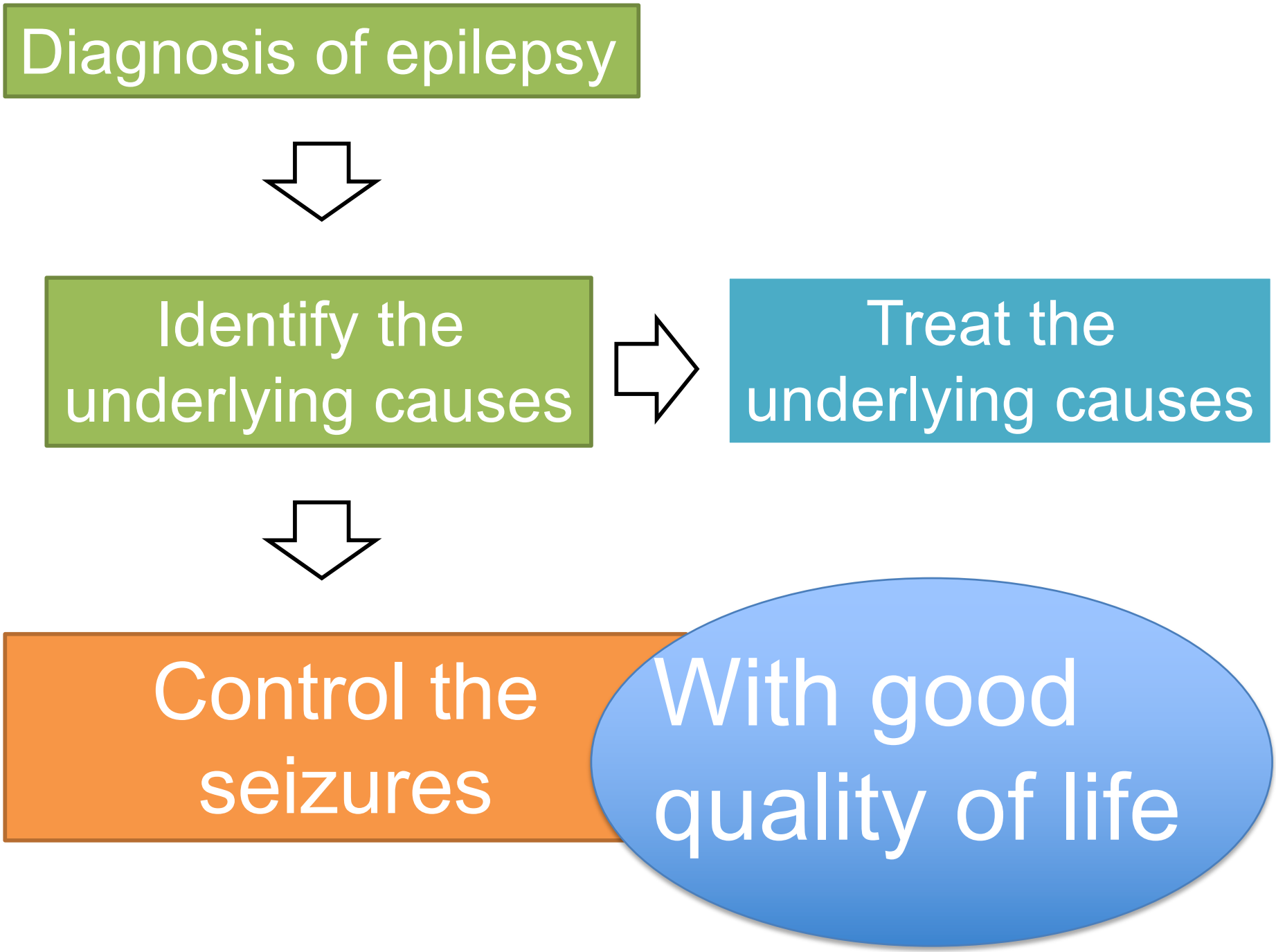
Mahidol University
Faculty of Medicine Siriraj Hospital

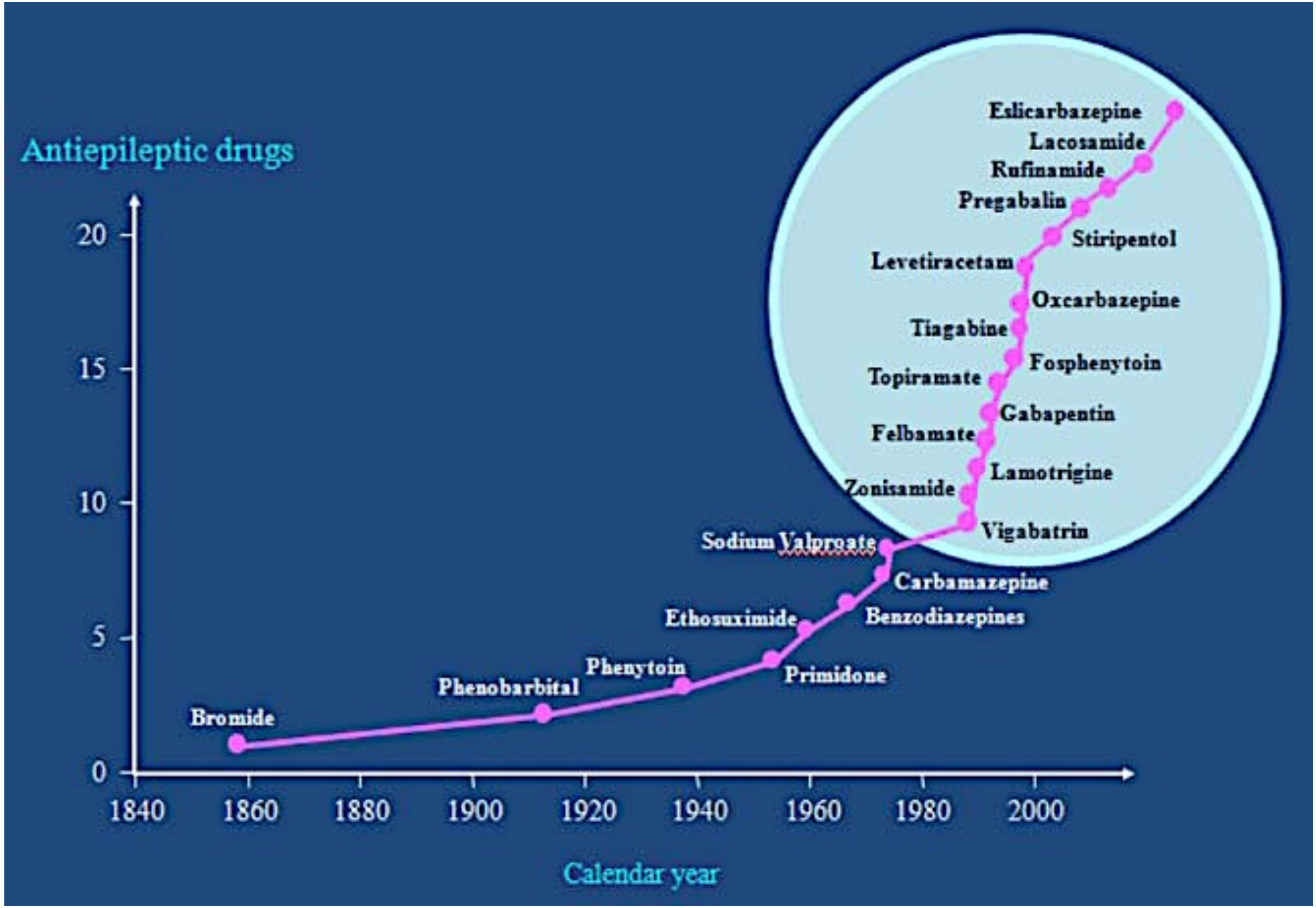
Selection of ASMs in special population

Kanokwan Boonyapisit, M.D.
Department of Medicine
Siriraj Hospital

GOAL OF EPILEPSY TREATMENT


Diagnosis of epilepsy
Identify the underlying causes
Treat the underlying causes
Control the seizures
With good quality of life

Antiepileptic drug development



New (2nd generation) AEDs

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

Advantage of 2nd gen. AEDs

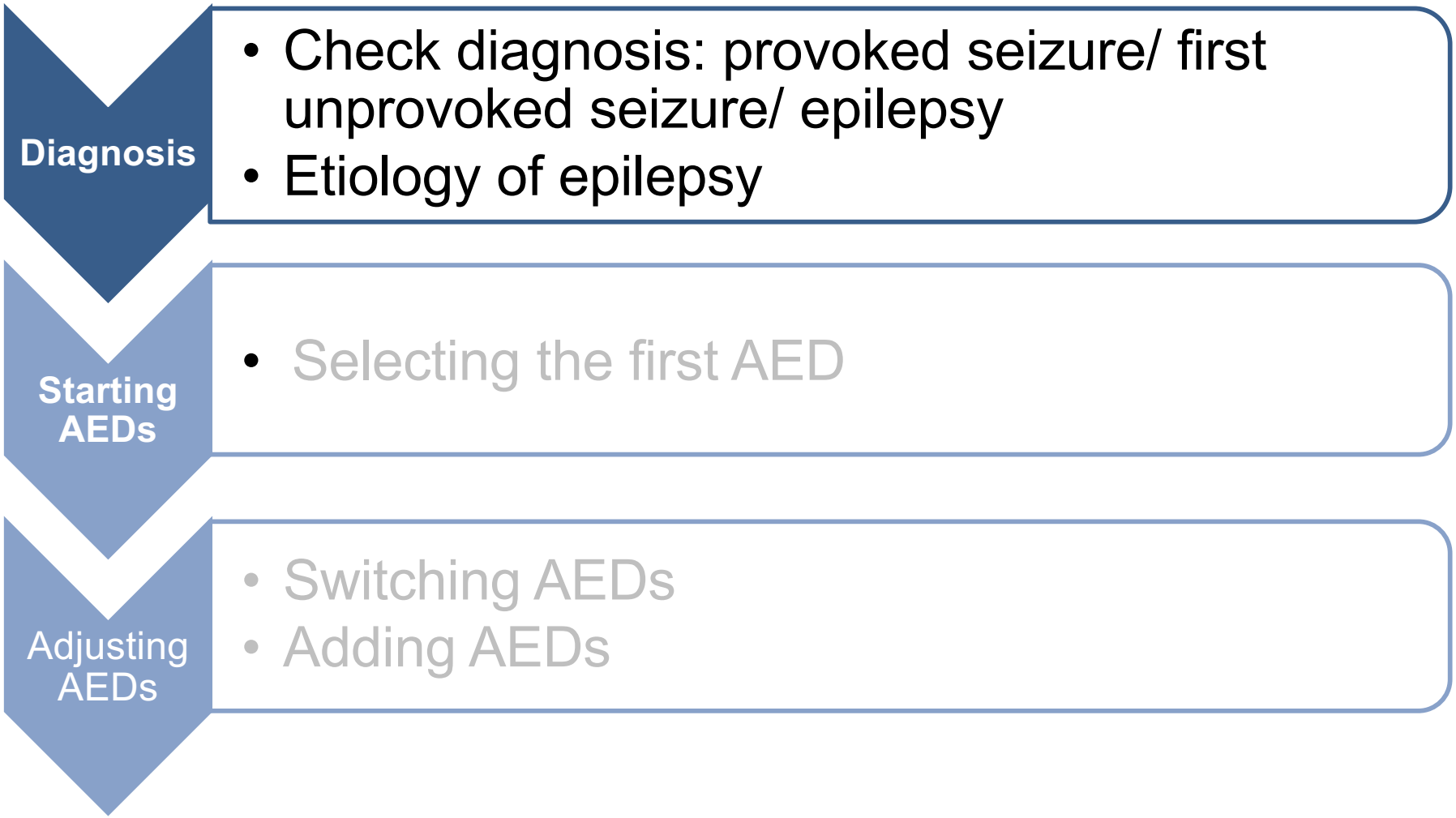
- Give clinician more choices of antiepileptic medications especially more choices of broad spectrum AEDs
- Better efficacy?
- Better tolerability?
- Better pharmacokinetic properties
- Low protein binding
- Most of the new AEDs are not strong hepatic enzyme inducers→ fewer drug interaction
- Fewer serious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

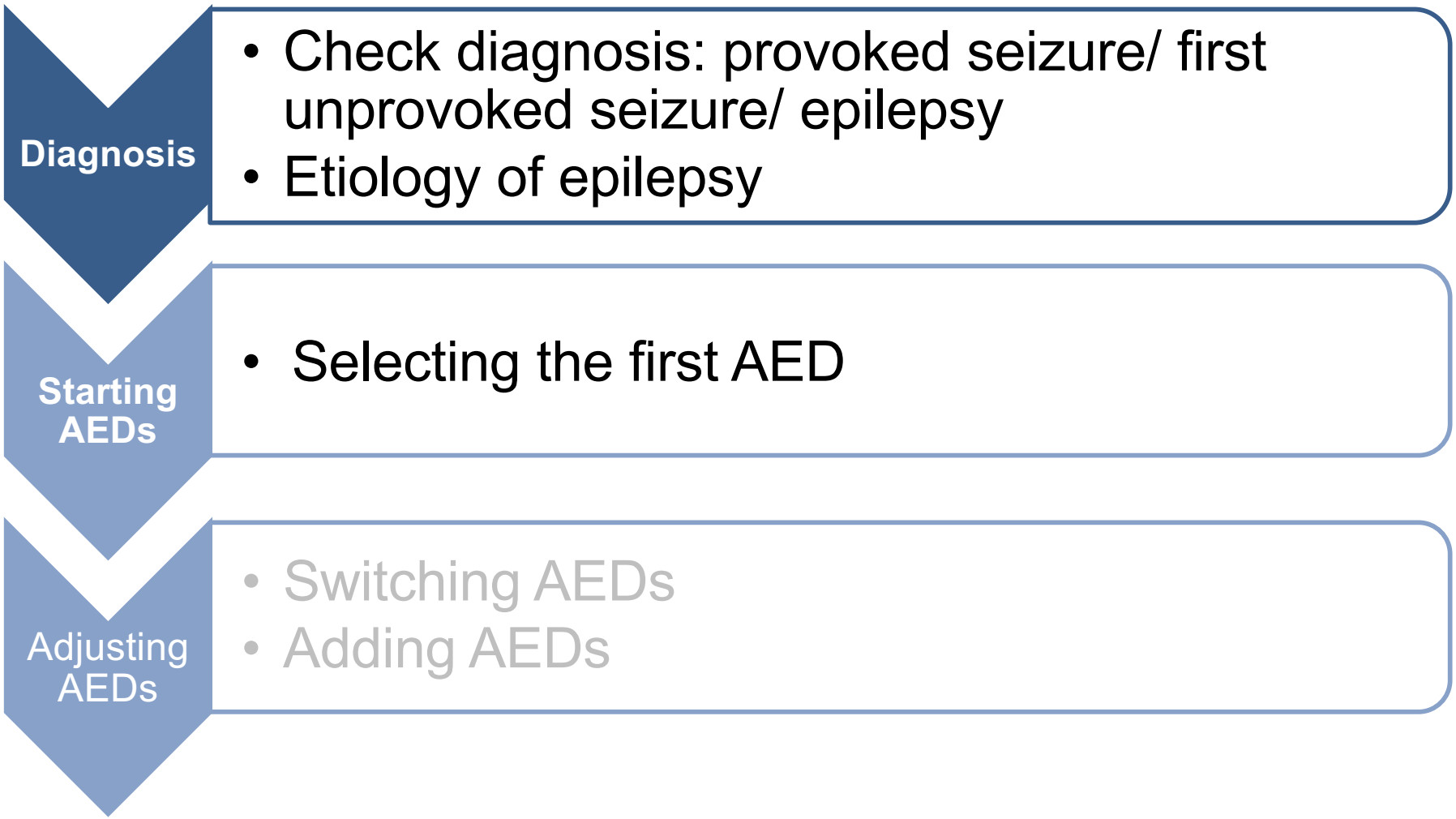
Newest (3rd generation) AEDs

- 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
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


Diagnosis
• Check diagnosis: provoked seizure/ first unprovoked seizure/ epilepsy
• Etiology of epilepsy
Starting AEDs
• Selecting the first AED
Adjusting AEDs
• Switching AEDs
• Adding AEDs


Diagnosis
• Check diagnosis: provoked seizure/ first unprovoked seizure/ epilepsy
• Etiology of epilepsy
Starting AEDs
• Selecting the first AED
Adjusting AEDs
• Switching AEDs
• Adding AEDs

SELECTING THE FIRST AED

Which medications?

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

AEDs

- Which AEDs are available?
- Cost
- Experience

Patient's profile

- Type of seizures
- Age
- Weight
- Occupation
- Underlying diseases
- Current medication
- Psychological profiles

Drug administration
Prone to which side effects
Potential drug interaction

Elderly

- Changes in pharmacokinetics of AEDs in the elderly
- Side effects of the AEDs esp. cognitive side effects
- Drug interaction
- Osteoporosis

Pharmacokinetic changes in the elderly

Lean body mass ↓

Total body water mass ↓

Proportion of fat ↓

↓

Volume distribution of hydrophilic drugs and lipophilic drugs ↓

↓

Serum drug concentrations ↑

Pharmacokinetic changes in the elderly

- Decreased albumin level leads to increased free fraction of drugs in the body.
- Measurement of total serum drug concentration may not reflect the true unbound drug level.
- Reduce hepatic metabolism (evidence is still unclear) and reduce renal excretion with reduction of creatinine clearance

Caution of SE of AEDs in elderly

AEDs	Special precautions
Phenobarbital	Drowsiness, cognitive dysfunction May reduce effects of other drugs (enzyme inducer)
Phenytoin	Reduced metabolism and clearance Reduced protein binding → increased free fraction Increase incidence of adverse effects PHT level may be increased by amiodarone, cimetidine, isoniazid, trazodone May reduce effects of other drugs (enzyme inducer)
Carbamazepine	Increase incidence of adverse effects May reduce effects of other drugs (enzyme inducer) Hyponatremia
Sodium valproate	Drowsiness, parkinsonism Thrombocytopenia
Oxcarbazepine	Increase incidence of adverse effects Hyponatremia
Topiramate	Cognitive side effects at higher dosage (can be avoided by slow titration)

Epilepsia, **(*):1–13, 2013
doi: 10.1111/epi.12074

SPECIAL REPORT

Updated ILAE evidence review of antiepileptic drug efficacy and effectiveness as initial monotherapy for epileptic seizures and syndromes

***Tracy Glauser, †Elinor Ben-Menachem, ‡Blaise Bourgeois, §Avital Cnaan, ¶Carlos Guerreiro, #Reetta Kälviäinen, **Richard Mattson, ††Jacqueline A. French, ‡‡Emilio Perucca, §§Torbjorn Tomson for the ILAE subcommission of AED Guidelines**

***Comprehensive Epilepsy Center, Division of Neurology, Cincinnati Children's Hospital Medical Center, University of Cincinnati College of Medicine, Cincinnati, Ohio, U.S.A.; †Institution for Clinical Neuroscience, Sahlgrenska Academy, University of Göteborg, Göteborg, Sweden; ‡Department of Neurology, The Children's Hospital and Harvard Medical School, Boston, Massachusetts, U.S.A.; §Division of Biostatistics and Study Methodology, Center for Translational Science, Children's National Medical Center, Washington, District of Columbia, U.S.A.; ¶Department of Neurology, University of Campinas (UNICAMP), Hospital das Clínicas, Campinas, Sao Paulo, Brazil; #Department of Neurology, Kuopio Epilepsy Center, Kuopio University Hospital, Kuopio, Finland; **Department of Neurology, Yale University School of Medicine, Yale New Haven Hospital, New Haven, Connecticut, U.S.A.; ††Comprehensive Epilepsy Center, New York University Langone Medical Center, New York, New York, U.S.A.; ‡‡Clinical Pharmacology Unit, Institute of Neurology, IRCCS C. Mondino Foundation, University of Pavia, Pavia, Italy; and §§Department of Clinical Neuroscience, Karolinska Institute, Stockholm, Sweden**

Glauser T, et al. Epilepsia 2013

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)
Adults with partial-onset seizures	4	1	34	Level A: CBZ, LEV, PHT, ZNS Level B: VPA Level C: GBP, LTG, OXC, PB, TPM, VGB Level D: CZP, PRM
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
Elderly adults with partial-onset seizures	1	1	3	Level A: GBP, LTG Level B: None Level C: CBZ Level D: TPM, VPA
Adults with generalized onset tonic–clonic seizures	0	0	27	Level A: None Level B: None Level C: CBZ, LTG, OXC, PB, PHT, TPM, VPA Level D: GBP, LEV, VGB

AEDs in the elderly

Study	Type of epilepsy	Discontinuation rates	Efficacy
KOMET (Pohlmann-Eden, 2016)	> 60 yo	LEV<VPA<CBZ	similar
Rowan, 2005	New onset epilepsy >60 yo VA population	LTG<GBP<CBZ	similar
Werhahn, 2015 (RCT)	New onset epilepsy >60 yo	LEV<LTG<CBZ	similar

WOMEN WITH EPILEPSY

Women with epilepsy

- Side effects of antiepileptic medications
  - Cosmetic side effects
  - Weight issues
  - Osteoporosis
  - Teratogenic effects
- Contraception
- Pregnancy
- Lactation
- How to advise the patients

Skin and cosmetic side effects

Side effects	AEDs	Time frame	Incidence	Reversible
Alopecia	VPA		0.5-4%/ up to 6%	
	CBZ, OXC	2-3 months		
Gum hypertrophy	PHT	Chronic use	10-40%	/
Hirsutism, hypertrichosis	PB			
	PHT			
Acne	VPA			
	PHT			
Dupuytren's Contracture, plantar fibromatosis	PB	Chronic use	Up to 5%	/

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

Weight issues from AEDs

Weight Gain	Weight Neutral	Weight Loss
Valproate	Lamotrigine	Topiramate
Gabapentin	Levetiracetam (?)	Zonisamide
Carbamazepine	Phenytoin	Felbamate
Tiagabine (?)		
Vigabatrin		

Body weight changes with AEDs

Side effects	AEDs	Time frame	Incidence	Extent
Weight gain	VPA	2-3 months and may be continue	Up to 30-40%	1-3% of BW Up to 8% of BW (with high dose)
	GBP		23%	
	PGB		18%	
	RTG			
Weight loss	TPM	Stabilize after 12-18 months	6-17% in leaflet (upto 60% in review)	Up to 7.5% of BW Dose dependent
	ZNS		3%	
	FBM			
	STP			

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

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	✓

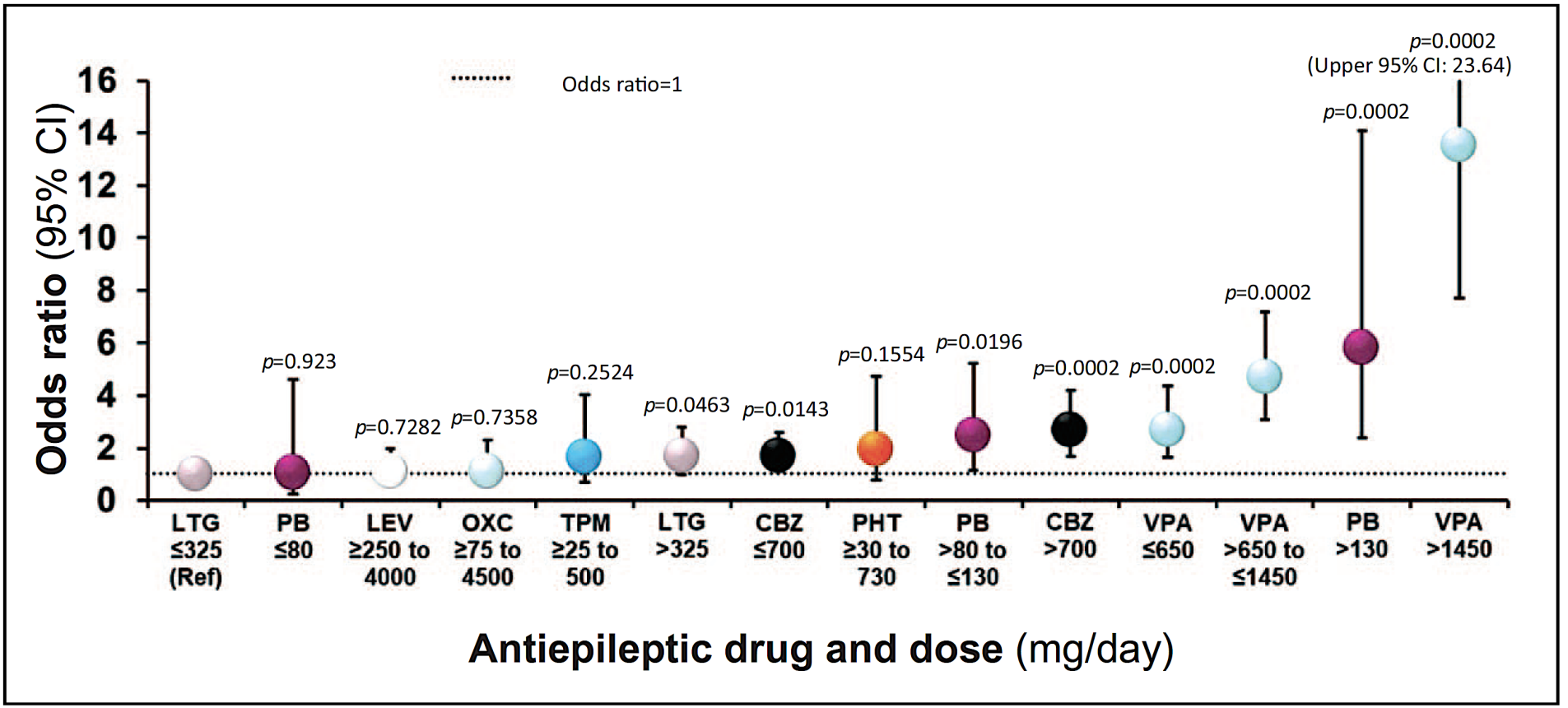


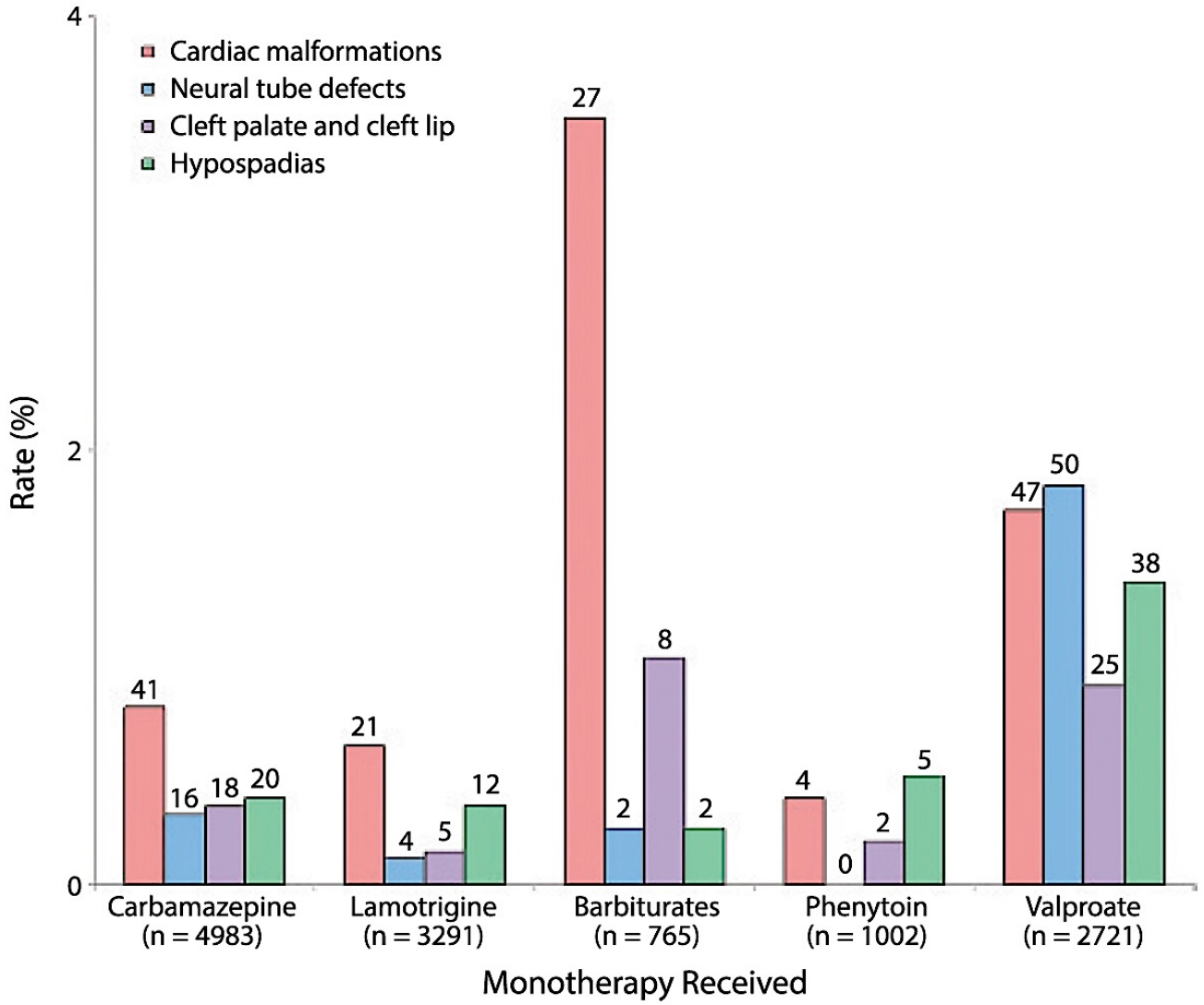
FIGURE 3. Risk of major congenital malformations (odds ratios with 95% confidence intervals) with different antiepileptic drug treatments compared with lamotrigine 325 mg/day or less. CBZ, carbamazepine; LEV, levetiracetam; LTG, lamotrigine; OXC, oxcarbazepine; PB, phenobarbital; PHT, phenytoin; Ref, reference; TPM, topiramate; VPA, valproate. Based on Data from [5▪▪].

Tomson T, Battino D, Bonizzoni E, et al. Comparative risk of major congenital malformations with eight different antiepileptic drugs: a prospective cohort study of the EURAP registry. Lancet Neurol 2018; 17:530–538.

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

Are there specific MCMs associated with specific AEDs?



Treatment for epilepsy in pregnancy: neurodevelopmental outcomes in the child (Review)

Bromley R, Weston J, Adab N, Greenhalgh J, Sanniti A, McKay AJ, Tudur Smith C, Marson AG

THE COCHRANE COLLABORATION®

Bromley R, et al. Cochrane Database of Systematic Reviews 2014, Issue 10. Art. No.: CD010236.

Characteristics of the studies

The review included 28 studies. Participants were women with epilepsy taking commonly used AEDs who were compared to either women without epilepsy or women who had epilepsy but who were not treated with AEDs. Comparisons were also made between children exposed to different AEDs in the womb. The evidence presented in this review was up to date to May 2014.

Results

- The evidence for younger children exposed to carbamazepine (CBZ) in the womb was conflicting, however this was likely to be due to differences in the way that these studies were carried out. In older children those exposed to CBZ were not poorer in their IQ than children who were not exposed. No link was found between the dose of CBZ and child ability.

- Both younger and older children exposed in the womb to sodium valproate (VPA) showed poorer cognitive development in comparison to children not exposed and children exposed to other AEDs. A link between dose of VPA and child ability was found in six studies; with higher doses of the drug linked to a lower IQ ability in the child. The level of this difference was likely to increase the risk of poorer educational levels.

- Children exposed to CBZ in the womb did not differ in their skills from children exposed to lamotrigine (LTG), however very few studies investigated this. There were also no differences between children exposed to phenytoin (PHT) in the womb and those exposed to CBZ or those exposed to LTG.

- There were very limited data on newer medications such as LTG, levetiracetam or topiramate.

Bromley R, et al. Cochrane Database of Systematic Reviews 2014, Issue 10. Art. No.: CD010236.

Conclusions

This review found that children exposed to VPA in the womb were at an increased risk of poorer neurodevelopment scores both in infancy and when school aged. The majority of evidence indicates that exposure in the womb to CBZ is not associated with poorer neurodevelopment. Data were not available for all AEDs that are in use or for all aspects of child neurodevelopment. This means decision making for women and their doctors is difficult. Further research is needed so that women and their doctors can make decisions based on research evidence about which medication is right for them in their childbearing years.

Bromley R, et al. Cochrane Database of Systematic Reviews 2014, Issue 10. Art. No.: CD010236.

Epilepsy and pregnancy

- ควรมีการให้ความรู้เกี่ยวกับโอกาสและความเสี่ยงที่จะเกิดความผิดปกติของเด็กในครรภ์สำหรับหญิงวัยเจริญพันธุ์ที่ต้องรับประทานยากันชัก เพื่อผู้ป่วยจะได้สามารถวางแผนและตัดสินใจเรื่องการตั้งครรภ์ล่วงหน้าได้

Epilepsy and pregnancy

- ควรวางแผนล่วงหน้าก่อนการตั้งครรภ์เนื่องจาก
  - ในกรณีที่มารดาไม่มีอาการชักนานเกิน 2 ปีอาจพิจารณาหยุดยากันชักได้
  - ในกรณีที่คุมอาการชักได้ดี และมารดารับประทานยากันชักมากกว่า 1 ชนิดอาจพิจารณาลดขนาดยาหรือลดยาเหลือ 1 ชนิด เพื่อลดโอกาสการเกิดผลข้างเคียงต่อทารกในครรภ์

Epilepsy and pregnancy

- ควรวางแผนล่วงหน้าก่อนการตั้งครรภ์เนื่องจาก
  - ควรหลีกเลี่ยงการใช้ยากันชักที่มี teratogenic effect สูง เช่น sodium valproate ในช่วงการตั้งครรภ์หากสามารถทำได้

Epilepsy and pregnancy

- ในขณะที่ผู้ป่วยตั้งครรภ์ไม่ควรปรับหรือเปลี่ยนยากันชัก เนื่องจากโอกาสที่จะเกิดอันตรายต่อมารดาและทารกในครรภ์หากผู้ป่วยเกิดการชักมีมากกว่าโอกาสการเกิดผลข้างเคียงต่อทารกในครรภ์
- ควรมีการตรวจคัดกรองความผิดปกติของเด็กในครรภ์มารดา โดยเฉพาะ malformation ที่พบได้บ่อยและรุนแรง เช่น neural tube defect

Epilepsy and pregnancy

- ในผู้หญิงวัยเจริญพันธ์ควรได้รับ folic acid supplementation ในขนาด 4-5 mg/d ซึ่งจากการศึกษาที่ผ่านมา อาจช่วยลดโอกาสการเกิด neural tube defects ได้บ้าง
- ในผู้ป่วยที่ได้รับ enzyme inducing AEDs เด็กแรกคลอดควรได้รับ vitamin K supplement หลังคลอดเช่นเดียวกับเด็กอื่นๆ

AEDs

- Which AEDs are available?
- Cost
- Experience

Patient's profile

- Type of seizures
- Age
- Weight
- Occupation
- Underlying diseases
- Current medication
- Psychological profiles

Drug administration
Prone to which side effects
Potential drug interaction

UNDERLYING DISEASE
CURRENT MEDICATION

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	Enzyme inducing AEDs	
On OCP	Enzyme inducing AEDs	
HLA 1502 +ve	CBZ	
Sulfa allergy	ZNS	

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

UNDERLYING DISEASE
CURRENT MEDICATION

HEPATIC/ RENAL DYSFUNCTION

AED	Protein binding %	T/2	Site of elimination	Remarks
Gabapentin	0	4-6	Renal, 100% Not metabolize	Dose dependent absorption
Lamotrigine	55	15-30	Hepatic, 90% Glucoronidation	Clearance increased by enzyme inducing AEDs, reduced by VPA
Topiramate	9-17	15-23	Renal, 40-70%	Fraction hepatically metabolized, increased by enzyme inducing AEDs
Levetiracetam	0	6-8	Renal, 66%; hydrolysis of acetamide gr, 34%	Metabolism is nonhepatic hydrolysis
Oxcarbazepine	40	4-9	Hepatic, 70% Hepatic conversion to active metabolite	Based upon 10 Hydroxy carbazepine (MHD), the major active metabolite
Zonisamide	40-60	24-60	Hepatic, 70%	Clearance increased by enzyme inducing AEDs
Pregabaline	0	6	Renal Not metabolize	

Effects	Older AEDs	New AEDs
Measurable increased in free fraction with hypoalbuminemia	PHT VPA	-
Metabolism affected by renal disease	PB	GBP, LEV, TPM
Metabolism affected by liver disease	CBZ, PHT, VPA	LTG, ZNS, OXC, TGB

UNDERLYING DISEASE
CURRENT MEDICATION

CARDIAC CONDITIONS

Using AEDs in cardiac conditions

- Side effects
- Drug interaction

IV AEDs for established SE

	Route of administration	Adult dose
Phenytoin	IV (<50 mg/min)	15-20 mg/kg
Fosphenytoin	IV (<100 mg PE/min)	15-20 mg PE/kg
Phenobarbital	IV (<100 mg/min)	10-20 mg/kg
Valproate	IV (50-100 mg/min)	20-30 mg/kg
Levetiracetam	IV (100 mg/min)	2000-4000 mg
Lacosamide	IV (30-60 min/ up to 15 min)	200-400 mg

Shorvon S. Curr Opin Neurol 2011;24:165–170

Interaction with cardiac drugs

- Phenytoin → ⬇ amiodarone level (CYP induction)
  ⬇ digoxin level (upreg. P-gp)
- Enzyme inducers
  → ⬇ calcium channel blocker level
  ⬇ beta blocker level
- Verapamil and diltiazem inhibits carbamazepine metabolism

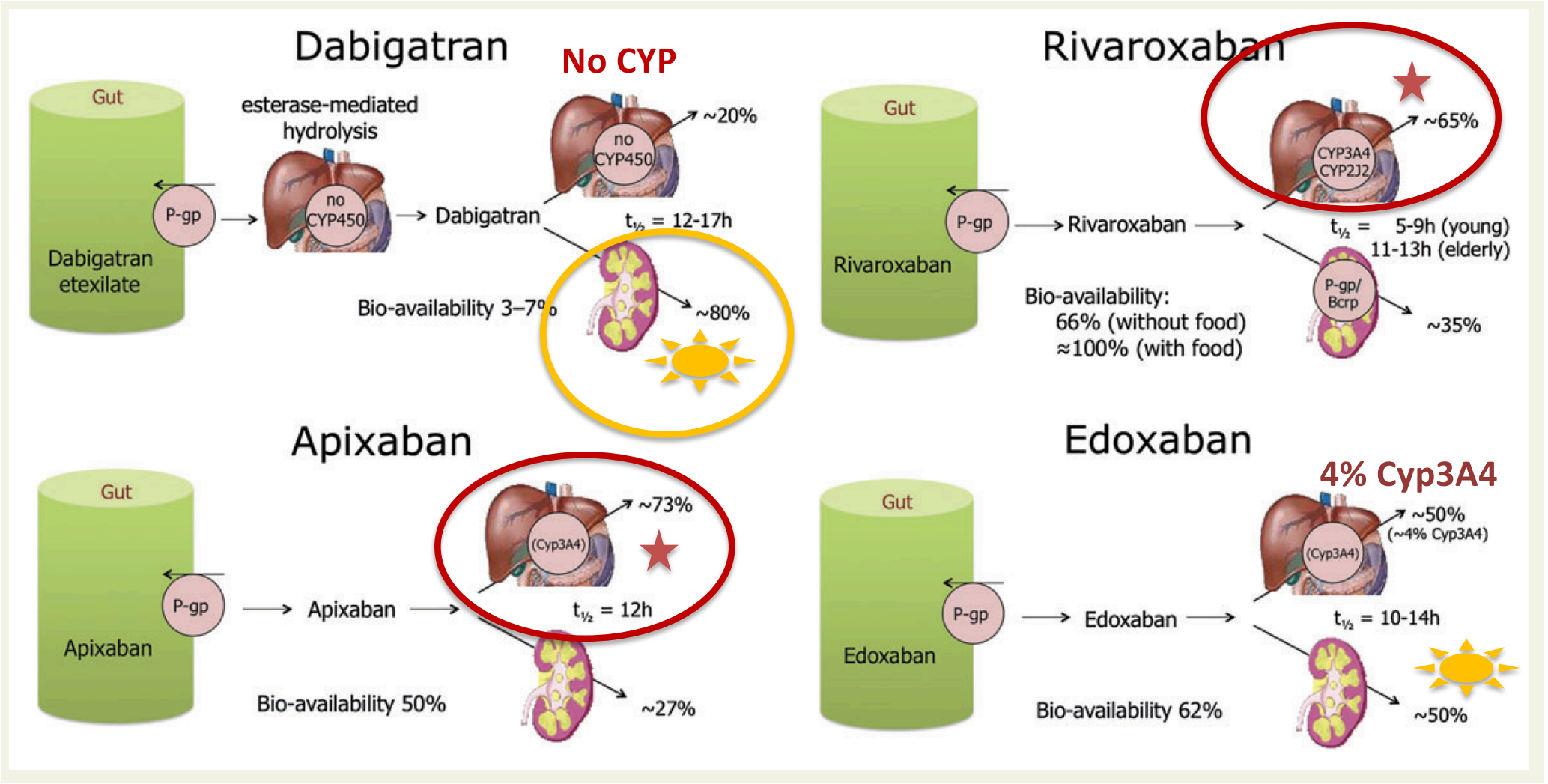
Drug interaction with warfarin

- Metabolites through CYP3A4, 2C9
- Phenytoin, phenobarbital and carbamazepine reduce the concentration of warfarin by up to 50-65%
- Phenobarbital and carbamazepine also reduce the anticoagulation effects of warfarin metabolites
- Newer AEDs do not have significant interaction with anticoagulant

Interaction between AEDs and NOACs

- Intestinal absorption and renal elimination of NOACs are dependent on the intestinal and renal permeability glycoprotein (P-gp) efflux transporter protein system
- Some NOACs are substrates of the hepatic CYP3A4 enzymes
- Induction of P-gp or CYP3A4 might decrease serum NOAC levels, reduce anticoagulant effects and lead to an increase in embolic risk.

Absorption and metabolism of the different new anticoagulant drugs



DE-RA

ESC European Society of Cardiology

Europace (2021) **00**, 1–65
doi:10.1093/europace/euab065

POSITION PAPER
EHRA PRACTICAL GUIDE

2021 European Heart Rhythm Association Practical Guide on the Use of Non-Vitamin K Antagonist Oral Anticoagulants in Patients with Atrial Fibrillation

Jan Steffel[1]*, Ronan Collins[2], Matthias Antz[3], Pieter Cornu[4], Lien Desteghe[5,6], Karl Georg Haeusler[7], Jonas Oldgren[8], Holger Reinecke[9], Vanessa Roldan-Schilling[10], Nigel Rowell[11], Peter Sinnaeve[12], Thomas Vanassche[12], Tatjana Potpara[13], A. John Camm[14], and Hein Heidbüchel[5,6]

Steffel J, et al. Europace 2021; 0:1-65

	Via[426, 539-541]	Dabigatran etexilate	Apixaban	Edoxaban	Rivaroxaban
P-gp substrate		Yes	Yes	Yes	Yes
CYP3A4 substrate		No	Yes (≈25%)	No (<4%)	Yes (≈18%)
Drug					
Brivaracetam	–	No relevant interaction known/assumed			
Carbamazepine	Strong CYP3A4/P-gp induction; CYP3A4 competition	-29% [542]	-50% (SmPC)	SmPC	SmPC
Ethosuximide	CYP3A4 competition	No relevant interaction known/assumed			
Gabapentin	–	No relevant interaction known/assumed			
Lacosamide	–	No relevant interaction known/assumed			
Lamotrigine	P-gp competition	No relevant interaction known/assumed			
Levetiracetam	P-gp induction; P-gp competition				
Oxcarbazepine	CYP3A4 induction; P-gp competition				
Phenobarbital	Strong CYP3A4/possible P-gp induction		SmPC	SmPC	SmPC
Phenytoin	Strong CYP3A4/P-gp induction; P-gp competition	SmPC [543]	SmPC	SmPC	SmPC
Pregabalin	–	No relevant interaction known/assumed			
Topiramate	CYP3A4 induction; CYP3A4 competition				
Valproic acid	CYP3A4/P-gp induction/inhibition				Ref 544
Zonisamide	CYP3A4 competition; weak P-gp inhibition	No relevant interaction known/assumed (SmPC)			

- Colour coding is based on the respective NOAC SmPC (**Summary of Product Characteristics)**, drug interaction databases, or expert opinion.
- The hatched colour coding indicates no clinical or PK data available.
- Some of the colour codes will likely require adaptation as more data become available over time.
- White: No relevant drug–drug interaction anticipated.
- Blue (dark): Contraindicated due to reduced NOAC plasma levels.
- Blue (light): Caution required, especially in case of polypharmacy or in the presence of >_2 light blue interactions due to reduced NOAC plasma levels.

Steffel J, et al. Europace 2021; 0:1-65

UNDERLYING DISEASE
CURRENT MEDICATION

INFECTIOUS CONDITIONS

Antibiotics/AEDs interaction

Drug groups	Drugs	Effects on AEDs
Antibiotics	Carbapenems	↓↓↓ VPA levels
	Macrolides	↑ CBZ levels
Antifungals	Fluconazole Itraconazole Ketoconazole	↑ CBZ levels ↑ PHT levels
Tuberculostatics	Rifampicin	↓ PHT, CBZ, VPA, LTG levels
	Isoniazid	↑ PHT, CBZ, VPA, LTG levels

Epilepsia Open

SHORT RESEARCH ARTICLE

Carbapenems and valproate: A consumptive relationship

*†Peter Bede, ‡Diane Lawlor, ‡Damodar Solanki, and *§Norman Delanty

Epilepsia Open, 2(1):107–111, 2017
doi: 10.1002/epi4.12030

Table 1. Summary of the demographic and clinical profile of the cases

Case	Age	Sex	Pre-meropenem VPA dose	Last pre-meropenem VPA level	Duration of meropenem therapy	VPA measured after initiation of meropenem	VPA level during meropenem therapy	Patient symptomatic of low VPA	Intervention	Normalization of VPA levels post-meropenem therapy
1	55	Female	800 mg BD	19	+14 days	24 h	8	Yes; seizures	Increased dose + bolus + alternative AED	*RIP*
2	42	Male	600 mg BD	41	10 days	24 h	<3	No	No	4 weeks
3	24	Female	600 mg TDS	45	3 days	72 h	9	Yes; seizures	Increased dose + bolus + alternative AED	*RIP*
4	42	Male	625 mg BD	N/A	24 + 7 days	Meropenem introduced first	6	Yes; seizures	Increased dose + bolus	4 weeks
5	78	Male	600 mg BD	27	3 days	72 h	9	No, but intubated	Meropenem discontinued	*RIP*
6	25	Male	1,300/1,200 mg	106	7 days	7 days	11	Yes; seizures	No	Checked 2 months later
7	69	Female	300 mg BD	40	10 days	72 h	<3	Yes; hypomania	Increased dose	8 days

AED, antiepileptic drug; BD, twice a day; RIP, patient deceased; TDS, three times a day.

UNDERLYING DISEASE
CURRENT MEDICATION

HIV INFECTION

Interaction between ARVs and AEDs

ARV	Protein binding (%)	Metabolism	Potential drugs that may have interaction with AEDs	AEDs that may have interaction with
NRTI	Min- 38	Gluc	↑Zidovudine	VPA
NNRTI	50-90	CYP450		
PI	>99	CYP450	↓Lopinavir/ Ritonavir	PHT

SPECIAL REPORT

Antiepileptic drug selection for people with HIV/AIDS: Evidence-based guidelines from the ILAE and AAN

*†Gretchen L. Birbeck, ‡Jacqueline A. French, §Emilio Perucca, ¶David M. Simpson, #Henry Fraimow, **Jomy M. George, ††Jason F. Okulicz, ‡‡David B. Clifford, §§Houda Hachad, and §§René H. Levy for the Quality Standards subcommittee of the American Academy of Neurology and the ad hoc task force of the Commission on Therapeutic Strategies of the International League Against Epilepsy

Epilepsia, 53(1):207–214, 2012

Recommendations

- AED–ARV administration may be indicated in up to 55% of people taking ARVs.
- Patients receiving phenytoin may require a lopinavir/ritonavir (PI) dosage increase of approximately 50% to maintain unchanged serum concentrations (Level C: one class II study).
- Patients receiving valproic acid may require a zidovudine (NRTI) dosage reduction to maintain unchanged serum zidovudine concentrations (Level C).
- Coadministration of valproic acid and efavirenz (NNRTI) may not require efavirenz dosage adjustment (Level C: one class II study).

Epilepsia, 53(1):207–214, 2012

Recommendations

- It may be important to avoid enzyme inducing AEDs in people on ARV regimens that include protease inhibitors or non nucleoside reverse transcriptase inhibitors because pharmacokinetic interactions may result in virologic failure, which has clinical implications for disease progression and development of ARV resistance. If such regimens are required for seizure control, patients may be monitored through pharmacokinetic assessments to ensure efficacy of the ARV regimen (Level C: one class II study).

Epilepsia, 53(1):207–214, 2012

UNDERLYING DISEASE
CURRENT MEDICATION

TRANSPLANT PATIENTS

Using AEDs in transplant patients

- CBZ, oxcarbazepine, PB, and PHT may reduce cyclosporine, tacrolimus, and corticosteroid blood levels with a delayed effect of up to 10 days.
- Azathioprine, mycophenolate mofetil, and OKT3 metabolism are not significantly affected by AEDs.

UNDERLYING DISEASE
CURRENT MEDICATION

ONCOLOGIC CONDITIONS

Potentials interaction between AEDs and chemotherapy

- Enzyme inducing AEDs have been shown to have effects on levels of chemotherapy that metabolite through CYP 450
- Taxanes, vinca alkaloids, methotrexate, teniposide, and camptothecin analogues such as irinotecan
- Tyrosine kinase inhibitors, target therapy

Vecht CJ, Wagner GL, Wilms EB. Lancet Neurol 2003;2:404–9.

Effects of AEDs on chemotherapy metabolism

Group	AEDs	CTD	Met	Factor changes in metabolism
Alkylating agents	EIAEDs	Cyclophosphamide	CYP	Cl ⇧ 210%
Taxanes	EIAEDs	Docetaxel Pacitaxel	CYP	Cl ⇧ 150%
Antimetabolites	EIAEDs	Methotrexate		AUC ⇩ 58%
Vinca alkaloids	EIAEDs	Vincristine	CYP	Cl ⇧ 160%
Camtothecin derivatives	EIAEDs	Irinotecans	CYP	Cl ⇧ 200-235%
	VPA	Irinotecans		Cl ⇧ 175%
	EIAEDs	Topotecans	CYP	Cl ⇧ 145%
Topoisomerase II inhibitors	EIAEDs	Etoposide	CYP	Cl ⇧ 145-175%
	EIAEDs	Teniposide	CYP	Cl ⇧ 200-245%

Current Pharmaceutical Design 2017; 23: 6464-87

Effects of AEDs on tyrosine kinase inhibitors

Drugs	AEDs	Target	Met	Factor changes in metabolism
Bortezomib	EIAEDs	Proteosome inhibitor	CYP	Cl ⇧ 275%
Dasatinib	EIAEDs	SCR, Bcr-Abl	CYP	AUC ⇩ 45%
Gefitinib	EIAEDs	EGFR	CYP	AUC ⇩ 45-63%
Imatinib	EIAEDs	Bcr-Abl, c-kit, PDGFR	CYP	Cl ⇧ 342-413%
Lapatinib	EIAEDs	EGFR, HER2	CYP	Cl ⇧ 883%
Evorolimus Sirolimus	EIAEDs	mTOR	CYP	AUC ⇩ 45%
Sorafenib	EIAEDs	c-kit, PDGFR, RAF	CYP	AUC ⇩ 36-49%
Tamoxifen	EIAEDs	Estrogen receptor	CYP	Dose ⇩ 46%

Neuro-Oncology Practice 2016; 3: 245–260

Effects of AEDs on steroid metabolism

AED	Steroid	No. of Patients	Change in Steroid Activity	Factor of Change	Reference
Carbamazepine	Prednisolone	6	Cl ↑	1.41	Bartoszek, 1987[96]
			T 1/2 ↓	0.64	
Phenobarbital		6	Cl ↑	1.79	Bartoszek, 1987[96]
			T 1/2 ↓	0.44	
Phenytoin		2	Cl ↑	1.77	Bartoszek, 1987[96]
			T 1/2 ↓	0.71	
Carbamazepine	Methylprednisolone	5	Cl ↑	3.09	Bartoszek, 1987[96]
			T 1/2 ↓	0.46	
Phenobarbital		5	Cl ↑	4.42	Bartoszek, 1987[96]
			T 1/2 ↓	0.46	
Phenytoin		2	Cl ↑	5.79	Bartoszek, 1987[96]
			T 1/2 ↓	0.29	
Phenytoin	Dexamethasone	15	Cl ↑	2.93	Chalk, 1984[97]
			T 1/2 ↓	0.54	
Phenytoin		6	Plasma Conc ↓	0.5	Wong, 1985[98]

Abbreviations: bid, bis in die; CBZ, carbamazepine; EIAEDs, enzyme-inducing anti-epileptic drugs; PB, phenobarbital; PCV: procarbazine, CCNU, vincristine; PHT, phenytoin; VPA, valproic acid; Cl, clearance; T $\frac{1}{2}$, plasma drug elimination half-life; AUC, area under time-concentration curve; MTD, maximum tolerated dose; nEI, MTD without EIAEDs; EI, MTD with EIAEDs and corresponding Cl, T $\frac{1}{2}$, or AUC.

Neuro-Oncology Practice 2016; 3: 245–260

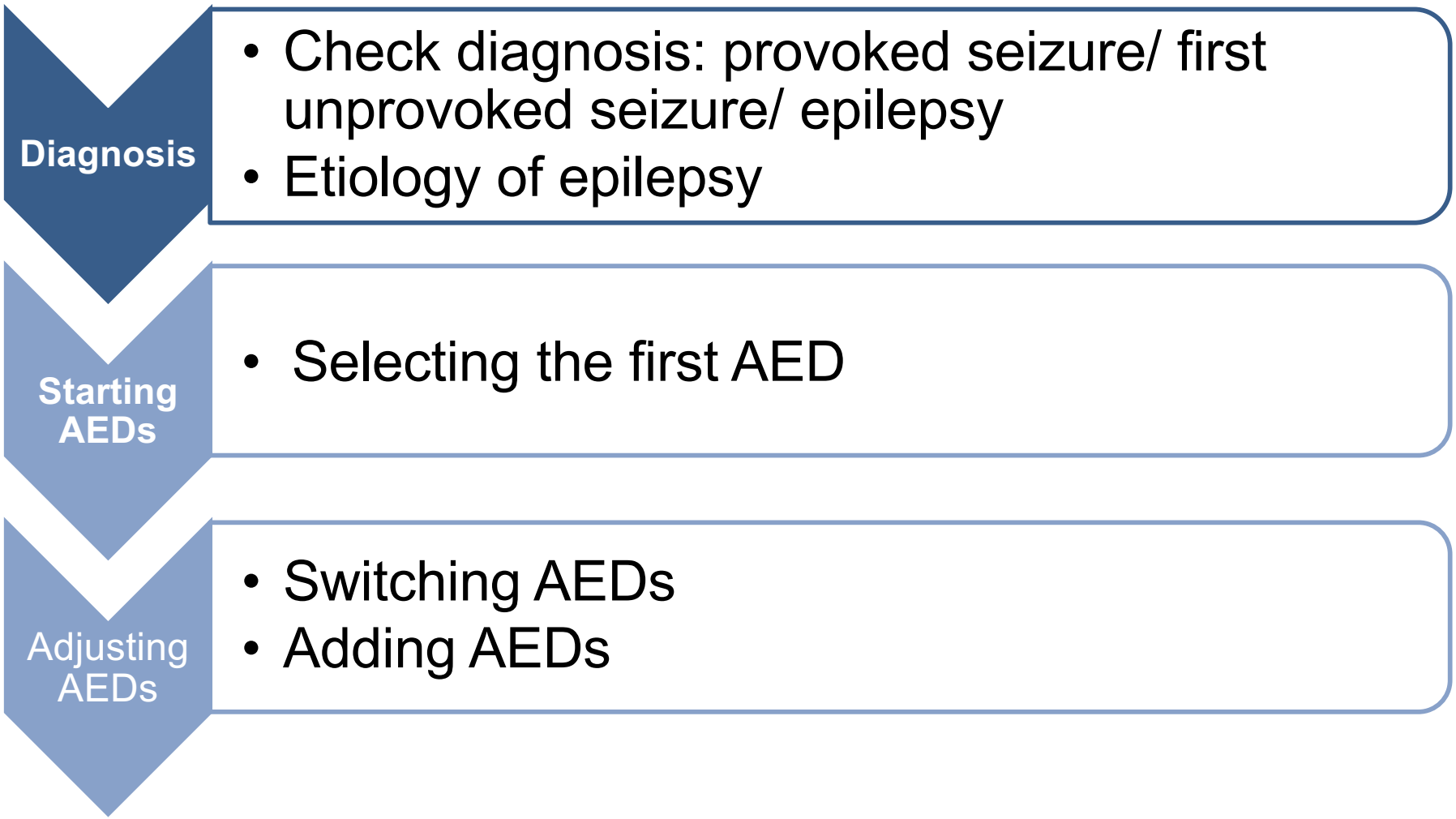
UNDERLYING DISEASE
CURRENT MEDICATION

PSYCHIATRIC COMORBIDITIES

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


Diagnosis
• Check diagnosis: provoked seizure/ first unprovoked seizure/ epilepsy
• Etiology of epilepsy
Starting AEDs
• Selecting the first AED
Adjusting AEDs
• Switching AEDs
• Adding AEDs

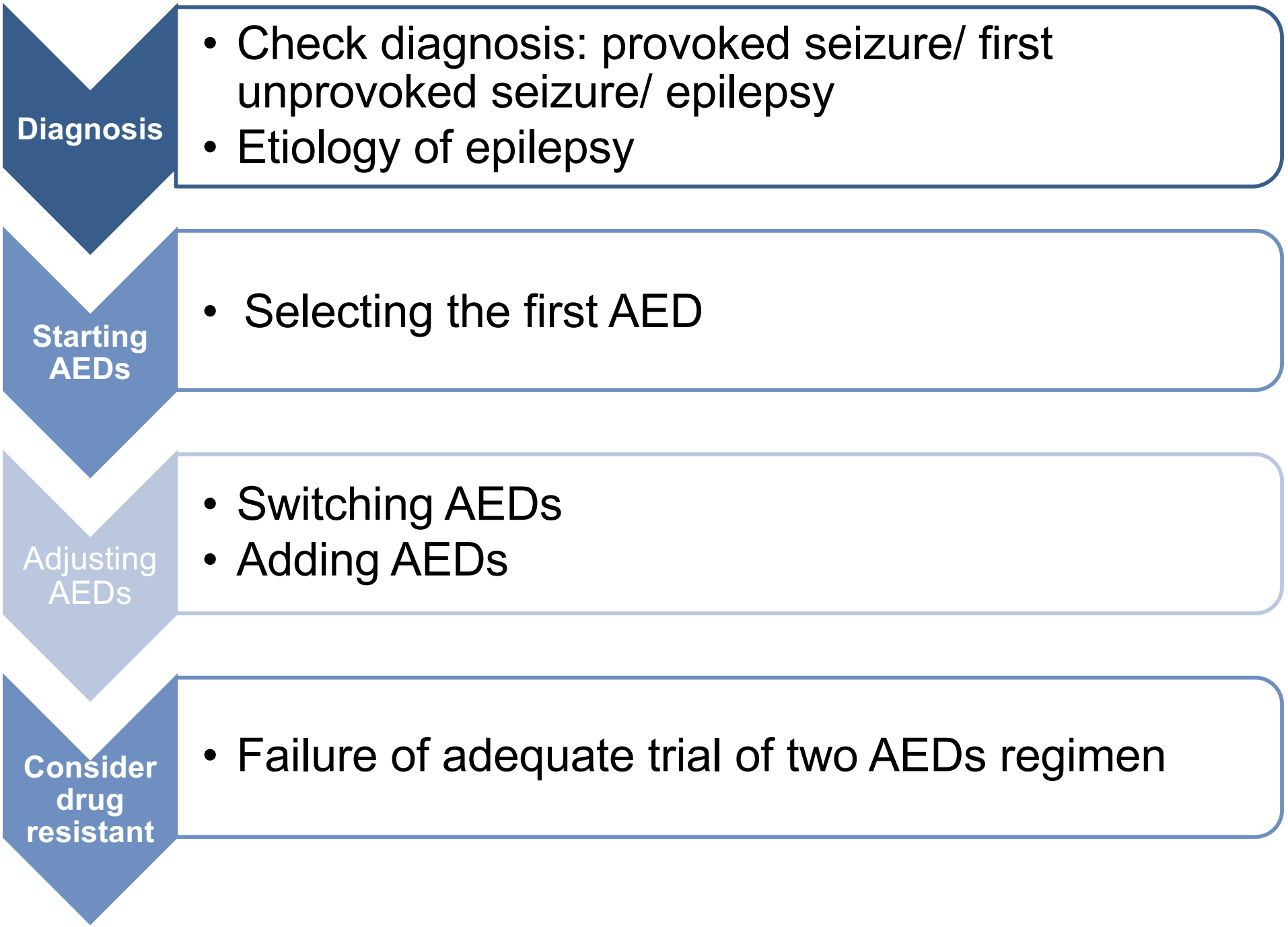
AEDs

- Which AEDs are available?
- Cost
- Experience

Patient's profile

- Type of seizures
- Age
- Weight
- Underlying diseases
- Current medication
- Occupation
- Psychological profiles

Drug administration
Prone to which side effects
Potential drug interaction


Diagnosis
• Check diagnosis: provoked seizure/ first unprovoked seizure/ epilepsy
• Etiology of epilepsy
Starting AEDs
• Selecting the first AED
Adjusting AEDs
• Switching AEDs
• Adding AEDs
Consider drug resistant
• Failure of adequate trial of two AEDs regimen