A position paper on breastfeeding by women with epilepsy – working group report

Joanna Jędrzejczak¹, Maria Wilińska², Ewa Kamińska³, Ryszard Lauterbach⁴, Ewa Helwich⁵, Teresa Jackowska⁶, Ewa Nagańska⁷, Natalia Jacyna⁸, Beata Majkowska-Zwolińska⁹,¹⁰

¹Department of Neurology and Epileptology, Centre of Postgraduate Medical Education, Warsaw
²Department of Neonatology, Centre of Postgraduate Medical Education, Warsaw
³Department of Pharmacology, Institute of Mother and Child, Warsaw
⁴Neonatal Department Jagiellonian University Medical College, Kraków
⁵Neonatology Department, Institute of Mother and Child, Warsaw
⁶Department of Pediatrics, Centre of Postgraduate Medical Education, Warsaw
⁷Department of Neurology and Epileptology, prof. W. Orłowski Independent Public Clinical Hospital, Centre of Postgraduate Medical Education, Warsaw
⁸Department of Neonatology, prof. W. Orłowski Independent Public Clinical Hospital, Warsaw
⁹Epilepsy Diagnostic and Therapeutic Center, Foundation of Epileptology, Warsaw
¹⁰Lazarski University, Warsaw

SUMMARY

Introduction. On the initiative of the General Board of the Polish Society of Epileptology a Working Group was established to develop an expert position on breastfeeding by women with epilepsy in Poland.
Aim. To facilitate a unified and rational approach to breastfeeding for women with epilepsy.
Methods. An ad hoc system was developed to classify available published evidence and expert opinions, which was used to evaluate recommendations on various aspects related to counselling, risk and safety of breastfeeding.
Discussion and conclusions. This position paper provides an educational, practical and organizational aspects. It will allow for the introduction of a uniform protocol of conduct in Poland, which in turn will improve the safety of the mother and her child.
Key words: women with epilepsy • breastfeeding recommendations • AEDs pharmacokinetics • safety
INTRODUCTION
On the initiative of the General Board of the Polish Society of Epileptology, in cooperation with the Polish Neonatal Society, the National Consultant for Neonatology and the National Consultant for Paediatrics, a Working Group was established to develop an expert position on breastfeeding by women with epilepsy in Poland. These recommendations are needed in medical care system so as to help guide management for women with epilepsy in Poland.

The breastfeeding of newborns of mothers with epilepsy is one of the interdisciplinary issues that should be familiar to all specialist involved in the care of a mother and her child during this particularly happy period of their lives. The conduct of neurologists, obstetricians-gynaecologists, neonatologists and paediatricians should be in accordance with a well-understood routine, but it should be a “live” document and routine so that new information so that it can be modified and supplemented accordingly. This position paper provides an educational, practical and organizational aspects. It will allow for the introduction of a uniform protocol of conduct in Poland, which in turn will improve the safety of the mother and her child.

The safety of breastfeeding while taking antiepileptic drugs (AEDs) is a serious concern for both women with epilepsy and their neurologists, obstetricians, neonatologists and paediatricians. Confirmation of these dilemmas is contained in the report “Practice parameter update” of the American Academy of Neurology statement regarding breastfeeding of newborns of mothers with epilepsy, which despite the passage of time is still valid: “The clinical consequences for the newborn of ingesting AEDs via breast milk remain underexplored and will continue to produce anxiety in women with epilepsy bearing children and all who care for these clinical dyads” (Harden et al., 2009).

Due to the limited data on the safety of using AEDs during lactation, mothers with epilepsy often receive conflicting advice and recommendations about breastfeeding from their physicians. There is a misconception that medicines taken by the mother always accumulate in the milk. There are also erroneous opinions that the baby’s exposure to possible harmful effects of the drug is higher during breastfeeding than during pregnancy. Because of the risk of the newborn being exposed to the possible adverse effects of AEDs via breast milk, epilepsy is still considered as a contraindication to breastfeeding regardless of the type of medicine the mother is taking.

A review of the literature indicates a significant degree of divergence of recommendations, which is the result of a limited number of studies and somewhat arbitrary findings.

In addition, some mothers are afraid that seizures may affect the safety of the breastfed child, and sleep disturbance may increase the risk of seizures.

In recent years, there has been much new information on this subject, encouraging epileptic mothers to breastfeed their newborns (Veiby et al., 2015; Birnbaum et al., 2019). “Most epileptologists agree that the known benefits of breastfeeding outweigh primarily the theoretical risk of exposure to most AEDs,” said Prof. Elizabeth E. Gerard, the lead author of the Maternal Outcomes and Neurodevelopmental Effects of Antiepileptic Drugs (MONEAD) project, during the annual American Epilepsy Society Conference in 2019 (Gerard and Pennell, 2019).

AIMS AND METHODS
To facilitate a unified and rational approach to breastfeeding for women with epilepsy, a group of experts in epileptology, neonatology and paediatrics held a joint meeting to reach a consensus on optimal treatment of women with epilepsy. An ad hoc system was developed to classify available published evidence and expert opinions, which was used to evaluate recommendations on various aspects related to counselling, risk and safety of breastfeeding. This position paper summarizes the available evidence for the inter-relationship between epilepsy, breastfeeding and offspring. It contains recommendations for physicians with regards to information and advice related to breastfeeding that should be provided to women with epilepsy.

In our opinion, it is advisable to develop a common therapeutic protocol for neurologists, neonatologists and paediatricians. We would like the prepared protocol to be present in all neurological, neonatological and paediatric wards.

Expert opinions presented in this article are based on a review of current literature on breastfeeding strategies by women with epilepsy, as well as on clinical experience and good medical practice of specialists with extensive experience in this subject. Each panellist presented their comments and the version presented here was created after a reaching consensus.
DISCUSSION

The benefits of breastfeeding for the baby and the mother

It is truism to state that breastfeeding ensures optimal and comprehensive nutrition for newborns. The benefits of breastfeeding for both the infant and the mother have been widely recognized by the World Health Organization (WHO, 2001). Both WHO (2001) and the American Academy of Pediatrics (2012) recommended exclusive natural feeding for the first six months of a child’s life, followed by continuing breastfeeding with the gradual introduction of local complementary foods, considering them the optimal model for feeding a young child.

According to general population data, approximately 97% of hospitalised women breastfeed after delivery. Furthermore, feeding with an infant formula in the neonatal ward itself occurs in more than half of newborns. After the child is discharged home, the share of mother's food in the infant's nutrition decreases dramatically. In the 6th month of life, only approximately 38% of Polish children are breastfed, and only 4% of them are exclusively breastfed (Królak-Olejnik et al., 2017). The basis for including complementary feeding is the insecurity of mothers about food sufficiency. However, some of the reasons for weaning were due to physicians' instructions consequent to concerns whereby undesirable medications were being taken by nursing mothers (Królak-Olejnik et al., 2017; Wilińska et al., 2005).

Effective release and maintenance of lactation at an optimal level in a woman after delivery depends largely on the attitude, knowledge and practical skills of medical staff, hospital practices in maternity wards and the awareness that many mothers need support and practical help in breastfeeding. One of the most important success factors in breastfeeding is the decision the woman makes on this topic while she is pregnant. The participation of physicians during pregnancy plays important role in this decision. In this regard, reliable knowledge about the actual feeding possibilities when taking medications is particularly needed, as well as the careful selection of optimal pharmacotherapy based on knowledge about the pharmacological properties of drugs.

Breast milk

Milk in the mammary gland is produced in the milk epithelium of the lactiferous alveoli. In the first days after delivery, the milk epithelial cells form the so-called loose intercellular bridges. These spaces allow the transport of high molecular weight substances, such as IgA, lysozyme, lactoferrin and other chemical substances directly from the mother's blood to milk. It is also possible to transfer large molecule drugs, but due to the small volume of food consumed by the child at this time, the total dose of the drug for the child is not large. After 3–4 days after delivery, these free spaces are tightly closed due to the natural decrease in progesterone concentration and under the influence of endogenous glucocorticosteroids.

This phenomenon determines the high concentration of protein in the colostrum. Colostrum is a thick, yellow discharge present in the mammary glands of a woman in the first days after childbirth. It is formed during pregnancy, approximately since the 20th week. Compared to mature milk, it is characterized by i.a. a higher content of protein, secretory immunoglobulin A (sIgA), Na, Cl, lactoferrin, cytokines, chemokines, trophic factors and oligosaccharides. It has a higher antioxidant potential than milk at any subsequent stage of lactation (Ma et al., 2017; Wilińska et al., 2015).

The composition of breast milk is dynamic, and changes during different times of the day (more fats at night, more carbohydrates during the day) and during one suckling act (more lactose in phase I milk, more fat in phase II milk). The composition of milk also changes at particular stages of lactation (Ballard and Morrow, 2013).

During the first 2–4 weeks after delivery, the level of milk secretion is adjusted to the needs of the baby (stabilization of lactation). Transitional milk becomes mature milk. It is bluish, watery and clearer. Its volume increases due to water; its caloric content, lactose and fat content also increases, and the protein concentration decreases. The task of the suckling child is to maintain food secretion at an appropriate level throughout breastfeeding. This balance between food production and the needs of the baby appears around the 6th week after delivery.

Mature milk differs in composition from the colostrum and the transitional milk. Table 1 presents a comparison of the concentration of selected milk components at various stages of lactation.

Many milk ingredients determine the specific immunity-strengthening and anti-inflammatory properties – among others: sIgA, lactoferrin, lysozyme, oligosaccharides, growth factors and viable breast milk cells.
The benefits of breastfeeding for the mother

Attaching the baby to the breast and releasing lactation accelerates the involution of the uterus after delivery, reduces vaginal bleeding and reduces the risk of postpartum anaemia. Lactation has a beneficial effect on a woman’s metabolism, mainly in the field of glucose and lipids, significantly reducing the risk of type II diabetes and cardiovascular diseases (Chowdhury et al., 2015).

Breastfeeding reduces the risk of pre-menopausal breast and ovarian cancer (Collaborative Group on Hormonal Factors in Breast Cancer, 2002).

Breastfeeding reduces the risk of pre-menopausal breast and ovarian cancer (Collaborative Group on Hormonal Factors in Breast Cancer, 2002).

Breastfeeding strengthens the bond between the mother and the child, which is associated with a cyclic release of endogenous oxytocin in the mother (Galbally et al., 2011).

The benefits of breastfeeding for the child

Breastfeeding improves the survival rate of newborns and children up to 5 years old (Sankar et al., 2015). In particular, breastfeeding reduces the number of deaths due to diarrhoea, especially in areas of the world with

Exclusive breastfeeding delays the resumption of normal ovulation and fertility, possibly due to elevated prolactin levels. This method is a highly effective global contraceptive program with 98.5–100% effectiveness (Peterson et al., 2000).

Breastfeeding strengthens the bond between the mother and the child, which is associated with a cyclic release of endogenous oxytocin in the mother (Galbally et al., 2011).

The benefits of breastfeeding for the child

Breastfeeding improves the survival rate of newborns and children up to 5 years old (Sankar et al., 2015). In particular, breastfeeding reduces the number of deaths due to diarrhoea, especially in areas of the world with

Table 1. Differences in composition of transitional and mature breast milk

| Component                | Transitional milk | Mature milk |
|--------------------------|-------------------|-------------|
| Lactose [g/L]            | 20–30             | 67          |
| Glucose [g/L]            | 0.2–1.0           | 0.2–0.3     |
| Oligosaccharides [g/L]   | 22–24             | 12–14       |
| Total proteins [g/L]     | 16                | 9           |
| Lactoferrin [g/L]        | 3.53              | 1.94        |
| slgA [g/L]               | 2.0               | 2.0         |
| IgM [g/L]                | 0.12              | 0.2         |
| IgG [g/L]                | 0.34              | 0.05        |
| Total lipids [%]         | 2                 | 3.5         |

Water soluble vitamins

| Vitamin C [mg/L]         | 100               |
| Thiamine [mcg/L]         | 200               |
| Riboflavin [mcg/L]       | 400–600           |
| Niacin [mg/L]            | 20                |
| Folate [mcg/L]           | 80–140            |
| Vitamin B12 [mcg/L]      | 0.5               |
| Pantothenic acid [mg/L]  | 2.0–2.5           |
| Biotin                   | 5.0–9.0           |

Fat soluble vitamins

| Retinol [mg/L]           | 2                 |
| Carotenoids [mg/L]       | 2                 |
| Vitamin K [mcg/L]        | 2–5               |
| Vitamin D [mcg/L]        | 0.33              |
| Vitamin E [mg/L]         | 8–12              |

Minerals

| Calcium [mg/L]           | 250               |
| Phosphorus [mg/L]        | 120–160           |
| Sodium [mg/L]            | 300–400           |
| Potassium [mg/L]         | 600–700           |
| Chloride [m/L]           | 600–800           |
| Iron [mg/L]              | 0.5–1.0           |
| Zinc [mg/L]              | 8–12              |
| Copper [mg/L]            | 0.5–0.8           |
| Manganese [mg/L]         | 5–6               |
| Selenium [mcg/L]         | 40                |

Table 1. Differences in composition of transitional and mature breast milk

| Component | Transitional milk | Mature milk |
|-----------|-------------------|-------------|
| Lactose [g/L] | 20–30             | 67          |
| Glucose [g/L]  | 0.2–1.0           | 0.2–0.3     |
| Oligosaccharides [g/L] | 22–24             | 12–14       |
| Total proteins [g/L] | 16                | 9           |
| Lactoferrin [g/L] | 3.53              | 1.94        |
| slgA [g/L]    | 2.0               | 2.0         |
| IgM [g/L]     | 0.12              | 0.2         |
| IgG [g/L]     | 0.34              | 0.05        |
| Total lipids [%] | 2                 | 3.5         |

Water soluble vitamins

| Vitamin C [mg/L] | 100 |
| Thiamine [mcg/L] | 200 |
| Riboflavin [mcg/L] | 400–600 |
| Niacin [mg/L]    | 20  |
| Folate [mcg/L]   | 80–140 |
| Vitamin B12 [mcg/L] | 0.5 |
| Pantothenic acid [mg/L] | 2.0–2.5 |
| Biotin           | 5.0–9.0 |

Fat soluble vitamins

| Retinol [mg/L] | 2 | 0.3–0.6 |
| Carotenoids [mg/L] | 2 | 0.2–0.6 |
| Vitamin K [mcg/L] | 2–5 | 2–3 |
| Vitamin D [mcg/L] | 0.33 |
| Vitamin E [mg/L] | 8–12 | 3–8 |

Minerals

| Calcium [mg/L] | 250 | 200–250 |
| Phosphorus [mg/L] | 120–160 | 129–140 |
| Sodium [mg/L]   | 300–400 | 120–250 |
| Potassium [mg/L] | 600–700 | 400–550 |
| Chloride [m/L]  | 600–800 | 400–450 |
| Iron [mg/L]     | 0.5–1.0 | 0.3–0.9 |
| Zinc [mg/L]     | 8–12   | 1–3     |
| Copper [mg/L]   | 0.5–0.8 | 0.2–0.4 |
| Manganese [mcg/L] | 5–6 | 3 |
| Selenium [mcg/L] | 40 | 7–33 |
low economic status (Lamberti et al., 2011; Hauck et al., 2011).

Naturally fed newborns less often suffer from infectious diseases, demonstrating the so-called dose-dependent effect. Breastfeeding reduces the incidence of respiratory infections caused by the respiratory syncytial virus (RSV), pneumonia, regardless of its aetiology, otitis, and gastrointestinal diseases. This beneficial effect of breastfeeding persists until the child’s school period (Shi et al., 2015; Li et al., 2014).

Data from epidemiological studies indicate a lower incidence of many chronic diseases in breastfed infants. These diseases include type I diabetes, chronic intestinal diseases, childhood leukaemia and dental caries (Patelarou et al., 2012; Amitay and Keinan-Boker, 2015; Tham et al., 2015).

Natural feeding reduces the risk of allergic diseases (Lodge et al., 2015).

Breastfeeding reduces the risk of obesity in school-age children, i.a. by affecting the appetite-regulating hormones such as ghrelin, leptin, and adiponectin. These substances reduce fat deposits and improve energy utilization (Horta et al., 2015; Kon et al., 2014).

Breastfeeding is associated with a higher intelligence quotient in children. It improves neurodevelopmental indicators in premature newborns (Vohr et al., 2006).

In the premature baby population, similarly to the full-term babies, natural feeding improves survival. It statistically significantly reduces the incidence of necrotising enterocolitis (NEC) and nosocomial infections.

The incidence and severity of retinopathy of prematurity and bronchopulmonary dysplasia, the indicators of the quality of care for premature newborns, are significantly lower. The degree of this reduction depends on the length and exclusiveness of breastfeeding (Zhou et al., 2015; Sullivan et al., 2010).

**Pharmacokinetics of antiepileptic drugs and bioavailability of the drug for the child**

When encouraging women with epilepsy to breastfeed, caution should always be exercised and the possible adverse effects on the newborn, which could be due to the direct effects of AEDs that pass into the breast milk, should be assessed.

Data on the use of AEDs by nursing women mostly come from small case series and case reports, and additionally are dispersed in various databases. Davanzo et al. (2013) collected available data for each AED from databases such as Hale’s “Drugs and Breast Milk” (2012), LactMed (2013), National Library of Medicine and MedLine Search (until 2013). When developing pharmacokinetic data, we also used the latest literature, including Hale’s Medications and Mothers’ Milk (2019), Drugs and Lactation Database (2018–2020 update), as well as the SmPCs of individual medicinal products.

Based on the available data, we present basic information on the pharmacokinetics of AEDs which will allow a more complete view of the safety of their use by mothers with epilepsy breastfeeding their children.

**Pharmacokinetic parameters of antiepileptic drugs**

- The concentration of the drug in the mother’s blood – passive transport is the basic mechanism of drug permeation from the mother’s blood to her milk and through the placental barrier to the foetus. The concentration of the drug in the mother’s blood is the most important factor determining the degree of excretion in milk. There is continuous bi-directional drug transport aiming to equalize its concentration in both of these compartments.
- The concentration of the drug in the mother’s blood is modified by its distribution to various tissues and organs of the body. A large volume of distribution is associated with a rapidly decreasing concentration of the drug in the mother’s blood and thus in her milk.
- Lipid solubility – lipophilicity is a factor that facilitates the transport of the drug through phospholipid barriers and into the breast milk fat.
- Binding to maternal plasma proteins – transport of the drug to milk depends on the degree of its binding to maternal plasma proteins. Only the free drug fraction diffuses through biological barriers. The fraction highly bound to the plasma proteins remains in circulation without reaching significant concentrations in tissues and other fluids.
- Molecular weight (MW) – the size of the molecule is a strong determinant of both the drug transfer from mother’s plasma to milk and the absorption from the child’s digestive tract into its circulation. Low molecular weight drugs (<200 g/mol) easily permeate from the blood vessel endothelium and the lactiferous alveoli epithelium into breast milk. Drugs with a large molecule hardly cross the lipid barrier of the cell membrane, which is inherently associated with blocking the drug’s access to breast milk.
- The degree of ionization – only the nonionized form of the drug overcomes biological barriers. Milk...
is more acidic (pH approx. 7.2) than the mother’s blood (pH approx. 7.4). This difference promotes the easy penetration of alkaline drugs into milk. These preparations fall into the so-called ionic trap, accumulating in the breast milk. Conversely, organic acids remain ionized and tend to persist in the mother’s circulation.

- Half-life $t_{0.5}$ – the shorter the better. Preferred are drugs with a $t_{0.5}$ of 1–3 hours.
- $t_{\text{max}}$ – time from taking the drug to reaching the maximum concentration ($C_{\text{max}}$) in the mother’s blood. During the period of the highest concentration of the drug, the mother should not breastfeed.
- pKa – pH value at which there is a balance between the ionized form and the non-ionized form of the drug. In general, drugs diffuse freely between the mother’s milk and blood, remaining in balance of concentration. It is a protective mechanism preventing the accumulation of the drug in the lactiferous alveolus. Low pKa means the possibility of a return from the milk to the mother’s plasma according to the current concentration difference. A drug that has a pKa higher than 7.2 does not undergo typical diffusion back into the mother’s plasma, i.e. it is sequestered in the milk.

**Bioavailability**

The bioavailability of a drug for a child is determined by the following parameters:

- RID (Relative Infant Dose). The drug dose the child receives during breastfeeding is the product of the concentration of the drug in mother’s milk ($C_m$) and the volume of milk consumed by the child per day ($V_m$). Drugs with RID <10% are generally safe.
- M/P ratio – the ratio of milk concentration to the maternal plasma concentration. The safe M/P ratio is <1. M/P ratio >1 indicates high penetration into milk. When assessing its size, it should be remembered that even when its value exceeds 1, the total daily dose taken by an infant with breast milk is almost always significantly lower than the therapeutic dose in infants (Verstegen et al., 2015). On the other hand, if the concentration in the plasma is low, the total dose of the drug taken by the child is small, although the ratio may be high.
- PPB ratio (maternal protein binding) – means the degree of binding of the drug to maternal plasma proteins. High binding to maternal plasma albumins results in poor drug excretion into breast milk.
- The volume of distribution ($V_d$) is the space of a woman’s body other than blood into which the drug permeates. The low volume of distribution indicates a very short drug presence in the body. In combination with a very short half-life, this means very fast elimination of the drug from the body.
- Oral bioavailability, i.e. absorption from the gastrointestinal tract, where the term “poor” means low absorption of the drug from milk through the child’s digestive tract into their blood.

**Conclusion**

Drug transfer to breast milk increases if the drug:

- reaches high maternal serum levels
- has a low molecular weight
- is poorly bound to plasma proteins (high drug free fraction)
- is lipophilic and easily crosses phospholipid membranes.

Pharmacokinetic parameters associated with high bioavailability of the drug for the child include:

- high relative dose of the drug (RID)
- long biological half-life
- high M/P ratio (not always)
- high distribution volume
- extended $t_{\text{max}}$
- high pKa

Pharmacokinetic and physicochemical properties of individual antiepileptic drugs (according to Hale, 2019; Davanzo et al., 2013; Veiby et al., 2015) as well as lactation risk assessment (according to Hale, 2019; Drugs and Lactation Database) are presented in tables 2, 3 and 4.

**Clinical parameters assessing the safety of AED during lactation**

In addition to the pharmacokinetic parameters of AEDs presented and discussed earlier, when assessing the safety of these drugs, it is worth to analyse clinical parameters such as:

1. **Theoretical Infant Dose** (TID), the theoretical dose in a newborn – is the maximum estimated amount of drug taken with breast milk; in other words, it is an estimate in milligrams per kilogram of the theoreti-
cal daily dose for the infant (according to the Atkinson formula: TID = daily mother’s milk consumption (150 ml/kg/day) × maximum concentration of the drug in the mother’s milk) (Atkinson et al., 1988).

2. The therapeutic dose in the neonatal period – the therapeutic dose in mg/kg/day, used in therapy during infancy. By comparing the TID dose with the therapeutic dose, the safety of the drug can be assessed. The therapeutic dose, which is higher than TID, ensures the safety of drugs during breastfeeding (Tables 5 and 6).

Davanzo et al. (2013) proposed 3 categories of drugs used during breastfeeding, i.e. safe: carbamazepine (CBZ), phenytoin (PHT), phenobarbital (PB), primidone (PRM), valproic acid and its salts (VPA); contraindicated: clonazepam (CLN), diazepam (DZP), ethosuximide (ESM), zonisamide (ZNS) and moderately safe: lamotrigine (LTG), gabapentin (GBP), levetiracetam (LEV), oxcarbazepine (OXC), tiagabine (TGB), topiramate (TPM), vigabatrin (VGB), lacosamide (LCM). The latter category has a less well documented safety profile due to the limited clinical experience and lack of research. These drugs can be used with caution. The mother should use the lowest dose possible. The infant should be monitored and, if possible, the concentration of the drug should be determined in the serum of the child. Two drugs, PB and PRM, which Da-
**Table 4.** New generation antiepileptic drugs (AEDs) – pharmacokinetic and physicochemical characteristics and lactation risk categories

| AED   | t_{1/2} [h] | t_{max} [h] | BA [%] | MW [g/mol] | RID [%] | M/P | PPB [%] | Vd [L/kg] | pKa | Hale’s (2019) lactation risk categories |
|-------|-------------|-------------|--------|------------|---------|-----|---------|-----------|-----|----------------------------------------|
| LTG   | 14–103 (mean 33 adults. monotherapy) | 1–4 | 98 | 256 | 9.2–18.27 | 0.057–1.47 | 55 | 09–1.3 | 5.7 | L2 |
| OXC   | 1.3–2.3 (OXC) 9 (MHD) | 4.5 | 100 | 252 | 1.5–1.7 | 0.5 | 40 | 0.7 | 10.7 | L3 |
| LEV   | 6–8 adults 5–6 children | 1.3 adults 0.5–1 children | 100 | 170 | 3.4–7.8 | 1 | <10 | 0.5–0.7 | _ | L2 |
| LCM   | 13 | 1–4 | 100 | 250 | NA | NA | <15 | 0.6 | 12.47 | L3 |

LTG – Lamotrigine; OXC – Oxcarbazepine; LEV – Levetiracetam; LCM – Lacosamide

t_{1/2} – half-life; t_{max} – time to maximum drug concentration; BA – bioavailability after oral administration; MW – molecular weight; RID – relative infant dose; M/P – milk to plasma ratio of a drug concentration; PPB – plasma protein binding; Vd – volume of distribution; pKa – the negative logarithm of the ionization constant of an acid; NA – no data

**Table 5.** Clinical parameters assessing the safety of older generation AEDs during lactation (Davanzo et al., 2013; Hale, 2019)

| AED   | TID [mg/kg/day] | Oral therapeutic dose in infants [mg/kg/day] | RID [%] | Hale’s (2019) lactation risk categories | Drug safety |
|-------|-----------------|--------------------------------------------|--------|----------------------------------------|-------------|
| CBZ   | 0.7             | 10–20                                      | 3.8–5.9 | L2 | safe |
| CLN   | 0.002           | 0.1–0.2                                    | 2.8    | L3 | contraindicated |
| DZP   | 0.05            | iv. 0.1–0.3 po. 0.5–1                      | 0.88–7.14 | L3 | contraindicated |
| PHT   | 0.4             | 5–8                                        | 0.6–7.7 | L2 | safe |
| ESM   | 11.5            | 15–40                                      | 31.4–73.5 | L4 | contraindicated |
| PB    | 0.4             | 3–4                                        | 24     | L4 | moderately safe |
| PRM   | 0.9             | 12–20                                      | 8.4–8.6 | L4 | moderately safe |
| VPA   | 0.7             | limited data in the neonatal period available | 0.99–5.6 | L3 | safe |

TID – theoretical infant dose; RID – relative infant dose

CBZ – Carbamazepine; CLN – Clonazepam; DZP – Diazepam; PHT – Phenytoin; ESM – Ethosuximide; PB – Phenobarbital; PRM – Primidone; VPA – Valproic acid

**Table 6.** Clinical parameters assessing the safety of new generation AEDs during lactation (Davanzo et al., 2013; Hale, 2019)

| AED   | TID [mg/kg/day] | Oral therapeutic dose in infants [mg/kg/day] | RID [%] | Hale’s (2019) lactation risk categories | Drug safety |
|-------|-----------------|--------------------------------------------|--------|----------------------------------------|-------------|
| GBP   | 1.7             | 10–15 (only pediatric dose available)       | 1.3–6.6 | L2 | moderately safe |
| LTG   | 0.7             | 1–6 with valproic acid 5–15 with enzyme inducing AEDs | 9.2 | L3 | moderately safe |
| LEV   | 3.9             | 5–10                                       | 3.4–7.8 | L3 | moderately safe |
| OXC   | b.d.            | 27.7–50 (<18 years)                        | 1.5–1.7 | L3 | moderately safe |
| TGB   | b.d.            | <12 years limited data available           | NA    | L3 | moderately safe |
| TPM   | 0.3             | 1–6 (<2 years)                             | 24.5   | L3 | moderately safe |
| VGB   | 0.1             | 25–50                                      | 1.5–2.7 | L3 | moderately safe |
| ZNS   | 1.9             | 5–8                                        | 28.9–36.8 | L4 | contraindicated |

TID – theoretical infant dose; RID – relative infant dose

GBP – Gabapentin; LTG – Lamotrigine; LEV – Levetiracetam; OXC – Oxcarbazepine; TGB – Tiagabine; TPM – Topiramate; VGB – Vigabatrin; ZNS – Zonisamide
vanzo et al. (2013) listed as safe during lactation, are described by other authors as moderately safe (Anderson, 2010) or potentially risky (Hale, 2019) due to the extremely long half-life and accumulation in the body of an infant. These drugs are currently very rarely used.

**Moderately safe new generation drugs**

**Lamotrigine**

LTG may accumulate in the blood of an infant due to the relatively large fraction of the drug not bound to plasma proteins and the metabolism occurring through glucuronidation, which in the child reaches full efficiency only around 20 months of age (Miyagi et al., 2007). Both blood concentrations and half-life (14–103 hours) show large inter-individual differences. Polytherapy also affects $t_{1/2}$. It is shortened by the combination with CBZ or PHT (adults – 14; children – 7; newborns and infants – 23 hours), while it extends the use of VPA (70, 45–50 and 136 hours, respectively).

During pregnancy, the drug reaches only slightly lower levels in the umbilical cord blood than in the mother’s blood (a reduction of approx. 16% on average). The reduction in maternal milk concentration is greater (by 33% on average), and in the baby’s blood by as much as 77% (according to various studies 15–45% of the mother’s concentration).

Although the drug concentration in milk is described as relatively high, in most studies there are no reports of obvious abnormalities in breastfed infants (Ohman et al., 2000; Page-Sharp et al., 2006). A case of adverse reaction related to LTG exposure via mother’s milk was reported in a 16-day-old newborn whose mother had the lamotrigine dose significantly increased during pregnancy (from a 450 mg/d dose to 875 mg/d) due to numerous seizures. On the 9th day after delivery, the mother showed toxic symptoms (concentration was not measured). The patient continued to feed until day 16, when the newborn had a severe apnoea incident (Nordmo et al., 2009). Cases of mild thrombocytopenia (Drugs and Lactation Database) and withdrawal syndrome (Anderson, 2020) have also been reported.

The concentration of the drug in milk decreases with the duration of lactation. A Norwegian study documents that the development of children born to mothers with epilepsy receiving LTG during pregnancy is better if they were breastfed after birth, compared to the control group of babies born from mothers who were artificially fed since birth. Development in categories of behaviour, motor skills, social contacts and speech were assessed at 6, 18 and 36 months of age. In general, the authors found lower development rates of children of mothers with epilepsy compared to the reference group of newborns of healthy mothers. Breastfeeding reduced these differences. Long-term breastfeeding (>6 months), compared to artificial feeding, has been associated with accelerated development in all of the mentioned categories. The positive effect of breastfeeding increased with its length (Veiby et al., 2013). Similarly, in a 3-year observation of the development of children of mothers receiving LTG during pregnancy and lactation, a beneficial effect of long-term breastfeeding on intelligence (IQ) was observed compared to shorter feeding (Meador et al., 2009).

**Child monitoring:** excessive sedation or irritability; reluctance to suckle, malnutrition, small weight gain; skin rash. Monitoring of liver enzymes activity and morphology as well as monitoring of LTG (Drugs and Lactation Database) levels may be indicated for “symptomatic” children.

**Oxcarbazepine**

The drug is rapidly metabolized to 10-hydroxycarbazepine (MHD) after ingestion, with a much longer half-life (9 h) than OXC. This metabolite is responsible for the antiepileptic activity of the drug. OXC is excreted in the urine in the form of metabolites – mainly MHD and its glucuronide derivative.

Transplacental transport of OXC occurs very easily, therefore the concentration of the drug in the blood of the pregnant and the foetal blood is almost equal. A significant reduction of the drug concentration is observed in the milk of lactating women. Due to this, from the 5th day after birth, the drug is practically undetectable in the blood of newborns (a decrease of 93% in relation to cord blood). No adverse effects were noted in the children of mothers using OXC except for withdrawal syndrome (Anderson, 2020). Bulau et al. (1988) are of the opinion that breastfeeding by patients treated with OXC is safe, but according to Hale (2019) – due to the lack of data – the drug belongs to category L3, i.e. probably safe.
**Child monitoring:** excessive sedation or irritability; reluctance to suckle, malnutrition, small weight gain; diarrhoea. If clinical signs increase, liver enzymes activity determination should be considered. In order to reduce the risk of coagulologic disorders (the drug affects the metabolism of vitamin K), a newborn at birth should, in addition to the standard dose of 1 mg vitamin K intramuscularly, receive an additional 1 mg of vitamin K orally every 3 days in the first 2 weeks of life.

**Levetiracetam**

The placental transport of the drug occurs easily, leading to comparable levels in the mother's blood and the umbilical cord blood. Due to the low molecular weight and low plasma protein binding, the drug readily passes into breast milk, however the plasma concentrations of infants are low.

In a report by Kramer et al. (2002), the authors write about the child's lower activity during feeding, inefficient suckling and reduced muscle tone in a child who is breastfed by a mother using polytherapy (including LEV). The easy penetration of the drug into the blood of the foetus and breast milk is confirmed by subsequent reports, however, they emphasize the rapid elimination of LEV by the child's body. In the subsequent days of life, the concentration in the child's blood drops sharply. Already on the 4th day after birth, the concentration remains at the detection threshold (Tomson et al., 2007; Johannessen et al., 2005).

**Child monitoring:** doses up to 3500 mg/d should not cause high concentration levels of LEV in the milk or adverse effects, especially after the child reaches 2 months of age (Drugs and Lactation Database). However, attention should be paid to the level of activity of the newborn, hyperactivity, activity at the breast, suckling efficiency and feeding efficiency (weight gain).

**Lacosamide**

Due to its relatively low molecular weight (250 g/mol), low plasma protein binding (<15%) and a low volume of distribution (0.6 L/kg), the drug may theoretically reach significant milk concentrations in lactating women. There is no accurate data on the permeation of the drug into breast milk. Observations to date have shown that after the administration of 200 mg/d, LCM reaches low levels in the milk, and its use for 7–9 months at a dose of 400 mg/day does not adversely affect the development of the breastfed infant (Anderson, 2020). The drug requires research, and caution should be exercised during its use by lactating women.

**Older generation antiepileptic drugs – contraindicated**

**Benzodiazepines (BDZ) – DZP and CLN**

DZP has a very long half-life (see Table 3). The drug is almost completely bound to plasma proteins and metabolized to 3 active compounds excreted in the urine, of which desmethyldiazepam has the t_{1/2} of 30–200 hours. The concentrations of the drug and its metabolite in the milk show individual differences (Wesson et al., 1985). Both DZP and its metabolites accumulate in the infant’s body, with the premature babies being at the greatest risk of toxicity.

There is a similarly long half-life (up to 60 hours) for CLN, which can also accumulate in an infant. Most authors believe that both DZP and CLN should not be used long-term in nursing mothers and only allow their single administration. If it is necessary to use BDZ, it is preferable to give lorazepam (LZP), which has a shorter t_{0.5} (adults 12–15 hours; infants up to 30 hours), reaches very low levels in breast milk and does not accumulate (Davanzo et al., 2013; Hale, 2019; Drugs and Lactation, Database; Veiby et al., 2015).

**Ethosuximide**

The drug’s plasma protein binding is negligible, and the half-life varies in children and adults (Table 3). ESM is extensively metabolised in the liver via cytochrome P450 to inactive metabolites excreted in the urine. The amount of ESM excreted into the milk is comparable to its concentration in the mother’s blood; the M/P ratio is approximately 1. RID reaches high values (31.4–73.5%), but Veiby et al. (2015) also report RID = 113%, which explains the high concentration in the serum of breastfed infants (15–40 mg/l) (Kuhnz et al., 1984).

ESM is considered potentially dangerous during lactation and requires monitoring during breastfeeding. Some believe that in nursing women should only be used when there is no alternative treatment (Davanzo
et al., 2013). Adverse effects included irritability, hyperactivity, drowsiness, and suckling disorders; in combination with PB or PRM cheiloschisis is mentioned.

**Child monitoring:** drowsiness, irritability, problems with suckling, weight loss, observation of psychomotor development (especially in premature babies), sometimes liver enzymes’ activity may need to be determined. Monitoring of infant serum concentration during breastfeeding is recommended to exclude toxicity.

**Older generation antiepileptic drugs – moderately safe**

**Phenobarbital**

It has a very long half-life in children (20–133 hours in infants and up to 500 hours in premature babies) (Taketomo et al., 2012) and a lower plasma protein binding in newborns when compared to adults (3–43% vs 51%) (Davanzo et al., 2013). This means that it can accumulate in newborns and infants. It is partly metabolised in the liver by cytochrome P450 enzymes and excreted both in an unchanged form and as metabolites. PB permeates into breast milk and reaches varying levels in it. In general, concentration levels in infant plasma account for 30% of the concentration in the maternal plasma (Hale, 2019), however cases have been reported where they have exceeded twice the maternal plasma concentration level.

Maintaining feeding can alleviate any abstinence in the newborn baby. Caution should be exercised, especially in polytherapy and after pausing or stopping breastfeeding (risk of convulsions).

**Child monitoring:** drowsiness, suckling reflex, adequate weight gain and development (especially in younger infants and in the case of polytherapy). Monitoring of concentration in the infant’s serum during breastfeeding is recommended to exclude toxicity.

**Primidone**

PRM is mainly metabolised to PB. The M/P ratio is 0.7. Serum concentrations of primidone and its metabolites in breastfed infants may be close to the therapeutic range value. The drug should be used with caution while breastfeeding, because it can accumulate in the body of an infant (Veiby et al., 2015).

**Child monitoring:** drowsiness, suckling reflex, adequate weight gain and development (especially in younger infants and in the case of polytherapy). Monitoring of infant serum concentration during breastfeeding is recommended to exclude toxicity.

**Older generation antiepileptic drugs – safe**

**Carbamazepine**

The drug is extensively metabolised in the liver by cytochrome P450 enzymes to several metabolites that are excreted in urine and faeces. CBZ and the pharmacologically active metabolite 10,11-epoxide (CBZ-E) are poorly excreted into breast milk, partly due to the high plasma protein binding. The M/P ratios of CBZ and CBZ-E are 0.69 and 0.79, respectively (Davanzo et al., 2013). CBZ concentrations in breast milk are moderate and vary: from 0.34 to 6 mg/L (Shimoyama et al., 2000). Other authors note the average concentrations in milk: CBZ – 7.1 mg/L, CBZ-E – 2.6 mg/L (Hale, 2019). The RID value is low (3.8–5.9%), similar to the concentration in the serum of infants, which are usually below the therapeutic range.

Breastfeeding is considered safe. Adverse reactions (somnolence, reduced suckling, rash, sporadic liver dysfunction cases) have rarely been reported.

**Child monitoring:** observation for the mentioned adverse reactions.

**Phenytoin**

PHT is considered a safe drug during lactation, because it binds substantially to plasma proteins (89%), it is excreted in breast milk to a small extent (M/P: 0.18–0.45) and it reaches low concentration levels in it (Hagg and Spigset, 2000; Shimoyama et al., 1998; Harden et al., 2009). It is metabolized in the liver by cytochrome P450 enzymes in hydroxylation and glucuronidation reactions, and then it is excreted in the urine, mainly in the form of inactive metabolites. The effect of PHT on a fed infant is considered to be minimal if maternal plasma concentration is <10 mg/L (Hale, 2019).

Extremely rare cases of hyperactivity (probably caused by the withdrawal syndrome) and methemoglobinemia, somnolence and suckling problems have been observed in children of mothers using PHT in polytherapy with PB or CBZ.

**Child monitoring:** observation for the mentioned adverse reactions.

**Valproic acid and its salts**

Due to almost complete plasma protein binding, the drug very poorly permeates into breast milk, thus ensuring safety during lactation (Meador et al., 2010). It is metabolized in the liver, mainly in the glucuronidation reaction, and excreted in the urine primarily in
the form of metabolites. VPA reaches the lowest concentration levels in infant blood of all AEDs, i.e. 0.7–1.5 mg/L (only 0.9–2.3% of maternal blood concentration) (Schaefer et al., 2007). M/P ratio is 0.01–0.3% (Veiby et al., 2015). The case of a breastfed infant with symptoms of thrombocytopenia, purpura and anaemia (Stahl et al., 1997) indicates the need for careful use of the drug during breastfeeding, although the relationship with the mother’s VPA intake (Drugs and Lactation Database) has not been completely confirmed. Due to the theoretical risk of hepatotoxic effects of the drug, an assessment of liver and bile duct function in late jaundice is justified.

**Child monitoring:** drowsiness, irritability, suckling problems, weight loss, sometimes liver enzymes activity determination may be required. Attention should also be paid to unusual bleeding.

It should be noted that the potentially adverse effects of the drug on the body of a newborn child depends on their age. Newborns, especially premature babies, are at the highest risk of side effects. This is not only due to the “anatomical leaks” of the mammary gland and the ability of its metabolism and elimination or excretion. Regarding maternal excretion, the drug elimination rate for premature babies born between 24–28 weeks of pregnancy is initially 5%; in premature babies born between 28–34 weeks – 10% and in newborns with 34–40 weeks of gestation, approximately 33%. In a full-term newborn baby, only after 2 months of life does the child’s ability to excrete the drug is identical to that of the mother. Hence, the number of complications associated with the activity of drugs contained in food is: in the first month of life – 67%, while over 6 months of age it is only 4% (Berlin and Briggs, 2005).

**The current state of breastfeeding of newborns of mothers with epilepsy**

Many factors influence a mother’s decision to breastfeed. Socio-economic factors such as the mother’s education, income, employment and social class affect both the initiation rate and the duration of breastfeeding (Quigley et al., 2012). Emotions and self-esteem are other factors that can influence breastfeeding decisions. Women with epilepsy may have higher rates of depression and anxiety especially during pregnancy and after delivery (Reiter et al., 2013). According to Norwegian studies, women with epilepsy were more likely to have perinatal depression (26.7%) or anxiety (22.4%) than women without epilepsy (18.9% and 14.8% respectively, p<0.001) and women with other chronic diseases (23.1% and 18.4% respectively, p = 0.03 and 0.01) (Bjørk et al., 2015; Turner et al., 2009).

It is extremely important to know the additional factors that may prevent one from making the decision to start or continue breastfeeding. According to a study which attempted to identify the causes of the lack of breastfeeding in women with epilepsy, such causes were only known in 17.6% of individuals (Al-faraj and Pang, 2019). These included the aforementioned fear of exposing the child to AEDs through breast milk, recommendations of medical staff (neurologists, obstetricians, neonatologists and paediatricians) not to breastfeed and technical difficulties affecting the unsuccessful attempts at breastfeeding and insufficient lactation. On the other hand, fear of children being exposed to AEDs through breast milk, frequent seizures and insufficient milk were the most common causes of early cessation of breastfeeding. Mothers with epilepsy who gave birth on time and whose seizures were controlled were more likely to engage in long-term breastfeeding. It seems that family support and clear advice from doctors can greatly enhance decision making with regards to breastfeeding.

The results of these studies also showed that a conversation with a neurologist about breastfeeding was conducted with approximately half of women with epilepsy (52.95%). However, 91% of patients reported having such a conversation with a nurse. Of 66% of the women who were under maternity care at the Beth Israel Deaconess Medical Center, only 13% received a lactation consultation before delivery compared with 58% of the healthy population. It is clear that the education on breastfeeding by a neurologist was significantly positively correlated with the decision on feeding (p < 0.005) and its initiation (p <0.05). In addition, the postnatal lactation consultation was also associated with a significantly higher percentage of breastfeeding initiation (p <0.05), compliance with breastfeeding recommendations after 6 weeks (p = 0.01) and after 3 months (p =0.01) (Al-faraj and Pang, 2019).

The rates of breastfeeding by women with epilepsy vary from country to country (Dyson et al., 2005). According to recent US data, women with epilepsy breastfeed their children less often than women in the general population (Gerard and Pennell, 2019; Al-faraj and Pang, 2019). The feeding initiation rate was 79%. Only 41% of women breastfeed for 3 months (Centers for Disease Control and Prevention, 2014).
The NEAD study shows that a total of 42% of women with epilepsy breastfeed for the first three months after delivery (Meador et al., 2010). The MONEAD study (continuation of the NEAD study) confirmed a lower percentage of nursing women with epilepsy for the first 3 months and subsequent 6 months (Gerard and Pennell, 2019; Al-faraj and Pang, 2019). It was shown that 51% of women with epilepsy (n = 102) started feeding after delivery, compared with 87% of healthy women (n = 113). After 6 weeks and 3 months in the group of women with epilepsy, these rates decrease to 38.2% and 36.2%, respectively, and after 6 months the decrease was even more visible. Only 18.6% of women with epilepsy continued breastfeeding. The above studies show that women with epilepsy are less likely to breastfeed than women without epilepsy. However, if they start breastfeeding, after three months they continue in a similar percentage as women without epilepsy – 34.5% and 28.6% respectively (breastfeeding only). It is for this reason that the educational aspect encouraging women with epilepsy to breastfeed is so important (Gerard and Pennell, 2019).

In Norway, approximately 90% of women start breastfeeding. After 6 months, the percentage of breastfeeding women in the groups with epilepsy and poly-therapy was <50%, in the group with LTG monotherapy – <60% and in the group with other AED monotherapies the control group (mothers without epilepsy) – <70%. The results may indicate that both mothers and their doctors were concerned about the safety of feeding while using a particular treatment (Veiby et al., 2015).

The breastfeeding rate for mothers with epilepsy in China in the study by Hao et al. (2017) was 59.4%, whereas in the healthy women population it was 95%. After three months, only 36.3% of mothers exclusively breastfed and 49.5% of women with epilepsy stopped breastfeeding. After six months, approximately only one-third (33.1%) continued breastfeeding their children, and 12.8% were exclusively breastfed (Hao et al., 2017). In contrast, in the Bhutan kingdom, a majority of women (97%) reported breastfeeding in the questionnaire survey (Halani et al., 2017).

In Poland, the work of Bosak et al. (2019) shows that in a group of 171 women with epilepsy, breastfeeding at any time was reported by 68.1%.

Antiepileptic drugs use safety
Exposure to AEDs through breast milk can potentially cause adverse effects or negatively affect the child’s development. Most studies on the transfer of AEDs to breast milk indicate that the drug concentration in the serum of the infant is well below the pharmacological effect limit.

As mentioned above, some drugs such as PB, BDZ, LTG and ESM can achieve high concentrations in the serum of breastfed infants. Therefore, breastfed infants should be monitored for adverse effects. However, adverse effects are still rarely reported in infants who are breastfed by mothers taking AEDs. Prospective studies have not show any negative developmental effects in children who were exposed to AEDs through their breast milk.

The degree of exposure of the baby to the drugs in the mother’s milk can be minimized by breastfeeding during periods when the concentration in the milk is low, reducing the maternal AED dose to pregnancy levels. Most AEDs are considered safe or moderately safe during breastfeeding. Mothers with epilepsy should be encouraged to breastfeed, provided that their children are carefully monitored.

Long-term effects of antiepileptic drugs’ use during breastfeeding
As emphasized earlier breastfeeding has beneficial effects, but there are concerns that breastfeeding during maternal AED therapy may be harmful to the child’s development in the long-term perspective. In 2010, Meador et al. published a report on the neurological development of children breastfed by mothers with epilepsy. Eighty four breastfed newborns were assessed for 3 to 24 months (average of 6 months) compared with 115 non-breastfed newborns. The results showed that at 3 years of age, the average IQ in the breastfed group was 99 compared to 98 in the non-breastfed group. The conclusion was that in the study assessing the intelligence quotient in children of mothers with epilepsy taking AEDs and breastfeeding their children, at the age of 3, no negative effects of drugs such as CBZ, LTG, PHT or VPA used during breastfeeding were found. Considering the fact that the intelligence quotient at the age of 6 allows better prediction of school results, the impact of the exposure to AED through breastfeeding on the cognitive functions of children at the age of 6 was examined. The study was conducted as a prospective observational multicentre study assessing the long-term neurodevelopmental effects of using AEDs. Pregnant women with epilepsy receiving monotherapy (CBZ, LTG, PHT or VPA) were registered from October 14,
1999 to April 14, 2004 (for 3.5 years) in the United States and Great Britain. At 6 years of age, the neurological status was assessed in 181 children born to those mothers for whom breastfeeding, and IQ data were available. All mothers included in this analysis continued to take the AED after delivery. A total of 42.9% of children were breastfed for an average of 7.2 months.

The indicators and duration of breastfeeding did not differ between the AED drug groups. Researchers evaluated the IQ in children aged 6 years who were exposed to the effects of AEDs. Linear regression analysis included the adjustment for other known factors that could affect the IQ results, including maternal intelligence quotient, specific AED monotherapy, drug dose, and folate use prior to pregnancy.

The IQ score was 4 points higher in the group of breastfed children compared to those who were not breastfed. In the remaining cognitive domains, only verbal skills differed significantly between breastfed and non-breastfed groups (p = 0.03). Thus, no negative effects of AED exposure through breast milk during breastfeeding were observed in six-year-old children, which is consistent with another recent study which studied 3 year old children (Meador et al., 2014; Meador et al., 2010).

The study by Veiby et al. (2013) may also provide additional evidence that long-term breastfeeding by mothers receiving AEDs is safe and even beneficial for their offspring. The development of motor skills and behaviour was assessed in a group of 223 infants of mothers receiving AEDs (CBZ, LTG, VPA). At the age of 6 months, impairment of motor skills was noted in 11.5% of offspring exposed to an AED, much more than in the reference group without epilepsy (4.8%). However, a reduced risk of impaired motor skills was observed in mothers nursing for 6 months when compared to the group of women who had stopped feeding before the age of 6 months. Infants who were breastfed for six months or more experienced greater weight gain and did not have as many autistic traits as the group breastfed for less than six months. The next assessments carried out at the age of 18 and 36 months did not show a negative impact of AEDs taken by the mother on the development of children in comparison with the group of children of healthy mothers.

It is worth emphasizing that in the study by Veiby et al. (2013) the mother’s IQ was not controlled and their results were based on the mother’s report; children were not individually examined as in the NEAD study. These positive effects of breastfeeding babies of mothers with epilepsy are consistent with the three latest large prospective cohort studies in the general population (Bernard et al., 2013; Belfort et al., 2013; Julvez et al., 2014). These studies found a significant relationship between the length of breastfeeding and subsequent positive psychosocial or emotional development of the child.

While the impact of breastfeeding on cognitive functions remains controversial (Jain et al., 2002; Walfisch et al., 2013), the presented study results may confirm the causal relationship between natural feeding and the improvement of the child’s cognitive functions (Christakis, 2013). Questions arise – is there a positive effect of feeding on cognitive deficits caused by the AED effect? Could breastfeeding be a modifiable factor in improving cognitive performance in children born to mothers who must take AEDs during pregnancy? The authors interpret their results carefully, emphasizing safety rather than the benefits of breastfeeding in this aspect. Nevertheless, the most important and safe interpretation of the above results is that breastfeeding is safe for women undergoing an AED monotherapy and should be strongly supported by neurologists, obstetricians, neonatologists and paediatricians.

Interesting research results were presented by Danish authors Sun et al. (2011) asking the question whether breastfeeding can reduce the risk of childhood epilepsy. The study investigated, based on the Danish birth register, 69,750 children born between 1997–2003. The study ended in 2008. Information on breastfeeding was provided by mothers during two computer-assisted telephone interviews at 6 and 18 months after birth. Information on epilepsy (hospitalized and outpatient patients) was obtained from the Danish national hospital register. The authors of this study showed that breastfeeding was associated with a reduced risk of epilepsy. Children breastfed for 3 to 5; 6 to 8; 9 to 12 and ≥13 months were 26, 39, 50 and 59%, respectively, less likely to develop epilepsy after the first year of life when compared to children breastfed for less than a month. This favourable trend continued even when children who had adverse effects in the neonatal period or children who were exposed to adverse effects during pregnancy were excluded. The observed beneficial, protective effect of breastfeeding may be completely random, nevertheless it is another reason to encourage breastfeeding.

It seems that the percentage of foetal malformations after exposure to AEDs in the uterus cannot be extrapolated to breastfeeding after delivery. Exposure to val-
proic acid during foetal organogenesis carries a much greater risk than during breastfeeding. Therefore, it is prudent to plan the safest drug before pregnancy in terms of the risk of potential teratogenicity and breastfeeding if a woman so wishes.

One should be aware of the limitations of studies as they involve a small number of patients. There are no data on the concentrations of the drug in breast milk or in the blood of children, there is also no randomization and no control group. Only the inclusion of all these factors in the analysis can allow a full estimation of the data on the safety of AEDs during breastfeeding. Previous studies do not provide a definitive answer, but there is agreement among epileptologists that we recommend breastfeeding to mothers with epilepsy while informing them about the risks and benefits.

RECOMMENDATIONS
- It is recommended that women with epilepsy breastfeed exclusively for the first 6 months after delivery and then continue breastfeeding until at least 12 months of the child’s age, with the gradual introduction of complementary foods. It is worth remembering that in infants with a high demand for iron, it is appropriate to introduce complementary foods (after 4 months) – a vegetable soup.
- Most AEDs are safe or moderately safe during lactation
- AED permeation into milk is inversely proportional to their binding to plasma proteins.
- In case of new AEDs, knowledge about the drug metabolism in newborns is required
- Neonates should be monitored for drowsiness, reduced suckling activity and poor weight gain, especially in the population of premature newborns
- In the event of suspicion of any adverse effects associated with the mother’s AED intake, it is recommended to monitor the drug’s concentration in the infant’s blood. Feeding should be recommended at the time of the lowest concentration of the drug in the mother’s blood, i.e. ingesting the drug immediately after feeding or before the newborn’s longest period of sleep.
- With increased drug effects in the infant, mixed feeding should be considered, i.e. with milk from a breast milk bank (if possible) or with ready-made milk. It may also be useful to plan a breastfeeding break to see if the symptoms disappear and then resurface when breastfeeding is resumed. In such cases, it is necessary to maintain lactation in the mother by systematically pumping off milk. The real risk of mother discontinuing breastfeeding should be considered.
- The adopted model of feeding a child in every situation must be agreed with the parents and accepted by them.
- In the postpartum period, adjustment of the mother’s dose should be considered if the dose was increased or decreased during pregnancy.
- Feeding safety aspects should be discussed.
- The following subjects should be discussed: risk of postpartum depression, insomnia, compliance with the physician’s AED intake recommendations. Medical procedures for women giving birth and during delivery may not interfere with the prescribed times for taking AEDs. This means that AEDs intake does not interfere with the fasting recommendation.
- A woman with epilepsy while in the maternity ward or neonatology ward should be under increased care and observation, in particular under the direct supervision of staff or relatives while using the bathroom. She should not leave the ward without informing the staff.

Management of a nursing mother taking AEDs – specific situations
1. Mother with epilepsy, not taking AEDs and with no seizures during pregnancy:
   • a healthy child can stay with the mother in the rooming-in system,
   • sleep deprivation should be prevented, which means uninterrupted sleep of the mother between 2–6 AM, the last breastfeeding is carried out around midnight, the next one on the next day after 6 o’clock; during that time the child is in the neonatal ward; it is recommended to secure pumped-off breast milk for night feeding, in individual cases night feeding directly from the breast is allowed, after determining the degree of risk and in consultation with the mother; the mother does not leave the bed;
   • medical staff hands over and collects the child and conducts general supervision of the feeding,
   • the mother should feed while lying down on a bed equipped with safety rails.
2. Mother with epilepsy, taking AEDs with no seizures during pregnancy:
   • a healthy child can stay with the mother in the rooming-in system,
   • sleep deprivation should be prevented, which means
uninterrupted sleep of the mother between 2–6 AM, the last breastfeeding is carried out around midnight, the next one on the next day after 6 o’clock; during that time the child is in the neonatal ward; it is recommended to secure pumped-off breast milk for night feeding,
• the mother should feed while lying down on a bed equipped with safety rails, it is recommended to monitor the newborn in terms of suckling efficiency and effectiveness.

3. Mother with epilepsy, taking AED and with seizures during pregnancy:
• a healthy child stays with their mother in the presence of third parties (family, medical staff); they spend the remaining time in the neonatology ward,
• sleep deprivation should be prevented, which means uninterrupted sleep of the mother between 2–6 AM, the last breastfeeding is carried out around midnight, the next one on the next day after 6 o’clock; during that time the child is in the neonatal ward; it is recommended to secure pumped-off breast milk for night feeding,
• the mother should feed while lying down on a bed equipped with safety rails, it is recommended to monitor the newborn in terms of suckling efficiency and effectiveness.

4. Mother with epilepsy, unknown course of the disease (no reliable data available):
• a healthy child stays with their mother in the presence of third parties (family, medical staff); they spend the remaining time in the neonatology ward,
• sleep deprivation should be prevented, which means uninterrupted sleep of the mother between 2–6 AM, the last breastfeeding is carried out around midnight, the next one on the next day after 6 o’clock; during that time the child is in the neonatal ward; it is recommended to secure pumped-off breast milk for night feeding,
• the mother should feed while lying down on a bed equipped with safety rails, it is recommended to monitor the newborn in terms of suckling efficiency and effectiveness.

CONFLICT OF INTEREST
Joanna Jędrzejczak received speaker’s honoraria and travel grants from Sanofi, Adamed and served as medical advisor UCB. Beata Majkowska-Zwolińska received speaker’s honoraria from Sanofi and UCB outside of the submitted work.

The other authors declare that they have nothing to disclose.

REFERENCES
Al-faraj A., Pang T.: Factors affecting breastfeeding patterns in women with epilepsy. Presented at: American Epilepsy Society 2019 Meeting; December 7–10; Baltimore, Maryland. Abstract 1.246. www.aesnet.org/annual_meeting/abstract_search#
American Academy of Pediatrics.: Breastfeeding and the use of human milk. Pediatrics, 2012, 3: 827–841.
Amitay E.A., Keinan-Boker L.: Breastfeeding and childhood leukemia incidence. The Journal of the American Medical Association. JAMA Pediatr., 2015, 169: e151025.
Anderson P.O.: Antiepileptic drugs during breastfeeding. Breastfeed Med., 2020, 15: 2–4.
Atkinson H.C., Begg E.J., Darlow B.A: Drugs in human milk. Clinical pharmacokinetic considerations. Clin. Pharmacokinet., 1988, 14: 217–240.
Ballard O., Morrow A.L.: Human Milk Composition. Nutrients and Bioactive Factors. Pediatr. Clin. N. Am., 2013, 60: 49–74.
Belfort M.B., Rifas-Shiman S.L., Kleinman K.P, Guthrie L.B., Bellinger D.C., Taveras M. et al.: Infant feeding and childhood cognition at ages 3 and 7 years: effects of breastfeeding duration and exclusivity. JAMA Pediatr., 2013, 167: 836–844.
Berlin C.M., Briggs G.G.: Drugs and chemicals in human milk. Semin. Fetal. Neonat. Med., 2005, 10: 149–159.
Bernard J.Y., De Agostini M., Forhan A., Alfaite T., Bonet M., Champion V. et al., EDEN Mother-Child Cohort Study Group: Breastfeeding duration and cognitive development at 2 and 3 years of age in the EDEN mother-child cohort. J. Pediatr., 2013, 163: 36–42.
Birnbaum A.K., Meador K.J., Karanam A., Brown C., May R.C., Gerard E.E. and MONEAD Investigator Group: Antiepileptic Drug Exposure in Infants of Breastfeeding Mothers With Epilepsy. JAMA Neurol., 2019, 30: e194443. doi: 10.1001/jama-neurol.2019.4443.
Bjørk M.H., Veiby G., Reiter S.C., Berle J.O., Daltveit A.K., Spigset O. et al.: Depression and anxiety in women with epilepsy during pregnancy and after delivery: a prospective population-based cohort study on frequency, risk factors, medication and prognosis. Epilepsia, 2015, 56: 28–39.
Bosak M., Cyranka K., Slowik A.: Hormonal contraception in patients with epilepsy. Ginekol Pol., 2019, 90: 61–65.
Buluş P., Paar W.D., von Unruh G.E.: Pharmacokinetics of oxcarbazepine and 10-hydroxy-carbazepine in the newborn child of an oxcarbazepine treated mother. Eur. J. Clin. Pharmacol., 1988, 34: 311–313.
Centers for Disease Control and Prevention: Breastfeeding
The Role of Oxytocin in Mother-Infant Relations: A Systematic Review of Human Studies

Breastfeeding and the risk for diarrhea morbidity in children with antiepileptic drugs. Epilepsia, 2002, 43 (suppl. 7): 105.

Harden C.L., Pennell P.B., Koppel B.S., Hovinga C.A., Gidal B., Meador K.J. et al.: Practice Parameter Update: Management Issues for Women With Epilepsy – Focus on Pregnancy (An Evidence-Based Review): Vitamin K, Folic Acid, Blood Levels, and Breastfeeding. Report of the Quality Standards Subcommittee and Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology and American Epilepsy Society. Neurology, 2009, 73: 142–149.

Hauck F.R., Thompson J., Tanabe K.O., Moon R.Y., Venne mann M.M.: Breastfeeding and Reduced Risk of Sudden Infant Death Syndrome: A Meta-analysis. Pediatrics, 2011, 128: 103–110; DOI: https://doi.org/10.1542/peds.2010-3000.

Horta B.L., de Mola C.L., Victora C.G.: Long-term consequences of breastfeeding on cholesterol, obesity, systolic blood pressure and type 2 diabetes: a systematic review and meta-analysis. Acta Paediatrica, 2015, 104: 30–37.

Jain A., Concato J., Leventhal J.M.: How good is the evidence linking breastfeeding and intelligence? Pediatrics, 2002, 109: 1044–1053.

Julevz J., Guxens M., Carsin A.E., Forns J., Mendez M., Turner M.C., Sunyer J.: A cohort study on full breastfeeding and child neuropsychological development: the role of maternal social, psychological, and nutritional factors. Dev. Med. Child. Neurol., 2014, 56: 148–156.

Johannessen S.I., Helge G., Brodtkorb E.: Levetiracetam concentrations in serum and in breast milk at birth and during lactation. Epilepsia, 2005, 46: 775–777.

Kon I.Y., Shilina N.M., Gmoshinskaya M.V., Ivanushkina T.A.: The Study of Breast Milk IGF-1, Leptin, Ghrelin and Adiponectin Levels as Possible Reasons of High Weight Gain in Breast-Fed Infants. Ann. Nutr. Metab., 2014, 65: 317–323.

Kuhnz W., Koch S., Jacob S., Hartmann 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: 671–677.

Kramer G., Hosli I., Glanzmann R., Holzgrewe W.: Levitiracetam accumulation in human breast milk. Epilepsia, 2002, 43 (suppl. 7): 105.

Królak-Olejnik B., Blasiak I., Szczygiel A.: Promotion of breastfeeding in Poland: the current situation. Journal of International Medical Research, 2017, 45: 1976–1984.

Lamberti L.M., Fischer Walker C.L., Noiman A., Victora C., Black R.E.: Breastfeeding and the risk for diarrhea morbidity and mortality. BMC Public Health, 2011, 11 (Suppl. 3): S15.

Li R., Dee D., Li C-M., Hoffman H.J., Grummer-Straw M.L.: Breastfeeding and Risk of Infections at 6 Years. American Academy of Pediatrics, 2014. www.pediatrics.org/cgi/doi/10.1542/peds.2014-0646D
Liporace J., Kao A., D’Abreu A.: Concerns regarding lamotrigine and breastfeeding. Epilepsy Behav., 2004, 5: 102–105.
Lodge C.J., Tan D.J., Lau M.X.Z., Dai X., Tham R., Lowe A.J. et al.: Breastfeeding and asthma and allergies: a systematic review and meta-analysis. Acta Pædiatrica, 2015, 104: 38–53.
Ma L., Shi H., Lian K., Diao Y., Chen Y., Ma C., Kang W.: Highly selective and sensitive determination of several antioxidants in human breast milk using high-performance liquid chromatography based on Ag(III) complex chemiluminescence detection. Food Chem., 2017, 218: 422–426.
Meador K.J., Baker G.A., Browning N., Clayton-Smith J., Combs-Cantrell D.T., Cohen M. et al.: Cognitive function at 3 years of age after fetal exposure to antiepileptic drugs. N. Eng. J. Med., 2009, 360: 1597–1605.
Meador K.J., Baker G.A., Browning N., Clayton-Smith J., Combs-Cantrell D.T., Cohen M. and NEAD Study Group: Effects of breastfeeding in children of women taking antiepileptic drugs. Neurology, 2010, 75: 1954–1960.
Miyagi S.J., Collier A.C.: Pediatric development of glucuronidation: the ontogeny of hepatic UGT1A4. Drug Metab. Dispos., 2007, 35: 1587–1592.
Nordmo E., Aronsen L., Waslmand K., Småbrekke L., Vorren K.: Concerns regarding lamotrigine in breastfeeding. JAMA Pediatr., 2014, 168: 729–736.
Page-Sharp M., Kristensen J., Hodding J.H., Kraus D.M. et al.: Exclusively Human Milk-Based Diet Is Associated with a Lower Rate of Necrotizing Enterocolitis than a Diet of Human Milk and Bovine Milk-Based Products. J. Pediatr., 2011, 158: 924–929.
Pennell P.B.: Use of Antiepileptic Drugs During Pregnancy: Evolving Concepts. Neurotherapeutics, 2016, 13: 811–820.
Peterson A.E., Perez-Escamilla R., Llabok M.H., Hight V., von Hertenz H., Van Look P.: Multicenter study of the lactational amenorrhea method (LAM) III: effectiveness, duration, and satisfaction with reduced client-provider contact. Contraception, 2000; 62: 221–230.
Quigley M.A., Hockley C., Carson C., Kelly Y., Renfrew M.J., Sacker A.: Breastfeeding is associated with improved child cognitive development: a population-based cohort study. J. Pediatr., 2012, 160: 25–32.
Reiter S.F., Veiby G., Dalveit A.K., Engels P.A., Gilhus N.E.: Psychiatric comorbidity and social aspects in pregnant women with epilepsy – the Norwegian Mother and Child Cohort Study. Epilepsy Behav., 2013, 29: 379–385.
Sankar M.J., Sinha B., Chowdhury R., Bhandari N., Taneya S., Martines J., Bahl R.: Optimal breastfeeding practices and infant and child mortality: a systematic review and meta-analysis. Acta Pædiatrica, 2015, 104: 3–13.
Schaefer Ch.: Antiepileptics. In: Ch. Schaefer, P. Peters, R.K. Miller (eds.) Drugs during Pregnancy and Lactation, 2nd ed., Elsevier 2007.
Sullivan S., Schanler R.L., Kim J.H., Patel A.L., Trawöger R., Kiechl-Kohlendorf U. et al.: An Exclusively Human Milk-Based Diet Is Associated with a Lower Rate of Necrotizing Enterocolitis than a Diet of Human Milk and Bovine Milk-Based Products. J. Pediatr., 2010, 156: 562–567.
Sun Y., Vestergaard M., Christensen J., Olsen J.: Breastfeeding and risk of epilepsy in childhood: a birth cohort study. J. Pediatr., 2011, 158: 924–929.
Taketomo C.K., Hodding J.H., Kraus D.M.: Pediatric and Neonatal Dosage Handbook. 19th edition. Lexicomp Drug Reference Handbooks, 2012.
Tham R., Bowatte G., Dharmage S.C., Tan D.J., Lau M.X.Z., Allen K.J., Lodge C.J.: Breastfeeding and the risk of dental caries: a systematic review and meta-analysis. Acta Pædiatrica, 2015, 104: 62–84.
Tomson T., Palm R., Källén 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: 1111–1116.
Breastfeeding in epilepsy – recommendations

Turner K., Piazzini A., Franz A., Marconi A.M., Canger R., Canevini M.P.: Epilepsy and postpartum depression. Epilepsia 2009, 50 (Suppl. 1): 24–27.

Veiby G., Engelsen B.A., 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: 1367–1374.

Veiby G., Bjork M., Engelsen B.A., Gilhus N.E.: Epilepsy and recommendations for breastfeeding. Seizure, 2015; 28: 57–65.

Verstegen R.H.J., Ito S.: Drugs in lactation. J. Obstet. Gynecol., 2019, 45: 522–531.

Vohr R., Poindexter B.B., Dusick A.M., McKinley L.T., Wright L.L., and NICHD Neonatal Research Network.: Beneficial Effects of Breast Milk in the Neonatal Intensive Care Unit on the Developmental Outcome of Extremely Low Birth Weight Infants at 18 Months of Age. Pediatrics, 2006, 118: e115–e123; DOI: https://doi.org/10.1542/peds.2005-2382.

Walfisch A., Sermer C., Cressman A., Koren G.: Breast milk and cognitive development: the role of confounders: a systematic review. BMJ Open, 2013, 3: e003259.

Wesson D.R., Camber S., Harkey M., Smith D.E.: Diazepam and desmethyldiazepam in breast milk. J. Psychoactive Drugs, 1985, 17: 55–56.

Wilinska M., Florczyk B., Kościelecka M.: Rola oddziału noworodkowego w popularizacji naturalnego karmienia – doświadczenia własne. Postępy Neonatologii, 2005, 2: 46–50.

Wilinska M., Borszewska-Kornacka M.K., Niemiec T., Jakiel G.: Oxidative stress and total antioxidant status in term newborns and their mothers. Ann. Agric. Environ. Med., 2015, 22: 736–740.

World Health Organization.: Global strategy for infant and young child feeding. Geneva, 2001: 1–5.

Zhou J., Shukla V.V., John D., Chen C.: Human Milk Feeding as a Protective Factor for Retinopathy of Prematurity: A Meta-analysis. Pediatrics, 2015, 136: e1576–e1586.