



Further Evidence Breastfeeding by Women With Epilepsy Is Safe: Are Mothers Getting the Message?

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Antiepileptic Drug Exposure in Infants of Breastfeeding Mothers With Epilepsy

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There is limited information on infant drug exposure via breastfeeding by mothers who are receiving antiepileptic drug therapy.

Objective: To provide direct, objective information on antiepileptic drug exposure through breast milk. **Design, Setting, and Participants:** This prospective cohort study was conducted between December 2012 and October 2016, with follow-up in children until 6 years of age at 20 sites across the United States. Data were collected via an observational multicenter investigation (Maternal Outcomes and Neurodevelopmental Effects of Antiepileptic Drugs) of outcomes in pregnant mothers with epilepsy and their children. Pregnant women with epilepsy who were aged 14 to 45 years, had pregnancies that had progressed to less than 20 weeks' gestational age, and had measured intelligence quotient (IQ) scores of more than 70 points were enrolled and followed up through pregnancy and 9 postpartum months. Their infants were enrolled at birth. Data were analyzed from May 2014 to August 2019. **Exposures:** Antiepileptic drug exposure in infants who were breastfed. **Main Outcomes and Measures:** The percentage of infant-to-mother concentration of antiepileptic drugs. Antiepileptic drug concentrations were quantified from blood samples collected from infants and mothers at the same visit, 5 to 20 weeks after birth. Concentrations of antiepileptic drugs in infants at less than the lower limit of quantification were assessed as half of the lower limit. Additional measures collected were the total duration of all daily breastfeeding sessions and/or the volume of pumped breast milk ingested from a bottle. **Results:** A total of 351 women (of 865 screened and 503 eligible individuals) were enrolled, along with their 345 infants (179 female children [51.9%]; median [range] age, 13 [5-20] weeks). Of the 345 infants, 222 (64.3%) were breastfed; the data collection yielded 164 matching infant-mother concentration pairs from 138 infants. Approximately 49% of all antiepileptic drug concentrations in nursing infants were less than the lower limit of quantification. The median percentage of infant-to-mother concentration for all 7 antiepileptic drugs and 1 metabolite (carbamazepine, carbamazepine-10,11-epoxide, levetiracetam, lamotrigine, oxcarbazepine, topiramate, valproate, and zonisamide) ranged from 0.3% (range: 0.2%-0.9%) to 44.2% (range: 35.2%-125.3%). In multiple linear regression models, maternal concentration was a significant factor associated with lamotrigine concentration in infants (Pearson correlation coefficient, 0.58; $P < .001$) but not levetiracetam concentration in infants. **Conclusions and Relevance:** Overall, antiepileptic drug concentrations in blood samples of infants who were breastfed were substantially lower than maternal blood concentrations. Given the well-known benefits of breastfeeding and the prior studies demonstrating no ill effects when the mother was receiving antiepileptic drugs, these findings support the breastfeeding of infants by mothers with epilepsy who are taking antiepileptic drug therapy.

Commentary

The benefits of breastfeeding are well established. Breastfed infants are at lower risk of respiratory infections, otitis media, gastroenteritis, and sudden infant death syndrome.¹ Children who were breastfed have lower rates of obesity, type 1 and type 2 diabetes mellitus, and acute leukemia.¹ They also may have higher intelligence quotient (IQ) scores than formula-fed infants.¹ For mothers, breastfeeding benefits include lower rates of postpartum depression and type 2 diabetes mellitus and long-term risk reduction of cardiovascular disease,

hypertension, breast, and ovarian cancer.¹ Economic considerations also favor breastfeeding over infant formula. Given these advantages, breastfeeding should be recommended unless there are clear and compelling contraindications. The American Academy of Pediatrics specifically recommends exclusive breastfeeding for the first 6 months.¹ In reality, 75% of women in the United States initiate breastfeeding, but at 6 months postpartum, only 43% are still doing any breastfeeding and only 13% exclusively breastfeeding.¹ Maternal education, socioeconomic status, and race influence the likelihood of



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breastfeeding, as do cultural and social mores.² Women with epilepsy face unique barriers and are even less likely to breastfeed.³⁻⁵ Their major concern is presumed to be that antiepileptic drug (AED) in breast milk could be harmful to their child. The 2009 American Academy of Neurology guideline on pregnancy management in women with epilepsy noted that the paucity of evidence around breastfeeding served as a source of anxiety for both women and health-care providers.⁶ One area of caution has been the potential for AED in breast milk to cause immediate dose-related adverse effects, such as sedation, irritability, liver dysfunction, or rash. Reports of such adverse events in exposed infants have been infrequent.⁷ Nevertheless, for those trying to calculate the likelihood of toxic exposure, the pharmacokinetic considerations are complex and published studies of concentration of AED in breast milk and/or infant serum have been limited in number and scope.⁷ A second potential concern is that extended exposure to AED via breastfeeding could adversely affect the developing brain, resulting in behavioral or intellectual impairment. However, previously published prospective data from the Neurodevelopmental Effects of Antiepileptic Drugs (NEAD) study of offspring of women with epilepsy taking monotherapy lamotrigine, carbamazepine, valproate, or phenytoin during pregnancy showed higher average IQ at 6 years of age those that were breastfed.⁸ Similarly, a large prospective cohort study from Norway found that babies exposed to AED during pregnancy who were continuously breastfed had better developmental outcomes at 18 months compared to those with limited or no breastfeeding.⁴ The authors of these studies concluded that women with epilepsy could be encouraged to breast feed, but it is not clear that rates of breastfeeding have improved over time.

Newly published data on AED levels in breastfeeding infants from the NEAD study should further increase support of breastfeeding by women with epilepsy. Birnbaum et al measured temporally matched maternal and breastfed infant serum AED levels in 164 pairs 5 to 20 weeks postpartum.⁹ A total of 82% of the women were on a monotherapy AED regimen. The most common AEDs were lamotrigine (n = 73) and levetiracetam (n = 63) and small numbers of mothers taking carbamazepine, oxcarbazepine, topiramate, valproate, and zonisamide. In 49% of the infants, the AED concentration was below the lower limit of detection. In single drug analysis, 71% of infants exposed to levetiracetam had undetectable serum levels, while 88.6% of infants exposed to lamotrigine had measurable levels. The median infant to mother AED concentration was 29% for lamotrigine, 44% for levetiracetam, 21% for valproate, and less than 20% for all of the other AED. A regression analysis of a subset of the pairs taking levetiracetam and lamotrigine found infant drug concentration was predicted by maternal serum concentration, but not by time between maternal drug dosing and feeding or by overall duration of breastfeeding. The authors noted that the levels of AED exposure to breastfed infants is very low compared to that which occurs during pregnancy and therefore would be unlikely to result in additional adverse neurodevelopmental impact.

As clinicians, we need to determine how to convert the growing body of evidence on the safety of breastfeeding for women taking AED into expanding the numbers who successfully breastfeed for the recommend 6 months or longer. Blanket recommendations to avoid breastfeeding out of an abundance of caution are no longer acceptable in the face of available data. Many other barriers still remain. First, many physicians lack the knowledge and training necessary to advise women on the benefits of breast feeding.¹ If this is true for family practitioners and pediatricians, then certainly most neurologists have an educational gap in this area. Providers can access free, up to date information about medications and breastfeeding through the National Library of Medicine LactMed database (<http://lactmed.nlm.nih.gov>). Second, there is abundant evidence that health-care providers are generally poor at accurately communicating with patients about medical risks and that this communication failure contributes to poor health-care decision-making.¹⁰ One area for improvement is how we as health-care providers frame the conversation around risk.¹⁰ Are you advising your patient that she could breastfeed, only to then excessively caution about the need to monitor for infant sedation or infant AED levels? A balanced discussion should include both the potential benefits as well as potential harms and avoid an unintended focus on atypically severe or uncommon outcomes. Finally, we should explore other barriers to breastfeeding in women with epilepsy outside of AED exposure. For example, women with epilepsy may fear that breastfeeding will increase sleep deprivation and potentially increase the risk of breakthrough seizures. In fact, parents who breastfed in the first 3 months of life have been shown to get both more sleep and less disrupted sleep compared to those feeding formula to their infants at night.¹¹ The best time to have these conversations with your own patients is prior to conception or prior to delivery, before the opportunity to start breastfeeding has been lost or breastfeeding interrupted. The good news: When health-care providers support breastfeeding and empower their patients with appropriate education, rates of breastfeeding improve.²

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