DSEN ABSTRACT

Comparative safety of anti-epileptic drugs during pregnancy: a systematic review and network meta-analysis of congenital malformations and prenatal outcomes

Summary

Epilepsy in pregnant women can cause frequent seizures, increasing the risk of pregnancy-related complications. Anti-epileptic drugs (AEDs) can mitigate these symptoms, but can also increase the risk of teratogenicity. We conducted a systematic review and network meta-analysis (NMA) to assess the comparative safety of in utero exposure to AEDs in infants and children. Our results suggest that newer generation AEDs, lamotrigine and levetiracetam, did not significantly increase risks of congenital malformations (CMs) or cardiac malformations when compared with control.

Implications

Across CM outcomes, many AEDs were associated with increased risk. However, caution is needed as the overall low quality of available studies on this subject limits definitive conclusions. There is also insufficient evidence to draw conclusions on the safety of polytherapy with newer generation AEDs. Further research is required to explore the risks of older and newer AEDs in both monotherapy and polytherapy.

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What is the current situation?

- AEDs are prescribed to reduce the severity of epilepsy or help manage other conditions such as pain, psychiatric disorders, and migraines.
- However, these agents can be transferred to the fetus via the placenta, increasing the risk of miscarriage and teratogenicity for pregnant women taking AEDs, including a 4–8% chance of giving birth to a child with a major CM.

What was the aim of the study?

- To compare the safety of in utero exposure to AEDs in infants and children through a systematic review and NMA.

How was the study conducted?

- MEDLINE, EMBASE, and the Cochrane CENTRAL Register of Controlled Trials were searched on March 18th, 2014; the search was updated on December 15th, 2015.
- Studies reporting at least one outcome of interest that included pregnant women taking AEDs for any indication were eligible.
- Two reviewers independently performed study selection and data abstraction of included articles. All discrepancies were resolved by a third reviewer.
- Two reviewers independently appraised quality using the Cochrane risk-of-bias tool and Newcastle-Ottawa Scale. Discrepancies were resolved by a third reviewer.
- Statistical analysis was conducted according to the International Society for Pharmacoeconomics and Outcomes Research (ISPOR) guidelines.

What did the study find?

- 96 studies with 58,461 patients were included for analysis across 3 CM outcomes (major, minor, and specific CMs [e.g., cardiac malformation]); and 3 pre-natal harms (fetal loss, preterm birth, and pre-natal growth retardation).
- AEDs associated with significantly increased risk of two or more types of CM include: carbamazepine, ethosuximide, gabapentin, phenobarbital, phenytoin, topiramate, and valproate.
- AEDs associated with significantly increased risk of one or more pre-natal harms include: clobazam, phenobarbital, topiramate, and valproate.
- Lamotrigine, levetiracetam, oxcarbazepine, and vigabatrin (newer generation AEDs) were not associated with significantly increased risks to physical development; however, this does not mean the risks have been completely ruled out.
- Counselling on teratogenic risks is advised for women of childbearing age receiving a first prescription for AEDs and before women continue with these agents during pregnancy.

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Link to protocol: Tricco et al. 2014