



Epilepsy in special group: women

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Special issues 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



Contraception



Contraception in epilepsy patients

- ❖ **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.



Contraception in epilepsy patients

- ❖ **AEDs that are non-enzyme inducing have no effect on oral contraceptives.**

- ❖ **Non-enzyme inducing AEDs:**
 - levetiracetam, gabapentin, tiagabine, valproic acid, zonisamide, pregabalin, vigabatrin, topiramate ≤ 200 mg.



Antiepileptic Drug	Effect on Hormonal Contraception	Affected by Hormonal Contraception?
Clonazepam, diazepam, ethosuximide, ezogabine, gabapentin, lacosamide, lorazepam, levetiracetam, pregabalin, vigabatrin, zonisamide	None	No
Carbamazepine, clobazam, eslicarbazepine, oxcarbazepine, phenobarbital, phenytoin, primidone, rufinamide	Decreased ethinyl estradiol levels Decreased progestin levels	Unknown
Topiramate	Decreased ethinyl estradiol levels (dose-dependent effect)	Unknown
Perampanel	Decreased progestin levels	Unknown
Lamotrigine	Decreased progestin levels	Decreased lamotrigine levels (with estrogen-containing contraception)
Valproate	No	Decreased valproate levels (with estrogen-containing contraception)

Contraceptive Method	Pregnancies Per Year ^a	Considerations for Women With Epilepsy
Intrauterine device (IUD)		
Copper IUD	<1%	No significant antiepileptic drug (AED) interactions Copper IUD may preclude 3-tesla MRI at some institutions
Levonorgestrel-releasing IUD	<1%	Levonorgestrel-releasing IUD reduces or eliminates menstrual bleeding
Combined hormonal contraception		
Combined oral contraceptive pills	9%	Not recommended with enzyme-inducing antiepileptic drugs (EIAEDs)
Vaginal ring	9%	Will reduce lamotrigine levels
Transdermal patch	9%	May be used to treat symptoms of polycystic ovary syndrome Transdermal patch may worsen seizure control ⁵⁹
Progesterone-only contraception		
Etonogestrel implant	0.05%	Efficacy of the etonogestrel implant may be reduced by EIAEDs
Depot medroxyprogesterone acetate injection	6%	The depot medroxyprogesterone acetate injection may offer seizure-control benefit in some patients if amenorrhea achieved The depot medroxyprogesterone acetate injection is associated with reversible bone loss
Progesterone-only pills	9% ^b	Progesterone-only pills require excellent compliance Efficacy of progesterone-only pills is reduced by EIAEDs and possibly lamotrigine and perampanel



Contraception in epilepsy patients

- ❖ **Oral contraceptives should contain >50 micrograms of estrogen in the combination and external methods to prevent insufficient protection.**
- ❖ **IUD can be used**



Pregnancy



Epilepsy and pregnancy

❖ ไม่มียากันชักตัวใดที่ปลอดภัยต่อเด็กในครรภ์
มากกว่าตัวอื่นอย่างแท้จริง



Malformation Risks of AEDs in Pregnancy

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

Registry	Study	Carbamazepine	Rate of Major Congenital	
			Gabapentin	Lamotrigine
Australian Pregnancy Registry	Vajda et al, 2014 ¹⁰	5.5% (346)	0% (14)	4.6% (307)
Danish Registry	Mølgaard-Nielsen, Hviid, 2011 ¹¹	NA	1.7% (59)	3.7% (1019)
International Registry of Antiepileptic Drugs and Pregnancy	Tomson et al, 2011 ¹²	5.6% (1402)	NA	2.9% (1280)
Finland National Birth Registry	Artama et al, 2005 ¹³	2.7% (805)	NA	NA
GlaxoSmithKline Lamotrigine Registry	Cunnington et al, 2011 ¹⁴	NA	NA	2.2% (1558)
North American AED Pregnancy Registry	Hernández-Díaz et al, 2012 ¹⁵	3.0% (1033)	0.7% (145)	2.0% (1562)
Norwegian Medical Birth Registry	Veiby et al, 2014 ¹⁶	2.9% (685)	NA	3.4% (833)
Swedish Medical Birth Registry	Tomson, Battino, 2012 ¹⁷	2.7% (1430)	0% (18)	2.9% (1100)
UK/Ireland pregnancy registry	Campbell et al, 2014 ¹⁸ Mawhinney et al, 2013 ¹⁹ Hunt et al, 2008 ²⁰ Morrow et al, 2006 ²¹	2.6% (1657)	3.2% (32)	2.3% (2098)

AED = antiepileptic drug; NA = not applicable.

Malformations With Individual Antiepileptic Drugs as Monotherapy (N =)

Levetiracetam	Oxcarbazepine	Phenobarbital	Phenytoin	Topiramate	Valproic Acid
2.4% (82)	5.9% (17)	0% (4)	2.4% (41)	2.4% (42)	13.8% (253)
0% (58)	2.8% (393)	NA	NA	4.6% (108)	NA
1.6% (126)	3.3% (184)	7.4% (217)	5.8% (103)	6.8% (73)	9.7% (1010)
NA	NA	NA	NA	NA	10.7% (263)
NA	NA	NA	NA	NA	NA
2.4% (450)	2.2% (182)	5.5% (199)	2.9% (416)	4.2% (359)	9.3% (323)
1.7% (118)	1.8% (57)	7.4% (27)	NA	4.2% (48)	6.3% (333)
0% (61)	3.7% (27)	14% (7)	6.7% (119)	7.7% (52)	4.7% (619)
0.7% (304)	NA	NA	3.7% (82)	9% (203)	6.7% (1290)

ยากันชัก

อัตราการเกิด congenital malformation

Carbamazepine	2.1-6.3%
Phenytoin	2.6-7.4%
Phenobarbital	2.9-6.5%
Sodium valproate	6.1-16.3%*
Lamotrigine	1.4-5.2%
Gabapentin	0.8-5.9%**
Topiramate	2-4.8%**
Levetiracetam	2% **

*หากใช้ sodium valproate ในขนาดไม่เกิน 700-1000 mg ต่อวัน
อัตราการเกิด malformation จะอยู่ในช่วง 6-9%



- ❖ 1. Wlodarczyk BJ, Palacios AM, George TM, Finnell RH. Antiepileptic drugs and pregnancy outcomes. *Am J Med Genet A*. 2012;158:2071-90.
- ❖ 2. Campbell E, Kennedy F, Russell A, Smithson WH, Parsons L, Morrison PJ, et al. Malformation risks of antiepileptic drug monotherapies in pregnancy: updated results from the UK and Ireland Epilepsy and Pregnancy Registers. *J Neurol Neurosurg Psychiatry*. 2014;85:1029-34.
- ❖ 3. Morrow J, Russell A, Guthrie E, et al. Malformation risks of antiepileptic drugs in pregnancy: a prospective study from the UK Epilepsy and Pregnancy Register. *J Neurol Neurosurg Psychiatry* 2006;77:193–8.



- ❖ 4. Hernández-Díaz S, Smith CR, Shen A, et al. Comparative safety of antiepileptic drugs during pregnancy. *Neurology* 2012;78:1692–9.
- ❖ 5. Tomson T, Battino D, Bonizzoni E, et al. Dose-dependent risk of malformations with antiepileptic drugs: an analysis of data from the EURAP epilepsy and pregnancy registry. *Lancet Neurol* 2011;10:609–17.
- ❖ 6. Cunnington MC, Weil JG, Messenheimer JA, et al. Final results from 18 years of the International Lamotrigine Pregnancy Registry. *Neurology* 2011;76:1817–23

SPECIAL REPORT

Management issues for women with epilepsy—Focus on pregnancy (an evidence-based review): II. Teratogenesis and perinatal outcomes

Report of the Quality Standards Subcommittee and Therapeutics and Technology Subcommittee of the American Academy of Neurology and the American Epilepsy Society

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Risk of congenital malformation using AED in 1st trimester

- ❖ **AEDs taken during the first trimester probably increase the risk of MCMs in the offspring of WWE (two adequately sensitive Class II studies) but it cannot be determined if the increased risk is from all AEDs or from only one or some AEDs**



Risk of congenital malformation using AED in 1st trimester

AEDs	MCM risk	Evidences
All AEDs	Prob. increased	2 class II (adeq.sensitive)
VPA monoRx	Prob. increased	1 class II
VPA polyRx	Prob. increased	1 class I
CBZ	Prob. does not	1 class I
LTG	Insuff. evidences	1 class I (inadeq.sensitive)
Other specific AEDs	Insuff. evidences	No class III



Risk of congenital malformation using AED in 1st trimester

- ❖ If possible, avoidance of the use of VPA as part of polytherapy during the first trimester of pregnancy should be considered to decrease the risk of MCMs (Level B)
- ❖ If possible, avoidance of the use of VPA monotherapy during the first trimester of pregnancy may be considered to decrease the risk of MCMs (Level C).



Polytherapy VS monotherapy

- ❖ **Polytherapy probably contributes to the development of MCMs in the offspring of WWE as compared to monotherapy (one Class I study)**
- ❖ **To reduce the risk of MCMs, avoidance of the use of AED polytherapy during the first trimester of pregnancy, if possible, compared to monotherapy should be considered (Level B).**

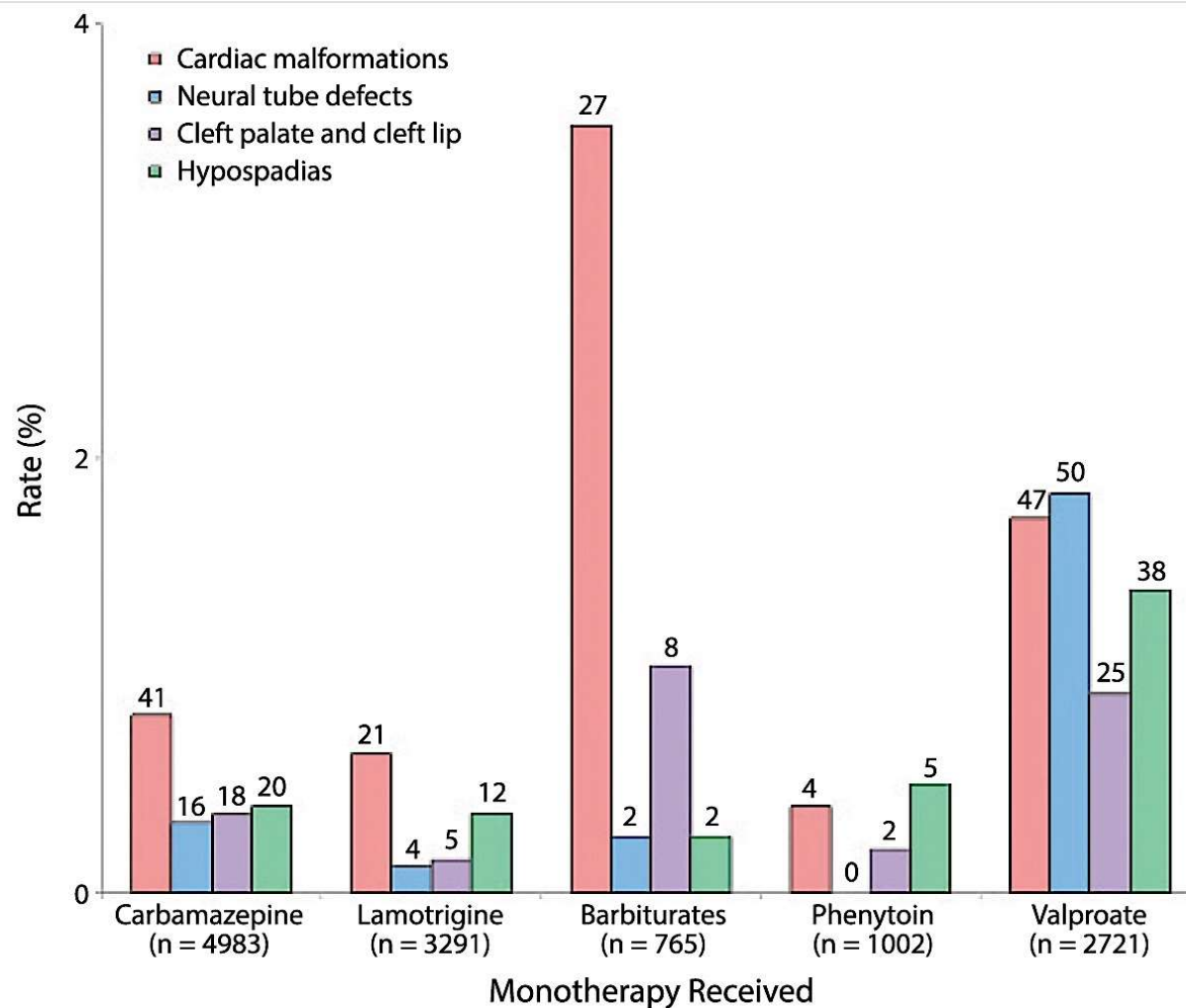


Are there specific MCMs associated with specific AEDs?

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?



ORIGINAL ARTICLE

Valproic Acid Monotherapy in Pregnancy and Major Congenital Malformations

Janneke Jentink, M.Sc., Maria A. Loane, M.Sc., Helen Dolk, Dr.P.H.,
Ingeborg Barisic, Dr.P.H., Ester Garne, M.D., Joan K. Morris, Ph.D.,
and Lolkje T.W. de Jong-van den Berg, Ph.D.,
for the EUROCAT Antiepileptic Study Working Group*

Jentink J, et al. N Engl J Med 2010;362:2185-93.

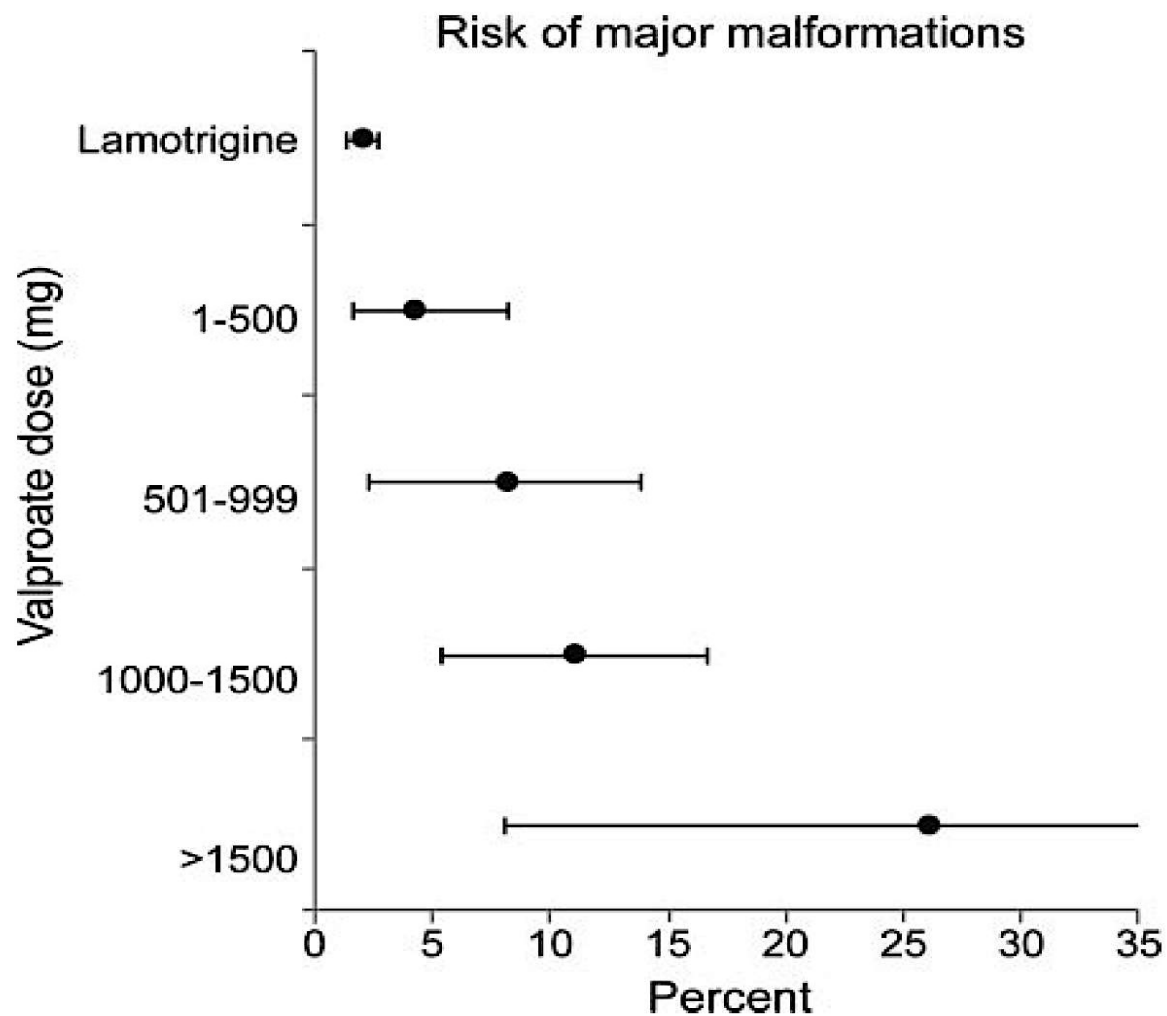


MCM	Adjusted OR	95% CI
Spina bifida	12.7	7.7-20.7
Atrial septal defect	2.5	1.4-4.4
Cleft palate	5.2	2.8-9.9
Hypospadia	4.8	2.9-8.1
Polydactyly	2.2	1.0-4.5
Craniosynostosis	6.8	1.8-18.8

Jentink J,et al. N Engl J Med 2010;362:2185-93.

Figure 1

Risk of major malformations by average valproate dose (mg) during the first trimester



North American AED Pregnancy Registry 1997-2011.

Hernández-Díaz S, et al. Neurology 2012;78;1692



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



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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.



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.

In utero exposure to levetiracetam vs valproate

Development and language at 3 years of age

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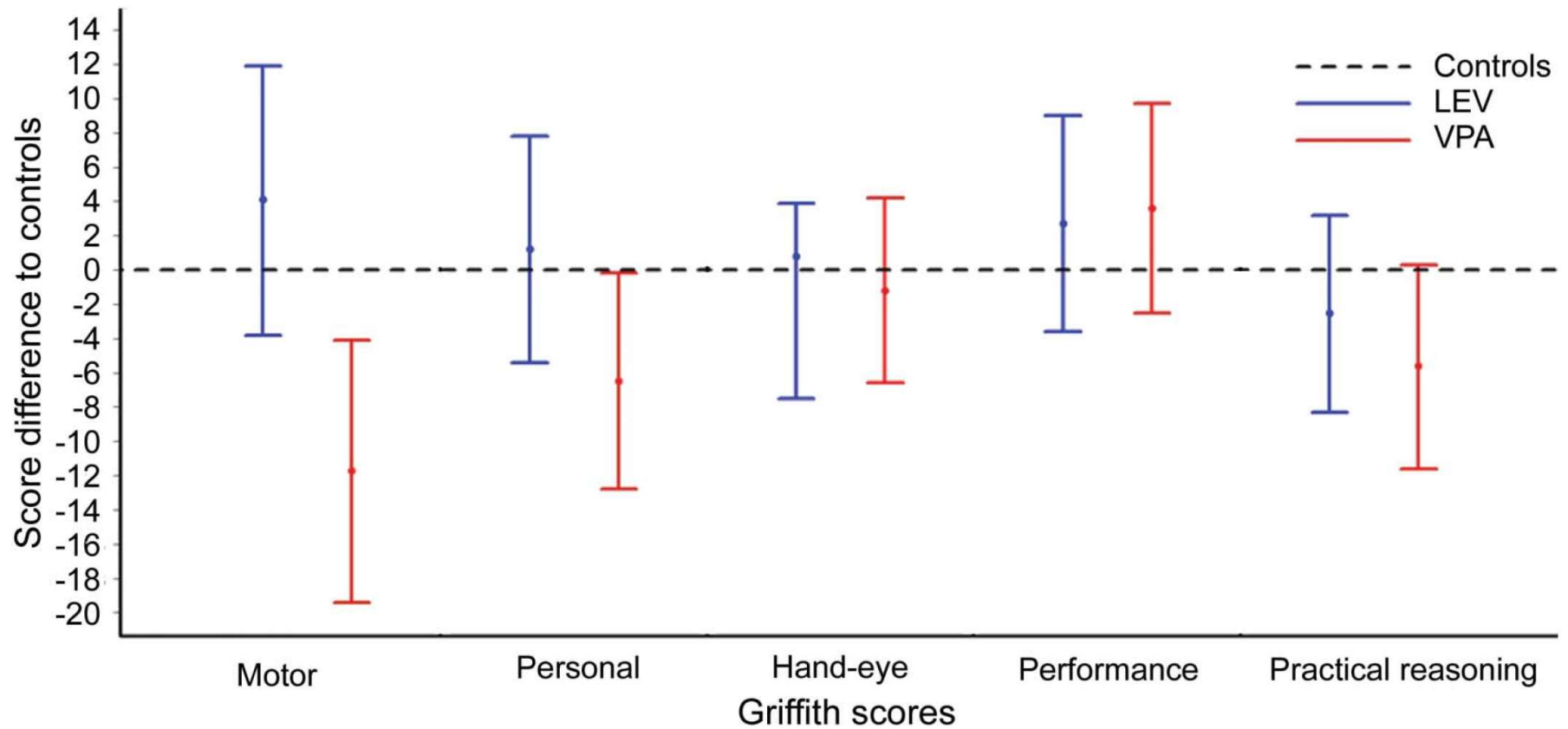
ABSTRACT

Objective: To compare the cognitive and language development of children born to women with epilepsy (WWE) exposed in utero to levetiracetam (LEV) or sodium valproate (VPA) and control children born to women without epilepsy not taking medication during pregnancy.

Methods: The children, aged between 36 and 54 months, were recruited from the United Kingdom and assessed using the Griffiths Mental Development Scales and the Reynell Language Development Scale. Maternal demographic and epilepsy information was also collected for use in statistical regression. This is an observational study with researchers not involved in the clinical management of the mothers enrolled.

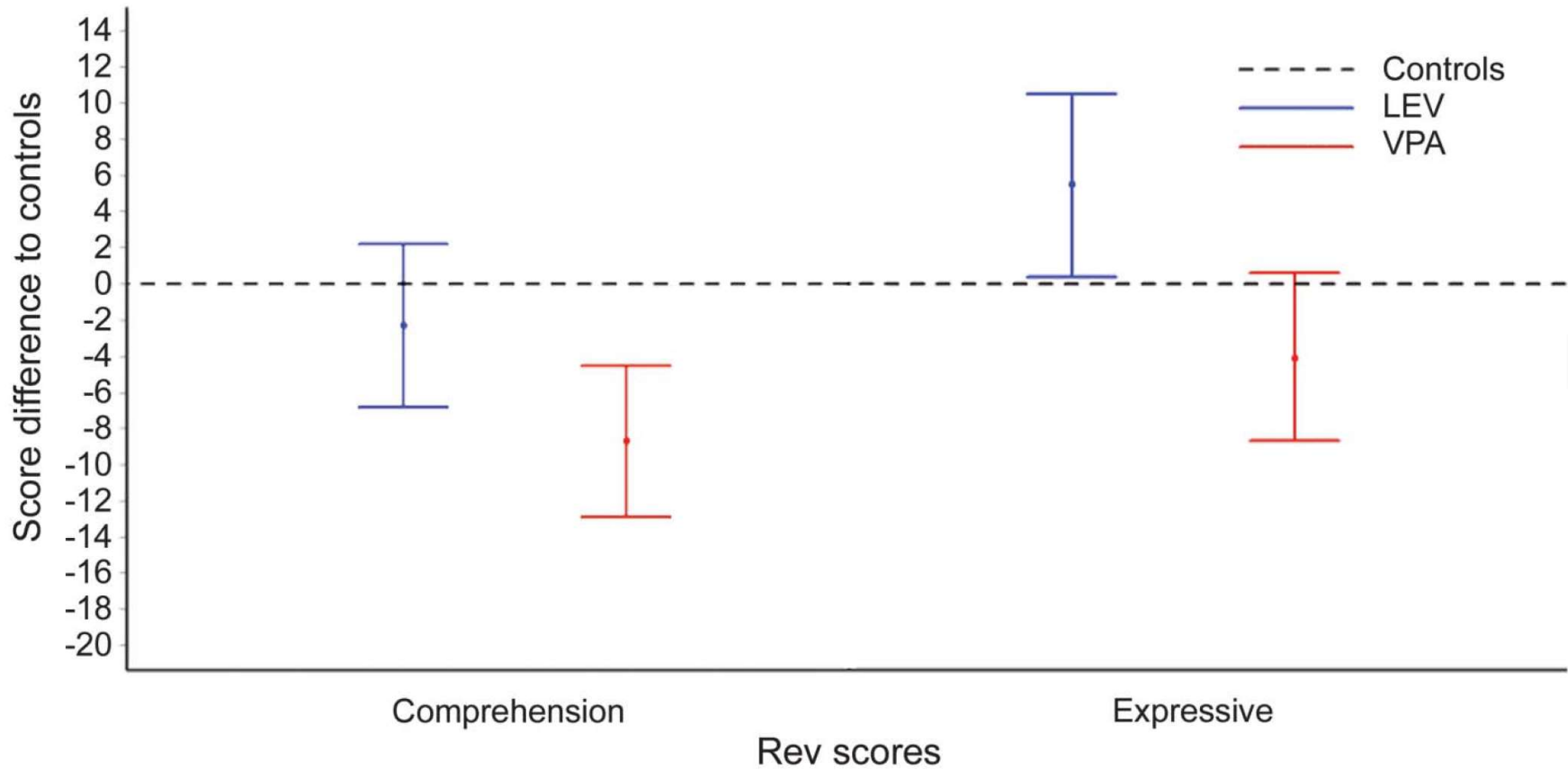
Results: After controlling for confounding variables, children exposed to LEV in utero ($n = 53$) did not differ from unexposed control children ($n = 131$) on any scale administered. Children exposed to VPA ($n = 44$) in utero scored, on average, 15.8 points below children exposed to LEV on measures of gross motor skills (95% confidence interval [CI] -24.5 to -7.1 , $p < 0.001$), 6.4 points below on comprehension language abilities (95% CI -11.0 to -1.8 , $p = 0.005$), and 9.5 points below on expressive language abilities (95% CI -14.7 to -4.4 , $p < 0.001$).

Conclusion: The current study indicates that children exposed to LEV in utero were superior in their language and motor development in comparison to children exposed to VPA. This information should be used collaboratively between health care professionals and WWE when deciding on women's preferred choice of antiepileptic drug. *Neurology*® 2014;82:213-221



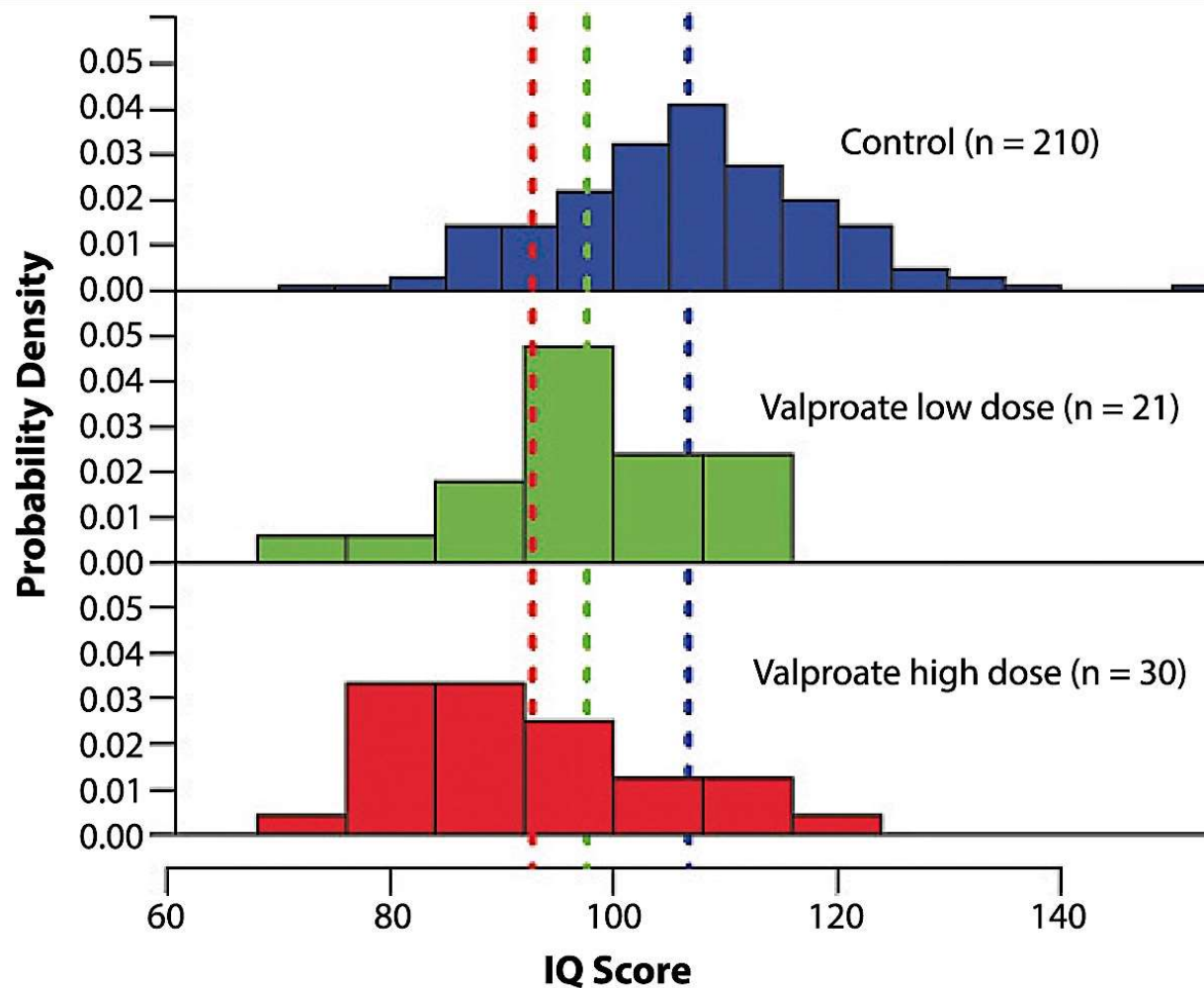
LEV = levetiracetam; VPA = sodium valproate.

Shallcross R, et al. Neurology 2014;82:213–221



LEV = levetiracetam; VPA = sodium valproate.

Shallcross R, et al. Neurology 2014;82:213–221



Baker G, et al, Neurology 2014



PHARMACOKINETIC OF AEDS DURING PREGNANCY



Changes in AEDs clearance or levels

AEDs	Level changes	Evidences
LTG	↓ >35%	1 class I, 2 class II
CBZ	↓ Up to 12%	1 class I
PHT	↓ Free PHT up to 16%	1 class I
OXC	↓ MHD conc. up to 36-61%	2 class III
LEV	↓ Up to 60%	1 class II
PB, VPA, ETX	Insufficient data	



BREAST FEEDING IN WOMEN WITH EPILEPSY



Breast milk penetration

- ❖ Valproate, phenobarbital, phenytoin, and carbamazepine may be considered as not transferring into breast milk to as great an extent as **primidone, levetiracetam, gabapentin, lamotrigine, and topiramate** (Level B when compared to primidone and levetiracetam and Level C when compared to gabapentin, lamotrigine, and topiramate).



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

- ✦ ในผู้หญิงวัยเจริญพันธุ์ควรได้รับ 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 phenobarbital, levetiracetam, gabapentin, lamotrigine, and topiramate
- ❖ Phenobarbital อาจจะมีผลทำให้เด็กง่วงซึมได้

A dramatic landscape photograph featuring a sunset or sunrise over a body of water. The sky is filled with dark, heavy clouds, with a bright, golden glow from the sun breaking through near the horizon. A seagull is captured in flight, its wings spread, against the dark sky. The water in the foreground is dark and textured. The overall mood is somber and contemplative.

THE END

Questions?