TREATMENTS OF INTRACTABLE EPILEPSY

Sathida Poonmaksatit, M.D.
Department of Pediatrics
King Chulalongkorn Memorial Hospital
8Sep2019

Outlines

- Definition of epilepsy and intractable epilepsy
- Medical management in epilepsy
- Surgical management in epilepsy

Epilepsy

Operational Definition (ILAE 2014)

ANY OF THE FOLLOWING CONDITIONS:

- At least TWO unprovoked (or reflex) seizures occurring > 24h apart
- ONE unprovoked (or reflex) seizure AND a probability of further seizures similar to the general recurrent risk after 2 unprovoked seizures (60%), occurring over the next 10 years
- Diagnosis of an epilepsy syndrome

Epilepsy is considered to be resolved for individuals who had an age-dependent epile psy syndrome but are now past the applicable age or those who have remained seizu re-free for the last 10 years, with no seizure medicines for the last 5 years.

DEFINITION: Intractable Epilepsy

- Drug-resistant epilepsy (DRE), refractory epilepsy
- 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

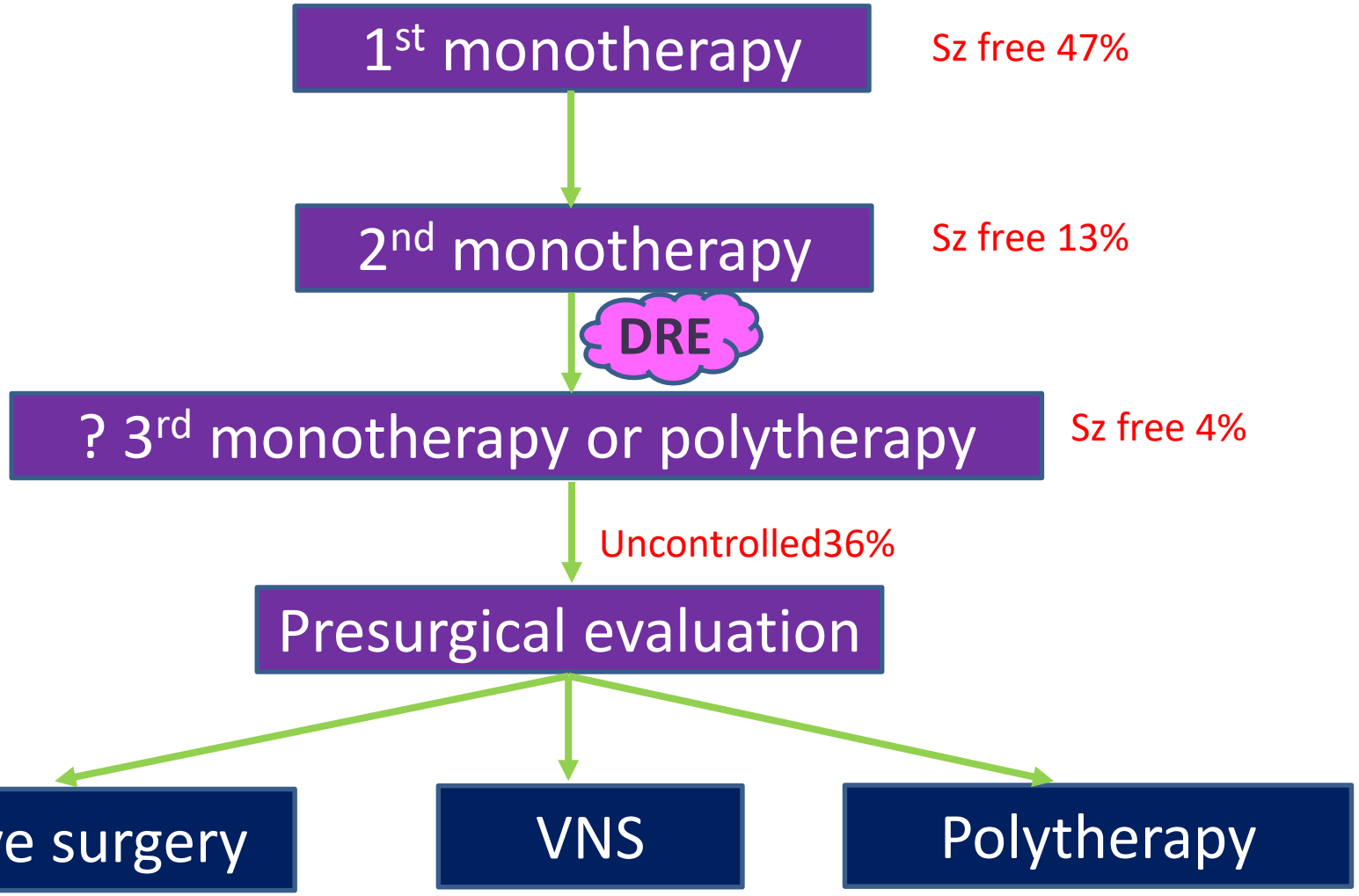
Key terms

- Appropriately chosen
- Adequate trials
- Sustained sz freedom

EPIDEMIOLOGY

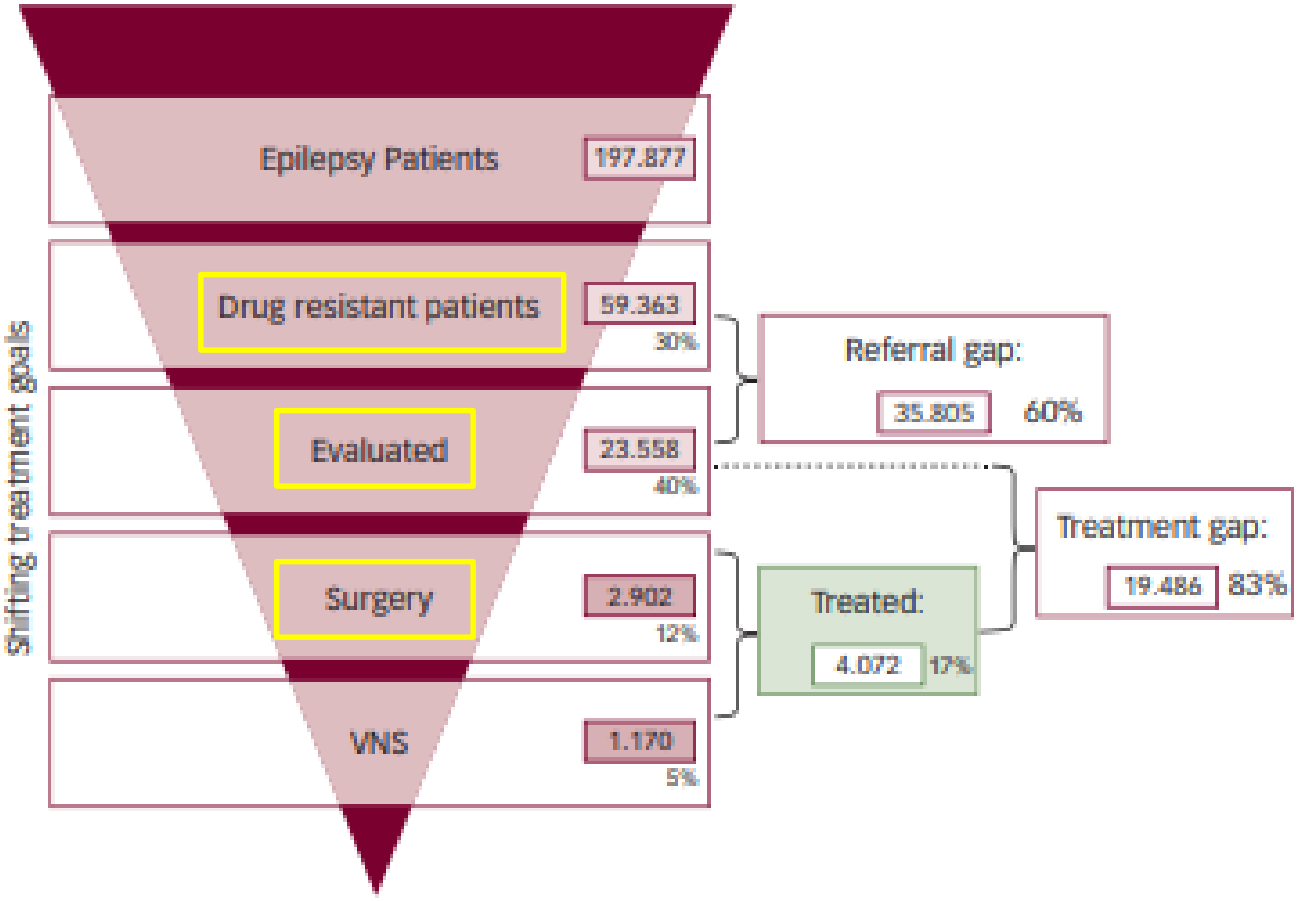
- Prevalence of epilepsy 0.5-1%
- 20-30% of epilepsy patients are refractory to treatment

Strategies for Management



Kwan P, et al. Epilepsia 2010

DRE Treatment Gap



VNS = vagus nerve stimulation.

Factors ass w/ drug resistance

- Age of onset (<1yo or >12yo)
- Focal seizures or multiple sz types
- High initial sz frequency
- MRI shows hippocampal atrophy (<10% achieve remission)
- Cortical dysplasia or dual pathology
- Neurologic deficits
- Fail first two AEDs at moderate or high doses

WiebeS, Jette N. Nat Rev Neurol 2012

Pseudo-resistance to AEDs

- Wrong diagnosis: syncope, PNES
- Wrong drugs
- Wrong dose
- Lifestyle issue: compliance, alcohol and substances

Complications of DRE

- Seizure-related injuries
- Disability and poor quality of life
- Increase mortality rate and risk of SUDEP

Treatment options for DRE

Medical

- AEDs
- Ketogenic diet
- Cannabidiol (CBD)

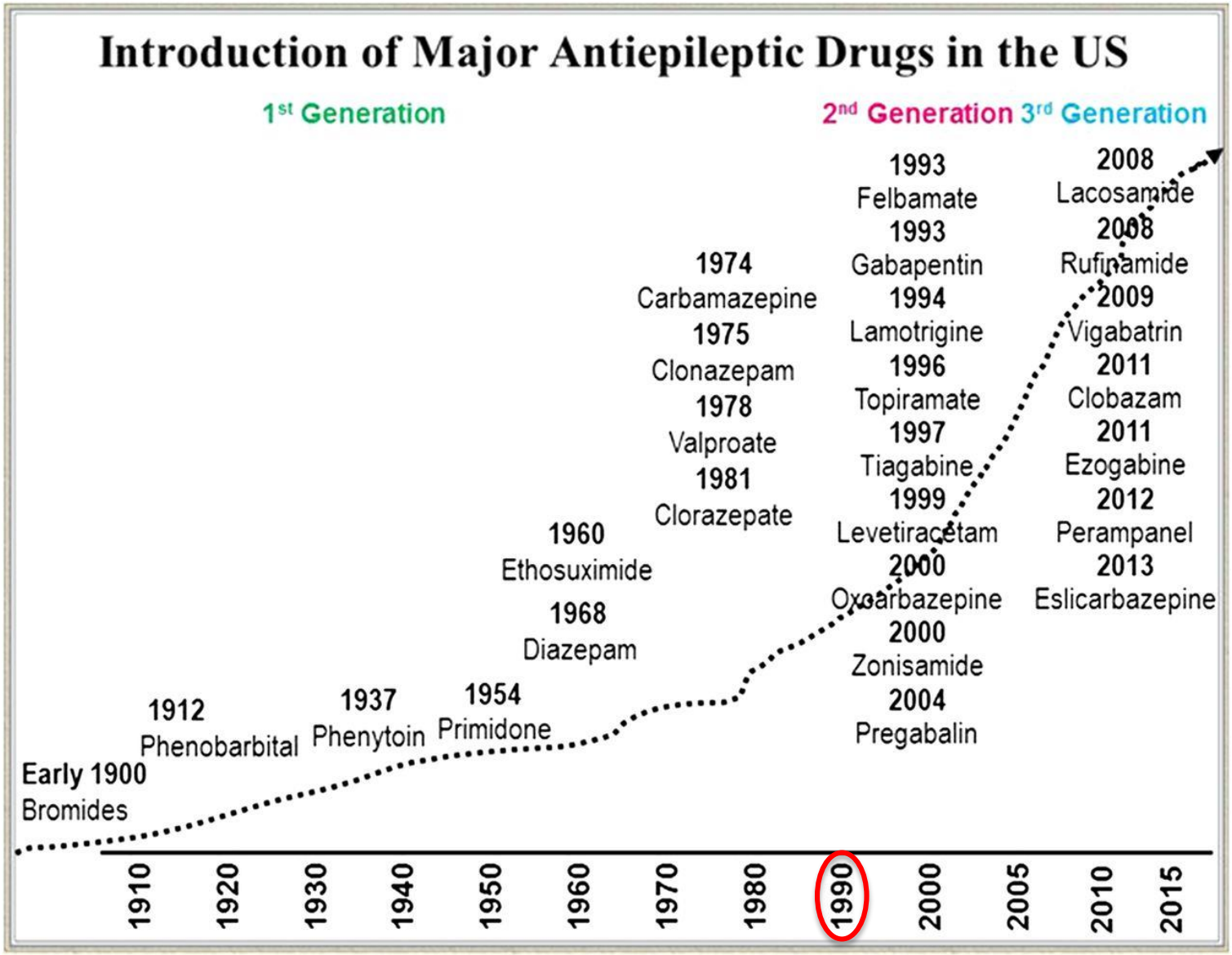
Surgical

- Resective: hemispherectomy, lobectomy
- Devices: VNS
- Palliative: Callosotomy

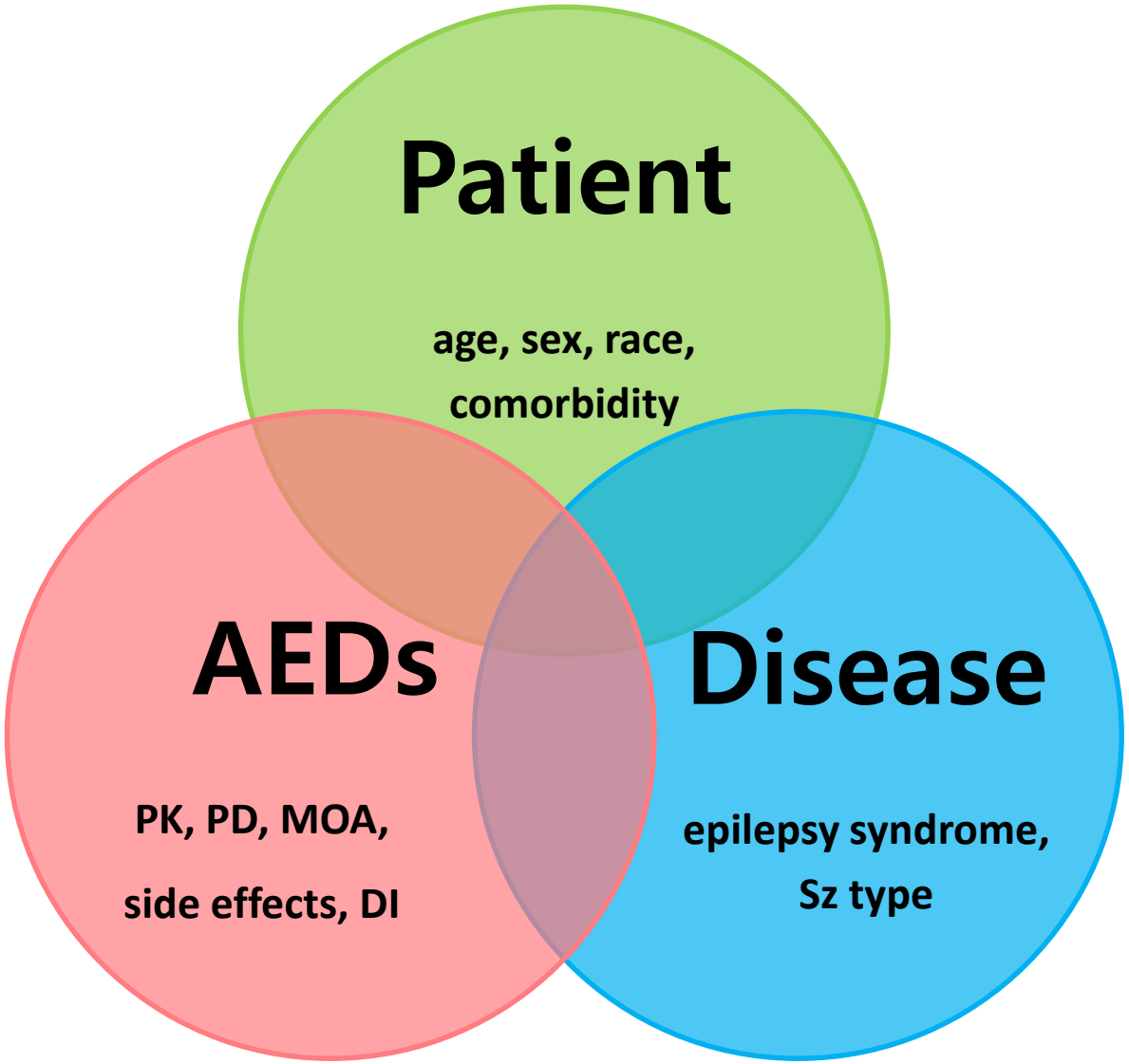
Medical management

Antiepileptic Drugs

AED development



Considerations for AED initiation



Mechanisms of action

Calcium channel blocker	
Ethosuximide	Low voltage-activated channel
Gabapentin Pregabalin	High voltage-activated channel
Carbonic anhydrase inhibition	
Acetazolamide	
GABAergic activity	
Barbiturates	Prolongs chloride channel opening
Benzodiazepines	Increases frequency of chloride channels
Tiagabine	Blocks synaptic GABA reuptake
Vigabatrin	Inhibits GABA-transaminase
Multiple targets	
Felbamate	Na channel, NMDA Rc, GABA A Rc
Rufinamide	
Sodium valproate	Na channel, NMDA Rc, GABA turnover
Topiramate	Na channel, AMPA/kainite Rc, GABA A Rc
Zonisamide	

Snaptic vesicle protin 2A modulator	
Brivaracetam	
Levetiracetam	
	Sodium channel blocker
Carbamazepine Eslicarbazepine Lamotrigine Oxcarbazepine Phenytoin	Fast-inactivated state
Lacosamide	Slow-inactivated state
AMPA antagonist	
Perampanel	

Alick S, Doyle A. Practical Neurol 2018

Pharmacokinetics of AEDs

AED	F (%)	V_d (L/kg)	Protein binding (%)	$T_{1/2}$ (h)	Renal (%)	Routes of elimination hepatic isozymes involved	Active metabolite
Carbamazepine	70–80	0.8–2	75	12–17	<1	CYP3A4 (major), CYP1A2, 2C8	Yes
Clobazam	87	0.9–1.4	85–93	10–30	nk	CYP2C19, 3A4	Yes
Clonazepam	90	3.2	85	22–40	<1	CYP3A4	Yes
Eslicarbazepine[a]	—	nk	30	20–24	66	UGT1A4, UGT1A9, UGT2B4, UGT2B7, UGT2B17	No
Ethosuximide	>90	0.6–0.7	0	25–60	20	CYP3A4 (major), 2E1	No
Ezogabine	60	2–3	80	6–10	20–30	UGT, NAT2	Yes
Felbamate	>90	0.7–1.0	22–25	20–23	50	UGT, CYP3A4 (20%), 2E1	No
Gabapentin	30–60	0.85	0	5–9	>90	None	No
Lacosamide	100	0.6	<15	13	40	Not identified	No
Lamotrigine	98	0.9–1.3	55	12–60	<1	UGT1A4	No
Levetiracetam	100	0.5–0.7	<10	6–8	66	Amidase	No
Oxcarbazepine	>90	nk	40–60	1–2.5	<1	Cytosolic arylketone reductase	Yes
MHD	—	0.7–0.8	33–40	8–11	20	UGT	No
Perampanel	100	1.1	95	60–130	30	CYP3A4/5, other CYPS	No
Phenobarbital	80–90	0.5–1.0	20–60	36–118	20	Glucosides, CYP2C9, 2C19, 2E1	No
Phenytoin	70–100	0.5–1.0	88–93	7–42	2	CYP2C9 (major), CYP2C19	No
Pregabalin	>90	0.5	0	5–6.5	>95	None	No
Primidone	>90	0.4–1.0	20–30	3–7	0	CYPs, isozyme not identified	Yes
Rufinamide	85	0.7	34	6–10	<2	Non–CYP-dependent hydrolysis	No
Stiripentol	25	nk	99	13	<1	UGT and CYPs, isozymes not identified	No
Tiagabine	90	1.0	96	3–8	<2	CYP3A4 (22%),	No
Topiramate	80	0.6–0.8	9–17	21	30	Not identified	No
Valproate	90	0.14–0.23	5–15	6–17	<5	β-Oxidation, UGT1A6, 1A9, 2B7, CYP2C9, 2C19	Yes
Vigabatrin	50–60	0.8	0	5–8	>90	None	No
Zonisamide	>90	0.8–1.6	40–60	27–70	35	NAT2, CYP3A4 (major), CYP2C19	No

[a] After administration of eslicarbazepine acetate.

CYP, Cytochrome P450; UGT, UDP-glucuronosyltransferase; NAT, N-acetyltransferase; nk,

AEDs for epilepsy syndromes

Table 4. Summary of studies and level of evidence for each seizure type and epilepsy syndrome

Seizure type or epilepsy syndrome	Class I studies	Class II studies	Class III studies	Level of efficacy and effectiveness evidence (in alphabetical order)
Children with partial-onset seizures	1	0	19	Level A: OXC Level B: None Level C: CBZ, PB, PHT, TPM, VPA, VGB Level D: CLB, CZP, LTG, ZNS
Children with generalized-onset tonic–clonic seizures	0	0	14	Level A: None Level B: None Level C: CBZ, PB, PHT, TPM, VPA Level D: OXC
Children with absence seizures	1	0	7	Level A: ESM, VPA Level B: None Level C: LTG Level D: None
Benign epilepsy with centrotemporal spikes (BECTS)	0	0	3	Level A: None Level B: None Level C: CBZ, VPA Level D: GBP, LEV, OXC, STM
Juvenile myoclonic epilepsy (JME)	0	0	1	Level A: None Level B: None Level C: None Level D: TPM, VPA

Glauser Y, et al. Epilepsia 2013

Dosage of AEDs

First-Generation Antiepileptic Drugs, Recommended Dosage, and Laboratory Monitoring

Drug	Starting Dose/Day	Maintenance Dose/ Day	Dosing Schedule	Half -life (hours)	Laboratory/Clinical Monitoring	Formulations
PHB	3 mg/kg	3-6 mg/kg	QD-BID	24-140	Sedation, CBC, LFT, serum levels	Suspension, pills, IV
PHT	4 mg/kg	4-8 mg/kg	QD-TID	7-42	CBC, LFT, serum levels	Suspension, capsule, IV
VPA	15 mg/kg	15-45 mg/kg	TID-QID	5-15	CBC, LFT	Sprinkle caps, tablets, suspension, IV
CBZ	10 mg/kg	10-35 mg/kg	TID	25-65	CBC, LFT	Suspension, capsule
ETX	15 mg/kg	15-40 mg/kg	QD-BID	30-40	CBC,LFT	Liquid, capsule

Second-Generation Antiepileptic Drugs, Recommended Dosage, and Laboratory Monitoring

Drug	Starting Dose/Day	Maintenance Dose/ Day	Dosing Schedule	Half-life (hours)	Laboratory/Clinical Monitoring	Formulations
FBM	15 mg/kg	15-45 mg/kg	TID	20-30	CBC, LFT	Suspension, pills
GBP	10 mg/kg	25-50 mg/kg	TID	4-7	Weight	Suspension, caps, IV
LTG	0.15-0.5 mg/kg	5-15 mg/kg (very slow titration)	BID	6-11	Rash, CBC, LFT	Pills (chewable and dispersible)
LEV	10 mg/kg	40-100 mg/kg	BID	6-8	Behavior	Pills, liquid, IV
OXC	8-10 mg/kg	30-46 mg/kg	BID	7-9	BMP, hyponatremia	Pills, suspension
TPM	1-3 mg/kg	5-9 mg/kg	BID	8-12	Weight, renal stones, cog-nition, ocular pressure	Pills, sprinkle capsules
ZNS	2-4 mg/kg	4-12 mg/kg	BID	63	None	Capsules

Advantages vs Disadvantages

Drug	Main issues	"Added benefits"
Levetiracetam	Irritability	No drug-drug interactions, minimal cognitive side effects, ? anti-epileptogenic
Lamotrigine	Rash, slow titration	Minimal teratogenic potential
Oxcarbazepine/ carbamazepine	Hyponatremia, osteoporosis, drug-drug interactions	Rapid titration, mood stabilizer
Topiramate	Weight loss, nephrolithiasis, cognitive slowing, slow titration	Weight loss, migraine prophylaxis, neuropathic pain
Valproic acid	Weight gain, thrombocytopenia, hepatotoxicity, pancreatitis, polycystic ovarian syndrome, teratogenicity	Migraine prophylaxis, mood stabilizer

AED polytherapy

- consider efficacy/benefit vs side effects
- other issues: cost, long-term side effects

Rational AED polytherapy1

- Lamotrigine and valproate

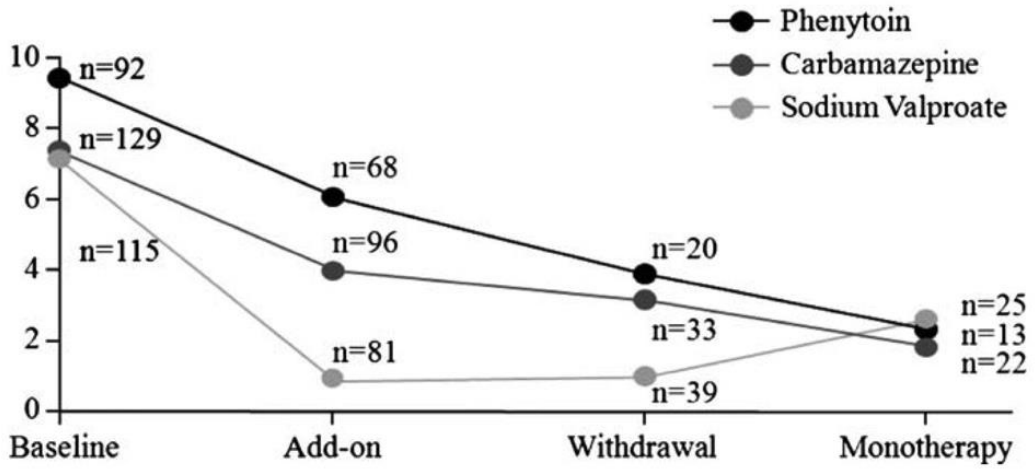


Fig. 2. Median monthly seizure counts for patients receiving add-on lamotrigine to baseline treatment with phenytoin, carbamazepine or sodium valproate. The study consisted of a 12-week "baseline phase" of the original baseline monotherapy, followed by the "add on phase" when lamotrigine was introduced with baseline medication unchanged. Patients showing at least 50% reduction in seizure frequency compared with baseline entered the 12-week "withdrawal phase" when the baseline antiepileptic drug was tapered off. Patients who successfully completed the withdrawal phase entered the lamotrigine "monotherapy phase" of 12 weeks duration.(reproduced from Ref. [71], with permission).

Brodie and Yuen. Epilepsy Res 1997

Rational AED polytherapy2

Drug combination	Level of evidence
Valproate and lamotrigine[25-29]	+++
Valproate and ethosuximide[30]	++
Lamotrigine and topiramate[31]	+
Lacosamide and levetiracetam[32,33]	++
Lamotrigine and levetiracetam[35,36]	++
Valproate and levetiracetam[34]	+
Valproate, clobazam and stiripentol[37]	+++
Valproate, lamotrigine and benzodiazepine[38]	++

Combinations containing enzyme-inducing drugs were excluded.
+++, from controlled trials; ++, from case series or observational studies; +, case reports.

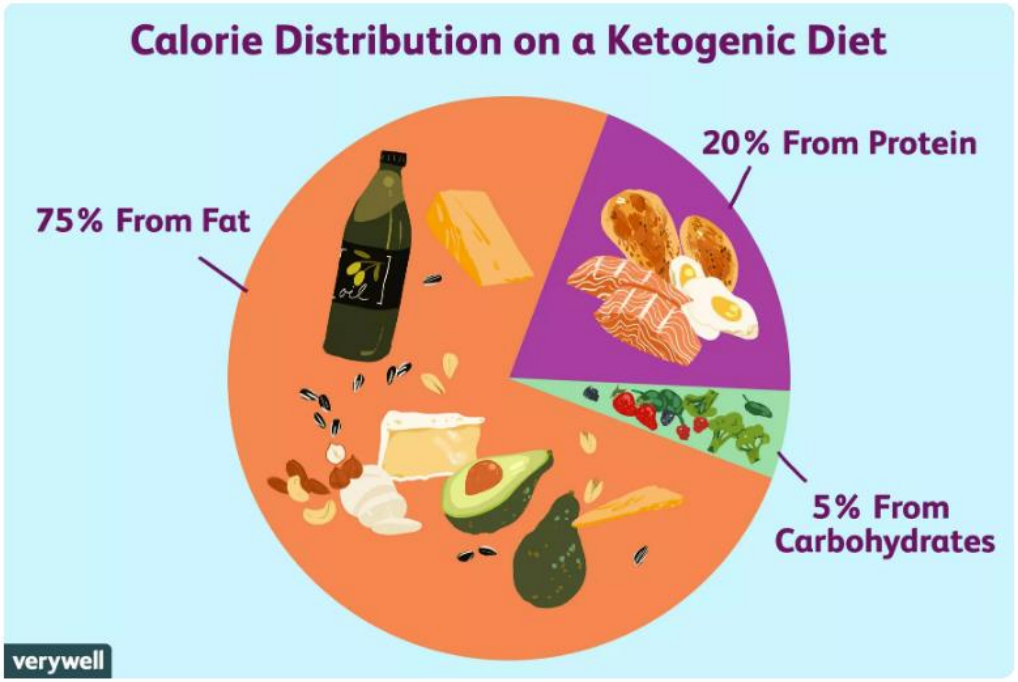
Park, et al. J Epilepsy Res 2019

Medical management

Ketogenic diet (KD)

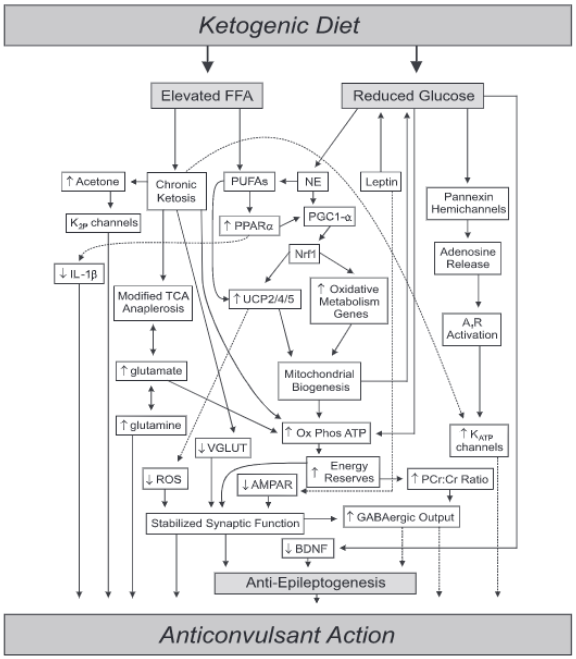
Ketogenic diet

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



Mechanism of action: hypotheses

- Direct anticonvulsant effect
- NTs and ion channel: enh GABA production
- Mitochondrial change: anti-oxidative, anti-inflammation
- Glycolytic restriction/increase in non-glucose source



JM Rho. Neuroscience Letter 2017

Indications for the KD

- Failure to control seizures after adding a second medication.
- Medically refractory epilepsy.
- First-line treatment for:
  - GLUT1 deficiency.
  - PDH deficiency.
- Metabolic disorders:
  - Phosphofructokinase deficiency.
  - Glycogen storage disease type V.
  - Mitochondrial respiratory chain complex disorders.
- Epileptic syndromes:
  - Myoclonic astatic epilepsy.
  - Seizures caused by tuberous sclerosis complex.
  - West syndrome refractory to vigabatrin or adrenocorticotropic hormone (ACTH).
  - Dravet syndrome.
- Symptomatic epilepsies:
  - Lafora body disease.
  - Seizures caused by Rett syndrome.
  - Landau-Kleffner syndrome.
  - Sub acute sclerosing panencephalitis.
  - Febrile infection-related epilepsy syndrome (FIRES).
  - Refractory status epilepticus.

Contraindications

- **Absolute:**
  - Carnitine deficiency
  - Carnitine palmitoyltranferase I or II deficiency
  - Carnitine translocase deficiency
  - β-oxidation defects
    - MCAD, LCAD, SCAD
    - Long-chain, medium-chain 3-hydroxyacyl-CoA deficiency
  - Pyruvate carboxylase deficiency
  - Porphyria
- **Relative:**
  - Inability to maintain adequate nutrition
  - Surgical candidates
  - noncompliance

Ketogenic diet

- Classical KD
  - Long-chain triglyceride
  - Ratio of fat (gram) to protein+carbohydrate (gram)
  - Typically used 4:1 or 3:1
- MCT KD
  - MCT oil based
  - Similar efficacy
  - Greater carb and protein allowance
  - Yield more ketone
  - But more expensive

Table 3. Comparison of the 4 Major Ketogenic Diets in Clinical Use (1000 kcal/d Provided)

Diet	Fat (g)	Protein (g)	Carbohydrate (g)
Classic long-chain triglyceride			
4:1	100	17	8
3:1	96	18	14
2:1	92	20	26
1:1	77	37	40
Medium-chain triglyceride oil diet	78	25	50
Low-glycemic-index treatment	67[a]	40-60[a]	40-60
Modified Atkins diet	72[a]	68-78[a]	10-20

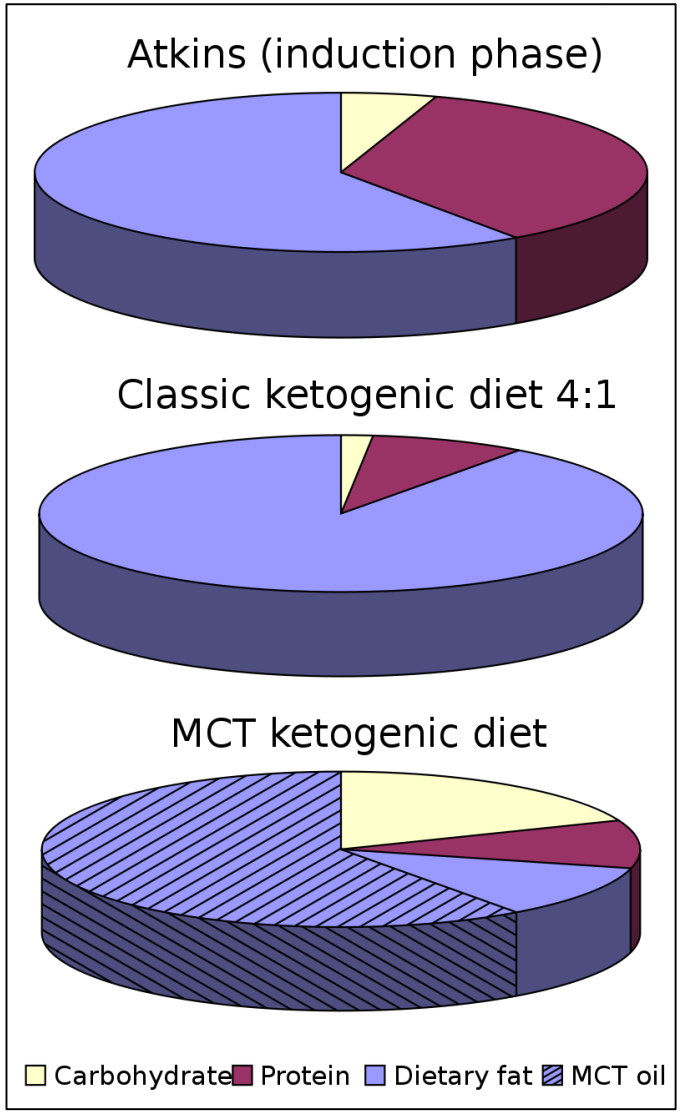
[a] Values are approximate.

Ketogenic diet

Table 3. Comparison of the 4 Major Ketogenic Diets in Clinical Use (1000 kcal/d Provided)

Diet	Fat (g)	Protein (g)	Carbohydrate (g)
Classic long-chain triglyceride			
4:1	100	17	8
3:1	96	18	14
2:1	92	20	26
1:1	77	37	40
Medium-chain triglyceride oil diet	78	25	50
Low-glycemic-index treatment	67[a]	40-60[a]	40-60
Modified Atkins diet	72[a]	68-78[a]	10-20

[a] Values are approximate.



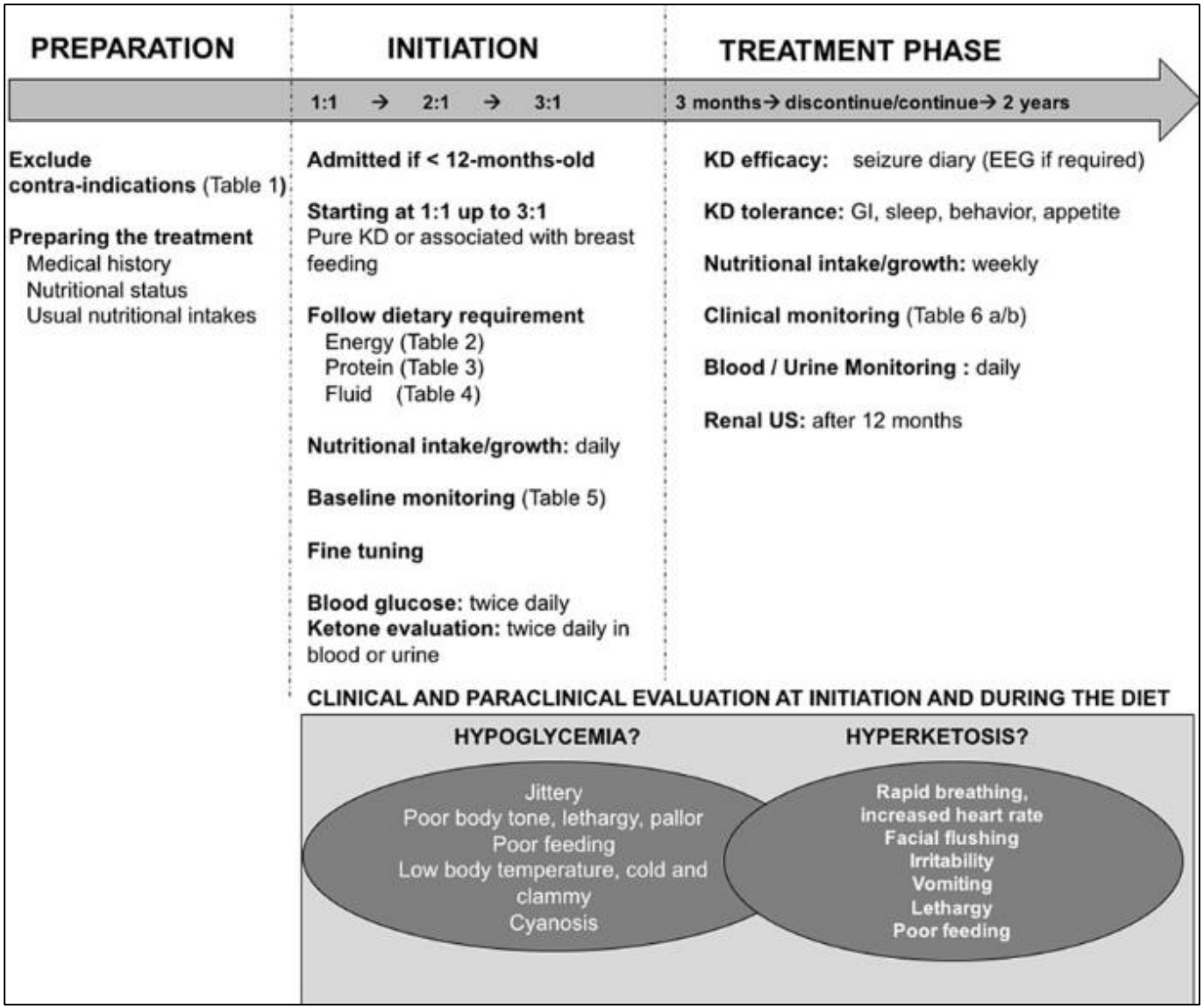
Ratio of caloric contributions

Side effects of KD

Side effect	Early/ late onset	Reported incidence (%)	References
Dehydration	Early	0.3–46.5	Kang *et al*[22]; Keene[23]
Gastrointestinal (vomiting/nausea, diarrhoea, abdominal pain, constipation)	Early and late	1.9–38.7	Kang *et al*[22]; Keene[23]
Increased infections	Early and late	0.8–20.9	Kang *et al*[22]; Keene[23]
Raised serum lipids	Early and late	2.6–27.1	Kang *et al*[22]; Keene[23]
Raised serum uric acid	Early and late	1.8–26.4	Kang *et al*[22]; Keene[23]
Hypoglycaemia	Early and late	0.8–7.0	Kang *et al*[22]; Keene[23]
Pancreatitis	Early and late	0.1–0.8	Kang *et al*[22]; Keene[23]
Osteopenia	Late	14.7	Kang *et al*[22]
Renal stones	Late	1.3–3.1	Kang *et al*[22]; Keene[23]
Acidosis	Early	0.8–1.9	Keene[23]
Gallstones	Not stated	0.4	Keene[23]
Elevated liver enzymes	Not stated	0.2	Keene[23]
Protein loss enteropathy	Not stated	0.2	Keene[23]
Lipoid aspiration pneumonia	Early and late	0.3–4.7	Kang *et al*[22]; Keene[23]
Cardiomyopathy	Late	0.8	Kang *et al*[22]
Hypoproteinaemia	Early and late	3.9–5.5	Kang *et al*[22]
Hypomagnesaemia	Early and late	4.7–10.9	Kang *et al*[22]
Hepatitis	Early and late	2.3–5.4	Kang *et al*[22]

Taken from Keene[23] (systematic review of 1066 cases) and Kang *et al*[22] (prospective study, 129 cases).

Overview of treatment with KD



Louw E, et al. Eur J Ped Neurol 2016

Diet discontinuation

- Use at lease 3.5 month for determining of efficacy
- If response, continue for at lease 2 years

Efficacy of KD

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

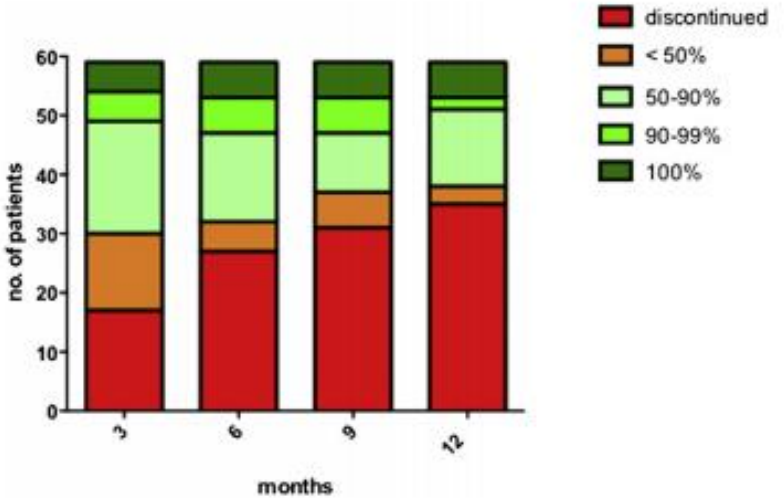


Fig. 1 – Seizure reduction distribution at 3,6,9 and 12 months after diet initiation.

Vehmeijer F OL, et al. Eur J Ped Neurol 2015

Surgical management

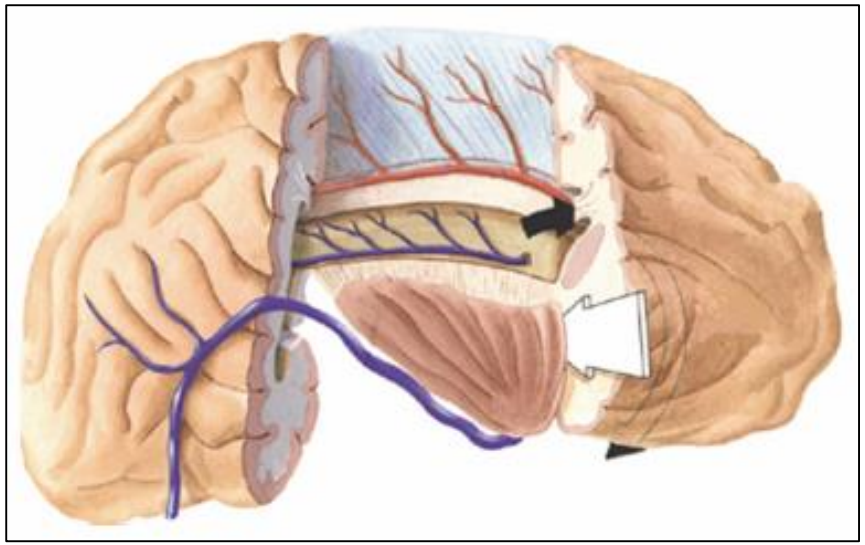
Surgical candidates

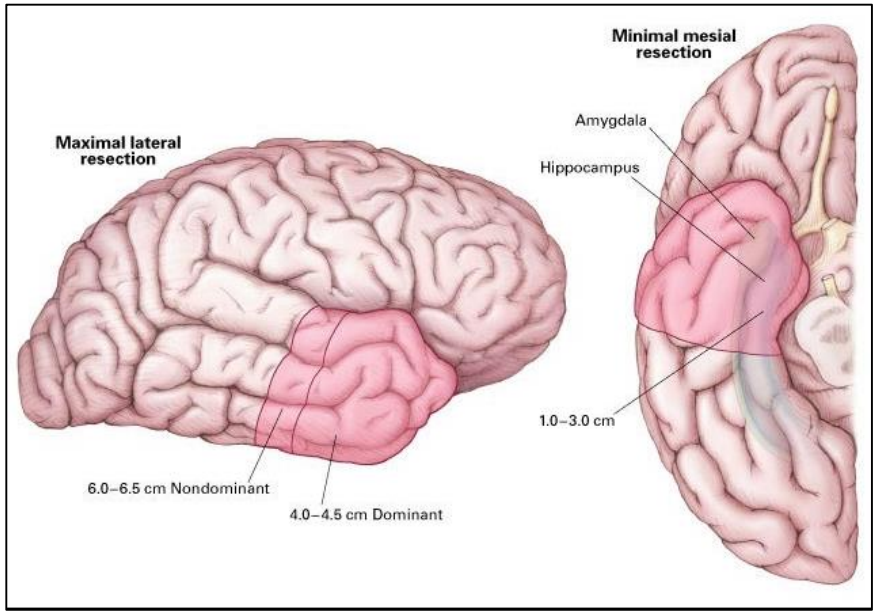
Most common criteria

- Sz frequency >1 per mo
- Failure of >2 AEDs
- Lesional epilepsy

Surgical procedures for DRE

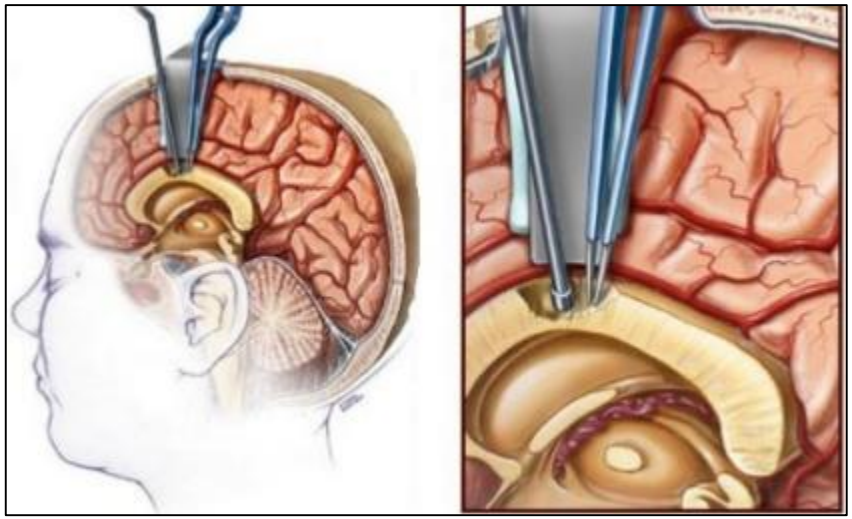
- Resective surgery
  - Hemispherectomy
  - Lobectomy
  - Lesionectomy

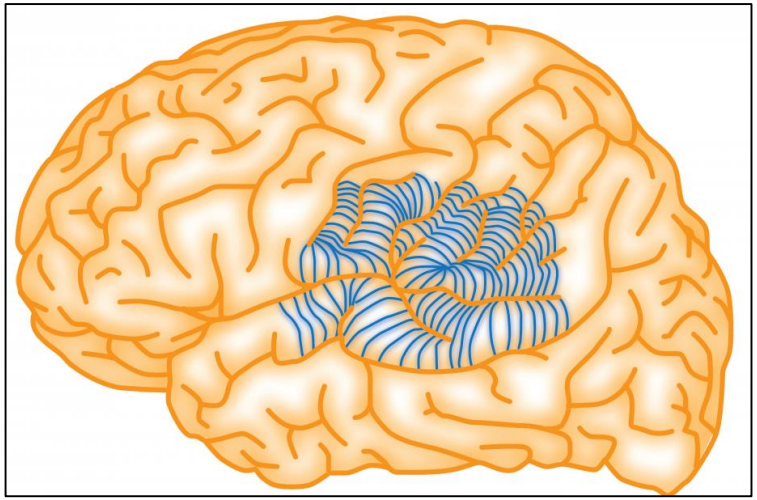




Surgical procedures for DRE

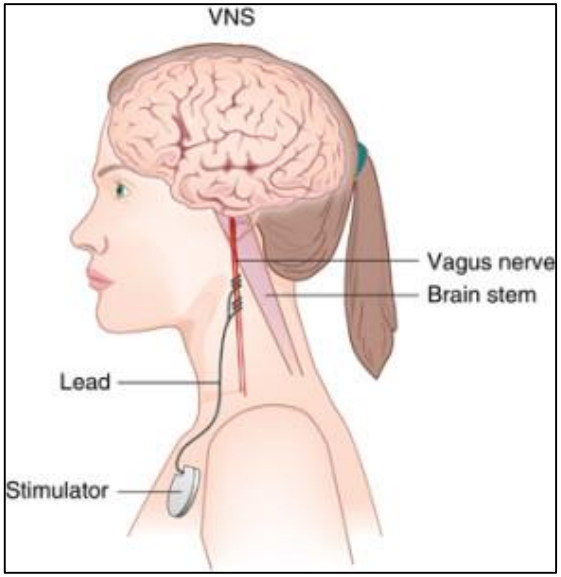
- Nonresective techniques
  - laser interstitial thermal therapy
  - gamma knife radiosurgery
- Functional/palliative
  - Callosotomy
  - Multiple subpial transections

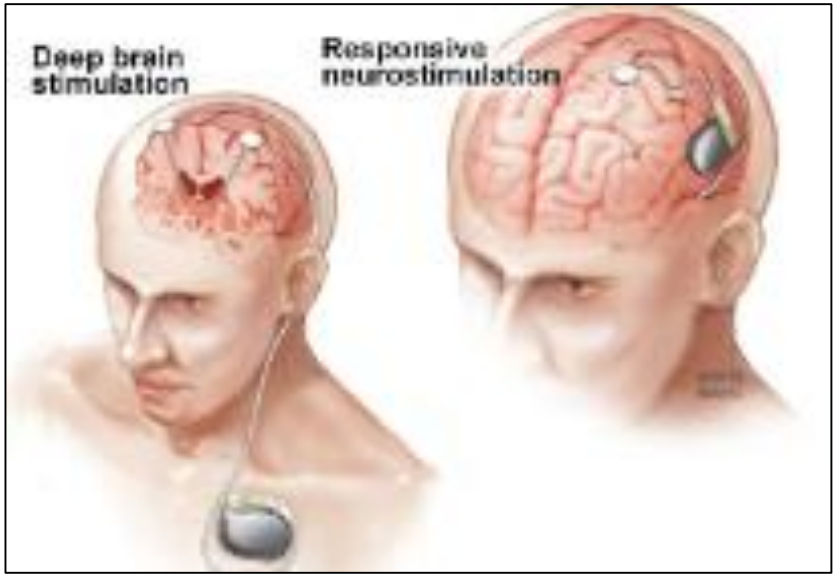




Surgical procedures for DRE

- Devices
  - VNS: FDA approved for epilepsy in 1997
  - RNS: FDA approved for partial onset epilepsy in 2013
  - DBS: for epilepsy in 2018





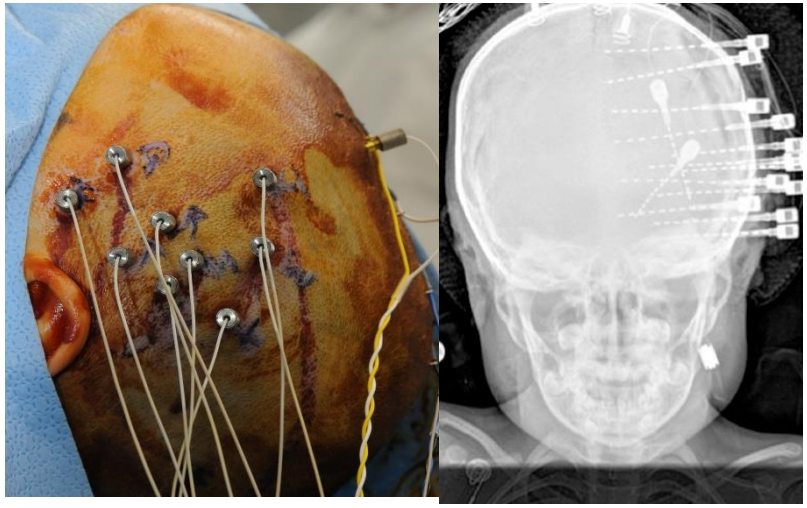
Rosa MA, Lisanby SH. 2012
Edward CA, et al. Mayo Clin Proc 2017

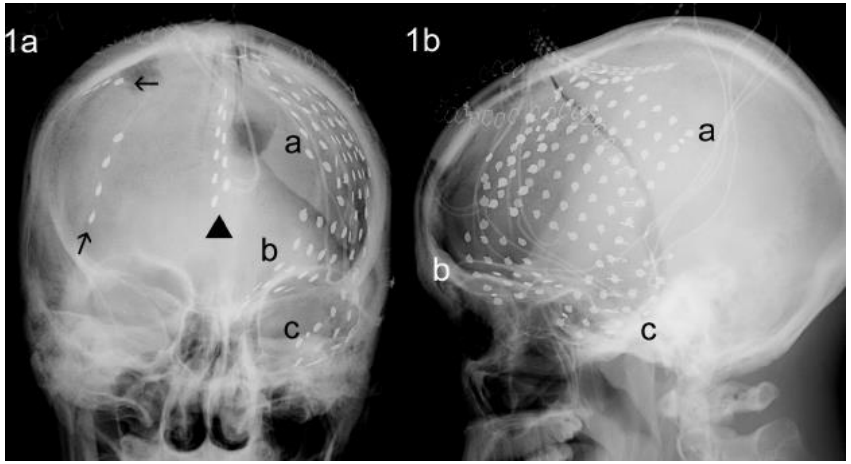
Presurgical Evaluations for DRE1

- Non-invasive evaluations
  - Video EEG monitoring
  - MRI
  - PET (Positron Emission Tomography)
  - Ictal SPECT (Single Proton Emission Computed Tomography)
  - Functional assessment: neuropsych, fMRI

Presurgical Evaluations for DRE2

- Invasive evaluations
  - Intracranial EEG monitoring
    - Subdural grid and depth electrode
    - Stereotactic EEG
  - Intra-operative Electrocorticography (ECoG)





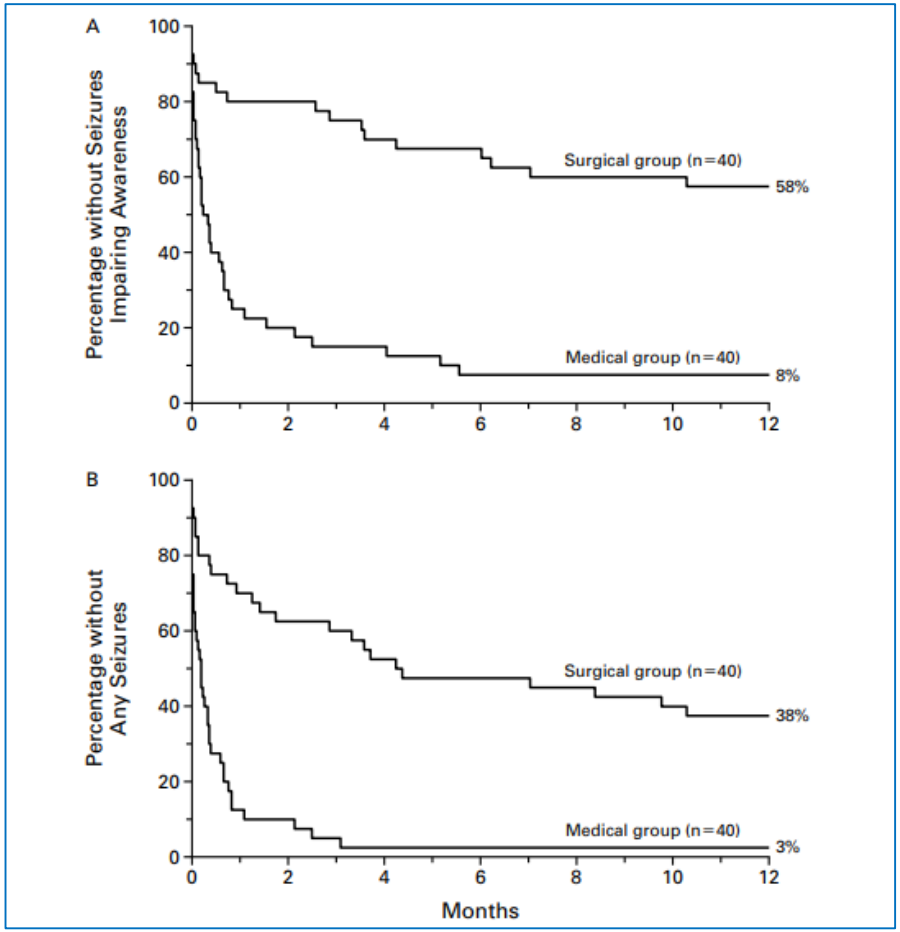
The New England Journal of Medicine

VOLUME 345 AUGUST 2, 2001 NUMBER 5

A RANDOMIZED, CONTROLLED TRIAL OF SURGERY FOR TEMPORAL-LOBE EPILEPSY

SAMUEL WIEBE, M.D., WARREN T. BLUME, M.D., JOHN P. GIRVIN, M.D., PH.D., AND MICHAEL ELIASZIW, PH.D., FOR THE EFFECTIVENESS AND EFFICIENCY OF SURGERY FOR TEMPORAL LOBE EPILEPSY STUDY GROUP*

- RCT, 80 pts with TLE
- Follow up 1 year
- Free of any sz:
  - 38% in sx gr
  - 3% in med gr
- No sz with impaired awareness
  - 58% in sx gr
  - 8% in med gr



Seizure outcome

in resective epilepsy surgery

Epilepsy Etiology/ Cause	Specific Pathology	Engel Class I Outcome[b]	Predictors of Favorable Outcome
Mesial temporal lobe epilepsy	Mesial temporal sclerosis and other causes	58–73%	Febrile seizures, mesial temporal sclerosis, abnormal MRI, tumor, EEG/MRI concordance
Tumor	Glioneuronal tumor	72–80%	Early intervention, gross total resection, lack of generalized seizures
	Low-grade glioma	67%	Gross total resection, early intervention
Malformation of cortical development	Focal cortical dysplasia	58%	Gross total resection, lack of generalized seizures, temporal location, abnormal MRI, type II classification
	Tuberous sclerosis	56–57%	Lack of intellectual disability, lack of generalized seizures, localized ictal EEG, EEG/MRI concordance
	Severe hemispheric epilepsy (hemispherectomy)	66–85%	Early intervention, young age, Sturge-Weber syndrome, lack of hemimegalencephaly, unilateral PET abnormality
Vascular malformation	Cavernous angioma	75%	Gross total resection, early intervention, small lesion, single lesion, lack of generalized seizures
	Arteriovenous malformation	70–91%	Early intervention, young age, gross total obliteration, lack of deep artery perforators

Nair DR. Continuum 2016

Upcoming treatment for DRE

Cannibidiol

Possible Mechanisms

- Decrease presynaptic glutamate release
- Non-endocannabinoid receptor
- 5HT1A agonist
- Glycine receptor agonist
- Increase anandamide

Evidences

Table 1 Study-level summaries of included randomised controlled trials

Study	Design	Sample	Treatment	Pharma. grade	Outcomes measured	Results	Adverse events and serious adverse events
Devinsky *et al*[26]	Randomised, double-blind, placebo-controlled trial	120 children and adolescents (mean age=9.8; range=2–18; 52% male) with Dravet syndrome (drug-resistant epilepsy)	20 mg/kg/day CBD or placebo, taken orally for 14 weeks, as an adjunctive treatment	Yes	Change in seizure frequency, caregiver global impression of change	- Three CBD patients achieved total seizure freedom during the test period, no placebo patients achieved seizure freedom (P=0.08). - Twenty-six CBD patients (~43%) had a >50% reduction in seizures, compared with 16 patients (~27%) in the placebo group. - Thirty-seven caregivers (~62%) judged their child's overall condition to be improved in the cannabidiol group, as compared with 20 (~34%) in the placebo group (P=0.02). - Nine CBD patients withdrew from the study, 8 of which were due to adverse events. In comparison, three placebo patients withdrew, with only one being due to adverse events.	Somnolence (36%) Diarrhoea (31%) Decreased appetite (28%) Fatigue (20%) Vomiting (15%) Fever (15%) Lethargy (13%) Upper respiratory tract infection (11%) Convulsion (11%) *Serious:* Elevated liver aminotransferase enzymes (20%) Status epilepticus (4.9%)
GW Pharmaceuticals [27]	Randomised, double-blind, placebo-controlled trial	225 patients (mean age=16; range=2–55) with Lennox-Gastaut syndrome (drug-resistant epilepsy)	i) 10 mg/kg/day CBD for 14 weeks	Yes	Change in seizure frequency, change in QoL and caregiver global impression of change	- Patients randomised to 10 mg/kg/day of CBD achieved a median reduction in monthly drop seizures of 37%, in comparison with 17% in those patients in the placebo group (P=0.0016). - One patient receiving 10 mg/kg/day CBD withdrew due to adverse events, as did one placebo patient.	All cause (83.6%) *Serious:* All cause (17.8%)
			ii) 20 mg/kg/day CBD for 14 weeks	Yes	Change in seizure frequency, change in QoL and caregiver global impression of change	- Patients taking 20 mg/kg/day of CBD showed a median reduction in monthly drop seizures of 42%, compared with 17% in the placebo group (P=0.0047). - Six patients receiving the higher dose (20 mg/kg/day) withdrew due to adverse events, compared with one placebo patient.	All cause (93.4%) *Serious:* All cause (17.1%)
Thiele *et al*[28]	Randomised, double-blind, placebo-controlled study	171 patients (mean age=15.4; range=2–45; 51.5% male) with Lennox-Gastaut syndrome (drug-resistant epilepsy)	20 mg/kg/day CBD or placebo, taken daily for 14 weeks, as an adjunctive treatment	Yes	Change in seizure frequency, caregiver impression of overall improvement	- Five of 86 CBD patients achieved complete seizure freedom during the maintenance period, compared with none in the placebo group. - Thirty-eight patients (~44%) taking CBD had >50% decrease in seizures, compared with 20 (~24%) patients taking placebo. - Forty-two (~58%) CBD patients were reported (by either themselves or a caregiver) to have achieved an improvement in their overall condition, compared with 29 (~34%) placebo patients. - Fourteen CBD patients withdrew from the study, compared with just one patient given placebo.	Diarrhoea (18.6%) Somnolence (15.1%) Fever (12.8%) Decreased appetite (12.8%) Vomiting (10.5%) *Serious:* All cause (23.3%)

Stockings E, et al. J Neurol Neurosurg Psychiatry 2018

Cannibidiol

Indications in EPILEPSY

- Adjunctive therapy in Dravet syndrome and LGS
- Adjunctive therapy in Refractory epilepsy

Guidance on cannabis for medical use, กรมการแพทย์ 2562

Questions!!

THANK YOU