MAHIDOL
UNIVERSITY
Wisdom of the Land

Rationale pharmacotherapy in Epilepsy

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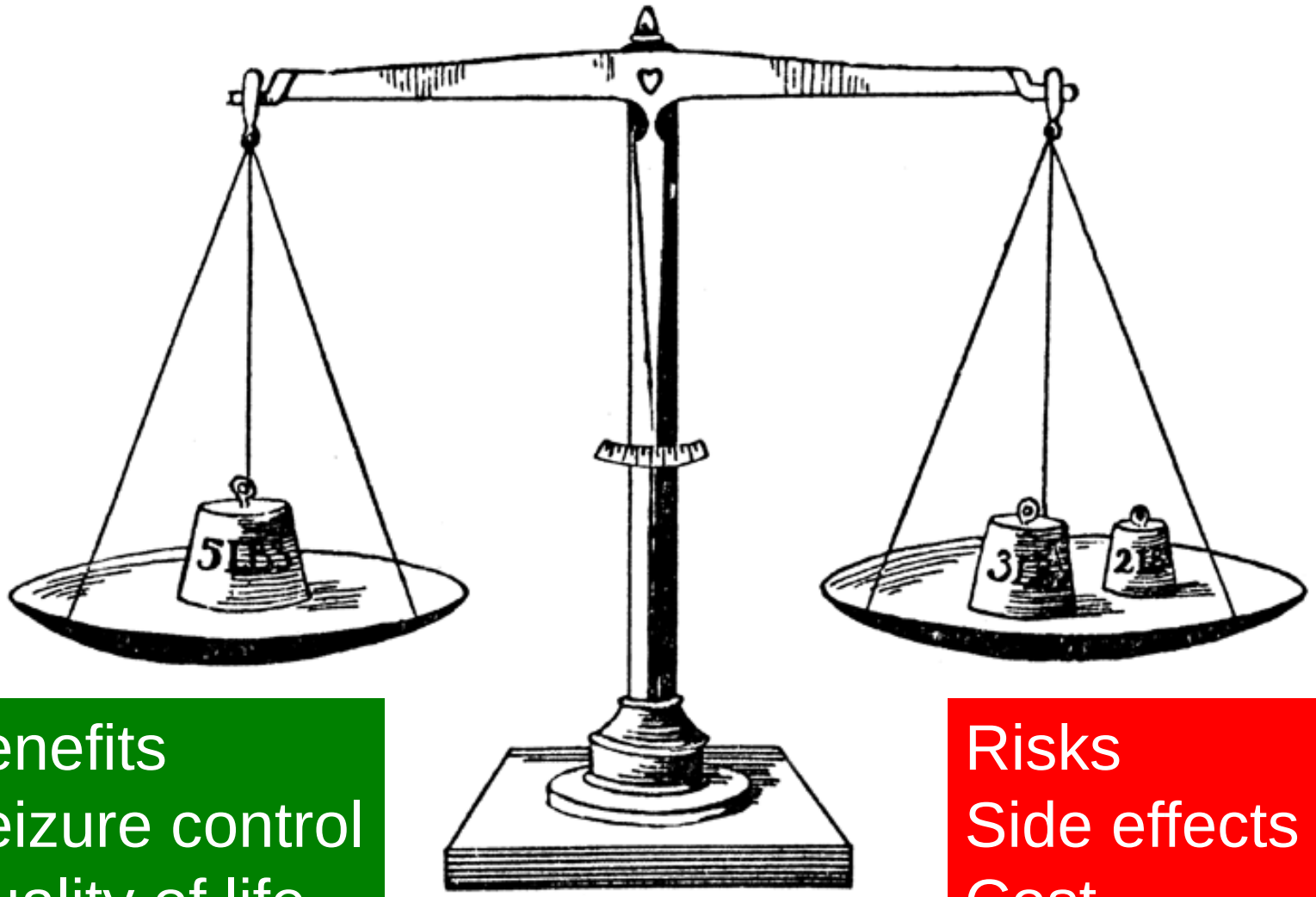


Benefits
Seizure control
Quality of life

Risks
Side effects
Cost

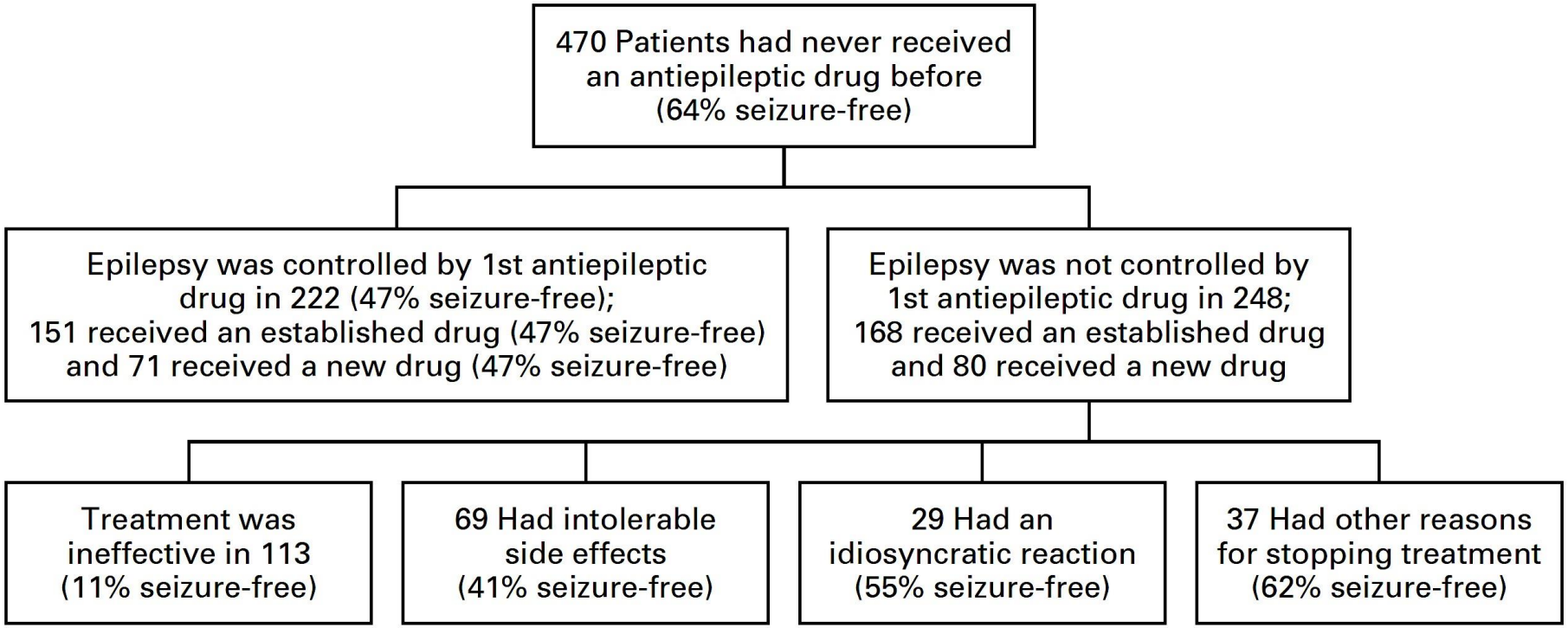
Treatment of epilepsy

- Antiepileptic drugs
- Epilepsy surgery
- Neurostimulation
  - Vagal nerve stimulation
  - Deep brain stimulation
  - Closed loop stimulation
- Other modalities: ketogenic diet

NATURAL HISTORY OF TREATED EPILEPSY

EARLY IDENTIFICATION OF REFRACTORY EPILEPSY

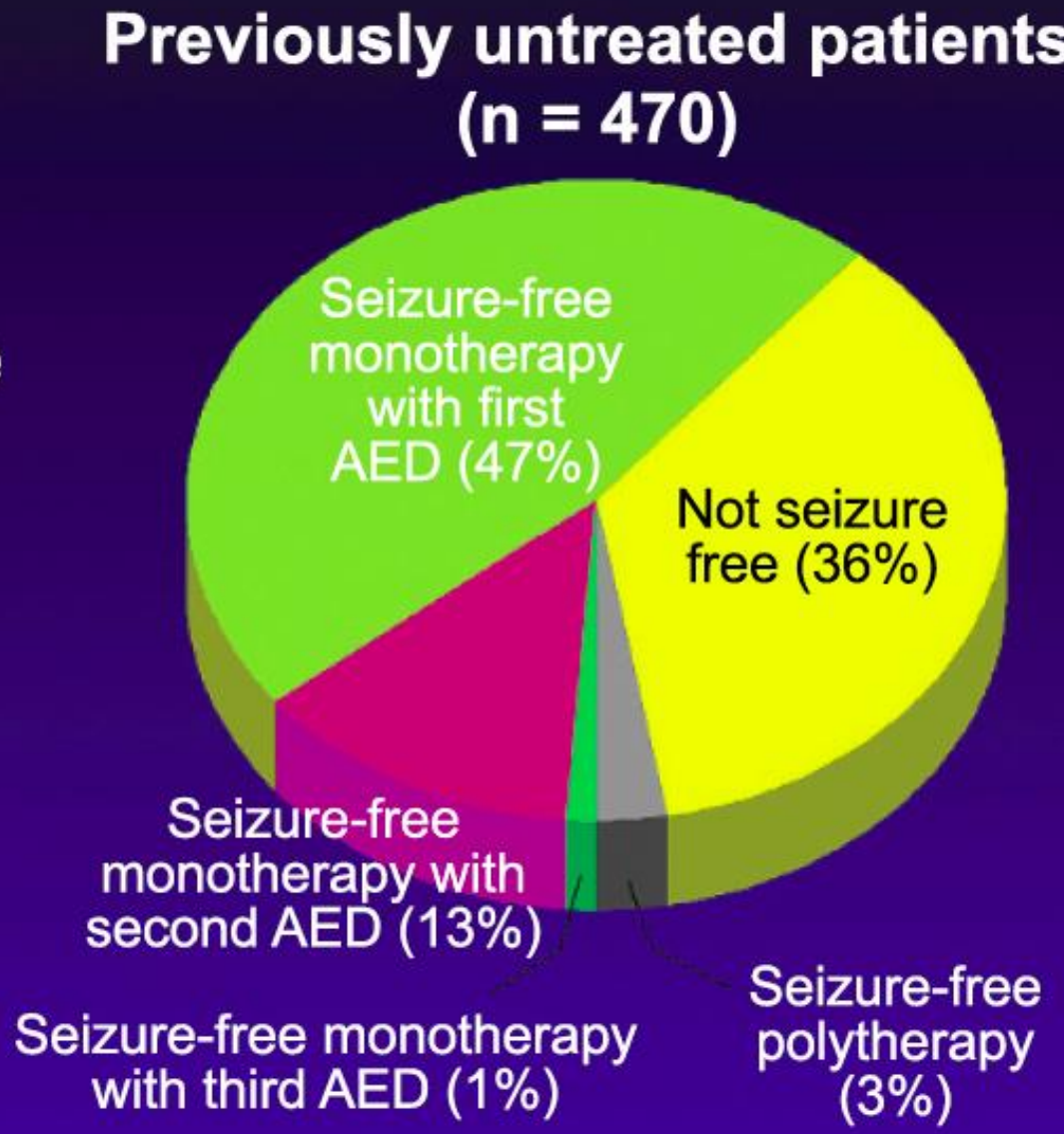
PATRICK KWAN, M.D., AND MARTIN J. BRODIE, M.D.



NEJM 2000;342:314-19

63% remained seizure free

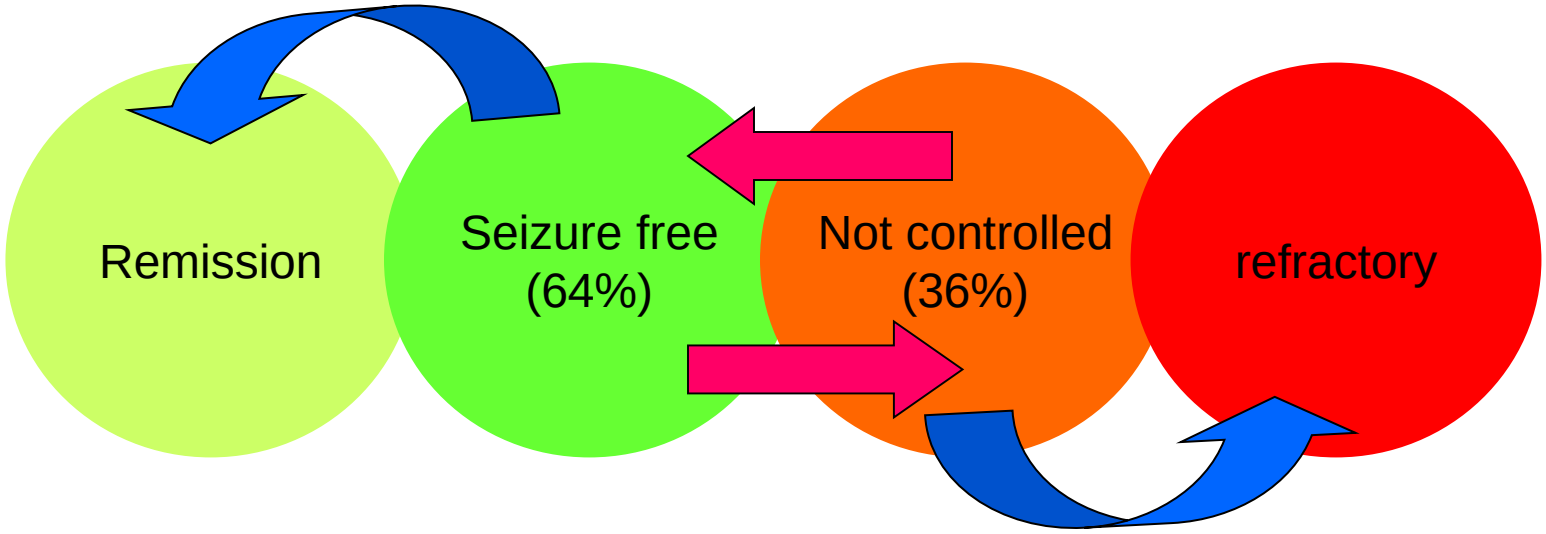
Seizure-free rates were similar between those treated with a single older AED (67%) and those treated with a newer AED (69%)



NEJM 2000;342:314-19

Nair D. Continuum 2016;22:157–172

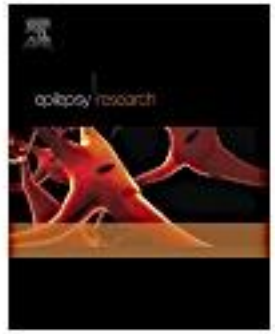
Natural history of treated epilepsy



1. There seem to be two class of patient :easy versus difficult to control de novo
2. Patient with difficult to control epilepsy commonly have underlying cerebral pathology and higher number (>20) of seizure prior to treatment

Epilepsy Research (2011) 96, 225–230

journal homepage: www.elsevier.com/locate/epilepsyres

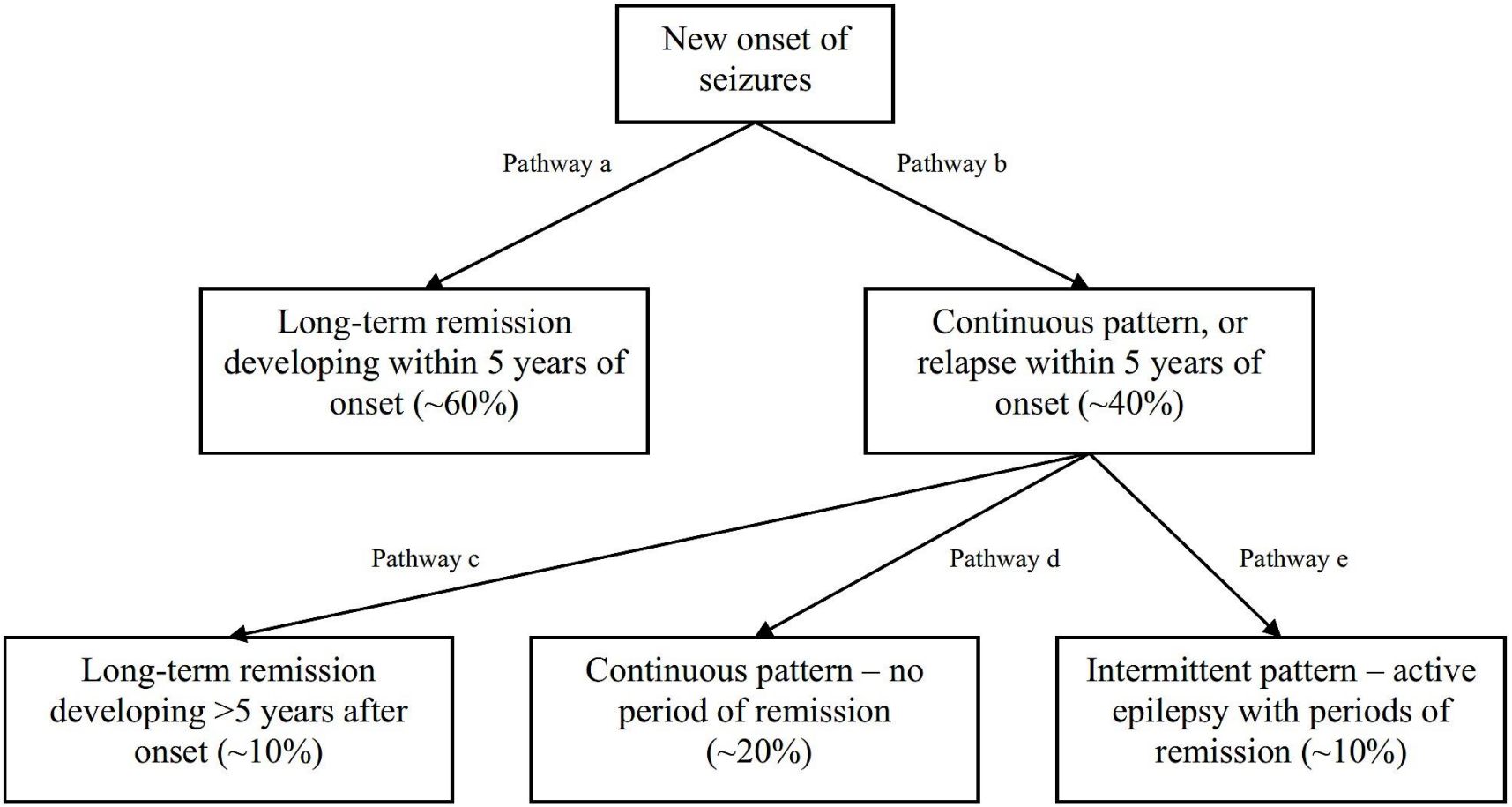


How refractory is refractory epilepsy? Patterns of relapse and remission in people with refractory epilepsy

Aidan Neligan[a], Gail S. Bell[a], Josemir W. Sander[a,b], Simon D. Shorvon[a,*]

[a] Department of Clinical & Experimental Epilepsy, UCL Institute of Neurology, Queen Square, London, WC1N 3BG, United Kingdom
[b] SEIN-Epilepsy Institutes in the Netherlands Foundation, Heemstede, The Netherlands

Neligan A, et al. Epilepsy research 2011;96:225-30



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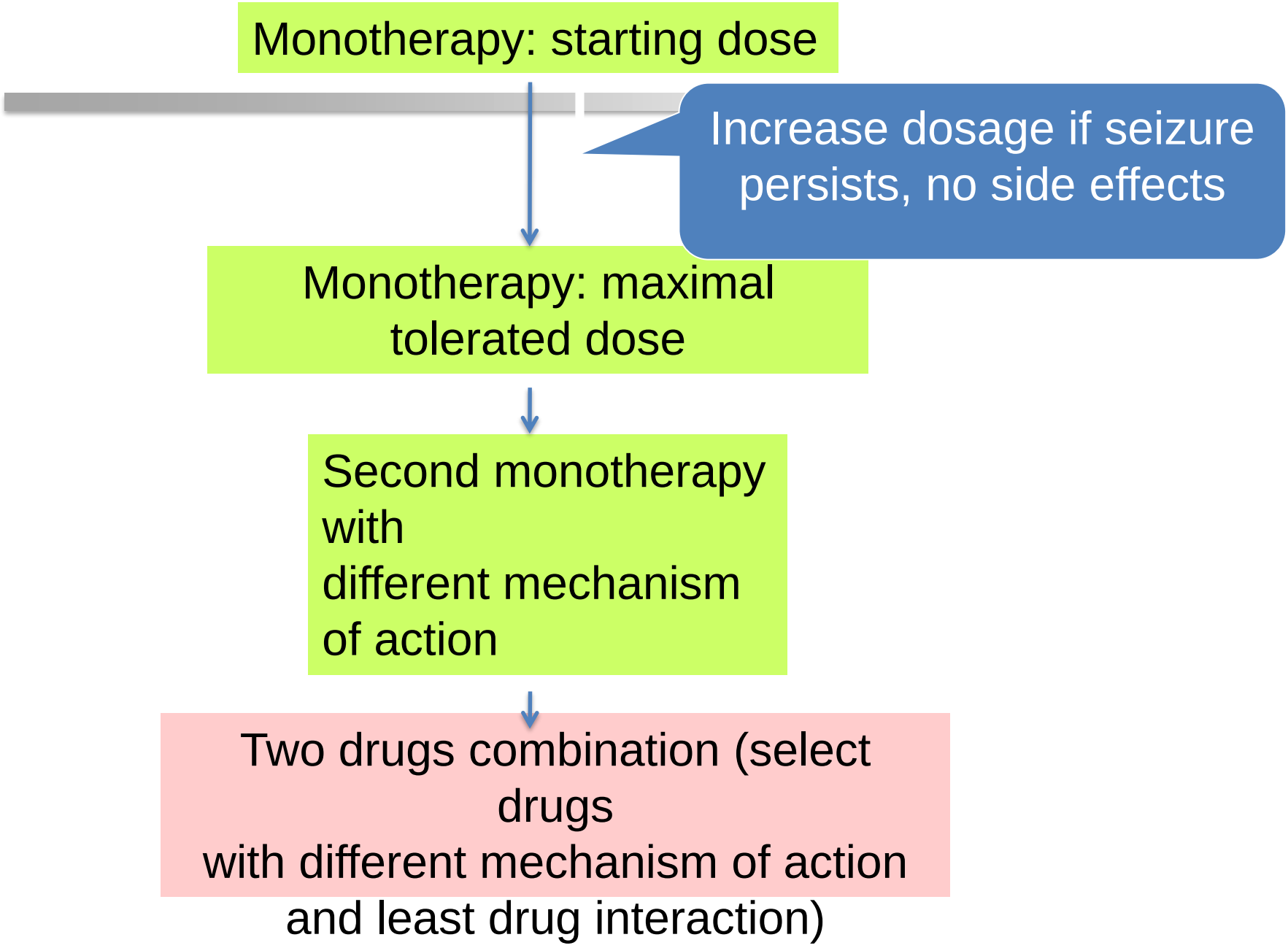
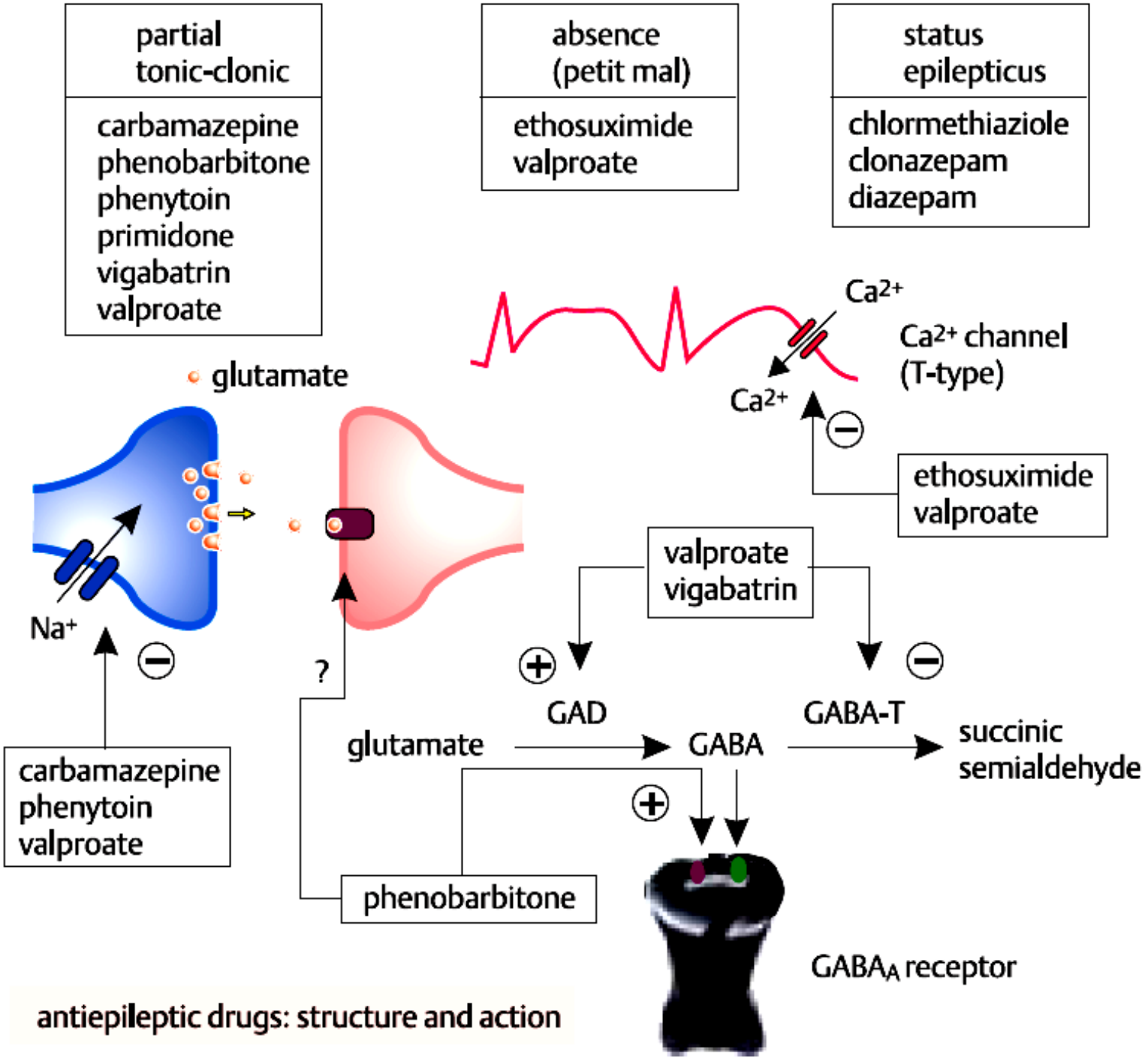

Monotherapy: starting dose
Increase dosage if seizure persists, no side effects
Monotherapy: maximal tolerated dose
Second monotherapy with different mechanism of action
Two drugs combination (select drugs with different mechanism of action and least drug interaction)

SELECTING THE AEDS: OPTION OF AVAILABLE AEDS

Traditional antiepileptic drugs

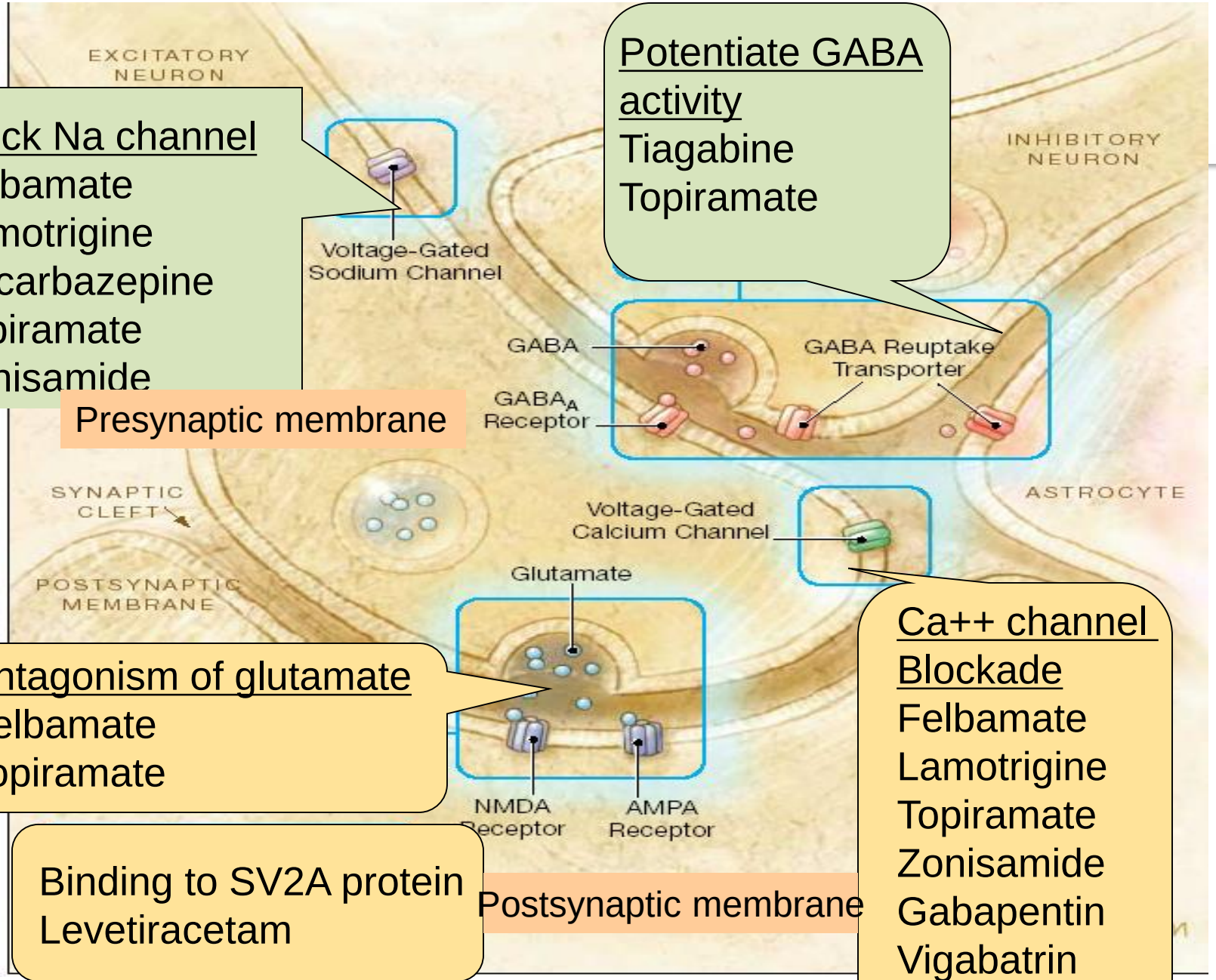
- Phenobarbital
- Phenytoin
- Carbamazepine
- Sodium valproate
- Benzodiazepine



antiepileptic drugs: structure and action

New (2nd generation) AEDs

- Felbamate (1993)
- Gabapentin (1993)
- Lamotrigine (1994)
- Topiramate (1996)
- Tiagabine (1997)
- Levetiracetam (1999)
- Oxcarbazepine (2000)
- Zonisamide (2000)
- Pregabalin (2005)
- Vigabatrin



Block Na channel
Felbamate
Lamotrigine
Oxcarbazepine
Topiramate
Zonisamide

Potentiate GABA activity
Tiagabine
Topiramate

Antagonism of glutamate
Felbamate
Topiramate

Ca++ channel Blockade
Felbamate
Lamotrigine
Topiramate
Zonisamide
Gabapentin
Vigabatrin
Pregabalin

Binding to SV2A protein
Levetiracetam

JAMA. 2004;291:605-614

Advantage of 2nd gen. AEDs

- Give clinician more choices of antiepileptic medications especially more choices of broad spectrum AEDs
- Better efficacy?
- Better tolerability?
- Better pharmacokinetic properties
- Low protein binding
- Most of the new AEDs are not strong hepatic enzyme inducers→ fewer drug interaction
- Fewer serious adverse events

Disadvantage of 2nd gen. AEDs

- Cost effectiveness
- Availability

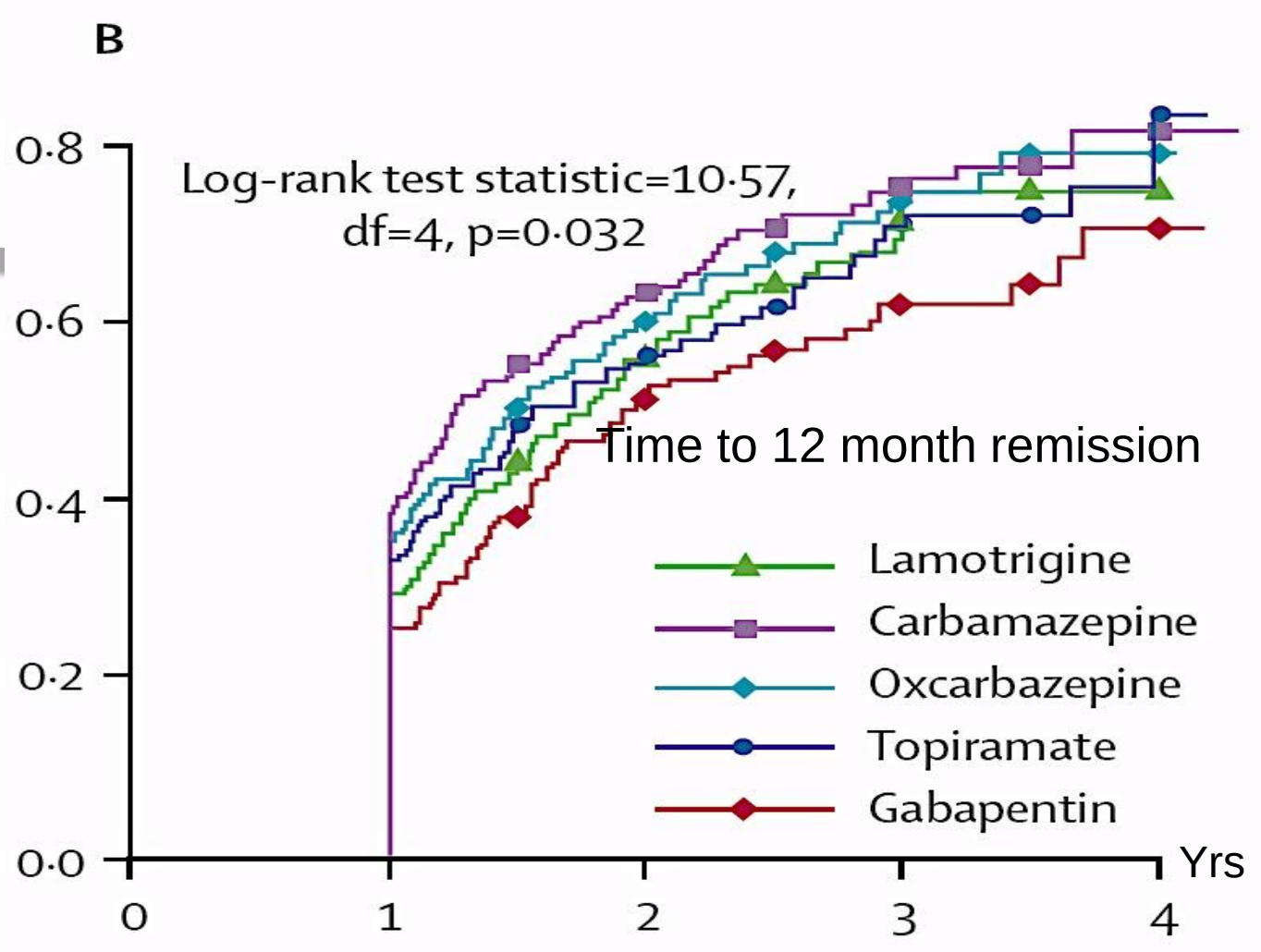
The SANAD study of effectiveness of carbamazepine, gabapentin, lamotrigine, oxcarbazepine, or topiramate for treatment of partial epilepsy: an unblinded randomised controlled trial

Anthony G Marson, Asya M Al-Kharusi, Muna Alwaidh, Richard Appleton, Gus A Baker, David W Chadwick, Celia Cramp, Oliver C Cockerell, Paul N Cooper, Julie Doughty, Barbara Eaton, Carrol Gamble, Peter J Goulding, Stephen J L Howell, Adrian Hughes, Margaret Jackson, Ann Jacoby, Mark Kellett, Geoffrey R Lawson, John Paul Leach, Paola Nicolaides, Richard Roberts, Phil Shackley, Jing Shen, David F Smith, Philip E M Smith, Catrin Tudur Smith, Alessandra Vanoli, Paula R Williamson, on behalf of the SANAD Study group.

Lancet 2007; 369: 1000–15

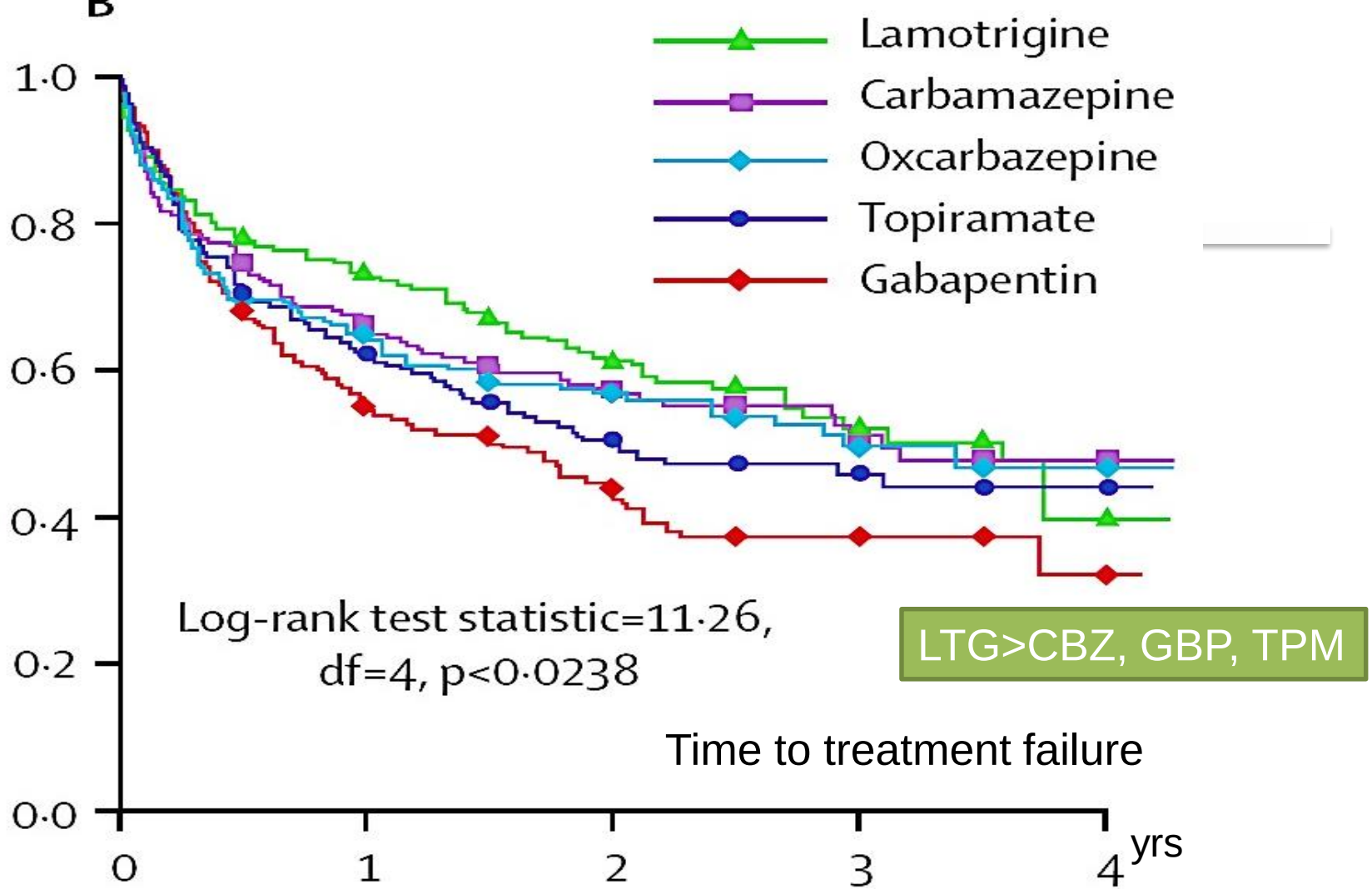
- Unblinded randomised controlled trial in hospital-based outpatient clinics in the UK
- Arm A recruited 1721 patients for whom carbamazepine was deemed to be standard treatment
- The patients were randomly assigned to receive carbamazepine, gabapentin, lamotrigine, oxcarbazepine, or topiramate.

Lancet 2007; 369: 1000–15



CBZ>GBP

	Carbamazepine	Gabapentin	Lamotrigine	Topiramate
Gabapentin	0·75 (0·63–0·90)	..		
Lamotrigine	0·91 (0·77–1·09)	1·21 (1·01–1·46)	..	
Topiramate	0·86 (0·72–1·03)	1·14 (0·95–1·37)	0·94 (0·78–1·13)	..
Oxcarbazepine†	0·92 (0·73–1·18)	1·37 (1·06–1·78)	1·15 (0·89–1·47)	1·10 (0·86–1·42)



	Carbamazepine	Gabapentin	Lamotrigine	Topiramate
Gabapentin	1·21 (0·99–1·48)	..		
Lamotrigine	0·78 (0·63–0·97)	0·65 (0·52–0·80)	..	
Topiramate	1·22 (0·99–1·49)	1·01 (0·83–1·23)	1·56 (1·26–1·93)	..
Oxcarbazepine†	1·04 (0·78–1·39)	0·75 (0·57–0·98)	1·15 (0·86–1·54)	0·90 (0·68–1·19)

- For time to treatment failure, lamotrigine was significantly better than carbamazepine (hazard ratio [HR] 0.78 [95% CI 0.63–0.97]), gabapentin (0.65 [0.52–0.80]), and topiramate (0.64 [0.52–0.79])

- For time to 12-month remission carbamazepine was significantly better than gabapentin (0.75 [0.63–0.90])

Lancet 2007; 369: 1000–15

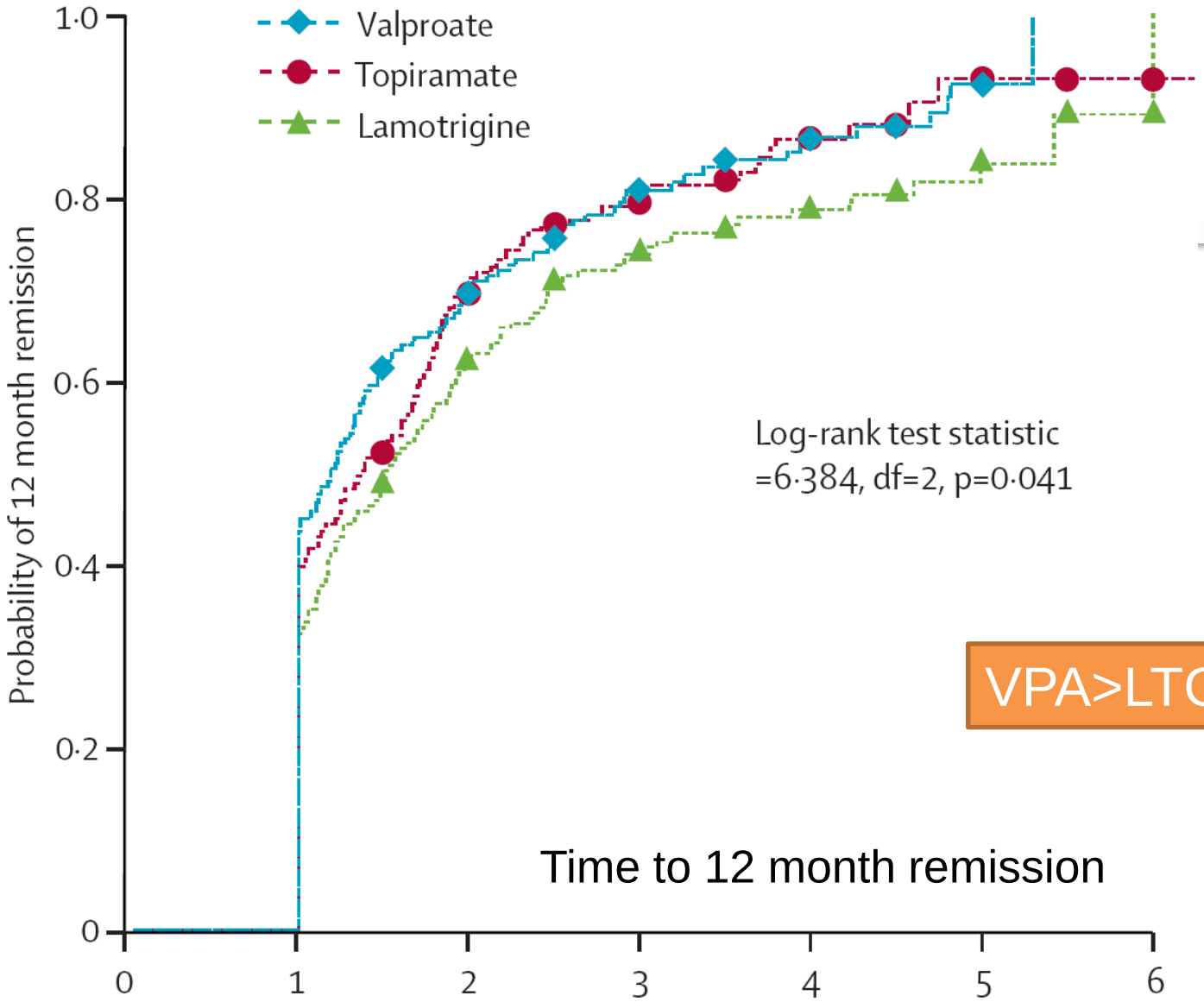
The SANAD study of effectiveness of valproate, lamotrigine, or topiramate for generalised and unclassifiable epilepsy: an unblinded randomised controlled trial

Anthony G Marson, Asya M Al-Kharusi, Muna Alwaidh, Richard Appleton, Gus A Baker, David W Chadwick, Celia Cramp, Oliver C Cockerell, Paul N Cooper, Julie Doughty, Barbara Eaton, Carrol Gamble, Peter J Goulding, Stephen J L Howell, Adrian Hughes, Margaret Jackson, Ann Jacoby, Mark Kellett, Geoffrey R Lawson, John Paul Leach, Paola Nicolaides, Richard Roberts, Phil Shackley, Jing Shen, David F Smith, Philip E M Smith, Catrin Tudur Smith, Alessandr a Vanoli, Paula R Williamson, on behalf of the SANAD Study group

Lancet 2007; 369: 1016–26

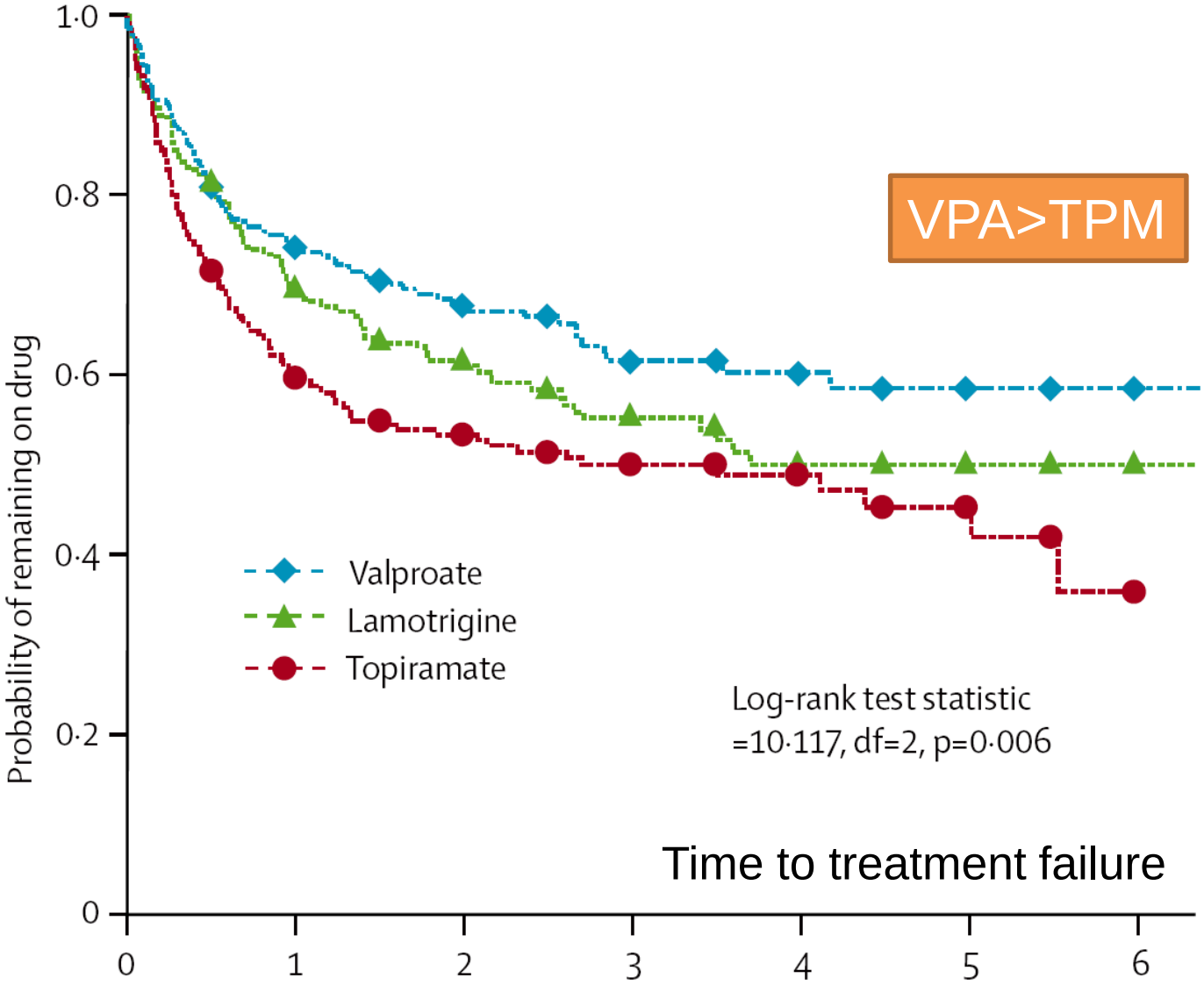
- An unblinded randomised controlled trial in hospital-based outpatient clinics in the UK.
- Arm B of the study recruited 716 patients for whom valproate was considered to be standard treatment.
- Patients were randomly assigned to valproate, lamotrigine, or topiramate between Jan 12, 1999, and Aug 31, 2004

Lancet 2007; 369: 1016–26



VPA>LTG

	Valproate	Lamotrigine
Lamotrigine	0·76 (0·62–0·94)	..
Topiramate	1·93 (0·76–1·15)	1·23 (0·99–1·51)



VPA>TPM

	Valproate	Lamotrigine
Lamotrigine	1·25 (0·94–1·68)	..
Topiramate	1·57 (1·19–2·08)	1·25 (0·96–1·64)

- For time to treatment failure, valproate was significantly better than topiramate (hazard ratio 1.57 [95% CI 1.19–2.08])

- For time to 12-month remission valproate was significantly better than lamotrigine (0.76 [0.62–0.94])

Lancet 2007; 369: 1016–26

Newest (3rd generation) AEDs

- Stiripentol (2007)
- Lacosamide (2008)
- Rufinamide (2008)
- Eslicarbazepine (2009)
- Vigabatrin (2009)
- Ezogabine (2011)
- Perampanel (2012)

Newest generation of antiepileptic medications: mechanism

Drugs	Related drugs	Mechanisms
Brivaracetam	Levetiracetam	10 fold higher affinity for SV2A than LEV
Eslicarbazepine	Carbamazepine	Less problem with drug interaction and toxic metabolites
Rufinamide	Lamotrigine	Acts on Na channels Prolonged inactive state of channels
Retigabine		Activate K current
Ganaxolone	Neurosteroids	Acts on postsynaptic and extrasynaptic GABA A receptors
Perampanel		Blocks AMPA receptors at “noncompetive site”
Lacosamide		Block Na channel in slow inactivated state

Advantage of 3rd gen. AEDs

- Give clinician more choices of antiepileptic medications especially more choices of AEDs with new mechanism
- Designed for high potency
- Better efficacy?
- Better tolerability?
- Better pharmacokinetic properties
- Low protein binding
- Fewer drug interaction
- Fewer serious adverse events?

Disadvantage of 3rd gen. AEDs

- Still need to watch for serious or new types of adverse effects, teratogenic side effects
- Cost effectiveness
- Availability

Retigabine: adverse effects

Blue discoloration of skin, lips, nails, retina

Example of new AED use

- Add on or monotherapy in patients with difficult to treat epilepsy
- More choices of broad spectrum AEDs and more choices of AEDs with new mechanisms
- More choices of IV AEDs
- In patients with multiple medications to avoid drug interaction (from using enzyme inducing AEDs)
- In patients with severe hepatic dysfunction or elevation of LFT

AEDs	Mechanism	Use and indication
Rufinamide	Na channel	Add-on for partial-onset seizures and in the LGS population
Lacosamide	Na channel	Adjunctive treatment for patients with pharmacoresistant partial epilepsy Case series in status epilepticus
Vigabatrin	Inh. GABA transaminase	Monotherapy in the treatment of infantile spasms and as adjunctive therapy for very resistant partial seizures (Black box warnings for VGB that concern the risks of developing irreversible visual field deficits in 30-40% of cases)
Perampanel	AMPA glutamate receptor antagonist	Add-on therapy for refractory partial onset seizures with or without generalization

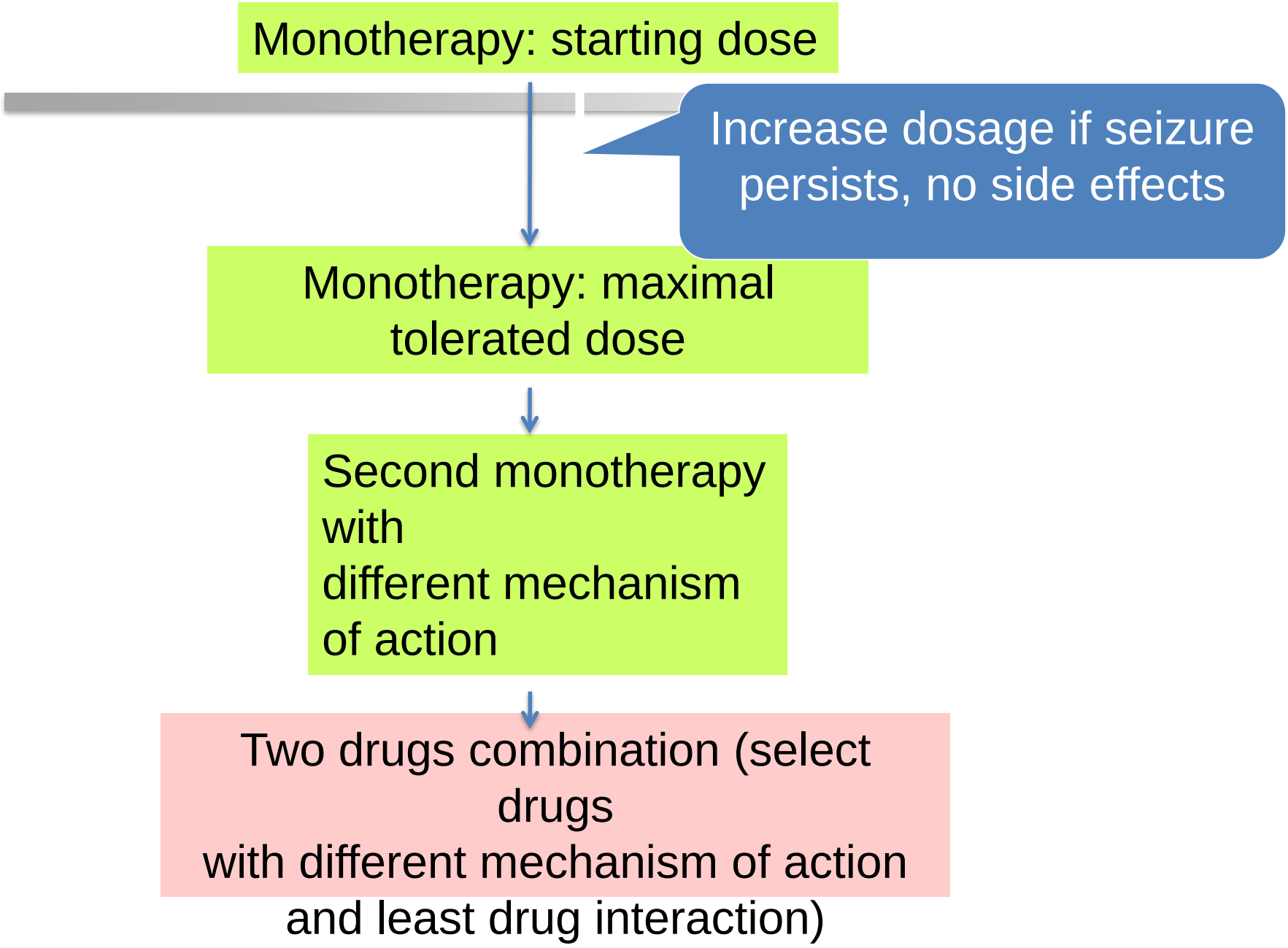
Ben-Menachem E. Epilepsia 2014;55(suppl1):3-8

AEDs	Mechanism	Use and indication
Eslicarbazepine	Na channel	Add-on treatment in refractory partial onset seizures
Briviracetam	SV2A	Add-on treatment in refractory partial onset seizures
Retigabine	Neuronal KCNQ agonist (opening of the VGKC, enhance the M-type potassium current)	Add-on therapy for patients with refractory partial onset seizures (Limited use due to the unexpected side effects of development of a blue hue to the skin and retina after long-term use)

Ben-Menachem E. Epilepsia 2014;55(suppl1):3-8

	Dosage/day (mg/d)	Expense/ month
Phenobarbital	120-180	30-45
Phenytoin	300	360
Carbamazepine original	400-1200	360-1200
Carbamazepine generic		150-450
Sodium valproate original	1000-3000	900-2700
Sodium valproate generic		300-900
Oxcarbazepine	600-1200	1050-3150
Lamotrigine	100-300	1230-3690
Topiramate	100-300	1320-3960
Zonisamide	100-300	1050-3150
Levetiracetam	1000-3000	2700-8100
Pregabalin original	150-600	2400-9600
Pregabalin generic		1740-6960
Lacosamide	100-400	3240-12960
Perampanel	2-8	1950-5880

SELECTING AEDS


Monotherapy: starting dose
Increase dosage if seizure persists, no side effects
Monotherapy: maximal tolerated dose
Second monotherapy with different mechanism of action
Two drugs combination (select drugs with different mechanism of action and least drug interaction)

Which medications?

- ลักษณะการชักและประเภทของโรคลมชักของผู้ป่วย
- การบริหารยา
- ผลข้างเคียงของยากันชัก
- Drug interaction กรณีที่ผู้ป่วยได้ยาหลายชนิดพร้อมกัน
- Special situations
  - Reproductive age
  - Elderly
  - Hepatic impairment
  - Renal impairment

Which medications?

- ลักษณะการชักและประเภทของโรคลมชักของผู้ป่วย
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- Special situations
  - Reproductive age
  - Elderly
  - Hepatic impairment
  - Renal impairment

Variables that lead to selection of a specific AED

AED-specific variables

- **Seizure or epilepsy syndrome**
- **specific efficacy**
- Dose-dependent adverse effects
- Idiosyncratic reactions
- Chronic toxicities
- Teratogenicity
- Pharmacokinetics
- Interaction potential
- Formulations

Patient-specific variables

- Genetic background
- Gender
- Age
- **Other medications**
- **Comorbidities**
- Insurance coverage
- Relative wealth
- Ability to swallow pills/tablets

Nation-specific variables

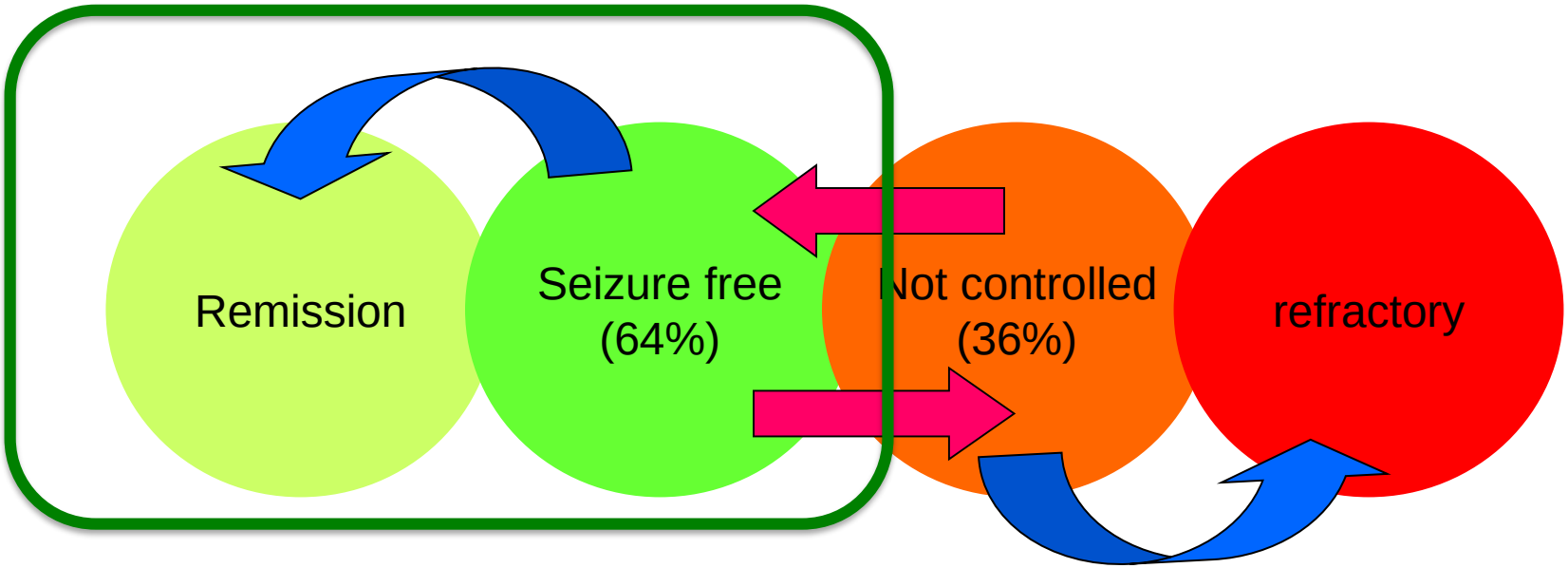
- **AED availability**
- **AED cost**
- **National policy**

Doctor-specific variables

Experience with the medications

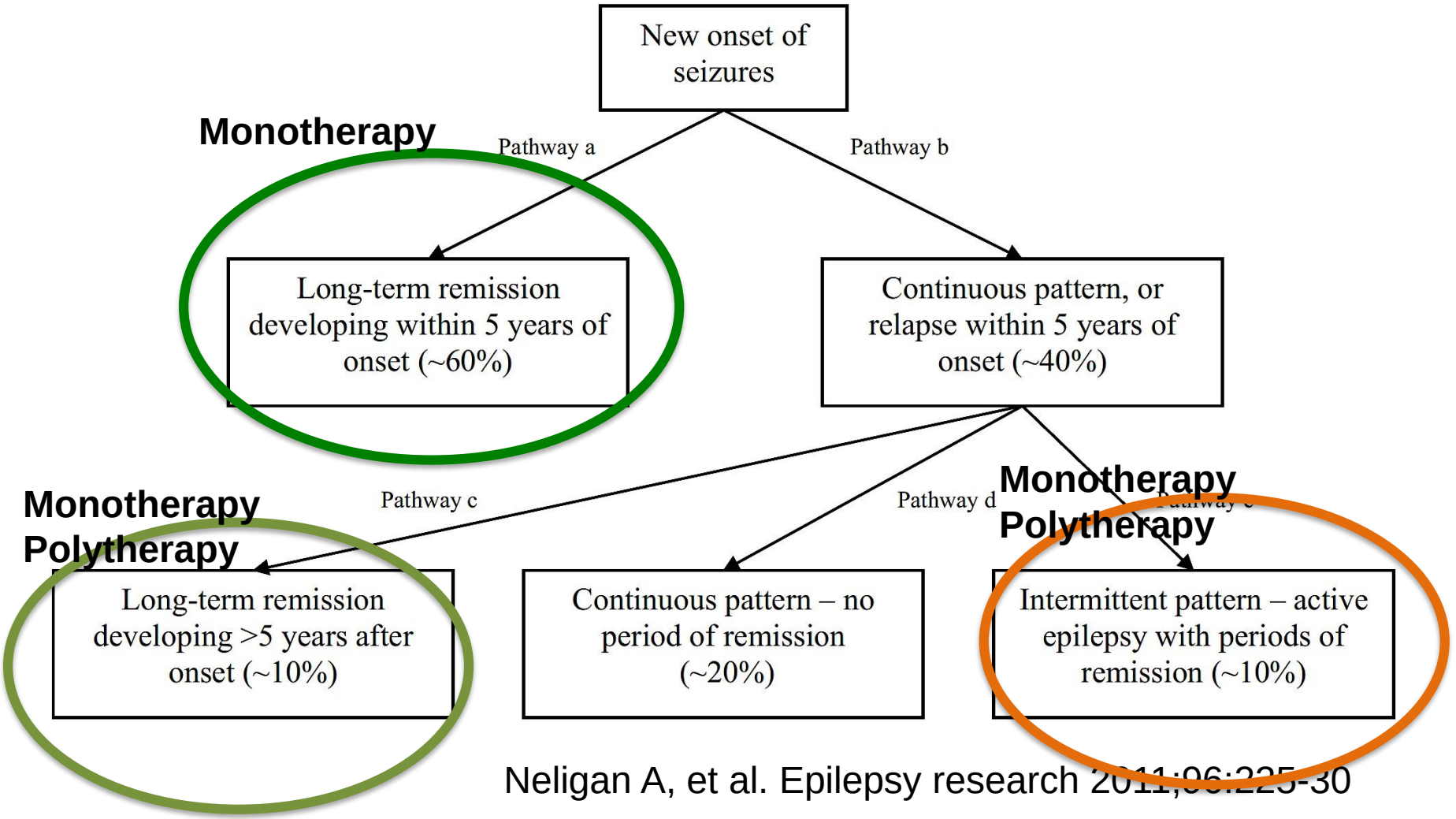
Tracy Glauser, et.al. ILAE Treatment Guidelines: Evidence-based Analysis of Antiepileptic Drug Efficacy and Effectiveness as Initial Monotherapy for Epileptic Seizures and Syndromes. Epilepsia;2006:47:1094–120.

Natural history of treated epilepsy



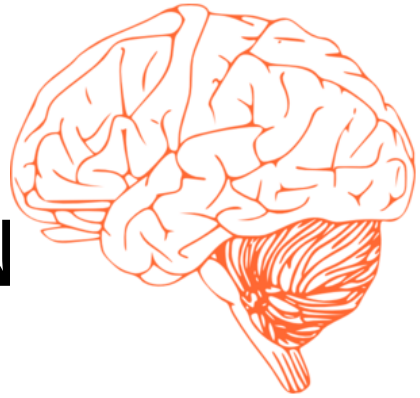
1. There seem to be two class of patient :easy versus difficult to control de novo
2. Patient with difficult to control epilepsy commonly have underlying cerebral pathology and higher number (>20) of seizure prior to treatment

Natural history of treated epilepsy



Neligan A, et al. Epilepsy research 2011;96:225-30

PRACTICAL ISSUES: WHAT SHOULD WE CONSIDER WHEN SELECTING AEDS?



THE DIAGNOSIS IS APPROPRIATE FOR THE CHOICE OF AEDS

Aggravation of seizures by AEDs

	CBZ	OXC	PHT	LTG	VPA	GBP	VGB	BDZ
Absence	+++	+	+++			+	++	
Myoclonic	+++	+	+++	+		+	+	
JME	++	+	++	+				
LGS/MAE	++	+	++	+		+	++	++
BECTS	+			+	+			
LKS/ESES	+		+					
ULD			+					

ชนิดของอาการชัก	Traditional AEDs	New AEDs
Absence	Sodium valproate	Lamotrigine Clonazepam
Myoclonic, atonic	Sodium valproate	Lamotrigine Topiramate Clonazepam Levetiracetam
Generalized tonic clonic	Phenobarbital Phenytoin Carbamazepine Sodium valproate	Lamotrigine Topiramate Oxcarbazepine Levetiracetam Gabapentin Clonazepam

ชนิดของอาการชัก	Traditional AEDs	New AEDs
Partial	Phenobarbital Phenytoin Carbamazepine Sodium valproate	Lamotrigine Topiramate Oxcarbazepine Levetiracetam Gabapentin Clonazepam Clobazam
Infantile spasm	Vigabatrin	Sodium valproate Topiramate Clonazepam Clobazam

STARTING AND TITRATING THE AEDS

Dosing schedule for AED

	t/2 (hrs)	Dosing schedule	Need slow titration
Phenytoin	20-30	OD	
Phenobarbital	96	OD	
Carbamazepine	10-20	Bid-tid	✓
Sodium valproate	8-12	Bid-tid	
Topiramate	20	Bid	✓
Lamotrigine	25-30	Bid	✓
Levetiracetam	7	Bid	
Zonisamide	63	OD-bid	
Oxcarbazepine	10	Bid-tid	✓
Gabapentin	5-7	Bid-tid	✓
Pregabalin	6	Bid-tid	✓

AWARE OF SIDE EFFECTS AND WHAT TO DO WHEN SE OCCURS?

Adverse effects traditional and new AEDs

	New	Traditional
Hypersensitivity/ rash	LTG, ZNM	PHT, CBZ, PB
Hematologic side effects	Less	CBZ, VPA
Elevation of LFT	Less	VPA
Electrolyte disturbances	OXC	CBZ
Teratogenic side effects	Similar or less	More with VPA
Cosmetic side effects	Wt gain with PGB, GBP	PHT (gum, hersutism) VPA (Wt gain)
Bone metabolism	Less	PHT, CBZ, PB, VPA
Cognitive side effects	TPM, ZNM	PB

Consider about psychiatric side effects in pts. with psychiatric comorbidities

Psychiatric comorbidities	Avoid	Consider
Mood lability/ bipolar disorder	-	LTG, CBZ, OXC, PHT, VPA
Anxiety	FLB, LEV, LTG, TGB	BZD, GBP, PBG
Depression	Barbiturates, LEV, PGB, TGB, TPM, VGB, ZNS	LTG
Psychosis	ETX, FLB, LEV, PHT, TGB, TPM, VGB, ZNS	-

Perucca P & Mula M. *Epilepsy Behav* 2013;26:440-9

RARE SIDE EFFECTS OF AEDS

Drugs	Adverse effects	Incidence	Year of marketing	Discovery of AE
CBZ	Aplastic anemia	~1:200,000	1963	1964
FBM	Aplastic anemia	1:7,500	1993	1994
PB	Shoulder hand syndrome	< 12%	1912	1934
PHT	Rickets and osteomalacia	< 5%	1938	1967
	Pseudolymphoma	82 cases reported in first 20 years		1940
TPM	Acute closed angle glaucoma	86 cases reported up to 2006	1994	2001
	Renal stones	~1%		1995
	Oligohydrosis	Few case reports		2001
VPA	Hepatotoxicity	1:600-1:50,000	1967	1977
VGB	Visual field defect	< 33%	1989	1997
ZNS	Oligohydrosis	1:5000 pt-yrs	1989	1996
	Renal stones	18:1000 pt-yrs		1993

Gaitatzis A, Sander JW. CNS Drugs 2013; 27:435–455

TERATOGENIC SIDE EFFECTS OF AEDS

Malformation Risks of AEDs in Pregnancy

- No AED 2-3%
- Monotherapy 3.7%-6%
- Polytherapy 6.1%-15%

ยากันชัก	อัตราการเกิด congenital malformation
Carbamazepine	2.1-6.3%
Phenytoin	2.6-7.4%
Phenobarbital	2.9-6.5%
Sodium valproate	6.1-16.3%*
Lamotrigine	1.4-5.2%
Gabapentin	0.8-5.9%**
Topiramate	2-4.8%**
Levetiracetam	2% **

*หากใช้ sodium valproate ในขนาดไม่เกิน 700-1000 mg ต่อวัน อัตราการเกิด malformation จะอยู่ในช่วง 6-9%

Are there specific MCMs associated with specific AEDs?

AEDs	MCMs	Evidences
PHT	Cleft palate	1 Class II study
CBZ	Posterior cleft palate	1 Class II study
VPA	Neural tube defects, facial cleft	1 Class I study
PB	Cardiac malformations	2 Class III studies

What should we do?

- Always warn the patient about rash and hypersensitivity reaction and note in the medical record!!
- Check HLA 1502 (if available) before using CBZ
- Find chance to counseling women in child bearing age regarding potential teratogenic side effect and what needed to be done esp. in patients on VPA→ Advice planned pregnancy
- Give folic acid to women in child bearing age

What should we do?

- Look (and ask) for cosmetic side effects in AEDs with potential cosmetic side effects
- Check CBC, LFT 1-2 times after start AEDs with potential hematologic side effects or elevated LFT
- Occasionally check sodium in elderly patients on CBZ (if needed)
- Replace calcium, vitamin D in patient on enzyme inducing AEDs with risk factors for osteoporosis

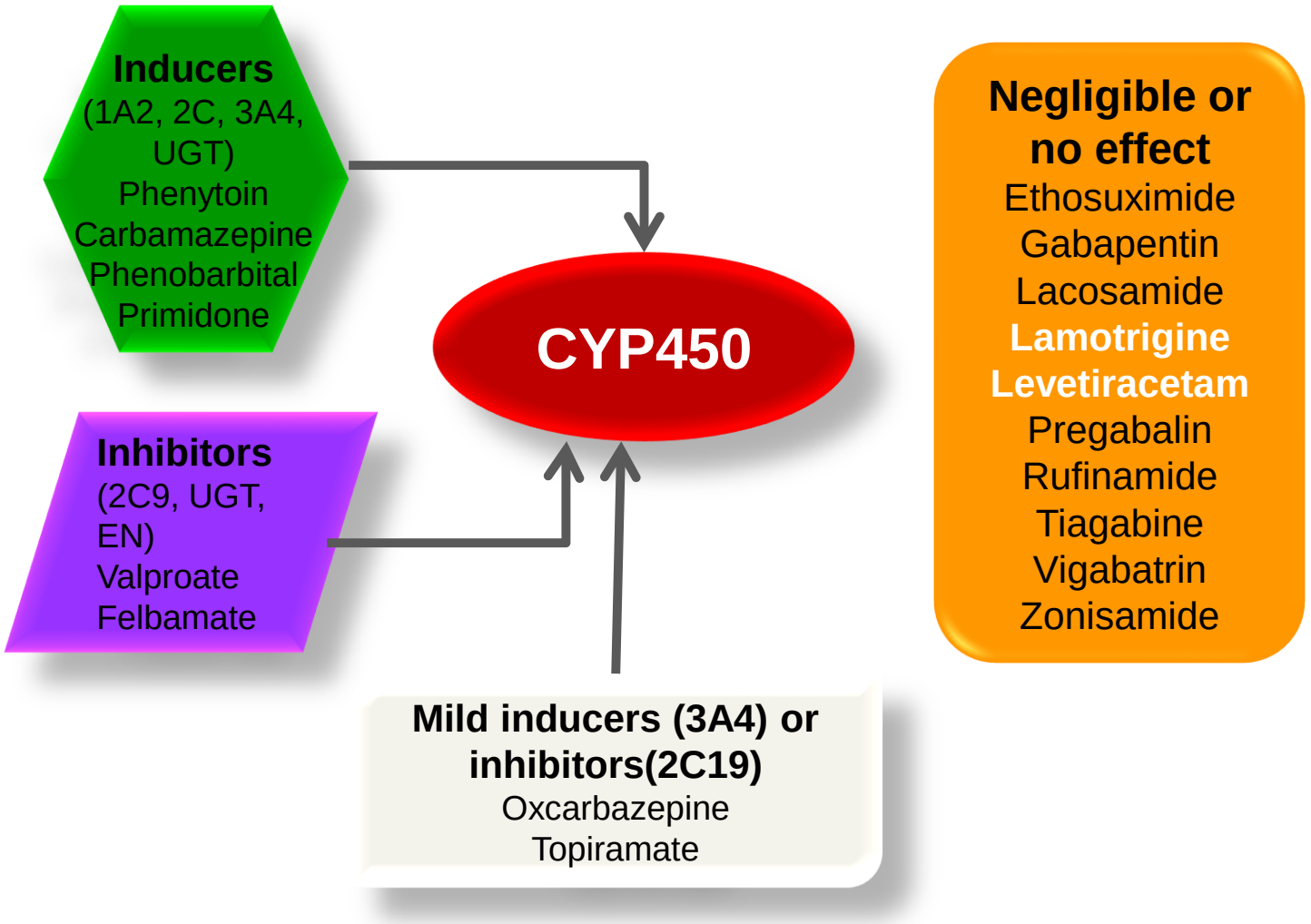
AWARE OF POTENTIAL DRUG INTERACTION

Metabolic pathways of AEDs

CYP 1A2	CYP 2C9	CYP 2C19	CYP 3A4
Carbamazepine*	Phenytoin	Phenytoin*	Carbamazepine
	Phenobarbital	Diazepam	Tiagabine
	Valproate*		Zonisamide
			Ethosuximide
			Felbamate

*Minor metabolic pathway.

Effect of Antiepileptic Drugs on the cytochrome P450 Interactions of AEDs



Asconape JJ. Neurol Clin 2010;28:843-52.

Effects on hepatic enzymes

Enzyme inhibitor	Enzyme inducer
Sodium valproate	Phenytoin
	Carbamazepine
	Phenobarbital

Interaction of AEDs with other drugs

Drugs	Met.	AEDs	Effects on other drug level
Warfarin	CYP3A4, CYP2C9	PHT, CBZ, PB	↓↓ warfarin level by 50-65%
OCP	CYP3A4	PHT, CBZ, PB	↓↓ OCP level
		OXC, LTG TPM>200mg/d	May ↓ OCP level (mild enzyme inducer)
Calcium channel blocker		PHT, CBZ, PB	May ↓ CCB level
Tacrolimus, cyclosporin, corticosteroid		PHT, CBZ, PB	May ↓ level
Zydovudine (NRTI)	Gluc.	VPA	May ↑ level
Lopinavir/ ritonavir (PI)	CYP	PHT	May ↓ level
Some chemotherapy*	CYP	PHT, CBZ, PB	May ↓ level

*Taxanes, vinca alkaloids, methotrexate, teniposide, and camptothecin analogues such as irinotecan

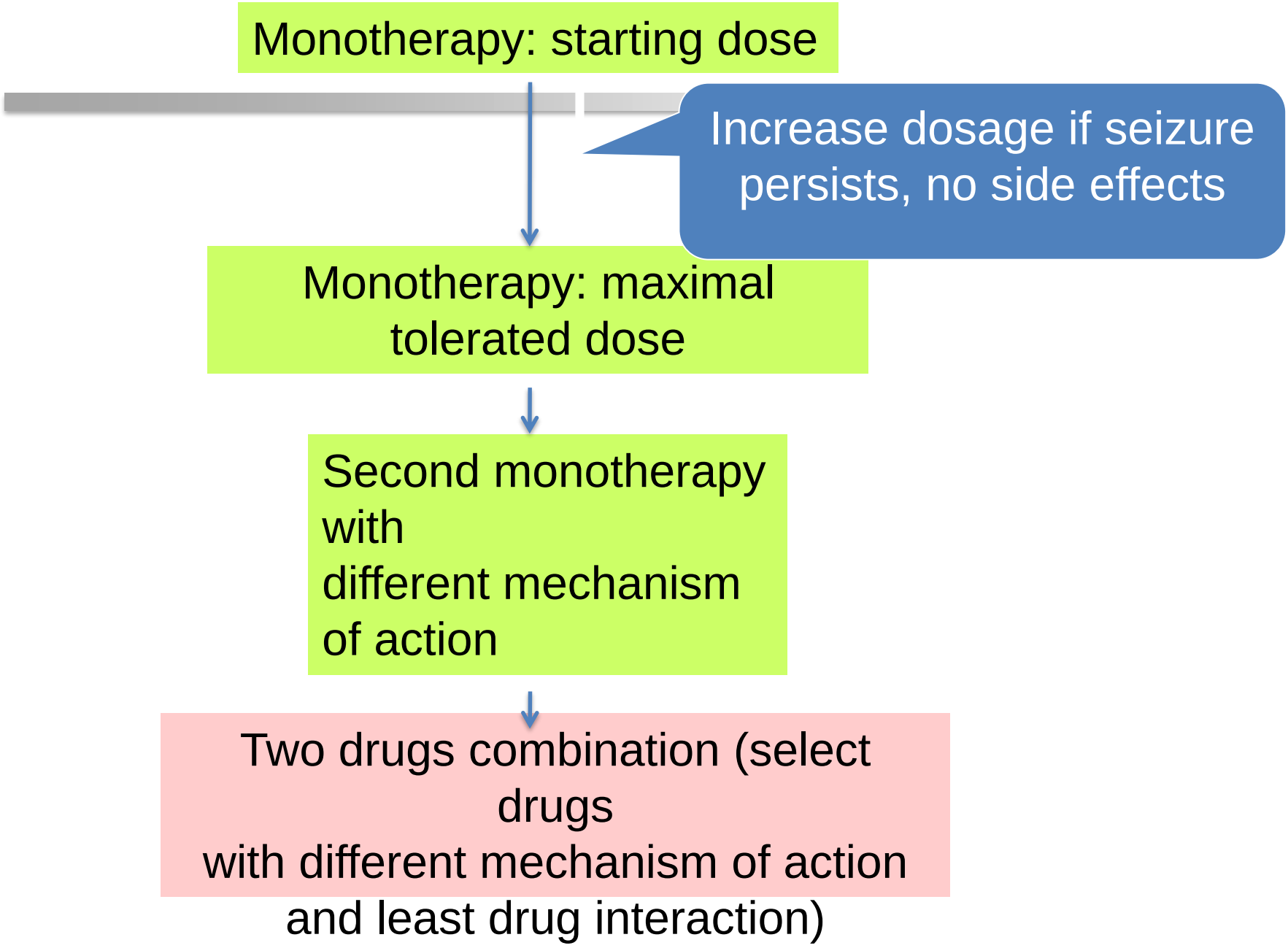
PATIENTS' COMORBIDITY GOES WELL WITH THE CHOICE OF AEDS

Matching AEDs with other comorbidities

	Avoid/ caution	Prefer
Migraine		VPA, TPM
Mood lability/ bipolar disorder	-	LTG, CBZ, OXC, PHT, VPA
Pain		CBZ, PGB, GBP
Anxiety	FLB, LEV, LTG, TGB	BZD, GBP, PGB
Depression	Barbiturates, LEV, PGB, TGB, TPM, VGB, ZNS	LTG
On warfarin, multiple medications	Enzyme inducing AEDs	
On OCP	Enzyme inducing AEDs	
HLA 1502 +ve	CBZ	
Sulfa allergy	ZNS	

Perucca P & MulaM. *Epilepsy Behav* 2013;26:440-9

IF THE 1ST AED DOES NOT WORK, WHAT TO DO NEXT?


Monotherapy: starting dose
Increase dosage if seizure persists, no side effects
Monotherapy: maximal tolerated dose
Second monotherapy with different mechanism of action
Two drugs combination (select drugs with different mechanism of action and least drug interaction)

How to adjust the medications?

- ก่อนจะพิจารณาเปลี่ยนหรือปรับยาในแต่ละขั้นตอนต้องคำนึงถึงสิ่งต่อไปนี้เสมอ
  - Is the diagnosis correct?
  - ยากันชักที่เลือกใช้เหมาะสมกับชนิดของการชักของผู้ป่วยหรือไม่?
  - Compliance
  - Avoid precipitating factors
  - Drug interaction

Epilepsia, 50(Suppl. 8):63–68, 2009
doi: 10.1111/j.1528-1167.2009.02238.x

REFRACTORY SEIZURES

Rational polytherapy

***Jacqueline A. French and †Edward Faught**

***New York University School of Medicine, New York, New York, U.S.A.; and †Birmingham Department of Veterans' Affairs Medical Center,
The University of Alabama School of Medicine, Birmingham, Alabama, U.S.A.**

Table 3. Patient scenarios that might favor sequential monotherapy (switching) versus polytherapy (adding)

Add	Switch
Inadequate control with two sequential monotherapies	Patient failed a single monotherapy at adequate doses
First AED appropriate, provided partial control	First AED has disadvantages (e.g., frequent monitoring, high cost, known teratogenicity in woman of childbearing age), or pregnancy is anticipated
No anticipated drug interactions	Drug interactions expected
Patient risk-averse, or consequences of seizure exacerbation are high	Seizure exacerbation not likely
Patient tolerating first AED	Patient not tolerating first AED

AED, antiepileptic drug.

Which drugs combination?

- Preferred drugs combination
  - VPA-LTG
  - Sodium channel blocker- broad spectrum
- Non favorable drugs combination
  - Same mechanism of action esp. sodium channel blocker

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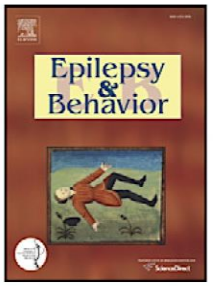


Review

Antiepileptic drug therapy: Does mechanism of action matter?

Martin J. Brodie [a,*], Athanasios Covanis [b], Antonio Gil-Nagel [c], Holger Lerche [d], Emilio Perucca [e,f], Graeme J. Sills [g], H. Steve White [h]

[a] *Epilepsy Unit, Western Infirmary, Glasgow, UK*
[b] *Neurology Department, Agia Sophia Children's Hospital, Thivon and Levadias, Goudi, Athens, Greece*
[c] *Epilepsy Programme, Hospital Ruber Internacional, Madrid, Spain*
[d] *Department of Neurology and Epileptology, Hertie Institute for Clinical Brain Research, University Hospital Tübingen, Tübingen, Germany*
[e] *Clinical Pharmacology Unit, Department of Internal Medicine and Therapeutics, University of Pavia*
[f] *National Institute of Neurology IRCCS C Mondino Foundation, Pavia, Italy*
[g] *Department of Molecular and Clinical Pharmacology, University of Liverpool, Liverpool, UK*
[h] *Department of Pharmacology and Toxicology, University of Utah, Salt Lake City, UT, USA*

- It is increasingly considered appropriate to treat patients established on a sodium channel blocker with
  - a drug that possess different mechanisms of action, such as levetiracetam and pregabalin, or
  - drugs that have multiple mechanisms of action, such as valproic acid, levetiracetam, topiramate, and zonisamide.

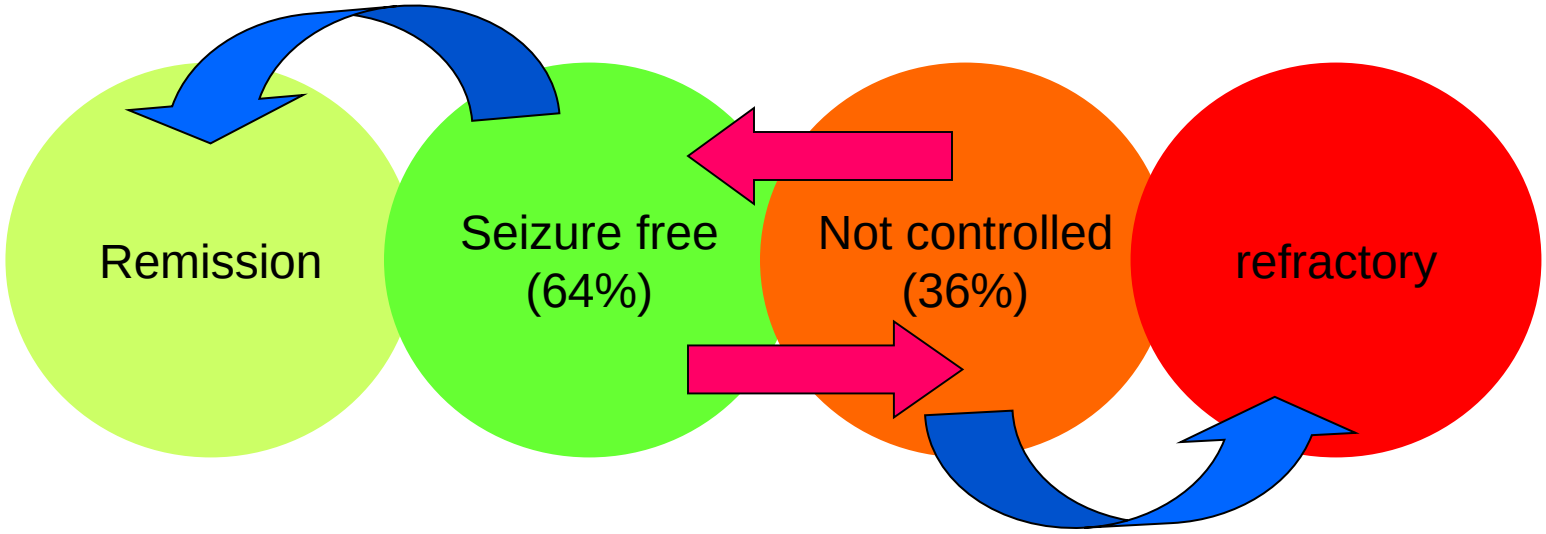
- If a patient tolerates the first or second drug well with a useful but suboptimal response, combination therapy could be considered, particularly if there is a high seizure density and demonstrable underlying pathology, such as mesial temporal sclerosis or cortical dysplasia

- Several duotherapy combinations should be tested before considering the addition of a third drug.
- Larger numbers of drugs should be avoided as it is unlikely that this strategy will produce a useful seizure reduction

- (2.) An additional AED may be used not just to treat the epilepsy, but to benefit comorbid conditions such as
- Neuropathic pain (gabapentin, pregabalin)
- Trigeminal neuralgia (carbamazepine, oxcarbazepine)
- Migraine (topiramate, valproic acid)
- Bipolar disorder (lamotrigine, valproic acid); and
- Anxiety (pregabalin, clobazam)

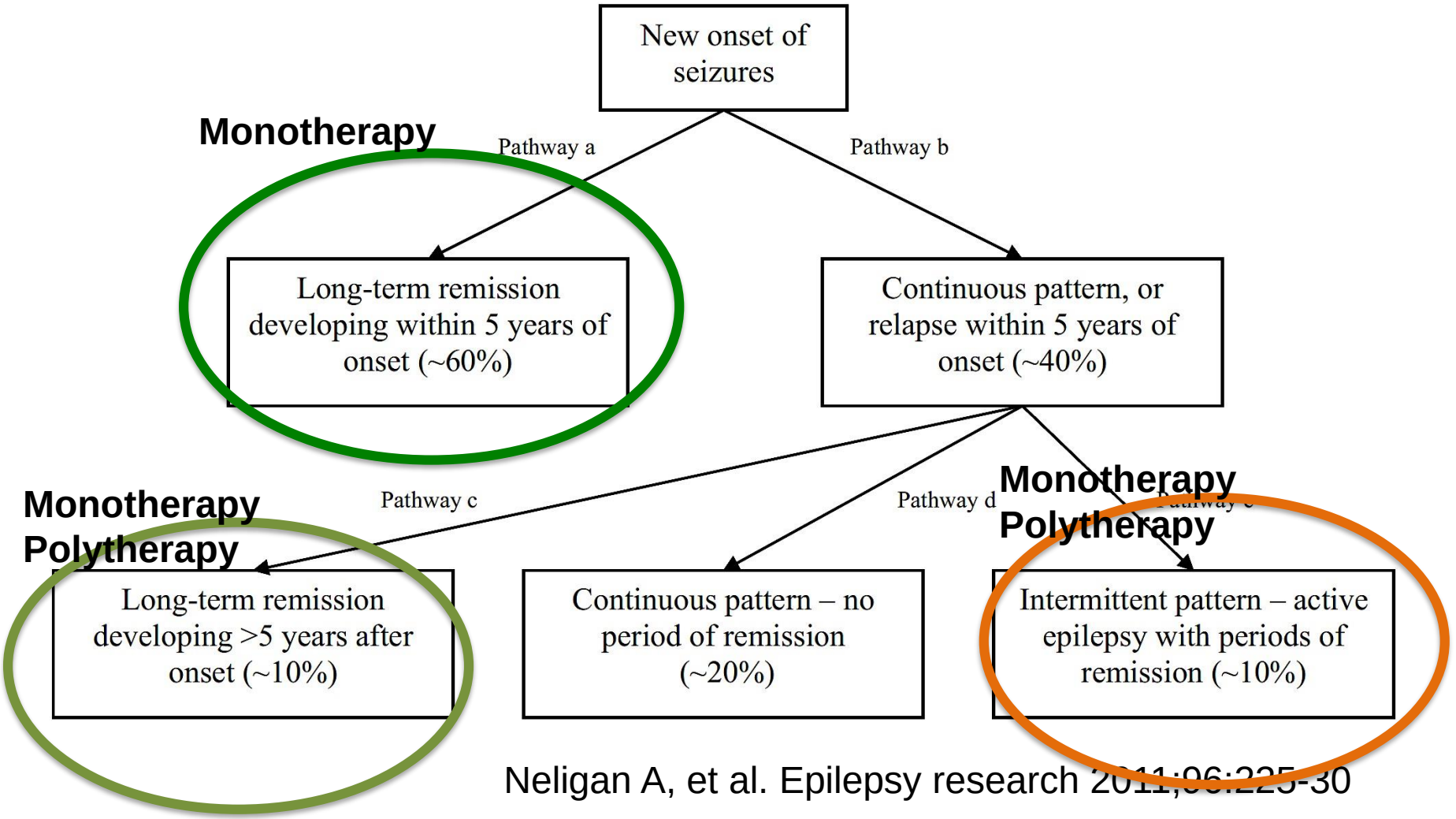
WHEN TO CONSIDER OTHER MODALITIES

Natural history of treated epilepsy



1. There seem to be two class of patient :easy versus difficult to control de novo
2. Patient with difficult to control epilepsy commonly have underlying cerebral pathology and higher number (>20) of seizure prior to treatment

Natural history of treated epilepsy



Neligan A, et al. Epilepsy research 2011;96:225-30

Results of Treatment Changes in Patients with Apparently Drug-Resistant Chronic Epilepsy

Anna L. Luciano, MD,[1–3] and Simon D. Shorvon, MA, MD, FRCP[1]

Objective: It has long been known that the response to treatment in newly diagnosed epilepsy is better than in chronic epilepsy. However, in the past 15 years, 8 major new antiepileptic drugs have been licensed, and the effect of this wider range of treatment options on prognosis has not been fully assessed. The aim of this study was to quantify the effect of adding a previously unused antiepileptic drug to the treatment regimen in adults with uncontrolled chronic epilepsy that had been resistant to previous antiepileptic drug treatment.

Methods: A total of 265 drug additions were studied in 155 adult patients with chronic epilepsy (defined as epilepsy active at least 5 years after and initiation of therapy).

Results: About 16% of all drug introductions resulted in seizure freedom (defined as seizure freedom at last follow-up for 12 months or longer), and a 50 to 99% seizure reduction occurred in a further 21%. Of the 155 patients, 28% were rendered seizure free by a drug introduction. Clinical factors associated with a better effect were fewer previously used antiepileptic drugs, shorter duration epilepsy, and idiopathic epilepsy.

Interpretation: This study provides a quantitative estimate of the value of changing drug therapy in patients in whom seizures were previously uncontrolled by previous therapy. The application of a systematic protocol to the treatment of chronic epilepsy will improve seizure control in a substantial proportion of cases. The rather nihilistic view that intractability is inevitable if seizure control is not obtained within a few years of the onset of therapy is incorrect.

Ann Neurol 2007;62:375–381

Luciano AL, Shorvon SD, et al. Ann Neurol 2007;62:375-81

Treatment Response to the Introduction of a Previously Unused Drug

265 Trials in 155 Patients

Less than 50% Reduction in Seizure Frequency, n (%)	50–99% Reduction in Seizure Frequency, n (%)	Seizure Freedom, n (%)	Proportion of the 155 Patients Rendered Seizure Free, n (%)
166 (63%)	56(21%)	43(16%)	43(28%)

Luciano AL, Shorvon SD, et al. Ann Neurol 2007;62:375-81

Factors That Influence the Treatment Response in All Patients

Patient Group	n[a]	50% or Less Reduction in Seizures, n (%)	Greater Than 50% Reduction in Seizures, n (%)	Seizure Free, n (%)	*p*
Number of drugs taken previously					0.001
<5 previous drugs	98	48 (49)	26 (27)	24 (24)	
≥5 previous drugs	167	118 (71)	30 (18)	19 (11)	
Cause of epilepsy				0.017	
Idiopathic	33	14 (42)	10 (30)	9 (27)	
Symptomatic	144	95 (66)	23 (16)	26 (18)	
Cryptogenetic	88	57 (65)	23 (26)	8 (9)	
Duration of epilepsy[b]					0.01
<10 years	51	27 (53)	9 (18)	15 (30)	
≥10 years	193	127 (66)	43 (22)	23 (12)	

[a]Number of drug additions. [b]In 35 patients, the duration of epilepsy was not exactly known; in 14, it was expressed as "long-standing," "since childhood," and therefore considered longer than 10 years.

Luciano AL, Shorvon SD, et al. Ann Neurol 2007;62:375-81

RESEARCH PAPER

Treatment changes in a cohort of people with apparently drug-resistant epilepsy: an extended follow-up

Aidan Neligan,[1] Gail S Bell,[1] Muaz Elsayed,[1] Josemir W Sander,[1,2] Simon D Shorvon[1]

- Of the 155 people in the original cohort, further follow-up was available on 139 (90%).
- The mean duration of follow-up was 6.7 years.
- During this period, 448 drug changes were made in 139 individuals

Neligan A, et al. J Neurol Neurosurg Psychiatry 2012;83:810-13

Table 2 Response to individual antiepileptic drug changes

Seizure outcome*	Antiepileptic drug changes (%) N = 448
<50% Reduction in seizure frequency	336 (75)
50%—99% Reduction in seizure frequency	74 (17)
Seizure freedom	37† (8)

Seizure outcome following 448 medication changes in 139 people in the extended follow-up.

At the time of last follow-up
26 (19%) were seizure-free
41 (29%) had a 50%-99% reduction in seizure frequency

Neligan A, et al. J Neurol Neurosurg Psychiatry 2012;83:810-13

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

SPECIAL REPORT

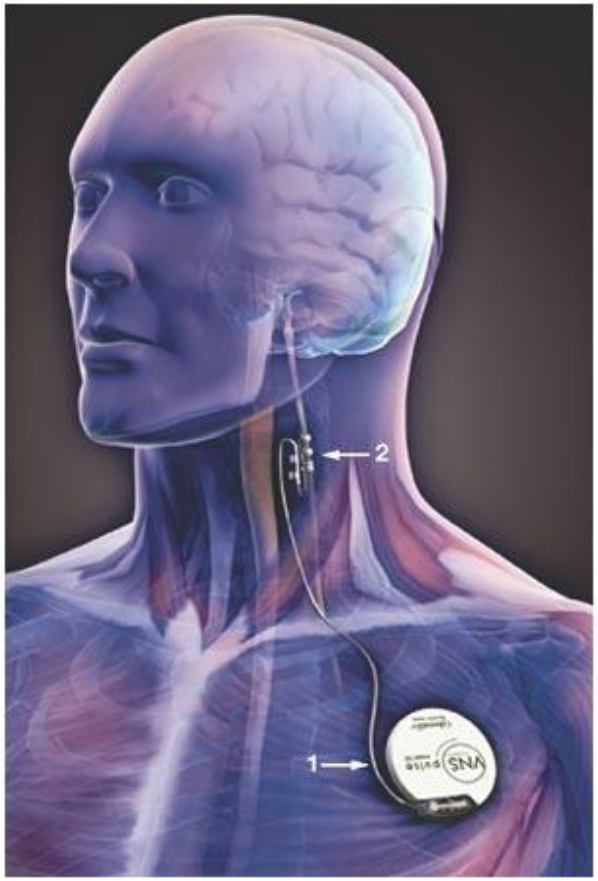
Definition of drug resistant epilepsy: Consensus proposal by the ad hoc Task Force of the ILAE Commission on Therapeutic Strategies

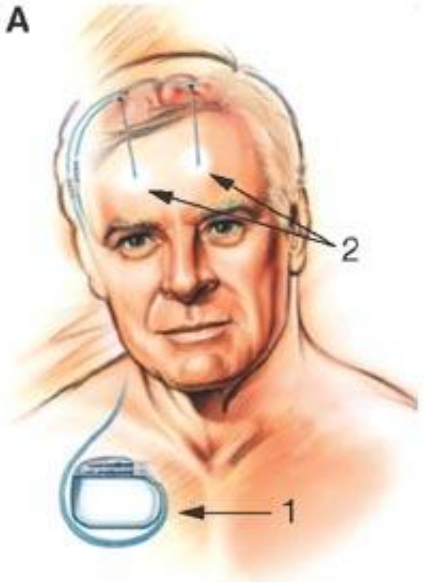
*[1]Patrick Kwan, †Alexis Arzimanoglou, ‡Anne T. Berg, §Martin J. Brodie, ¶W. Allen Hauser, #[2]Gary Mathern, **Solomon L. Moshé, ††Emilio Perucca, ‡‡Samuel Wiebe, and §§[2]Jacqueline French

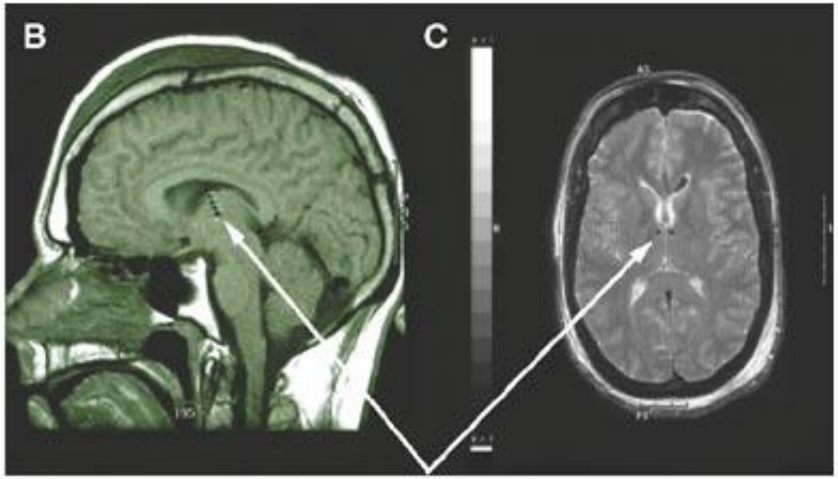
Drug resistant epilepsy may be defined as failure of adequate trials of two tolerated and appropriately chosen and used AED schedules (whether as monotherapies or in combination) to achieve sustained seizure freedom.

Treatment of medical refractory epilepsy

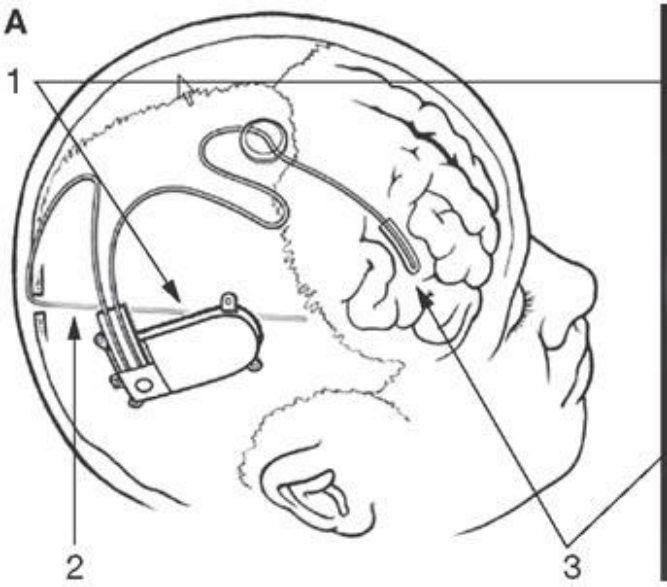
- Epilepsy surgery
- Neurostimulation
  - Vagal nerve stimulation
  - Deep brain stimulation
  - Closed loop stimulation
- Other modalities: ketogenic diet

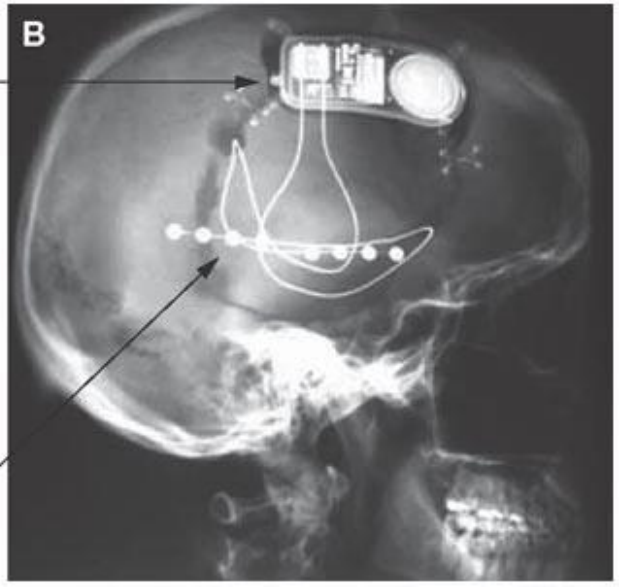






Stimulating electrodes



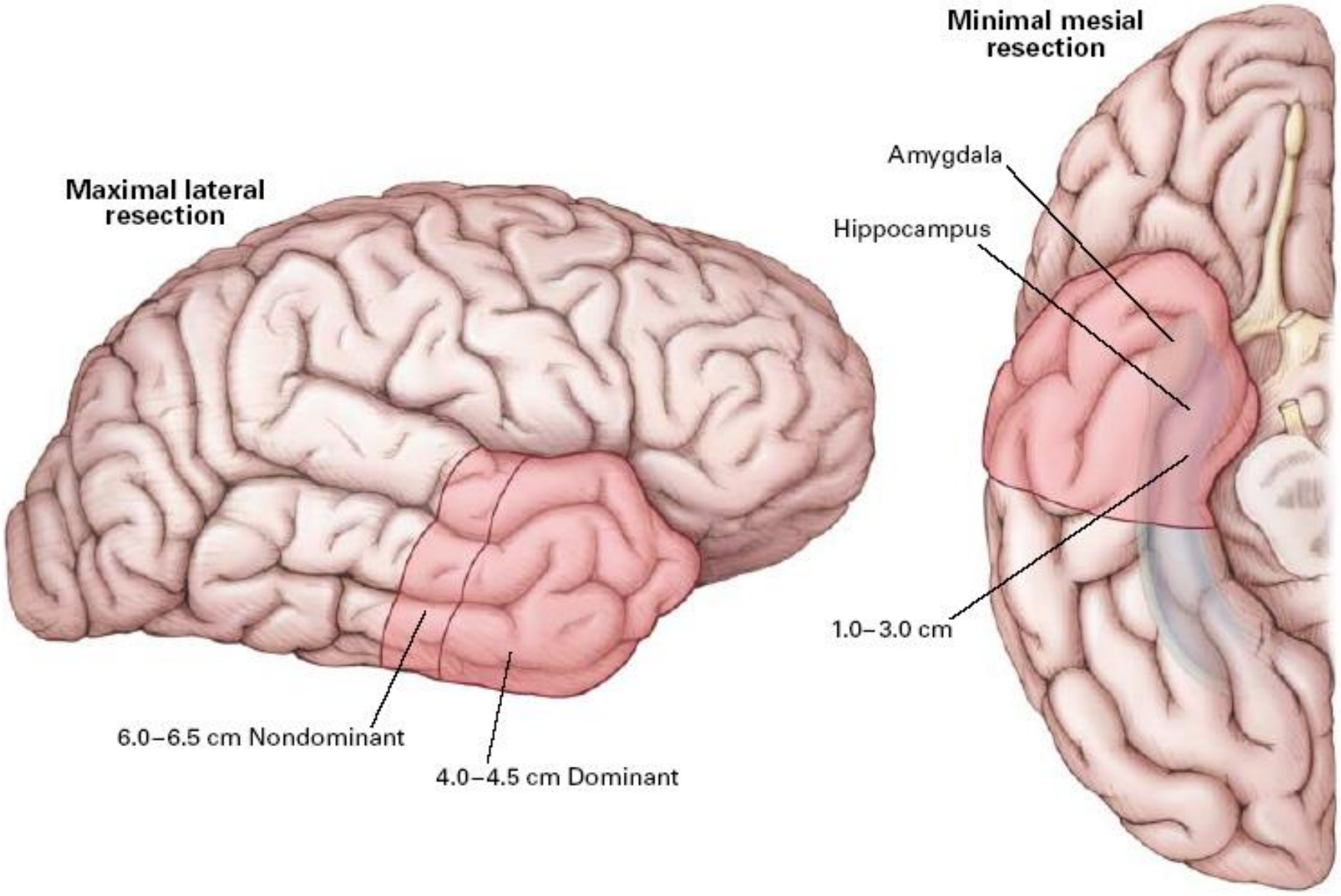


The New England Journal of Medicine

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*


Maximal lateral resection
6.0–6.5 cm Nondominant
4.0–4.5 cm Dominant
Minimal mesial resection
Amygdala
Hippocampus
1.0–3.0 cm

RCT OF SURGERY FOR TLE

- Eighty patients with temporal-lobe epilepsy
- Randomly assigned to surgery (40 patients) or treatment with antiepileptic drugs for one year (40 patients).
- The primary outcome was freedom from seizures that impair awareness of self and surroundings.
- Secondary outcomes were the frequency and severity of seizures, the quality of life, disability, and death.

RCT OF SURGERY FOR TLE

- At one year, the cumulative proportion of patients who were free of seizures impairing awareness was 58 percent in the surgical group and 8 percent in the medical group ($P<0.001$).
- The patients in the surgical group had fewer seizures impairing awareness and a significantly better quality of life ($P<0.001$) than the patients in the medical group.
- Four patients (10 percent) had adverse effects of surgery. One patient in the medical group died.

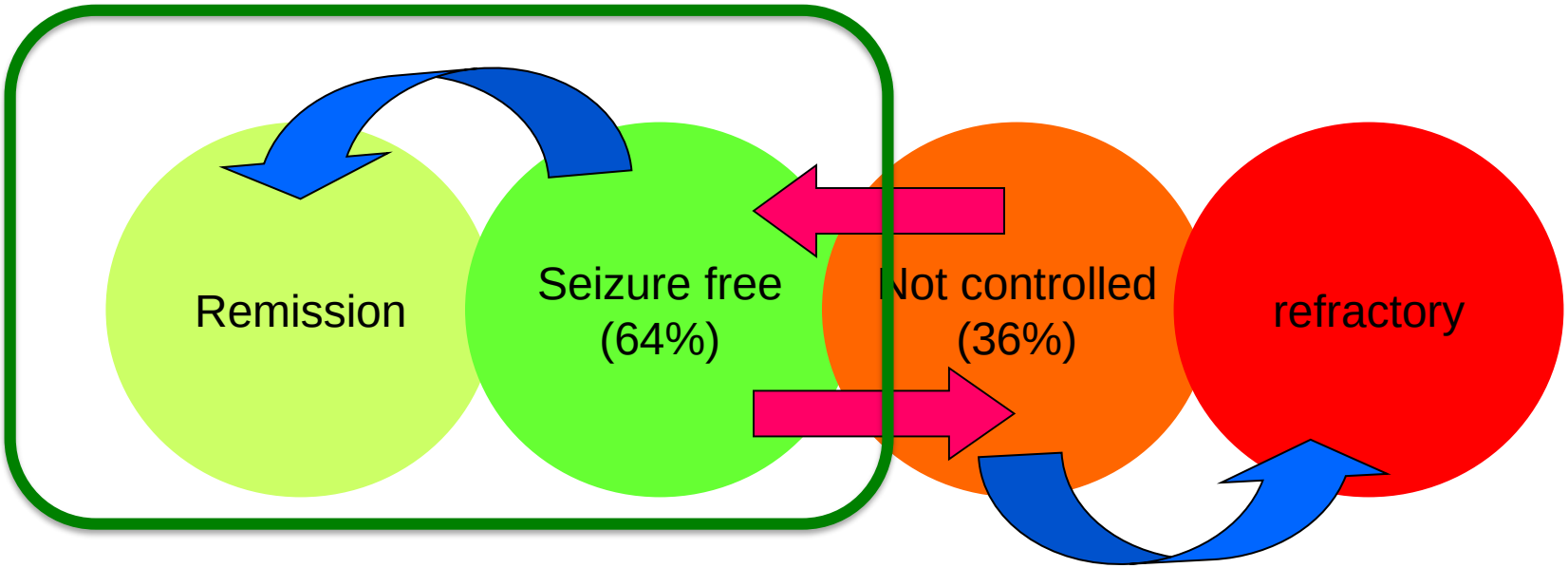
Outcome of temporal lobe epilepsy surgery

Studies	Yr	No.	F/U	Seizure free (%)	
Controlled trials					
Wiebe, et al	2001	36	1	64	8% with medical Rx
Gilliam, et al	1999	94	1	65	
Bien, et al	2001	148	4.8	62	7.5% with medical Rx
Series					
Radhakrishnan, et al	1998	175	3.6	77	
Jeha, et al	1999	371	5.5	63	
Jeong, et al	1999	93	1.5	84	
Wieser, et al	2001	369	7.2	67	
Spencer, et al	2005	297	4.6	68	
Cohen-Godol, et al	2006	372	6.2	74	
Al Kaylani, et al	2007	150	6	78	

Outcome of extratemporal epilepsy surgery

Studies		No.	F/U	Seizure free (%)	
Metaanalysis					
Tellez Zenteno, et al	2005	772		31	Exclude hemispherectomy, callosotomy
Ansari, et al	2007	95		34	Children mean age 4.5
Lerner, et al	2009	854		62	Cortical dysplasia, include TLE
Series					
Holmes, et al	2000	126	3	43	
Janszky, et al	2000	61	1.8	49	FLE
Chung, et al	2005	74	2.2	58	
Cohen- Godol, et al	2006	27	6.2	42	
Boesebeck, et al	2007	81	2	41	
Binder, et al	2008	52	6.7	69	OLE
Elsharkawy, et al	2008	218	5	53	

Natural history of treated epilepsy



1. There seem to be two class of patient :easy versus difficult to control de novo
2. Patient with difficult to control epilepsy commonly have underlying cerebral pathology and higher number (>20) of seizure prior to treatment

Variables that lead to selection of a specific AED

AED-specific variables

- **Seizure or epilepsy syndrome**
- **specific efficacy**
- Dose-dependent adverse effects
- Idiosyncratic reactions
- Chronic toxicities
- Teratogenicity
- Pharmacokinetics
- Interaction potential
- Formulations

Patient-specific variables

- Genetic background
- Gender
- Age
- **Other medications**
- **Comorbidities**
- Insurance coverage
- Relative wealth
- Ability to swallow pills/tablets

Nation-specific variables

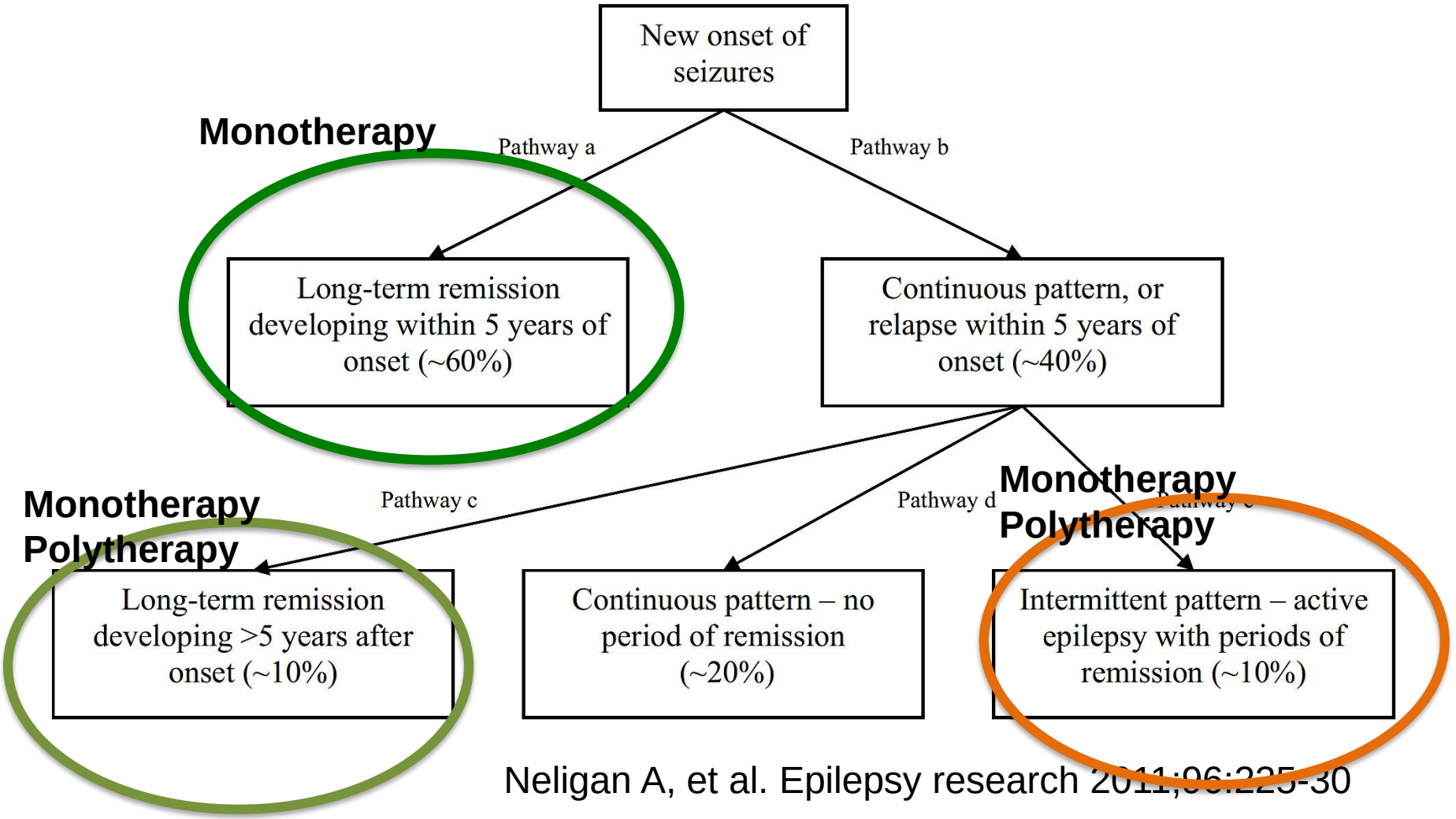
- **AED availability**
- **AED cost**
- **National policy**

Doctor-specific variables

Experience with the medications

Tracy Glauser, et.al. ILAE Treatment Guidelines: Evidence-based Analysis of Antiepileptic Drug Efficacy and Effectiveness as Initial Monotherapy for Epileptic Seizures and Syndromes. Epilepsia;2006:47:1094–120.

Natural history of treated epilepsy



Neligan A, et al. Epilepsy research 2011;96:225-30

Practical issues: what should we consider when using AEDs?

- 1. The diagnosis is appropriate for the choice of AEDs
- 2. Starting and Titrating the AEDs
- 3. If the 1st AED does not work, what to do next?
- 4. Blood tests and levels, when to check
- 5. Aware of side effects and what to do when SE occurs?
- 6. Aware of drug interaction
- 7. When to consider other modalities?