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Review

Epilepsy and recommendations for breastfeeding

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ABSTRACT

Purpose: The objective of this paper is to provide a synopsis of benefits and potential harmful effects of exposure to antiepileptic drugs (AEDs) via breastmilk, and present recommendations for breastfeeding in women with epilepsy.
Methods: The article is based on a discretionary selection of English language articles retrieved by a literature search in the PubMed database, the LactMed database, and the authors' clinical experience.
Results: Breastfeeding is associated with benefits for the infant, including nutrition, protection against infectious and immunological disease, and promotion of development and psychological attachment. Exposure to AEDs via breastmilk could potentially produce side effects or negatively affect development. Most studies on AED transfer through breastmilk report infant serum levels well below the limit of an expected pharmacological effect. Some drugs have the potential to reach significant serum levels in breastfed infants, such as barbiturates, benzodiazepines, lamotrigine, and ethosuximide. Thus, breastfed infants should be monitored for side effects. Still, adverse symptoms are rarely reported in breastfed infants of mothers taking AEDs, and prospective studies have failed to demonstrate any negative developmental effects in children that have been exposed to AEDs via breastmilk. The nursing infant's degree of drug exposure can be minimized by breastfeeding when drug concentrations in the milk are low, reducing maternal AED dosage to prepregnancy levels, and administering mixed nutrition.
Conclusion: Most AEDs are considered safe or moderately safe during breastfeeding. Mothers with epilepsy should be encouraged to breastfeed, provided careful monitoring of the infant.

1. Introduction

The safety of breastfeeding while taking antiepileptic drugs (AEDs) is a major concern for pregnant women with epilepsy and their doctors. Exposure to AEDs in the womb is associated with an increased risk of congenital malformations [1–4], growth restriction [3,5], and neurodevelopmental delay in the child [6–10]. Proposed teratogenic mechanisms of action include folic acid antagonism, induction of apoptosis, oxidative stress, and receptor-mediated effects on brain cell proliferation, migration, differentiation, and synaptogenesis [11,12]. The central nervous system (CNS) is more vulnerable towards teratogenic agents than other organs, due to length of time over which developmental processes proceed, also including the postnatal period [13]. The formation of the blood–brain barrier is not completed until well after birth, leaving the brain relatively unprotected against toxic substances during this period [13]. Thus, prolonged exposure to maternal AEDs via breastmilk could theoretically pose an additional risk to the infant who has already been exposed during pregnancy.

Conversely, the beneficial effects of breastfeeding for both mother and child are widely documented and acknowledged. Breastfeeding is an essential biological function of humans and the normative standard of infant feeding [14]. Restricting a mother's natural inclination to breastfeed must therefore be justified by evidence that any harmful effect is likely to outweigh the advantages. Counselling women with epilepsy with regard to breastfeeding is a challenging task since they have to choose between an artificial food source or exposing their infant to a CNS acting drug.

Due to limited data on AEDs' safety during lactation, mothers with epilepsy have often received conflicting breastfeeding advice from their neurologist, paediatrician or gynaecologist.

In 2009, the American Academy of Neurology (AAN) updated their practice parameter for the management of women with epilepsy during pregnancy, but did not give any specific recommendations concerning breastfeeding [15].

Abbreviations: AED, antiepileptic drug; CNS, central nervous system.

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The aim of this paper is to provide an updated synopsis of AEDs and their safety during the lactation period, as well as to present practical recommendations for women with epilepsy who are motivated to breastfeed.

2. Methods

The recommendations are based on a discretionary selection of articles retrieved by literature search in the PubMed database performed on September 15, 2014. English language articles only were included. The search terms 'breastfeeding', 'breastmilk', and 'lactation' were linked to the terms 'antiepileptic drugs' and 'epilepsy', as well as search terms of the individual antiepileptic drugs. Information from the online LactMed database was also included. The authors' scientific and clinical experience of work with women with epilepsy has influenced the evaluation and recommendations.

3. Benefits of breastfeeding in the general population

Human milk and its bioactive components are ideally adapted to the needs of the nursing child, and is the ultimate nutrient source for infants [16]. Human milk enhances growth and development, as well as long-term child and adult health. Breastfeeding reduces the risk of infectious diseases in infancy, such as lower respiratory tract and gastrointestinal infections [14]. Other benefits include a lower risk of sudden infant death syndrome [17], allergic disease [18,19], and possibly inflammatory bowel disease [20]. Breastfeeding also protects against childhood leukaemia [21], reduces the risk of obesity, and type 1 and 2 diabetes [22–24].

The association between breastmilk and neurocognitive abilities in infants remains controversial. Many studies have investigated this relationship, but the reported findings have been conflicting [25]. On average, breastfed children score several points higher on tests of cognitive function compared to those who solely received formula milk [26]. However, maternal factors such as socioeconomic status, education, and intelligence represent major confounders for the association between breastfeeding and cognitive child development [14].

Breastfeeding is nevertheless an important aspect of the psychological mother–child relationship and promotes attachment security. Mothers who breastfeed demonstrate more sensitive parenting behaviour in early infancy [27]. Breastfeeding is also associated with positive effects on maternal health and well-being, including prolonged lactational amenorrhea, a reduced risk of postpartum depression, type 2 diabetes mellitus, and breast and ovarian cancer, as well as beneficial economic aspects [25,28].

4. Breastfeeding practice in women with epilepsy

Many factors influence a mother's decision to breastfeed. It is a common misconception that drugs taken by the mother are retained in the breastmilk [29]. Amongst women taking AEDs, some believe that the drug exposure for the child is higher during breastfeeding than pregnancy. Many are concerned that breastmilk will produce an unnecessary prolonged drug exposure for the infant, and regard formula milk as a safer alternative. Sleep-deprivation and missed medication during the postpartum period increase the risk of seizures [30]. Thus, some mothers fear that seizures might affect the safety of breastfeeding, or that breastfeeding could affect the risk of seizures.

Socioeconomic factors such as maternal education, income, employment, and social class affect both the initiation rate and duration of breastfeeding [28,31]. Women with epilepsy are at increased risk of having adverse outcome for such factors [5,32], probably affecting their ability or motivation to breastfeed. Indeed, Meador et al. [33] showed that breastfeeding mothers with epilepsy had higher IQ compared to those not breastfeeding. Emotional status and self-esteem may represent determinants for a mother's capacity to breastfeed. Women with epilepsy are especially vulnerable during pregnancy and in the post-partum period, with higher rates of depression and anxiety [32,34,35]. Hence, personal support and advice from family and health care workers can be essential for a mother in coping with the emotional and practical challenges of breastfeeding [30].

The child's developmental status may affect the practical aspects of breastfeeding, as AEDs during pregnancy are associated with delayed motor and social skills in the child during the lactation period [36]. In infants with inadequate developmental resources, i.e. reduced suckling or latching abilities, failure to succeed with breastfeeding can occur even if the mothers are motivated to do so.

Rates of breastfeeding vary between and within countries [28]. In the US, the initiation rate is 79%, with only 41% exclusively breastfeeding at 3 months [37]. The NEAD study group reported that overall 42% of women with epilepsy were breastfeeding at 3 months [33]. In Scandinavia, where the initiation rates of breastfeeding are around 90%, women with epilepsy have higher breastfeeding rates, as shown using data from the Norwegian Mother and Child Cohort Study (Fig. 1). In this study, women using either AED polytherapy or lamotrigine monotherapy had substantially lower breastfeeding rates compared to both non-epileptic controls as well as women taking other AED monotherapy. This indicates that the mothers and their physicians had safety concerns regarding specific drug groups.

5. Pharmacokinetic considerations

To affect the nursing infant, any drug used by the mother has to transfer through the breastmilk and reach the child's systemic

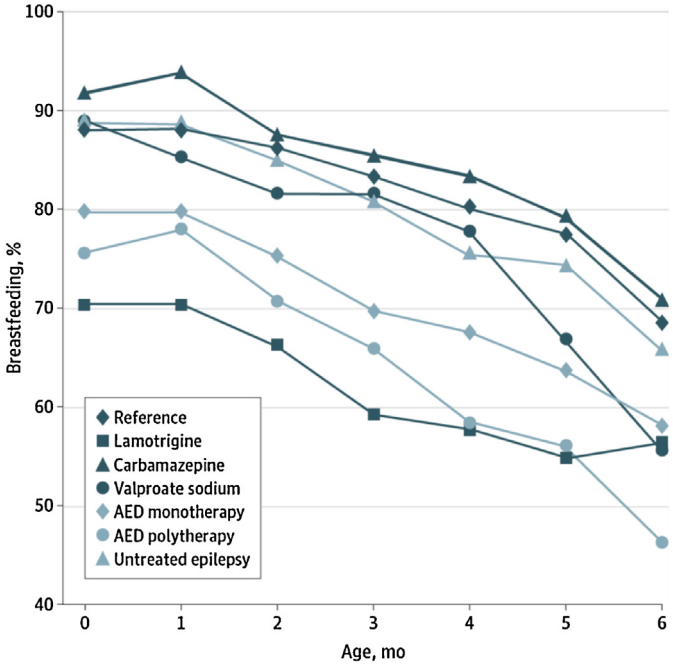

Fig. 1. Exclusive or mixed breastfeeding at ages 0–6 months. Frequency of breastfeeding in epilepsy groups and the reference group at 0 to 6 months after delivery. AED indicates antiepileptic drug.

blood circulation in such an amount that it can produce a pharmacological effect. Key determinants for the drug-dose to the infant are maternal plasma concentrations, degree of drug transfer to breastmilk, and the amount of milk that the infant ingests.

Maternal plasma levels and the *timing of breastfeeding* will be decisive for the concentration of a drug in the milk at the time of breastfeeding [29]. The passage of drugs between maternal plasma and breastmilk is mainly based on principles of passive diffusion across lipid membranes, following a gradient from high to low. As a consequence, the concentration of free unbound drug in the breastmilk is in constant balance with maternal plasma. When a drug reaches its highest concentration in the mother's blood, it will with a short delay also peak in the breastmilk. Conversely, as a drug is gradually eliminated by the mother, it will diffuse from the breastmilk and back into the plasma [29]. Drugs that are excreted into breastmilk in significant amounts are typically characterized by high maternal plasma concentrations, a low degree of protein binding, low molecular weight, and a high fat solubility [38].

The amount of breastmilk that the infant ingests will determine the final drug dose to the infant. However, the actual amount of drug that enters the child's systemic circulation also depends on the absorption, distribution, metabolism, and elimination of the drug by the infant [39]. This is especially relevant for infants younger than 2–3 months, and for premature infants in particular, since an immature capacity to metabolize and excrete substances can potentially lead to drug accumulation [29].

There are methods to calculate the infant's exposure to maternal drugs during lactation.

The milk/plasma (M/P) ratio is the relation between drug concentrations in the breast milk vs. maternal plasma, and expresses the degree of drug transfer into the breastmilk. An M/P ratio greater than 1 indicates that the drug is concentrated in breastmilk. However, this ratio alone has limited clinical value, as it does not always reflect the child's actual level of exposure, that is, the amount of drug that eventually reaches the infant's systemic circulation [40].

The infant's *theoretical dose* can be calculated by multiplying drug concentration in the milk with the volume of milk consumed by the child each day. To assess the risk of side effects, this estimated dose can be compared with the therapeutic paediatric dose [40]. Alternatively, if the therapeutic paediatric dose is not known, the theoretical infant dose can be compared to the mother's weight-adjusted dose; the so called *relative infant dose*. Estimated infant doses of less than 10 percent of the recommended paediatric dose, or relative to the mother's dose, are generally considered to be clinically insignificant [29,40].

In clinical practice, representative sampling or calculation of drug levels in breastmilk may not be easily obtainable. A practical and accurate way to assess the child's level of drug exposure is to measure the *infant's plasma concentrations*, and compare this to the recommended age-adjusted plasma levels, if known.

6. Safety of specific AEDs

In general, there are limited safety data for specific AEDs during lactation. Most recommendations are based on studies where the degree of penetration into breastmilk or infant serum levels have been measured, in combination with clinical experience, case reports on observed side effects, and pharmacokinetic considerations for the different drugs.

A number of resources are available to obtain information on the safety of various drugs in relation to breastfeeding. Recommendations from pharmacological drug companies are often not helpful, as this information may be constrained by legal considerations. Unfortunately, the AAN practice parameter update in 2009 did not include specific recommendations for breastfeeding in mothers taking AEDs, due to lack of scientific evidence on safety [15].

Many countries have individual guidelines for the follow-up of women with epilepsy during the puerperium. An accredited online source is the 'Drugs and Lactation Database' (LactMed) from the U.S. National Institute of Health, which is updated monthly and includes information on drug levels in breast milk and infant blood, as well as adverse effects in nursing infants [41].

The regularly revised 'Medications and Mother's Milk' by Hale et al. [42] is often recommended as general literature regarding breastfeeding and medications. In this manual, drugs are classified into five lactation risk categories, ranging from 'Safest' to 'Contraindicated' (L1–L5). In line with this classification, most AEDs can be divided into three main risk categories during breastfeeding; 'L2 – safe', 'L3 – moderately safe', or 'L4 – possibly hazardous'.

6.1. Safe AEDs

6.1.1. Phenytoin

Phenytoin is highly protein-bound in plasma and has a low degree of penetration into breastmilk, with a reported M/P ratio ranging from 0.1 to 0.6 [43]. Phenytoin is considered compatible with breastfeeding, with rarely reported side effects and low infant serum levels if maternal concentrations remain within the therapeutic range [43,44]. Case reports of adverse effects mainly include infants whose mothers were using phenytoin in combination with other AEDs [41].

6.1.2. Valproate

Valproate has a high degree of plasma protein-binding, and is excreted into breastmilk in very low concentrations with an M/P ratio of 0.01–0.3 [44]. Serum levels in breastfed infants are low, and no definite adverse reactions have been reported with maternal monotherapy [41].

However, due to a theoretical risk of hepatotoxicity, it is sometimes recommended that infants should be monitored for jaundice or other signs of liver dysfunction. A case of an infant with thrombocytopenia has been reported, but the correlation with maternal valproate use was unclear [45].

6.1.3. Carbamazepine

Carbamazepine has a moderately high degree of protein-binding in plasma and transfers into breastmilk to some degree, with an M/P ratio of 0.2–0.7 [44]. However, the serum concentrations of carbamazepine and its active epoxide metabolite are generally below the therapeutic range in nursing infants, and side effects are rarely reported [43,46]. A few case reports of liver dysfunction with jaundice and elevated liver enzymes, as well as reports of poor suckling and reduced weight gain, have been described in breastfed infants of mothers using carbamazepine as monotherapy [46–49].

6.2. Moderately safe AEDs

6.2.1. Lamotrigine

Lamotrigine is 55% protein-bound in maternal plasma and penetrates into breastmilk in moderate amounts, with a mean M/P ratio of 0.4 (range 0.1–1.4) [50]. Infants have a limited capacity to metabolize lamotrigine via hepatic UDP glucuronidation, which in combination with reduced plasma protein-binding can result in high serum concentrations in the breastfed neonate. Serum levels in breastfed infants are variable; on average 18% of maternal levels (range 10–27%), indicating that a clinically relevant risk of side effects is present. The free and unbound fraction of lamotrigine is even higher, with infant serum levels around 31% of maternal

levels (range 13–48%) [50]. However, adverse effects in infants are rarely reported, and lamotrigine exposure via breastmilk appears to be well tolerated [41]. Mild thrombocytosis has been described [50], as well as withdrawal symptoms related to abrupt termination of breastfeeding [51]. Maternal lamotrigine dose is often increased during pregnancy to account for increased drug-clearance. After delivery, immediate reduction of lamotrigine back to the initial prepregnancy dose is important to ensure that the breastfed infant's drug exposure is minimized. One case report describes serious apnoea in an infant whose mother used high doses of lamotrigine after delivery [52].

Lamotrigine is compatible with breastfeeding, but the child should be monitored for rash, poor suckling, and drowsiness. Infant serum levels should be measured if side effects are suspected [41].

6.2.2. Oxcarbazepine

Oxcarbazepine has a relatively low degree of penetration into breastmilk, with an M/P ratio around 0.5 [53]. Oxcarbazepine's primary route of elimination is through hepatic glucuronidation and could therefore, similar to lamotrigine, be expected to reach high serum levels in nursed infants. However, serum concentrations of oxcarbazepine and its active monohydroxy derivative (eslicarbazepine) appear to be low in breastfed infants [53–55], and there are no case reports on side effects [41]. Adverse effects during lactation are not expected, but due to limited clinical experience and data, oxcarbazepine is still classified as moderately safe.

6.2.3. Levetiracetam

Levetiracetam has a very low degree of protein-binding in plasma, a low molecular weight, and is transferred to breastmilk in extensive amounts with an M/P ratio of 1.0 (range 0.8–1.6) [56,57]. Still, serum concentrations in breastfed infant are low, indicating that levetiracetam is efficiently eliminated by the neonate [56,57]. There are no reports of adverse effects in nursed infants whose mothers were using levetiracetam monotherapy. Levetiracetam is therefore regarded as well compatible with breastfeeding [41].

6.2.4. Topiramate

Topiramate has a low molecular weight, a plasma protein-binding of 15%, and is significantly transferred into breastmilk with an M/P ratio of 0.9 (range 0.7–1.1) [58]. Limited data suggest that serum levels in breastfed infants are low with maternal doses at 200 mg daily or less [41,58]. A case report of a breastfed infant whose mother was treated with topiramate describes diarrhoea and reduced weight gain, probably caused by topiramate exposure via breastmilk [59].

6.2.5. Gabapentin

Gabapentin has a low molecular weight and minimal protein-binding in plasma. It has high penetration into breast milk, with an M/P ratio of 1.1 (range 0.5–2.0) [60]. Data from nine suckling infants showed that maternal gabapentin doses up to 2100 mg daily produced low infant serum concentrations between 4 and 12% of the mother's levels, and with no adverse effects in the neonates [60–62].

6.2.6. Pregabalin

Pregabalin has low molecular weight and low protein-binding in plasma, and is expected to transfer extensively into breastmilk. Very limited data from one mother–infant pair found an M/P ratio of around 1.0, but infant serum levels of only 8% of the mother's level, suggesting an efficient elimination in the newborn [63].

6.2.7. Vigabatrin

Vigabatrin has a low molecular weight and is not protein-bound. Data from two mother–infant pairs found a mean M/P ratio for the active (*S*)-enantiomer of 0.2 (range 0.04–0.2) and for the inactive (*R*)-enantiomer of 0.6 (range 0.1–0.9). The maximum dose to breastfed infants was estimated to be 0.6–1.0% of the maternal dose for the active (*S*)-enantiomer [64]. These limited data indicate that vigabatrin is compatible with breastfeeding.

6.2.8. Tiagabine

There are very limited published data on tiagabine during lactation. Tiagabine is highly protein-bound in plasma, and should be expected to be excreted into breastmilk in low amounts. One case report describes successful breastfeeding while taking tiagabine [65].

6.3. Possibly hazardous AEDs

6.3.1. Phenobarbital

Phenobarbital has a low to moderate transfer to breastmilk with an M/P ratio of 0.3–0.5 [43]. Due to an extremely long half-life and low degree of protein-binding in neonates, phenobarbital has the potential to accumulate during breastfeeding. In one case-report the infant's free drug fraction actually exceeded the mother's serum levels [66]. Yet, the estimated theoretical infant dose with phenobarbital during breastfeeding is much lower than the recommended paediatric dosage [67]. Thus, treatment with phenobarbital should be considered compatible with breastfeeding, but careful monitoring is warranted in breastfed infants. In case of suspected side effects such as drowsiness or poor weight gain, limiting or discontinuing breastfeeding might be justified [41].

6.3.2. Primidone

Primidone serves as a prodrug for its major active metabolite phenobarbital, and has relatively high excretion into breastmilk with an M/P ratio of 0.7 [67]. Similar to phenobarbital it has the potential to accumulate and produce high serum levels in breastfed neonates [41,66]. Caution is recommended during breastfeeding with particular attention to infant sedation or poor weight gain.

6.3.3. Benzodiazepines

Diazepam, midazolam, and lorazepam are used as treatment of acute epileptic seizures. *Diazepam* and its active metabolite are excreted into breastmilk with an M/P ratio of 0.5 (range 0.2–2.8) [68,69]. There is usually no need to wait to resume breastfeeding after a single dose of diazepam [41]. However, diazepam can accumulate in breastfed infants with repeated or continuous maternal administration due to a long half-life and slowed elimination in neonates. The half-life of diazepam is about 80 h in premature infants, 30 h in full-term newborns, and up to 20 h in older infants [29]. Sedative effects such as drowsiness and reduced weight gain have been reported in nursed infants of mothers taking diazepam daily [41]. *Midazolam* has a similar potential to accumulate in infants with prolonged use, but data on safety while breastfeeding are lacking [41]. *Lorazepam* produces low levels in breastmilk, and probably has a lower risk of side effects in nursed infants due to shorter half-life relative to other benzodiazepines [41].

Clobazam and clonazepam are used in the treatment of chronic epilepsy. *Clobazam* and its active metabolite have a high plasma protein-binding and relatively low penetration into breastmilk with an M/P ratio of 0.1–0.4 [44]. Data on side effects are lacking, but short-term use is considered to carry a low risk of adverse effects in breastfed infant [41]. *Clonazepam* has a low degree of transfer to breastmilk with an M/P ratio of about 0.3, but have the potential to accumulate in nursed infants due to a long half-life [67]. Sedative effects in breastfed infants have sporadically been

reported with clonazepam [41]. Prolonged use of clonazepam should be avoided during lactation and alternative shorter-acting drugs be considered.

A recent cohort study indicated that side effects in breastfed infants rarely occurs with maternal intake of the various benzodiazepines [70].

6.3.4. Ethosuximide

Ethosuximide has a high penetration into breastmilk, with an M/P ratio of 0.8–1.0 [43]. The relative infant dose has been calculated to be on average 62% of the maternal dose (range 32–113%), and serum levels in breastfed infants range from 24 to 75% of the mother's levels. This indicates that a clinically relevant risk of side effects is present [41]. Sedation, hyperexcitability, feeding problems and poor weight gain have been reported in neonates exposed to ethosuximide via breastmilk, but mainly for infants whose mothers also used co-medication with other AEDs [71]. There are no reports on adverse effects with ethosuximide as monotherapy. Still, careful monitoring during breastfeeding is recommended due to risk of high infant serum levels and potential toxicity [41].

6.3.5. Zonisamide

Zonisamide has a significant excretion into breastmilk with an M/P ratio of about 0.8 (range 0.7–0.9) [72–74]. Furthermore, neonates have a low capacity to eliminate zonisamide with an estimated half-life of 100 h [74]. Limited information suggests that zonisamide can reach high serum levels in breastfed infants during the neonatal period, but with a rapid decline during the first month of life. There are no reports of adverse events [41]. Zonisamide is compatible with breastfeeding provided careful monitoring, especially in exclusively breastfed infants.

6.3.6. Felbamate.

There are no studies available on felbamate during breastfeeding. Due to the complete lack of safety data and the risk of serious side effects in adults, including aplastic anaemia and acute liver failure, the recommendation is that felbamate is incompatible with breastfeeding [44].

6.3.7. Other AEDs

There are no evidence-based safety data on breastfeeding while taking *perampanel*, *lacosamide*, or *eslicarbazepine*. Special caution is recommended while breastfeeding, with attention to potential side effects such as drowsiness, or reduced suckling or weight gain in the infant. As eslicarbazepine is the main active metabolite of oxcarbazepine, no adverse effects are expected in breastfed infants for this drug [41].

7. Postnatal developmental effects

AEDs during pregnancy are associated with increased risk of congenital malformations and adverse development in the child. While maternal factors such as socioeconomic status and epilepsy type and severity may play a role, the risk is mainly mediated by the in utero drug exposure. AEDs might theoretically produce similar effects during the postnatal period. Thus, in addition to potential side effects in neonates such as drowsiness and poor feeding, AEDs via breastmilk could have an impact on the child's cognitive development and behaviour. Unfortunately, data on breastfeeding status have rarely been collected in studies on women with epilepsy and their offspring. Potential developmental effects of AEDs through breastmilk have only been systematically explored by two studies [33,36,75].

7.1. Development during the breastfeeding period

A recent prospective population-based study by Veiby et al. addressed infant development and breastfeeding status during the first months of life. A large cohort of women with and without epilepsy recruited during early pregnancy were followed until three years after delivery [36]. Validated, standardized screening tools completed by the mothers were used to determine whether the child reached developmental milestones at the expected age. The mothers also reported detailed information about breastfeeding during the first year. Among 223 children of mothers taking AEDs, continuous breastfeeding was associated with a more favourable development at age 6 months compared to those with discontinued or no breastfeeding (Fig. 2B). This was significant also for the subgroups whose mothers used AED polytherapy or lamotrigine monotherapy (Fig. 2C and D).

7.2. Development after the breastfeeding period

The NEAD study is a prospective and controlled multicenter-study that investigated long-term neurodevelopment in children of women with epilepsy taking monotherapy with commonly used AEDs during pregnancy. The children have been evaluated by AED-blinded assessment of cognitive outcomes at different ages. Breastfed children were compared to those with discontinued or no breastfeeding. In 199 children at 3 years of age, Meador et al. [33] found mean IQ scores of 99 and 98 for breastfed vs. nonbreastfed children. Furthermore, the investigators found identical IQ scores for breastfed vs. nonbreastfed children of mothers taking lamotrigine, whereas breastfed children whose mothers used valproate or carbamazepine scored several IQ points higher. At age 6 years, the investigators reported similar results for 181 children, with an overall significantly higher IQ in breastfed vs. nonbreastfed children (Table 1) [75].

The NEAD study group also assessed various developmental domains at age 6 years, and found that breastfed children in the AED exposed group had enhanced verbal abilities compared to those with discontinued or no breastfeeding during infancy [75].

The population-based cohort study by Veiby et al. [36] also examined postnatal development after the breastfeeding period. In children of mothers taking AEDs, breastfeeding during infancy was associated with less risk of impaired development at 18 months of age, and especially for autistic traits. At 36 months of age, there was no longer any apparent difference between the breastfed vs. nonbreastfed groups.

7.3. Postnatal weight gain

One cohort study addresses the risk of low weight gain in infants exposed to AEDs via breastmilk. Veiby et al. found that breastfeeding was associated with a lower risk of weight below the 10th percentile during early infancy. This was significant also for the subgroups exposed to lamotrigine monotherapy or AED polytherapy (Fig. 3A). The breastfed vs. nonbreastfed groups did not differ in weight at 6 months of age (Fig. 3B) [36].

8. Discussion and recommendations

It is generally recommended that women should breastfeed their infants at least for 12 months, and preferably exclusively for the first 6 months [76]. Breastfeeding is the optimal feeding method for infants, providing a variety of nutritional, immunological, developmental, and psychological benefits. Such benefits could be of particular importance in children of women with epilepsy. However, breastfeeding is often considered 'elective' in

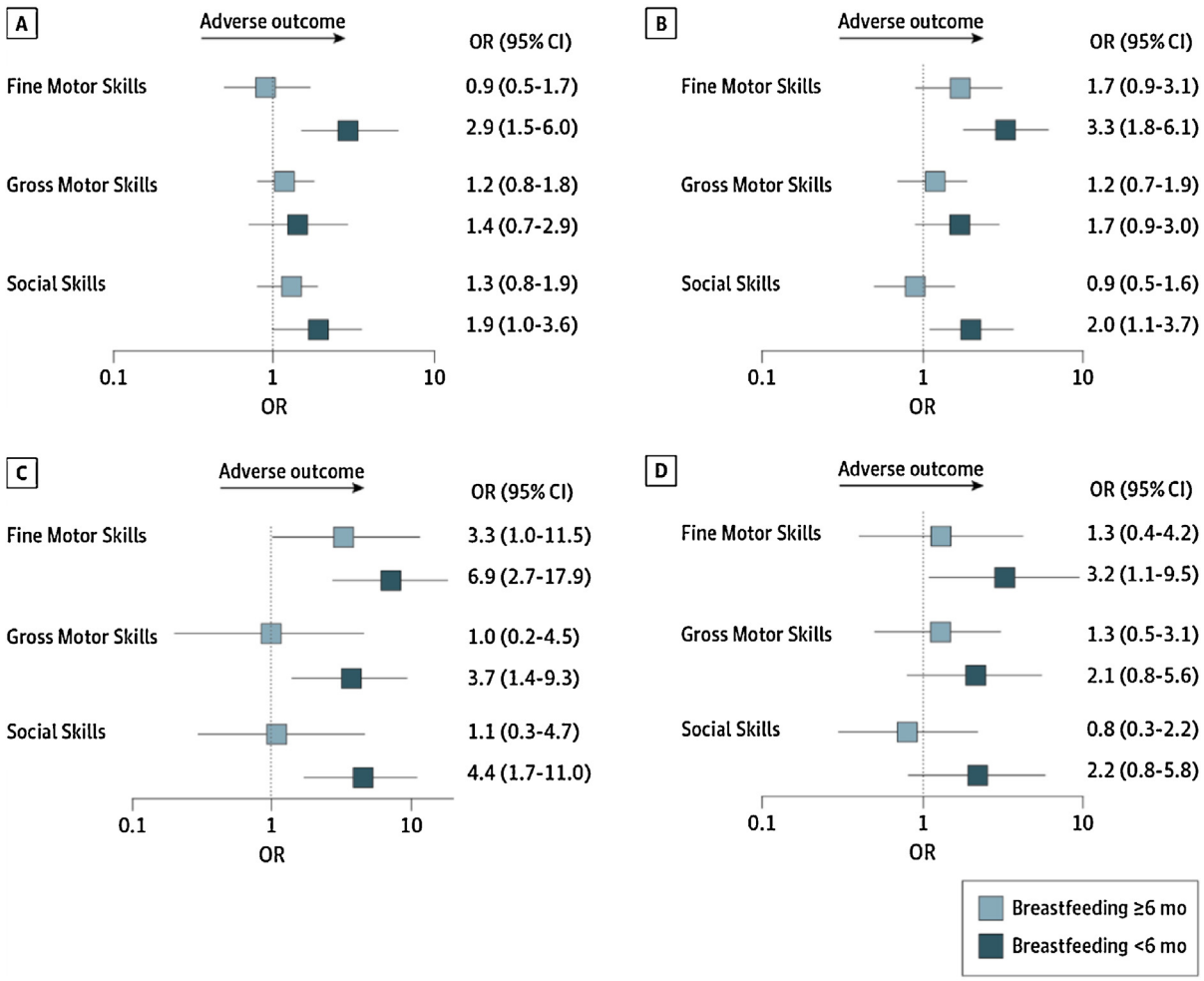

Fig. 2. Risk of Adverse development score at 6 months in children of mothers with epilepsy according to breastfeeding. Epilepsy groups with no maternal antiepileptic drug use (A), maternal antiepileptic drug use (B), maternal antiepileptic drug polytherapy (C), and maternal lamotrigine monotherapy (D) were examined. Odds ratios (ORs) with 95% CIs were adjusted for maternal age, parity, smoking, folate use, education, anxiety/depression, and child malformation.

epilepsy populations due to concerns about toxic effects of AED exposure via breastmilk [77].

The amount of AED that is transferred to the child can be difficult to predict, and systematic prospective studies on safety of individual AEDs while breastfeeding is sorely needed, especially for recently marketed anticonvulsants. Studies that have examined AEDs via breastmilk generally report infant serum concentrations well below the level where a pharmacological effect can be expected, and adverse events are rarely observed. This also applies for many of the AEDs that have a high penetration into breastmilk. Some AEDs have the potential to reach significant serum levels in breastfed infants, i.e. barbiturates, benzodiazepines, lamotrigine, and ethosuximide, and careful monitoring of side effects is necessary. However, in most cases, the amount of drug that reaches the child's systemic circulation is not clinically relevant. Most published data on side effects in breastfed neonates are

Table 1
Adjusted IQs at age 6 years across antiepileptic drugs (AEDs) comparing breastfed vs nonbreastfed children.[a]

AED group	IQ, mean (95% CI)			*P* value
	Breastfed	Nonbreastfed	Difference	
All AEDs	108 (105–111) (*n* = 78)	104 (101–106) (*n* = 103)	4 (0 to 8)	.04
Carbamazepine	107 (101–113) (*n* = 23)	105 (99–110) (*n* = 24)	2 (−6 to 11)	.61
Lamotrigine	113 (110–117) (*n* = 27)	110 (107–113) (*n* = 34)	3 (2 to 8)	.23
Phenytoin	104 (99–110) (*n* = 17)	108 (103–113) (<*n* = 20)	−4 (−12 to 4)	.23
Valproate	106 (97–115) (n = 11)	94 (88–100) (*n* = 25)	12 (1 to 24)	.04

[a] Adjusted for other significant factors in the model (i.e., maternal IQ, AED group, AED dosage, periconception folate use, and breastfeeding) plus the propensity score. The following were not significant: Socioeconomic status, educational level, race/ethnicity, seizure or epilepsy type, maternal age, number of convulsions (none vs >5), United Kingdom site, any use of alcohol during pregnancy, any use of tobacco during pregnancy, employment (at the time of enrollment), pregnancy complications, prior pregnancy complications, prior pregnancy birth defects, and whether the pregnancy was unwanted.

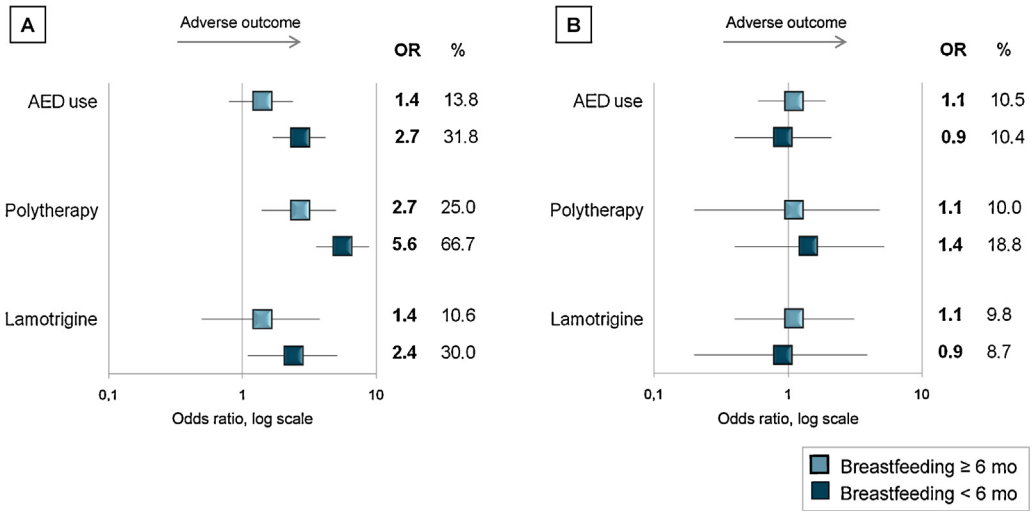

Fig. 3. Risk of weight below the 10th percentile at 6 weeks (A) and 6 months (B) in children of mothers with epilepsy according to breastfeeding. Odds ratios (ORs) were adjusted for low birth weight, preterm delivery, maternal education, age, parity and smoking.
The figure is based on data from Veiby et al. [36].

case-reports, where a causal relationship between the symptoms and the child's drug exposure is difficult to establish [29]. In any case, the infant's drug exposure is invariably much lower than during pregnancy. Some even argue that AEDs via breastmilk could have a beneficial tapering effect for the infant that has already been exposed in utero, minimizing the child's total experience of side effects over time. Discontinued breastfeeding has been associated with withdrawal symptoms in neonates of mothers taking high dose barbiturates [78].

Two prospective studies have evaluated the risk of adverse development in children exposed to AEDs via breastmilk [33,36,75]. Both studies were unable to demonstrate any deleterious effects of breastfeeding, even with adjustment for potential confounders such as maternal education, IQ, folate use, AED dose, and maternal depression or anxiety. Still, a mother's motivation or ability to breastfeed may be influenced by residual factors that could be important for child development and behaviour. Only a minority of the marketed AEDs were examined, and the studies were also limited by small sample sizes within each AED group. However, as both studies found a more favourable outcome in those that were breastfed, it is unlikely that larger samples would reveal any major negative effects on development. Thus, the developmental effects that have been associated with in utero exposure to AEDs should not be extrapolated to exposure during lactation. Any adverse cognitive effects of AEDs via breastmilk remain purely theoretical, in contrast to the many well-documented benefits of breastfeeding.

The general expert opinion is that women with epilepsy taking AEDs should be encouraged to breastfeed, based on the assumption that the manifold advantages of breastmilk outweigh any harm from a modest drug exposure [77]. In order to succeed with breastfeeding, measures should be undertaken to reduce the risk of infant side effects, as well as support the mother, and prevent seizures during the postpartum period (Table 2).

The child should be monitored closely when the mother is using an AED that has the potential to accumulate in breastfed infants. If side effects are suspected, repeated infant serum levels should be measured [79]. It may also be useful to schedule a period without breastfeeding to observe if the infant's symptoms disappear, or if the symptoms return when breastfeeding is resumed [29]. If regarded necessary, a solution to minimize the infant's drug dose is to administer mixed nutrition with some breastmilk and some formula milk. This is relevant for recently marketed AEDs with an undetermined safety profile. For drugs with a short half-life, the infant's exposure can be reduced by breastfeeding when milk concentrations are low, i.e. immediately before the next drug dose [79]. To avoid high maternal serum concentrations, it is important to ensure that AEDs where the dose is increased during pregnancy are swiftly tapered off postpartum. An algorithm for dose adjustment during pregnancy and postpartum has been proposed for lamotrigine [80].

Safety and care of the newborn are very important issues for mothers with epilepsy [81]. Special attention towards postpartum depression may be essential to succeed with breastfeeding and promote mother–infant attachment. Planning to avoid sleep

Table 2
Recommendations for breastfeeding in mothers taking antiepileptic drugs.

Breastfeeding should be encouraged	Most AEDs are compatible with breastfeeding with a safe or moderately safe risk of side effects in the infant. Online information: http://toxnet.nlm.nih.gov/newtoxnet/lactmed.htm
Observe the infant	Monitor for drowsiness, reduced suckling activity, and poor weight gain; especially infants that are premature or in poor health. If side effects are suspected, consider analysis of drug serum-levels in the infant. Evaluate if developmental milestones are reached as expected
Consider mixed nutrition	For AEDs with undetermined breastfeeding safety, or if side effects are suspected in the infant, consider mixed nutrition with partial breastfeeding and formula milk supplement.
Breastfeed at the lowest drug level	Take AED immediately after breastfeeding, or immediately before the infant's longest sleep period.
Consider postpartum dose adjustment	If maternal AED drug dose has been increased during the pregnancy, ensure postpartum dose tapering until the mother's optimal serum-level is reached.
Discuss safety issues	Discuss measures that may prevent maternal depression, sleep deprivation, and missed medications postpartum. Suggest safe breastfeeding techniques in case of seizures.

deprivation can prevent seizures during the postpartum period, and safe breastfeeding techniques in the event of seizures or myoclonic attacks should be discussed, that is, the mother can be advised to breastfeed in a supine position, where the infant would be protected against traumatic injury.

9. Conclusions

Providing balanced information about the benefits and potential risks of breastfeeding while taking AEDs is an important and challenging task. In most cases, the benefits of breastfeeding outweigh any harm from a modest exposure to AEDs via breastmilk. Breastfeeding should generally be encouraged in women with epilepsy. However, women taking AEDs are particularly vulnerable during pregnancy and after delivery, and it is important not to impose pressure by too aggressive promotion of breastfeeding. In situations where harmful effects of AEDs via breastmilk are a major concern, formula milk or mixed nutrition might be the appropriate solution. In our experience, most women with epilepsy are highly motivated to breastfeed their infants and grateful to receive support and advice in this regard.

Conflict of interest

G. Veiby has received congress travel support from GSK and UCB Pharma and lecture fee from GSK. B.A. Engelsen has received congress travel support from GSK and lecture fee from Lundbeck. M. Bjørk has received congress travel support from GSK and UCB Pharma and lecture fee from GSK. N.E. Gilhus has received lecture fee from Octapharma, Baxter, and Merck Serono.

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