Choosing AEDs in special situations

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Which medications?

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

Special situations

Special situations

- **Hepatic and renal dysfunction**
- **Other medical conditions**
  - Transplant patients
  - HIV infected patients
  - Patients with brain tumor
- **Psychiatric patients**
- **Elderly**
- **Women**

Hepatic and renal dysfunction

Hepatic dysfunction

Factors affecting hepatic clearance

- **The extent of drug binding to the blood component**
- **Hepatic blood flow**
- **Hepatic metabolic activity**

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

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	

Dosing adjustment for patients with impaired hepatic function

- **There is insufficient information available to make recommendations on the necessity of dosage adjustment**

Patients with impaired hepatic function

- **Free fractions of diazepam, PHT, and VPA increase as a result of reduced circulating albumin concentrations. Frequent serum determinations of free fractions and gradual dose regulations are required.**

Renal dysfunction

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

Dosing adjustment for patients with impaired renal function

Creatinine clearance (mL/min)	Dosage (mg)
Gabapentin	
>60	400 tid
30-60	300 bid
15-30	300 od
<15	300 every other day
hemodialysis	200-300* supplement
Levetiracetam	
>80	500-1500 bid
50-80	500-1000 bid
30-50	250-750 bid
<30	250-500 bid
hemodialysis	500-1000*q 24 hr then 250-500 mg supplement

***with supplement dose after HD**

Dosing adjustment for patients with impaired renal function

Creatinine clearance (mL/min)	Dosage (mg)
Topiramate	
>70	Normal dosage
10-70	Decrease dosage 50%
<10	Decrease dosage 75%
hemodialysis	Consider supplement

***with supplement dose after HD**

Using AEDs in patients with other medical conditions

Metabolic pathways of AEDs

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

*Minor metabolic pathway.

Effects on hepatic enzymes

Enzyme inhibitor	Enzyme inducer
Sodium valproate	Phenytoin
	Carbamazepine
	Phenobarbital

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

Between AEDs

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

Interaction with other drugs

- **Interaction between CYP3A4 inhibitors and carbamazepine**
- **Warfarin**
- **OCPs**
- **Psychiatric drugs**
- **Cardiac drugs**
- **Chemotherapy and immunosuppressive agents**

Commonly used medications that inhibit the CYP3A4

Erythromycin	Fluvoxamine
Clarithromycin	Nefazodone
Troleandomycin	Sertraline
Cimetidine	Ritonavir
Diltiazem	Indinavir
Verapamil	Nelfinavir
Fluconazole	Omeprazole
Itraconazole	Propoxyphene
Ketoconazole	

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.

Interaction with cardiac drugs

- **Phenytoin → ↑ amiodarone level**
  ↓ digoxin level
- **Enzyme inducers**
  → ↓ calcium channel blocker level
  ↓ beta blocker level
- **Verapamil and diltiazem inhibits carbamazepine metabolism**

Drug Class	Interactions with AEDs
Antiarrhythmics	Inductor AEDs enhances antiarrhythmics metabolism; phenytoin decreases amiodarone metabolism.
Hypotensive agents	Inductor AEDs enhances beta-blockers and calcium-antagonist metabolism; verapamil and diltiazem inhibit carbamazepine metabolism.
Digoxin	Phenytoin increases digoxin metabolism.
Lipid-lowering drugs	Inductor AEDs enhance lipid-lowering agents metabolism.
Immunosuppressants	Phenytoin, carbamazepine, and barbiturates enhance tacrolimus, sirolimus, and methylprednisolone metabolism.
Antivirals	Inductor AEDs enhance anti-HIV agents metabolism; anti-HIV agents increase carbamazepine, gabapentin, levetiracetam, and lamotrigine levels.
Antibiotics	Carbapenems decrease valproate levels; macrolides increase carbamazepine levels.
Antifungal	Antifungals enhance carbamazepine and phenytoin levels.
Tuberculostatics	Rifampicin enhances phenytoin, carbamazepine, valproate, ethosuximide, and lamotrigine metabolism; isoniazide inhibits it.

Drug interaction with warfarin

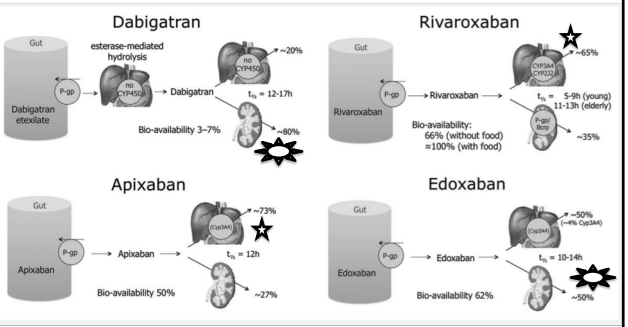
- Metabolites through CYP3A4, 2C9
- Phenytoin, phenobarbital and carbamazepine reduce the concentration of warfarin by up to 50-65%
- Phenobarbital and carbamazepine also reduce the anticoagulation effects of warfarin metabolites
- Newer AEDs do not have significant interaction with anticoagulant

Interaction between AEDs and NOACs

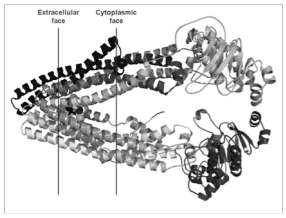
Table 2 Non-VKA oral anticoagulant drugs, approved for prevention of systemic embolism or stroke in patients with non-valvular AF

	Dabigatran	Apixaban	Edoxaban	Rivaroxaban
Action	Direct thrombin inhibitor	Activated factor Xa inhibitor	Activated factor Xa inhibitor	Activated factor Xa inhibitor
Dose	150 mg BID 110 mg BID[a,b] (75 mg BID)[b]	5 mg BID 2.5 mg BID[a]	60 mg OD[c] 30 mg OD[a]	20 mg OD 15 mg OD[a]
Phase III clinical trial	RE-LY[25]	ARISTOTLE[26] AVERROES[27]	ENGAGE-AF[28]	ROCKET-AF[29]

Absorption and metabolism of the different new anticoagulant drugs



P-glycoprotein



- Permeability glycoprotein
- Also known as multidrug resistance protein 1 (MDR1) or ATP-binding cassette sub-family B member 1 (ABCB1) or cluster of differentiation 243 (CD 243)
- Important protein of the cell membrane that pumps foreign substances out of cells
- ATP-dependent efflux pump with broad substrate specificity
- Encoded by the ***ABCB1*** gene

P glycoprotein expression

- **Intestinal epithelium: pumps xenobiotics (eg. toxins or drugs) back into the intestinal lumen**
- **Liver cells: pumps xenobiotics into bile ducts**
- **Cells of the proximal tubules of the kidney: pumps xenobiotics into urinary filtrate (in the proximal tubule)**
- **Capillary endothelial cells composing the blood brain barrier and blood testis barrier :pumps back into the capillaries**

P-gp transports various substrates across the cell membrane

- Drugs such as colchicine, desloratadine, tacrolimus and quinidine.
- Chemotherapeutic agents such as topoisomerase inhibitors (i.e. etoposide, doxorubicin), microtubule-targeted drugs (i.e. vinblastine), and tyrosine kinase inhibitors (i.e. gefitinib, sunitinib)
- Lipids
- Steroids
- Peptides
- Bilirubin
- Cardiac glycosides like digoxin
- Immunosuppressive agents
- Glucocorticoids like dexamethasone
- HIV-type 1 antiretroviral therapy agents like protease inhibitors and nonnucleoside reverse transcriptase inhibitors

Europace (2015) **17**, 1467–1507
doi:10.1093/europace/euv309

EHRA PRACTICAL GUIDE

Europace (2015) 17, 1467–1507

Updated European Heart Rhythm Association Practical Guide on the use of non-vitamin K antagonist anticoagulants in patients with non-valvular atrial fibrillation

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	via	Dabigatran	Apixaban	Edoxaban	Rivaroxaban
Fungostatics					
Fluconazole	Moderate CYP3A4 inhibition	No data yet	No data yet	No data yet	+42% (if systemically administered)[247]
Itraconazole; Ketoconazole; Posaconazole; Voriconazole;	potent P-gp and BCRP competition; CYP3A4 inhibition	+140-150% (US: 2 × 75 mg if CrCl 30-50 ml/min)	+100%[60]	+87-95%[64] (reduce NOAC dose by 50%)	Up to +160%[247]
Immunosuppressive					
Cyclosporin; Tacrolimus	P-gp competition	Not recommended	No data yet	+73%	Extent of increase unknown
Antiphlogistics					
Naproxen	P-gp competition	No data yet	+55%[254]	No effect (but pharmacodynamically increased bleeding time)	No data yet
Antacids					
H2B; PPI; Al-Mg-hydroxide	GI absorption	Minus 12-30%[45, 53, 58]	No effect[55]	No effect	No effect[241, 242]
Others					
Carbamazepine[###]; Phenobarbital[###]; Phenytoin[###]; St John's wort[###]	P-gp/ BCRP and CYP3A4/CYP2J 2 inducers	minus 66%[223]	minus 54%[SmPC]	minus 35%	Up to minus 50%

ESC European Society of Cardiology
European Heart Journal (2018) **39**, 1330–1393
doi:10.1093/eurheartj/ehy136
SPECIAL ARTICLE
European Heart Journal 2018;39:1330–1393

The 2018 European Heart Rhythm Association Practical Guide on the use of non-vitamin K antagonist oral anticoagulants in patients with atrial fibrillation

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	Via[142,145,146]	Dabigatran etexilate	Apixaban[130]	Edoxaban	Rivaroxaban
P-gp substrate		Yes	Yes	Yes	Yes
CYP3A4 substrate		No	Yes (≈25%)	No (<4%)	Yes (≈18%)
Drug					
Carbamazepine	Strong CYP3A4/P-gp induction; CYP3A4 competition	SmPC	−50%[SmPC]	−35%[SmPC]	SmPC, Ref.[147]
Ethosuximide	CYP3A4 competition; No relevant interaction known/assumed				
Gabapentin	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/P-gp induction; P-gp competition		SmPC	SmPC	SmPC
Phenytoin	Strong CYP3A4/P-gp induction; P-gp competition	SmPC, Ref.[148]	SmPC	SmPC	SmPC
Pregabalin	No relevant interaction known/assumed				
Topiramate	CYP3A4 induction; CYP3A4 competition				
Valproic acid	CYP3A4/P-gp induction				Ref.[149]
Zonisamide	CYP3A4 competition; No relevant interaction known/assumed				

Epilepsy Research 126 (2016) 98–101
Contents lists available at www.sciencedirect.com
Epilepsy Research
journal homepage: www.elsevier.com/locate/epilepsyres
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Short communication

Interactions between non-vitamin K oral anticoagulants and antiepileptic drugs

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ARTICLE INFO
Article history:
Received 12 April 2016
Received in revised form 1 June 2016
Accepted 24 June 2016
Available online 9 July 2016
Keywords:
Atrial fibrillation
Stroke
Seizure
Drug-drug interaction

ABSTRACT
Atrial fibrillation (AF) is a frequent cause of stroke. Secondary prophylaxis by oral anticoagulants (OAC) is recommended after stroke in AF-patients. OAC can be achieved by vitamin-K antagonists (VKAs) or non-vitamin K antagonist oral anticoagulants (NOACs) like dabigatran, rivaroxaban, apixaban or edoxaban. Seizures are frequent after stroke, and antiepileptic drugs (AEDs) are indicated. The review, based on a literature research, aims to give an overview about pharmacokinetic knowledge and clinical data about drug–drug interactions (DDIs) between NOACs and AED.
Carbamazepine, levetiracetam, phenobarbital, phenytoin and valproic acid might decrease the effect of NOACs by inducing P-glycoprotein (P-gp) activity. Carbamazepine, oxcarbazepine, phenytoin, phenobarbital and topiramate might decrease the effect of NOACs by inducing CYP3A4 activity. Controversial data – inhibition as well as induction of CYP3A4 – were found about valproic acid.
The relevance of these DDIs is largely unknown since there are only sporadic case reports available. To increase the knowledge about DDIs between NOACs and AEDs we suggest subgroup analyses addressing effects and safety of VKAs versus NOACs in patients with AF on AEDs, in case they have been included in previously completed or still ongoing trials or registries. This could be easily feasible and would be desirable in view of the large data already accumulated.

Epilepsy Research 2016;126:98–101

Antiepileptic drugs and evidence of their effects on the activity of P-glycoprotein and CYP 3A4

Antiepileptic drug	P-GP	Evidence	CYP 3A4	Evidence
Carbamazepine	↑ (Giessmann et al., 2004)	Humans	↑ (Puranik et al., 2013)	Humans
Ethosuximide	NR		NR	
Gabapentin	NR		NR	
Lamotrigine	No effect (Wang-Tilz et al., 2006)	Animals	NR	
Levetiracetam	↑ (Moerman et al., 2011)	Animals	No effect (Nicolas et al., 1999)	In vitro
Oxcarbazepine	NR		↑(Andreasen et al., 2007)	Humans
Phenobarbital	↑ (Jing et al., 2010)	Animals	↑ (Ohno et al., 2009)	In vitro
Phenytoin	↑ (Alvariza et al., 2014)	Animals	↑ (Lim et al., 2004)	Humans
Pregabalin	NR		NR	
Topiramate	No effect (Wang-Tilz et al., 2006)	Animals	↑ (Nallani et al., 2003)	In vitro
Valproic acid	↑ (Eyal et al., 2006)↓ (Tang et al., 2004)	In vitro	↑ (Cerveny et al., 2007)↓ (Wen et al., 2001)	In vitro
Zonisamide	NR		NR	a

↑ = Inducer.
↓ = Inhibitor.
NR = not reported.

Epilepsy Research 2016;126:98–101

Antiepileptic drugs and reports about interaction with NOACs

Antiepileptic drug	Dabigatran	Rivaroxaban	Apixaban	Edoxaban
Carbamazepine	NR	1 CR (Risselada et al., 2013)	NR	NR
Ethosuximide	NR	NR	NR	NR
Gabapentin	NR	NR	NR	NR
Lamotrigine	NR	NR	NR	NR
Levetiracetam	NR	NR	NR	NR
Oxcarbazepine	NR	1 CR (Serra et al., 2015)	NR	NR
Phenobarbital	CS (Chin et al., 2014)	NR	NR	NR
Phenytoin	CS (Chin et al., 2014)CR (Wiggins et al., 2016)	NR	NR	NR
Pregabalin	NR	NR	NR	NR
Topiramate	NR	NR	NR	NR
Valproic acid	NR	1 CR (Stöllberger and Finsterer, 2014)	NR	NR
Zonisamide	NT	NR	NR	NR

CR = Case report.
CS = clinical series.
NR = not reported.

Epilepsy Research 2016;126:98–101

Epilepsy Research (2011) 94, 18–25

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

Antiepileptic drugs modulate P-glycoproteins in the brain: A mice study with ^{11}C-desmethylloperamide

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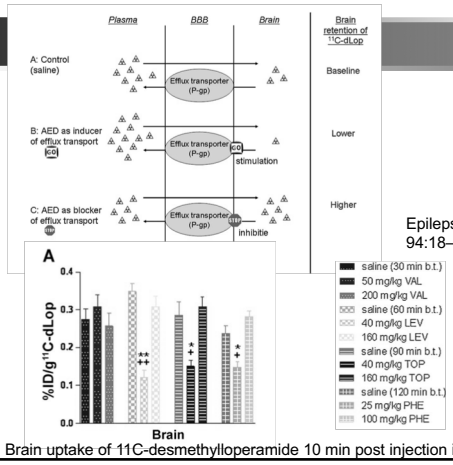
Received 5 July 2010; received in revised form 1 December 2010; accepted 27 December 2010
Available online 31 January 2011

Epilepsy Research 2011;94:18—25

- **11C-desmethylloperamide (11C-dLop), a radiolabelled substrate of P-gp, was intravenously administrated after pretreatment with saline or AEDs (sodium valproate, levetiracetam, topiramate and phenytoin) at their human therapeutic and four times their therapeutic dose**

Epilepsy Research 2011;94:18—25



Epilepsy Research 2011; 94:18—25

Brain uptake of 11C-desmethylloperamide 10 min post injection in wild-type mice

	Via[142,145,146]	Dabigatran etexilate	Apixaban[130]	Edoxaban	Rivaroxaban
P-gp substrate		Yes	Yes	Yes	Yes
CYP3A4 substrate		No	Yes (≈25%)	No (<4%)	Yes (≈18%)
Drug					
Carbamazepine	Strong CYP3A4/P-gp induction; CYP3A4 competition	SmPC	–50%[SmPC]	–35%[SmPC]	SmPC, Ref.[147]
Ethosuximide	CYP3A4 competition; No relevant interaction known/assumed				
Gabapentin	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/P-gp induction; P-gp competition		SmPC	SmPC	SmPC
Phenytoin	Strong CYP3A4/P-gp induction; P-gp competition	SmPC, Ref.[148]	SmPC	SmPC	SmPC
Pregabalin	No relevant interaction known/assumed				
Topiramate	CYP3A4 induction; CYP3A4 competition				
Valproic acid	CYP3A4/P-gp induction				Ref.[149]
Zonisamide	CYP3A4 competition; No relevant interaction known/assumed				

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.**

HIV patients

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

Brain tumors

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**

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

Potentials interaction between AEDs and chemotherapy

- **In a study of 716 children with ALL, 40 children who were on enzyme-inducing AEDs had worse event-free survival (hazard ratio 2.67 [95% CI, 1.50 to 4.76]), hematological relapse (3.40 [1.69 to 6.88]) and CNS relapse (2.90 [1.01 to 8.28]).**
- **These children were found to have a higher clearance of teniposide and methotrexate.**

Relling MV, Pui CH, Sandlund JT, et al. Lancet 2000;356:285–90

Potentials interaction between AEDs and chemotherapy

- In a study on glioblastoma multiforme treated with adjuvant CCNU after surgery and radiotherapy, patients receiving enzyme-inducing AEDs (carbamazepine in80% of patients) had a significantly shorter survival,10.8 versus 13.9 months, than patients treated withnon-enzyme-inducing AEDs (valproic acid in 80% of patients)

Oberndorfer S, et al. J Neurooncol 2005;72:255–60

Patients with brain tumors

- Enzyme-inducing AEDS can interfere with the level of concomittent chemotherapy and should be avoided.
- Valproic acid may be considered as a first-line agent, although physicians should be aware of the potentially enhanced toxicity of concomitant agents that share the same P-450 coenzyme metabolic pathway.

Patients with brain tumors

- Newer AEDs that do not metabolite through CYP 450 system also can be used.
- More evidence is still needed.

Issues in epilepsy treatment in the elderly

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

Issues in epilepsy treatment in the 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

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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

SPECIAL ARTICLE LEVEL OF RECOMMENDATION

Practice guideline update summary: Efficacy and tolerability of the new antiepileptic drugs I: Treatment of new-onset epilepsy

Report of the Guideline Development, Dissemination, and Implementation Subcommittee of the American Academy of Neurology and the American Epilepsy Society

Andres M. Kanner, MD, Eric Ashman, MD, David Gloss, MD, MPH&TM, Cynthia Harden, MD, Blaise Bourgeois, MD, Jocelyn F. Bautista, MD, Bassel Abou-Khalil, MD, Evren Burakgazi-Dalkilic, MD, Esmeralda Llanas Park, MD, John Stern, MD, Deborah Hirtz, MD, Mark Nespeca, MD, Barry Gidal, PharmD, Edward Faught, MD, and Jacqueline French, MD

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Neurology® 2018;91:74-81. doi:10.1212/WNL.0000000000005755

Neurology 2018;91:74-81

	Level A	Level B	Level C	Level U
New onset focal epilepsy or unclassified GTC > 60 yo		LTG	GBP	
New onset focal epilepsy or unclassified GTC in adult			LEV ZNS	GBP OXC TPM CLB All 3rd gen AEDs
New onset focal epilepsy or unclassified GTC in children	no recommendations can be made regarding TPM use at the studied doses (400 mg/d), particularly in new-onset epilepsy and pediatric patients.			
New onset generalized epilepsy and unclassified GTC seizures in adult and children	Evidence is insufficient to compare efficacy of LTG and TPM with that of VPA in children and adults with new-onset or relapsing GE (1 Class III study).			
Monotherapy in adults and adolescents with new-onset focal, GE, or unclassified GTC seizures	Evidence is insufficient to compare efficacy of CBZ-CR, LEV, and VPA-ER in adolescents and adults with new-onset GE and focal epilepsy (1 Class III study).			
Childhood absence epilepsy	LTG is probably not as effective as ETS or VPA for treating absence seizures (1 Class I study). Attention disturbances are more common with VPA use.			

Neurology 2018;91:74-81

Malformation Risks of AEDs in Pregnancy

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

CURRENT OPINION

Teratogenicity of antiepileptic drugs

Torbjörn Tomson[a], *Dina Battino*[b], *and Emilio Perucca*[c]

Purpose of review
We review data on the comparative teratogenicity of antiepileptic drugs (AEDs), focusing on major congenital malformations (MCMs), intrauterine growth restriction, impaired cognitive development, and behavioral adverse effects following prenatal exposure.

Recent findings
Prospective registries and meta-analyses have better defined the risk of MCMs in offspring exposed to individual AEDs at different dose levels. Valproate is the drug with the highest risk, whereas prevalence of MCMs is lowest with lamotrigine, levetiracetam, and oxcarbazepine. For valproate, phenobarbital, phenytoin, carbamazepine, and lamotrigine, the risk of MCMs is dose-dependent. Prenatal exposure to valproate has also been confirmed to cause an increased risk of cognitive impairments and autistic traits. In a population-based study, the risk of AED-induced autistic traits was attenuated by periconceptional folate supplementation.

Summary
The risk of adverse fetal effects differs in relation to the type of AED and for some AEDs also the daily dose. Although for MCMs the risk is primarily associated with the first trimester of gestation, influences on cognitive and behavioral development could extend throughout pregnancy. Available information now permits a more rational AED selection in women of childbearing potential, and evidence-based counseling on optimization of AED treatment before conception.

Keywords
antiepileptic drugs, behavior, cognition, congenital malformations, epilepsy, pregnancy

Curr Opin Neurol 2019, 32:246–252

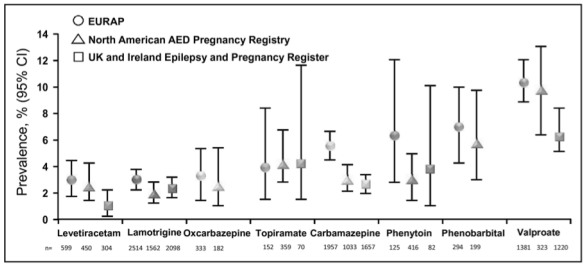
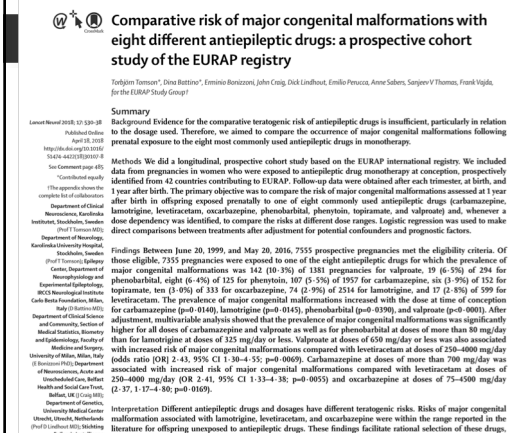


FIGURE 1. Prevalence (%; and 95% confidence intervals, CI) of major congenital malformations with eight different antiepileptic drug monotherapies based on data from three prospective registries [2,4,5**].



Comparative risk of major congenital malformations with eight different antiepileptic drugs: a prospective cohort study of the EURAP registry

Torbjörn Tomson*, Dina Battino*, Emminio Bonizzoni, John Craig, Dick Lindhout, Emilio Perucca, Anne Sabers, Sanjeev V Thomas, Frank Vajda, for the EURAP Study Group†

Lancet Neurol 2018; 17: 530–38
Published Online April 18, 2018 http://dx.doi.org/10.1016/S1474-4422(18)30107-8
See Comment page 495
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Summary

Background Evidence for the comparative teratogenic risk of antiepileptic drugs is insufficient, particularly in relation to the dosage used. Therefore, we aimed to compare the occurrence of major congenital malformations following prenatal exposure to the eight most commonly used antiepileptic drugs in monotherapy.

Methods We did a longitudinal, prospective cohort study based on the EURAP international registry. We included data from pregnancies in women who were exposed to antiepileptic drug monotherapy at conception, prospectively identified from 42 countries contributing to EURAP. Follow-up data were obtained after each trimester, at birth, and 1 year after birth. The primary objective was to compare the risk of major congenital malformations assessed at 1 year after birth in offspring exposed prenatally to one of eight commonly used antiepileptic drugs (carbamazepine, lamotrigine, levetiracetam, oxcarbazepine, phenobarbital, phenytoin, topiramate, and valproate) and, whenever a dose dependency was identified, to compare the risks at different dose ranges. Logistic regression was used to make direct comparisons between treatments after adjustment for potential confounders and prognostic factors.

Findings Between June 20, 1999, and May 20, 2016, 7555 prospective pregnancies met the eligibility criteria. Of those eligible, 7355 pregnancies were exposed to one of the eight antiepileptic drugs for which the prevalence of major congenital malformations was 142 (10·3%) of 1381 pregnancies for valproate, 19 (6·5%) of 294 for phenobarbital, eight (6·4%) of 125 for phenytoin, 107 (5·5%) of 1957 for carbamazepine, six (3·9%) of 152 for topiramate, ten (3·0%) of 333 for oxcarbazepine, 74 (2·9%) of 2514 for lamotrigine, and 17 (2·8%) of 599 for levetiracetam. The prevalence of major congenital malformations increased with the dose at time of conception for carbamazepine (p=0·0140), lamotrigine (p=0·0145), phenobarbital (p=0·0390), and valproate (p<0·0001). After adjustment, multivariable analysis showed that the prevalence of major congenital malformations was significantly higher for all doses of carbamazepine and valproate as well as for phenobarbital at doses of more than 80 mg/day than for lamotrigine at doses of 325 mg/day or less. Valproate at doses of 650 mg/day or less was also associated with increased risk of major congenital malformations compared with levetiracetam at doses of 250–4000 mg/day (odds ratio [OR] 2·43, 95% CI 1·30–4·55; p=0·0069). Carbamazepine at doses of more than 700 mg/day was associated with increased risk of major congenital malformations compared with levetiracetam at doses of 250–4000 mg/day (OR 2·41, 95% CI 1·33–4·38; p=0·0055) and oxcarbazepine at doses of 75–4500 mg/day (2·37, 1·17–4·80; p=0·0169).

Interpretation Different antiepileptic drugs and dosages have different teratogenic risks. Risks of major congenital malformation associated with lamotrigine, levetiracetam, and oxcarbazepine were within the range reported in the literature for offspring unexposed to antiepileptic drugs. These findings facilitate rational selection of these drugs, taking into account comparative risks associated with treatment alternatives. Data for topiramate should be interpreted cautiously because of the small number of exposures in this study.

Lancet Neurol 2018; 17: 530–38

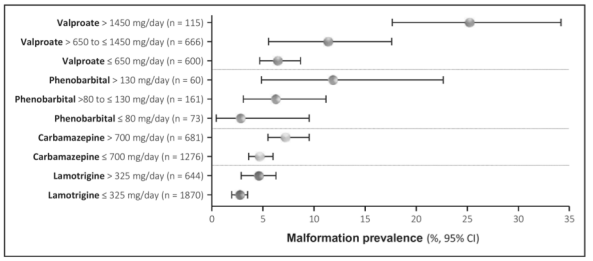

FIGURE 2. Dose dependency of major congenital malformations (%; and 95% confidence intervals) with four antiepileptic drug monotherapies. Based on Data from [5**].

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.

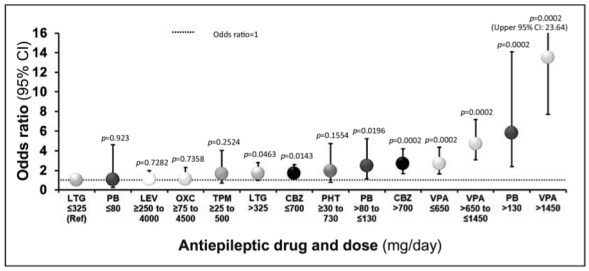

FIGURE 3. Risk of major congenital malformations (odds ratios with 95% confidence intervals) with different antiepileptic drug treatments compared with lamotrigine 325 mg/day or less. CBZ, carbamazepine; LEV, levetiracetam; LTG, lamotrigine; OXC, oxcarbazepine; PB, phenobarbital; PHT, phenytoin; Ref,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

ARTICLE

Risks of 23 specific malformations associated with prenatal exposure to 10 antiepileptic drugs

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Neurology® 2019;93:e167-e180. doi:10.1212/WNL.0000000000007696

- The cohort included 1,886,825 pregnancies, 2,997 exposed to lamotrigine, 1,671 to pregabalin, 980 to clonazepam, 913 to valproic acid, 579 to levetiracetam, 517 to topiramate,512 to carbamazepine, 365 to gabapentin, 139 to oxcarbazepine, and 80 to phenobarbital
- Exposure to valproic acid was associated with 8 specific types of MCMs (e.g., spina bifida, OR 19.4, 95% CI 8.6–43.5), and exposure to topiramate was associated with an increased risk of cleft lip (6.8, 95% CI 1.4–20.0)
- No significant association for lamotrigine, levetiracetam, carbamazepine, oxcarbazepine, and gabapentin

Table 4 Number, frequency (per 1,000 pregnancies), and crude ORs according to tertiles of cumulative dose

	Tertile 1[a]		Tertile 2[b]		Tertile 3[c]	
	n (‰)	OR (95% CI)	n (%)	OR (95% CI)	n (%)	OR (95% CI)
Valproic acid						
Spina bifida	0 (0)	0.0 (0.0–30.4)	1 (3.26)	9.9 (0.3–56.0)	5 (16.45)	50.9 (16.4–120.8)
Ventricular septal defect	2 (6.85)	2.8 (0.3–10.0)	4 (13.33)	5.4 (1.5–14.0)	3 (10.34)	4.2 (0.9–12.3)
Atrial septal defect	2 (6.85)	3.9 (0.5–14.3)	5 (16.67)	9.6 (3.1–22.7)	8 (27.59)	16.1 (6.9–32.2)
Pulmonary valve atresia	1 (3.42)	42.0 (1.1–239.6)	0 (0.00)	0.0 (0.0–124.0)	1 (3.45)	42.3 (1.1–241.2)
Hypoplastic left heart syndrome	0 (0.00)	0.0 (0.0–89.4)	2 (6.67)	57.8 (6.9–213.0)	0 (0.00)	0.0 (0.0–90.0)
Cleft palate	0 (0.00)	0.0 (0.0–16.3)	1 (3.33)	5.3 (0.1–29.7)	2 (6.90)	11.0 (1.3–40.0)
Anorectal atresia	1 (3.42)	11.7 (0.3–66.2)	1 (3.33)	11.4 (0.3–64.4)	1 (3.45)	11.8 (0.3–66.7)
Hypospadias	1 (7.81)	1.6 (0.0–9.2)	0 (0.00)	0.0 (0.0–5.6)	7 (64.22)	14.2 (5.5–30.3)
Clonazepam						
Microcephaly	1 (3.14)	9.8 (0.2–55.5)	0 (0.00)	0.0 (0.0–31.7)	2 (6.47)	20.3 (2.4–74.5)
Phenobarbital						
Ventricular septal defect	1 (37.04)	15.4 (0.4–93.6)	1 (40.00)	16.6 (0.4–102.1)	0 (0.00)	0.0 (0.0–48.8)
Pregabalin						
Coarctation of aorta	1 (1.83)	4.4 (0.1–24.6)	1 (1.83)	4.4 (0.1–24.5)	2 (3.57)	8.5 (1.0–31.1)
Topiramate						
Cleft lip with or without cleft palate	1 (6.00)	6.8 (0.2–38.7)	0 (0.00)	0.0 (0.0–20.9)	2 (11.63)	13.4 (1.6–49.0)

Abbreviations: CI = confidence interval; OR = odds ratio
[a] Tertile 1: valproic acid ≤26,667 mg, clonazepam ≤40 mg, phenobarbital ≤3,000 mg (50 mg/d), pregabalin ≤1,820 mg, and topiramate ≤1,447 mg.
[b] Tertile 2: valproic acid 26,667 to 48,000 mg, clonazepam 40 to 50 mg, phenobarbital 3,000 to 5,100 mg, pregabalin 1,820 to 4,387 mg, and topiramate 1,447 to 3,400 mg.
[c] Tertile 3: valproic acid >48,000 mg, clonazepam >50 mg, phenobarbital >5,100 mg, pregabalin >4,387 mg, and topiramate >3,400 mg.

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.

WHAT WE SHOULD DO?

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 หลังคลอดเช่นเดียวกับเด็กอื่น ๆ

Epilepsy and lactation

- ยากันชักส่วนมากไม่ได้ excrete ออกมาในน้ำนมมากนัก จึงมีผลน้อยต่อเด็ก ยกเว้น phenobabital, levetiracetam, gabapentin,lamotrigine, and topiramate
- Phenobarbital อาจจะมีผลทำให้เด็กง่วงซึมได้

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