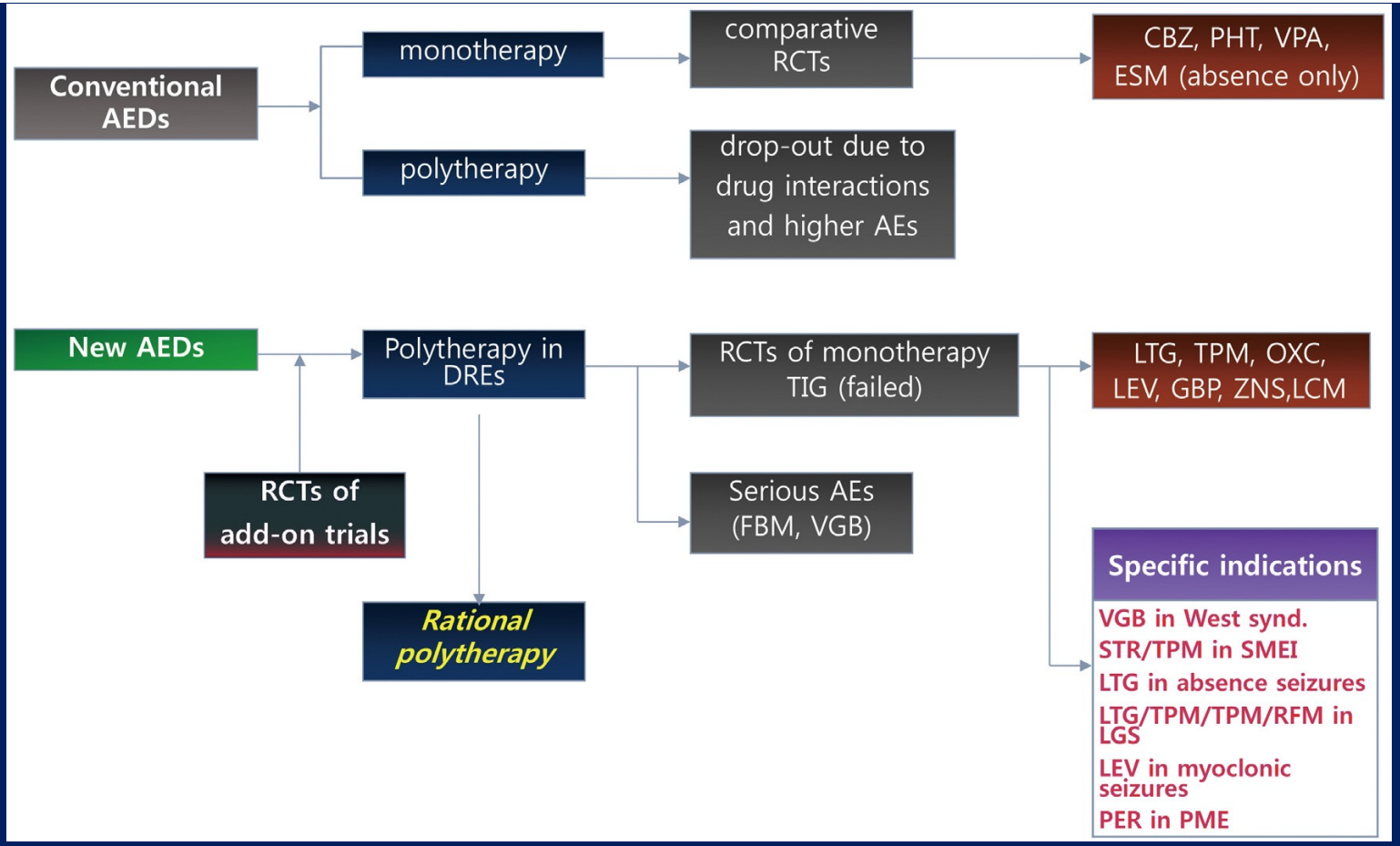
Surgical workup

Surgery

Not surgery

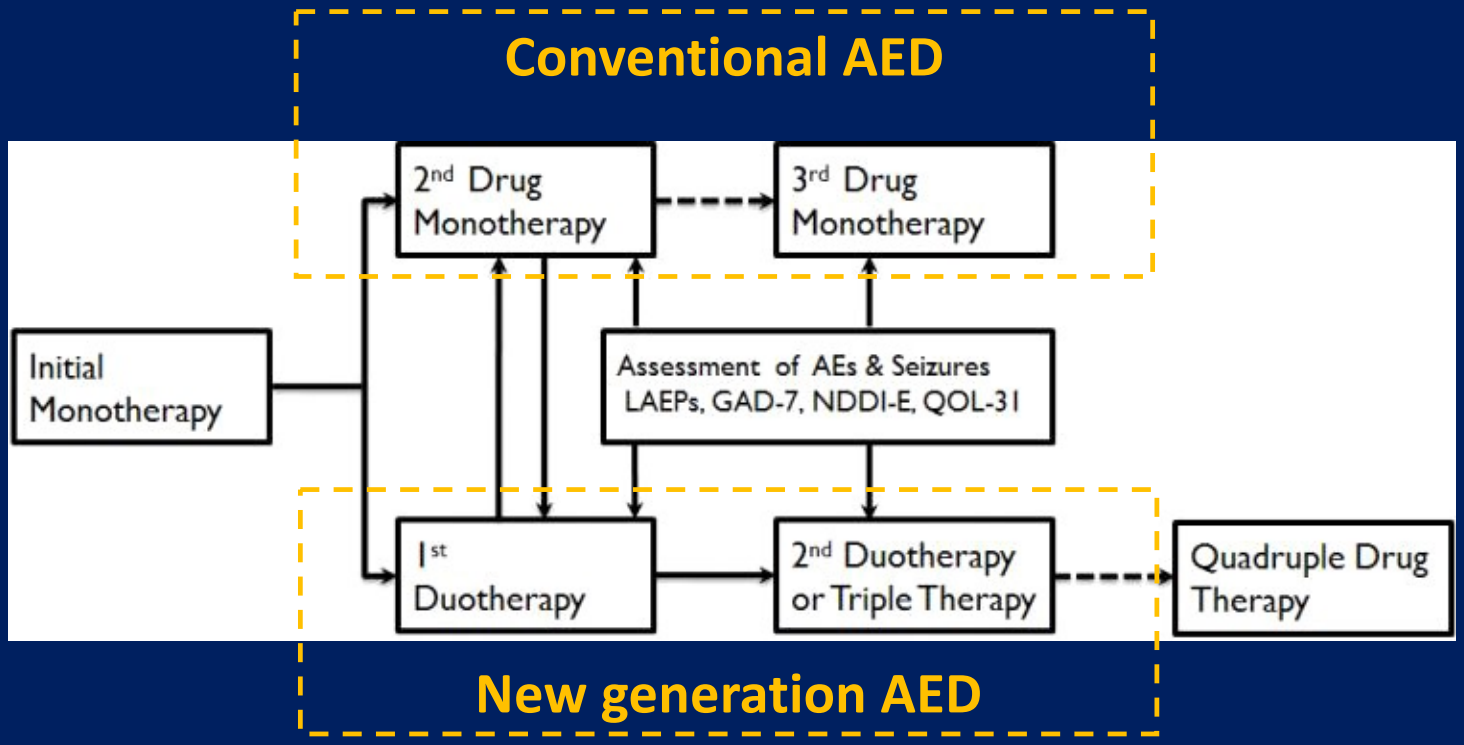
Pathway of epilepsy management





Lee BI, et al. Epilepsy Research 2019; 106-5

Sequential AED trials epilepsy



Park KM, et al. J of Epilepsy Research 2019;9:14-26

Treatment Response with AEDs

Old	Newer (2nd gen)
Phenobarbital 1919	Felbamate 1993
Phenytoin 1938	**Gabapentin 1993**
Primidone 1954	**Lamotrigine 1994**
Ethosuximide 1960	**Topiramate 1996**
Carbamazepine 1974	Tiagabine 1997
Valproic acid 1978	**Levetiracetam 1999**
	Oxcarbazepine 2000
	Zonisamide 2000

Treatment Response with AEDs

Drug #	% Seizure free	
1st mono	**47.2**	**+13%**
2nd mono	**60.2**	**+4%**
3rd mono or combination	**64**	

36% (~1/3) of patients have resistant to medication

Kwan & Brodie. NEJM 2000;342:314-9

3rd gen AEDs

Old	Newer (2nd gen)	Newest (3rd gen)
Phenobarbital 1919	Felbamate 1993	**Pregabalin 2005**
Phenytoin 1938	**Gabapentin 1993**	Rufinamide 2009
Primidone 1954	**Lamotrigine 1994**	**Lacosamide 2009**
Ethosuximide 1960	**Topiramate 1996**	Vigabatrin 2009
Carbamazepine 1974	Tiagabine 1997	**Clobazam 2011**
Valproic acid 1978	**Levetiracetam 1999**	Ezogabine 2011
	Oxcarbazepine 2000	**Perampanel 2012**
	Zonisamide 2000	Eslicarbazepine 2014

Pattern of treatment response

Table 1 Seizure-free rates with successive antiepileptic drug regimens

Drug regimens	No. of patients	Seizure-free on monotherapy	Seizure-free on combination	Total no. seizure-free	% of cohort seizure-free	% Seizure-free on regimen
First	1,098	543	0	543	49.5	49.5
Second	398	101	45	146	13.3	36.7
Third	168	26	15	41	3.7	24.4
Fourth	68	6	5	11	1.0	16.2
Fifth	32	1	3	4	0.4	12.5
Sixth	16	1	1	2	0.2	12.5
Seventh	9	1	1	2	0.2	22.2
Eighth	3	0	0	0	0.0	0.0
Ninth	2	0	0	0	0.0	0.0

SZ freedom does not differ substantially whether an established or a new-generation AED is used.

Brodie MJ, et al. Neurology 2012;78:1548–54

Epilepsia, 51(6):1069–1077, 2010
doi: 10.1111/j.1528-1167.2009.02397.x

SPECIAL REPORT

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

"Drug-resistant or Medically intractable epilepsy"

- "a failure of adequate trials of **2 tolerated, appropriately chosen** and used anticonvulsant drug schedules (whether as **monotherapy or in combination**) to achieve sustained seizure freedom."

Kwan P, et al. Epilepsia 2010

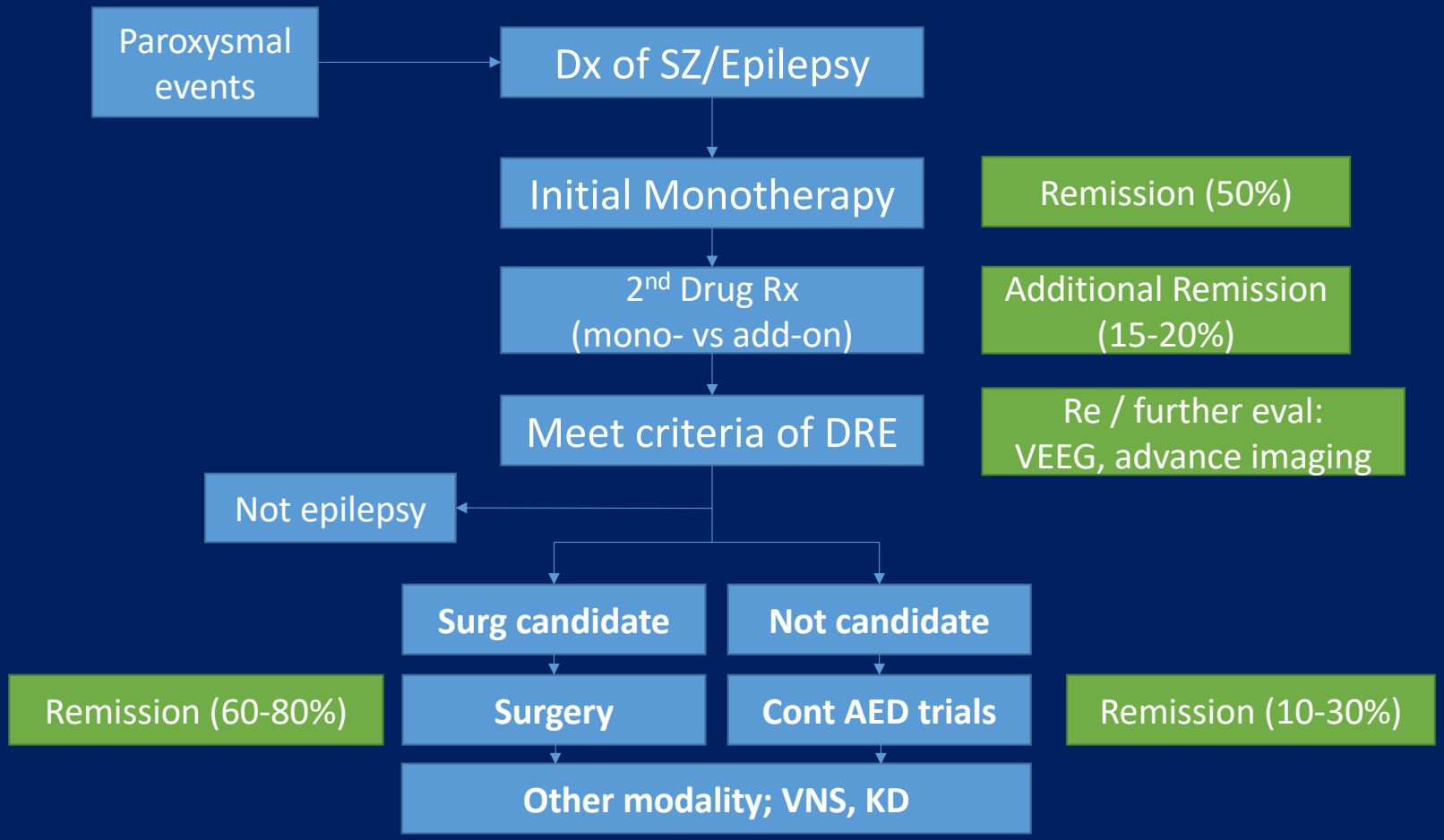
Exclude pseudoresistance

Table 1. Some Reasons for Pseudoresistance to Antiepileptic Drug Therapy.

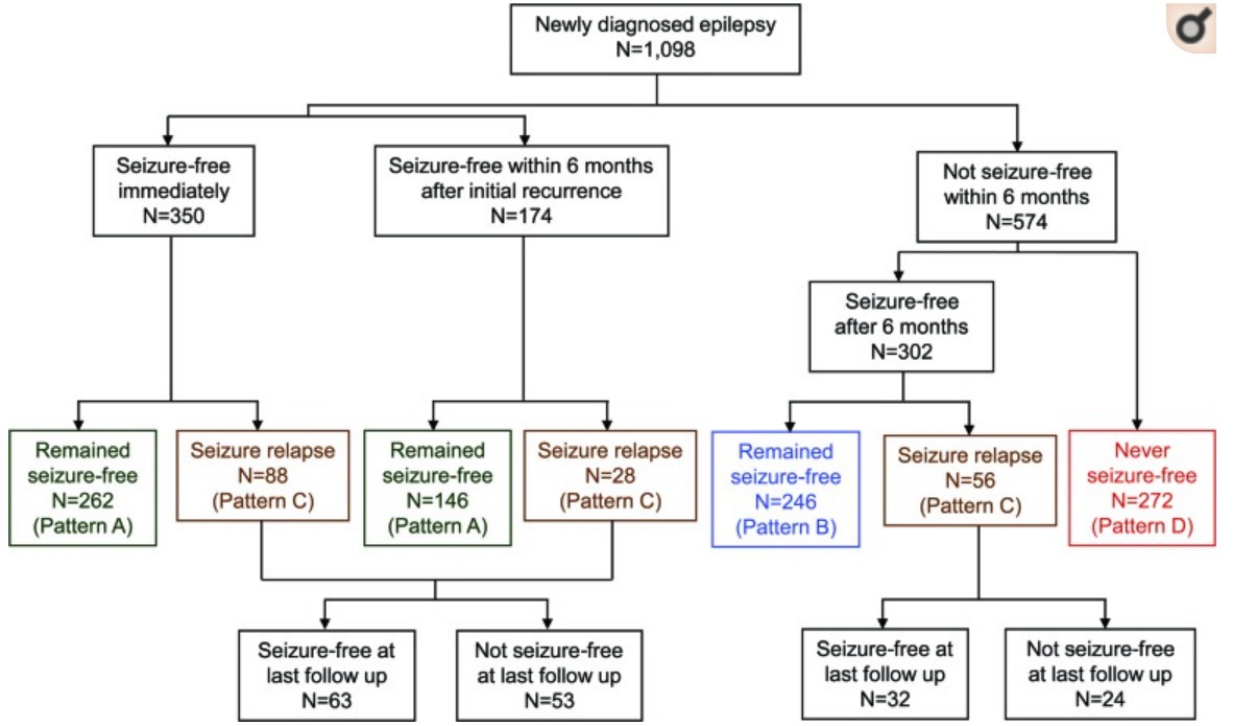
Reason	Examples
Wrong diagnosis	Syncope, cardiac arrhythmia, or other conditions; psychogenic nonepileptic seizures
Wrong drug (or drugs)	Inappropriate for seizure type; pharmacokinetic or pharmacodynamic interactions
Wrong dose	Too low (overreliance on "therapeutic" blood levels); side effects preventing drug increase
Lifestyle issues	Poor compliance with medication; alcohol or drug abuse

Kwan P, et al. N Engl J Med 2011;365:919-26.

Pathway of epilepsy management



Pattern of treatment response

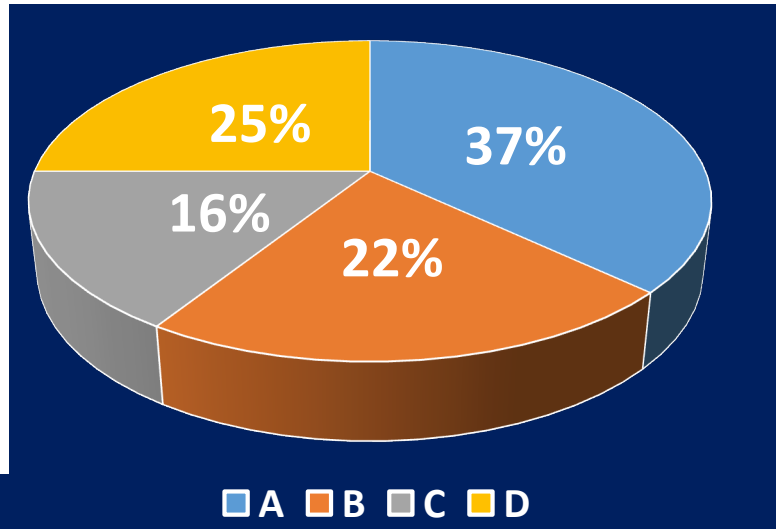


Pattern A: Early and sustained

Pattern B: Delayed and sustained

Pattern C: Fluctuating course

Pattern D: Never SZ-free



Neurology. 2012 May 15; 78(20): 1548–1554.

Rational polytherapy

- 1st AED fails due to lack of tolerability → 2nd mono
- 1st AED fails due to inefficiency
  - →Add-on (partially effective from 1st AED)
  - →2nd mono (totally ineffective from 1st AED)
- 2nd mono should be considered in
  - ○Elder, women w/ child bearing age
  - ○Compliance challenging
  - ○Cost

Add-on: consider different MOA and co-morbidity

Rational Combination of AEDs

Recommend

: Na-Channel blocker + GABAergic

: Na-Channel blocker + multiple mechanism AED

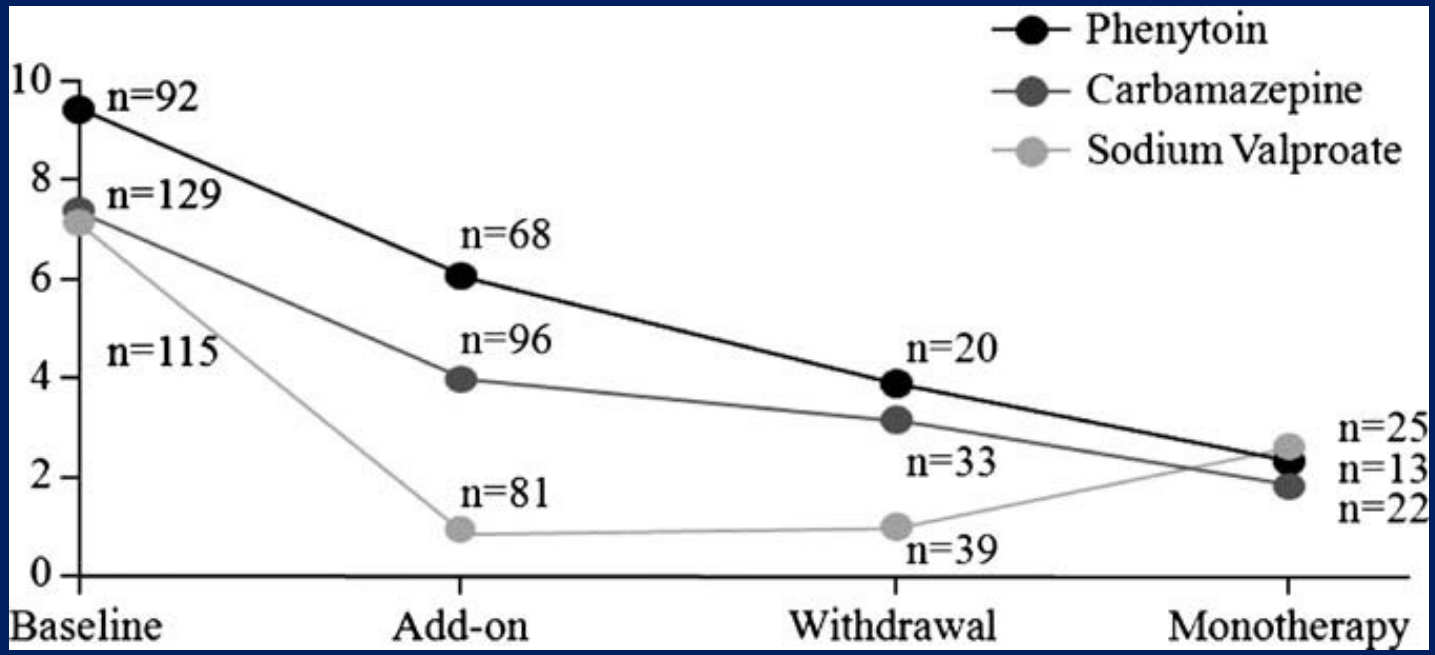
: Valproate + Lamotrigine

Not recommend

: Na-Channel blocker + Na-Channel blocker

→ more neurotoxic side-effects; dizziness, diplopia and ataxia

Synergistic effect of VPA + LTG



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

Synergistic combination regimen

Combination regimen	LOE	Remarks
VPA + LTG	+++	
VPA + ETX	++	In absence
LTG + TPM	+	
LCS + LEV	++	
LTG + LEV	++	
VPA + LEV	+	
VPA + clobazam + stiripentol	+++	In Dravet syndrome
VPA + LTG + BZP	++	In epileptic encephalopathy

+++	controlled trials
++	case series or observational studies
+	case reports

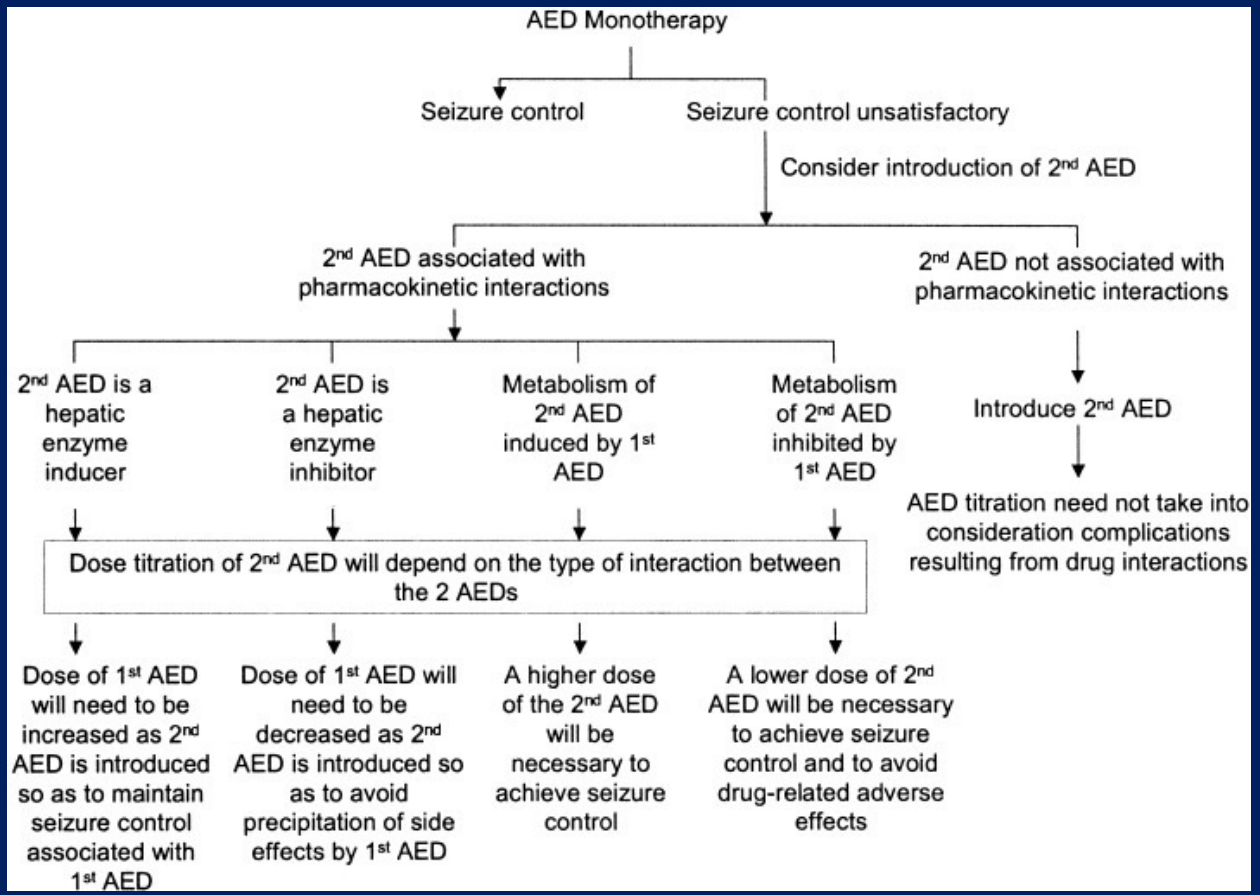
Lee BI, et al. Epilepsy Research 2019; 106-5

Guidance for combining AEDs

1. Establish optimal dose of baseline agent
2. Add drug with multiple mechanisms
3. Avoid combining similar MOA
4. Titrate new agent slowly and carefully
5. Be prepared to reduce dose of original drug
6. Replace less effective drug if response still poor
7. Try range of different duo therapies
8. Add 3rd drug if still suboptimum

M.J. Brodie. Seizure 20 (2011) 369–375

Interaction between 1st & 2nd AEDs



Expected changes in plasma concentration when new AED

◊ Enz inducer
□ Enz inhibitor

Effect of → / On ↓	PB◊	PHT◊	PRM◊	ESM	CBZ◊	VPA□	FBM□	VGB	GBP	LTG	TPM◊	TGB	OXC◊	LEV	PGB	ZNS	LCS
PB	-	↑	-	-	-	↑	↑	↓	-	-	-	-	↑	-	-	-	-
PHT	↑↓	-	↑↓	-	↑↓	-	↑	↓	-	-	↑	-	↑	-	-	-	-
PRM	↓	↓	-	-	↓	↑	-	↓	-	-	-	-	-	-	-	-	-
ESM	↓	↓	↓	-	↓	↑	-	-	-	-	-	-	-	-	-	-	-
CBZ	↓	↓	↓	-	-	↑	↓	↑	-	-	-	-	↓	-	-	↑	-
VPA	↓	↓	↓	↓	↓	-	↑	-	-	-	↓	-	-	-	-	-	-
FBM	↓	↓	↓	-	↓	↑	-	-	-	-	-	-	-	-	-	-	-
VGB	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
GBP	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
LTG	↓	↓	↓	-	↓	↑	-	-	-	-	-	-	↓	-	-	-	-
TPM	↓	↓	↓	-	↓	↓	-	-	-	-	-	-	-	-	-	-	-
TGB	↓	↓	↓	-	↓	-	-	-	-	-	-	-	-	-	-	-	-
OXC	↓	↓	↓	-	↓	-	-	-	-	-	-	-	-	-	-	-	-
LEV	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
PGB	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
ZNS	↓	↓	↓	-	↓	-	-	-	-	-	-	-	-	-	-	-	-
LCS	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
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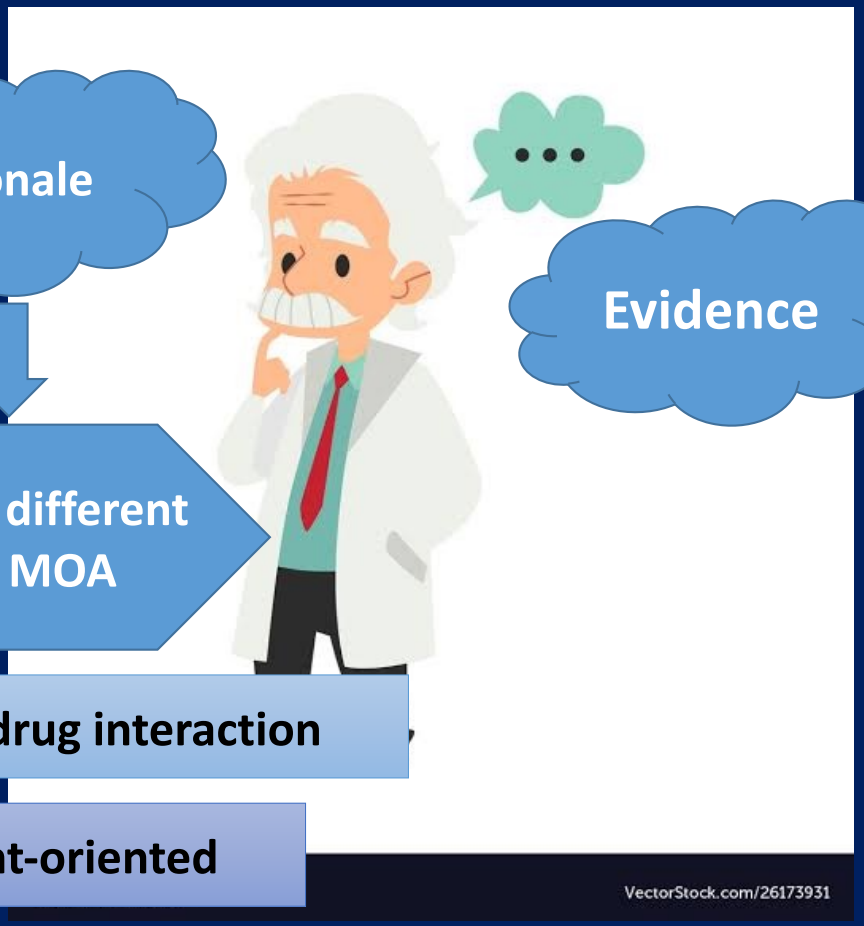
Expert Opin. Pharmacother. (2010) 11(7)

Rationale polytherapy



Combine different AED's MOA

Drug-drug interaction

Patient-oriented

Patient-oriented: To choose, To avoid

Co-morbidity	Choose	Avoid
Obesity	TPM, ZNS	VPA, PGB, GBP, PER
Migraine	TPM, VPA, ZNS, PGB, GBP	
Skin rash	LEV, GBP, PGB, TPM, VPA, PER, LCM	LTG, OXC, CBZ, PHT, PB
Neuropathic pain	PGB, GBP, CBZ, OXC, PHT	
Depression +/- Behav/Psych	LTG, CBZ, OXC, VPA, PGB	LEV, PV, PRM, TPM, ZNS, PER
Cognitive dysfn	LTG, LEV, OXC	PB, TPM, ZNS
Concomitant drugs	GBP, LEV, PGB, VPA	EI-drugs
Osteoporosis	LTG, LEV	EI-drugs, TPM, VPA, ZNS
Tremor	TPM, PER	VPA

Patient-oriented: To choose, To avoid

Co-morbidity	Choose	Avoid
Restless legs syndrome	GBP, PGB, CZP	
Renal stone		TPM, ZNS
Glaucoma		TPM
Hematological disorder		CBZ, VPA
Hyponatremia		OXC, ESL, CBZ
Hepatic disease	New AEDs	VPA
Renal disease	Old AEDs	
Cardiac arrhythmia		CBZ, LTG, LCM, PHT
Cancer	VPA, LEV, PER	EI-drugs
Heat stroke		TPM, ZNS

Epilepsy Care

Seizure

Epilepsy diagnosis

Medication trials

Imaging for pathology

Medical intractability

Surgical Consideration

Surgical workup

Surgery

Not surgery

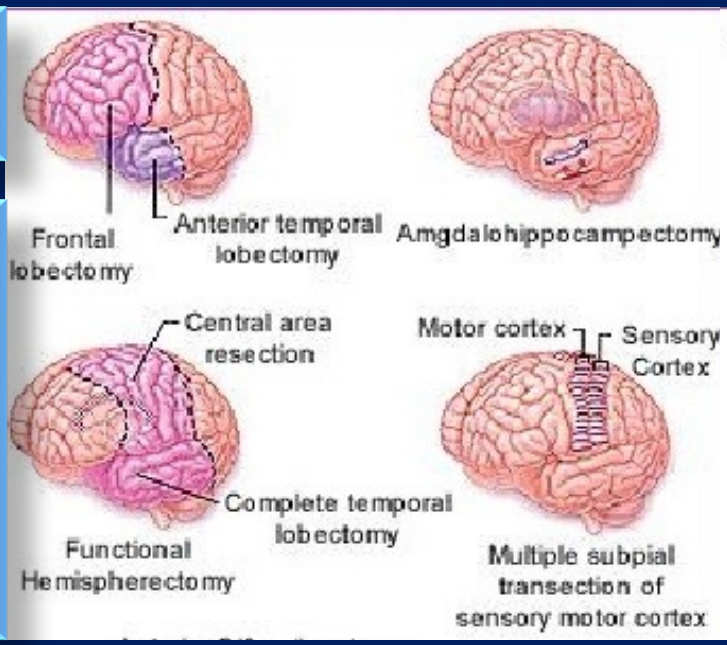
Treatment Alternatives for DRE:

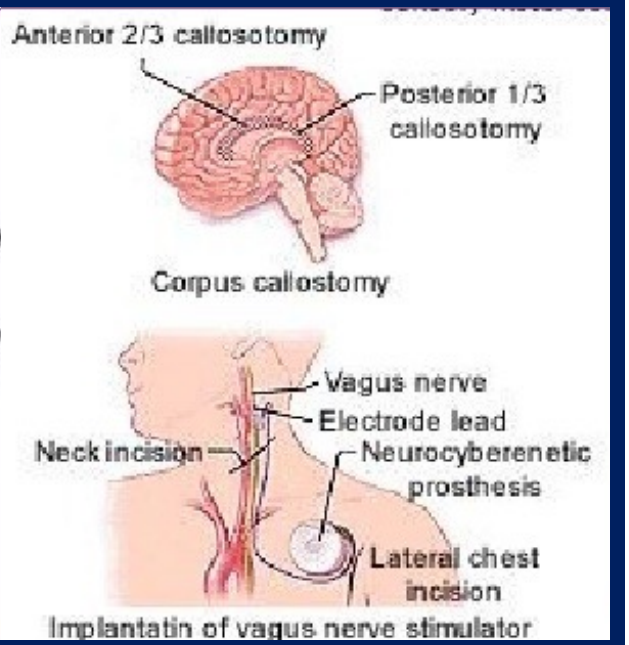
Surgery	Non-Surgery
- Resective surgery - Palliative surgery - Non-resective technique	Diet - Ketogenic diet

Type of surgical procedure

Surgery

- Resective surgery
- Palliative surgery
- Non-resective technique





Resective surgery

Resect **epileptogenic zone** to eliminate or reduce SZ

Without causing deficits

Indication

DRE with SZs that interfere daily living

The progression timeline should reach > 2 years, except in patients with life-threatening SZs or in children

Epilepsies that can be treated with surgery

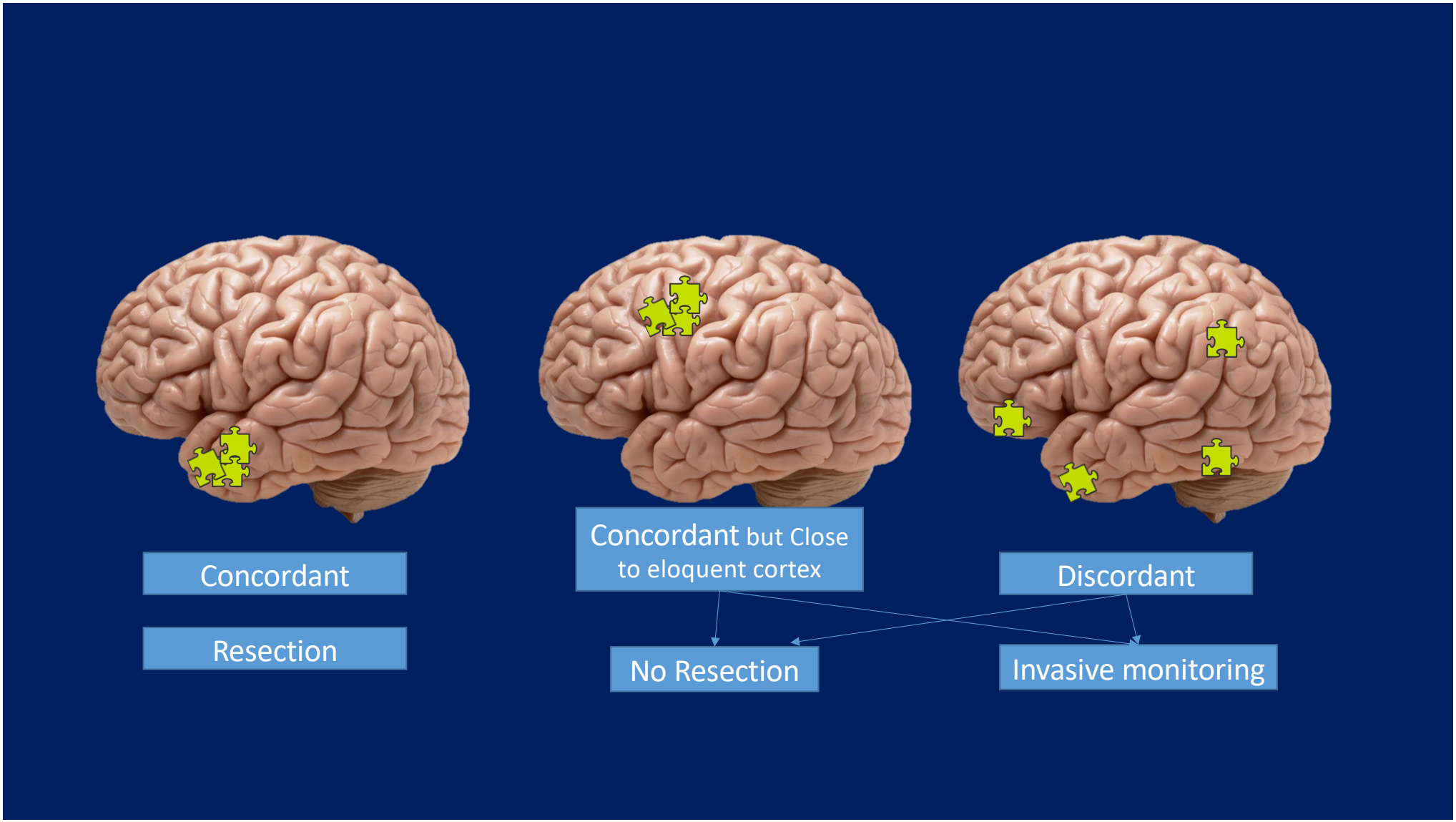
Contraindication

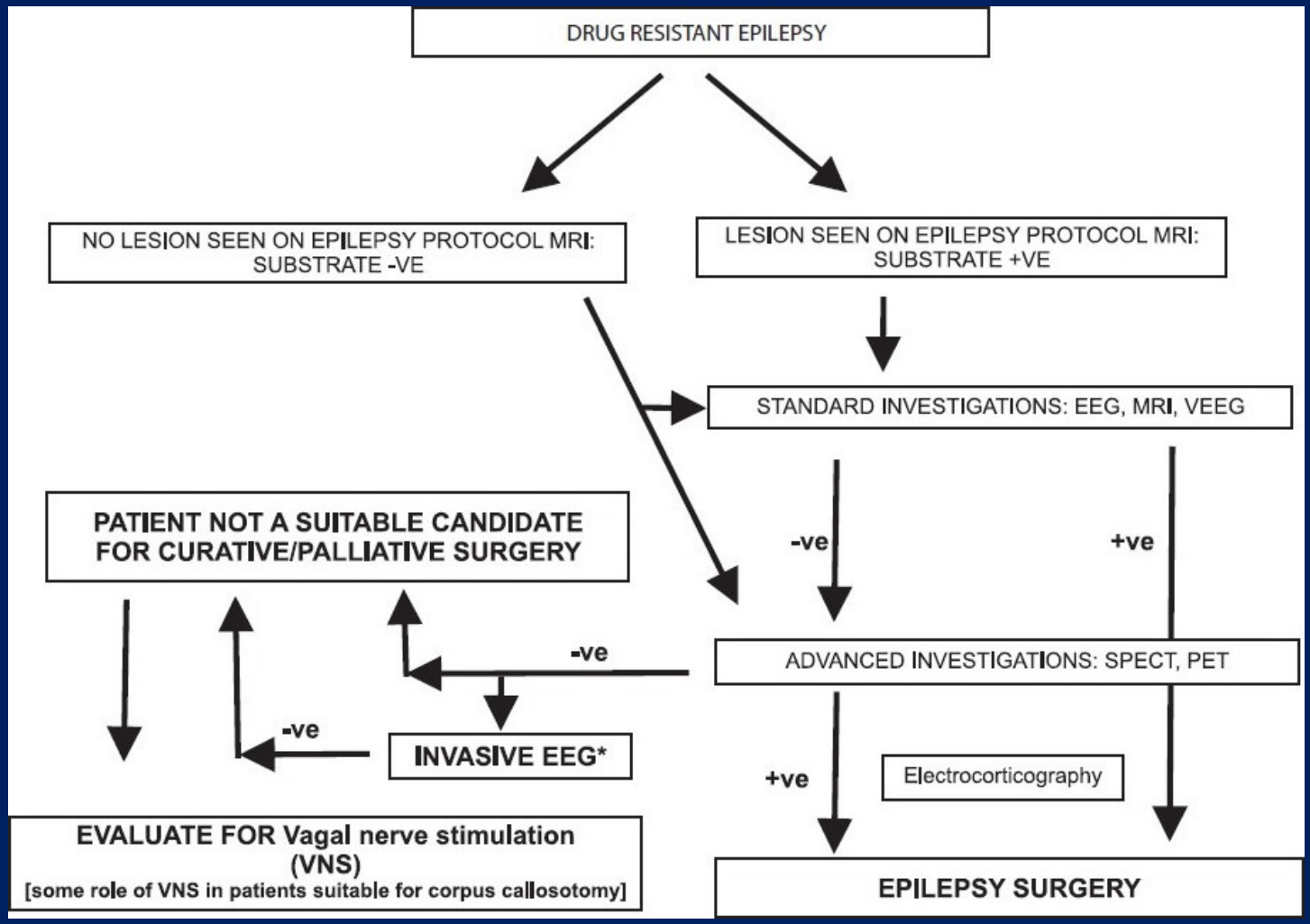
No absolute C/I

1. Age; in elderly should be carefully assessed
2. Etiology; progressive neurological disease, except Rasmussen encep
3. Concerning comorbidity that high risk for surgery
4. Concomitant psychiatric disorder: if it may compromise the result
5. IQ < 70 shows poorer prognosis; but not absolute C/I

Presurgical evaluation: Goal

- To localize the cortical area that generates seizures.
- → **“epileptogenic zone” (EZ)**
- → zone whose resection is necessary and sufficient to eliminate seizures
- So “epileptogenic zone” cannot be certainly determined until the patient seizure free after resective surgery.


Concordant
Resection
Concordant but Close to eloquent cortex
No Resection
Discordant
Invasive monitoring



Annals of Indian Academy of Neurology 2010 13(2):87-93

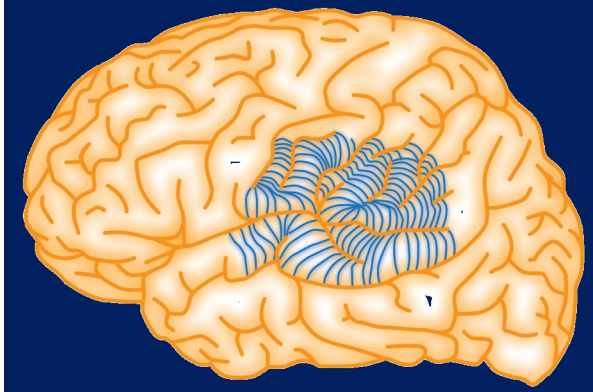
Results of epilepsy surgery

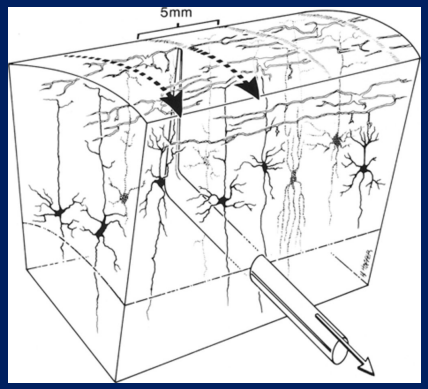
Procedure	SZ free%
Surgically treatable syndromes	
Mesial TLE -> amygdalohippocampectomy w/ or w/o ATL	70-80%
Neocortical epilepsy with single circumscribed lesion -> lesionectomy - Temporal - Extratemporal	 70-80% 60-70%
Poorer outcomes	
Neocortical epilepsy with single poorly-circumscribed lesion: - Temporal - Frontal - Parietal - Occipital	 66% 27-34% 46% 46%
Non-lesional epilepsy - Temporal - Extratemporal	 60% 35%

Neurología. 2015;30 (7):439-446

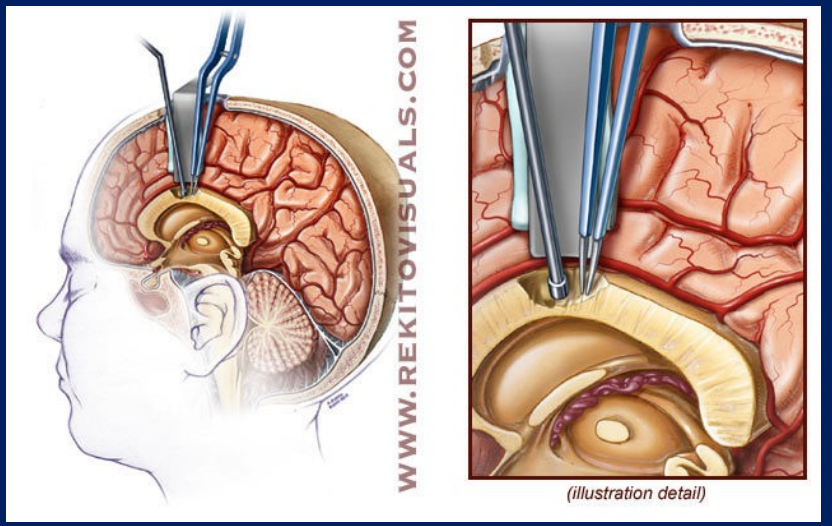
Palliative surgery

- Multiple subpial transection
  - Exclusively in eloquent area; Landua-Kleffner syndrome
  - 55% SZ free, 4% with deficit





- Corpus callosotomy
  - Partial or total
  - For atonic SZ
  - 70% shows SZ reduction



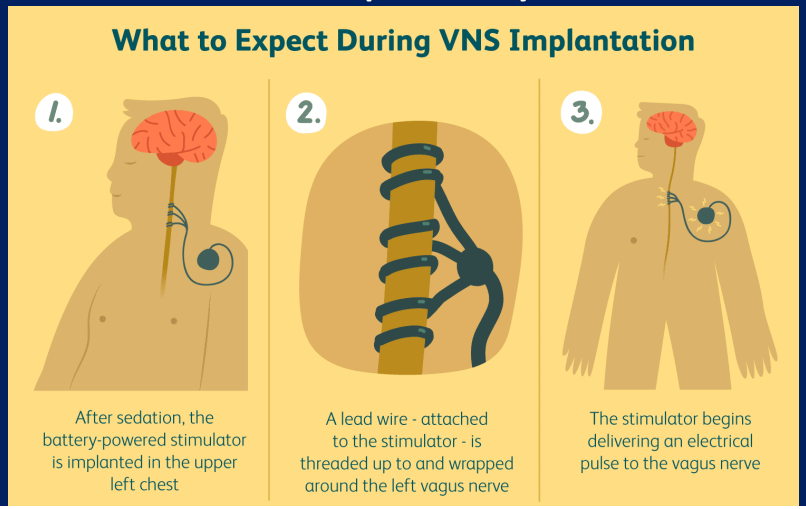
Non resection techniques

- Vagus nerve stimulation
- Deep brain stimulation
- Trigeminal nerve stimulation
- Gamma knife radiosurgery

Non-surgical candidate

Vagus nerve stimulation

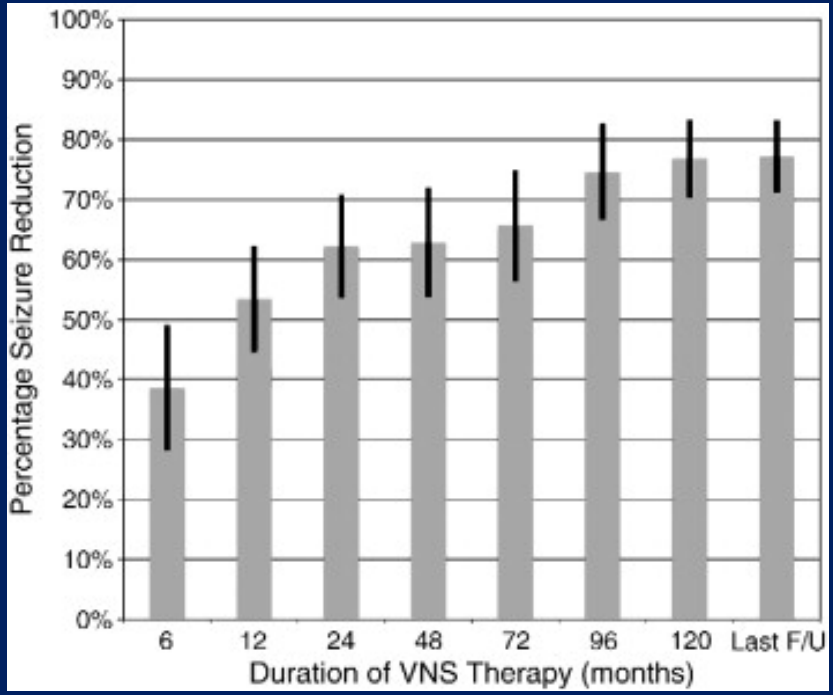
- Not surgical candidate
  - Both focal and generalized epilepsy
- Median SZ reduction 44.6%
- 50.6% of patients – SZ reduction > 50%
- 4.6% - SZ free
- SZ reduction 60% in pt < 6 years old



J Neurosurg. 2011;115:1248—55

Efficacy of vagus nerve stimulation over time: Review of 65 consecutive patients with treatment-resistant epilepsy treated with VNS >10 years

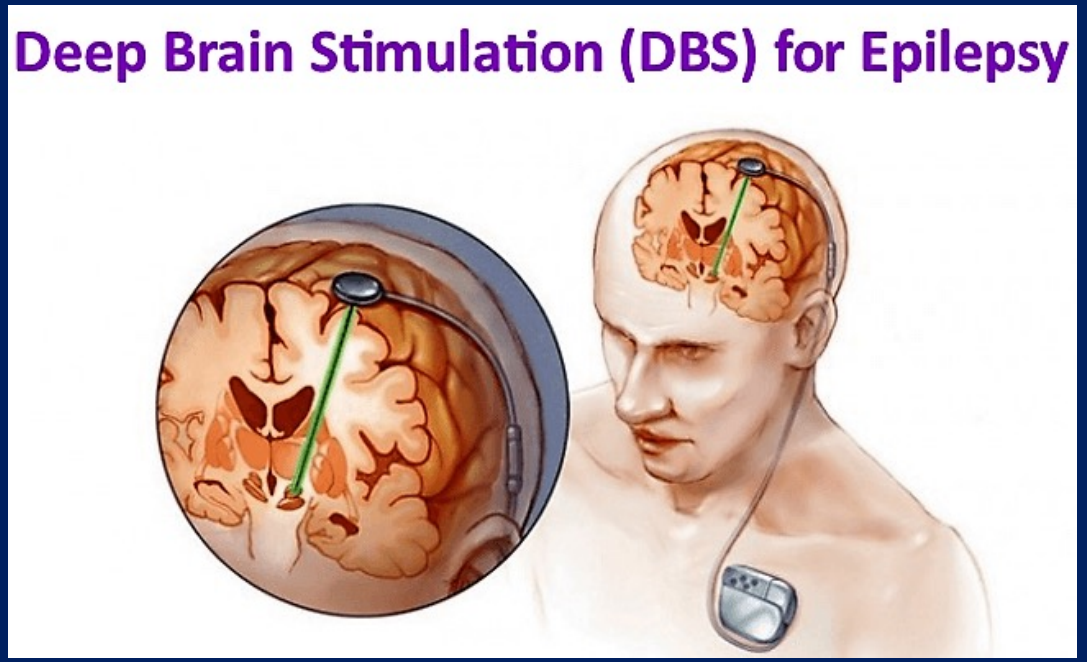
Robert E. Elliott [a,*], Amr Morsi [a], Omar Tanweer [a], Bartosz Grobelny [a], Eric Geller [b], Chad Carlson [c], Orrin Devinsky [b,c,d], Werner K. Doyle [a,b]



Epilepsy & Behavior 20 (2011) 478–483

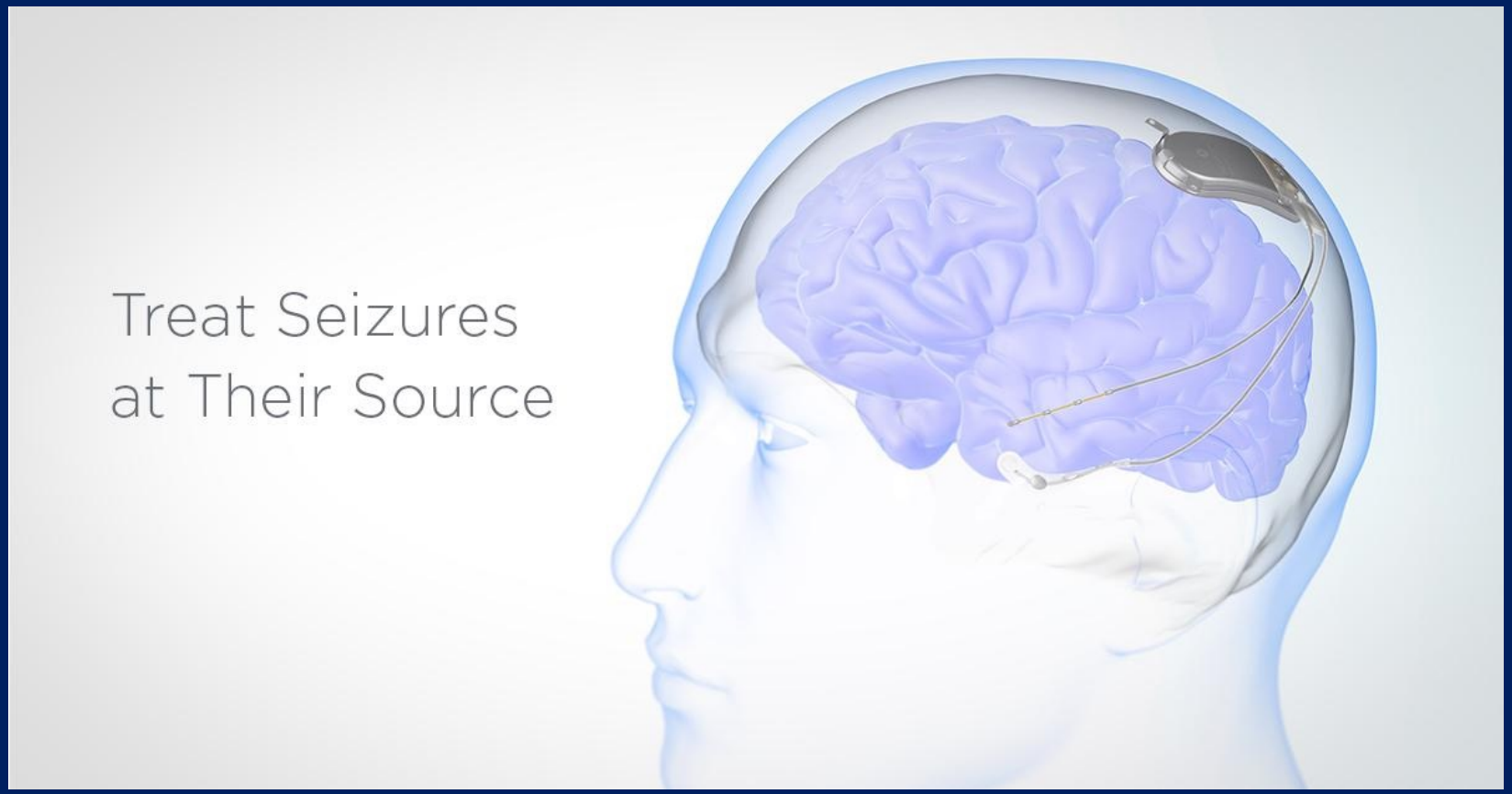
Deep brain stimulation

- Potentially regulate cortical/subcortical circuit
- Targeted at
  - anterior nuclei of thalamus
  - Caudate nucleus
  - Hypothalamus
  - Cerebellum
- In ATN;
  - 56% SZ reduction
  - 54% of pt - >50% SZ reduction

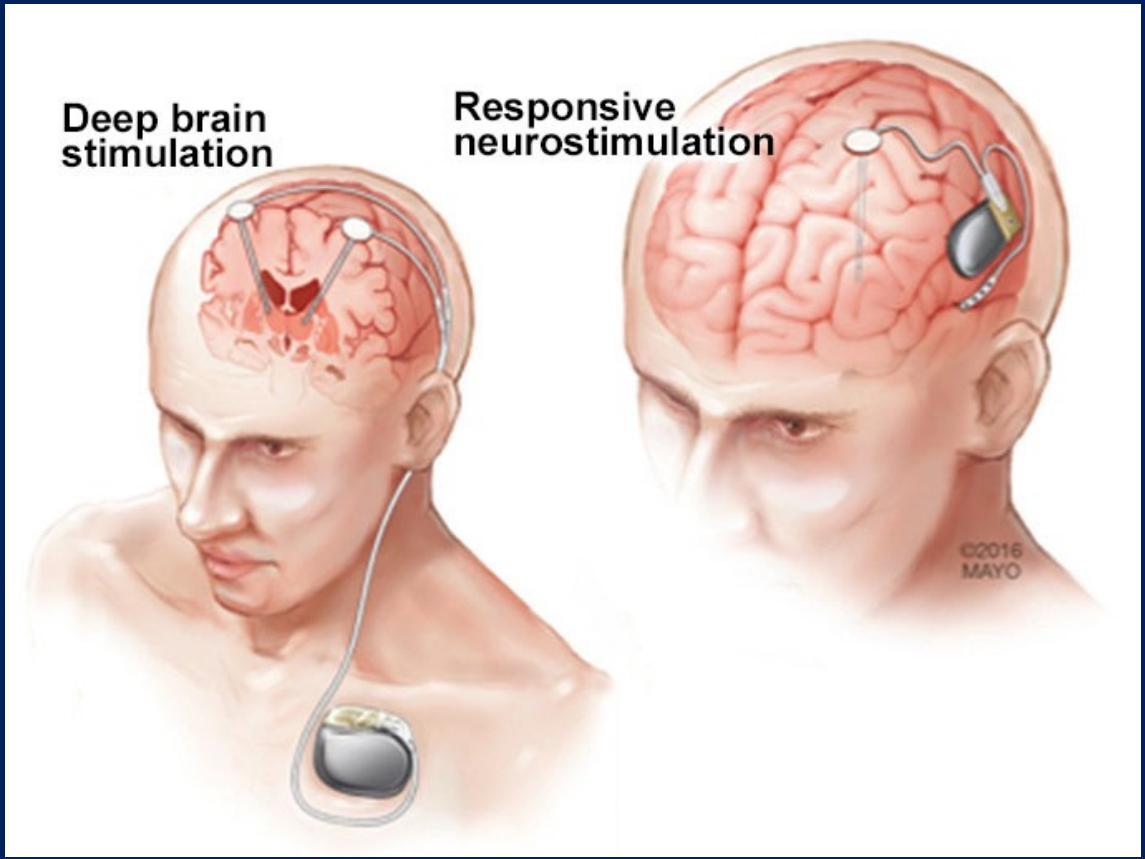


Epilepsia. 2010;51:899-908

Responsive neurostimulation



DBS vs RNS


Deep brain stimulation
Responsive neurostimulation
©2016 MAYO

Treatment Alternatives for DRE: Outline

Surgery	Non-Surgery
- Resective surgery - Palliative surgery - Non-resective technique	Diet - Ketogenic diet

Ketogenic diet

Ketogenic diet

- High fat -- Adequate protein -- Low carb
- Commonly used in epileptic children

- Force the brain to use “ketone” instead of glucose as a fuel.
- KD promotes synthesis of glutamine (precursor of GABA)

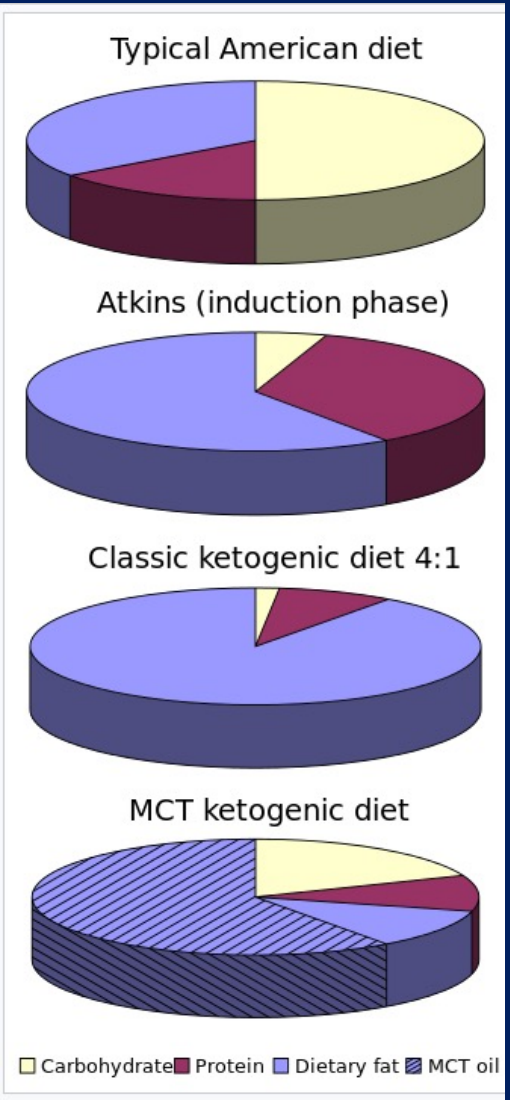
Table 1. Example of Typical Ketogenic Diet Meals Using a 1100 kcal, 4:1 Ketogenic Diet (for a Typical 4-Year-Old Child)

Breakfast
- 90 g ketogenic pudding
- 44 g cream cheese
- 13 g eggs
- 29 g heavy cream
- 10 g strawberries

Lunch
- 40 g 36% heavy cream
- 8 g medium-chain triglyceride oil (mixed into cream)
- Dark meat chicken salad
  - 20 g dark meat chicken
  - 8 g mayonnaise
- 20 g avocado

Dinner
- 35 g 36% heavy cream
- Ground beef and cheese
  - 11 g ground beef
  - 10 g cheese
  - 8 g butter
- 26 g cooked broccoli
- 11 g butter

Snack
- Ketogenic chocolate candy
  - 3 g cocoa
  - 6 g butter
  - 6 g coconut oil



Efficacy

- 50% SZ reduction; >50% of pts
- 90% SZ reduction; 1/3 of pts

- Respond in 2 wks
- Recommendation to try 3 mo

J Child Neurol. 2009;24:979-988

Table 4. Potential Beneficial Indications for Dietary Therapy (Adapted From Ref 5)

Probable Benefit (at Least 2 Publications)
Glucose transporter protein 1 (GLUT-1) deficiency
Pyruvate dehydrogenase deficiency (PDHD)
Myoclonic-astatic epilepsy (Doose syndrome)
Tuberous sclerosis complex
Rett syndrome
Severe myoclonic epilepsy of infancy (Dravet syndrome)
Infantile spasms
Selected mitochondrial disorders
Children receiving only formula (infants or enterally fed patients)
Suggestion of benefit (one case report or series)
Landau-Kleffner syndrome
Lafora body disease
Combined use with vagus nerve stimulation
Combined use with zonisamide

J Child Neurol. 2009;24:979-988

Treatment Alternatives for DRE: Take home messages

Rational polyRx	Surgery	Non-Surgery
	- Resective surgery - Palliative surgery - Non-resective technique	Diet - Ketogenic diet