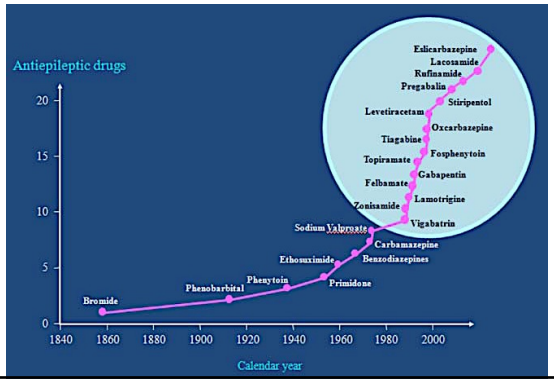
Mahidol University
Faculty of Medicine Siriraj Hospital

Choosing AEDs in Special Situations

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

THREE GENERATIONS OF AEDS

Antiepileptic drug development



SELECTING THE FIRST AED

Which medications?

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

CHOOSING AEDS IN PATIENTS WITH MEDICAL COMORBIDITIES

Special situations

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

Hepatic and renal dysfunction

Seizures and epilepsy in this condition

- More acute seizures and status epilepticus precipitated by metabolic causes
- Need to differentiate between alteration of consciousness from metabolic encephalopathy and nonconvulsive status epilepticus (Clinically and EEG)

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.

Patients with impaired hepatic function

- Caution should be taken if VPA is used inpatients with liver disease.
- Hepatic dysfunction is less of a concern with PB, gabapentin, levetiracetam, topiramate, and zonisamide.

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**

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

	% Renal excretion	%Protein binding	Dosing in renal impairment	HD
PHT	<5	90	NA	NA*
CBZ	1-3	75	NA	NA
PB	25	20-45	CrCL<10 ↓ dose	HD: Dose before and 50 % dose after HD PD: 50 % of the normal dose CRRT: No sufficient data; no initial dose adjustment is needed; possible significant removal by CRRT
VPA	<7	80-90	NA	NA
Clona zepam	<2	85	NA	NA
OXC	20-30	40	CrCl< 30: Initiate at 50 % starting dose (300 mg/day) then titrate cautiously	HD: No data PD: No data CRRT: No data; possibly removed

Seizure 2020;76:143–152

	% Renal excretion	%Protein binding	Dosing in renal impairment	HD
LEV	66	<10	See table	HD: 500−1000 mg/day + supplement al dose post dialysis (250−500 mg) PD: Dose for CrCl < 10 CRRT: Significantly removed; suggested dosage 1000 mg q12h
LTG	10	55	Start at low dose and titrate cautiously	HD: No sufficient data; start at low dose and titrate cautiously; give dose post dialysis. PD: No data; start at low dose and titrate cautiously CRRT: No data; start at low dose and titrate cautiously
TPM	50	13-41	See table	HD: 100−200 mg/day + supplemental dose post dialysis (50−100 mg) PD: 100−200 mg/day CRRT: No data; possibly removed

Seizure 2020;76:143–152

	% Renal excretion	%Protein binding	Dosing in renal impairment	HD
GBP	100	<10	See table	HD: Dose based on CrCl + supplemental dose post dialysis (125−350 mg) PD: Initiate dosing as in patients with CrCl <15 CRRT: Initiate dosing as in patients with CrCl 15-50
PGB	90	-	CrCl 30-60: 75−300 mg/day CrCl 15-30: 25−150 mg/day CrCl <15: 25−75 mg/day	HD: Dose based on CrCl + supplemental dose post dialysis (25−150 mg) PD: No data; Initiate dosing as in patients with CrCl <15 CRRT: No data; likely to be significantly removed by CRRT

Seizure 2020;76:143–152

	% Renal excretion	%Protein binding	Dosing in renal impairment	HD
LCM	40	<15	CrCl > 30: No dosage adjustment needed CrCl< 30: 50−300 mg/d	HD: 50−300 mg/d + supplemental dose post dialysis PD: No data CRRT: No sufficient data; likely removed by CRRT; no initial dose adjustment needed
PER	-	95	CrCl > 30: No dosage adjustment needed CrCl< 30: No data	HD: No data PD: No data CRRT: No data; less likely to be removed

Seizure 2020;76:143–152

AEDs that can cause renal stone

- Topiramate
- Zonisamide

USING AEDS IN PATIENTS WITH OTHER MEDICAL CONDITIONS

Metabolic pathways of AEDs

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

*Minor metabolic pathway.

Perampanel

Effects on hepatic enzymes

Enzyme inhibitor	Enzyme inducer
Sodium valproate	Phenytoin
	Carbamazepine
	Phenobarbital

Oxcarbazepine
Topiramate >200 mg/d

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
↓ 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	

USING AEDS IN PATIENTS WITH 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

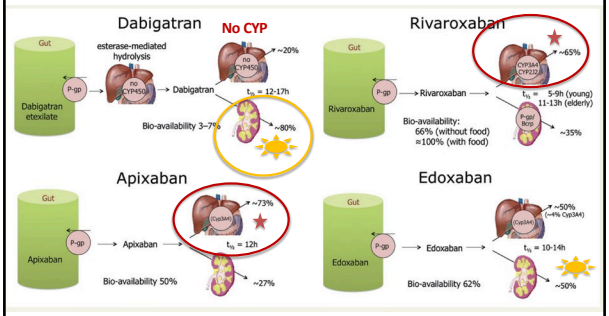
Interaction between AEDs and NOACs

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

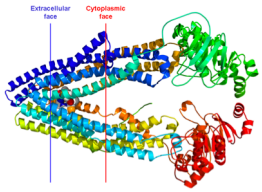
	Dabigatran	Apixaban	Edoxaban	Rivaroxaban
Action	Direct thrombin inhibitor	Activated factor Xa inhibitor	Activated factor Xa inhibitor	Activated factor Xa inhibitor
Dose	150 mg BID 110 mg BID[a,b] (75 mg BID)[b]	5 mg BID 2.5 mg BID[a]	60 mg OD[c] 30 mg OD[a]	20 mg OD 15 mg OD[a]
Phase III clinical trial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

- 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



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

Hein Heidbuchel[1]*, Peter Verhamme[2], Marco Alings[3], Matthias Antz[4], Hans-Christoph Diener[5], Werner Hacke[6], Jonas Oldgren[7], Peter Sinnaeve[2], A. John Camm[8], and Paulus Kirchhof[9,10]

Advisors:, Azhar Ahmad, M.D. (Boehringer Ingelheim Pharma), Jutta Heinrich-Nols, M.D. (Boehringer Ingelheim Pharma), Susanne Hess, M.D. (Bayer Healthcare Pharmaceuticals), Markus Müller, M.D., Ph.D. (Pfizer Pharma), Felix Münzel, Ph.D. (Daiichi-Sankyo Europe), Markus Schwertfeger, M.D. (Daiichi-Sankyo Europe), Martin Van Eickels, M.D. (Bayer Healthcare Pharmaceuticals), and Isabelle Richard-Lordereau, M.D. (Bristol Myers Squibb/Pfizer)

Document reviewers:, Gregory Y.H. Lip, (Reviewer Coordinator; UK), Chern-En Chiang, (Taiwan), Jonathan Piccini, (USA), Tatjana Potpara, (Serbia), Laurent Fauchier, (France), Deirdre Lane, (UK), Alvaro Avezum, (Brazil), Torben Bjerregaard Larsen, (Denmark), Guiseppe Boriani, (Italy), Vanessa Roldan-Schilling, (Spain), Bulent Gorenek, (Turkey), and Irene Savelieva, (UK, on behalf of EP-Europace)

	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 x 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%[253]	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

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

Advisors: Martin van Eickels, M.D. (Bayer Healthcare), Jutta Heinrich-Nols, M.D. (Boehringer Ingelheim), Markus Müller, M.D., Ph.D. (Pfizer), Wolfgang Zierhut M.D. (Daiichi-Sankyo) and Poushali Mukherjea, Ph.D. (Bristol-Myers Squibb)

Document reviewers (ESC scientific document group): Gregory YH Lip (EHRA Review Coordintaor; UK, Denmark), Jeffrey Weitz (Canada), Laurent Fauchier (France), Deirdre Lane (UK), Giuseppe Boriani (Italy), Andreas Goette (Germany), Roberto Keegan (Argentina), Robert MacFadyen (Australia), Chern-En Chiang (Taiwan), Boyoung Joung (Korea), and Wataru Shimizu (Japan)

SmPC= Summary of product characteristics

	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				

USING AEDS IN PATIENTS WITH 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

Potential mechanism of interaction between VPA and carbapenems

- Carbapenems enhance the glucuronidation of VPA by increasing uridine diphosphate-glucuronic acid levels, resulting in decreased serum levels of VPA
- Multidrug-resistance proteins on adenosine triphosphate-binding cassette transporters on erythrocyte membranes may be inhibited by carbapenems. Therefore, VPA is not effluxed out of the erythrocytes, which results in decreased serum levels of VPA
- When VPA is given orally, its absorption into the intestinal lumen may be restricted by intravenously administered carbapenem antibiotics. This may relate to the inhibition of the membrane transporter in intestinal cells

HIV PATIENTS

Drug	Protein Binding (%)	Metabolism
Older AEDs		
Phenobarbital	45	CYP450
Phenytoin	90	CYP450-2C
Carbamazepine	~75	CYP450-3A, 2C
Valproate	90	Gluc
Newer AEDs		
Gabapentin	Minimal	Nil
Lamotrigine	55	Gluc, CYP450
Oxcarbazepine	40	Gluc, CYP450
Topiramate	Minimal	CYP450-3A
Levetiracetam	Minimal	Enzymatic hydrolysis
Tiagabine	96	Hydrolysis
Zonisamide	Minimal	Gluc, CYP450
Pregabalin	Minimal	Negligible
HAART		
NRTI	Minimal to ~38	Gluc
NNRTI	50–99	CYP450
PI	>90	CYP450

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

USING AEDS IN 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.

USING AEDS IN BRAIN TUMOR AND ONCOLOGIC PATIENTS

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 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 ½, 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 ½, or AUC.

Neuro-Oncology Practice 2016; 3: 245–260

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 in 80% 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

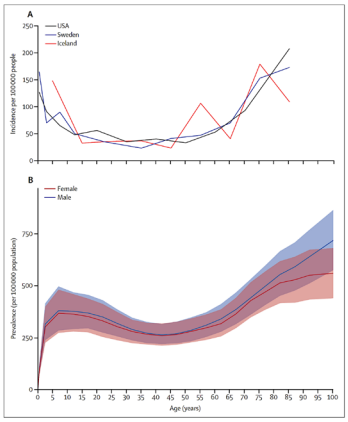
Patients with brain tumors

- 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.

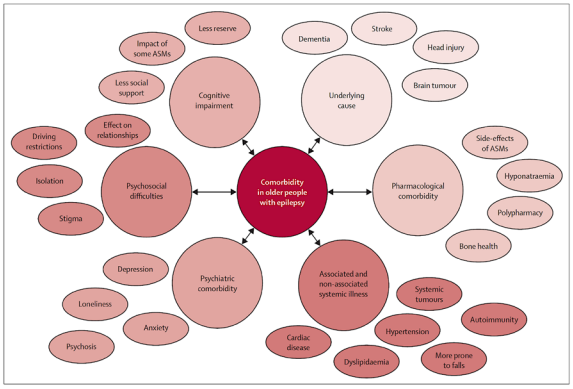
Patients with brain tumors

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

USING AEDS IN ELDERLY PATIENTS



Lancet 2020; 395: 735–48



Lancet 2020; 395: 735–48

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

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

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

Table 4. Summary of studies and level of evidence for each seizure type and epilepsy syndrome

Seizure type or epilepsy syndrome	Class I studies	Class II studies	Class III studies	Level of efficacy and effectiveness evidence (in alphabetical order)
Adults with partial-onset seizures	4	1	34	Level A: CBZ, LEV, PHT, ZNS Level B: VPA Level C: GBP, LTG, OXC, PB, TPM, VGB Level D: CZP, PRM
Children with partial-onset seizures	1	0	19	Level A: OXC Level B: None Level C: CBZ, PB, PHT, TPM, VPA, VGB Level D: CLB, CZP, LTG, ZNS
Elderly adults with partial-onset seizures	1	1	3	Level A: GBP, LTG Level B: None Level C: CBZ Level D: TPM, VPA
Adults with generalized onset tonic–clonic seizures	0	0	27	Level A: None Level B: None Level C: CBZ, LTG, OXC, PB, PHT, TPM, VPA Level D: GBP, LEV, VGB

AEDs in the elderly

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

USING AEDS IN PATIENTS WITH OTHER MORBIDITIES

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

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.

USING AEDS IN WOMEN WITH EPILEPSY

Special issues in women with epilepsy

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

TERATOGENIC SIDE EFFECTS OF AEDS

Malformation Risks of AEDs in Pregnancy

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

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

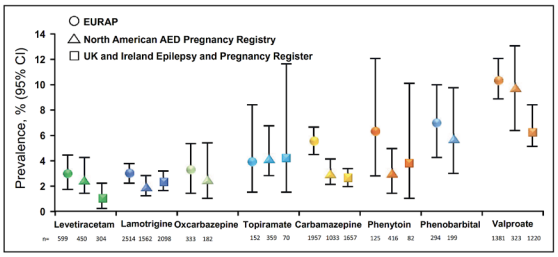
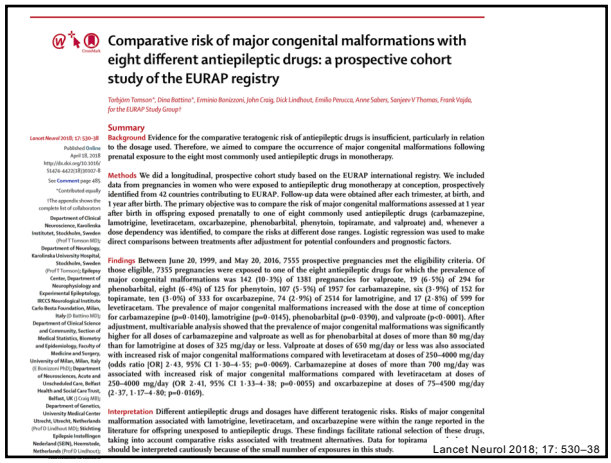


FIGURE 1. Prevalence (%; and 95% confidence intervals, CI) of major congenital malformations with eight different antiepileptic drug monotherapies based on data from three prospective registries [2,4,5▪▪].



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

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

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See Comment page 485

*Contributed equally
†The appendix shows the complete list of collaborators
Department of Clinical Neuroscience, Karolinska Institutet, Stockholm, Sweden (Prof T Tomson MD); Department of Neurology, Karolinska University Hospital, Stockholm, Sweden (Prof T Tomson); Epilepsy Center, Department of Neurophysiology and Experimental Epileptology, IRCCS Neurological Institute, Carlo Besta Foundation, Milan, Italy (D Battino MD); Department of Clinical Science and Community, Section of Medical Statistics, Biometry and Epidemiology, Faculty of Medicine and Surgery, University of Milan, Milan, Italy (E Bonizzoni PhD); Department of Neurosciences, Acute and Unscheduled Care, Belfast Health and Social Care Trust, Belfast, UK (J Craig MD); Department of Genetics, University Medical Center Utrecht, Utrecht, Netherlands (Prof D Lindhout MD); Stichting Epilepsie Instellingen Nederland (SEIN), Heemstede, Netherlands (Prof D Lindhout); Department of Pharmacology and Toxicology, University of Pavia, Pavia, Italy (Prof E Perucca MD); Department of Neurology, Epilepsy Center, University Hospitals Leuven, Leuven, Belgium (A Sabers MD); Department of Neurology, Christian Medical College, Vellore, India (S V Thomas MD); Department of Neurology, Medical University of Vienna, Vienna, Austria (Prof F Vajda MD)

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

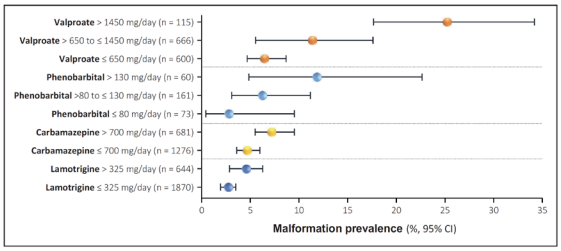

FIGURE 2. Dose dependency of major congenital malformations (%; and 95% confidence intervals) with four antiepileptic drug monotherapies. Based on Data from [5▪▪].

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.

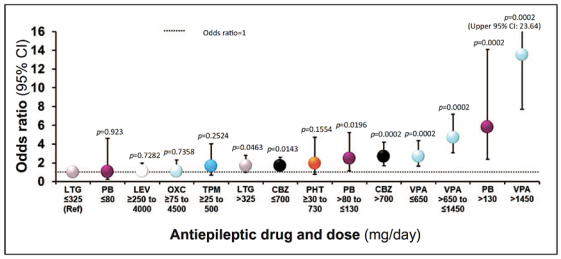

FIGURE 3. Risk of major congenital malformations (odds ratios with 95% confidence intervals) with different antiepileptic drug treatments compared with lamotrigine 325 mg/day or less. CBZ, carbamazepine; LEV, levetiracetam; LTG, lamotrigine; OXC, oxcarbazepine; PB, phenobarbital; PHT, phenytoin; Ref,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

Pierre-Olivier Blotière, MSc, Fanny Raguideau, PharmD, Alain Weill, MD, Elisabeth Elefant, MD, Isabelle Perthus, MD, Véronique Goulet, MD, PhD, Florence Rouget, MD, Mahmoud Zureik, MD, PhD, Joël Coste, MD, PhD, and Rosemary Dray-Spira, MD, PhD

Correspondence
Pierre-Olivier Blotière
pierre-olivier.blotiere@assurance-maladie.fr

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

- ในขณะที่ผู้ป่วยตั้งครรภ์ไม่ควรปรับหรือเปลี่ยนยากันชักเนื่องจากโอกาสที่จะเกิดอันตรายต่อมารดาและทารกในครรภ์หากผู้ป่วยเกิดการชักมีมากกว่าโอกาสการเกิดผลข้างเคียงต่อทารกในครรภ์
- ควรมีการตรวจคัดกรองความผิดปกติของเด็กในครรภ์มารดา โดยเฉพาะ malformation ที่พบได้บ่อยและรุนแรง เช่น neural tube defect

Epilepsy and pregnancy

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

Epilepsy and lactation

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

Special situations

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

Questions