Mahidol University
Faculty of Medicine Siriraj Hospital

SI-NEURO

Selection of ASMs in special population

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

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

WOMEN WITH EPILEPSY

PWECP “People with epilepsy of childbearing potential”

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

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

Effects of exogenous hormone on AEDs metabolism

- Metabolism of lamotrigine is increased approximately 50% by cotreatment with combined oral contraceptive pills
- The clearance of valproic acid is also increased with COCs.
- Clearance of LTG appeared to affect by estradiol-containing preparations but not by progesterone-only containing compounds

Malformation Risks of AEDs in Pregnancy

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

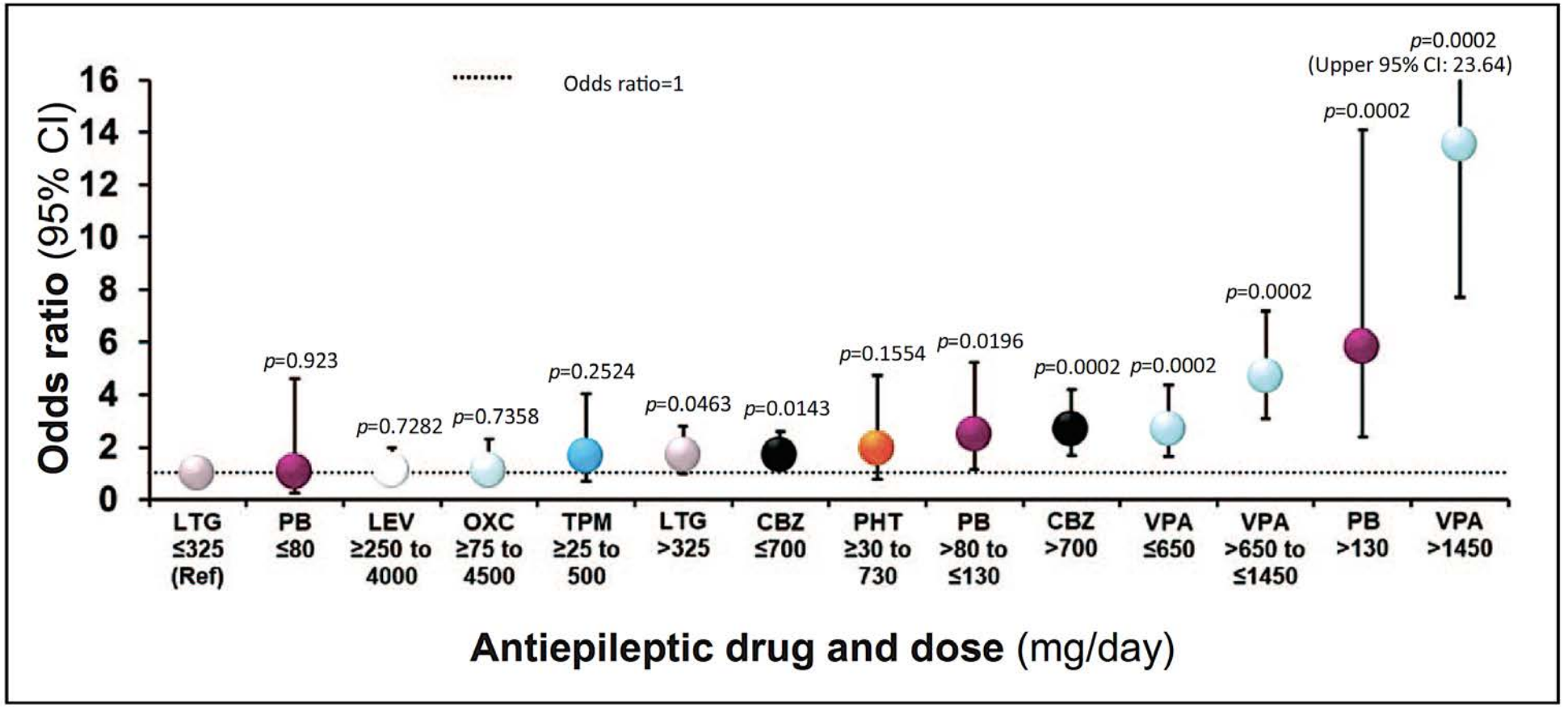


FIGURE 3. Risk of major congenital malformations (odds ratios with 95% confidence intervals) with different antiepileptic drug treatments compared with lamotrigine 325 mg/day or less. CBZ, carbamazepine; LEV, levetiracetam; LTG, lamotrigine; OXC, oxcarbazepine; PB, phenobarbital; PHT, phenytoin; Ref,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

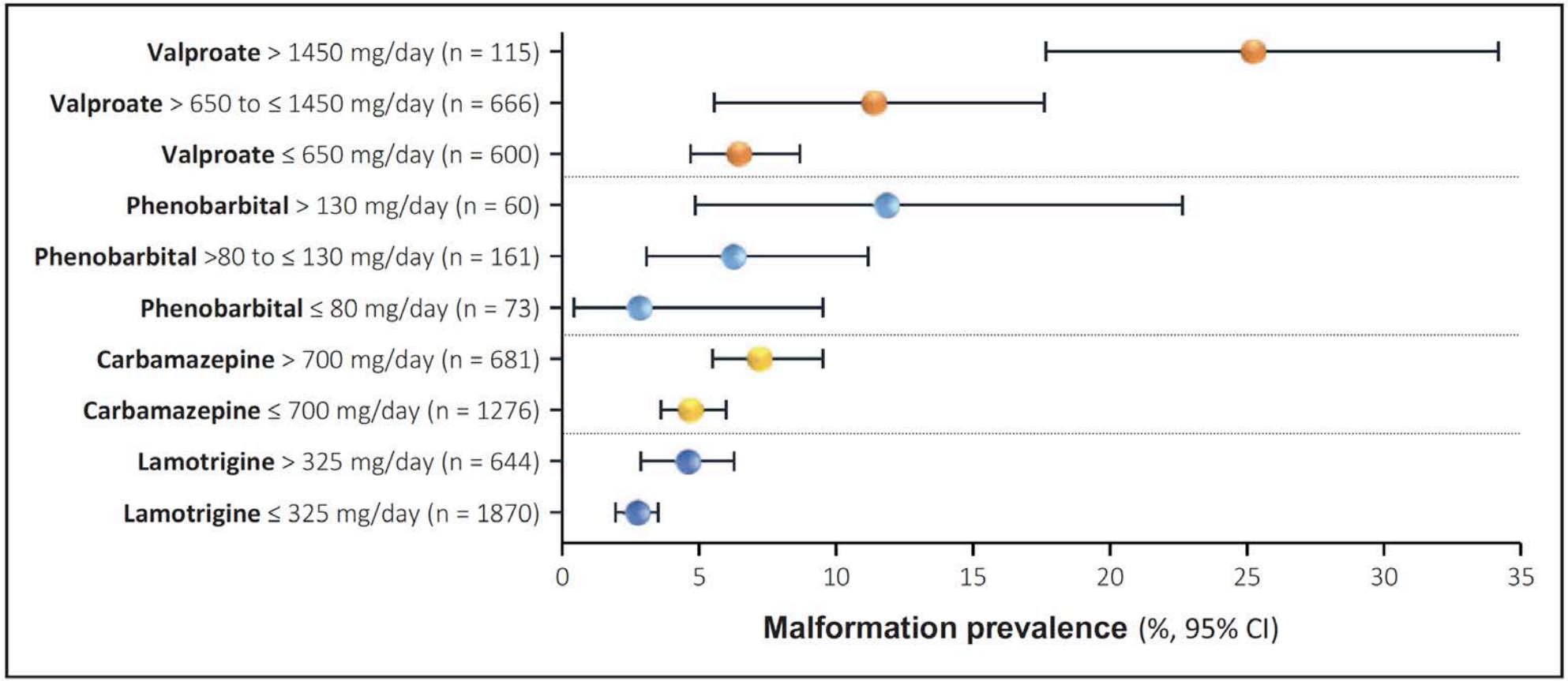


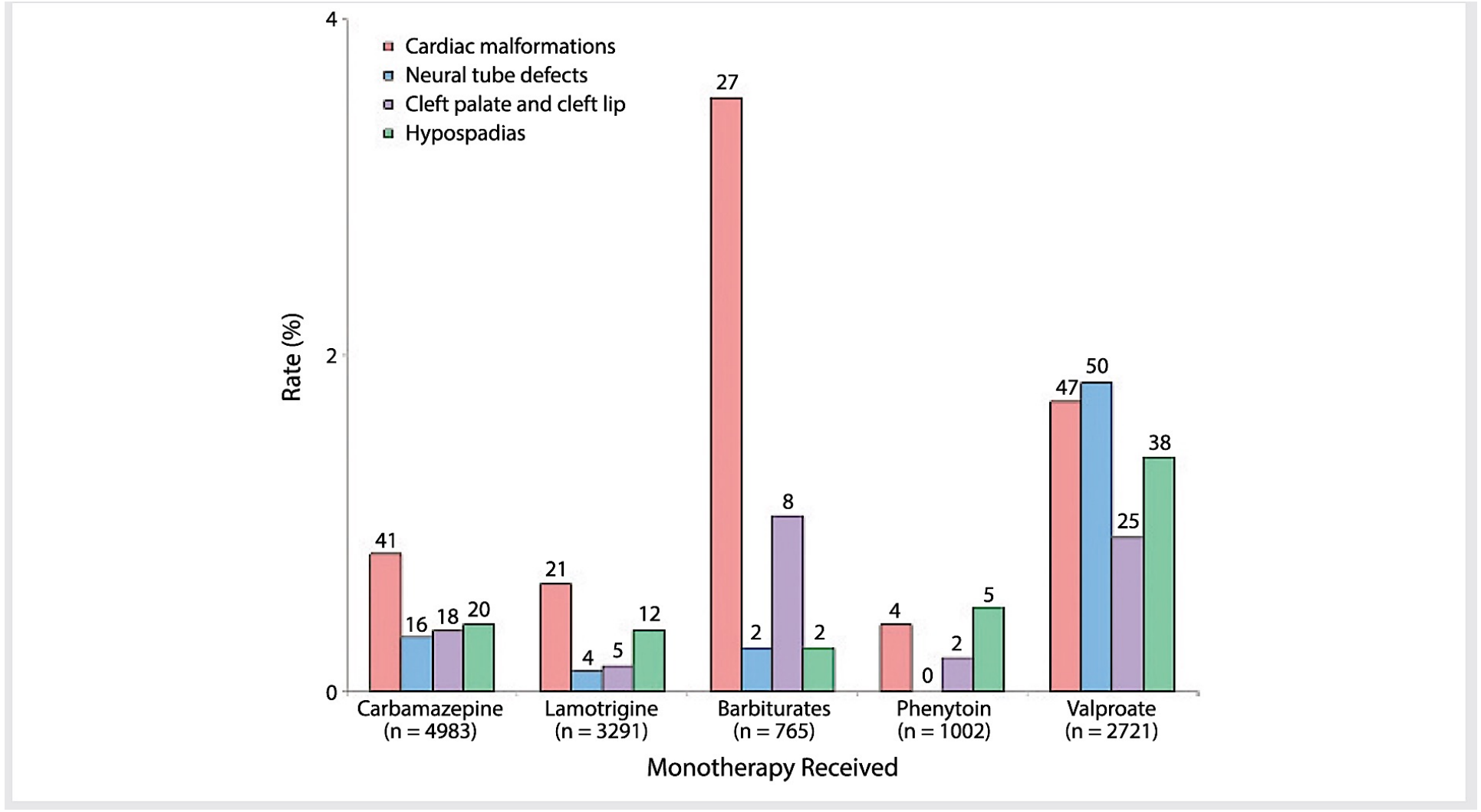
FIGURE 2. Dose dependency of major congenital malformations (%; and 95% confidence intervals) with four antiepileptic drug monotherapies. Based on Data from [5▪▪].

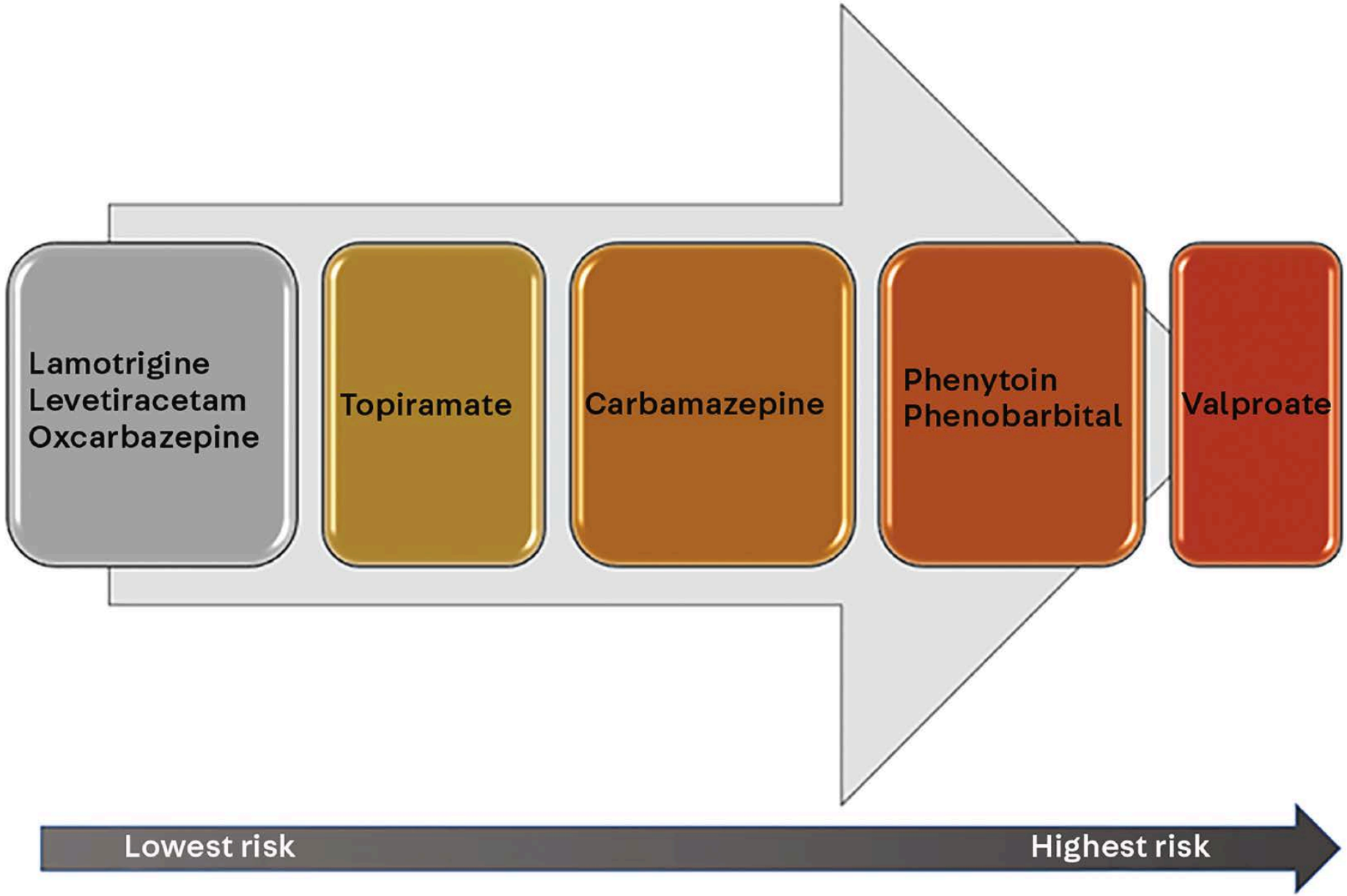
Tomson T, Battino D, Bonizzoni E, et al. Comparative risk of major congenital malformations with eight different antiepileptic drugs: a prospective cohort study of the EURAP registry. Lancet Neurol 2018; 17:530–538.

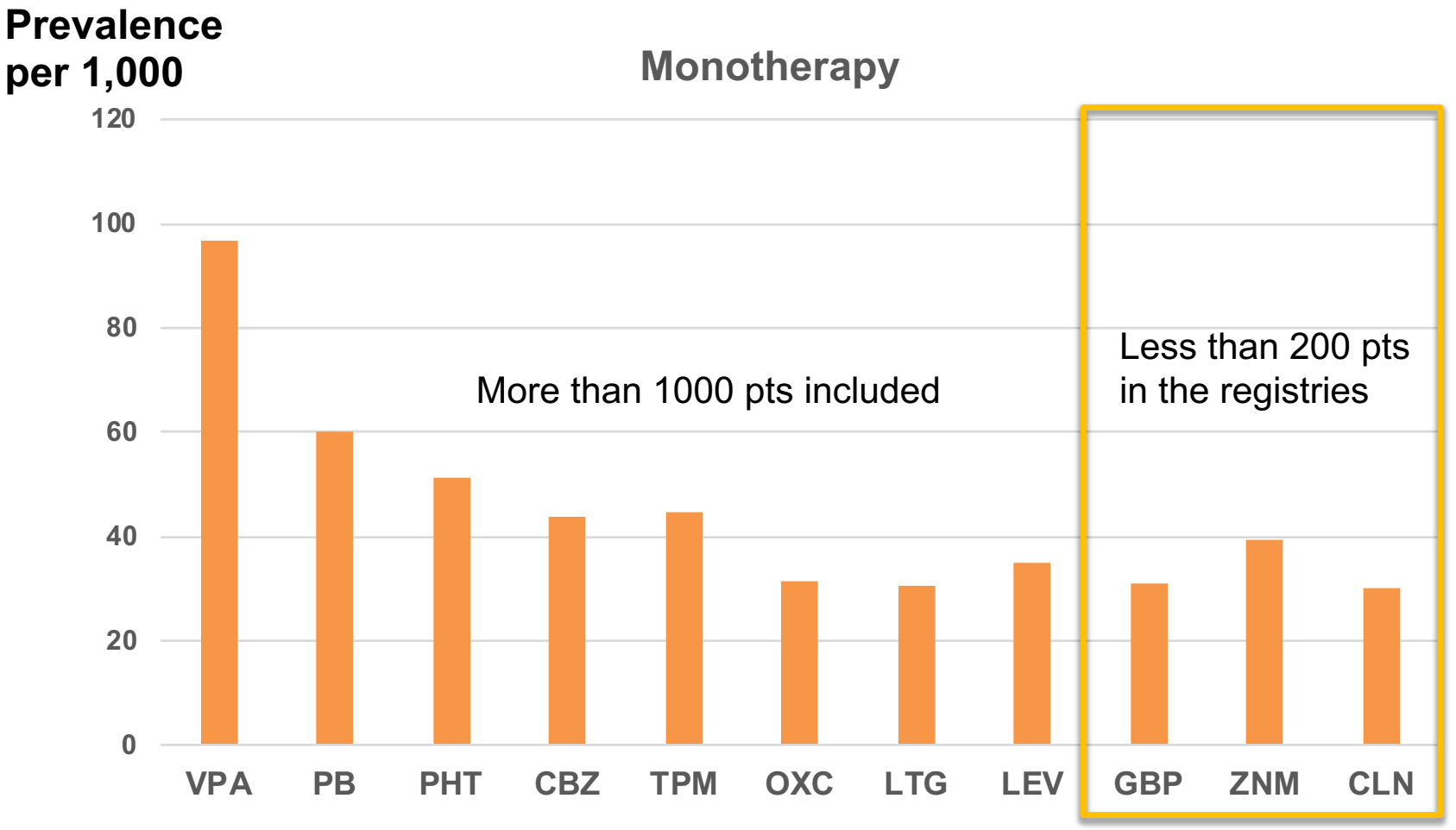
Are there specific MCMs associated with specific AEDs?

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

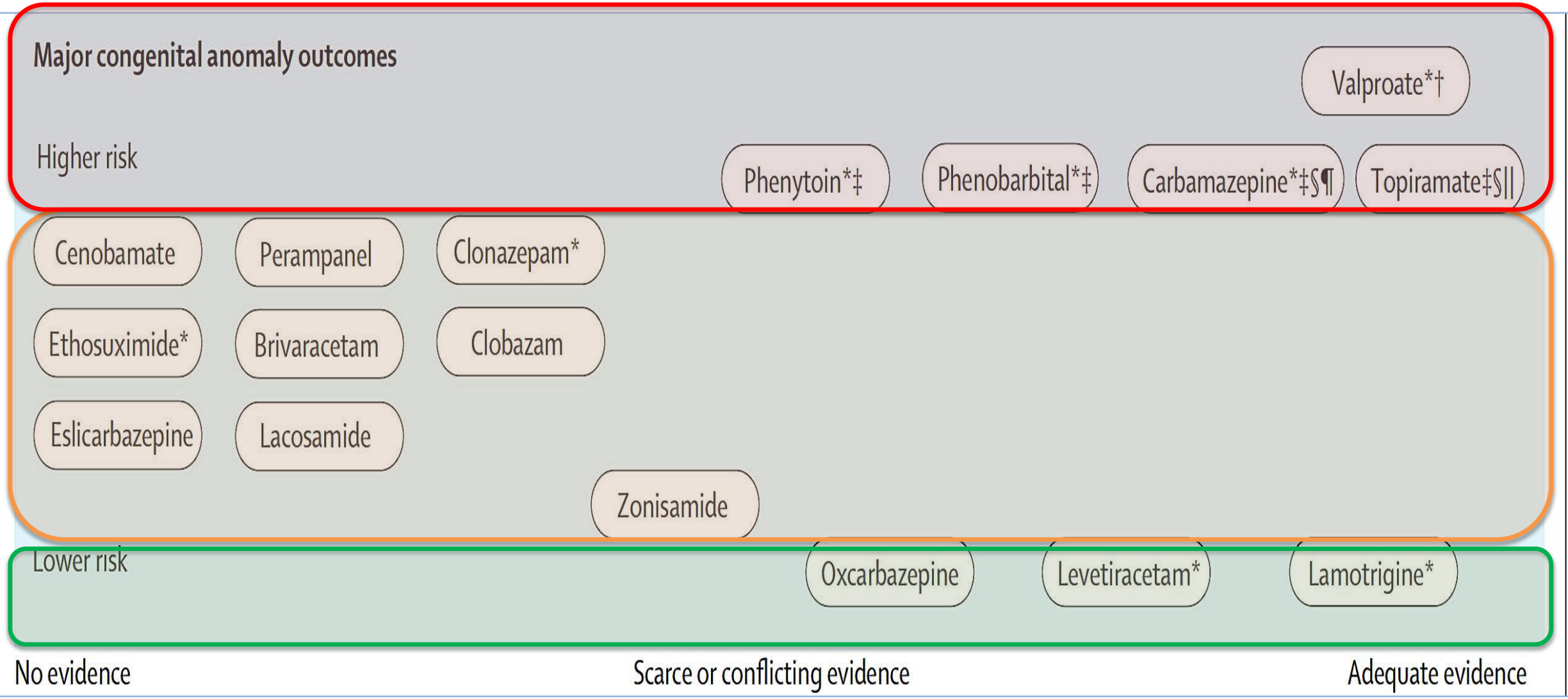
Are there specific MCMs associated with specific AEDs?




Lamotrigine
Levetiracetam
Oxcarbazepine
Topiramate
Carbamazepine
Phenytoin
Phenobarbital
Valproate
Lowest risk
Highest risk



Neurology 2024;102:e209279



Bjork MH, et al. Lancet Neurol 2025; 24: 601–13

SPECIAL ARTICLE

Teratogenesis, Perinatal, and Neurodevelopmental Outcomes After In Utero Exposure to Antiseizure Medication

Practice Guideline From the AAN, AES, and SMFM

Alison M. Pack, MD, MPH, Maryam Oskoui, MD, MSc, Shawniqua Williams Roberson, MEng, MD, Diane K. Donley, MD, Jacqueline French, MD, Elizabeth E. Gerard, MD, David Gloss, MD, MPH&TM, Wendy R. Miller, PhD, RN, CCRN, Heidi M. Munger Clary, MD, MPH, Sarah S. Osmundson, MD, MS, Brandy McFadden, Kaitlyn Parratt, MBBS (Hons 1), Page B. Pennell, MD, George Saade, MD, Don B. Smith, MD, Kelly Sullivan, PhD, Sanjeev V. Thomas, MD, DM, Torbjörn Tomson, MD, Mary Dolan O'Brien, MLIS, PMP, Kylie Botchway-Doe, Heather M. Silsbee, MWC, and Mark R. Keezer, MDCM, PhD

Correspondence
American Academy of Neurology
guidelines@aan.com

Neurology® 2024;102:e209279. doi:10.1212/WNL.0000000000209279

Recommendation 3 Statements

3A. Clinicians must counsel their patients with epilepsy that the birth prevalence of any MCM in the general population is approximately 2.4%–2.9%, providing a comparison framework for their individual risk (Level A).

3B. Clinicians must consider using lamotrigine, levetiracetam, or oxcarbazepine in PWECP when appropriate based on the patient's epilepsy syndrome, likelihood of achieving seizure control, and comorbidities, to minimize the risk of MCMs (Level A).

3C. Clinicians must avoid the use of valproic acid in PWECP to minimize the risk of MCMs (composite outcome) or NTDs, if clinically feasible (Level A).

3D. Clinicians must counsel PWECP who are treated with, or are considering starting, valproic acid that the risk of any MCM is the highest with valproic acid as compared with other studied ASMs (Level A).

Pack AM, et al. Neurology 2024;102:e209279

3E. To reduce the risk of cardiac malformations, clinicians must avoid the use of phenobarbital in PWECP, if clinically feasible (Level A).

3F. To reduce the risk of oral clefts, clinicians should avoid the use of phenobarbital and topiramate in PWECP, if clinically feasible (Level B).

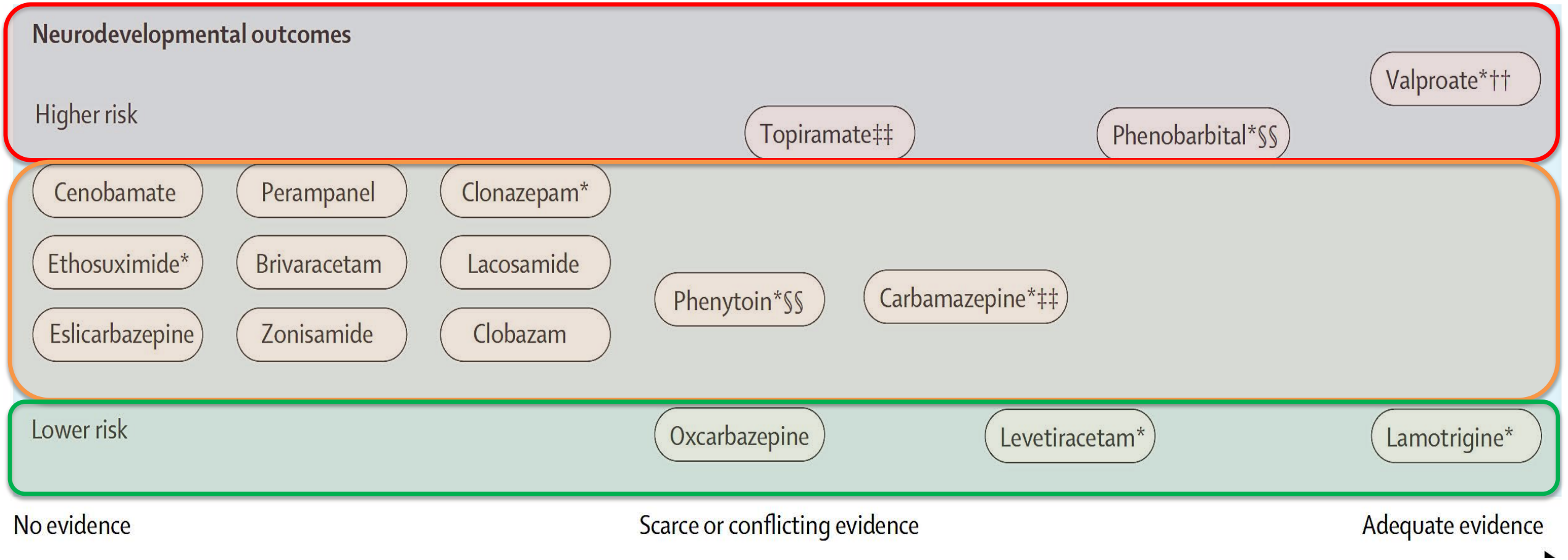
3G. To reduce the risk of urogenital and renal malformations, clinicians should avoid the use of valproic acid in PWECP, if clinically feasible (Level B).

3H. To enable early detection and timely intervention of MCMs, obstetricians should recommend fetal screening for MCMs (e.g., a detailed anatomical ultrasound, where available) for PWECP who are treated with any ASM during pregnancy (Level B).

3I. To enable early detection and timely intervention of congenital heart defects, obstetricians should recommend screening cardiac investigations of the fetus among PWECP who are treated with phenobarbital during pregnancy (Level B).

Pack AM, et al.
Neurology 2024;102:e209279

Neurodevelopmental outcome



Bjork MH, et al. Lancet Neurol 2025; 24: 601–13

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

- 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.

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Table 4 Global IQ With Exposure to ASM Monotherapy

ASM	Total sample size	I^2	Included studies	Global IQ mean (95% CI)	RMD compared with reference (95% CI)
Carbamazepine	316	86.0	2 Class I,[50,51] 4 Class III[52-55]	100.4 (95.8–105.1)	6.53 (0.39–12.67) Low confidence in evidence
Lamotrigine	129	77.0	1 Class I,[51] 1 Class III[55]	105.8 (100.9–110.6)	11.85 (5.53–18.15) Moderate confidence in evidence, upgraded for magnitude of effect
Levetiracetam	42	NA	1 Class III[56]	99.0 (95.0–103.0)	6.3 (0.9–11.7) Very low confidence in evidence
Phenytoin	76	84.8	1 Class I,[51] 1 Class III[53]	103.2 (93.0–113.4)	9.29 (−1.63 to 20.21) Very low confidence in evidence, downgraded for imprecision
Topiramate	27	NA	1 Class III[56]	100.5 (95.8–105.2)	6.58 (0.37–12.80) Very low confidence in evidence
Valproic acid	173	69.0	2 Class I,[50,51] 2 Class III[53,56]	93.9 (89.1–97.9)	Reference

Abbreviations: ASM = antiseizure medication; I^2 = a statistical measure of study heterogeneity; NA = not applicable; RMD = raw mean difference.

Pack AM, et al. Neurology 2024;102:e209279

Recommendation 5 Statements

5A. To reduce the risk of poor neurodevelopmental outcomes, including ASD and lower IQ, in children born to PWECP, clinicians must avoid the use of valproic acid in PWECP, if clinically feasible (Level A).

5B. Clinicians must counsel PWECP who are treated with, or are considering starting, valproic acid that in utero exposure to valproic acid is likely or possibly associated with a decrease in full scale, verbal, and non-verbal IQ, as compared with other studied ASMs (i.e., carbamazepine, gabapentin, lamotrigine, levetiracetam, phenytoin, and topiramate) (Level A).

Pack AM, et al. Neurology 2024;102:e209279

5C. Clinicians must counsel PWECP who are treated with, or are considering starting, valproic acid that in utero exposure to valproic acid is possibly associated with an increased risk of ASD as compared with other studied ASMs (i.e., carbamazepine, clonazepam, levetiracetam, and lamotrigine) (Level A).

5D. Clinicians should implement age-appropriate developmental screening in children exposed to any ASM in utero born to PWECP (Level B).

Pack AM, et al. Neurology 2024;102:e209279

Overview

New measures to avoid topiramate exposure in pregnancy

Further restrictions on use; pregnancy prevention programme to be put in place

On 11 October 2023, the CMDh[1] endorsed new measures recommended by EMA's safety committee (PRAC) in September to avoid exposure of children to topiramate-containing medicines in the womb, because the medicine may increase the risk of neurodevelopmental problems after exposure during pregnancy. Topiramate is already known to cause serious birth defects when used during pregnancy.

Topiramate containing medicines are used in the European Union (EU) for the treatment of epilepsy and prevention of migraine. In some EU countries, the medicine is also used in combination with phentermine for weight reduction. At present, topiramate must not be used to prevent migraine or manage body weight during pregnancy and patients who can become pregnant must use effective birth control when using topiramate.

For patients using topiramate for the treatment of epilepsy, the medicine should not be used during pregnancy unless there is no other suitable treatment available.

The CMDh has also agreed to additional measures, in the form of a pregnancy prevention programme, to avoid exposure of children to topiramate in the womb. These measures will inform any woman or girl who is able to have children of the risks of taking topiramate during pregnancy and the need to avoid becoming pregnant while taking topiramate.

Healthcare professionals should ensure that all patients who can become pregnant are fully aware of the risks of taking topiramate during pregnancy. Alternative treatment options should be considered and the need for topiramate treatment should be reassessed at least annually.

The CMDh is a medicines regulatory body representing the European Union (EU) Member States, Iceland, Liechtenstein and Norway.

https://www.ema.europa.eu/en/medicines/human/referrals/topiramate

GOV·UK

Home > Drug Safety Update

Topiramate (Topamax): introduction of new safety measures, including a Pregnancy Prevention Programme

Topiramate is now contraindicated in pregnancy and in women of childbearing potential unless the conditions of a Pregnancy Prevention Programme are fulfilled. This follows a review by the MHRA which concluded that the use of topiramate during pregnancy is associated with significant harm to the unborn child. Harms included a higher risk of congenital malformation, low birth weight and a potential increased risk of intellectual disability, autistic spectrum disorder and attention deficit hyperactivity disorder in children of mothers taking topiramate during pregnancy.

From: Medicines and Healthcare products Regulatory Agency

Published 20 June 2024

General advice for healthcare professionals:

- topiramate should not be used:
  - in pregnancy for prophylaxis of migraine
  - in pregnancy for epilepsy unless there is no other suitable treatment
- topiramate should not be used in women of childbearing potential unless the conditions of the Pregnancy Prevention Programme are fulfilled. This aims to ensure that all women of childbearing potential:
  - are using highly effective contraception
  - have a pregnancy test to exclude pregnancy before starting topiramate
  - are aware of the risks from use of topiramate
- please see specific advice for prescribers and advice for dispensers
- ensure women of childbearing potential sign the Risk Awareness Form, you will receive materials including the Risk Awareness Form by post in the coming weeks to use in the implementation of the Pregnancy Prevention Programme
- report suspected adverse drug reactions associated with topiramate to the Yellow Card scheme

https://www.gov.uk/drug-safety-update/topiramate-topamax-introduction-of-new-safety-measures-including-a-pregnancy-prevention-programme

References

1. Bjørk MH and others. Association of Prenatal Exposure to Antiseizure Medication with Risk of Autism and Intellectual Disability. JAMA Neurology 2022: volume 79, pages 672 to 681. ↩ ↩2
2. Cohen JM and others. Comparative Safety of Antiseizure Medication Monotherapy for Major Malformations. Annals of Neurology 2023: volume 93, pages 551 to 562. ↩
3. Hernandez-Diaz S and others. Fetal growth and premature delivery in pregnant women on anti-epileptic drugs. Annals of Neurology 2017: volume 82, pages 457to 465. ↩
4. Blotière PO and others. Risk of early neurodevelopmental outcomes associated with prenatal exposure to the antiepileptic drugs most commonly used during pregnancy: a French nationwide population-based cohort study. BMJ Open 2020: volume 10, page e034829. ↩
5. Bromley RL and others. Cognition in school-age children exposed to levetiracetam, topiramate, or sodium valproate. Neurology 2016: volume 87, pages 1943 to 1953. ↩
6. Dreier JW and others. Prenatal Exposure to Antiseizure Medication and Incidence of Childhood- and Adolescence-Onset Psychiatric Disorders. JAMA Neurology 2023: volume 80, pages 568 to 577. ↩
7. Hernandez-Diaz S and others. Topiramate during pregnancy and the risk of neurodevelopmental disorders in children. Pharmacoepidemiology and Drug Safety 2022: volume 31, page 11. [Full study unavailable at time of review] ↩
8. Knight R and others. Adaptive behaviour in children exposed to topiramate in the womb. A thesis submitted to the University of Manchester for the degree of Doctor of Clinical Psychology in the Faculty of Biology, Medicine, and Health. 2020. ↩

https://www.gov.uk/drug-safety-update/
topiramate-topamax-introduction-of-new-safety-measures-including-a-pregnancy-prevention-programme

Research

JAMA Neurology | Original Investigation

Association of Prenatal Exposure to Antiseizure Medication With Risk of Autism and Intellectual Disability

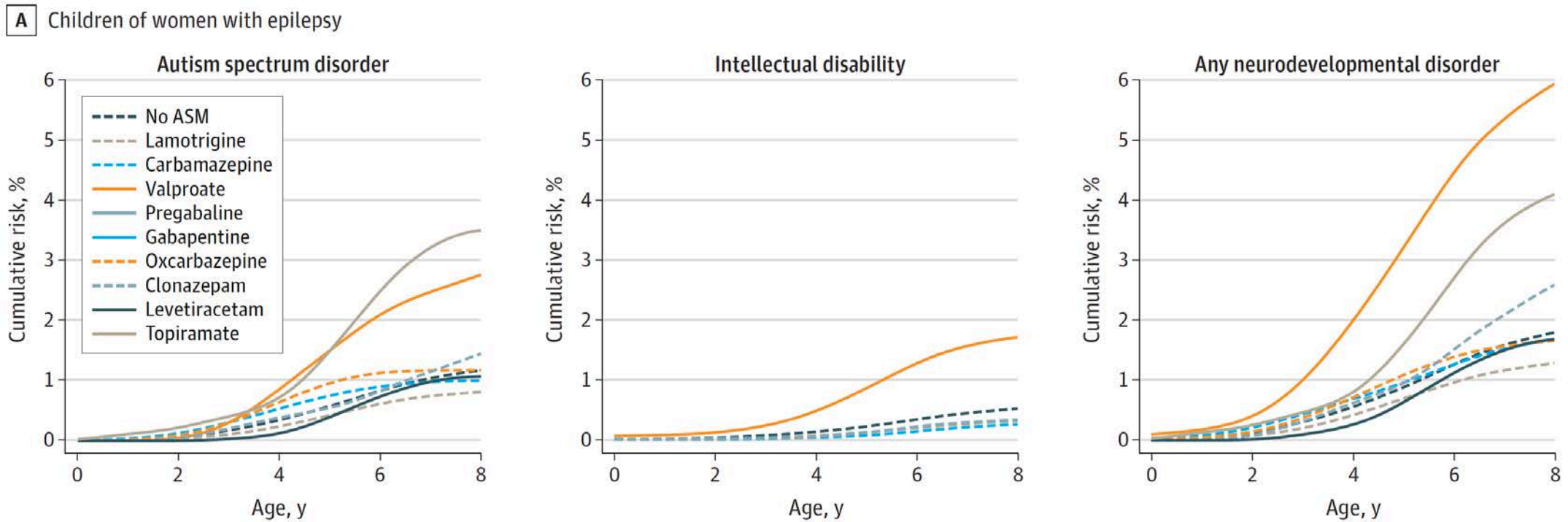
Marte-Helene Bjørk, MD, PhD; Helga Zoega, PhD; Maarit K. Leinonen, MD, PhD; Jacqueline M. Cohen, PhD; Julie Werenberg Dreier, PhD; Kari Furu, PhD; Nils Erik Gilhus, MD, PhD; Mika Gissler, PhD; Óskar Hálfdánarson, PhD; Jannicke Igland, PhD; Yuelian Sun, PhD; Torbjörn Tomson, MD, PhD; Silje Alvestad, MD, PhD; Jakob Christensen, MD, PhD

The Nordic register-based study of antiepileptic drugs in pregnancy (SCAN-AED)
Design: Population-based cohort study using health register and social register data from Denmark, Finland, Iceland, Norway, and Sweden (1996-2017; analysis performed February 2022)
Included 4,494,926 alive-born children with available mother-child identities and maternal prescription data

Main outcome: Estimated cumulative incidence at age 8 years in exposed and unexposed children.
Cox regression adjusted for potential confounders yielded adjusted hazard ratios (aHRs) with 95%CIs for autism spectrum disorder (ASD), intellectual disability (ID), or any neurodevelopmental disorder (ASD and/or ID)

Bjork MH, et al. JAMA Neurol. 2022;79(7):672-681

Figure 1. Cumulative Incidence of Neurodevelopmental Disorders After Prenatal Exposure to Antiseizure Medication (ASM)



Bjork MH, et al. JAMA Neurol. 2022;79(7):672-681

Table 3. Risk of Any Neurodevelopment Disorder (ND)[a] After Prenatal Antiseizure Medication (ASM)[b] Exposure by Dose Compared With Unexposed Children

Mean daily dose[c]	Total, No.	With ND, No.	Adjusted hazard ratio (95% CI)[d]
No ASM	4 462 418	68 295	1 [Reference]
Lamotrigine, mg[b]			
<150	4933	108	1.46 (1.20-1.76)
≥150	4267	51	1.01 (0.76-1.32)
Carbamazepine, mg[b]			
<500	2012	71	1.74 (1.38-2.20)
≥500	1492	42	1.48 (1.09-2.00)
Valproate, mg[b]			
<750	1982	97	2.27 (1.86-2.77)
≥750	945	103	5.64 (4.65-6.84)
Oxcarbazepine, mg[b]			
<500	396	16	1.54 (0.95-2.52)
≥500	1169	36	1.64 (1.19-2.28)
Topiramate, mg[b]			
<100	717	16	1.71 (1.04-2.79)
≥100	129	6	2.93 (1.32-6.55)

■ 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

Male reproductive age

Potential risk of neurodevelopmental disorders in children born to men treated with valproate medicines: PRAC recommends precautionary measures

12 January 2024

EMA's safety committee (PRAC) is recommending precautionary measures for the treatment of male patients with valproate medicines.

News Human Pharmacovigilance Referrals

In reaching its conclusion, the PRAC reviewed data from a retrospective observational study carried out by companies that market valproate as an obligation following a previous review of valproate use during pregnancy. The Committee also considered data from other sources, including non-clinical (laboratory) studies and scientific literature, and consulted patients and clinical experts.

The retrospective observational study used data from multiple registry databases in Denmark, Norway and Sweden and focused on birth outcomes in children born to men who were taking valproate or taking lamotrigine or levetiracetam (other medicines to treat conditions similar to those treated with valproate) around the time of conception.

The results of the study suggest there may be an increased risk of neurodevelopmental disorders in children born to men taking valproate in the 3 months before conception. Neurodevelopmental disorders are problems with development that begin in early childhood, such as autism spectrum disorders, intellectual disability, communication disorders, attention deficit/hyperactivity disorders and movement disorders.

The data showed that around 5 out of 100 children had a neurodevelopmental disorder when born to fathers treated with valproate compared with around 3 out of 100 when born to fathers treated with lamotrigine or levetiracetam. The study did not investigate the risk in children born to men who stopped using valproate more than 3 months before conception.

- European Medicines Agency. PRAC non-interventional imposed PASS final study report assessment report: valproate and related substances (sodium valproate, valproic acid, valproate semisodium, valpromide, valproate magnesium). 2024, European Medicines Agency.
- European Medicines Agency. A post-authorization safety study (PASS) to evaluate the paternal exposure to valproate and the risk of neurodevelopmental disorders including autism spectrum disorder as well as congenital abnormalities in offspring—a population-based retrospective study. 2023, European Medicines Agency.
- Christensen J, Trabjerg BB, Dreier JW. Valproate use during spermatogenesis and risk to offspring. *JAMA Netw Open* 2024; **7:** e2414709.
- Tomson T, Muraca G, Razaz N. Paternal exposure to antiepileptic drugs and offspring outcomes: a nationwide population-based cohort study in Sweden. *J Neurol Neurosurg Psychiatry* 2020; **91:** 907–13

Review

Management of reproductive risks in people with epilepsy

Marte Helene Bjørk, Cristine Cukiert, Bruna Nucera, Rebecca L Bromley

Lancet Neurol 2025; 24: 601–13

	Comparison	HR (95% CI)
Composite of neurodevelopmental diagnoses		
PAS Study (2023)[37,38]		
Denmark	Valproate *vs* levetiracetam and lamotrigine	1·34 (0·79–2·25)
Sweden	Valproate *vs* levetiracetam and lamotrigine	1·54 (0·95–2·51
Norway	Valproate *vs* levetiracetam and lamotrigine	1·52 (0·93– 2·49)
All studied countries	Valproate *vs* levetiracetam and lamotrigine	1·76 (0·83–3·71)*
Christensen et al (2024)[39]		
Denmark	Valproate *vs* general population comparator	1·10 (0·88–1·37)
Autistic spectrum disorder diagnoses		
Tomson et al (2020)[40]		
Sweden	Valproate *vs* general population control	1·4 (0·6–3·1)
PAS Study (2023)[37,38]		
Denmark	Valproate *vs* levetiracetam and lamotrigine	0·76 (0·30–1·89)
Sweden	Valproate *vs* levetiracetam and lamotrigine	2·68 (1·17–6·12)
Norway	Valproate *vs* levetiracetam and lamotrigine	Not reported
All studied countries	Valproate *vs* levetiracetam and lamotrigine	1·52 (0·83–2·81)*
Christensen et al (2024)[39]		
Denmark	Valproate *vs* general population comparator	0·92 (0·65–1·30)
Intellectual disability diagnoses		
Tomson et al (2020)[40]		
Sweden	Valproate *vs* general population control	1·6 (0·5–5·1)
Attention deficit hyperactivity diagnoses		
Tomson et al (2020)[40]		
Sweden	Valproate *vs* general population control	1·4 (0·7–2·8)

HR=hazard ratio. *Pooled HR.

Table 1: **Findings from population-based studies regarding use of valproate by men during spermatogenesis and offspring neurodevelopmental outcomes**

Lancet Neurol 2025; 24: 601–13

Epilep

Systematic review

Paternal exposure to antiseizure medications and offspring outcomes: a systematic review

Eliza Honybun ,[1,2] Genevieve Rayner,[1,2] Charles B Malpas ,[1,3] Terence J O'Brien,[3,4,5] Frank J Vajda,[3,4,5] Piero Perucca,[2,4,5,6] Emilio Perucca[2,4]

Results Of 923 studies identified by the search and screened by title and abstract, 26 underwent full-text review and 10 met eligibility criteria. There was limited evidence available, but there appeared to be no clear evidence for an adverse impact of paternal ASM use on offspring outcomes.

Honybun E, et al. J Neurol Neurosurg Psychiatry 2024;0:1–11

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ While maternal use of some antiseizure medications carries an elevated risk of adverse outcomes for the developing fetus, it is unclear whether paternal exposure to these drugs also carries risks for the offspring.

WHAT THIS STUDY ADDS

⇒ Our systematic review shows that evidence for any risk to the offspring resulting from paternal exposure to antiseizure medications is scarce and inconsistent, with most studies showing no increased risk compared with unexposed controls. Therefore, the available evidence does not justify major concerns.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ The results of our study inform the counselling of males with epilepsy and highlight the need for more research in this area, focusing in particular on risks associated with individual medications.

Advising the PWECP

"People with epilepsy of childbearing potential"

Epilepsy and pregnancy

- ควรมีการให้ความรู้เกี่ยวกับโอกาสและความเสี่ยงที่จะเกิดความผิดปกติของเด็กในครรภ์สำหรับหญิงวัยเจริญพันธุ์ที่ต้องรับประทานยากันชัก เพื่อผู้ป่วยจะได้สามารถวางแผนและตัดสินใจเรื่องการตั้งครรภ์ล่วงหน้าได้
- แนะนำวิธีการคุมกำเนิดที่เหมาะสม
- ??ควรมีการให้ความรู้เกี่ยวกับโอกาสและความเสี่ยงที่จะเกิดความผิดปกติของการพัฒนาการของเด็กสำหรับชายวัยเจริญพันธุ์ที่ต้องรับประทานยากันชักsodium valproate เพื่อผู้ป่วยจะได้สามารถวางแผนและตัดสินใจเรื่องการมีบุตรล่วงหน้าได้

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
  - ควรหลีกเลี่ยงการใช้ยากันชักที่มี teratogenic effect สูง เช่น sodium valproate phenobarbital, topiramate ในช่วงการตั้งครรภ์หากสามารถทำได้
  - ยากันชักบางชนิด ได้แก่ sodium valproate, topiramate อาจมีผลต่อ neurodevelopmental outcome ในเด็กได้

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
- ??ในผู้หญิงวัยเจริญพันธ์ควรได้รับ folic acid supplementation ในขนาด >0.4 mg/d (0.4-0.8 mg/d or 0.4-4 mg/d) ซึ่งจากการศึกษาที่ผ่านมา อาจช่วยลดโอกาสการเกิด neural tube defects ได้บ้าง และช่วยให้ neurodevelopmental outcome ดีขึ้น

Epilepsy and lactation

- ยากันชักส่วนมากไม่ได้ excrete ออกมาในน้ำนมมากนัก จึงมีผลน้อยต่อเด็ก ยกเว้น phenobabital, gabapentin, lamotrigine, and topiramate
- ยังไม่มีหลักฐานชัดเจนว่ายากันชักเหล่านี้ในน้ำนมมีผลกับ cognition ของเด็ก
- แนะนำให้มารดาสามารถ breast feeding ได้
- Phenobarbital อาจจะมีผลทำให้เด็กง่วงซึมได้

ELDERLY WITH EPILEPSY

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 ↑

Decreased Volume distribution: What should we do?

Lean body mass ↓

Total body water mass ↓

Proportion of fat ↓

Volume distribution o ic 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

UNDERLYING DISEASES
CONCOMITTENT 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

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

Effects on hepatic enzymes

Enzyme inhibitor	Enzyme inducer
Sodium valproate	Phenytoin
	Carbamazepine
	Phenobarbital

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)

Effects of enzyme inducing drugs on the concentration and clearance of concurrent AEDs

Effect on Concurrent AED Serum Concentration	Approximate Change in AED Clearance
↓ Ethosuximide	↑ 20–50%
↓ Valproate	↑ Two- to fourfold
↓ Lamotrigine	↑ Two- to fourfold
↓ Topira	40–50%
↓ Tiaga	Two- to fourfold
↓ Felbamate	↑ 50%
↓ Zonisamide	↑ 30–50%
↓ Oxcarbazepine	↑ 25–40%
Levetiracetam	No change

Enzyme inducing AEDs→
↓↓ VPA, LTG level

Between AEDs

- Enzyme inhibitors
- Sodium valproate→ ↑↑↑ lamotrigine
- Topiramate, oxcarbazepine→ ↑ phenytoin

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

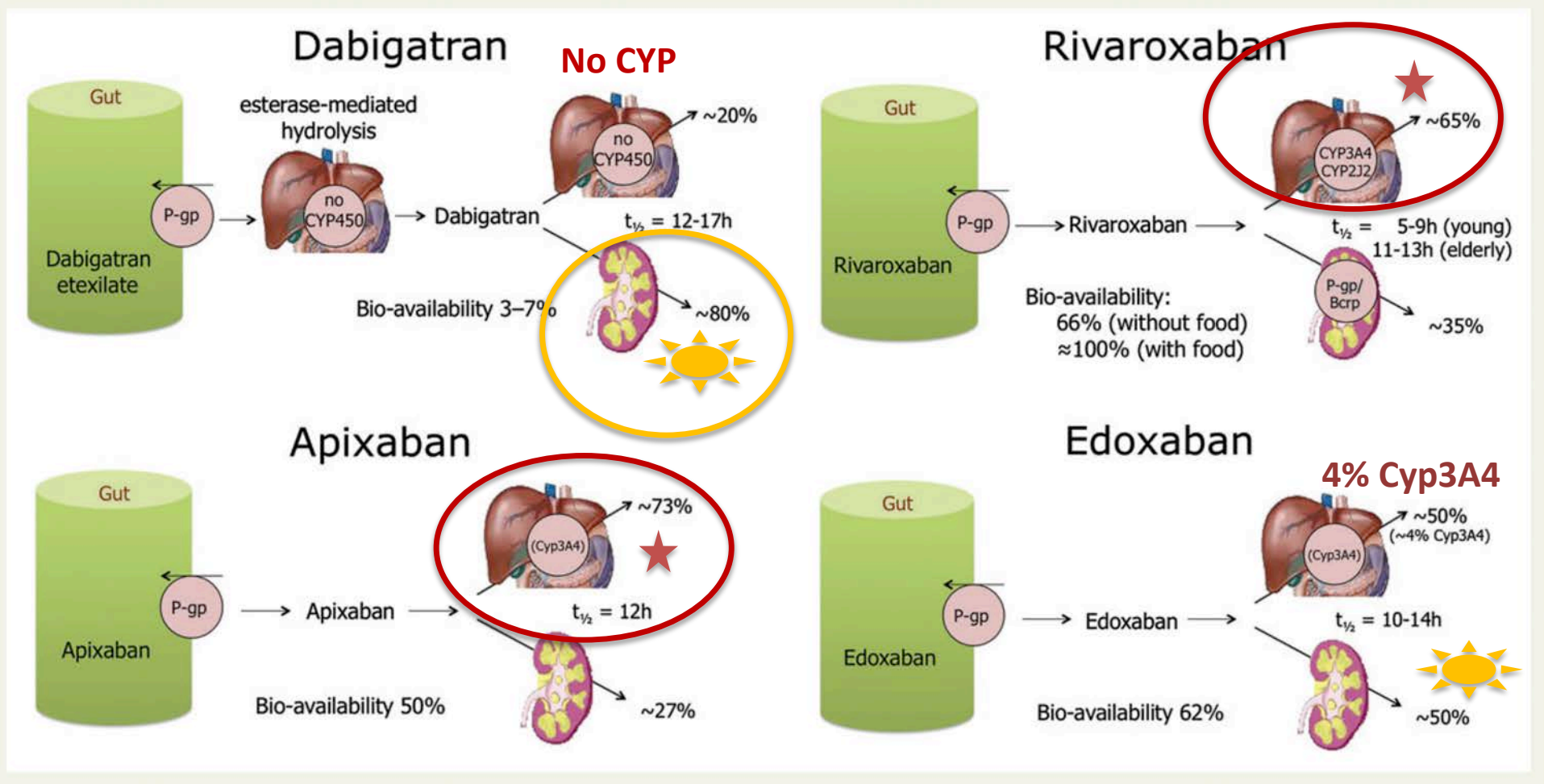
Drug interaction with warfarin

- 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)			

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.

Epilepsia Open 2017;2:107-11

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
MM	Bortezomib	EIAEDs	Proteosome inhibitor	CYP	Cl ⇧ 275%
CML, ALL (Ph+)	Dasatinib	EIAEDs	SCR, Bcr-Abl	CYP	AUC ⇩ 45%
NSCLC	Gefitinib	EIAEDs	EGFR	CYP	AUC ⇩ 45-63%
CML, ALL (Ph+) GIST	Imatinib	EIAEDs	Bcr-Abl, c-kit, PDGFR	CYP	Cl ⇧ 342-413%
HER-2 +ve metas breast CA	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

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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

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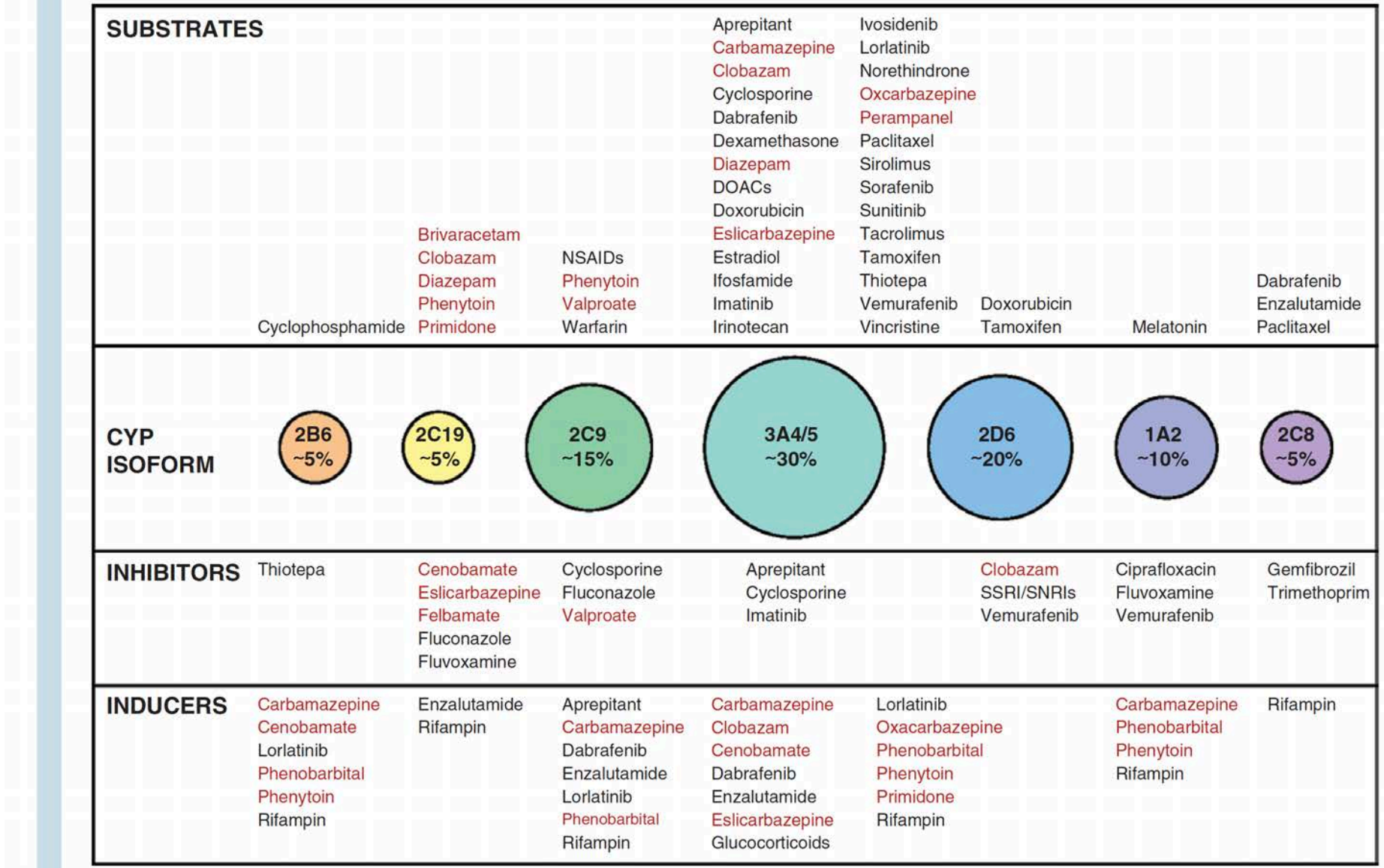

https://doi.org/10.1093/neuonc/noad154

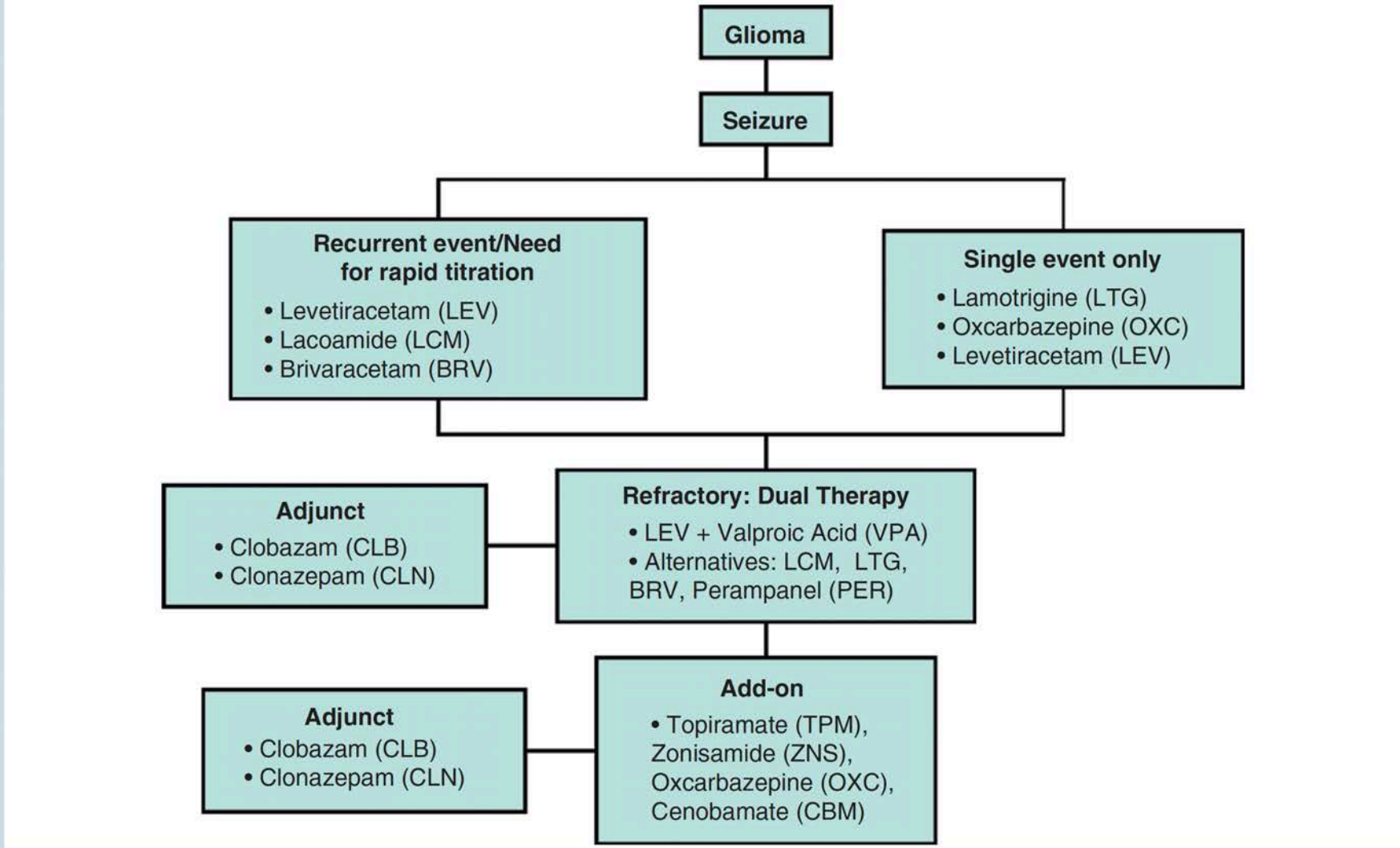

Figure 4. Proposed algorithm for ASM selection in glioma-related epilepsy. In polytherapy, ASMs with different mechanisms of action should be chosen to minimize adverse effects.

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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

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