

# Intake of anticonvulsant drugs by women with epilepsy during pregnancy and breastfeeding: advantages and disadvantages

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## Abstract

Anti-epileptic drugs (AED) are being widely used in neurological practice. These are being prescribed as standard treatment not only of epilepsy, but also in various non-epileptic conditions, such as psychic illnesses and chronic pain.

The main issue for women with epilepsy and their doctors during the AED administration is child and mother's safety during pregnancy and breastfeeding. Anti-epileptic treatment during these periods could have an unfavourable impact on the frequency of mother's seizures and child's psychomotor development. Breastfeeding-related risks during the AED administration remain theoretical, bearing in mind the insufficient data from the limited previously undertaken research. In view of the established benefits from breastfeeding for babies' long-term health in the general population, breastfeeding is to be promoted, with discretion on whether this should be balanced, individual, with monitoring of AED concentration in mother's milk and mother and breastfed child's serum.

## Keywords

anti-epileptic drugs, pregnancy, lactation, monitoring, risks

## Introduction

The action mechanism of most anti-epileptic drugs (AED) is complex and impacts numerous areas; knowing this is highly significant to ensure the right choice by the doctor. The common factor shared by the different presumable mechanisms for numerous drugs includes the opportunity for modulating the exciting and inhibiting neurotransmission via effects on to the voltage-gated ion channels, synaptic plasticity, heterogeneous receptors and metabolism of neurotransmitters (Kuzmanova et al. 2014). The complexity of AED action creates prerequisites for opti-

mal treatment choice when treating women of child-bearing age.

The topic of this review is the presence of certain risks and benefits of AED intake during pregnancy and lactation by women with epilepsy as a summary of the available literature data.

The use of AED by pregnant women with epilepsy could not be avoided even though it is possible in the case of other diseases. The administration of some AED during pregnancy is related to the increased risk of congenital malformations, growth inhibition and child's neurological development slowdown (Veiby et al. 2009, 2013a; Tomson

et al. 2011). The accurate combination of different AED when polytherapy is necessary also lowers the risk of future malformations of the foetus.

In recent years, doctors have been promoting breastfeeding by women taking AED, while also taking into account the ensuing physiological benefits. They promote the usage of folic acid at higher daily doses that starts even before pregnancy since it is believed to improve children's neurological development. These research works are necessary especially for the newer AED for which no data have been accumulated in clinical practice. Some authors establish developmental disturbances of children exposed to AED through mother's milk, yet opinions have been stated that unfavourable cognitive effects of AED during breastfeeding remain purely theoretical unlike the numerous well-established benefits of breastfeeding (Veiby et al. 2013b, 2015). Thus, for example, the intake of high doses of barbiturates during pregnancy and subsequent breastfeeding results in favourable effects for the child since it prevents the symptoms of medicinal deprivation (Rauchenzauner et al. 2011).

## AED administration during pregnancy by women with epilepsy

Women with epilepsy do not suspend their treatment with AED after pregnancy confirmation, because of the profound risk of fainting (Meador 2014). This necessitates the right selection of drugs being used by women with epilepsy at child-bearing age. In recent years, there have been data from research works that establish the risks related to the intake of the various types and doses of AED. In view of teratogenicity, the new AED have better parameters that results in their increased use by women of this age range (Reimers 2014). In the case of many drugs during pregnancy and after birth, significant pharmacokinetic changes occur. In the case of pregnancy onset, oftentimes we need to increase the AED doses because of the risk of mother's seizures becoming more frequent. On the other hand, the use of higher doses or serum concentrations correspondingly could result in foetus injuries. We aim at using as low as possible, yet therapeutic, AED doses.

The incidence of major congenital malformations is associated with early AED exposure, polytherapy of anti-seizure medication, the dose and type of AED, low serum folate concentrations and low maternal level of education (Li et al. 2022). A meta-analysis including 65,533 pregnancies in women with epilepsy exposed to carbamazepine, lamotrigine, **phenobarbital**, **phenytoin** or valproate showed that the overall incidence of congenital malformations in children born to women with epilepsy is approximately threefold that of healthy women (7.08% compared to 2.28%), with the highest incidence for AED polytherapy (16.78%) (Meador et al. 2008). In view of some AED, it was established that they bear a higher teratogenic risk (for example, **Valproate**), whereas in view of other drugs, data are still missing. The use of valproate

significantly increases the risk of major defects. These include spina bifida, atrial septal defect, cleft palate, hypospadias, polydactyly and craniosynostosis. There are case reports of intra-uterine growth restriction, infant hepatic toxicity and foetal distress, neurodevelopmental associations – foetal exposure to valproate in utero is associated with the risk of autism spectrum disorders (Macfarlane and Greenhalgh 2018). Minor dysmorphic features, such as epicanthic folds, small mouth, abnormal philtrum, dysplastic ears, hypoplastic digits and nails, were described in AED-exposed infants. It was observed that children exposed to valproate, **carbamazepine** and polytherapy had more minor dysmorphic features compared to other groups (Kini et al. 2006).

Based on registers for epilepsy and pregnancy in the United Kingdom and Ireland, we found that, from the exposure to **levetiracetam** of 304 women on monotherapy and 367 women on polytherapy in the first trimester, the malformation frequency in the group with monotherapy was 0.70% (95% CI 0.19–2.51) and in the group of polytherapy, it was 5.56% (95% CI 3.54–8.56) (Mawhinney et al. 2013). In the case of **topiramate**, the malformation per cent is communicated as 4.2% to 4.9% for monotherapy, with increased risk of cleft lip and cleft palate and hypospadias (Margulis et al. 2012). The Australian register of pregnancy provides information about an especially high percentage of malformations during the intake of topiramate when being used as polytherapy, in 14.1% with relatively high risk of 4.32% (95% CI 1.57–11.05) compared to the ones without therapy (Vajda et al. 2014). Prospective cohort research in Canada, Europe and Korea provides information about 223 women exposed to **gabapentin** and 223 controls (Fujii et al. 2013; Pennell 2016). The degree of malformations is similar in both groups (4.1% in the gabapentin group), yet the gabapentin group has higher levels of premature births. Low birth weight and neonatal complications, 38%, have been received in intensive care for new-borns or crèches for special needs versus only 2% in the control group (Pennell 2016). Results have been communicated about higher number of malformations in pregnancy after exposure to **pregabalin** compared to the control population (Winterfeld et al. 2016).

## AED administration during breastfeeding by women with epilepsy

The favourable effects of breastfeeding for the mother as well as for the child have been widely documented and recognised. Breastfeeding is a fundamental biological function and feeding standard for babies (Tomson et al. 2011). Many factors impact the decision made by the mother with epilepsy to breastfeed, whereas the main consideration is that breastfeeding would extend the child's exposure to AED. We take into consideration the interruption of mother's sleep because of breastfeeding and the increase of risk of seizures. Based on the reviewed litera-

ture, we present data about the transfer of various AED from plasma in mother's milk and in what concentration these were found in baby's plasma, as well as data about undesired reactions during breastfeeding and risk of foetal malformations.

## Classic anticonvulsants

**Phenytoin** is drug that is greatly connected to plasma proteins and penetrates in breast milk to very low degree, whereas the milk/maternal serum concentration ratio ranged from 0.1 to 0.6 (Tomson 2005). Phenytoin serum concentrations are measurable only in two out of six breastfed babies; the ratio serum concentration of baby/mother is 0.01. It is perceived as compatible with breastfeeding with rarely communicated side effects (Bar-Oz et al. 2000).

**Phenobarbital** has low to moderate transfer in breast milk with ratio 0.3–0.5 (Tomson 2005). After examining 37 women, the ratio of concentration of milk/mother's serum varies from 0.16 to 0.70, whereas most ratios are around 0.40 (Tomson et al. 2022). The reported side effects during breastfeeding with the drug are signs of lethargy in the baby (Pote et al. 2004).

**Primidone** contains main active metabolites and has a relatively high transfer in breast milk with the ratio of 0.7 (Davanzo et al 2013a). In 36 monitored women, the ratio of serum concentration of primidone in milk/mother varies from 0.48 to 1.1, whereas most ratios are between 0.7 and 0.8 (Tomson et al. 2022). There is information about two babies with continuous difficulties while eating and cases of sedation have also been reported (Kaneko et al. 1982).

**Valproate** is connected to a great degree to plasma proteins and is excreted in breast milk in very low concentrations, whereas the milk/maternal serum concentration ratio ranged from 0.01 to 0.3 (Bar-Oz et al. 2000). In 56 women, ratios of valproate concentration in breast milk/mother's serum vary from 0.01 to 0.10, whereas most figures are around 0.025 (Kacirova et al. 2019). The ratios of serum concentrations of breastfed babies/mothers have been reported in 34 pairs mother-child and vary from babies' levels below the quantification level to 0.25, with the majority being around 0.1 (Birnbaum et al. 2020). Due to the theoretical risk of hepatotoxicity, sometimes it is recommended for breastfed babies to be monitored for jaundice (Veiby et al. 2015).

**Carbamazepine** has moderately high degree of connectedness to proteins in plasma and transfers in breast milk to some degree, with ratios of 0.2–0.7 (Bar-Oz et al. 2000). In 72 cases, the ratios of carbamazepine concentration in mother's milk/serum are from 0.13 to 1.5, whereas in most cases, it is below 0.5 (Kacirova et al. 2021). There are several cases of liver dysfunction with jaundice and increased liver enzymes, whereas the role of carbamazepine through breastfeeding in these cases has not been fully clarified (Veiby et al. 2015).

**Ethosuximide** has high penetration in breast milk, with a ratio of 0.8–10 (Tomson 2005). During research,

we have established concentrations for breastfed babies on average of 62% of the mother's concentration (32–113%), demonstrating there is clinically significant risk of side effects (Drug and Lactation 2014). There are reports about 12 pairs of mother-child and ratios from 0.3 to 0.75 (Soderman and Rane 1986; Tomson and Villen 1994).

**Benzodiazepines.** It was established that Diazepam is excreted in breast milk with the ratio of 0.5 (0.2–2.8) (Dusci et al. 1990). The undesired manifestations are sedative effects, sleepiness and slowed weight gain (Drug and Lactation 2014). Midazolam has similar accumulation in breastfed babies during continuous use, whereas Lorazepam is with low levels in breast milk, because of its shorter half-life (Drug and Lactation 2014). Clonazepam is also accumulated in breastfed babies because of the long half-life (Davanzo et al. 2013).

## New anticonvulsants

The new AED transfer in mother's milk varies depending on their physicochemical properties. Approximately 30% of mother's serum concentrations have been observed in lamotrigine and topiramate, and in single reports about brivaracetam, lacosamide and perampanel.

**Lamotrigine** passes from blood in breast milk, varies between 40% and 60% and is related to the dose taken by the mother (Newport et al. 2008). Serum concentrations of lamotrigine in new-born babies are approximately equal to the lamotrigine concentrations of the mother. There are other reports about much lower concentrations of lamotrigine in breastfed babies/mothers that vary from 0.03 to 0.5 (Fotopoulou et al. 2009; Clark et al. 2013). In 92 cases, the ratios of lamotrigine concentration in breast milk compared to mother's serum vary from 0.18 to 1.4, with average values in most research works within the range from 0.6 to 0.7 (Ohman et al. 2000; Newport et al. 2008; Paulzen et al. 2019). In 166 couples of mother-child, the ratios of serum concentrations of breastfed babies/mothers are from 0.2 to 0.9, whereas the average value is around 0.3 (Nordmo et al. 2009; Bedussi et al. 2018). When monitoring 50 couples of mother/baby in these research works, no side effects were noted (Reimers 2014). By way of exception, in the case in which the breastfed child has an episode of apnoea, the mother used Lamotrigine in a daily dose of 850 mg (Nordmo et al. 2009). Additionally, slight thrombocytosis as well as symptoms of deprivation, related to sudden breastfeeding termination have been described (Popescu et al. 2005; Newport et al. 2008). No cognitive deficits were found in monitoring the average IQ between 30 breastfed and 36 non-breastfed children aged three (Meador et al. 2010). Research has been reported that includes 35 breastfed babies who did not establish side effects at different ages of the child (Page-Sharp et al. 2006; Prakash et al. 2016).

**Oxcarbazepine** has relatively low degree of transfer to breast milk, with a ratio of around 0.5 (Bulau et al. 1988). When examining six couples of mother/child, we found

serum concentrations of baby/mother from 0.002 to 0.009 (0.003 on average) (Antonucci et al. 2018). The serum concentrations of the reported babies did not exceed 5% of the mother's plasma levels and no harmful effects were established (Eisenschenk 2006; Lutz et al. 2007). Serum concentrations of oxcarbazepine and its active production (eslicarbazepine) are low in breastfed babies and there are no communications of cases on side effects (Ohman and Tomson 2003; Lutz 2007). Due to the limited clinical experience and insufficient data, at present, oxcarbazepine is classified as moderately safe.

**Levetiracetam** is connected to a very low degree to proteins in plasma and passes in breast milk in significant quantities, in the ratio of 1.0 (0.8–1.6) (Johannessen et al. 2005). In 82 cases, the ratios of levetiracetam concentration in breast milk/mother's serum is from 0.58 to 1.79, whereas the average values in most research are around 1.0 (Kacirova et al. 2021; Dinavitser et al. 2022). On the other hand, serum concentrations in breastfed babies are low and this demonstrates that levetiracetam is being effectively eliminated by the new-born child. Although there are rare reports about side effects of breastfeeding, there is a communicated case of hypotony in one of eight breastfed babies (Johannessen et al. 2005). Three cases of sedation have been communicated in 16 children breastfed by mothers on levetiracetam, which disappeared after passing to partial breast-feeding (Dinavitser et al. 2022). Large-scale prospective research of 84 breastfeeding women who take levetiracetam does not demonstrate unfavourable effects at the age of two (Meador et al. 2021).

**Topiramate** has low connection to plasma proteins of around 15% with significant passage in breast milk, on average 0.9 (0.7–1.1) (Ohman et al. 2002). In 31 women, the ratios of topiramate concentration in breast milk/mother's serum are from 0.62 to 2.43 with an average of 1.0 (Kacirova et al. 2021). It is supposed that serum levels of breastfed babies are low if the mother takes the drug at below 200 mg daily or less (Ohman et al. 2002). There is a report on a case of a breastfed baby with diarrhoea and slow weight gain, probably caused by the exposure to topiramate through breast milk (Westergren et al. 2014).

**Gabapentin** passes in breast milk at a high percentage, with an average ratio of 1.1 (0.5–2.0). While researching nine breastfed babies (daily dose to 2100 mg), we established low serum concentrations in breastfed babies from 4% to 12% of mother's levels (Ohman and Tomson 2009). In seven mother-child couples, the serum concentrations of breastfed babies/mothers were with an average ratio of 0.1 (Kristensen et al. 2006).

**Pregabalin** has low molecular weight and poor connection to proteins in plasma and transfers to high degree in breast milk, correspondingly. In 10 breastfeeding mothers with administration of pregabalin for three days, the average ratio of serum concentrations in breast milk/mother was 0.76 (Lockwood et al. 2016). One mother-baby couple established a ratio of around 1.0, yet the baby's serum levels were only 8% of the mother's level (Ohman et al. 2011).

**Brivaracetam.** There are limited data about concentrations in breast milk or serum concentrations in breastfed babies. When examining two couples of mother-child, the serum concentrations in breastfed babies were below the quantification level on the fifth day up to three weeks after the birth of one baby, whereas the ratio of serum concentration of baby/mother was from 0.18 to 0.20 in the other case. There are no data about side effects in breastfeeding children by mothers undergoing treatment with brivaracetam (Landmark et al. 2021).

**Lacosamide.** In one case, the ratio concentration of lacosamide in breast milk/mother's serum was 0.1 (Ylikotila et al. 2015). In the second reported case, the ratio of serum concentration of breast milk/mother was 0.80–0.86 and the ratio of serum concentration of baby/mother was 0.27–0.28 (Landmark et al. 2021). There are no data about development disturbances of children breastfed by mothers who take lacosamide.

## Discussion

The main risks related to AED administration during pregnancy are related to increased risk of congenital malformations of the foetus, whereas the unfavourable side effects during breastfeeding are sleepiness and poor diet. It is hard to foresee the AED quantity passed to the child because of the low number of research reports in the field. There are few authors who have systematically studied the effects on to the child's development while it was exposed to AED through mother's milk (Meador et al. 2010, 2014). After the onset of pregnancy, the most important changes are kidney blood flow increase by 50–80%, increase in serum concentration of oestrogens and increase in total water and fat stocks in the body (Reimers 2014). The kidney blood flow significantly increases as soon as two weeks after fertilisation and could result in accelerated kidney elimination of drugs, especially the ones that are excreted mainly unmodified through the kidneys. In addition to bodily fluid and fat increase, what is essential is the low serum albumin that results in the increase in the free fraction of the drugs. Usually, these changes subside up to two weeks after birth. With changes in metabolism and elimination of drugs, AED serum concentrations correspondingly also recover within the same period that requires recovery of the initial doses (Sabers et al. 2012; Reisinger et al. 2013). The best researched drug use amongst all new AED during pregnancy is Lamotrigine. Its serum concentrations go down by 40–60% during pregnancy, whereas most lowered values occur as soon as during the first trimester. The recovery of Lamotrigine serum concentrations is expected up to two weeks after birth. Oxcarbazepine or its active metabolite licarbazepine goes down by 30–40%, while serum concentrations of levetiracetam go down by 40–60% during pregnancy, most probably because of accelerated kidney elimination, their recovery being up to one week after birth (Westin et al. 2008). Eslicarbazepine



follows the same elimination pathways like licarbazepine which suggests a similar decrease of its serum concentrations (Reimers 2014). The concentrations of topiramate go down by 30–40% (Ohman et al. 2009).

Literature contains a large volume of data about foetal malformations related to mothers using AED during pregnancy and, in recent years, they also started communicating data about foetal malformations during pregnancy with the use of some new AED. We have established the basic teratogenic action mechanisms, based on antagonism of folic acid, apoptosis induction, oxidative stress and receptor-mediated effects on proliferation, migration, differentiation and synaptogenesis of brain cells (Ikonomidou and Turski 2010). More and more research works in recent years report on the absence of danger for the child when being breastfed by a mother who uses new AED. The new AED could impact the hormonal homeostasis and pass in mother's milk, whereas once again, the best researched drugs are lamotrigine, levetiracetam and oxcarbazepine. Despite this, there are significant data supporting the favourable effects of breastfeeding for the child as well as for the mother (Ip et al. 2009).

It is hard to define the relationship between AED exposure through breastfeeding and breastfed child's symptoms if there are undesired reactions. The examples are reports on unfavourable effects as sedation during breastfeeding with ethosuximide, phenobarbital and primidone, yet no data have been documented about children breastfed with AED and without side effects (Tomson et al. 2022). Veiby et al. (2013b) performed prospective population research on baby development while he or she was breastfed during the first months of his/her life. A large group of women has been monitored with and without epilepsy during early pregnancy and after birth for a period of three years. In the case of 223 children of mothers who intake AED, continuous breastfeeding is related to more favourable child's development at the age of 6 months compared to the ones with suspended or missing breastfeeding. This is significant for the sub-groups with mothers who used lamotrigine as poly- or monotherapy (Veiby et al. 2013b). Shawahna and Zaid (2022) established the presence of all researched AED in mother's milk (carbamazepine, ethosuximide, gabapentin, lamotrigine, levetiracetam, phenobarbital, primidone, topiramate and valproate) while reporting relatively high values of baby's relative dose with ethosuximide and lamotrigine. Bearing this in mind, they express an opinion on the need for monitoring breastfed babies exposed to ethosuximide, phenobarbital and primidone (Shawahna and Zaid 2022). Another prospective cohort research that includes children exposed to lamotrigine established that continuous breastfeeding is related to lesser developmental disturbance at the age of six and eighteen months compared to the ones who have not been breastfed or were breastfed for less than six months (Veiby et al. 2013a).

The information is about sedation or over-excitement, feeding problems and poor weight gain in the case of new-

borns exposed to ethosuximide via mother's milk, yet in most cases, the mother is on polytherapy (Kuhnz et al. 1984). The treatment with phenobarbital and phenytoin is perceived as compatible with breastfeeding, yet we should closely monitor the child. Both drugs have accumulation potential and produce high serum levels in breastfed newborns (Kuhnz et al. 1988). Most authors are of the opinion that benefits from breastfeeding exceed the low risk of side effects related to AED.

## Clinical recommendations

The concentration and type of medications are to be specified even before becoming pregnant and to be maintained adequately during pregnancy. During pregnancy, we should systematically examine the serum AED levels of the mother in order to maintain them within the therapeutic limits. During pregnancy, especially drugs with higher teratogenic risk (for example, Valproate, Topiramate) should be avoided. The accurate combination of different AED when polytherapy is necessary also lowers the risk of future malformations of the foetus. The usage of folic acid at higher daily doses is recommended starting even before pregnancy since it is believed to improve children's neurological development. This is necessary especially for the newer AED in view of which no data have been accumulated in clinical practice.

Breastfeeding is to be promoted in the case of women on AED, bearing in mind its benefits for babies' long-term health in the general population. At present, oxcarbazepine, levetiracetam, gabapentine and lacosamide are classified as moderately safe during breastfeeding. The provision of information about benefits and potential risks is essential in order for the mother and the attending doctor to arrive at the right decision.

## Conclusion

The intake of anti-epileptic drugs by women with epilepsy during pregnancy and breastfeeding has its advantages and disadvantages. Unlike other diseases, treatment for epilepsy during pregnancy cannot be suspended. The selection of anticonvulsants is of paramount importance during this period in order to lower the risk of congenital malformations and subsequent slowdown of psychomotor development of the child.

Breastfeeding decision-making is a responsible process that should not endanger children's health and development in the long run. Discretion on this matter should be balanced, tailored and it should be possible to monitor the AED concentrations in mother's serum, in her breast milk, as well as the serum levels of drugs in the breastfed baby. Monitoring and collecting such information in future research projects is a challenging task.

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