Mahidol University
Faculty of Medicine Siriraj Hospital

SI-NEURO

Special Considerations in Special Epilepsy Populations

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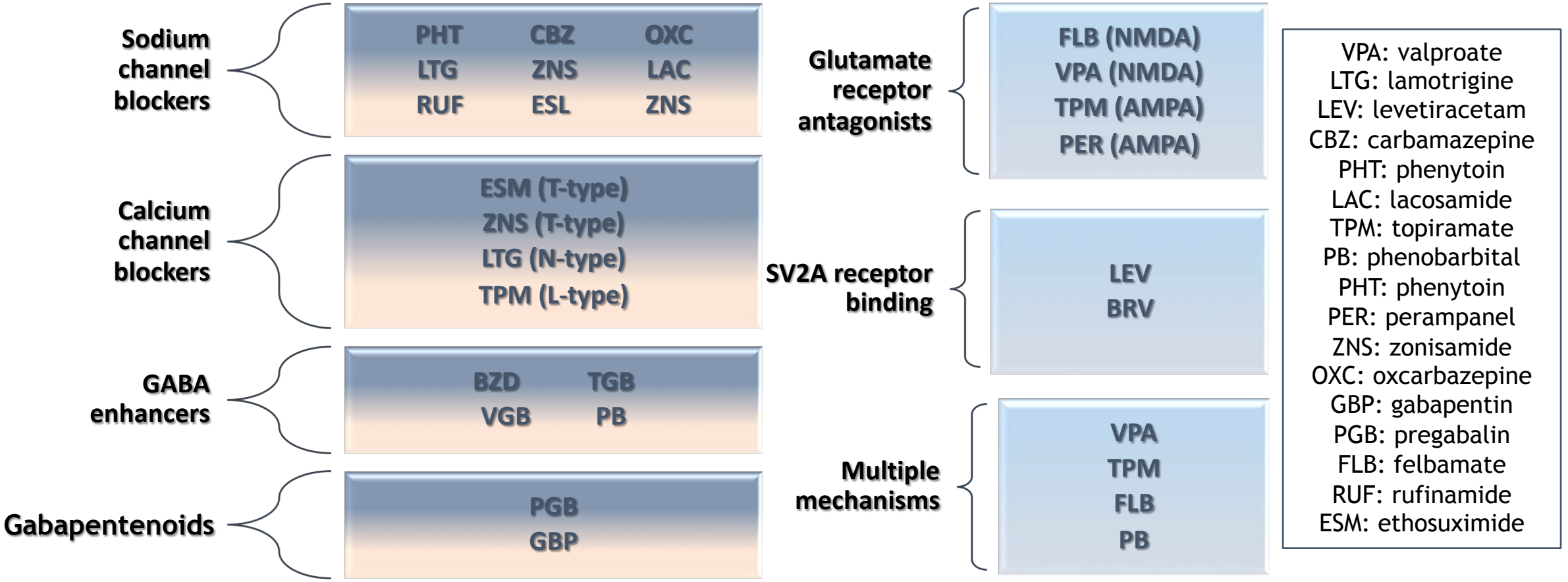
Department of Medicine
Siriraj Hospital

Mechanisms of action of ASMs



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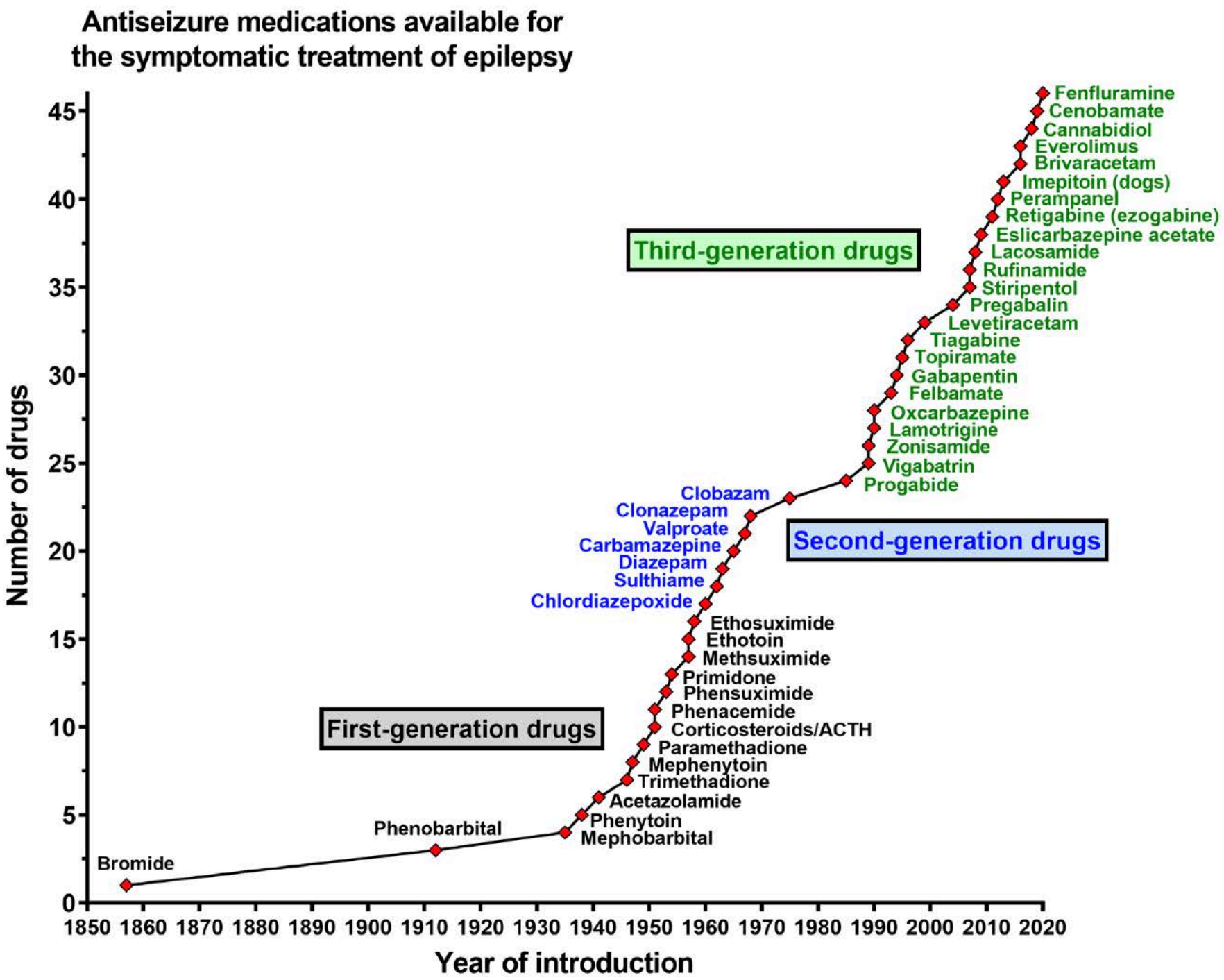
Loscher W, et al. CNS Drugs 2016;30:1055-77. 2. Stafstrom, C. Current opinion in Neurology 2010, 23:157-163.



Everolimus
Cannabidiol
Cenobamate
Fenfluramine

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

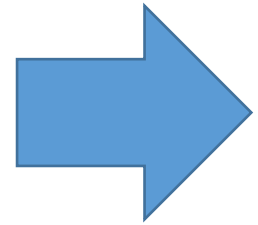
Selecting ASMs in special populations

- Special issues in this population
- Side effects that are most concerned in this population
- Drug interaction issues in this population

Case 1

- 23 year-old woman with JME

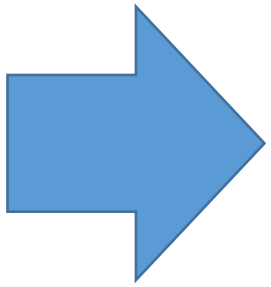
Phenytoin	Lamotrigine
Carbamazepine	Topiramate
Phenobarbital	Levetiracetam
Sodium valproate	Pregabalin
	Zonisamide
	Lacosamide
	Perampanel



Case 2

- 28 year-old married woman with JME, who is planning to have children

Phenytoin	Lamotrigine
Carbamazepine	Topiramate
Phenobarbital	Levetiracetam
Sodium valproate	Pregabalin
	Zonisamide
	Lacosamide
	Perampanel



Case 2

- What to consider in this case after delivery a baby?

Case 3

- 19 year-old man with JME

Phenytoin	Lamotrigine
Carbamazepine	Topiramate
Phenobarbital	Levetiracetam
Sodium valproate	Pregabalin
	Zonisamide
	Lacosamide
	Perampanel

National Patient Safety Alert

Medicines & Healthcare products Regulatory Agency

Valproate: organisations to prepare for new regulatory measures for oversight of prescribing to new patients and existing female patients

Date of Issue:	28 November 2023	Reference No:	NatPSA/2023/013/MHRA

This alert is for action by: Integrated Care Boards (in England), Health Boards (in Scotland), Health Boards (in Wales), and Health and Social Care Trusts (in Northern Ireland)

This is a safety critical and complex National Patient Safety Alert. Implementation should be coordinated by an executive lead for quality (or equivalent) in Integrated Care Boards in England, Health Boards in Scotland, Health Social Care Trusts in Northern Ireland, alongside the Chief Pharmacist (or equivalent) and sup organisations involved in the prescribing of valproate and clinical leads in neurology, psychiatry autism, contraception and sexual health, and general practice, with others included to meet loc

Explanation of identified safety issue:

The MHRA is asking organisations to put a plan in place to implement **new regulatory measures** for sodium valproate, valproic acid and valproate semisodium (valproate). This follows a comprehensive review of safety data, advice from the Commission on Human Medicines and an expert group, and liaison with clinicians and organisations.

Due to the known significant risk of serious harm to a baby after exposure to valproate in pregnancy, these measures aim to ensure valproate is only used if other treatments are ineffective or not tolerated, and that any use of valproate in women of childbearing potential who cannot be treated with other medicines is in accordance with the Pregnancy Prevention Programme (PPP). Given these and other risks of valproate, these measures also aim to reduce initiation of valproate to only in patients for whom no other therapeutic options are suitable.

The regulatory change in January 2024, for oral valproate medicines, means that:

A. Valproate must not be started in new patients (male or female) younger than 55 years, unless two specialists independently consider and document that there is no other effective or tolerated treatment, or there are compelling reasons that the reproductive risks do not apply.

B. At their next annual specialist review, women of childbearing potential and girls should be reviewed using a revised valproate Risk Acknowledgement Form, which will include the need for a second specialist signature if the patient is to continue with valproate and subsequent annual reviews with one specialist unless the patient's situation changes

Advise leaders that current safety measures for valproate continue to apply, including the valproate PPP for any girls and women of childbearing potential. See December 2022 Drug Safety Update for further information, including advice for clinicians to consider all other suitable therapeutic options before newly prescribing valproate in patients younger than 55.

Advise leaders in general practice and pharmacy that teams should continue to prescribe and dispense valproate but also discuss the current warnings and upcoming measures relating to valproate with their patients and consider together how it affects the patient's individual circumstances. New educational materials should be integrated into local guidance to ensure patients are able to make an informed choice.

Actions required

When: To begin as soon
31 January 2024

1. Designate a new or
   implementation of th
   providers, with overs
   This group should in
   a. An appointed cha
      the actions in th
   b. Representation f
      specialities nam
      departments.
   c. A mechanism by
      informed by pati

2. The group should be
   progress towards:
   a. Updating all loca
      prescribing of va
      position, includi
      responsibilities
      organisations, a
      the risk forms
   b. Commissioning
      needs of the aff
      people most at
   c. Reviewing the r
      with the existing
      of childbearing
   d. Commissioning/determining the local pathways of care for women of childbearing potential and girls in relation to the prescribing and review of valproate.
   e. Planning for and identification of clinical resource to meet the identified needs of the population and implement the new regulatory measures.

3. Based upon the findings of the above, the group should produce an Action and Improvement Plan by the alert deadline that is communicated with all relevant staff to ensure smooth implementation of the new regulatory measures and to allow for continuous improvement in care of patients who are considering or being prescribed valproate, including ongoing improvement, monitoring and audit.

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https://doi.org/10.1093/brain/awae128 BRAIN 2024: 147; 3426–3441 | 3426

BRAIN
ORIGINAL ARTICLE

Morbidity and mortality risks associated with valproate withdrawal in young adults with epilepsy

Gashirai K. Mbizvo,[1,2,3] Tommaso Bucci,[1,4] Gregory Y. H. Lip[1,5,†] and Anthony G. Marson[2,3,†]

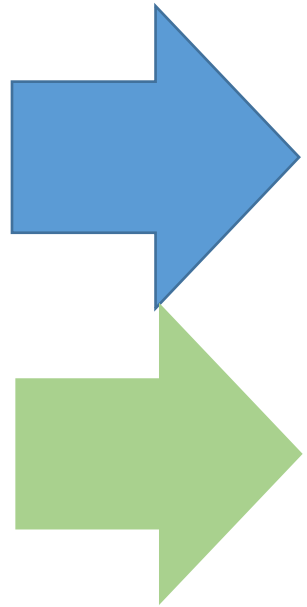
[†]These authors contributed equally to this work.

Valproate withdrawal was associated with significantly increased risks of emergency department attendance [HRs overall: 1.236 (CI 1.159–1.319)],
- hospital admission [HRs overall: 1.160 (CI 1.081–1.246)]
- falls [HRs overall: 1.179 (CI 1.041–1.336)]
- injuries [HRs overall: 1.095 (CI 1.021–1.174)]
- burns [HRs overall: 1.592 (CI 1.084–2.337)]
- new-onset depression [HRs overall 1.323 (CI 1.119–1.565)].

Case 4

- 67 year-old man with CAD, AF, CKD, H/O post stroke epilepsy
- on warfarin

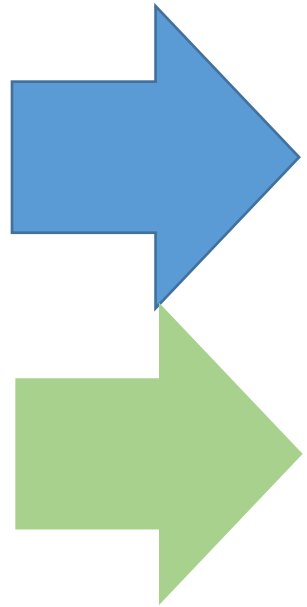
Phenytoin	Lamotrigine
Carbamazepine	Topiramate
Phenobarbital	Levetiracetam
Sodium valproate	Pregabalin
	Zonisamide
	Lacosamide
	Perampanel



Case 5

- 67 year-old man with CAD, AF, CKD, H/O post stroke epilepsy
- on apixaban

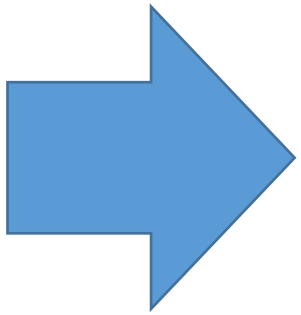
Phenytoin	Lamotrigine
Carbamazepine	Topiramate
Phenobarbital	Levetiracetam
Sodium valproate	Pregabalin
	Zonisamide
	Lacosamide
	Perampanel



Case 6

- 72 year-old man was recently diagnosed with multiple myeloma, planning to start on bortezomib

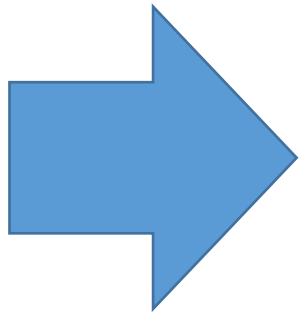
Phenytoin	Lamotrigine
Carbamazepine	Topiramate
Phenobarbital	Levetiracetam
Sodium valproate	Pregabalin
	Zonisamide
	Lacosamide
	Perampanel



Case 7

- 23 year old woman with focal epilepsy from MTS, who was diagnosed with MG and was started on prednisolone and MMF

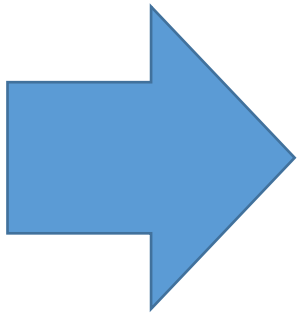
Phenytoin	Lamotrigine
Carbamazepine	Topiramate
Phenobarbital	Levetiracetam
Sodium valproate	Pregabalin
	Zonisamide
	Lacosamide
	Perampanel



Case 8

- 38 year old man with HIV

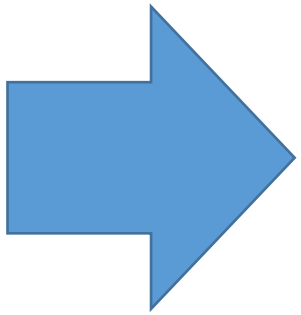
Phenytoin	Lamotrigine
Carbamazepine	Topiramate
Phenobarbital	Levetiracetam
Sodium valproate	Pregabalin
	Zonisamide
	Lacosamide
	Perampanel



Case 9

- 80 year old man with moderate AD

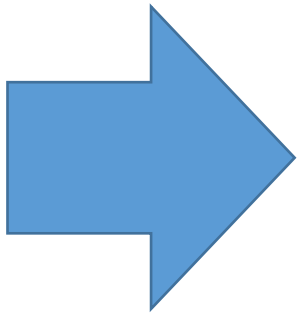
Phenytoin	Lamotrigine
Carbamazepine	Topiramate
Phenobarbital	Levetiracetam
Sodium valproate	Pregabalin
	Zonisamide
	Lacosamide
	Perampanel



Case 10

- 42 year old woman with anxiety, MDD

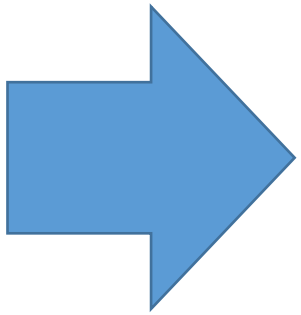
Phenytoin	Lamotrigine
Carbamazepine	Topiramate
Phenobarbital	Levetiracetam
Sodium valproate	Pregabalin
	Zonisamide
	Lacosamide
	Perampanel



Case 11

- 34 year old woman with focal epilepsy and migraine

Phenytoin	Lamotrigine
Carbamazepine	Topiramate
Phenobarbital	Levetiracetam
Sodium valproate	Pregabalin
	Zonisamide
	Lacosamide
	Perampanel



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

Malformation Risks of AEDs in Pregnancy

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

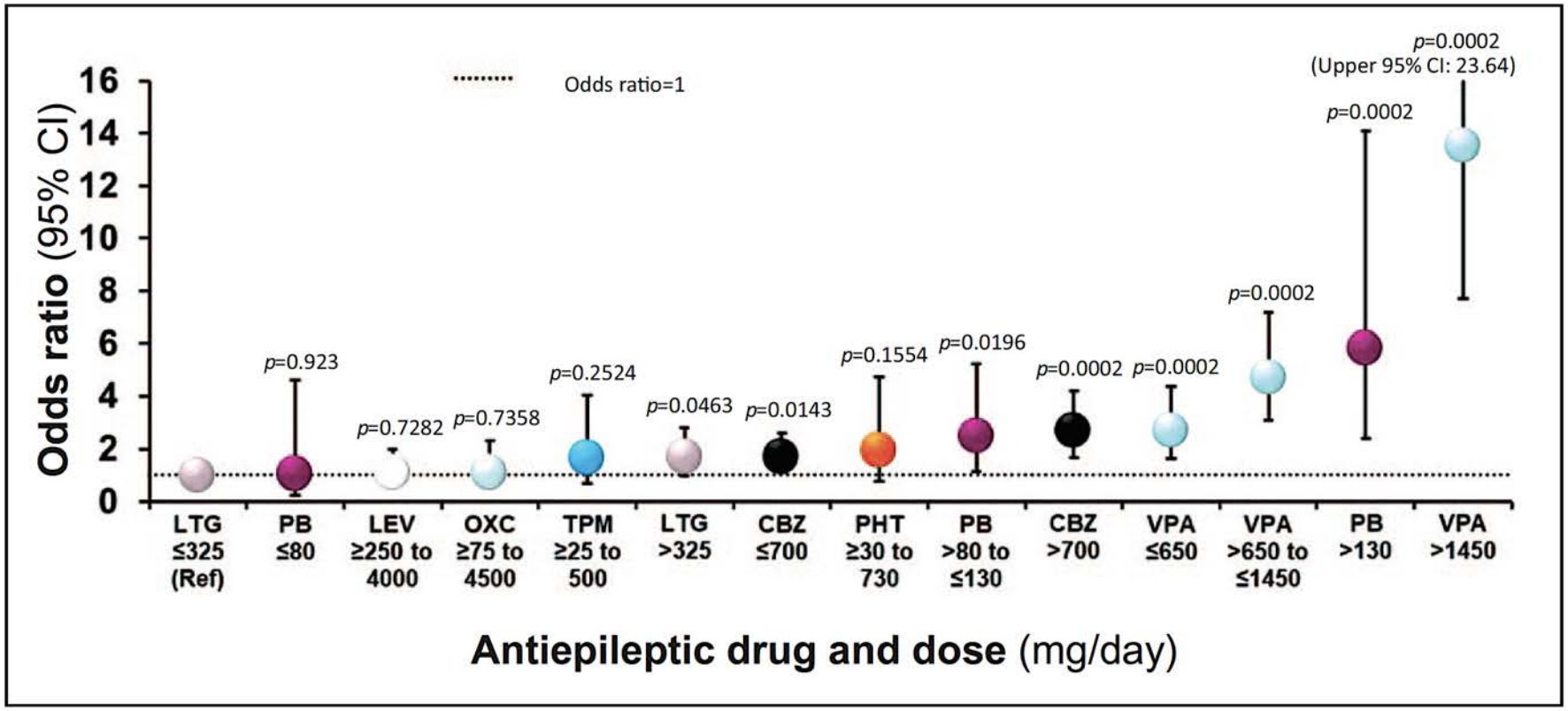


FIGURE 3. Risk of major congenital malformations (odds ratios with 95% confidence intervals) with different antiepileptic drug treatments compared with lamotrigine 325 mg/day or less. CBZ, carbamazepine; LEV, levetiracetam; LTG, lamotrigine; OXC, oxcarbazepine; PB, phenobarbital; PHT, phenytoin; Ref, 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.

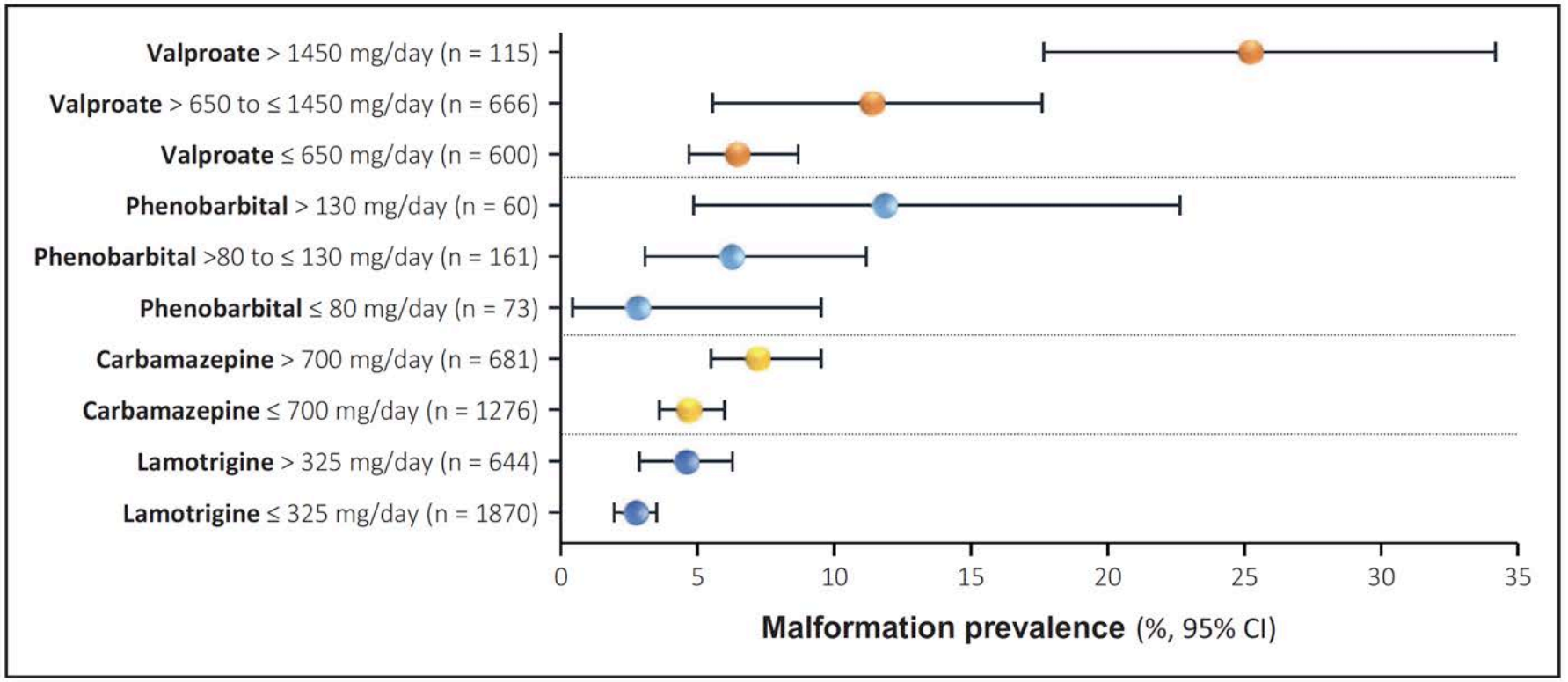


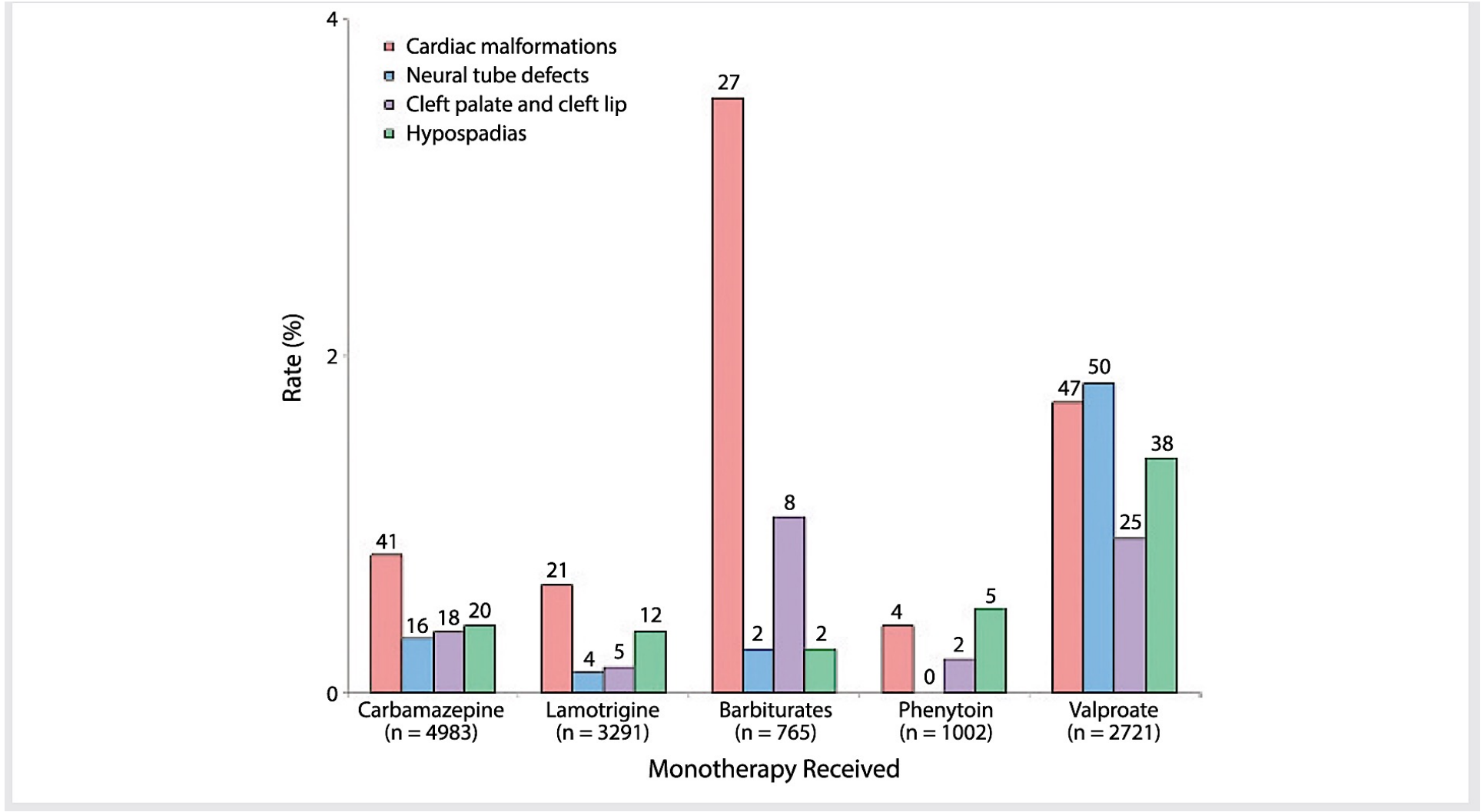
FIGURE 2. Dose dependency of major congenital malformations (%; and 95% confidence intervals) with four antiepileptic drug monotherapies. Based on Data from [5▪▪].

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.

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

■ Seminar in epileptology

Epileptic Disord 2022; 24 (6): 1020-1032

Epileptic Disorders

Breastfeeding while on treatment with antiseizure medications: a systematic review from the ILAE Women Task Force

Torbjörn Tomson[1], Dina Battino[2], Rebecca Bromley[3], Silvia Kochen[4], Kimford J. Meador[5], Page B. Pennell[6], Sanjeev V. Thomas[7]

Epileptic Disord 2022; 24:1021-32

Concentration of ASM in breastmilk

Low <10%	Approx. 30%	High > 30%
carbamazepine gabapentin levetiracetam oxcarbazepine phenytoin valproate clonazepam	lamotrigine topiramate brivaracetam lacosamide perampanel	ethosuximide phenobarbital zonisamide

Percentage of maternal serum concentration

Epileptic Disord 2022; 24:1021-32

- Prospective long-term follow-up studies of developmental outcomes among children that have been breastfed by mothers taking ASMs are sparse and have mainly involved children whose mothers were taking carbamazepine, lamotrigine, levetiracetam, phenytoin or valproate while breastfeeding.
- None of these studies indicated poorer outcome among breastfed children compared with those who were not breastfed

Although these studies have not indicated poorer outcome among breastfed children compared with those who were not breastfed, further data on long-term outcomes are needed to draw firm conclusions.

- It is concluded that breastfeeding should in general be encouraged in women taking ASMs, given the well-established benefits of breastfeeding with regard to both short- and long-term infant health in the general population.
- Counselling needs to be individualized including information on the current knowledge regarding the woman's specific ASM treatment.

Epileptic Disord 2022; 24:1021-32

Actions to reduce the risk of maternal seizures and risks associated with seizures

Reducing the risk of maternal seizures

- Optimize ASM dose, taking into account post-delivery related changes in pharmacokinetics as well as the possible need for intensified treatment due to sleep deprivation and other stressors
- Promote adherence to prescribed medication
- Reduce, as far as possible, sleep deprivation and other seizure-provoking factors; consider sharing the feeding, in particular, during night-time by having someone else share responsibility for feeding using a bottle of pumped breastmilk or formula

Reducing risks to the infant associated with maternal seizures

- Sit in a low position while breastfeeding (soft surface on the floor or low bed)
- Engage a "feeding buddy" to observe while feeding, in particular, during the first period after delivery until the situation has become stable regarding seizure control
- Do not bathe the infant alone

Epileptic Disord 2022; 24:1021-32

Drug interaction with OCPs

- AEDs that cause induction of CYP 3A4 increase metabolism of oral contraceptives resulting in failure of contraceptives.
- Potent enzyme inducing AEDs:
  - phenytoin, carbamazepine, primidone, phenobarbital.
- Less-potent enzyme inducing AEDs:
  - oxcarbazepine, lamotrigine
  - topiramate >200 mg.

Table 1. Recommendations for Use of Hormonal Contraceptives and Enzyme-inducing AEDs from the *US Medical Eligibility Criteria for Contraceptive Use* and Expert Opinion

	US Medical Eligibility Criteria for Contraceptive Use Category[a]				
EI-AEDs	COCs, Contraceptive Patch (Evra) and Ring (NuvaRing)[b]	POP[b]	Progestin Implant (Implanon)[b,c]	DMPA Injection (Depo-Provera)[d]	LNG-IUS (Mirena)[d]
Carbamazepine (Tegretol)	3	3	2	1	1
Felbamate (Felbatol)	NA	NA	NA	NA	NA
Oxcarbazepine (Trileptal)	3	3	2	1	1
Phenobarbital	NA	NA	NA	NA	NA
Phenytoin (Dilantin)	3	3	2	1	1
Primidone (Mysoline)	3	3	2	1	1
Topiramate (Topamax)	3	3	2	1	1
Rufinamide (Banzel)	NA	NA	NA	NA	NA
Lamotrigine (Lamictal)	3	1	1	NA	1

Guillemette T, et al. J Midwifery Womens Health 2012;57:290–5

Options of contraception in patients taking EIAEDs

- Intrauterine device (IUD) is an excellent choice, and, given the safety and high contraceptive efficacy, an IUD is a favorable option
- Levonorgestrel IUD prevents pregnancy by local hormonally mediated changes and is unlikely to be impacted by enzyme-inducing AEDs.
- Intramuscular medroxyprogesterone acetate is another long-acting reversible contraceptive that is likely adequate with coadministration of enzyme-inducing AEDs, because the concentration of progestin is high enough that efficacy is maintained but is often not considered a first-line option due to its side effect

Guillemette T, et al. J Midwifery Womens Health 2012;57:290–5

Women with epilepsy

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

Elderly with Epilepsy

Elderly

- Changes in pharmacokinetics of AEDs in the elderly
- Side effects of the ASMs, which elderly are more susceptible to occur eg. cognitive side effects
- Drug interaction
- Osteoporosis

Decreased Volume distribution: What should we do?

Lean body mass ↓

Total body water mass ↓

Proportion of fat ↓

Volume distribu… …pophilic drugs ↓

Beware of increased drug level and side effects esp. loading dose in frail elderly

…Serum drug concentrations ↑

$$\text{Level} = \frac{\text{loading dose (mg)}}{\text{Vd (L/kg)x weight (kg)}}$$

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 ASMs 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 at higher dosage
Oxcarbazepine	Increase incidence of adverse effects Hyponatremia
Topiramate	Cognitive side effects at higher dosage (can be avoided by slow titration)

Interaction between AEDs and drugs for dementia

Table 2. Interactions Between Medications for Alzheimer Disease and Antiepileptic Drugs[a]

Alzheimer Medications	PHT	CBZ	PB	BZD	VPA	OXC	LEV	TOP	GBP	LTG	ZNS	PGB
Donepezil (D)	↓	↓	↓	—	—	↓	—	—	—	—	—	—
Galantamine (G)	↓	↓	↓	—	—	↓	—	—	—	—	—	—
Rivastigmine (R)	none	none	none	none	none	none	none	none	none	none	—	none
Tacrine (T)	none	none	none	none	none	none	none	none	none	none	—	none
Memantine (M)	none	none	none	none	none	none	none	none	none	none	—	none

Jenssen S, Schere D. American Journal of Alzheimer's Disease & Other Dementias 2010;25:18-26

Elderly

- Changes in pharmacokinetics of AEDs in the elderly
- Side effects of the ASMs, which elderly are more susceptible to occur eg. cognitive side effects
- Drug interaction
- Osteoporosis

Patients with Underlying Medical Conditions

Medical conditions

- Side effects of the ASMs, which each conditions are more susceptible to occur eg. cognitive side effects
- Drug interaction
- Matching ASMs with other comorbidities

Effects on hepatic enzymes

Enzyme inhibitor	Enzyme inducer
Sodium valproate	Phenytoin
	Carbamazepine
	Phenobarbital
	Weak enzyme inducer at higher dose
	Oxcarbazepine
	Topiramate (>200mg)
	Perampanel (>8-12 mg)

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

Cardiac conditions

Using AEDs in cardiac conditions

- Side effects
- Drug interaction

IV loading precautions in patients with cardiac conditions for ASMs with Na channel action

	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

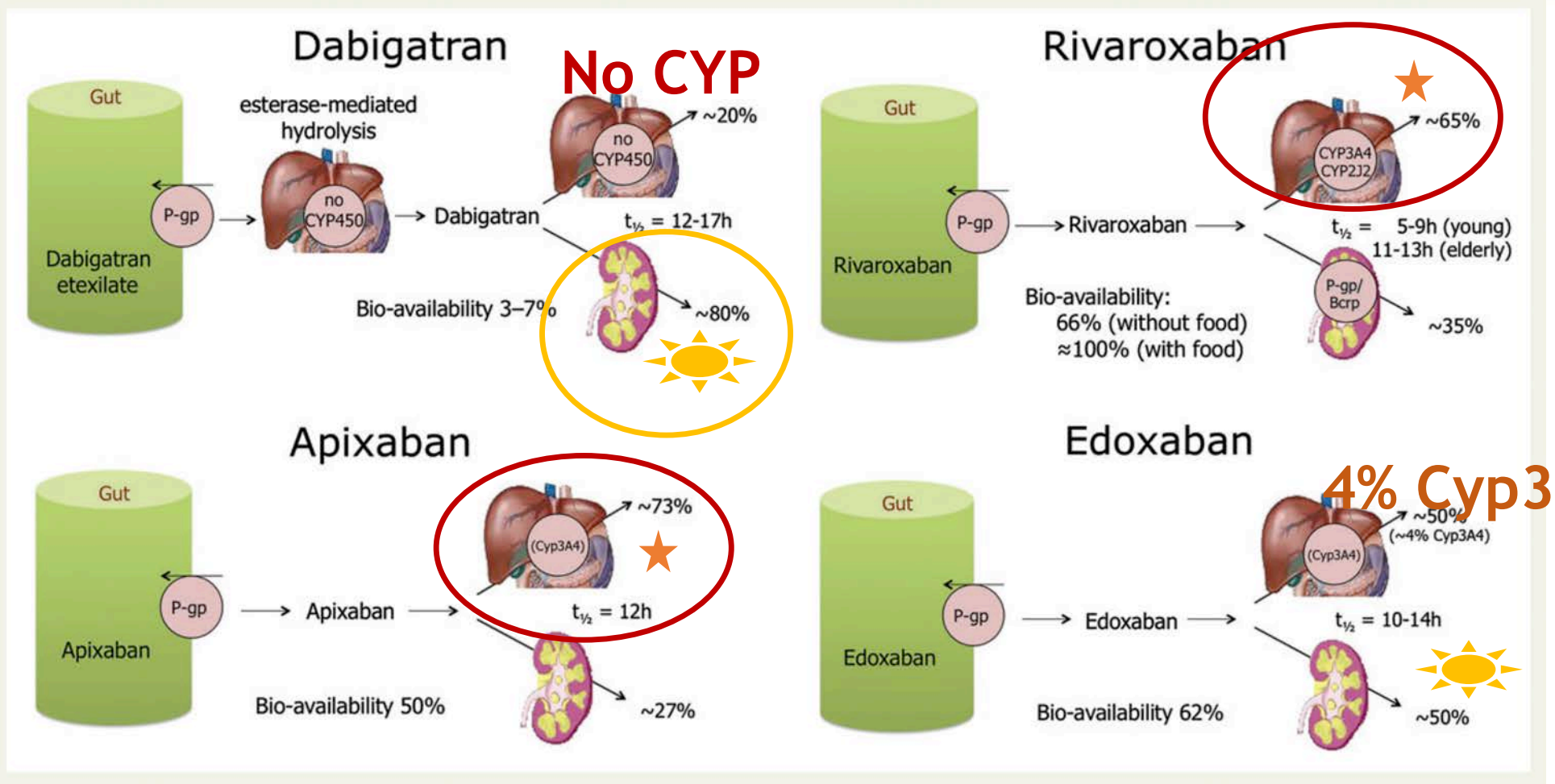
Drug interaction with warfarin

- 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)			

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.

Epilepsia Open 2017;2:107-11

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	Potential reaction with IAEDs	
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

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.

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, targeted 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

Neuro-Oncology

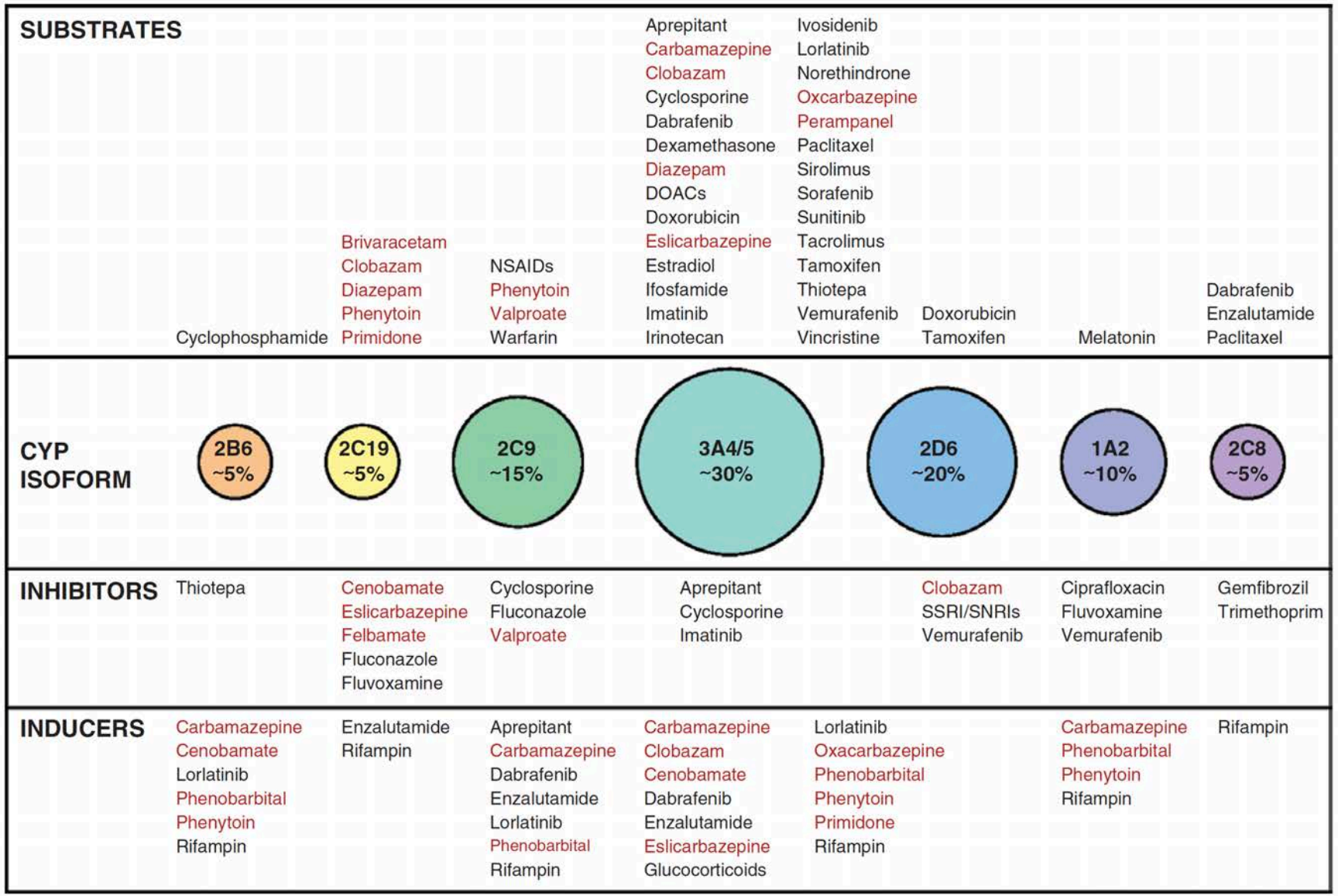
XX(XX), 1–18, 2023 | https://doi.org/10.1093/neuonc/noad154 | Advance Access date 12 September 2023

Brain tumor-related epilepsy management: A Society for Neuro-oncology (SNO) consensus review on current management

Edward K. Avila[†], Steven Tobochnik[†], Sara K. Inati, Johan A. F. Koekkoek, Guy M. McKhann, James J. Riviello, Roberta Rudà, David Schiff, William O. Tatum, Jessica W. Templer, Michael Weller, and Patrick Y. Wen

All author affiliations are listed at the end of the article

https://doi.org/10.1093/neuonc/noad154



https://doi.org/10.1093/neuonc/noad154

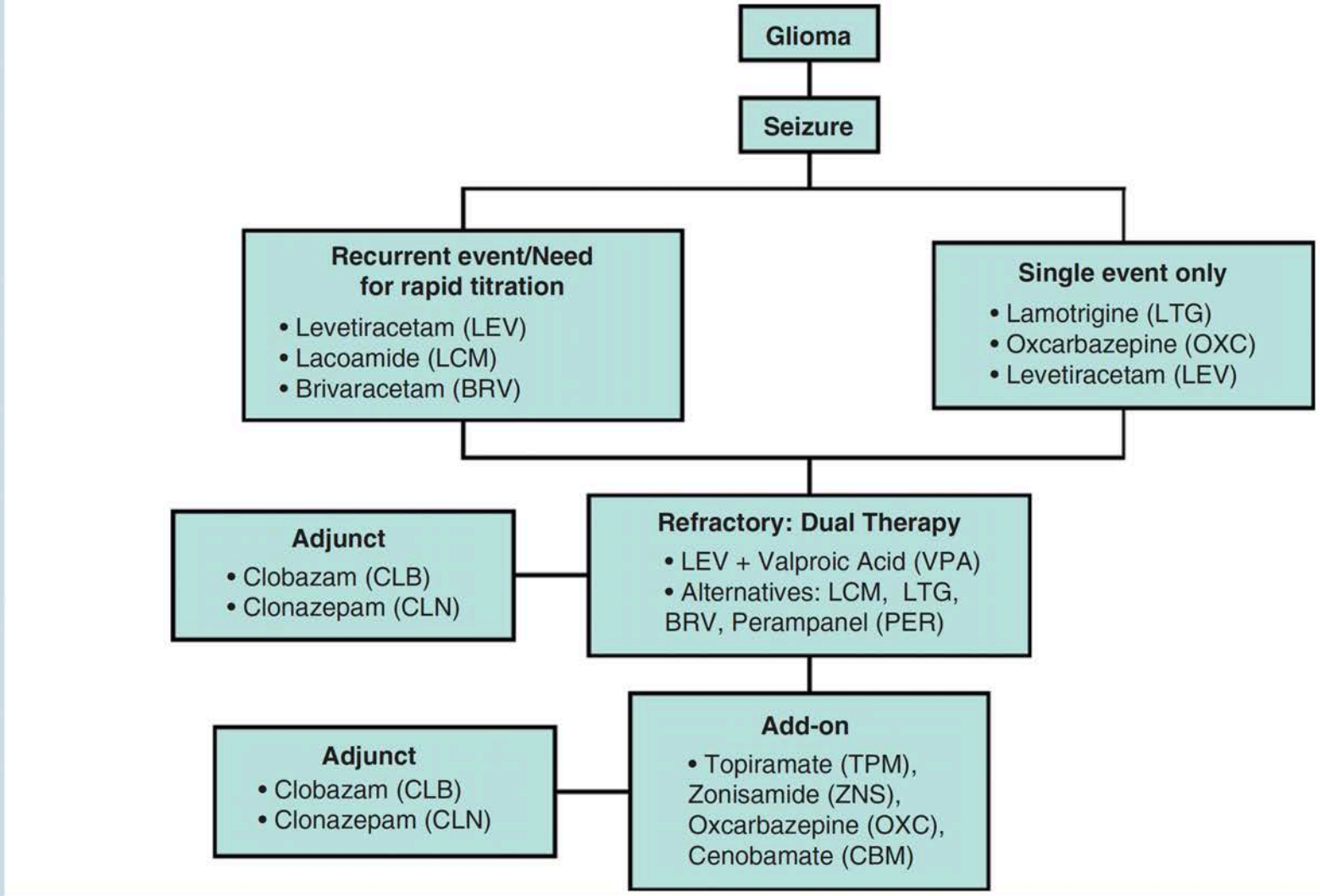


Figure 4. Proposed algorithm for ASM selection in glioma-related epilepsy. In polytherapy, ASMs with different mechanisms of action should be chosen to minimize adverse effects.

https://doi.org/10.1093/neuonc/noad154

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

Medical conditions

- Side effects of the ASMs, which each conditions are more susceptible to occur eg. cognitive side effects
- Drug interaction
- Matching ASMs with other comorbidities

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

Matching AEDs with other comorbidities

	Avoid/ caution	Prefer
Obesity	VPA, PGB, GBP	TPM, ZNS
Cognitive dysfunction	PB, TPM, ZNS	LTG, LEV, OXC
Restless leg syndrome	-	GBP, PGB, CZP
Tremor	VPA	TPM, PER
Gait ataxia	CBZ, PHT	-
Parkinson disease	-	ZNS
Multiple concomitant drugs	Enzyme inducing AEDs	-

Park KM, Kim SE, Lee BI. Journal of Epilepsy Research 2019; 9: 14-26

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

Question

คณะแพทยศาสตร์ศิริราชพยาบาล มหาวิทยาลัยมหิดล

THANK YOU FOR YOUR ATTENTION