Mahidol University
Faculty of Medicine Siriraj Hospital

Reproductive Health and Epilepsy in Women and Adolescent

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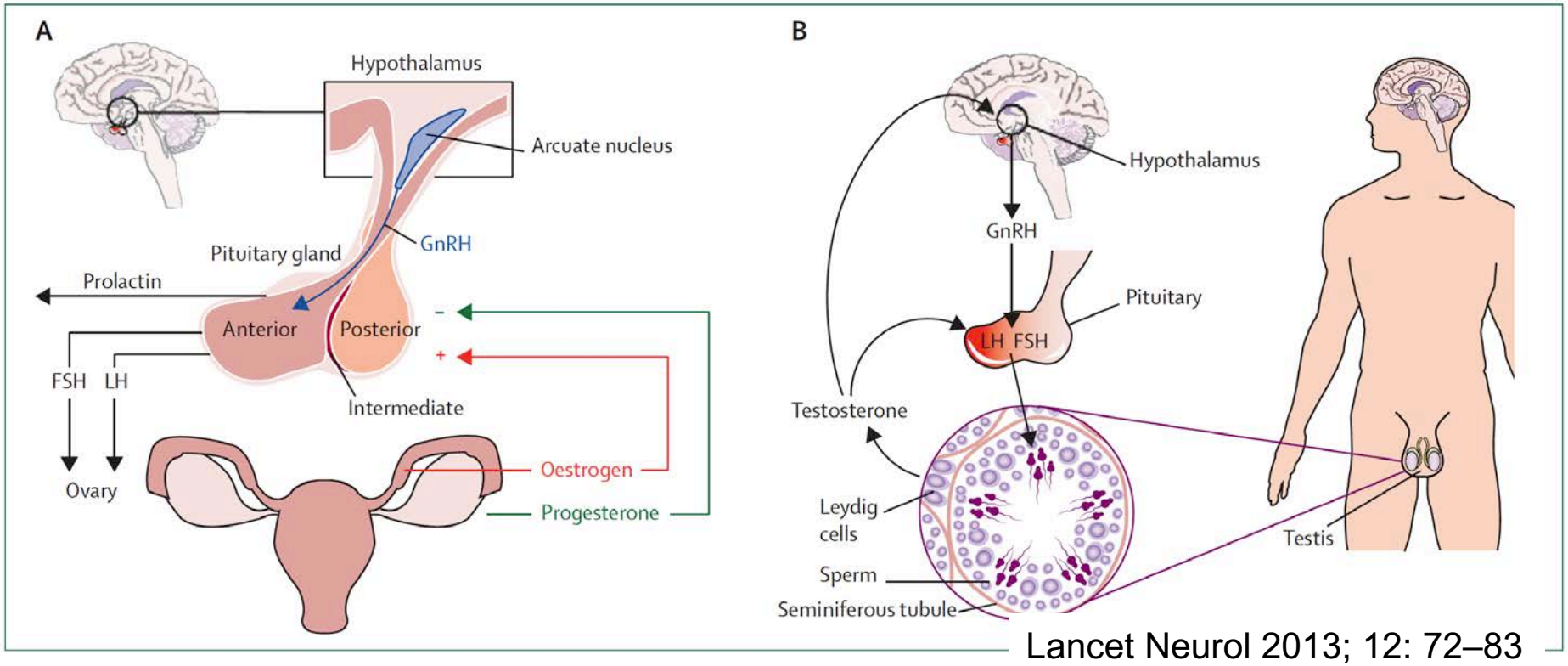
HORMONAL ABNORMALITIES IN PEOPLE WITH EPILEPSY

Reproductive dysfunction in patients with epilepsy

- Increased rates of PCOS
- Decreased libido
- Infertility
- Early menopause

Sex Steroid Hormone Axis



Lancet Neurol 2013; 12: 72–83

- Regions of the limbic cortex esp. amygdala, have extensive reciprocal connections with the hypothalamus and can modulate the hypothalamic-pituitary gonadal axis
- GnRH-cell population is vulnerable to injury by seizures in animal studies
- Dysfunction of GnRH cells →abnormal GnRH release → abnormal released of FSH, LH → hypogonadotrophic hypogonadism

Effects of AEDs on reproductive hormones

- Enzyme-inducing AEDs and directly alter concentrations of reproductive hormones
- EIAEDs also induce production of sex hormone-binding globulin→ reduces concentrations of free reproductive hormones in serum
- Decreased levels of free testosterone have been reported in men taking carbamazepine, phenytoin, oxcarbazepine and in those with untreated epilepsy

Herzog AG, et al. Neurology 2005; 65: 1016–20.
Isojrvi JIT, et al. Neurology 2004; 62: 247–53.
Bauer J, et al.J Neurol 2011;258: 1080–84.

Effects of AEDs on female reproductive system

Effects of AEDs on female reproductive system.

	Hormonal disturbances	PCOS	PCO	Menstrual disorders	Sexual dysfunction
Valproic Acid	YES [62]	YES [29,63,64]	NO (primates) [65]	YES [36,63]	NO [68]
Carbamazepine	YES [14,72]	NO [73]	NO [74]	YES [72,75]	YES [78]
Phenobarbital	YES [32]				
Phenytoin	YES [80]				
Oxcarbazepine		NO [82]	YES [82]		
Lamotrigine	NO [79,83]	NO [24]	NO [24]		NO [79,84]
Levetiracetam	NO [79]				NO [79]
Topiramate					YES [86]
Gabapentin					YES [88]
Pregabalin					YES [89]

PCOS = Polycystic Ovaries Syndrome, PCO = polycystic ovaries.

Markoula S, et al. Epilepsy & Behavior 2020;113 :107563

Effects of AEDs on reproductive hormones

- Sexual dysfunction occurs up to 4 times more frequently in people with epilepsy compared with people who do not have epilepsy

Rathore C, Radhakrishnan K. Neurol Clin 2022;40(4):869-889.

Effects of ASMs on male reproductive system

Effects of AEDs on male reproductive system.

	Hormonal disturbances	Sperm abnormalities	Sexual dysfunction
Valproic Acid	YES [114,115]	YES [114]	YES [117]
Carbamazepine	YES [114,116]	YES [114]	YES [107,119]
Phenytoin	YES [119]	YES [120], NO [98]	
Phenobarbital	YES [121]	NO [120]	
Primidone			YES [124]
Oxcarbazepine	YES (dose > 900 mg/day) [125]	YES [114], improvement [127]	YES [128,129,130,131]
Lamotrigine	NO [79,127,132]	NO [127]	YES [79], NO [127]
Levetiracetam	NO [79,127,133,134]	YES [133,134], NO [127]	YES [133,135], NO [79,127]
Topiramate			YES [86]
Pregabalin	NO (Healthy population) [142]		

Markoula S, et al. Epilepsy & Behavior 2020;113 :107563

CRITICAL REVIEW AND INVITED COMMENTARY

Caring for transgender patients with epilepsy

Emily L. Johnson and Peter W. Kaplan

Epilepsia, 58(10):1667–1672, 2017
doi: 10.1111/epi.13864

Table 1. Effects of common AEDs on hormone levels

AED	Free testosterone reduced by AED	Estrogens reduced by AED
Carbamazepine	Yes[18,19]	Yes[34]
Clobazam	ND	ND
Eslicarbazepine	Likely	Yes[35]
Ezogabine/retigabine	ND	No[36]
Gabapentin	No[37]	No[38]
Lacosamide	Likely no	No[39]
Lamotrigine	No[2]	No[a] (reduced by estrogen)[40]
Levetiracetam	May be increased[21]	No[41]
Oxcarbazepine	Likely	Yes[35]
Perampanel	ND	No[a35]
Phenobarbital	Yes[18,19]	Yes[42]
Phenytoin	Yes[18,19]	Yes[34]
Rufinamide	ND	Yes[35]
Topiramate	No[43]	Yes[b35]
Valproate	May be increased[44]	No[45]
Zonisamide	Possible[46]	No[47]

ND = no data.
[a]Reduces progesterone (perampanel at 12 mg).
[b]Dose-dependent.

Table 2. Commonly prescribed regimens for gender-affirming therapy

	Male-to-female	Female-to-male
Starting in adolescence	GnRH analog OR Depot medroxyprogesterone Oral 17-β-estradiol starting at 5ug/kg/day, increasing up to 2 mg/day[7]	GnRH analog OR Depot medroxyprogesterone Intramuscular testosterone starting at 25 mg/m^2 every 2 weeks, increasing up to 100 mg/m^2 every 2 weeks[7]
Starting in adulthood	Spironolactone OR cyproterone acetate Oral or transdermal estrogens such as 17-β-estradiol[7]	Testosterone (transdermal or parenteral) May add: Depot medroxyprogesterone[7]

Epilepsia, 58(10):1667–1672, 2017

MANAGEMENT OF FOR EPILEPSY PATIENTS OF REPRODUCTIVE AGE

Person-centred reproductive counselling in people with epilepsy should start before any chance of pregnancy and be regularly repeated

Counseling people with epilepsy of childbearing potential (12 years and older) about

- Drug-to-drug interactions with contraception
- Folic acid supplementation
- Potential antiseizure medication effects on fetal and child development
- Encourage pre-planned pregnancy

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 ASMs:
  - phenytoin, carbamazepine, primidone, phenobarbital.
- Less-potent enzyme inducing ASMs:
  - Oxcarbazepine (>1500 mg)
  - Lamotrigine
  - Topiramate (>200 mg)
  - Perampernel (>8 mg)
  - Clobazam
  - Felbamate
  - Eslicarbazepine
  - Rufinamide

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

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

COC, combined oral contraceptives; DMPA, depot medroxyprogesterone acetate;
LNG-IUS, levonorgestrel-releasing intrauterine system; POP, progestin-only pill.
Categories: 1 = no restriction for use of method, 2 = advantages of method outweigh theoretical or proven risks,
3 = theoretical or proven risks outweigh advantages of method, and 4 = unacceptable health risk of method if used.

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

Options of contraception in patients taking EIASMs

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

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

Effects of exogenous hormone on ASMs metabolism

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

Teratogenic Side Effects of ASMs

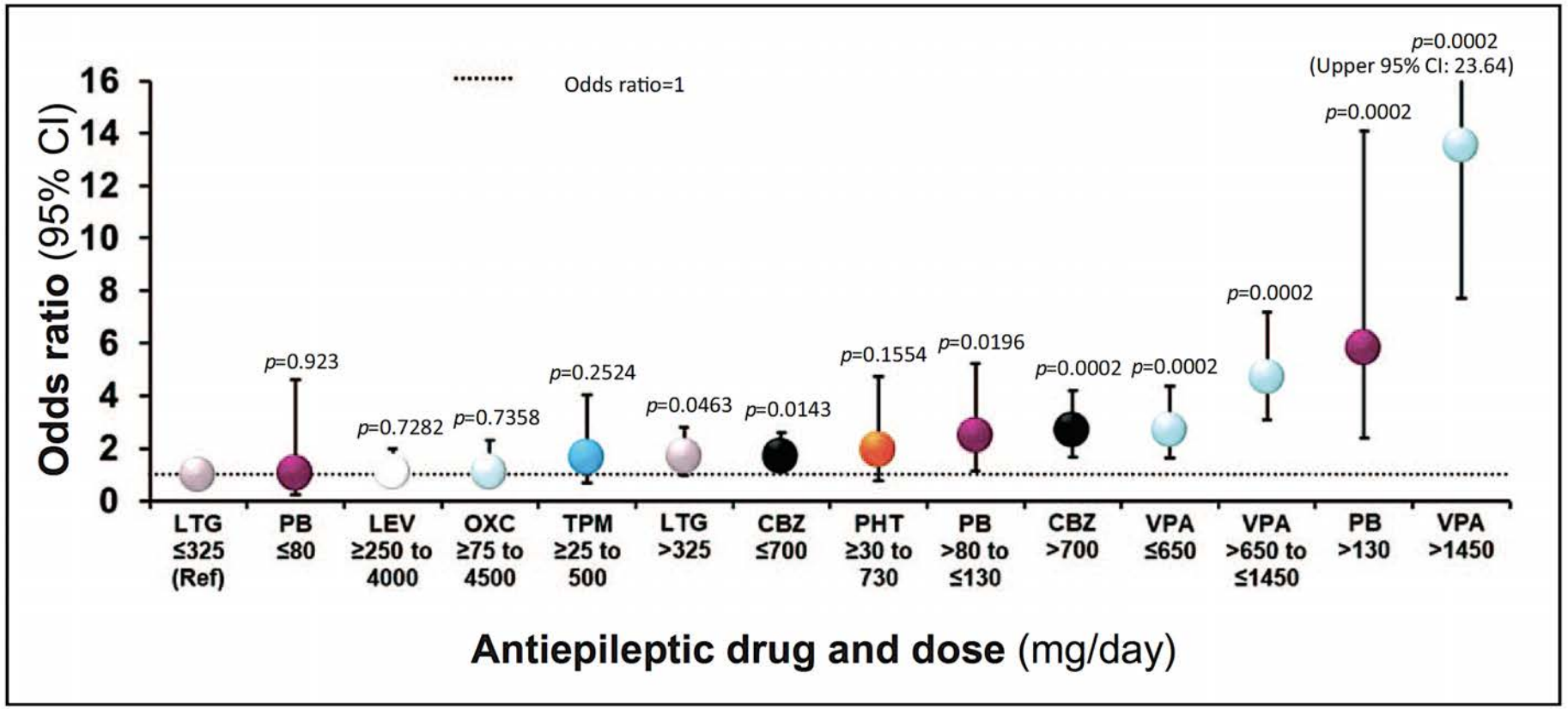


FIGURE 3. Risk of major congenital malformations (odds ratios with 95% confidence intervals) with different antiepileptic drug treatments compared with lamotrigine 325 mg/day or less. CBZ, carbamazepine; LEV, levetiracetam; LTG, lamotrigine; OXC, oxcarbazepine; PB, phenobarbital; PHT, phenytoin; Ref, reference; TPM, topiramate; VPA, valproate. Based on Data from [5▪▪].

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

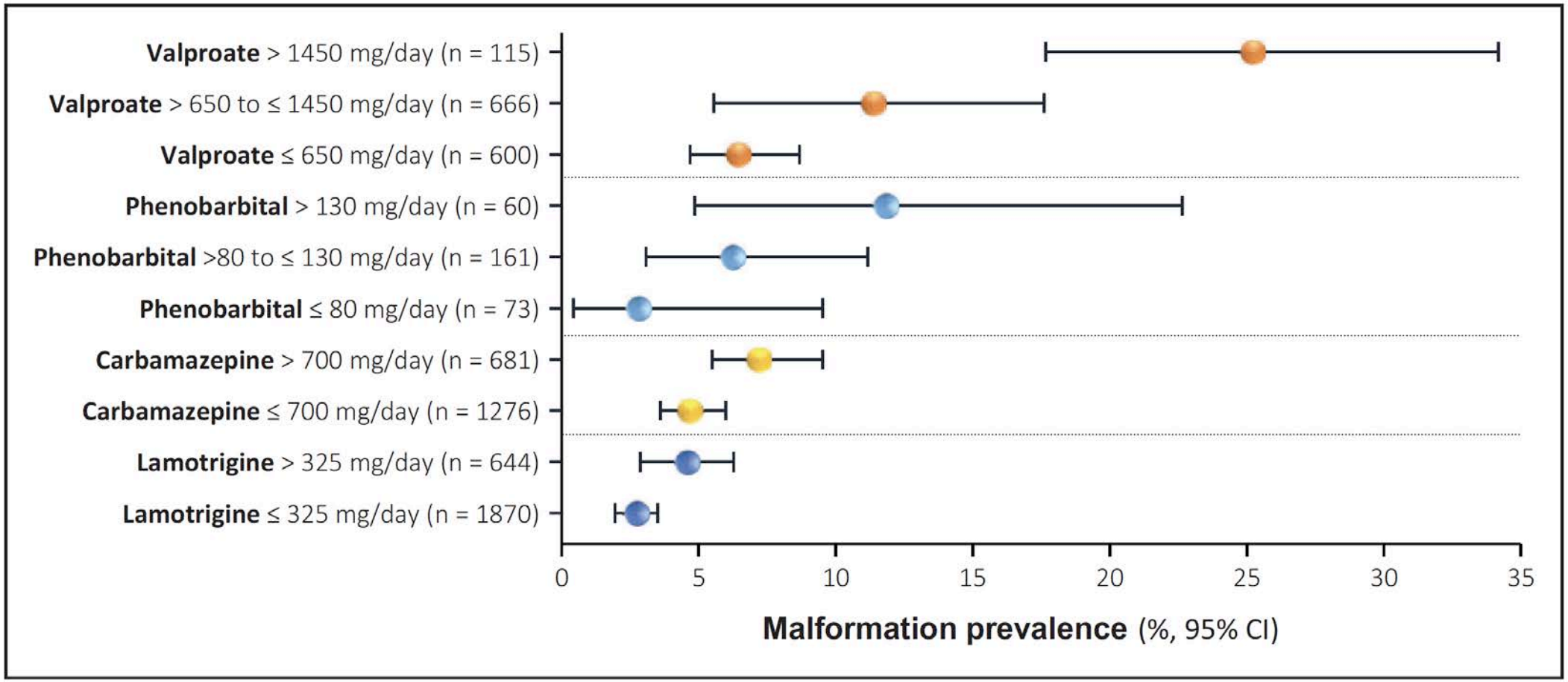


FIGURE 2. Dose dependency of major congenital malformations (%; and 95% confidence intervals) with four antiepileptic drug monotherapies. Based on Data from [5▪▪].

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

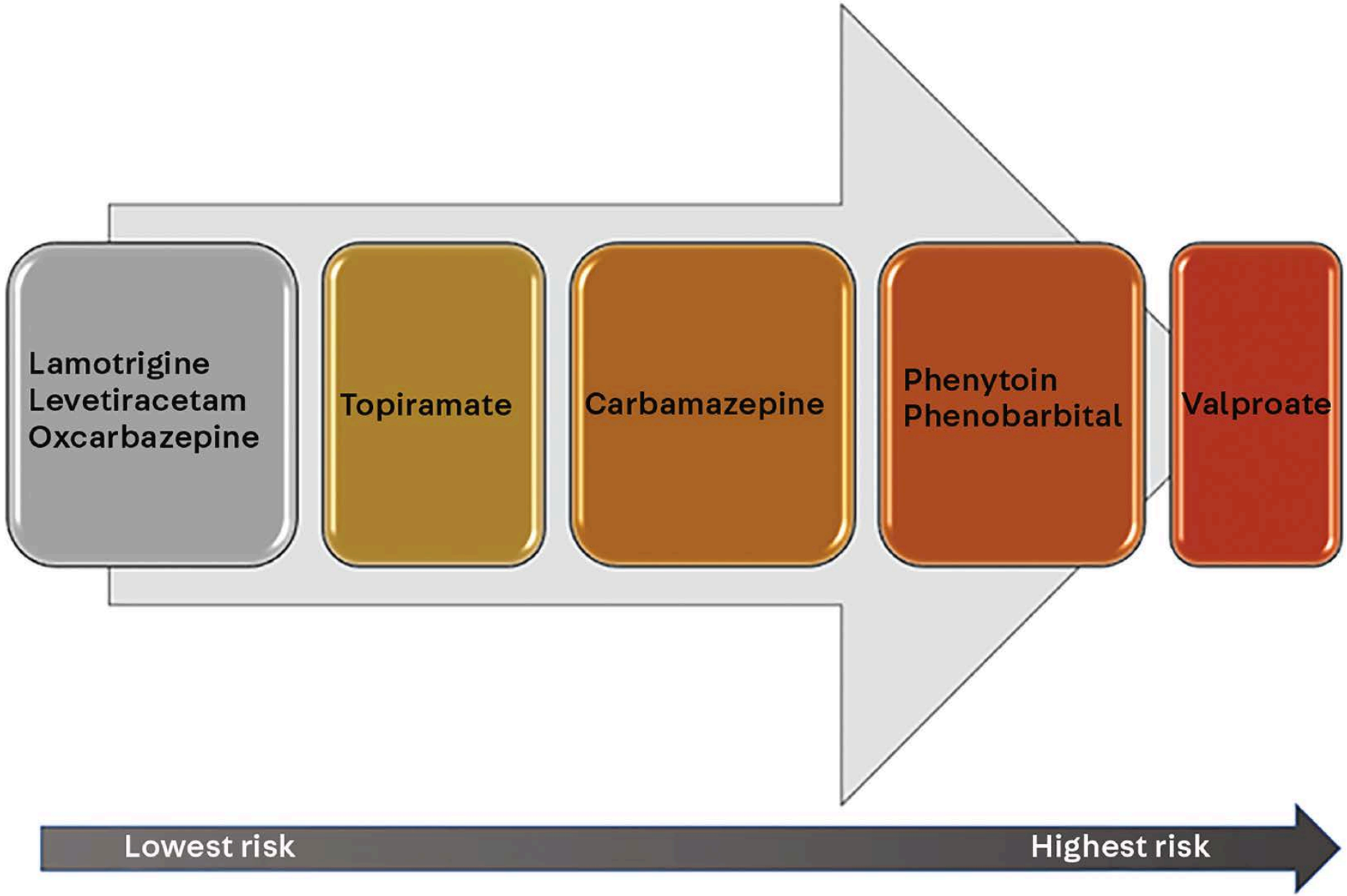
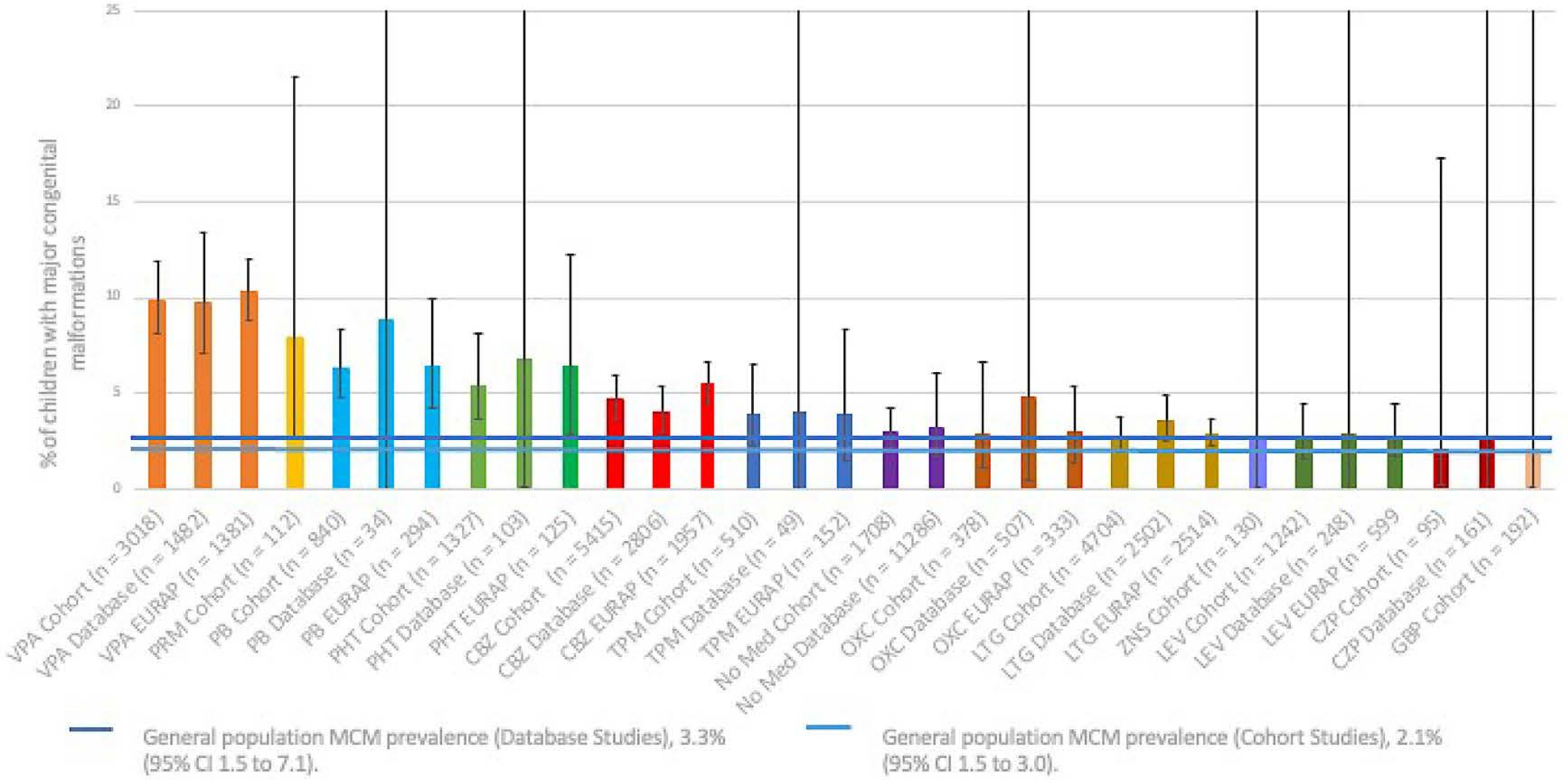
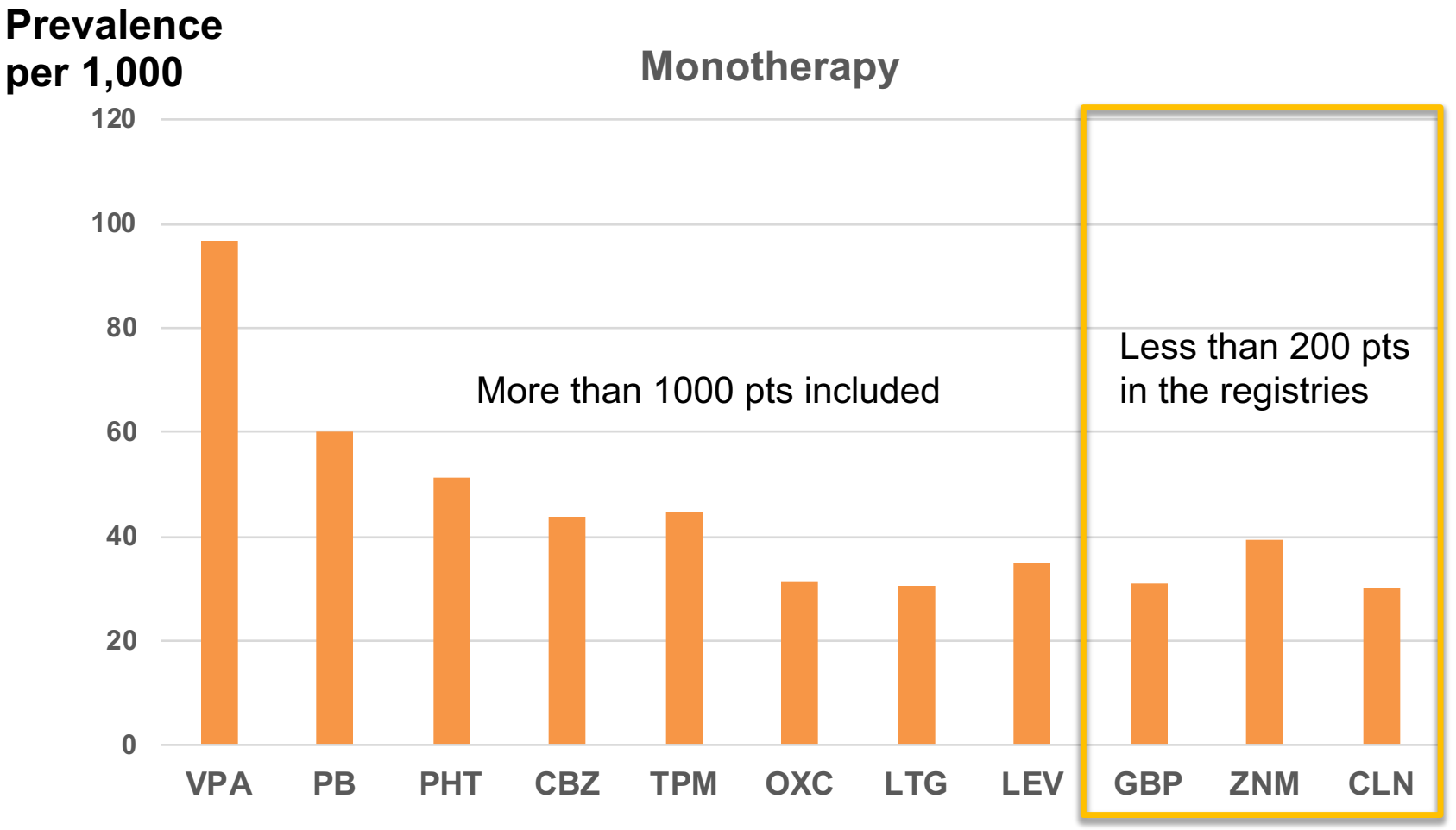

Lamotrigine
Levetiracetam
Oxcarbazepine
Topiramate
Carbamazepine
Phenytoin
Phenobarbital
Valproate
Lowest risk
Highest risk

Figure 3. Prevalence and 95% CI of major congenital malformations for each anti-seizure medication by data source

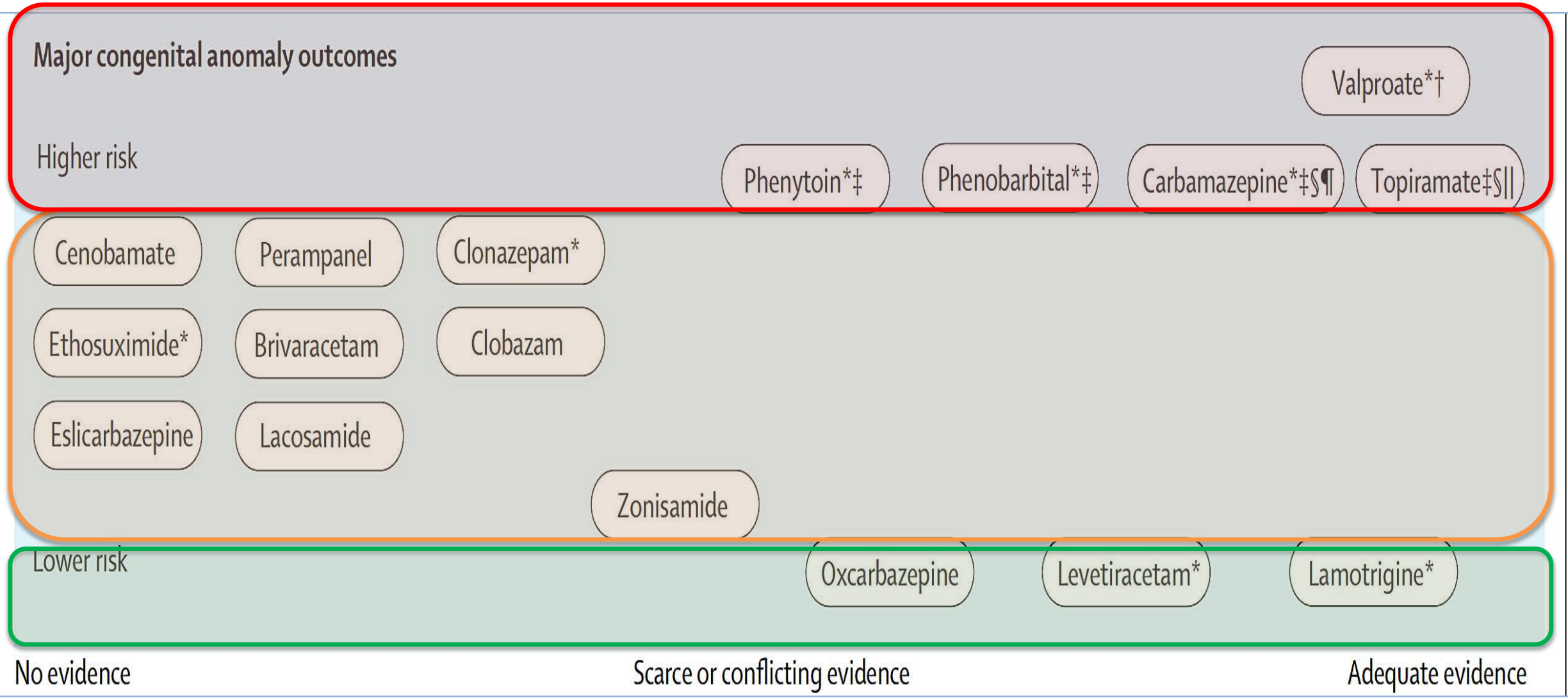


Individual cases ma
topiramate (TPM), l

Bromley R, et al. Cochrane Database of Systematic Reviews 2023, Issue 8. Art. No.: CD010224.



Neurology 2024;102:e209279

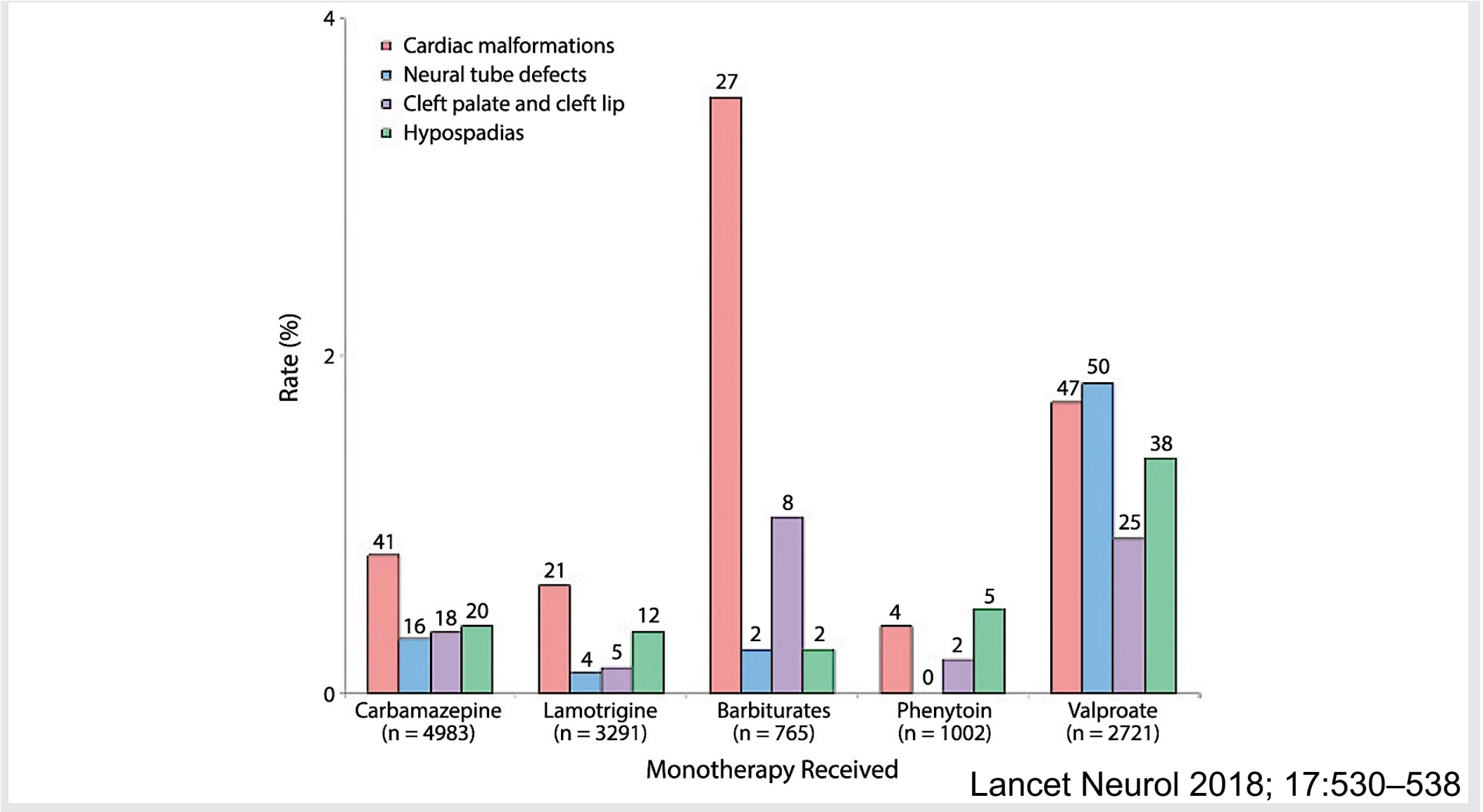


Bjork MH, et al. Lancet Neurol 2025; 24: 601–13

Are there specific MCMs associated with specific ASMs?

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 ASMs?



Lancet Neurol 2018; 17:530–538

SPECIAL ARTICLE

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

Practice Guideline From the AAN, AES, and SMFM

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

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

Recommendation 3 Statements

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

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

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

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

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

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

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

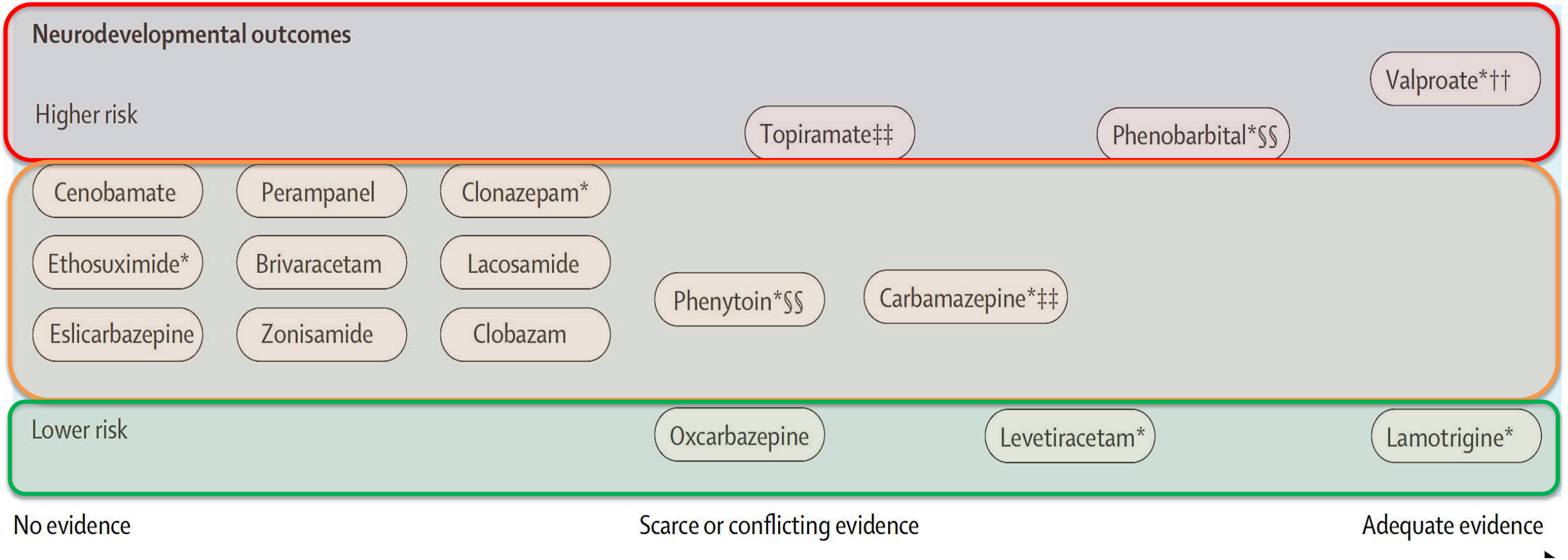
3G. To reduce the risk of urogenital and renal malformations, clinicians should avoid the use of valproic acid in PWECP, if clinically feasible (Level B).

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

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

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

Neurodevelopmental outcome



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

Treatment for epilepsy in pregnancy: neurodevelopmental outcomes in the child (Review)

Bromley R, Weston J, Adab N, Greenhalgh J, Sanniti A, McKay AJ, Tudur Smith C, Marson AG

THE COCHRANE COLLABORATION®

Bromley R, et al. Cochrane Database of Systematic Reviews 2014, Issue 10. Art. No.: CD010236.

Characteristics of the studies

The review included 28 studies. Participants were women with epilepsy taking commonly used AEDs who were compared to either women without epilepsy or women who had epilepsy but who were not treated with AEDs. Comparisons were also made between children exposed to different AEDs in the womb. The evidence presented in this review was up to date to May 2014.

Results

- The evidence for younger children exposed to carbamazepine (CBZ) in the womb was conflicting, however this was likely to be due

- Both younger and older children exposed in the womb to sodium valproate (VPA) showed poorer cognitive development in comparison to children not exposed and children exposed to other AEDs. A link between dose of VPA and child ability was found in six studies; with higher doses of the drug linked to a lower IQ ability in the child. The level of this difference was likely to increase the risk of poorer educational levels.

- Children exposed to CBZ in the womb did not differ in their skills from children exposed to lamotrigine (LTG), however very few studies investigated this. There were also no differences between children exposed to phenytoin (PHT) in the womb and those exposed to CBZ or those exposed to LTG.

- There were very limited data on newer medications such as LTG, levetiracetam or topiramate.

Bromley R, et al. Cochrane Database of Systematic Reviews 2014, Issue 10. Art. No.: CD010236.

The NEW ENGLAND JOURNAL of MEDICINE

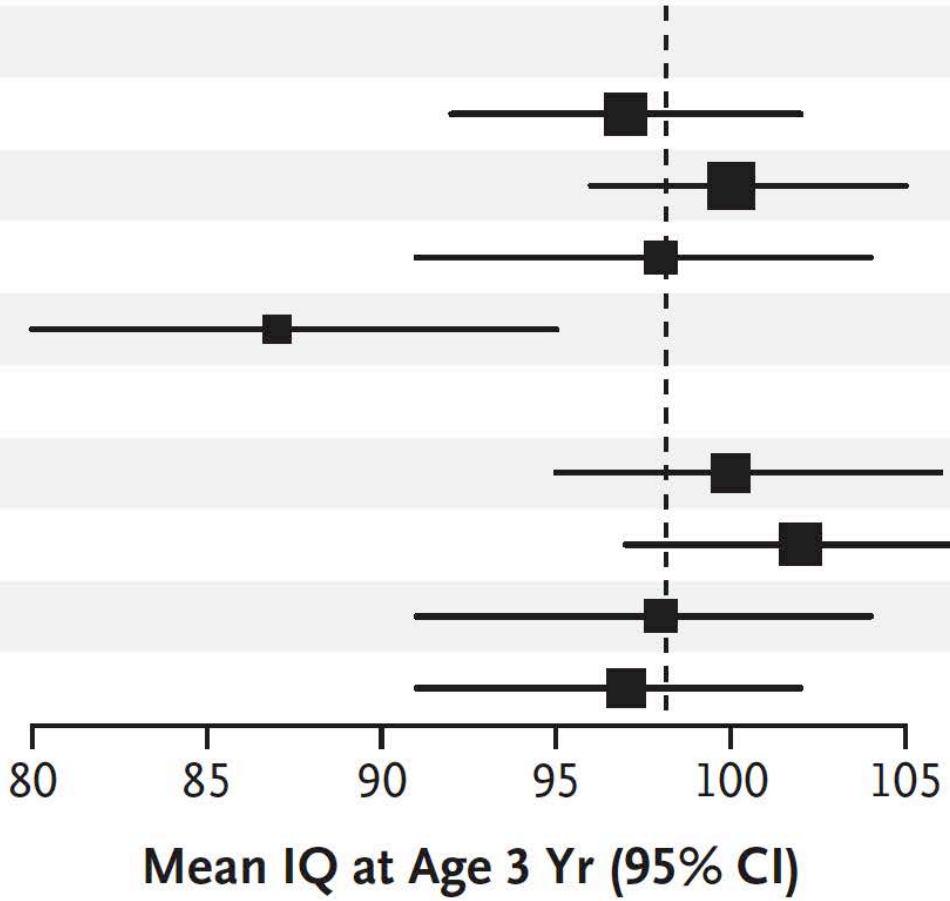
ESTABLISHED IN 1812 APRIL 16, 2009 VOL. 360 NO. 16

Cognitive Function at 3 Years of Age after Fetal Exposure to Antiepileptic Drugs

Kimford J. Meador, M.D., Gus A. Baker, Ph.D., Nancy Browning, Ph.D., Jill Clayton-Smith, M.D., Deborah T. Combs-Cantrell, M.D., Morris Cohen, Ed.D., Laura A. Kalayjian, M.D., Andres Kanner, M.D., Joyce D. Liporace, M.D., Page B. Pennell, M.D., Michael Privitera, M.D., and David W. Loring, Ph.D., for the NEAD Study Group*

IQ Scores of Children Who Were Exposed to Antiepileptic Drugs In Utero, According to Drug and Dose

Antiepileptic Drug	No. of Children	Mean IQ
High dose		
Carbamazepine	47	97
Lamotrigine	52	100
Phenytoin	28	98
Valproate	22	87
Low dose		
Carbamazepine	46	100
Lamotrigine	48	102
Phenytoin	27	98
Valproate	39	97



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

Table 4 Global IQ With Exposure to ASM Monotherapy

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

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

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

Recommendation 5 Statements

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

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

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

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

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

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

Overview

New measures to avoid topiramate exposure in pregnancy

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

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

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

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

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

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

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

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

GOV·UK

Home > Drug Safety Update

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

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

From: Medicines and Healthcare products Regulatory Agency

Published 20 June 2024

General advice for healthcare professionals:

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

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

Advice for healthcare professionals to provide to patients:

- new measures are being introduced because there is evidence that taking topiramate during pregnancy can increase the risk to the baby of congenital malformation, low birth weight, intellectual disability, autistic spectrum disorder and attention deficit hyperactivity disorder
- use effective birth control (contraception) at all times during your treatment with topiramate and for at least 4 weeks after the last dose
- topiramate may interact with some hormonal contraceptives. Your General Practitioner (GP), specialist, sexual health and contraception clinic or contraception service in community pharmacy will discuss which method of birth control is best for you
- if you are thinking about having a baby, make an appointment with your GP. Do not stop using topiramate and contraception before you have talked to your doctor
- if you think you are pregnant and are taking topiramate for epilepsy, do not stop using topiramate. This may cause your seizures to start again or happen more often and last longer. Make an urgent appointment with your GP or epilepsy team (within a few days)
- if you think you are pregnant and are taking topiramate for migraine prevention, stop taking topiramate straight away and contact your GP
- it is important to visit your doctor to review your treatment at least once each year
- always read the safety leaflet that comes with your medicine and consult the new Patient Guide for information about the risk of topiramate use during pregnancy

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

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

Research

JAMA Neurology | Original Investigation

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

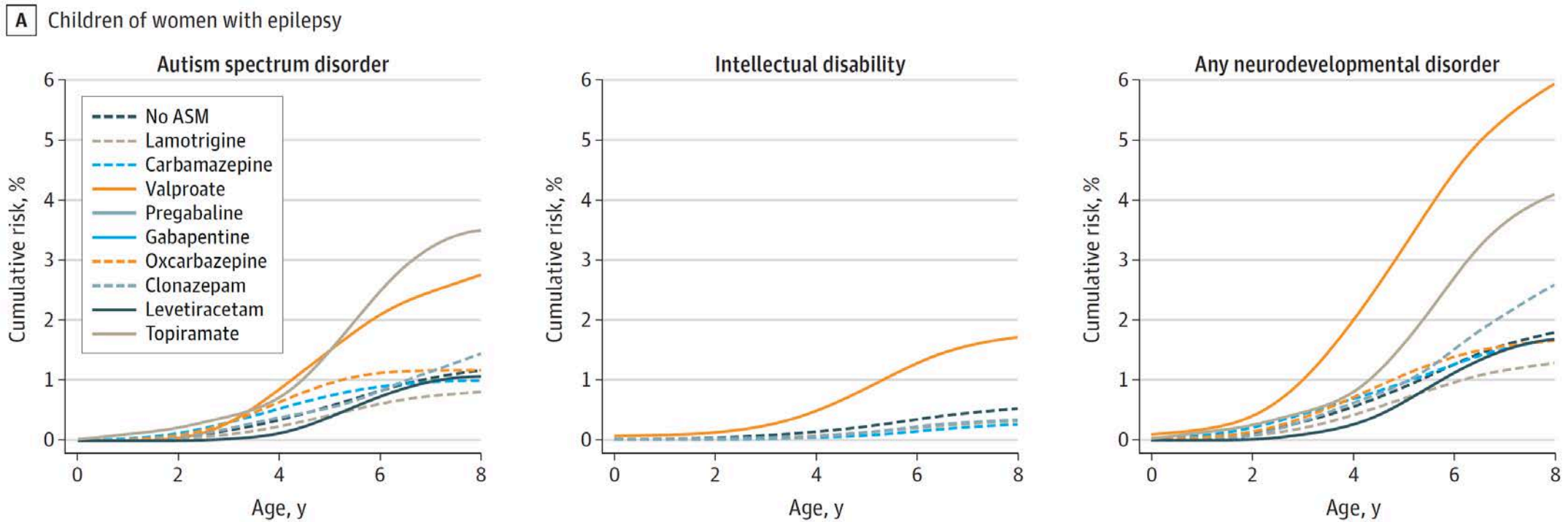
Marte-Helene Bjørk, MD, PhD; Helga Zoega, PhD; Maarit K. Leinonen, MD, PhD; Jacqueline M. Cohen, PhD; Julie Werenberg Dreier, PhD; Kari Furu, PhD; Nils Erik Gilhus, MD, PhD; Mika Gissler, PhD; Óskar Hálfdánarson, PhD; Jannicke Igland, PhD; Yuelian Sun, PhD; Torbjörn Tomson, MD, PhD; Silje Alvestad, MD,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

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

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

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

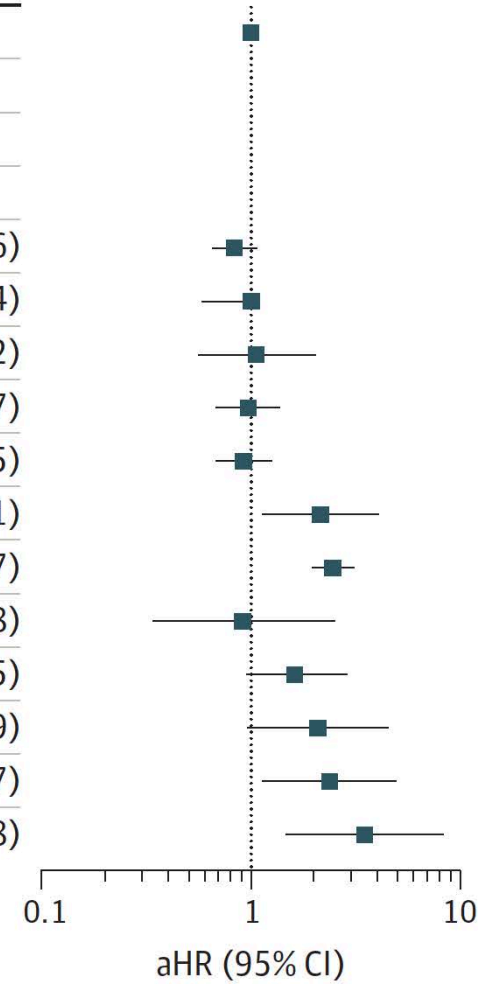
Figure 1. Cumulative Incidence of Neurodevelopmental Disorders After Prenatal Exposure to Antiseizure Medication (ASM)



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

A Children of women with epilepsy

Exposure	8-y Incidence, %	No. with ND	aHR (95% CI)
Unexposed, n = 21 634	2.4	443	1 [Reference]
Pregabalin, n = 91	NA	<5	NA
Gabapentin, n = 110	NA	<5	NA
Phenobarbital, n = 45	NA	<5	NA
Lamotrigine, n = 5073	1.8	81	0.83 (0.65-1.06)
Clonazepam, n = 318	4.5	15	1.00 (0.58-1.04)
Levetiracetam, n = 1004	2.1	10	1.06 (0.56-2.02)
Oxcarbazepine, n = 1429	2.0	[a]	0.97 (0.68-1.37)
Carbamazepine, n = 2609	1.9	65	0.92 (0.68-1.25)
Topiramate, n = 246	5.1	10	2.13 (1.13-4.01)
Valproate, n = 1884	6.5	152	2.44 (1.94-3.07)
Lamotrigine + levetiracetam, n = [a]	1.6	[a]	0.91 (0.34-2.48)
Valproate + lamotrigine, n = 312	5.5	[a]	1.65 (0.95-2.85)
Lamotrigine + oxcarbazepine, n = [a]	4.3	[a]	2.07 (0.96-4.49)
Lamotrigine + topiramate, n = 123	7.5	[a]	2.35 (1.13-4.87)
Levetiracetam + carbamazepine, n = [a]	5.7	[a]	3.46 (1.46-8.18)



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

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

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

JAMA Neurology | Original Investigation

Prenatal Exposure to Antiseizure Medication and Incidence of Childhood- and Adolescence-Onset Psychiatric Disorders

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

Design: A prospective, population-based register study assessed 4,546,605 singleton children born alive in Denmark, Finland, Iceland, Norway, and Sweden from January 1, 1996, to December 31, 2017.
38,661 children of mothers with epilepsy were identified. Data analysis was performed from August 2021 to January 2023.
Exposure: Prenatal exposure to ASM was defined as maternal prescription fills from 30 days before the first day of the last menstrual period until birth
Main outcome: Diagnosis of psychiatric disorders (a combined end point and 13 individual disorders).
Estimated adjusted hazard ratios (aHRs) using Cox proportional hazards regression and cumulative incidences with 95%CIs are reported.

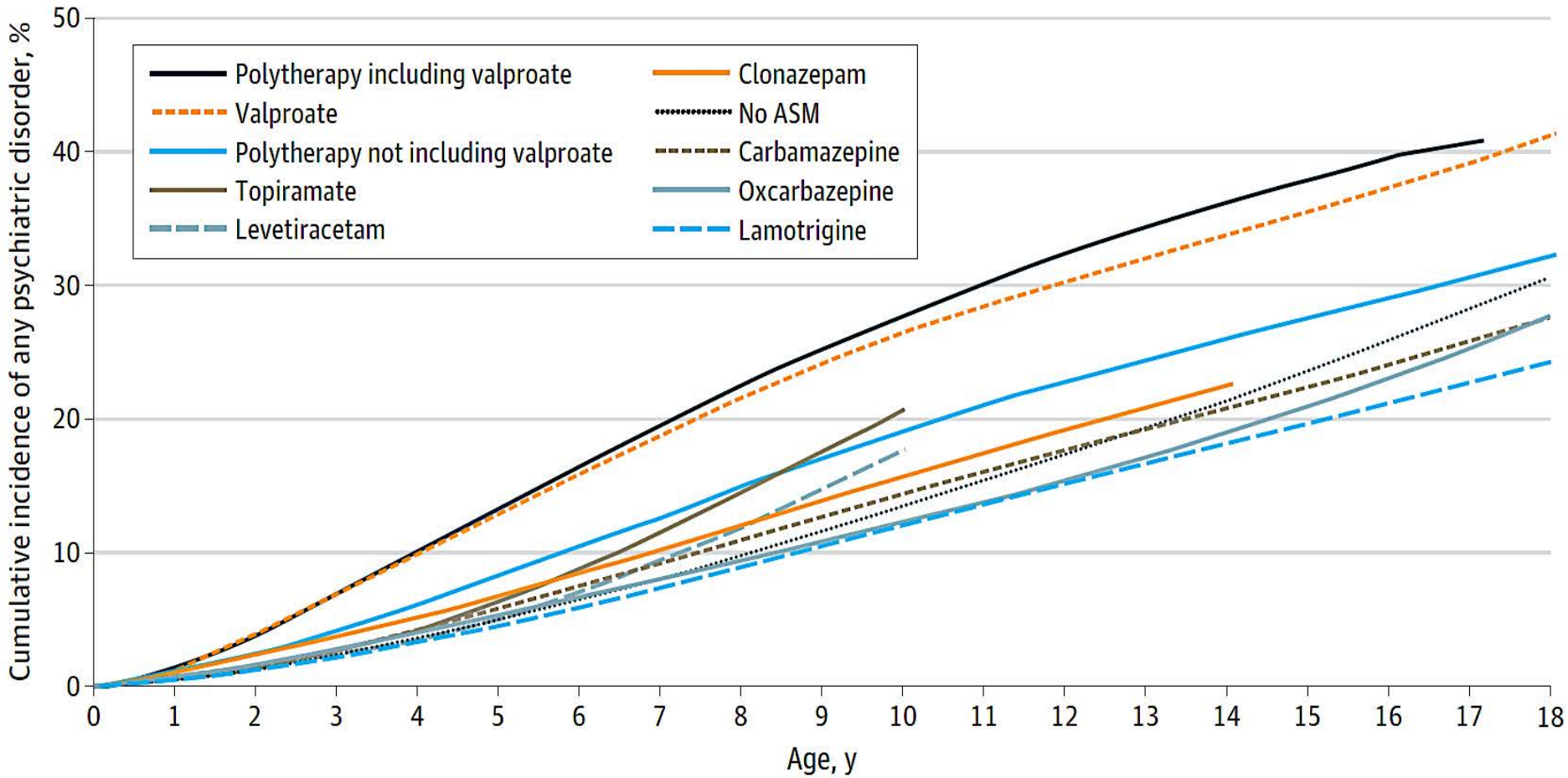
Dreier JW, et al. JAMA Neurol. 2023;80:568-577

Table 2. Incidence Rates, Hazard Ratios, and Cumulative Incidence at 10 and 18 Years of Age of the Combined Psychiatric End Point in Children Exposed and Unexposed to ASM During Pregnancy, Based on 38 661 Children of Mothers With Epilepsy in 5 Nordic Countries (1996-2017)

Exposure	No. of children	No. of children with psychiatric disorder	Incidence rate per 10 000 person-years (95% CI)	aHR (95% CI)		Cumulative incidence, % (95% CI)	
				Basic[a]	Full[b]	Age 10 y	Age 18 y
No ASM	22 203	1892	132.9 (127.1-139.0)	1 [Reference]	1 [Reference]	13.9 (13.2-14.6)	31.3 (28.9-33.6)
Any ASM[c]	16 458	2201	178.9 (171.6-186.5)	1.12 (1.05-1.20)	1.17 (1.09-1.25)	17.4 (16.6-18.2)	30.8 (29.2-32.3)
Monotherapies							
Valproate	1952	515	304.6 (279.4-332.1)	1.71 (1.52-1.92)	1.80 (1.60-2.03)	27.2 (24.9-29.4)	42.1 (38.2-45.8)
Lamotrigine	5288	389	117.0 (105.9-129.2)	0.87 (0.78-0.97)	0.91 (0.82-1.02)	12.4 (11.1-13.8)	24.1 (19.7-28.7)
Levetiracetam	1061	59	130.7 (101.3-168.7)	1.14 (0.87-1.48)	1.30 (0.99-1.71)	17.6 (12.2-23.8)	NA
Carbamazepine	2665	391	156.4 (141.7-172.7)	0.94 (0.83-1.07)	1.06 (0.93-1.22)	15.0 (13.4-16.7)	27.3 (24.5-30.1)
Oxcarbazepine	1460	197	144.2 (125.4-165.9)	0.78 (0.65-0.92)	0.85 (0.71-1.02)	12.3 (10.4-14.4)	27.1 (23.1-31.2)
Topiramate	290	34	182.0 (130.1-254.8)	1.31 (0.92-1.85)	1.34 (0.94-1.90)	20.4 (14.0-27.7)	NA
Clonazepam	339	64	189.0 (147.9-241.4)	1.26 (0.97-1.64)	1.08 (0.83-1.42)	15.8 (11.7-20.5)	35.1 (26.2-44.1)
Pregabalin	120	8	164.1 (82.1-328.1)	1.61 (0.80-3.26)	1.06 (0.52-2.16)	NA	NA
Gabapentin	138	16	190.6 (116.8-311.1)	1.48 (0.90-2.42)	1.30 (0.78-2.18)	NA	NA
Polytherapies							
Without valproate	2092	295	205.1 (183.0-229.9)	1.33 (1.17-1.51)	1.32[d] (1.15-1.51)	21.0 (18.6-23.5)	31.7 (27.5-36.0)
With valproate	822	202	311.9 (271.7-358.0)	1.86 (1.58-2.19)	1.85 (1.56-2.18)[d]	28.7 (25.0-32.5)	NA[e]

Dreier JW, et al. JAMA Neurol. 2023;80:568-577

Figure 1. Cumulative Incidence of the Combined Psychiatric End Point According to Prenatal Antiseizure Medication (ASM) Exposure



Dreier JW, et al. JAMA Neurol. 2023;80:568-577

No. of children followed up																			
No ASM	22 203	20 520	18 676	16 888	15 182	13 397	11 721	10 041	8338	6767	5272	3868	2552	1856	1466	1148	869	620	400
Monotherapies																			
Valproate	1952	1935	1878	1807	1729	1634	1532	1419	1297	1160	1015	853	724	619	542	463	382	306	227
Lamotrigine	5288	4894	4452	4010	3549	3158	2722	2317	1927	1543	1189	847	546	374	279	207	151	88	61
Levetiracetam	1061	947	782	630	510	397	302	230	162	109	62								
Carbamazepine	2665	2608	2504	2397	2276	2144	2001	1846	1693	1499	1336	1139	944	820	733	642	535	428	328
Oxcarbazepine	1460	1446	1369	1293	1216	1133	1060	968	876	806	740	663	569	489	417	347	280	210	147
Topiramate	290	276	262	244	216	191	170	141	115	90	70								
Clonazepam	339	NA	327	320	306	290	274	263	243	218	194	167	136	113	101				
Polytherapies																			
Without valproate	2092	1951	1780	1637	1475	1316	1177	1060	899	785	658	556	446	357	299	253	202	161	110
With valproate	822	800	748	702	662	622	573	535	473	413	372	322	278	240	214	186	154	124	

The cumulative incidence curves are unadjusted. Different lengths of the curves reflect differences in available follow-up data for the ASMs. NA indicates not applicable.

Dreier JW, et al. JAMA Neurol. 2023;80:568-577

Pregnancy

- The odds of mortality during pregnancy is 5–12 times greater among PWECP as compared with pregnant people without epilepsy
- Among 202 pregnancy-related deaths in the United Kingdom from 2013 to 2015
  - Most patients had uncontrolled seizures, and some patients had stop ASMs during pregnancy

Recommendation 2 Statements

2A. Clinicians must minimize the occurrence of convulsive seizures (generalized tonic-clonic seizures and focal-to-bilateral tonic-clonic seizures) in PWECP during pregnancy to minimize potential risks to the birth parent (e.g., seizure-related mortality) and to the fetus (Level A).

2B. Once a PWECP is already pregnant, clinicians should exercise caution in attempting to remove or replace an ASM that is effective in controlling generalized tonic-clonic or focal-to-bilateral tonic-clonic seizures, even if it is not an optimal choice with regards to the risk to the fetus (e.g., valproic acid) (Level B).

2C. Clinicians should monitor ASM levels in PWECP throughout pregnancy as guided by individual ASM pharmacokinetics and patient clinical presentation (Level B).

2D. Clinicians should adjust the dose of ASMs at their clinical discretion during the pregnancy in response to (1) decreasing serum ASM levels or (2) worsening seizure control (observed or anticipated based on the clinician's judgment and known pharmacokinetics of ASMs in the pregnant state) (Level B).

2E. Clinicians treating PWECP using acetazolamide, eslicarbazepine, ethosuximide, lacosamide, nitrazepam, perampanel, piracetam, pregabalin, rufinamide, stiripentol, tiagabine, or vigabatrin should counsel their patients that there are limited data on pregnancy-related outcomes for these drugs (Level B).

AED	Decrease in serum concentration	Decrease in serum free (unbound) concentration	Recommendations to perform therapeutic drug monitoring, if available
Phenobarbital	Up to 55%	Up to 50%	Yes
Phenytoin	60 - 70%	20 - 40%	Yes, free concentration
Carbamazepine	0 - 12%	None	Optional
Valproate	Up to 23%	None	Optional, free concentration if done
Oxcarbazepine monohydroxy-derivative (MHD)	36 - 62%	N/A	Yes
Lamotrigine	0.77 of population: 69% decrease 0.23 of population: 17% decrease	N/A	Yes
Gabapentin	Insufficient data	N/A	Yes
Topiramate	Up to 30%	N/A	Yes
Levetiracetam	40 - 60%, with maximal decrease reached in first trimester	N/A	Yes
Zonisamide	Up to 35% but little data	N/A	Yes

N/A: not applicable.

Tomson T, et al. Epileptic Disord 2019; 21 (6): 497-517

Recommendation 4 Statements

4A. Clinicians should counsel PWECP that the prevalence of intrauterine death does not differ among different ASM exposures in monotherapy (Level B).

4B. Clinicians should avoid the use of valproic acid or topiramate in PWECP to minimize the risk of offspring being born SGA, if clinically feasible (Level B).

4C. To enable early identification of fetal growth restriction, obstetricians should recommend screening of fetal growth throughout pregnancy among PWECP who are treated with valproic acid or topiramate (Level B).

Breast feeding

	Decrease in total plasma concentration (%)	Ratio of infant/ maternal plasma concentration [20]
Phenytoin	25–50[a]	0.1–0.6
Phenobarbital	25–50	0.3–0.5
Ethosuximide	[c]	0.8–1.0
Carbamazepine	<25	0.1–0.3
Valproate	25–50[b]	0.01–0.1
Oxcarbazepine MHD	>50	0.5
Vigabatrin	[c]	[c]
Lamotrigine	>50	0.4–0.8
Gabapentin	[c]	0.7–1.3
Topiramate	[c]	0.7–1.1
Tiagabine	[c]	[c]
Levetiracetam	>50	0.8–1.3
Pregabalin	[c]	[c]
Zonisamide	25–50	0.5–0.9

MHD, monohydroxy metabolite.
[a] Unbound concentration declines <25%.
[b] Unbound concentration often unchanged.
[c] Published data lacking.

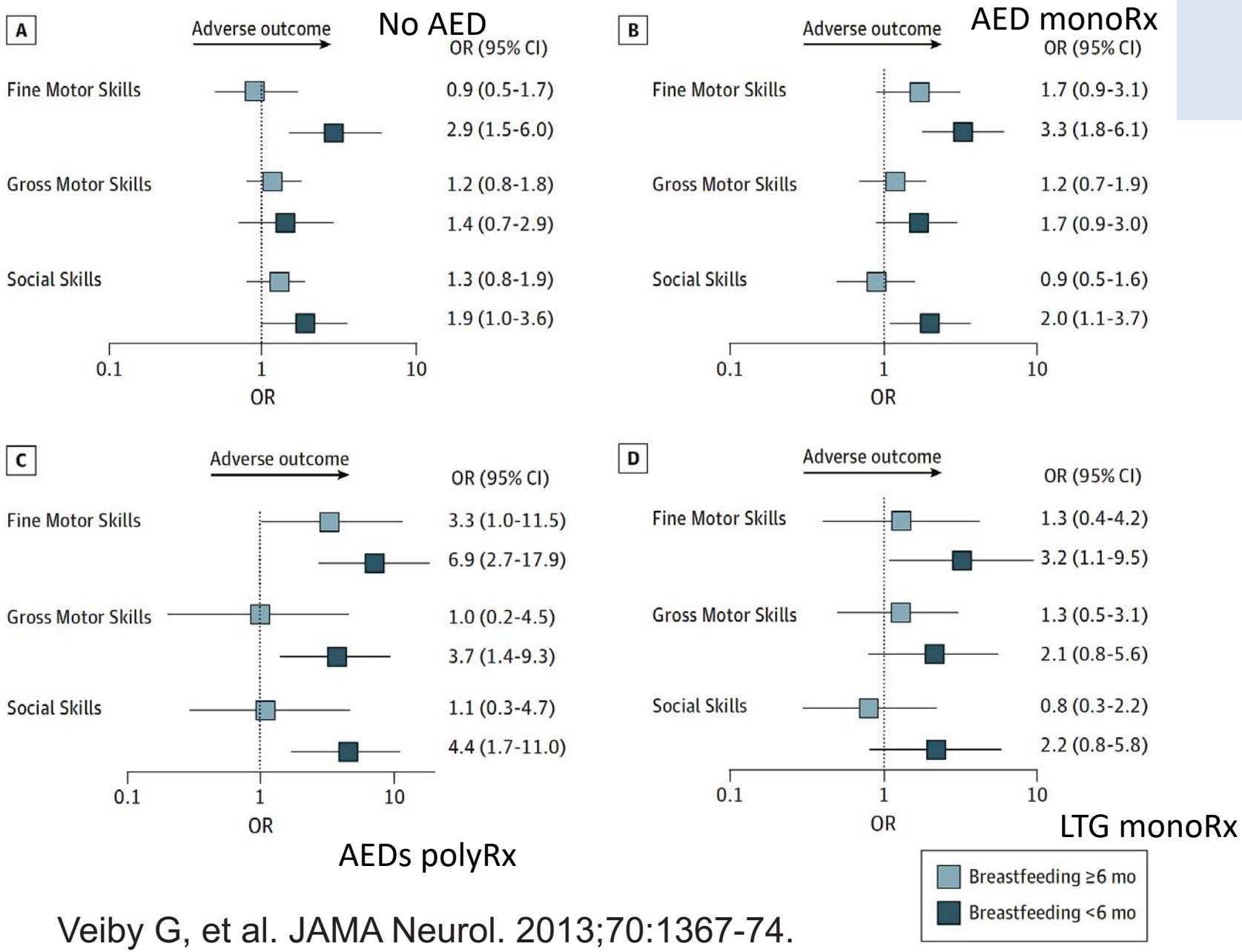
Current Opinion in Neurology 2009, 22:157–161

	Number of participants	Key findings
Meador et al (2010, 2013):[20,101] prospective, observational, multicentre study		
Carbamazepine	47	Higher IQ and enhanced verbal abilities at age 6 years in breastfed children
Lamotrigine	61	As above
Phenytoin	37	As above
Valproate	36	As above
Veiby et al (2013):[102] prospective, cohort study in Norway		
Carbamazepine	48	Continuous breastfeeding linked to less impaired development at age 6 months and 18 months compared with no breastfeeding, with similar development at 36 months to those who had discontinued earlier
Lamotrigine	71	As above
Valproate	27	As above
Lattanzi et al (2017):[95] case series		
Lacosamide	3	Normal milestones at age 18 months, 24 months, and 36 months
Meador et al (2025):[35] prospective, observational, multicentre study		
Lamotrigine	97	Development at 2 years of age did not differ between children of women with epilepsy taking antiseizure medications and children of women without epilepsy
Levetiracetam	70	As above
Bromley et al (2023):[26] prospective, observational, multicentre study		
Lamotrigine	106	Development at age 2 years did not differ (regarding cognitive, language, or motor developmental scores) compared with the control group
Levetiracetam	70	As above

IQ=intelligence quotient.

Table 3: **Studies of neurodevelopmental outcomes in breastfed infants of mothers taking antiseizure medications**

Figure 2. Risk of Adverse Development Score at 6 Months in Children of Mothers With Epilepsy According to Breastfeeding



Veiby G, et al. JAMA Neurol. 2013;70:1367-74.

Research

Original Investigation

Meador KJ, et al. JAMA Pediatr. 2014;168:729-736
the Neurodevelopmental Effects of Antiepileptic Drugs (NEAD) study group

Breastfeeding in Children of Women Taking Antiepileptic Drugs

Cognitive Outcomes at Age 6 Years

Table 3. Adjusted IQs at Age 6 Years Across Antiepileptic Drugs (AEDs) Comparing Breastfed vs Nonbreastfed Children[a]

	IQ, Mean (95% CI)			
AED Group	Breastfed	Nonbreastfed	Difference	*P* Value
All AEDs	108 (105 to 111) (n = 78)	104 (101 to 106) (n = 103)	4 (0 to 8)	.04
Carbamazepine	107 (101 to 113) (n = 23)	105 (99 to 110) (n = 24)	2 (−6 to 11)	.61
Lamotrigine	113 (110 to 117) (n = 27)	110 (107 to 113) (n = 34)	3 (2 to 8)	.23
Phenytoin	104 (99 to 110) (n = 17)	108 (103 to 113) (n = 20)	−4 (−12 to 4)	.23
Valproate	106 (97 to 115) (n = 11)	94 (88 to 100) (n = 25)	12 (1 to 24)	.04

CONCLUSIONS AND RELEVANCE No adverse effects of AED exposure via breast milk were observed at age 6 years, consistent with another recent study at age 3 years. In our study, breastfed children exhibited higher IQ and enhanced verbal abilities. Additional studies are needed to fully delineate the effects of all AEDs.

■ Seminar in epileptology

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

Epileptic Disorders

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

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

Epileptic Disord 2022; 24:1021-32

Concentration of ASM in breastmilk

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

Percentage of maternal serum concentration

Epileptic Disord 2022; 24:1021-32

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

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

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

Epileptic Disord 2022; 24:1021-32

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

Reducing the risk of maternal seizures

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

Reducing risks to the infant associated with maternal seizures

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

Epileptic Disord 2022; 24:1021-32

Folic acid supplementation

SPECIAL ARTICLE

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

Practice Guideline From the AAN, AES, and SMFM

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

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

Recommendation 6 Statements

6A. Clinicians should prescribe at least 0.4 mg of folic acid supplementation daily preconceptionally and during pregnancy to any PWECP treated with an ASM to decrease the risk of NTDs in the offspring (Level B).

6B. Clinicians must prescribe at least 0.4 mg of folic acid supplementation daily preconceptionally and during pregnancy to any PWECP treated with an ASM to possibly improve neurodevelopmental outcomes such as ASD and global IQ in the offspring (Level A).

6C. Clinicians should counsel PWECP treated with an ASM that adherence to recommended folic acid supplementation preconceptionally and during pregnancy is important to minimize the risk of MCMs and poor neurodevelopmental outcomes (Level B).

Research

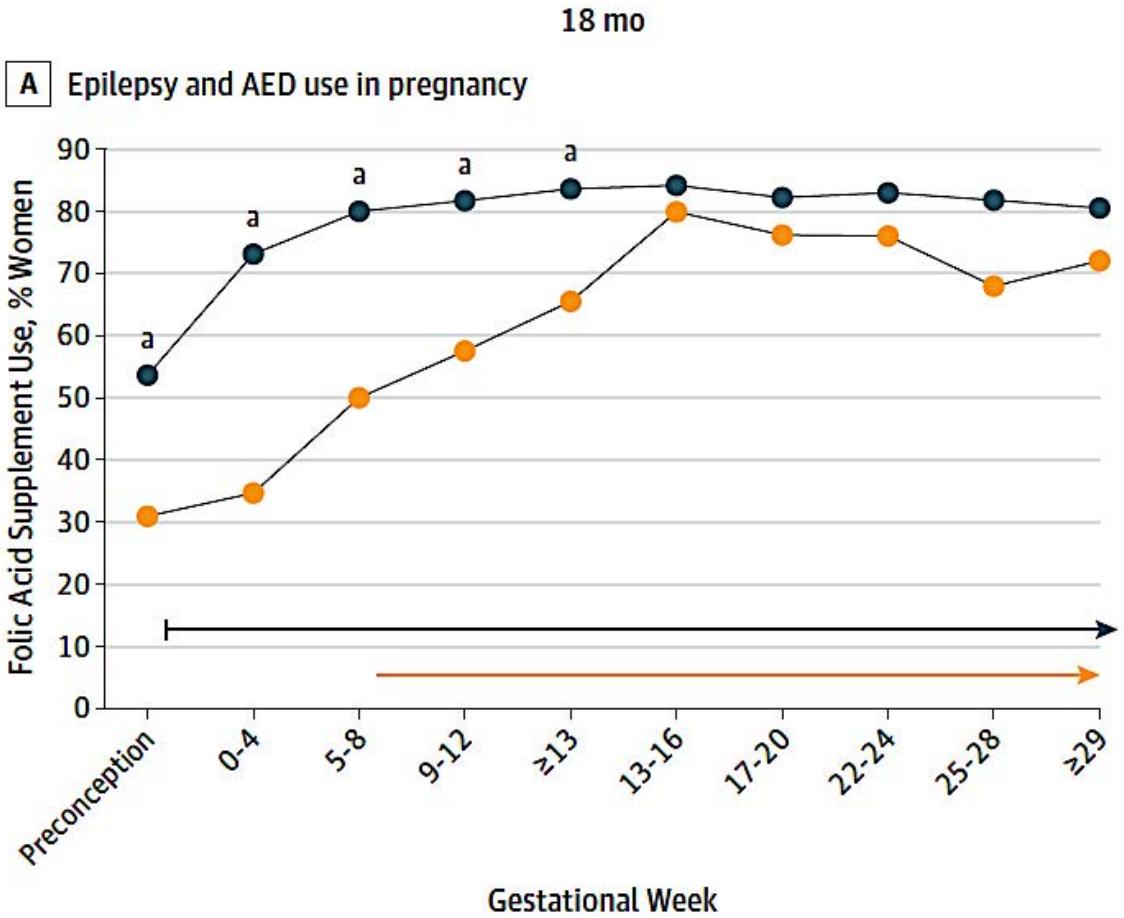
JAMA Neurology | Original Investigation

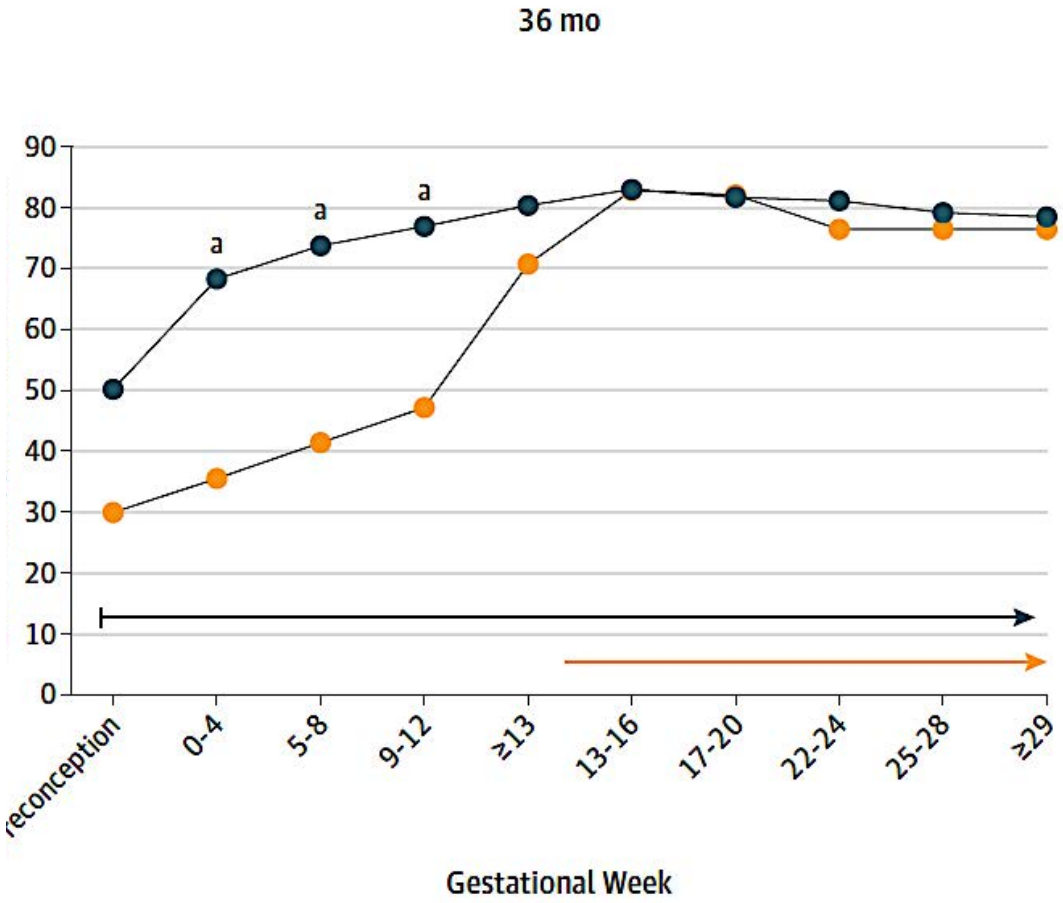
Association of Folic Acid Supplementation During Pregnancy With the Risk of Autistic Traits in Children Exposed to Antiepileptic Drugs In Utero

Marte Bjørk, MD, PhD; Bettina Riedel, MD, PhD; Olav Spigset, MD, PhD; Gyri Veiby, MD, PhD; Eivind Kolstad, MD; Anne Kjersti Daltveit, MD, PhD; Nils Erik Gilhus, MD, PhD

DESIGN: The population-based, prospective Norwegian Mother and Child Cohort Study approached Norwegian-speaking women attending routine ultrasonographic examinations from June 1999 through December 31, 2008 (163,844 of 277,702 women refused). Children aged 18 to 36 months of women with available information on use of AEDs and of folic acid supplementation (n = 104,946) were included in the analysis from March 1, 2016, through June 13, 2017.
EXPOSURES: Maternal folic acid supplementation 4 weeks before to 12 weeks after conception. Plasma folate concentration was analyzed at gestational weeks 17 to 19.
MAIN OUTCOMES: Autistic traits were evaluated using the Modified Checklist for Autism in Toddlers and Social Communication Questionnaire. Folate concentrations and folic acid doses were associated with the degree of autistic traits.

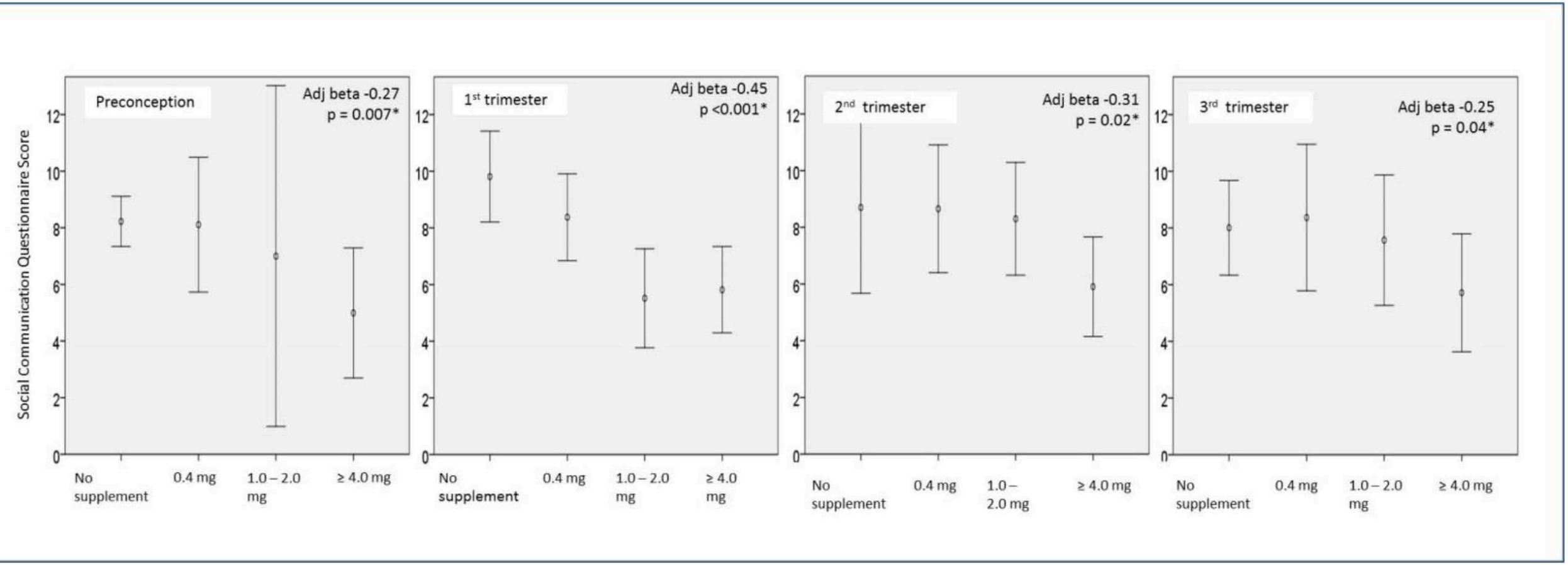
Bjork M, et al. JAMA Neurol. 2018;75(2):160-168





Bjork M, et al. JAMA Neurol. 2018;75(2):160-168

eFigure 1. Degree of Autistic Traits at 36 Months of Age According to Folic Acid Dose Used Before and During Pregnancy



Bjork M, et al. JAMA Neurol. 2018;75(2):160-168

Conclusions

Folic acid supplementation in early pregnancy is associated with a reduced risk of autistic traits in children of mothers with epilepsy using AEDs. The benefit of folic acid supplements was not restricted to children exposed to valproate. Folic acid intake was critical during the first 12 gestational weeks. We detected a dose-effect association for the degree of autistic traits. Unplanned pregnancies are common in the epilepsy cohort, and folic acid supplements should be taken continuously by all women taking AEDs if they could become pregnant.

Bjork M, et al. JAMA Neurol. 2018;75(2):160-168

Fetal antiepileptic drug exposure and cognitive outcomes at age 6 years (NEAD study): a prospective observational study

*Kimford J Meador, Gus A Baker, Nancy Browning, Morris J Cohen, Rebecca L Bromley, Jill Clayton-Smith, Laura A Kalayjian, Andres Kanner, Joyce D Liporace, Page B Pennell, Michael Privitera, David W Loring, for the NEAD Study Group**

Methods:
- Prospective, observational, assessor-masked, multicentre study, we enrolled pregnant women with epilepsy on antiepileptic drug monotherapy (carbamazepine, lamotrigine, phenytoin, or valproate) between October, 1999, and February, 2004, at 25 epilepsy centres in the UK and the USA.
- 305 mothers and 311 children (six twin pairs) in the primary analysis. 224 children completed 6 years of follow-up (6-year-completer sample).

Primary outcome: IQ at 6 years of age (age-6 IQ) in all children, assessed with linear regression adjusted for maternal IQ, antiepileptic drug type, standardised dose, gestational birth age, and use of periconceptional folate.

Meador KJ, et al. Lancet Neurol 2013; 12: 244–52

Table 2: Differences from valproate in mean IQ scores in all children in the study (n=311) and in children at 6 years of age (n=224)

	Carbamazepine	Lamotrigine	Phenytoin	Valproate
Total-enrolled				
Participants	94 (30%)	100 (32%)	55 (18%)	62 (20%)
Mean IQ*	105 (102–108)	108 (105–110)	108 (104–112)	97 (94–101)
Difference	7 (3–12)	10 (6–15)	10 (5–16)	NA
p value†	0·0015	0·0003	0·0006	NA
Age-6-completers				
Participants	61 (27%)	74 (33%)	40 (18%)	49 (22%)
Mean IQ*	106 (103–109)	108 (105–111)	109 (105–113)	98 (95–102)
Difference	8 (3–13)	10 (6–15)	11 (5–16)	NA
p value†	0·0010	0·0003	0·0004	NA

Meador KJ, et al. Lancet Neurol 2013; 12: 244–52

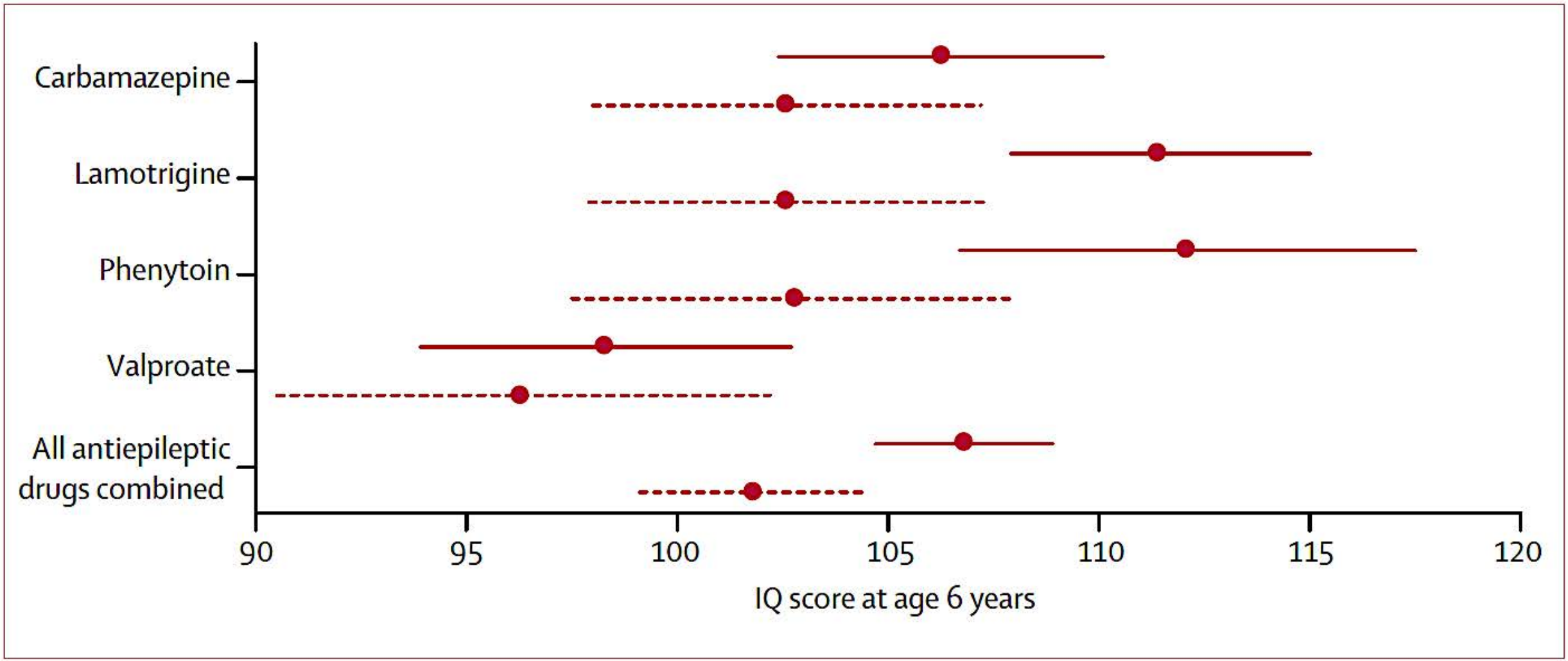


***Figure 3*: Child IQ at 6 years, by exposure to maternal antiepileptic drug use and periconceptional folate**

Meador KJ, et al. Lancet Neurol 2013; 12: 244–52

Problems with high-dose folic acid??

Research

JAMA Neurology | Original Investigation

Cancer Risk in Children of Mothers With Epilepsy and High-Dose Folic Acid Use During Pregnancy

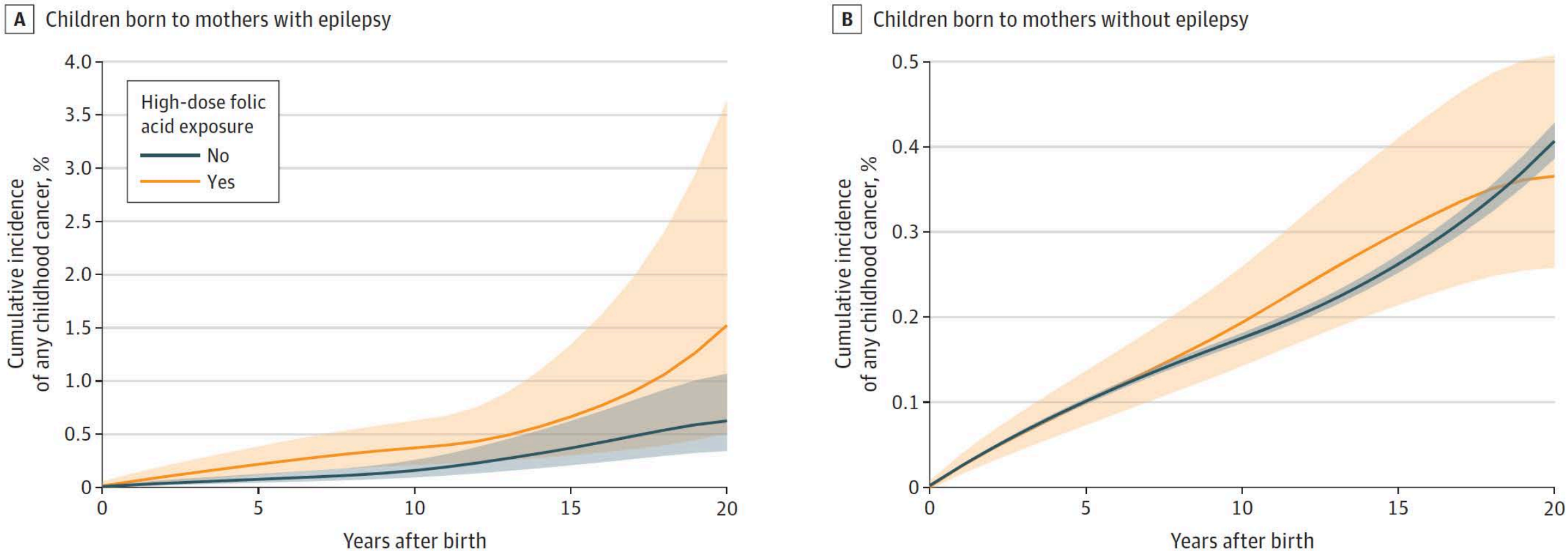
Håkon Magne Vegrim, MD; Julie Werenberg Dreier, PhD; Silje Alvestad, MD, PhD; Nils Erik Gilhus, MD, PhD; Mika Gissler, PhD; Jannicke Igland, PhD; Maarit K. Leinonen, MD, PhD; Torbjörn Tomson, MD, PhD; Yuelian Sun, MD, PhD; Helga Zoega, MA, PhD; Jakob Christensen, MD, PhD, DrMedSci; Marte-Helene Bjørk, MD, PhD

DESIGN: Observational cohort study conducted with nationwide registers in Denmark, Norway, and Sweden from 1997 to 2017. Analyses were performed in 2022.
Mother-child pairs were identified in medical birth registers and linked with information from patient, prescription, and cancer registers, and sociodemographic information from statistical agencies, and were categorized by maternal diagnosis of epilepsy. The study population consisted of 3,379,171 children.
EXPOSURES: Maternal prescription fills for high-dose folic acid tablets (1mg daily) between 90 days before pregnancy start and birth.
MAIN OUTCOMES: First onset of childhood cancer at younger than 20 years. Cox proportional hazards models were used to calculate adjusted hazard ratios with corresponding 95%CIs, adjusted for potential confounders.

Table 2. Association Between Maternal Epilepsy, Filled Prescription of High-Dose Folic Acid, and Risk of Childhood Cancer in the Offspring[a]

Maternal epilepsy	High-dose folic acid	Live births	Childhood cancer cases	Incidence rate per 100 000 person-years (95% CI)	Cumulative incidence at 20 y (95% CI)[b]	Crude HR (95% CI)
Yes	Yes	5934	18	42.5 (26.8-67.5)	1.5 (0.5-3.6)	2.4 (1.3-4.5)
	No	21 850	29	18.4 (12.8-26.5)	0.6 (0.3-1.1)	1 [Reference]
No	Yes	46 646	69	20.0 (15.8-25.4)	0.4 (0.3-0.5)	1.1 (0.9-1.4)
	No	3 304 741	4927	18.9 (18.4-19.5)	0.4 (0.4-0.4)	1 [Reference]

Figure 2. Cumulative Incidence of Childhood Cancer



Cumulative incidence of first onset of childhood cancer recorded from birth until 20 years of age with or without maternal prescription fill for high-dose folic acid for mothers with or without a diagnosis of epilepsy. The graph lines were smoothed owing to the Danish Data Protection Act to prevent identification of individuals.

Conclusions

In this cohort study, an association was found between increased risk of cancer among children of mothers with epilepsy and maternal use of high-dose folic acid. In contrast, prenatal exposure to high-dose folic acid was not associated with an increased
mothers without

Results of this study should be considered when the risks and benefits of folic acid supplements for women with epilepsy are discussed and before decisions about optimal dose recommendations are made. Because of the combined use of ASM and folic acid in high doses in mothers with epilepsy, future studies should investigate possible etiologic mechanisms between folic acid and ASM exposure in pregnancy and the risk of cancer.

Received: 6 June 2023 | Accepted: 9 June 2023

DOI: 10.1111/epi.17680

COMMENTARY

Unjustified allegation on cancer ris mothers with epilepsy taking high- pregnancy—No proof of a causal re

Randi von Wrede[1] | Juri-Alexander Witt[1] | St
Anita Devlin[5,6] | Lieven Lagae[7] | Anthony Ma
Terence J. O'Brien[11] | Jun Park[12] | Rainer Surge
Samuel Wiebe[17] | Christoph Helmstaedter[1]

Wrede RV, et al. Epilepsia. 2023;64:2239–2243.

Key points

- Serious methodological flaws do not allow conclusions about cancer risks in the offspring of mothers with epilepsy and high-dose folic acid supplementation.
- One major issue is the implausibility of the epilepsy diagnoses given the very high number of pregnant women with epilepsy without antiseizure medication.
- Further major concerns include inconclusive dose calculations and the fact that over-the-counter self-supplementation of folic acid was not considered.
- Non-critical reporting of the results and causal misinterpretation will negatively impact counseling and adherence.
- Continuation of an adjusted antiseizure medication and supplementation of 0.4-0.8 mg folic acid per day is highly recommended during pregnancy.

DOI: 10.1111/epi.17717

Epilepsia™

COMMENTARY

High-dose folic acid and cancer risk; unjustified concerns by von Wrede and colleagues regarding our paper

Marte-Helene Bjørk[1,2] | Torbjörn Tomson[3] | Julie Werenberg Dreier[4] | Silje Alvestad[1,5] | Nils Erik Gilhus[1,2] | Mika Gissler[6,7] | Jannicke Igland[8] | Maarit K. Leinonen[6] | Yuelian Sun[9] | Håkon Magne Vegrim[1] | Helga Zoega[10,11] | Jakob Christensen[12,1]

Abstract

Women using antiseizure medication in pregnancy are often advised to use (1mg to 5 mg) to reduce the risk of tera-
a report showing an association between
se folic acid in relation to pregnancy and
The report has sparked a debate about
be recommended in pregnancy in women
n this Commentary, we explain our find-
eport, and answer recent questions that
have emerged.

We are in full agreement with von Wrede et al. that women with epilepsy "should be encouraged to continue ASM as well as supplement folic acid with 0.4–0.8 mg per day before and while pregnant." We note that they do not recommend the higher folate doses suggested in some guidelines and that were assessed in our study, that is, folic acid doses of 1 mg or more per day.

Epilepsia. 2023;64:2244–2248.

Male reproductive age

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

12 January 2024

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

News Human Pharmacovigilance Referrals

EMA's safety committee (PRAC) is recommending precautionary measures for the treatment of male patients with valproate medicines. These measures are to address a potential increased risk of neurodevelopmental disorders in children born to men treated with valproate during the 3 months before conception. Valproate medicines are used to treat epilepsy, bipolar disorders and, in some EU countries, migraine.

The PRAC recommends that valproate treatment in male patients is started and supervised by a specialist in the management of epilepsy, bipolar disorder or migraine.

Doctors should inform male patients who are taking valproate about the possible risk and discuss the need to consider effective contraception, for both the patient and their female partner. Valproate treatment of male patients should be reviewed regularly to consider whether it remains the most suitable treatment, particularly when the patient is planning to conceive a child.

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

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

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

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

The possible risk in children born to men treated with valproate in the 3 months before conception is lower than the previously confirmed risk in children born to women treated with valproate during pregnancy. It is estimated that up to 30 to 40 out of 100 preschool children whose mothers took valproate during pregnancy may have problems with early childhood development, such as being slow to walk and talk, being intellectually less able than other children, and having difficulty with language and memory.

The study data on male patients had limitations, including differences between the groups in the conditions for which the medicines were used and in follow-up times. The PRAC could therefore not establish whether the increased occurrence of these disorders suggested by the study was due to valproate use. In addition, the study was not large enough to identify which types of neurodevelopmental disorders children could be at increased risk of developing. Nonetheless, the Committee considered precautionary measures were warranted to inform patients and healthcare professionals.

The potential risk of neurodevelopmental disorders and the precautionary measures will be reflected in updates to the product information and educational material for valproate medicines.

Valproate (Belvo, Convulex, Depakote, Dyzantil, Epilim, Epilim Chrono or Chronosphere, Episenta, Epival, and Syonell▼): updated safety and educational materials to support patient discussion on reproductive risks

Updated safety and educational materials are now available to support the implementation of the regulatory measures announced in the November 2023 National Patient Safety Alert and the September 2024 Drug Safety Update. They also include previous updates to product information on the risk of low birth weight in children exposed to valproate during pregnancy.

From: Medicines and Healthcare products Regulatory Agency

Published 10 June 2025

Advice for Healthcare Professionals:

- updated safety and educational materials are now available to support healthcare professionals and patients to implement the existing regulatory requirements
- the updates reflect:
  - precautionary advice on the potential risk of neurodevelopmental disorders in children fathered by men taking valproate around the time of conception
  - a risk of lower weight at birth for the gestational age in children exposed to valproate during pregnancy
- healthcare professionals should review the new materials and integrate them into their clinical practice when referring patients and when prescribing or dispensing valproate

As a reminder

- valproate must not be started in new patients (male or female) younger than 55 years unless two specialists independently consider and document that there is no other effective or tolerated treatment, or there are compelling reasons that the reproductive risks do not apply
- valproate must not be prescribed to any woman or girl able to have children unless the conditions of the Pregnancy Prevention Programme (PPP) are followed
- as a precaution, recommend that male patients use effective contraception (condoms, plus contraception used by the female sexual partner) throughout the valproate treatment period and for 3 months after stopping valproate, to allow for one completed sperm cycle not exposed to valproate. For further information see the September 2024 Drug Safety Update
- report suspected adverse reactions associated with valproate on Yellow Card

Advice for Healthcare Professionals to Provide to Patients:

- do not stop taking valproate without advice from a specialist. This is because epilepsy or bipolar disorder may worsen without treatment
- women and girls who are able to have children and who are taking valproate must follow the conditions of the Pregnancy Prevention Programme
- as a precaution it is recommended that male patients taking valproate should use effective contraception (condoms, plus contraception used by the female sexual partner) throughout the valproate treatment period and for 3 months after stopping valproate
- if you are on valproate, please attend any offered appointments to discuss your treatment plan and talk to a healthcare professional if you are concerned. If you wish to discuss family planning, please contact a healthcare professional
- consult the Patient Information Leaflet and Patient Guide for men or Patient Guide for women for information about the risks of valproate – also the MHRA information page for information resources

VALPROATE GUIDE FOR MALE PATIENTS

Read this guide along with the patient information leaflet which is included in each box of your medicine

This medicine will be referred to as valproate throughout this guide and covers the brands Epilim, Depakote, Convulex, Episenta, Epival, Sodium Valproate, Syonell, Belvo & Dyzantil.

Do not stop taking valproate unless your specialist tells you to - this is because your condition may become worse, including an increased risk of seizure in those being treated for epilepsy and increased risk of relapse in those treated for bipolar disorder.

What are the risks to male patients of taking valproate?

Valproate is used to treat epilepsy and bipolar disorder.

Valproate can potentially cause:

- Male infertility (may be reversible after treatment is stopped or the dose is reduced for some patients).
- Toxic effects on the testes (testicles) of animals, such as reduction in testes weight - it is unclear what this means for humans.

What are the risks of taking valproate when conceiving a child?

A study suggests a possible risk of neurodevelopmental conditions (problems with early childhood development) in children born to fathers treated with valproate in the 3 months before conception.

In this study, around 5 children in every 100 had such disorders when born to fathers treated with valproate, as compared to around 3 children in every 100 when born to fathers treated with lamotrigine or levetiracetam (other medicines that can be used to treat your condition).

The study has limitations and therefore it is not clear if the increased risk for neurodevelopmental conditions suggested by this study is caused by valproate.

The study was not large enough to show which particular type of disorder children may be at risk of developing.

The risk for children born to fathers who stopped valproate treatment 3 months (the time needed to form new sperm) or longer before conception is not known.

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

Review

Management of reproductive risks in people with epilepsy

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

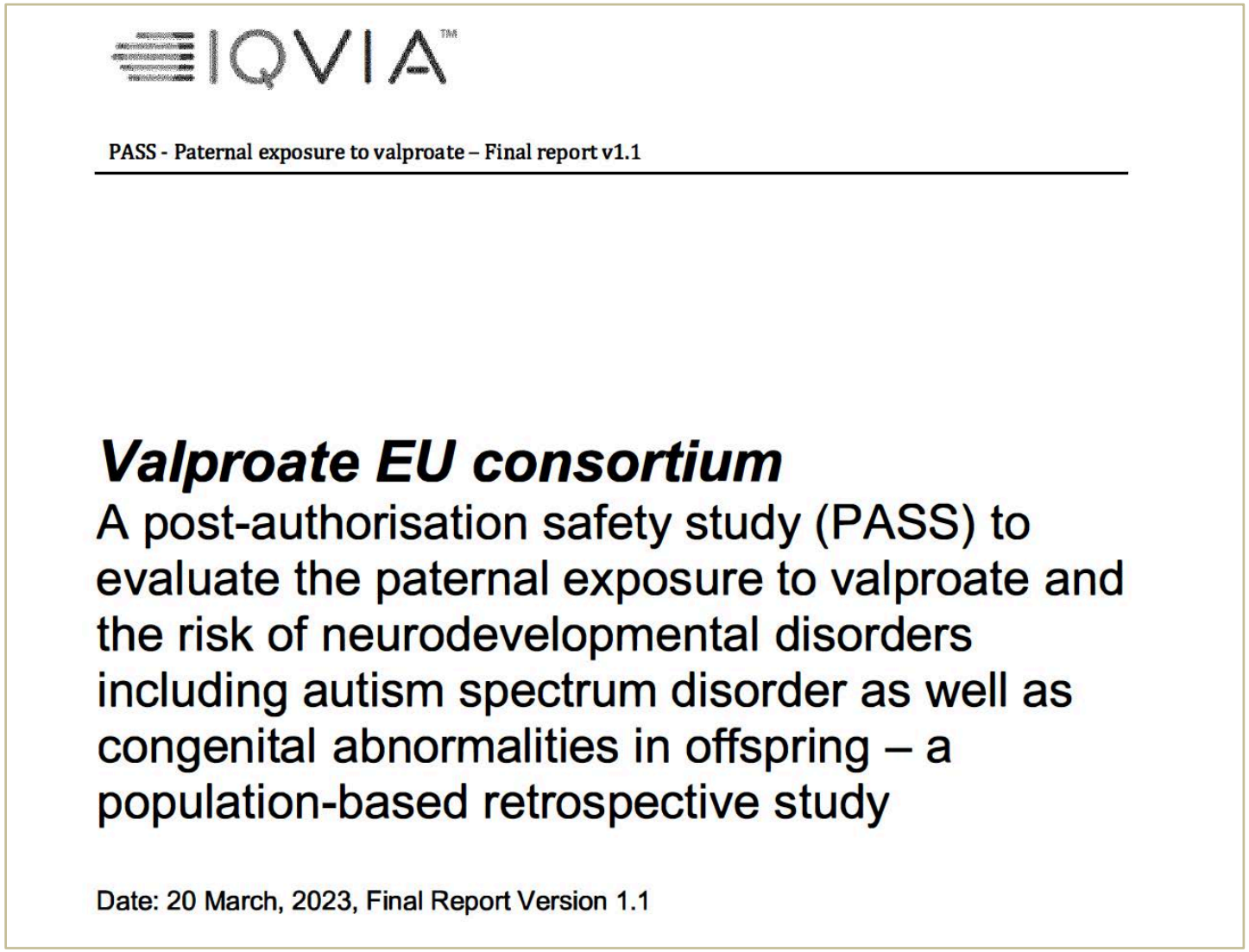
Lancet Neurol 2025; 24: 601–13

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

HR=hazard ratio. *Pooled HR.

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

Lancet Neurol 2025; 24: 601–13



European Medicines Agency. A post-authorization safety study (PASS) to evaluate the paternal exposure to valproate and the risk of neurodevelopmental disorders including autism spectrum disorder as well as congenital abnormalities in offspring—a population-based retrospective study. 2023, European Medicines Agency

13. Conclusions

This comprehensive real-world retrospective study provides the first data on NDD and CM in offspring paternally exposed to valproate during spermatogenesis, compared to those exposed to lamotrigine/levetiracetam. The pooled HR, indicated a moderate risk (HR 1.47, 95% CI: 1.10, 1.96) of NDD including ASD in offspring paternally exposed to valproate compared to those paternally exposed to lamotrigine/levetiracetam.

The pooled risk of congenital malformations suggested no higher risk in offspring paternally exposed to valproate when compared to those exposed to lamotrigine/levetiracetam. Due to the considerable heterogeneity observed, these findings should also be interpreted with caution.

Overall, this retrospective observational study has several limitations, including the difference in follow-up duration between the 2 groups and the different time period of exposure.

European Medicines Agency. A post-authorization safety study (PASS) to evaluate the paternal exposure to valproate and the risk of neurodevelopmental disorders including autism spectrum disorder as well as congenital abnormalities in offspring—a population-based retrospective study. 2023, European Medicines Agency

Table 1: Meta-analysis of the adjusted hazard ratios obtained from the PS-weighted Cox regression model; primary outcome NDD including ASD

NDD*	Denmark	Sweden	Norway	Meta-analysis Pooled HR
N Valproate	678	841	325	
N	38	47	13	
N lamotrigine/levetiracetam	1118	1334	910	
n	36	34	21	
valproate vs lamotrigine/levetiracetam	1.34 (0.79, 2.25)	1.54 (0.95, 2.51)	1.76 (0.83, 3.71)	1.50 (1.09, 2.076)

NDD*: neurodevelopmental disorders

Legend: Hazard Ratio of the outcome between the 2 exposure groups (valproate versus lamotrigine/levetiracetam composite monotherapy) were presented for each country separately and combined (meta-analysis). 95% CI: 95% confidence intervals.

Table 3 Meta-analysis of the hazard ratios obtained from the crude Cox regression model; primary outcome[1]

NDD	Crude Cox model Hazard Ratio						
	Sweden	Norway	Denmark	Meta-analysis (random effect)	P-value	Meta-analysis (fixed effect)	P-value
Number of events/Number of offspring: valproate group	49/930	15/398	43/793				
Number of events/Number of offspring: lamotrigine/levetiracetam group	41/1425	23/1018	41/1157				
I^2 (95% CI)				0.00 (0.00-0.90)	0.4315		
Crude HR (95% CI): valproate vs lamotrigine/levetiracetam	1.16 (0.76, 1.76)	1.60 (0.81, 3.15)	0.94 (0.60, 1.46)	1.13 (0.85-1.49)	0.3982	1.13 (0.85-1.49)	0.3982

CI: Confidence interval; HR: Hazard ratio; NDD: Neurodevelopmental disorders;
Legend: Hazard ratio of the outcome between the 2 exposure groups (valproate vs lamotrigine/levetiracetam composite monotherapy) is presented for each country separately and combined (meta-analysis). The 95% CI is presented as well. The meta-analysis was based on results from the crude model from all countries.
[1] The results reported in this table comprise the crude HR (95% CI) without excluding influential subjects and this approach represented a deviation from the study protocol

JAMA Network Open

Original Investigation | Neurology

Valproate Use During Spermatogenesis and Risk to Offspring

Jakob Christensen, DrMedSci; Betina B. Trabjerg, MSc; Julie Werenberg Dreier, PhD

This nationwide cohort study included 1,235,353 singletons born in Denmark between January 1, 1997, and December 31, 2017, identified in the Medical Birth Register; 1336 children had fathers who had filled prescriptions for valproate during spermatogenesis.
Congenital malformations were identified in the first year of life and neurodevelopmental disorders were identified from 1 year of age until December 31, 2018. Statistical analysis was performed March 2024.

Christensen J, et al. JAMA Network Open. 2024;7(6):e2414709

Among 1,235,353 live births (634,415 boys [51.4%] and 600,938 girls [48.6%]), 1336 children (0.1%) had fathers who filled prescriptions for valproate during spermatogenesis.
The median follow-up was 10.1 years (IQR, 5.1-14.8 years) for valproate-exposed children and 10.3 years (IQR, 5.2-15.6 years) for valproate-unexposed children.

When comparing the risk among valproate-exposed children with that among unexposed children,
- ARR of major congenital malformations was 0.89 (95%CI, 0.67-1.18)
- AHR of neurodevelopmental disorders was 1.10 (95%CI, 0.88-1.37)
- AHR of autism spectrum disorder was 0.92 (95%CI, 0.65-1.30).

CONCLUSIONS AND RELEVANCE In all analyses based on this large Danish cohort study, results suggest that exposure to valproate during spermatogenesis was not associated with offspring risk of congenital malformations or neurodevelopmental disorders, including autism spectrum disorder.

Christensen J, et al. JAMA Network Open. 2024;7(6):e2414709

ORIGINAL RESEARCH

Paternal exposure to antiepileptic drugs and offspring outcomes: a nationwide population-based cohort study in Sweden

Torbjörn Tomson ,[1] Giulia Muraca,[2,3] Neda Razaz[3]

- Using nationwide Swedish registries, we included 1,144,795 births to 741,726 fathers without epilepsy and 4544 births to 2955 fathers with epilepsy.
- 2,087 (45.9%) were born to fathers with epilepsy who had dispensed an AED during the conception period.
- The incidence rate of MCM, autism spectrum disorder, attention deficit hyperactivity disorder (ADHD) and intellectual disability in offspring was analysed.

Tomson T, Muraca G, Razaz N. J Neurol Neurosurg Psychiatry 2020;91:907–13

- Offspring of fathers exposed to AEDs did not show an increased risk of MCM (adjusted OR 0.9, 95% CI 0.7 to 1.2), autism (adjusted HR (aHR) 0.9, 95% CI 0.5 to 1.7), ADHD (aHR 1.1, 95% CI 0.7 to 1.9) or intellectual disability (aHR 1.3, 95% CI 0.6 to 2.8) compared with offspring of fathers with epilepsy not exposed to AEDs.

- Offspring of fathers with epilepsy who used valproate in monotherapy during conception, rates of autism (2.9/1000 child-years) and intellectual disability (1.4/1000 child-years) were slightly higher compared with the offspring of fathers with epilepsy who did not use AEDs during conception (2.1/1000 child-years autism, 0.9/1000 child-years intellectual disability)

- In the propensity-score adjusted analyses, no statistically significant increased risk of adverse outcomes was found

Conclusions: Paternal AED use during conception is not associated with adverse outcomes in the offspring.

Tomson T, Muraca G, Razaz N. J Neurol Neurosurg Psychiatry 2020;91:907–13

Table 4 Risk of adverse outcomes in the offspring born to fathers with epilepsy who used antiepileptic drug (AED) in monotherapy during conception

Offspring outcome	No. (%)	Rate/1000 child-years	Crude estimate (95% CI)	Adjusted estimate (95% CI)*
Major malformation†				
Valproate	22 (4.8)	–	1.0 (0.6 to 1.5)	0.9 (0.6 to 1.5)
Carbamazepine	32 (5.5)	–	1.1 (0.8 to 1.7)	1.0 (0.6 to 1.5)
Other	23 (3.8)	–	0.8 (0.4 to 1.2)	0.7 (0.4 to 1.1)
Unexposed	121 (4.9)	–	1 (Reference)	1 (Reference)
Autism spectrum disorder‡				
Valproate	8 (1.7)	2.9	1.4 (0.6 to 3.0)	1.4 (0.6 to 3.1)
Carbamazepine	8 (1.4)	2.1	1.0 (0.4 to 2.1)	1.0 (0.4 to 2.1)
Other	2 (0.3)	0.6	0.3 (0.1 to 1.3)	0.3 (0.1 to 1.3)
Unexposed	32 (1.3)	2.1	1 (Reference)	1 (Reference)
Attention deficit hyperactivity disorder‡				
Valproate	10 (2.2)	3.6	1.0 (0.5 to 2.1)	1.4 (0.7 to 2.8)
Carbamazepine	9 (1.5)	2.4	0.6 (0.3 to 1.3)	0.9 (0.4 to 1.9)
Other	4 (0.7)	1.2	0.4 (0.2 to 1.1)	0.5 (0.2 to 1.5)
Unexposed	51 (2.1)	3.4	1 (Reference)	1 (Reference)
Intellectual disability‡				
Valproate	4 (0.9)	1.4	1.5 (0.5 to 4.7)	1.6 (0.5 to 5.1)
Carbamazepine	2 (0.3)	0.5	0.5 (0.1 to 2.4)	0.6 (0.1 to 2.9)
Other	4 (0.7)	1.2	1.3 (0.4 to 4.1)	1.4 (0.5 to 4.3)
Unexposed	14 (0.6)	0.9	1 (Reference)	1 (Reference)

Systematic review

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

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

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

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

WHAT IS ALREADY KNOWN ON THIS TOPIC

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

WHAT THIS STUDY ADDS

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

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

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

Advising the PWECP

"People with epilepsy of childbearing potential"

Epilepsy and pregnancy

- ควรมีการให้ความรู้เกี่ยวกับโอกาสและความเสี่ยงที่จะเกิดความผิดปกติของเด็กในครรภ์สำหรับหญิงวัยเจริญพันธุ์ที่ต้องรับประทานยากันชัก เพื่อผู้ป่วยจะได้สามารถวางแผนและตัดสินใจเรื่องการตั้งครรภ์ล่วงหน้าได้
- แนะนำวิธีการคุมกำเนิดที่เหมาะสม
- ??ควรมีการให้ความรู้เกี่ยวกับโอกาสและความเสี่ยงที่จะเกิดความผิดปกติของเด็กสำหรับชายวัยเจริญพันธุ์ที่ต้องรับประทานยากันชักsodium valproate เพื่อผู้ป่วยจะได้สามารถวางแผนและตัดสินใจเรื่องการมีบุตรล่วงหน้าได้

Epilepsy and pregnancy

- ควรวางแผนล่วงหน้าก่อนการตั้งครรภ์เนื่องจาก
  - ในกรณีที่มารดาไม่มีอาการชักนานเกิน 2 ปีอาจพิจารณาหยุดยากันชักได้
  - ในกรณีที่คุมอาการชักได้ดี และมารดารับประทานยากันชักมากกว่า 1 ชนิดอาจพิจารณาลดขนาดยาหรือลดยาเหลือ 1 ชนิด เพื่อลดโอกาสการเกิดผลข้างเคียงต่อทารกในครรภ์

Epilepsy and pregnancy

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

Epilepsy and pregnancy

- ในขณะที่ผู้ป่วยตั้งครรภ์ไม่ควรปรับหรือเปลี่ยนยากันชัก เนื่องจากโอกาสที่จะเกิดอันตรายต่อมารดาและทารกในครรภ์หากผู้ป่วยเกิดการชักมีมากกว่าโอกาสการเกิดผลข้างเคียงต่อทารกในครรภ์
- ควรมีการตรวจคัดกรองความผิดปกติของเด็กในครรภ์มารดา โดยเฉพาะ malformation ที่พบได้บ่อยและรุนแรง เช่น neural tube defect

Epilepsy and pregnancy

- ในผู้หญิงวัยเจริญพันธ์ควรได้รับ folic acid supplementation ในขนาด 4-5 mg/d ซึ่งจากการศึกษาที่ผ่านมา อาจช่วยลดโอกาสการเกิด neural tube defects ได้บ้าง
- ??ในผู้หญิงวัยเจริญพันธ์ควรได้รับ folic acid supplementation ในขนาด >0.4 mg/d (0.4-0.8 mg/d) ซึ่งจากการศึกษาที่ผ่านมา อาจช่วยลดโอกาสการเกิด neural tube defects ได้บ้าง และช่วยให้ neurodevelopmental outcome ดีขึ้น

Epilepsy and lactation

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

Questions

Questions