■ 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]

[1] Department of Clinical Neuroscience Karolinska Institutet, Stockholm, Sweden
[2] Fondazione I.R.C.C.S. Istituto Neurologico CARLO BESTA, Milan, Italy
[3] Division of Neuroscience and Experimental Psychology, School of Biological Sciences, Faculty of Biology, Medicine and Health, University of Manchester, Manchester Academic Health Science Centre, Manchester, UK; Royal Manchester Children's Hospital, Central Manchester University Hospitals NHS Foundation Trust, Manchester Academic Health Science Centre, Manchester, UK
[4] Epilepsy Center, ENyS, CONICET, Hosp. El Cruce, Hosp. R. Mejía, Univ Buenos Aires, Argentina
[5] Department of Neurology & Neurological Sciences, Stanford University, Palo Alto, CA, USA
[6] Department of Neurology, University of Pittsburgh School of Medicine, Pittsburgh, PA, USA
[7] Department of Neurology, Institute for Communicative and Cognitive neurosciences, Trivandrum, Kerala State, India

Received June 21, 2022; Accepted September 6, 2022

• **Correspondence:**
Torbjörn Tomson
Department of Clinical Neuroscience,
Karolinska Institutet,
Department of Neurology,
Karolinska University Hospital,
SE 171 76 Stockholm, Sweden
<torbjorn.tomson@regionstockholm.se>
<torbjorn.tomson@sll.se>

doi:10.1684/epd.2022.1492

ABSTRACT

We carried out a systematic review of published information on transfer of antiseizure medications (ASMs) into breastmilk, ASM serum concentrations in breastfed infants, and the wellbeing of infants breastfed by mothers on ASM treatment. Information was extracted from 85 relevant articles. No data on ASM levels in breastmilk or in breastfed infants was identified for cannabidiol, cenobamate, clobazam, eslicarbazepine-acetate, everolimus, felbamate, fenfluramine, retigabine, rufinamide, stiripentol, tiagabine, and vigabatrin. For ASMs, with available information on levels in breastfed infants, very low concentrations (in the order of 10% or less of maternal serum concentrations) were reported for carbamazepine, gabapentin, levetiracetam, oxcarbazepine, phenytoin, valproate, and clonazepam. Slightly higher levels (up to approximately 30% of maternal serum concentrations) have been observed with lamotrigine and topiramate, and in single case reports for brivaracetam, lacosamide, and perampanel. High infant levels (30% up to 100% of maternal serum concentrations) have been reported with ethosuximide, phenobarbital and zonisamide. Adverse infant effects during breastfeeding by mothers on ASMs appear to be rare regardless of the type of ASM, but systematic study is limited. Prospective long-term follow-up studies of developmental outcomes among children who have been breastfed by mothers taking ASMs are sparse and have mainly involved children whose mothers were taking carbamazepine, lamotrigine, levetiracetam, phenytoin or valproate as monotherapy while breastfeeding. 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.

Key words: epilepsy, breastfeeding, antiseizure medications, lactation

ILAE Curriculum: Competences and learning objectives

- 2. Counseling
- 2.6.3 Provide guidance regarding post-partum and child care (L2)
- 3. Pharmacological treatment
- 3.3.1 Define treatment strategies considering issues specific to pre-menopausal women (L2)
- 3.2 Demonstrate up-to-date knowledge about special aspects of pharmacological treatment

While breastfeeding is recommended for women in the general population, women with epilepsy appear to be less likely to breastfeed their infants compared to women in the general population [1]. This is unfortunate given the well-known benefits of breastfeeding to the mother as well as to the infant (http://www.who.int/topics/breastfeeding/en/) and is probably related to concerns among mothers and/or their health providers that exposure to antiseizure medications (ASMs) through breastmilk might have a negative impact on their infants [1].

A recent meticulous systematic review reported levels of nine ASMs in breast milk of lactating women with epilepsy and calculated theoretical doses and relative infant dose through breast milk for these ASMs [2]. This information, and the fact that ASM concentrations can be detected in breast milk as well as in infants breastfed by mothers taking ASM, is of great value for health care providers as well as for women with epilepsy.

In line with the educational mission of the Seminar series of this journal, we carried out a more pragmatic systematic review as a basis for this paper's ambition to provide clinicians as well as women with epilepsy practical recommendations regarding breastfeeding while on ASMs. Our review covered 16 ASMs including some of the most recently approved. Our focus was on ASM concentrations in breast milk and in plasma of breastfed infants. Unlike previous systematic reviews, we also reviewed information on reports of adverse effects during breastfeeding as well potential impact on more long-term development of the child.

Methods

Review questions

The questions of the systematic review were the following: (i) What are the concentrations of different ASMs in breastmilk of mothers taking ASM? (ii) What are the serum concentrations of different ASMs in infants who are breastfed by mothers taking ASMs? (iii) What is the infant/maternal serum concentration ratio of different ASMs? (iv) Are there immediate or long-term adverse effects on the child associated with breastfeeding while on ASMs?

Types of studies and participants

We selected case reports, case series and other clinical studies that included original data on ASM concentrations in breastmilk, ASM serum concentrations in breastfed infants, and/or clinical outcomes such as adverse events or developmental outcomes in infants breastfed by mothers on ASMs whether as treatment for epilepsy or other indications or as healthy subjects. Reviews and meta-analyses were included only for the purpose of identifying original publications.

Systematic review for evidence

- ***PubMed database search***

The search terms "breastfeeding", "breastmilk", and "lactation" were linked to the terms "antiepileptic drugs" and "epilepsy", as well as search terms of the individual ASMs. We restricted the search to human studies and to articles providing data in English.

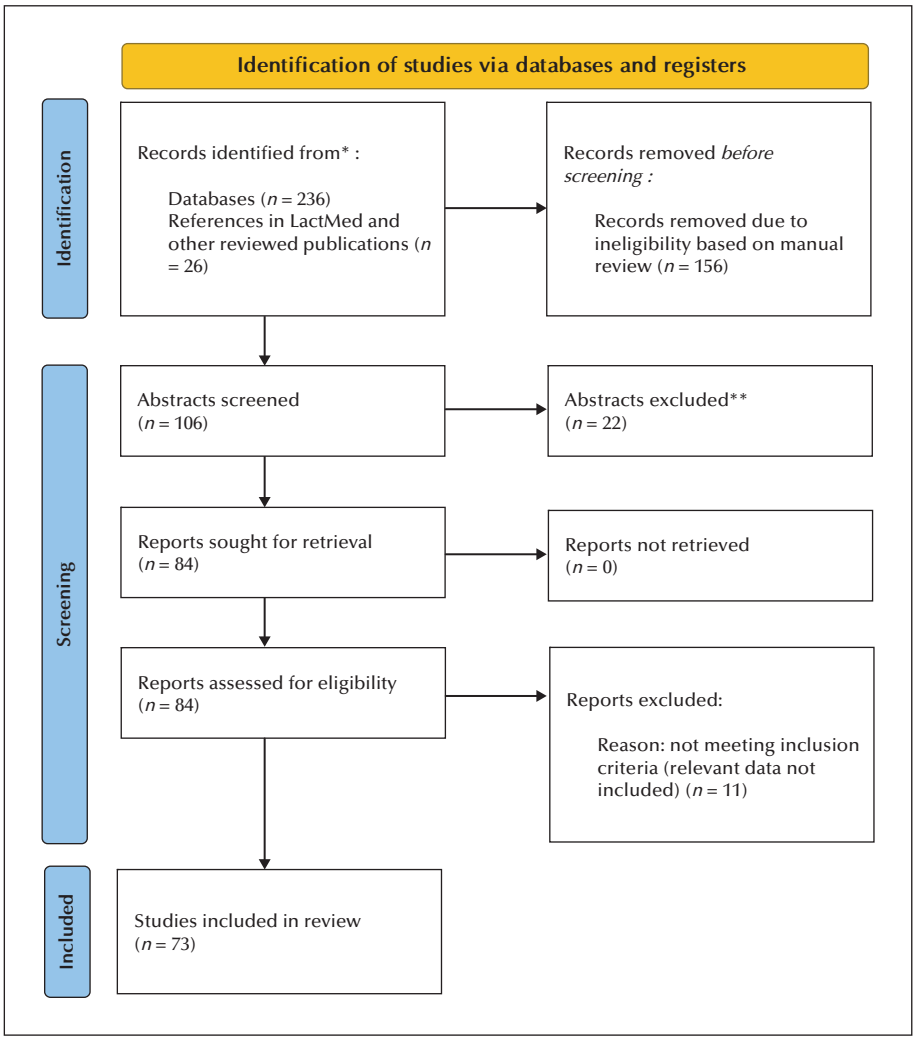
The panel searched the OVID MEDLINE databases up to November 2019 and then updated the search in July 2021 for relevant peer-reviewed articles that met our inclusion criteria.

We searched the "grey literature" in the form of LactMED and validated our results via the lists of references in LactMed. For the same purpose, we also cross-checked our search results against the articles included in the recently published systematic review by Shawahna and Zaid [2].

Two review panel members independently reviewed the article titles and abstracts for potential relevance. If there were any initial disagreements for final inclusion after the full-text review, consensus was achieved by discussion between the two panelists. Data extraction from the selected publications was made on a standardized Excel form.

Results

The MEDLINE search identified 235 publications of which 106 potentially relevant articles were selected for screening of abstracts. Of the reviewed abstracts, a total of 85 articles were included in the final review of the full-text articles. Of these, 72 articles were found to include information relevant to the review questions (*figure 1*).



■ **Figure 1.** Prisma flow diagram.

In the following, we summarize the retrieved information on different ASMs in alphabetical order. For each ASM, we report maternal milk/serum concentration ratios, infant/maternal serum concentration ratios, and information on clinical outcomes. Many of the cited publications did not report individual data. Hence, we have not been able to conduct a meta-analysis based on individual data. Instead, many of the ratios presented below are estimated averages of published aggregate ratios.

Brivaracetam

Information on concentrations in breastmilk or serum concentrations in breastfed infants is limited to two mother-child pairs [3]. In those, milk/maternal serum concentration ratios ranged from 0.61 to 0.75 on five days to five weeks postpartum. Serum concentrations in breastfed infants were below the level of quantification at five days to three weeks postpartum in one infant, whereas the infant/maternal serum concentration ratio was 0.18 to 0.20 in the other [3]. We have not identified any publications based on systematic follow-up of the wellbeing or later neurodevelopmental outcome of infants breastfed by mothers taking this medication.

Carbamazepine

Available information on maternal serum and milk concentrations as well as on serum concentrations in breastfed infants is extensive. Based on 72 published cases, the carbamazepine milk/maternal serum concentration ratios have ranged from 0.13 to

1.5, with the vast majority being below 0.5 [4–10]. Infant/maternal serum concentration ratios were reported in 66 mother-child pairs, and ranged from 0.04 to 0.7, with a reported average in individual studies in most cases below 0.1 [4, 5, 8, 10–14]. Adverse events with possible association with breast feeding have rarely been published. However, one case of hepatic dysfunction [8], one case of vomiting and regurgitation at 40 days of age [13], and one case of cholestatic hepatitis have been reported [12], but the role of carbamazepine exposure through breastfeeding for these events is unclear.

The prospective, observational, multi-center study, Neurodevelopmental Effects of Anti-epileptic Drugs (NEAD), assessed children of mothers on carbamazepine during pregnancy and lactation at 3 (n=58) and 6 (n=47) years of age [15, 16]. Almost half of the children were breastfed. There was no indication of poorer outcome among breastfed children compared with those who were not breastfed [16]. In fact, IQ was higher and verbal abilities were enhanced at six years old among previously breastfed children across all included ASMs (carbamazepine, lamotrigine, phenytoin, and valproate), and after correction for key covariates such as maternal IQ [16]. In a prospective, Norwegian cohort study comprising 223 children exposed to ASMs during pregnancy, continuous breastfeeding in children of women using ASMs was associated with less impaired development at ages six and 18 months compared with those with no breastfeeding [17]. Although these outcomes in relation to breastfeeding were not reported relative to individual ASMs, the most frequently used were lamotrigine, carbamazepine and valproate.

Clonazepam

In a single published case, the clonazepam milk/maternal serum concentration ratio was 0.35, and the infant/maternal serum concentration ratio 0.2 [18]. Serum concentrations of clonazepam were detectable in only 1/11 infants breastfed by mothers treated with clonazepam [19]. There are no reports of adverse effects or longer-term neurodevelopmental outcomes.

Ethosuximide

Based on 16 published cases, the ethosuximide milk/maternal serum concentration ratios have ranged from 0.8 to 1.0, with an average of 0.9 [20–24]. Infant/maternal serum concentration ratios were reported in 12 mother-child pairs, and ranged from 0.3 to 0.75 [20–22, 24]. There is one report of an infant with sedation, poor suckling and poor weight gain while breastfed by a mother taking ethosuximide in combination with primidone and valproate [21]. Otherwise, there are no reports of adverse events in relation to breastfeeding. No data was identified to inform on the longer-term health or neurodevelopmental outcomes of children breastfed while the mother was taking ethosuximide.

Gabapentin

Based on seven published cases, the gabapentin milk/maternal serum concentration ratios have ranged from 0.7 to 1.3, with an average of 1.0 [25, 26]. Infant/maternal serum concentration ratios were reported in seven mother-child pairs, with an average of 0.1 [26]. There were no reports of adverse events in relation to breastfeeding. No data was identified to inform on the longer-term health or neurodevelopmental outcomes of children breastfed on gabapentin.

Lacosamide

Lacosamide milk/maternal serum concentration ratio was 0.1, and infant/maternal serum concentration ratio 0.05 in one reported case [27]. In a second reported case, milk/maternal serum concentration ratio was 0.80-0.86 and the infant/maternal serum concentration ratio 0.27-0.28 [3]. The three breastfed infants were noted to have met normal developmental milestones at 18, 24, and 36 months, respectively [28].

Lamotrigine

Available information on maternal serum and milk concentrations as well as on serum concentrations in breastfed infants is extensive. Based on 92 published cases, the lamotrigine milk/maternal serum concentration ratios have ranged from 0.18 to 1.4, with averages in most studies in the order of 0.6 to 0.7 [29–34]. Infant/maternal serum concentration ratios were reported in 166 mother-child pairs, and ranged from 0.2 to 0.9, with a reported average in individual studies in most cases at around 0.3 [29–32, 34–39]. Adverse effects of breastfeeding have rarely been reported. However, there is one case report of episodes of apnea in a breastfed infant [38] and one case of anemia at 40 days after birth, which normalized after stopping breastfeeding [39].

The prospective NEAD study included 61 children of mothers on lamotrigine during pregnancy, 44% of whom were breastfed with testing at six years of age [16]. As above, the breastfed group for all ASMs demonstrated higher IQ and verbal abilities at six years compared to those who were not breastfed [16]. The prospective Norwegian cohort study included children exposed to lamotrigine with the finding that continuous breastfeeding in children of women using ASMs was associated with less impaired development

at ages six and 18 months compared with those with no breastfeeding or breastfeeding for less than six months [17]. A retrospective study found no difference in health outcomes over one month after birth in 20 infants of mothers breastfeeding while on treatment with lamotrigine compared to outcomes in 20 breastfed infants of healthy mothers [40]. Other studies including altogether 35 breastfed infants found no adverse events at different ages [31, 35, 37, 41].

Levetiracetam

Available information on maternal serum and milk concentrations as well as on serum concentrations in breastfed infants is extensive. Based on 82 published cases, the levetiracetam milk/maternal serum concentration ratios have ranged from 0.58 to 1.79, with averages in most studies in the order of 1.0 [27, 42–45]. Infant/maternal serum concentration ratios were reported in 121 mother-child pairs, and ranged from below the level of quantification in infant serum to a ratio of 0.71, with a reported average in individual studies in most cases at around 0.1 [14, 27, 42–45]. Adverse effects of breastfeeding have rarely been reported. However, there is a case report of hypotonia in one of eight breastfed infants [42]. Three cases of sedation were reported among 16 children breastfed by mothers taking levetiracetam, which resolved shortly after switching to partial breastfeeding [45]. A large prospective study, of which 84 breastfeeding women were on levetiracetam, did not show overall adverse effects at age two years across all ASMs [46].

Oxcarbazepine

In three reported cases, the breastmilk/maternal serum concentration ratio of the 10-hydroxy-oxcarbazepine metabolite was 0.5-0.8 [47–49]. Infant/maternal serum concentration ratios in a series of six mother-child pairs ranged from 0.002 to 0.009 (median: 0.003) [13]. In two case reports, serum concentration in the breastfed infant was below the level of quantification [47, 48]. Adverse effects have not been attributed to breastfeeding [50, 51]. No data was identified to inform on the longer-term health or neurodevelopmental outcomes of children breastfed on oxcarbazepine.

Perampanel

Information on concentrations in breastmilk or serum concentrations in breastfed infants is limited to one mother-child pair [3]. In this case, milk/maternal serum concentration ratios ranged from 0.10 to 0.17 at five days and five weeks postpartum, respectively. The infant/maternal serum concentration ratio was 0.16 to 0.27, five days and five weeks postpartum [3]. We have not identified any publications based on systematic follow-up of the wellbeing and longer-term neurodevelopment of infants breastfed by mothers taking this medication.

Phenobarbital

Based on data from 37 women, the milk/maternal serum concentration ratio ranged from 0.16 to 0.70 with most ratios in the order of 0.40 [5, 52–54]. Infant/maternal serum concentration ratios ranged in the largest series of 24 women from 0.8 to 0.9, five days after delivery [52]. In one case report, the ratio was 1.9. The high ratio was obtained two and a half hours after intake of phenobarbital, 19 days after birth. The breastfed infant showed signs of adverse effects in the form of lethargy [54]. No data was identified to inform on the longer-term health or neurodevelopmental outcomes of children breastfed on phenobarbital.

Phenytoin

Based on data from 15 women, the milk/maternal serum concentration ratio ranged from 0.13 to 0.18 [5, 55]. Serum concentrations of phenytoin were measurable in only two of six breastfed infants; the infant/maternal serum concentration ratio was 0.01 in these two pairs [55]. The prospective NEAD study included 77 children of mothers on phenytoin during pregnancy, 46% of whom were breastfed with testing at six years of age [16]. As above, the breastfed group for all ASMs demonstrated higher IQ and verbal abilities at six years compared to those who were not breastfed [16].

Pregabalin

Information on pregabalin is limited to data obtained from 10 healthy lactating women who were administered pregabalin for three days. The average milk/maternal serum concentration ratio was 0.76 [56]. There are no data on pregabalin concentration in breastfed infants or on the longer-term child health and neurodevelopmental outcomes.

Primidone

Based on 36 women, the milk/maternal primidone serum concentration ratio ranged from 0.48 to 1.1, with the majority being between 0.7 and 0.8 [5, 6, 57, 58]. The ratio of primidone-derived phenobarbital was 0.41 in four women [57]. Information on infant serum levels and outcomes in infants breastfed by mothers on treatment with primidone is very

limited. Two infants with prolonged feeding difficulties have been reported [59]. One of the mothers was on treatment with primidone in combination with phenytoin, phenobarbital and sulthiame. The highest serum concentrations of phenobarbital were measured at 12.7 mg/L at one month, but primidone levels were not reported. The second mother was on combination treatment with primidone and phenytoin, but infant drug levels were not reported. There are some additional case reports of sedation attributed to breast-feeding while on primidone treatment [60]. No data was identified to inform on the longer-term health or neurodevelopmental outcomes of children breastfed on primidone.

Topiramate

Based on data from 31 women, the milk/maternal serum concentration ratios of topiramate ranged from 0.62 to 2.43 with an average of 1.0 [61, 62]. Infant/maternal serum concentrations have been reported in 28 mother-child pairs and ranged from undetectable infant topiramate concentrations to a ratio of 0.7, with an average in the order of 0.25 [14, 61, 62]. There is one case report of diarrhea in an infant during breastfeeding from a mother on topiramate treatment [63], while no adverse effects were observed among six breastfed infants [61, 64]. No data was identified to inform on the longer-term health or neurodevelopmental outcomes of children exposed to topiramate through breastmilk.

Valproate

Based on data from 56 women, the milk/maternal serum concentration ratios of valproate ranged from 0.01 to 0.10, with most on average in the range of 0.025 [65–71]. Infant/maternal serum concentration ratios were reported in 34 mother-child pairs and ranged from infant levels below the level of quantification to 0.25, with the majority being in the range of 0.1 [6, 14, 67, 68, 70, 72]. The prospective NEAD study included 36 children of mothers on valproate during pregnancy, with only 31% of whom were breastfed, with testing at six years of age [16]. For the valproate group alone, the breastfed group demonstrated higher IQ and verbal abilities at six years compared to those who were not breastfed [16]. This is in addition to the finding for all ASMs combined. Additionally, valproate was one of the most frequently used ASMs in the Norwegian cohort study, which reported that continuous breastfeeding in children of women using ASMs was associated with less impaired development at ages six and 18 months compared with those with no breastfeeding or breastfeeding for less than six months [17].

Zonisamide

Based on three mothers taking zonisamide, the milk/maternal serum concentration ratio ranged from 0.70 to 1.03 [73, 74]. The infant/maternal serum concentration ratio was determined in five infant-mother pairs during breastfeeding while on zonisamide and was on average 0.44, ranging from 0.17 to 1.25 [14, 75]. No data was identified to inform on the longer-term health or neurodevelopmental outcomes of children breastfed on zonisamide.

Summary and general comments on reported data in relation to previous publications

The recently published systematic review by Shawahna and Zaid [2] is characterized by methodological rigor and a focus on studies enabling calculations of relative infant dose (RID) but also providing data on ASM levels in breastmilk and ratios between concentrations in breastmilk and maternal plasma. Their main findings were detectable concentrations in breastmilk of all investigated ASMs (carbamazepine, ethosuximide, gabapentin, lamotrigine, levetiracetam, phenobarbital, primidone, topiramate, and valproate) and comparatively high RIDs with ethosuximide and lamotrigine. They also recommended vigilance regarding signs of adverse effects of breastfeeding in infants exposed to ethosuximide, phenobarbital and primidone [2]. Our current review used a more pragmatic approach and a broader scope with an educational mission aiming at practical clinical recommendations. Thus, we accepted articles (including case reports) even if the reported data did not permit calculations of RIDs, as long as information was provided on ASM levels in breastmilk, ASM serum concentrations in breastfed infants, and/or clinical outcomes such as adverse events or developmental outcomes in infants breastfed by mothers on ASMs. Instead of calculating RIDs, we gave priority to reporting infant/maternal plasma concentration ratios. All 15 studies included in the previous systematic review [2] were included among the 73 publications in current review and we report on seven ASMs not included in that review.

Our approach has certain limitations in addition to the less strict search article selection criteria. These include no consideration of timing of sampling in relation to maternal intake of medication, or in relation to time after birth. Nor did we systematically consider maternal ASM dose or whether the ASM was administered as monotherapy or taken in combination with other ASMs. For the reasons explained in the

Methods section, our analysis was qualitative rather than quantitative. We believe, however, that our inclusive methodology provides complementary information to that of the previous more strict systematic review [2], and that this is useful for health care providers as well as for women taking ASMs.

Data on drug levels in breastmilk and infant serum

Data on breastmilk and infant ASM levels is extensive (>50 mother-child pairs) for carbamazepine, lamotrigine, levetiracetam and valproic acid.
For ethosuximide, phenobarbital, phenytoin, and topiramate, information has been published for more than 10 mother-child pairs, while for gabapentin, oxcarbazepine, pregabaline, primidone, and zonisamide, breastmilk and infant serum concentration data is limited to 2-10 mother-child pairs. The corresponding information is restricted to 1-2 case reports for brivaracetam, clonazepam, lacosamide, and perampanel.
No relevant breastfeeding data was identified for cannabidiol, cenobamate, clobazam, eslicarbazepine-acetate, everolimus, felbamate, fenfluramine, retigabine, rufinamide, stiripentol, tiagabine, and vigabatrin.

Serum concentrations in breastfed infants

Information on ASM serum concentrations in breastfed infants provides the best estimate of drug exposure and thus the potential for pharmacological (adverse) effects. It is a function of the passage of the ASM into breastmilk, the amount ingested and absorbed by the nursed infant, and the infant's capacity to eliminate the ingested drug.
Very low concentrations (in the order of 10% or less of maternal serum concentrations) have consistently been reported for carbamazepine, gabapentin, levetiracetam, oxcarbazepine, phenytoin, valproate, and clonazepam. Slightly higher levels (up to approximately 30% of maternal serum concentrations) have been seen with lamotrigine and topiramate, and in single case reports for brivaracetam, lacosamide, and perampanel. High infant levels (30% up to 100% of maternal serum concentrations) have been reported with ethosuximide, phenobarbital, and zonisamide. It should, however, be noted that there are individual cases in which infant serum levels may be considerably higher than the averages given above.

Adverse events during breastfeeding

Information on adverse events during breastfeeding is mainly based on case reports in which the causal relationship between exposure to ASMs through breastmilk and symptoms in the infant are difficult to determine. Additionally, even when such relationship appears plausible, a bias towards reporting adverse outcomes rather than uneventful breastfeeding cases makes it impossible to estimate the true frequency of such adverse effects of breastfeeding. Keeping these limitations in mind, the available reports indicate that adverse effects such as sedation and poor suckling may occasionally occur during breastfeeding with ethosuximide, phenobarbital, and primidone. Nevertheless, it seems very likely that, in the majority of cases, women also on these medications can breastfeed their infants without adverse effects.

Systematic long-term follow-up of neurodevelopment

Prospective long-term follow-up studies of developmental outcomes among children that have been breastfed by mothers taking ASMs are sparse [15–17, 46], 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 [15–17, 46]. In fact, among children of mothers treated with valproate, IQ at six years of age was higher in those who had been breastfed compared to those who had not [16]. Similar data on long-term developmental outcomes are lacking for other ASMs. It should also be noted that the prospective studies have been restricted to follow-up of children who have been exposed to ASMs already *in utero*, whereas there are no data on children exposed through breastfeeding *de novo* postpartum by mothers starting on ASMs after delivery.

Recommendations

Given the well-established benefits of breastfeeding with regards to both short- and long-term neonatal health in the general population and the data from studies showing no adverse neurodevelopmental effects in children of mothers taking ASMs, breastfeeding should in general be encouraged in women taking ASMs. However, women should be counselled regarding the scarcity of information on ASM levels in breastfed infants for a large number of ASMs, and the fact that studies have not investigated any impact on longer-term health or neurodevelopment for an even larger number ASMs. Counselling needs to be individualized including information on

the current knowledge regarding the woman's specific ASM treatment. The LactMed database is a useful resource for physicians to check for updated information on individual ASMs and other medications.

Precautions regarding breastfeeding with selected ASMs

In general, the exposure of the infant to ASMs through breastfeeding, and the corresponding infant drug levels, is considerably lower than exposure during pregnancy. However, as presented in this review, for some ASMs, notably ethosuximide and phenobarbital, serum concentrations in the breastfed infant can occasionally reach levels at which pharmacological effects may occur. This does not mean that women on these ASMs should be advised against breastfeeding, but they should be informed of potential adverse effects such as poor suckling and weight gain, drowsiness and sedation. If such effects are suspected, measuring ASM levels in the infant should be considered regardless of which ASM the mother is taking, and amounts may potentially be reduced by combining with feeding of formula.

Where resources are available, it is reasonable to consider measuring serum concentrations in the breastfed infant if the mother is treated with an ASM for which no data on infant drug levels are available. However, this should preferably be in the context of an established research project.

ASM exposure of the infant through breastfeeding can be minimized through simple measures:

1. If the ASM dose has been increased during pregnancy to maintain stable serum concentrations, it is important to consider dose reduction soon after delivery.
2. Taking the medication immediately after breastfeeding or immediately before the baby's longest sleep period will enable breastfeeding at the time of the lowest maternal ASM levels. This is relevant particularly if the mother is on a medication known to be associated with high exposure.
3. If infant serum levels are high and felt to be contributing to symptoms of sedation, then consider potentially reducing amounts by combining with some formula feeding.

General recommendations regarding safety measures during breastfeeding in mothers at risk of seizures

There are also infant and maternal safety issues related to breastfeeding beyond infant exposure to ASMs. Under unfortunate circumstances, maternal seizures could potentially harm the infant, and stress and sleep deprivation due to breastfeeding could trigger seizures. Some suggestions for mitigating such risks are given in *table 1*.

▼ **Table 1.** 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

Case 1

Maud is 27 years old. She is on treatment with lamotrigine for juvenile myoclonic epilepsy with a history of tonic-clonic seizures until her lamotrigine dose was increased to 200 mg/day three years ago. During pregnancy, her lamotrigine dose has been gradually increased to 450 mg/day in response to declining drug levels. She has remained seizure-free and delivered a healthy baby and is now considering breastfeeding.

Comment:

The passage of lamotrigine into breastmilk is rather extensive, and the newborn's capacity to eliminate lamotrigine is not fully developed. Hence, lamotrigine concentrations in newborns breastfed by mothers on high doses of lamotrigine can occasionally approach levels considered to be pharmacologically active in patients with epilepsy. However, reports of adverse effects are rare and long-term developmental data are reassuring, so there is no reason to advise against breastfeeding. Nevertheless, a reduction in lamotrigine dose should be considered soon after delivery to avoid exposure to unnecessarily high drug levels when maternal pharmacokinetics are normalized after pregnancy.

Case 2

Vera has a focal epilepsy with a previous history of focal unaware as well as focal to bilateral tonic-clonic seizures. She has been seizure-free for two years (including during pregnancy) on eslicarbazepine-acetate at 800 mg/day. She has delivered and is now considering breastfeeding.
Comment:
There is no information published on milk levels or levels in infants breastfed by mothers while on treatment with eslicarbazepine-acetate. However, the active moiety of eslicarbazepine acetate is the same as for oxcarbazepine for which available data suggest low levels in breastfed infants. It is therefore reasonable to support Vera's wish to breastfeed. Since eslicarbazepine-acetate is dosed once daily (in the evening), Vera is recommended to take her medication immediately after the last feeding of her baby, before night-time sleep.

Conclusion

This systematic review has revealed important gaps in knowledge regarding infant exposure to many ASMs through breastfeeding, and in particular, long-term neurodevelopmental outcomes in children who have been breastfed by mothers taking ASMs. However, the available information does not suggest an increase in risk of adverse events that outweigh the well-established benefits of breastfeeding in general. Hence, although further research is indicated, in particular, regarding the second and third-generation ASMs, breastfeeding should in general be encouraged also in women taking ASMs. Future research should prioritize assessment of infant exposure through breastfeeding by mothers under treatment with any of the >15 marketed ASMs for which no or very limited information is available. Systematic observational studies on long-term outcomes after breastfeeding with most ASMs are also urgently needed. ■

Key points

- No data on ASM levels in breastmilk or in breastfed infants was found for cannabidiol, cenobamate, clobazam, eslicarbazepine-acetate, everolimus, felbamate, fenfluramine, retigabine, rufinamide, stiripentol, tiagabine, and vigabatrin.
- Very low infant drug levels (in the order of 10% or less of maternal serum concentrations) are reported for carbamazepine, gabapentin, levetiracetam, oxcarbazepine, phenytoin, valproate, and clonazepam.
- Slightly higher levels (up to approximately 30% of maternal serum concentrations) have been observed with lamotrigine and topiramate, and in single case reports for brivaracetam, lacosamide, and perampanel.
- High infant levels (30% up to 100% of maternal serum concentrations) have been reported with ethosuximide, phenobarbital and zonisamide.
- Adverse infant effects during breastfeeding by mothers on ASMs appear to be rare regardless of the type of ASM, but systematic study is limited.
- Prospective long-term follow-up studies have not indicated poorer developmental outcomes among breastfed children whose mothers were taking carbamazepine, lamotrigine, levetiracetam, phenytoin or valproate.
- Long-term follow-up studies of development of children of mothers using other ASMs during breastfeeding are lacking.
- Despite incomplete information, breastfeeding should in general be encouraged in women taking ASMs, given the well-established benefits of breastfeeding.
- Taking the medication immediately after breastfeeding or immediately before the baby's longest sleep period will enable breastfeeding at the time of the lowest maternal ASM levels.
- Precautions to reduce risks should seizures occur during breastfeeding may include sitting in a low position on a soft surface.

Supplementary material.

Supplementary data and summary slides accompanying the manuscript are available at www.epilepticdisorders.com.

Acknowledgements and disclosures

This report was written by experts selected by the International League Against Epilepsy (ILAE) and was approved for publication by the ILAE. Opinions expressed by the authors, however, do not necessarily represent the policy or position of the ILAE.
TT reports grants from Eisai, GSK, UCB, Bial, Sanofi, Angelini Pharma, GW Pharma, Teva, advisory board honoraria from Angelini Pharma and GW Pharma, and speaker's honoraria from Eisai, Sanofi, Sun Pharma, and from UCB, outside the submitted work. KJM has received research support from the National Institutes of Health, Eisai, and Medtronic Inc; the Epilepsy Study Consortium pays his university for his research consultant time related to Eisai, GW Pharmaceuticals, NeuroPace, Novartis, Supernus, Upsher-Smith Laboratories, UCB Pharma, and Vivus Pharmaceuticals. In addition, KJM is Co-I and Director of Cognitive Core of the Human Epilepsy Project for the Epilepsy Study Consortium. KJM is also on the editorial boards for Neurology, Cognitive & Behavioral Neurology, Epilepsy & Behavior, and Epilepsy & Behavior Case Reports. PBP has received research support from the National Institutes of Health and royalties from UpToDate, Inc. DB received

grants from Eisai, GSK, UCB, Bial, Sanofi, Angelini Pharma, GW Pharma, Teva. SK has received research support from the National Science and Technology Ministry, National Health Ministry. SVT received research grants from the Government of India and Kerala State through his Institution. SVT had received honorarium for Wiley Publishing house and British Medical Journal (India). SVT is on the editorial board of Epilepsy Research journal. RB has no conflicts to declare.

References

1. Johnson EL, Burke AE, Wang A, Pennell PB. Unintended pregnancy, prenatal care, newborn outcomes, and breastfeeding in women with epilepsy. *Neurology* 2018; 91: E1031-9.

2. Shawahna R, Zaid L. Concentrations of antiseizure medications in breast milk of lactating women with epilepsy: a systematic review with qualitative synthesis. *Seizure: European Journal of Epilepsy* 2022; 98: 57-70.

3. Landmark CJ, Rektorli L, Burns ML, Revdal E, Johannessen SI, Brodtkorb E. Pharmacokinetic data on brivaracetam, lacosamide and perampanel during pregnancy and lactation. *Epileptic Disord* 2021; 23: 426-31.

4. Pynnönen S, Sillanpaa M. Carbamazepine and mother's milk. *Lancet* 1975; 306: 563.

5. Kaneko S, Sato T, Suzuki K. The levels of anticonvulsants in breast milk. *Br J Clin Pharmacol* 1979; 7: 624-7.

6. Niebyl JR, Blake DA, Freeman JM, Luff RD. Carbamazepine levels in pregnancy and lactation. *Obstet Gynecol* 1979; 53: 139-40.

7. Froescher W, Eichelbaum M, Niesen M, Dietrich K, Rausch P. Carbamazepine levels in breast milk. *Ther Drug Monit* 1984; 6: 266-71.

8. Merlob P, Mor N, Litwin A. Transient hepatic dysfunction in an infant of an epileptic mother treated with carbamazepine during pregnancy and breast feeding. *Ann Pharmacother* 1992; 26: 1563-5.

9. Shimoyama R, Ohkubo T, Sugawara K. Monitoring of carbamazepine and carbamazepine 10,11-epoxide in breast milk and plasma by high-performance liquid chromatography. *Ann Clin Biochem* 2000; 37(Pt2): 210-5.

10. Kacirova I, Grundmann M, Brozmanova H. Therapeutic monitoring of carbamazepine and its active metabolite during the 1st postnatal month: Influence of drug interactions. *Biomed Pharmacother* 2021; 137: 111412.

11. Wisner KL, Perel JM. Serum levels of valproate and carbamazepine in breastfeeding mother-infant pairs. *J Clin Psychopharmacol* 1998; 18: 167-9.

12. Frey B, Braegger CP, Ghelfi D. Neonatal cholestatic hepatitis from carbamazepine exposure during pregnancy and breast feeding. *Ann Pharmacother* 2002; 36: 644-7.

13. Antonucci R, Cuzzolin L, Manconi A, Cherchi C, Oggiano AM, Locci C, *et al*. Maternal carbamazepine therapy and unusual adverse effects in a breastfed infant. *Breastfeed Med* 2018; 13: 155-7.

14. Birnbaum AK, Meador KJ, Karanam A, Brown C, May RC, Gerhard EE, *et al*. Antiepileptic drug exposure in infants of breastfeeding mothers with epilepsy. *JAMA Neurol* 2020; 77: 441-50.

15. Meador KJ, Baker GA, Browning N, Clayton-Smith J, Combs-Cantrell DT, Cohen M, *et al*. Effects of breastfeeding in children of women taking antiepileptic drugs. *Neurology* 2010; 75: 1954-60.

16. Meador KJ, Baker GA, Browning N, Cohen MJ, Bromley RL, Clayton-Smith J, *et al*. Breastfeeding in children of women taking antiepileptic drugs: cognitive outcomes at age 6 years. *JAMA Pediatr* 2014; 168: 729-36.

17. Veiby G, Engelsen BA, Gilhus NE. Early child development and exposure to antiepileptic drugs prenatally and through breastfeeding: a prospective cohort study on children of women with epilepsy. *JAMA Neurol* 2013; 70: 1367-74.

18. Soderman P, Matheson I. Clonazepam in breast milk. *Eur J Pediatr* 1988; 147: 212-3.

19. Birnbaum CS, Cohen LS, Bailey JW, Grush LR, Robertson LM, Stowe ZN. Serum concentrations of antidepressants and benzodiazepines in nursing infants: a case series. *Pediatrics* 1999; 104: e11.

20. Rane A, Tunell R. Ethosuximide in human milk and in plasma of a mother and her nursed infant. *Br J Clin Pharmacol* 1981; 12: 855-8.

21. Kuhnz W, Koch S, Jacob S, Hartman A, Helge H, Nau H. Ethosuximide in epileptic women during pregnancy and lactation period. Placental transfer, serum concentration in nursed infants. *Br J Clin Pharmacol* 1984; 18: 671-7.

22. Soderman P, Rane A. Ethosuximide and nursing. *Acta Pharmacol Toxicol (Copenh)* 1986; 59(Suppl 5 Pt 2): Abstract513.

23. Meyer FP, Quednow B, Potrafki A, Walther H. The perinatal pharmacokinetics of anticonvulsant drugs. *Zentralbl Gynakol* 1988; 110: 1195-205.

24. Tomson T, Villen T. Ethosuximide enantiomers in pregnancy and lactation. *Ther Drug Monit* 1994; 16: 621-3.

25. Ohman I, Vitols S, Tomson T. Pharmacokinetics of gabapentin during delivery, in the neonatal period, and lactation: does a fetal accumulation occur during pregnancy? *Epilepsia* 2005; 46: 1621-4.

26. Kristensen JH, Ilett KF, Hackett LP, Kohan R. Gabapentin and breastfeeding: a case report. *J Hum Lact* 2006; 22: 426-8.

27. Ylikotila P, Ketola RA, Timonen S, Malm H, Ruuskanen JO. Early pregnancy cerebral venous thrombosis and status epilepticus treated with levetiracetam and lacosamide throughout pregnancy. *Reprod Toxicol* 2015; 57: 204-6.

28. Lattanzi S, Cagnetti C, Foschi N, Provinciali L, Silvestrini M. Lacosamide during pregnancy and breastfeeding. *Neurol Neurochir Pol* 2017; 51(3): 266-9.

29. Tomson T, Öhman I, Votils S. Lamotrigine in pregnancy and lactation: a case report. *Epilepsia* 1997; 38: 1039-41.

30. Öhman I, Vitols S, Tomson T. Lamotrigine in pregnancy: pharmacokinetics during delivery, in the neonate, and during lactation. *Epilepsia* 2000; 41: 709-13.

31. Newport DJ, Pennell PB, Calamaras MR, Ritchie JC, NewmanM, Knight B, *et al*. Lamotrigine in breast milk and nursing infants: determination of exposure. *Pediatrics* 2008; 122: e223-31.

32. Fotopoulou C, Kretz R, Bauer S, Schefold JC, Schmitz B, Dudenhausen JW, *et al*. Prospectively assessed changes in lamotrigine-concentration in women with epilepsy during pregnancy, lactation and the neonatal period. *Epilepsy Res* 2009; 85: 60-4.

33. Paulzen M, Stingl JC, Augustin M, Sussmannhausen H, Franz C, Grunder G, *et al*. Comprehensive measurements of intrauterine and postnatal exposure to lamotrigine. *Clin Pharmacokinet* 2019; 58: 535-43.

34. Kacirova I, Grundmann M, Brozmanova H. A short communication: lamotrigine levels in milk, mothers and breast-fed infants during the 1st postnatal month. *Ther Drug Monit* 2019; 41: 401-4.

35. Rambeck B, Kurlemann G, Stodieck SRG, May TW, Jurgens U. Concentrations of lamotrigine in a mother on lamotrigine treatment and her newborn child. *Eur J Clin Pharmacol* 1997; 51: 481-4.

36. Liporace J, Kao A, D'Abreu A. Concerns regarding lamotrigine and breast-feeding. *Epilepsy Behav* 2004; 5: 102-5.

37. Page-Sharp M, Kristensen JH, Hackett LP, Beran R, Rampono J, Hale TW, *et al*. Transfer of lamotrigine into breast milk. *Ann Pharmacother* 2006; 40: 1470-1.

38. Nordmo E, Aronsen L, Wasland K, Småbrekke L, Vorren S. Severe apnea in an infant exposed to lamotrigine in breast milk. *Ann Pharmacother* 2009; 43: 1893-7.

39. Bedussi F, Relli V, Faraoni L, Eleftheriou G, Giampreti A, Gallo M, *et al*. Normocytic normochromic anaemia and asymptomatic neutropenia in a 40-day-old infant breastfed by an epileptic mother treated with lamotrigine: Infant's adverse drug reaction. *J Paediatr Child Health* 2018; 54: 104-5.

40. Yashima K, Obara T, Matsuzaki F, Suzuki C, Saeki M, Koyama M, *et al*. Evaluation of the safety of taking lamotrigine during lactation period. *Breastfeed Med* 2021; 16: 432-8.

41. Prakash C, Hatters-Friedman S, Moller-Olsen C, North A. Maternal and fetal outcomes after lamotrigine use in pregnancy: a retrospective analysis from an urban maternal mental health centre in New Zealand. *Psychopharmacol Bull* 2016; 46: 63-9.

42. Johannessen SI, Helde G, Brodtkorb E. Levetiracetam concentrations in serum and in breast milk at birth and during lactation. *Epilepsia* 2005; 46: 775-7.

43. Tomson T, Palm R, Kallen K, Ben-Menachem E, Söderfeldt B, Danielsson B, *et al*. Pharmacokinetics of levetiracetam during pregnancy, delivery, in the neonatal period, and lactation. *Epilepsia* 2007; 48: 1111-6.

44. Kacirova I, Grundmann M, Brozmanova H. Umbilical cord, maternal milk, and breastfed infant levetiracetam concentrations monitoring at delivery and during early postpartum period. *Pharmaceutics* 2021; 13: 398.

45. Dinavitser N, Kohn E, Berlin M, Brandriss N, Bar-Chaim A, Keidar R, *et al*. Levetiracetam in lactation:how much is excreted into the human breast milk? *Br J Clin Pharmacol* 2022; 88(1): 199-205.

46. Meador KJ, Cohen MJ, Loring DW, May RC, Brown C, Robalino CP, *et al*, Maternal Outcomes and Neurodevelopmental Effects of Antiepileptic Drugs Investigator Group. . Two-year-old cognitive outcomes in children of pregnant women with epilepsy in the Maternal Outcomes and Neurodevelopmental Effects of Antiepileptic Drugs Study. *JAMA Neurol* 2021; 78(8): 927-36.

47. Bülau P, Paar WD, von Unruh GE. Pharmacokinetics of oxcarbazepine and 10-hydroxy-carbazepine in the newborn child of an oxcarbazepine-treated mother. *Eur J Clin Pharmacol* 1988; 34: 311-3.

48. Lutz UC, Wiatr G, Gaertner HJ, Bartels M. Oxcarbazepine treatment during breast-feeding: a case report. *J Clin Psychopharmacol* 2007; 27: 730-2.

49. Chen CY, Li X, Ma LY, Wu P-H, Zhou Y, Feng Q, *et al*. *In utero* oxcarbazepine exposure and neonatal abstinence syndrome: case report and brief review of the literature. *Pharmacotherapy* 2017; 37: e71-5.

50. Gentile S. Oxcarbazepine in pregnancy and lactation. *Clin Drug Investig* 2003; 23: 687.

51. Eisenschenk S. Treatment with oxcarbazepine during pregnancy. *Neurologist*. 2006; 12: 249-54.

52. Gomita Y, Furuno K, Araki Y, Yamatogi Y, Ohtahara S. Phenobarbital in sera of epileptic mothers and their infants. *Am J Ther* 1995; 2: 968-71.

53. Shimoyama R, Ohkubo T, Sugawara K. Characteristics of interaction between barbiturate derivatives and various sorbents on liquid chromatography and determination of phenobarbital in Japanese human breast milk. *J Liq Chromatogr Relat Technol* 2000; 23: 587-99.

54. Pote M, Kulkarni R, Agarwal M. Phenobarbital toxic levels in a nursing neonate. *Indian Pediatr* 2004; 41: 963-4.

55. Steen B, Rane A, Lonnerholm G, Falk O, Elwin CE, Sjöqvist F. Phenytoin excretion in human breast milk and plasma levels in nursed infants. *Ther Drug Monit* 1982; 4: 331-4.

56. Lockwood PA, Pauer L, Scavone JM, Allard M, Mendes da Costa L, Alebic-Kolbah T, *et al*. The pharmacokinetics of pregabalin in breast milk, plasma, and urine of healthy postpartum women. *J Hum Lact* 2016; 32: NP1-8.

57. Nau H, Rating D, Hauser I, Jäger-Roman E, Göpfert-Geyer I, Helge H. Placental transfer at birth and postnatal elimination of primidone and metabolites in neonates of epileptic mothers. In: Janz D, Bossi L, Dam M, *et al*, eds. *Epilepsy, pregnancy and the child*. New York: Raven Press, 1982.

58. Meyer FP, Quednow B, Potrafki A, Walther H. The perinatal pharmacokinetics of anticonvulsant drugs. *Zentralbl Gynakol* 1988; 110: 1195-205.

59. Granström ML, Bardy AH, Hiilesmaa VK. Prolonged feeding difficulties of infants of primidone mothers during neonatal period: preliminary results from the Helsinki study. In: Janz D, Dam M, Richens A, *et al*, eds. *Epilepsy, pregnancy and the child*. New York: Raven Press, 1982.

60. Kaneko S, Suzuki K, Sato T, Ogawa Y, Nomura Y. The problems of antiepileptic medication in the neonatal period: Is breastfeeding advisable? In: Janz D, Bossi L, Dam M, *et al*. *Epilepsy, pregnancy and the child*. New York: Raven Press, 1982.

61. Öhman I, Vitols S, Luef G, Söderfeldt B, Tomson T. Topiramate kinetics during delivery, lactation, and in the neonate: preliminary observations. *Epilepsia* 2002; 43: 1157-60.

62. Kacirova I, Grundmann M, Brozmanova H, Koristkowa K. Monitoring topiramate concentrations at delivery and during lactation. *Biomed Pharmacother* 2021; 138: 111446.

63. Westergren T, Hjelmeland K, Kristoffersen B, Johannessen SI, Kalikstad B. Probable topiramate-induced diarrhea in a 2-month-old breast-fed child - A case report. *Epilepsy Behav Case Rep* 2014; 2: 22-3.

64. Gentile S. Topiramate in pregnancy and breastfeeding. *Clin Drug Investig* 2009; 29: 139-41.

65. Dickinson RG, Harland RC, Lynn RK, Smith WB, Gerber N. Transmission of valproic acid (Depakene) across the placenta: half-life of the drug in mother and baby. *J Pediatr*. 1979; 94: 832-5.

66. Nau H, Rating D, Koch S, Häuser I, Helge H. Valproic acid and its metabolites: placental transfer, neonatal pharmacokinetics, transfer *via* mother's milk and clinical status in neonates of epileptic mothers. *J Pharmacol Exp Ther* 1981; 219: 768-77.

67. Bardy AH, Granstrom ML, Hiilesmaa VK. Valproic acid and breast-feeding. In: Janz D, Bossi L, Dam M, *et al*, eds. *Epilepsy, pregnancy and the child*. New York: Raven Press 1982.

68. von Unruh GE, Froescher W, Hoffmann F, Niesen M. Valproic acid in breast milk: how much is really there? *Ther Drug Monit* 1984; 6: 272-6.

69. Nau H, Helge H, Luck W. Valproic acid in the perinatal period: decreased maternal serum protein binding results in fetal accumulation and neonatal displacement of the drug and metabolites. *J Pediatr* 1984; 104: 627-34.

70. Philbert A, Pedersen B, Dam M. Concentration of valproate during pregnancy, in the newborn and in breast milk. *Acta Neurol Scand* 1985; 72: 460-3.

71. Kacirova I, Grundmann M, Brozmanova H. Valproic acid concentrations in nursing mothers, mature milk, and breastfed infants in monotherapy and combination therapy. *Epilepsy Behav* 2019; 95: 112-6.

72. Wisner KL, Perel JM. Serum levels of valproate and carbamazepine in breastfeeding mother-infant pairs. *J Clin Psychopharmacol* 1998; 18: 167-9.

73. Shimoyama R, Ohkubo T, Sugawara K. Monitoring of zonisamide in human breast milk and maternal plasma by solid-phase extraction HPLC method. *Biomed Chromatogr* 1999; 13: 370-2.

74. Ando H, Matsubara S, Oi A, Usui R, Suzuki M, Fujimura A. Two nursing mothers treated with zonisamide: should breast-feeding be avoided? *J Obstet Gynaecol Res* 2014; 40: 275-8.

75. Ohman I, Tomson T. Pharmacokinetics of zonisamide in neonatal period and during lactation. *Basic Clin Pharmacol Toxicol* 2011; 109(Suppl 1): 73-AbstractP55.

TEST YOURSELF

(1) For which of the following newer generation ASMs have some data been published on drug levels in the breastfed infant?

A. Lacosamide
B. Cenobamate
C. Fenfluramine
D. Cannabidiol

(2) For which of the following ASMs have infant/mother serum concentrations not been reported to exceed 30%?

A. Zonisamide
B. Carbamazepine
C. Phenobarbital
D. Ethosuximide

(3) Reassuring data have been reported on IQ, at age six, of previously breastfed children of mothers taking which of the following ASMs during lactation?

A. Carbamazepine
B. Lamotrigine
C. Valproate
D. Phenytoin
E. All of the above

(4) Which of the following statements regarding breastfeeding by mothers on ASMs is correct?

A. The benefits of breastfeeding generally outweigh the risks associated with ASM exposure
B. Adverse effects of breastfeeding have rarely been reported
C. ASM exposure to the infant can be reduced if the mother takes her medication immediately after breastfeeding
D. All of the above

(5) Which of the following statements is correct?

A. Infant exposure to ASMs through breastfeeding is generally lower than that to the fetus in mothers taking ASMs during pregnancy and lactation
B. Special precautions are rarely justified to reduce risks to the infant should the mother have a seizure while breastfeeding
C. Women with epilepsy are as likely to breastfeed their infants as mothers in general

Note: Reading the manuscript provides an answer to all questions. Correct answers may be accessed on the website, www.epilepticdisorders.com.