JAMA Clinical Evidence Synopsis

Maternal Use of Antiepileptic Agents During Pregnancy and Major Congenital Malformations in Children

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CLINICAL QUESTION Is maternal use of antiepileptic drugs during pregnancy associated with major congenital malformations in children?

BOTTOM LINE Certain antiepileptic drugs were associated with increased rates of congenital malformations (eg, spina bifida, cardiac anomalies). Lamotrigine (2.31% in 4195 pregnancies) and levetiracetam (1.77% in 817 pregnancies) were associated with the lowest risk and valproate was associated with the highest risk (10.93% in 2565 pregnancies) compared with the offspring of women without epilepsy (2.51% in 2154 pregnancies).

Introduction

This JAMA Clinical Evidence Synopsis summarizes a Cochrane review[1] regarding monotherapy treatment of epilepsy during pregnancy. Most women with epilepsy require continued antiepileptic drug treatment during pregnancy and evidence regarding the risks associated with different antiepileptic drugs is important to inform treatment decisions.

Evidence Profile

No. of studies: 50 studies (31 contributing to meta-analysis); 49 observational cohort studies and 1 randomized clinical trial, which randomized women to 1 of 2 treatments vs no therapy; however, some refused their group assignment and took no medication

Study years: published: 1974-2014; conducted: 1969-2013

No. of patients: 18 767

Race/ethnicity: Not reported

Age range: Neonatal to 12 months

Setting: Hospitals

Countries: Argentina, Australia, Bulgaria, Canada, Croatia, Denmark, Finland, France, Germany, India, Israel, Italy, Japan, Jordan, Mexico, the Netherlands, Poland, Saudi Arabia, Spain, Sweden, Turkey, United Kingdom, United States

Comparisons: Children exposed to monotherapy antiepileptic drugs vs other monotherapy antiepileptic drugs; and children exposed to monotherapy antiepileptic drugs vs no antiepileptic drugs

Primary outcomes: The number of major congenital malformations (a structural deformity present at birth affecting any region of the body)

Secondary outcomes: The number of specific major congenital malformations within the following classifications: neural tube malformations (eg, spina bifida, anencephaly), cardiac malformations (eg, atrial septal defect, pulmonary atresia), orofacial or craniofacial malformations (eg, cleft lip, craniosynostosis), skeletal and limb malformations (eg, congenital scoliosis, polydactyly)

Summary of Findings

For the children of women without epilepsy, the rate of major congenital malformation was 2.51%. Random-effects modeling was used to calculate the rates when there was a significant level of variance across the studies from which the data were drawn. For the antiepileptic drug exposure groups, valproate was associated with the highest prevalence of major congenital malformation (10.93% [95% CI, 8.91%-13.13%]; 235 of 2565 children). Major congenital malformations were reported in 96 of 4195 children (2.31% [95% CI, 1.87%-2.78%]) exposed to lamotrigine.

Lamotrigine was associated with lower rates of major congenital malformations vs carbamazepine (risk difference [RD], 0.01 [95% CI, 0 to 0.02]), topiramate (RD, −0.02 [95% CI, −0.04 to 0]), and valproate (RD, 0.06 [95% CI, 0.05 to 0.07]) (absolute rates appear in the **Table**). Levetiracetam was associated with a 1.77% (95% CI, 0.98% to 2.79%; 14 of 817 children) rate of major congenital malformations. Levetiracetam was associated with lower rates of congenital malformations than carbamazepine (RD, 0.01 [95% CI, 0 to 0.02]), topiramate (RD, −0.02 [95% CI, −0.04 to 0]), and valproate (RD, 0.07 [95% CI, 0.05 to 0.09]).

Phenobarbital was associated with higher rates of cardiac malformations vs levetiracetam (RD, −0.02 [95% CI, −0.04 to 0]), lamotrigine (RD, −0.02 [95% CI, −0.04 to 0]), and phenytoin (RD, −0.03 [95% CI, −0.05 to 0]). Valproate exposure was associated with a higher rate of neural tube defects vs carbamazepine (RD, −0.02 [95% CI, −0.02 to −0.01]), lamotrigine (RD, 0.01 [95% CI, 0.01 to 0.02]), and levetiracetam (RD, 0.01 [95% CI, 0.01 to 0.02]). Valproate was associated with a higher rate of cardiac malformations vs phenytoin (RD, 0.02 [95% CI, 0.01 to 0.04]), lamotrigine (RD, 0.02 [95% CI, 0.01 to 0.02]), and levetiracetam (RD, 0.02 [95% CI, 0.01 to 0.03]). There was evidence of a dose-response relationship for valproate, but a similar relationship was not found for other antiepileptic drugs.[1]

An updated search in January 2017 identified only 1 eligible publication[2]; however, this study was linked to a study that had

Table. Absolute Rates and Risk Differences for Major Congenital Malformation Rates According to Antiepileptic Drug (AED) Therapy

AED Comparison[a]			Drug 1		Drug 2			
Drug 1	Drug 2	No. of Studies	No. of Children	No. of Malformations	No. of Children	No. of Malformations	Risk Ratio (95% CI)[b]	Absolute Risk Difference (95% CI)[b]
Carbamazepine	Valproate	25	4549	167	2529	229	0.41 (0.34 to 0.50)	-0.05 (-0.07 to -0.04)
Carbamazepine	Levetiracetam	3	3051	92	817	14	1.84 (1.03 to 3.29)	0.01 (0 to 0.02)
Carbamazepine	Lamotrigine	7	3385	108	4164	94	1.34 (1.01 to 1.76)	0.01 (0 to 0.02)
Valproate	Gabapentin	3	1814	149	190	2	6.21 (1.91 to 20.23)	0.08 (0.05 to 0.11)
Valproate	Levetiracetam	3	1814	149	817	14	5.82 (3.13 to 10.81)	0.07 (0.05 to 0.09)
Valproate	Lamotrigine	7	2021	174	4164	94	3.56 (2.77 to 4.58)	0.06 (0.05 to 0.07)
Valproate	Topiramate	3	1814	149	473	19	2.35 (1.40 to 3.95)	0.05 (0.03 to 0.08)
Valproate	Oxcarbazepine	4	676	74	238	5	3.71 (1.65 to 8.33)	0.08 (0.04 to 0.11)
Valproate	Phenobarbital	20	1137	128	626	38	1.59 (1.11 to 2.29)	0.04 (0.01 to 0.08)
Valproate	Phenytoin	21	2319	212	1137	55	2.00 (1.48 to 2.71)	0.05 (0.03 to 0.08)
Gabapentin	Phenobarbital	2	159	1	204	11	0.12 (0.02 to 0.96)	-0.05 (-0.08 to -0.01)
Levetiracetam	Phenobarbital	2	513	12	204	11	0.43 (0.20 to 0.96)	-0.03 (-0.06 to 0.01)
Lamotrigine	Phenobarbital	4	1959	44	282	17	0.32 (0.17 to 0.61)	-0.04 (-0.07 to -0.01)
Lamotrigine	Phenytoin	5	4082	94	624	25	0.53 (0.34 to 0.84)	-0.02 (-0.04 to 0)
Levetiracetam[c]	Phenytoin[c]	3	817	14	566	21	0.49 (0.26 to 0.92)	-0.02 (-0.04 to 0)
Levetiracetam	Topiramate	3	817	14	473	19	0.50 (0.26 to 0.97)	-0.02 (-0.04 to 0)
Lamotrigine	Topiramate	3	3975	93	473	19	0.56 (0.34 to 0.94)	-0.02 (-0.04 to 0)

[a] Only comparisons that reached significance in the fixed-effects model were included. Details on all comparisons appear in Weston et al.[1]

[b] Calculations were completed using RevMan software and weighted depending on their variance in the calculations; therefore, the raw data in some cases cannot be used to calculate the risk differences.

[c] Comparison was not significant in the random-effects model.

already been included, had incomplete information, and did not alter the results of the review.

Discussion

These results can inform discussions with patients about treatment options for the management of epilepsy during pregnancy. Minimizing seizures should be balanced against the risk of child malformation. Although the overall rates of congenital malformations were small, congenital malformations have a substantial effect on the child and family.

Limitations

The quality of the included studies varied and, given the observational design, all were at high risk of certain biases. Data were limited for comparisons including levetiracetam, topiramate, and other newer antiepileptic drugs and for all antiepileptic drugs when investigating specific types of malformation.

Comparison of Findings With Current Practice Guidelines

The American Academy of Neurology, the American Epilepsy Society, and the International League Against Epilepsy[3,4] recommend the cautious use of valproate in women and the results reported herein support this position.

Areas in Need of Future Study

Analysis of larger data sets for the investigation of specific malformation types following exposure to the now widely used newer antiepileptic drugs (eg, levetiracetam and lamotrigine) are needed.

ARTICLE INFORMATION

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Submissions: We encourage authors to submit papers for consideration as a JAMA Clinical Evidence Synopsis. Please contact Dr McDermott at mdm608@northwestern.edu.

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