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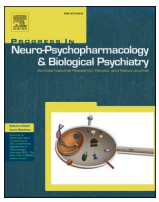

# Transfer of anticonvulsants and lithium into amniotic fluid, umbilical cord blood & breast milk: A systematic review & combined analysis

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ABSTRACT

*Objective:* Data on the ability of anticonvulsants and lithium to enter fetal and newborn circulation has become increasingly available; here we estimated penetration ratios in a series of matrices from combined samples of pregnant/breastfeeding women treated with anticonvulsants or lithium.
*Methods:* We conducted a systematic literature search in PubMed/EMBASE for studies with concentrations of anticonvulsants/lithium from maternal blood, amniotic fluid, umbilical cord blood and/or breast milk. Penetration ratios were calculated by dividing the concentrations in amniotic fluid, umbilical cord plasma or breast milk by the maternal concentrations. When data from multiple studies were available, we calculated combined penetration ratios, weighting studies' mean by study size.
*Results:* Ninety-one eligible studies for brivaracetam, carbamazepine, clonazepam, ethosuximide, gabapentin, lacosamide, lamotrigine, levetiracetam, lithium, oxcarbazepine, perampanel, phenobarbital, phenytoin, pregabalin, primidone, topiramate, valproate, vigabatrin and zonisamide were identified. For amniotic fluid, the highest penetration ratios were estimated for levetiracetam (mean 3.56, range 1.27–5.85, $n = 2$) and lowest for valproate (mean 0.11, range 0.02–1.02, $n = 57$). For umbilical cord plasma, oxcarbazepine had the highest ratio (mean 1.59, range 0.11–4.33, $n = 12$) with clonazepam having the lowest (mean 0.55, range 0.52–0.59, $n = 2$). For breast milk, the highest ratios were observed for oxcarbazepine (mean 3.75, range 0.5–7.0, n = 2), whereas the lowest were observed for valproate (mean 0.04, range 0.01–0.22, $n = 121$).
*Discussion:* We observed substantial variability between anticonvulsants and lithium regarding their ability to enter fetal/newborn circulation. Assessing concentrations of anticonvulsants and lithium in maternal samples can provide a surrogate of fetal/infant exposure, although patterns of concentration-dependent effects for maternal/neonatal safety are lacking.

## 1. Introduction

Anticonvulsants for treatment of epileptic seizures, as mood stabilizers in bipolar disorder or as augmentation strategy in treatment-resistant major depressive disorder and schizophrenia represent a commonly prescribed pharmacological treatment in peripartum women (Pariente et al., 2016). Concerns around maternal and neonatal safety present a significant challenge for clinicians (Cohen et al., 2019), particularly as there is an increasing awareness of the significant teratogenic potential of valproate (Patel et al., 2018). In light of this awareness, recent pharmacoepidemiological evidence suggests a shift in anticonvulsant prescription trends in an effort to minimize teratogenic

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risks (Ajinkya et al., 2021; Hochbaum et al., 2022). There is a red warning not to use valproate in women with childbearing potential. Nevertheless, implementation of regulatory authorities' restrictions has not always been successful (Ajinkya et al., 2021) and exposure for women of childbearing age to anticonvulsants with teratogenic potential remains significant in several countries (Goldspink et al., 2020; Kikuchi et al., 2022). Apart from valproate, there is evidence suggesting increased risk for congenital malformations for ethosuximide, topiramate, phenobarbital, phenytoin and carbamazepine (Veroniki et al., 2017). However, clinical experience as well as scientific evidence regarding the safety of the majority of anticonvulsants during pregnancy is still considered limited (Schaefer, 2011) and in most cases, peripartum anticonvulsant treatment requires an effective weighing of risks, benefits and alternatives to treatment (Veroniki et al., 2017). Further evidence is required to characterize high-risk cohorts accounting for potential confounders (Veroniki et al., 2017). On the other hand, compared to women with adequate seizure control under anticonvulsants, untreated epilepsy has been associated with poor seizure control during pregnancy (Jiménez et al., 2022; Vajda et al., 2022), which in turn may adversely affect the fetal development (Sveberg et al., 2015). Likewise, discontinuing mood stabilizers proximate to conception in women with bipolar disorders was related with twofold higher relapse risk compared to treatment continuation during pregnancy (Viguera et al., 2007b), with infants of mothers with untreated bipolar disorder being at increased fetal growth restriction risk (Bodén et al., 2012).

Regarding mechanisms of anticonvulsant adverse fetal/newborn effects, several hypotheses based on the distinct pharmacologic profile of each agent have been postulated (Hernandez-Diaz and Levin, 2014); for example, the role of anticonvulsant-associated low folate levels has received much attention (Veroniki et al., 2017), whereas newer hypotheses suggest direct effect on DNA synthesis of developing cells (Hernandez-Diaz and Levin, 2014). While mechanisms underlying adverse fetal effects of anticonvulsants remain poorly understood, the assessment of fetal/newborn anticonvulsant exposure might assist in assessing potential risk. In fact, there is some evidence of pharmacokinetic correlates for anticonvulsants and mood stabilizers' adverse effects on fetal health. For example, a higher third trimester maternal plasma concentration of total valproate was correlated with a higher risk of neonatal hypoglycemia one hour postpartum and the development of neonatal withdrawal symptoms correlated positively with the maternal plasma concentration of the free fraction of valproate at delivery (Ebbesen et al., 2000). Furthermore, five women carrying a fetus with spina bifida aperta had higher total valproate serum concentrations during pregnancy compared to women with unaffected fetuses (Omtzigt et al., 1992). In another cohort of pregnant women taking valproate, inverse correlations were reported between birth length and both maternal and umbilical cord concentrations (Kacirova et al., 2015). There is also a considerably body of literature suggesting higher rates of fetal adverse reactions including central nervous system complications in infants with high lithium serum levels (Newmark et al., 2019; Newport et al., 2005).

Additionally, there is robust data that anticonvulsant bioavailability may be drastically affected during pregnancy due to pregnancy-related changes in metabolism (Pennell et al., 2022); in turn, these changes can greatly impact anticonvulsant efficacy, e.g. changes in seizure frequency or relapse of affective symptoms when anticonvulsants are prescribed as mood stabilizers (Clark et al., 2013). Therapeutic drug monitoring (TDM) (Baughman Jr. and Randinitis, 1970; Brent and Wisner, 1998), i.e. quantification of anticonvulsant and lithium concentrations in different matrices of pregnant or lactating mothers, including maternal blood, amniotic fluid, umbilical cord blood and breast milk, can enable a comprehensive assessment of the ability of the prescribed medications to enter the fetal and newborn circulation (Schoretsanitis et al., 2020) and thus provide quantitative data for assessing risk.

Passive diffusion is considered a common fetal transfer pathway for anticonvulsants (Pacifici and Nottoli, 1995), however the drug's specific physicochemical properties determine the degree of diffusion (Hutson et al., 2011). Regarding passage into breast milk, the drug's physicochemical profile as well as milk-related variables, such as pH and lipid content, may play an important role (Whitby and Smith, 2005). Despite the growing concerns regarding safety of anticonvulsant treatment of pregnant and breastfeeding women and the potential of routine TDM within the context of good clinical practice, practical recommendations on TDM as part of anticonvulsant treatment in these patients are limited.

### 1.1. Aims of the study

The aims of the study were to systematically review TDM data for anticonvulsants and lithium in maternal blood samples (plasma or serum), amniotic fluid, umbilical cord blood samples (plasma or serum), and breast milk, to evaluate excretion patterns into these matrices to inform clinical decision-making.

## 2. Material and methods

The study was conducted with use of PRISMA guidelines (Hutton et al., 2015) and registered with PROSPERO (registration number CRD42020181838). Studies with concentrations of anticonvulsants or lithium in maternal blood (serum or plasma), amniotic fluid, umbilical cord blood (serum or plasma), or breast milk were identified in the PubMed and EMBASE databases using the following search strategy: (antiepileptic OR "mood stabilizer" OR anticonvulsant OR barbexaclone OR brivaracetam OR carbamazepine OR cenobamate OR "chloral hydrate" OR clobazam OR clonazepam OR diphenylhydantoin OR divalproex OR divalproate OR erlosamide OR eslicarbazepine OR ethosuximide OR ethadione OR etiracetam OR felbamate OR gabapentin OR mesuximide OR metharbital OR lacosamide OR lamotrigine OR levetiracetam OR lithium OR oxcarbazepine OR perampanel OR phenobarbital OR phenytoin OR pregabalin OR primidone OR rufinamide OR topiramate OR valproate OR "valproic acid" OR vigabatrin OR zonisamide) AND (blood OR serum OR plasma) AND (umbilical OR amniotic OR milk OR lactat* OR pregnan* OR antepart* OR postpart*). Data on blood (serum or plasma) concentrations in infants of anticonvulsant-treated mothers were not the focus of this review, although we included them for reasons of completeness. Both databases were searched in February 2022 for articles since data inception by two authors (CTS and GS). References from identified works were scrutinized for further reports.

### 2.1. Inclusion criteria

We included studies containing drug concentration data for anticonvulsants or lithium from maternal blood, amniotic fluid, umbilical cord blood or breast milk in pregnant or breastfeeding women. Lithium was included for reasons of comprehensiveness, as many anticonvulsants are also prescribed as mood stabilizers in bipolar disorder treatment. There were no restrictions regarding main diagnosis, daily dosage or duration of anticonvulsant/lithium treatment.

### 2.2. Data extraction

Data including sample sizes, daily doses of anticonvulsants or lithium, concomitant use of drugs with inducing properties, drug concentrations (mean and ranges or standard deviations depending on how data were reported) of anticonvulsants or lithium in maternal blood, amniotic fluid, umbilical cord blood and breast milk (fore-milk and hind-milk separately when available) were independently extracted by two authors (CTS and GS). When concentration values were reported in substance concentration units (e.g. nmol/L) conversion factors were used to convert to mass concentration units (ng/mL) (Hiemke et al., 2018). The term "blood" here refers to concentrations measured in

plasma or serum. We also report infant blood (serum or plasma) concentrations when available for reasons of completeness, although it was not part of the search strategy.

### 2.3. Outcomes & statistical analysis

The primary outcomes were the penetration ratios of anticonvulsants or lithium into amniotic fluid, umbilical cord blood and breast milk, i.e. the concentrations in amniotic fluid, umbilical cord blood or breast milk, divided by the concentrations in maternal blood. Ratios were estimated for medications as parent drugs without considering active metabolites. For example, for oxcarbazepine and phenobarbital we estimated ratios when these two anticonvulsants were prescribed as such and not when estimated as active metabolites (of carbamazepine and primidone respectively). When concentrations in both hind-milk and fore-milk were reported, we used the mean milk concentrations as the primary outcome and consequently estimated ratios for fore-milk and hind-milk separately. In case of multiple assessments from one single patient lacking area under the time-concentration curve values (Hochbaum et al.), we estimated mean concentrations for ratio calculation. When enantiomer concentrations were provided, we used their sum (Tran et al., 1998). When data from multiple studies were available, we estimated combined (pooled) penetration ratios for every matrix, with the mean of each study being weighted by the sample size, so that larger studies were given more weight (Schoretsanitis et al., 2020; Schoretsanitis et al., 2021). We performed a subgroup analysis estimating combined penetration ratios in women with anticonvulsant or lithium monotherapy or with concomitant use of non-interacting drugs versus women with concomitant use of drugs with inducing properties, excluding patients with missing information on type (or lack) of co-medications. The subgroup analysis was necessary due to the high frequency of anticonvulsant polypharmacy (Baftiu et al., 2018) and the strong inducing properties of several anticonvulsants on a number of metabolic pathways; in the group of co-medications with strong inducing properties we considered carbamazepine, phenytoin, phenobarbital and primidone (Hiemke et al., 2018). Patients treated concomitantly with valproate were not considered in any group of this subgroup analysis given valproate's complex interaction potential with both inhibiting and inducing properties (Bennett and Shad, 2021; McGrane et al., 2022). We also aimed to perform subgroup analyses for different formulations of lithium and valproate (immediate- vs prolonged-release), when formulation was specified. We reported % differences in penetration ratios between patients treated with vs. without concomitant medications with inducing properties. Penetration ratios and ranges were visualized using Matplotlib, which is a plotting library of Python.

### 2.4. Quality assessment

The quality of the included studies was assessed using the ClinPK guidelines (Kanji et al., 2015), which is well established in the evaluation of reporting for pharmacokinetic studies.

## 3. Results

The search yielded 4176 articles from PubMed, 3500 additional articles from Embase, 10 additional articles from article references and two additional articles from the authors' own collections, leading to a total of 6860 articles after 828 duplicates were removed (Supplementary Fig. 1). Abstract screening resulted in rejection of 6670 of these. Full-text screening led to rejection of another 99 articles due to either lack of TDM data in maternal blood and/or amniotic fluid, umbilical cord blood or breast milk ($n = 42$), reviews ($n = 23$), overlapping data ($n = 22$), no anticonvulsants/lithium ($n = 7$) or the lack of TDM data in an analyzable form (no individual patient data or means/ranges, $n = 5$). Finally, 91 articles were selected and used for data extraction (Supplementary Fig. 1).

Concentrations of anticonvulsants in maternal blood and in amniotic fluid, umbilical cord blood, breast milk and/or infant plasma are summarized in Table 1. One study is not presented in Table 1, as apart from data of penetration ratios no further information was provided (Kuhnz et al., 1988).

### 3.1. Excretion into amniotic fluid

In a total of 196 patients, data were available allowing the calculation of penetration ratios into amniotic fluid for the following medications: carbamazepine, ethosuximide, lamotrigine, levetiracetam, lithium, phenytoin, primidone and valproate. Amniotic fluid samples were collected at birth in five trials (MacKay et al., 1976; Meyer et al., 1988; Paulzen et al., 2019; Paulzen et al., 2014; Pynnönen et al., 1977) and at amniocentesis in the first or second trimester in two trials (Omtzigt et al., 1992; Omtzigt et al., 1993).The highest penetration ratios were reported for levetiracetam (combined mean 3.56, range 1.27–5.85, $n = 2$), lithium (mean 1.61, no range, $n = 1$) and primidone (combined mean 1.12, range 0.62–2.28, n = 7), while the lowest ratios were reported for valproate (combined mean 0.11, 0.02–1.02, $n = 57$), phenytoin (combined mean 0.39, range 0.17–0.6, $n = 2$) and carbamazepine (combined mean 0.77, range 0.03–0.85, $n = 110$) (Supplementary Table 1, Fig. 1a).

For the subgroup analysis of penetration ratios in patients prescribed with or without concomitant inducers, only data for carbamazepine and valproate were available, with penetration ratios in patients with inducers being 66.7% of the ratios in patients without concomitant inducer use for both anticonvulsants (Supplementary Table 2, Fig. 1b). For the subgroup analysis of penetration ratios in patients prescribed different lithium and valproate formulations, no studies specified on used formulations, so that no analyses were performed.

### 3.2. Excretion in umbilical cord plasma

In a total of 761 patients, data were available allowing the calculation of penetration ratios into umbilical cord for the following medications: brivaracetam, carbamazepine, clonazepam, ethosuximide, lacosamide, lamotrigine, levetiracetam, lithium, oxcarbazepine, phenobarbital, phenytoin, primidone, topiramate, valproate, vigabatrin and zonisamide (Supplementary Table 1, Fig. 2a). The highest penetration ratios were reported for oxcarbazepine (combined mean 1.59, range 0.11–4.33, $n = 12$), followed by valproate (combined mean 1.56, range 0.64–4.64, $n = 139$) and levetiracetam (combined mean 1.14, range 0.56–2.17, $n = 51$). On the other hand, the lowest ratios were observed for clonazepam (combined mean 0.55, range 0.52–0.59, $n = 2$), vigabatrin (combined mean 0.66, range 0.10–1.21, n = 2) and phenytoin (combined mean 0.66, range 0.16–2.12, $n = 82$) (Fig. 2a).

For the subgroup analysis of penetration ratios in patients prescribed with or without concomitant inducers, the largest differences were reported for vigabatrin, levetiracetam and zonisamide (Fig. 2b), where penetration ratios in patients receiving concomitant inducing medications were 8.3, 77.3 and 80.0% respectively of ratios in patients without concomitant inducer use (Supplementary table 2). For the subgroup analysis of penetration ratios in patients prescribed different lithium and valproate formulations, no studies specified on used formulations, so that no analyses were performed.

### 3.3. Excretion into breast milk

In a total of 797 patients, data were available allowing the calculation of penetration ratios into breast milk for the following medications: brivaracetam, carbamazepine, clonazepam, ethosuximide, gabapentin, lacosamide, lamotrigine, levetiracetam, lithium, oxcarbazepine, perampanel, phenobarbital, phenytoin, pregabalin, primidone, topiramate, valproate, vigabatrin and zonisamide (Supplementary Table 1, Fig. 3a).

**Table 1**
Concentrations of anticonvulsants and lithium (in alphabetical order) in maternal serum/plasma, amniotic fluid, umbilical cord serum/plasma and infant serum/plasma.

| | Reference | n | Daily dose (mg) | Quantification method | Maternal serum/plasma concentration (ng/mL)[a] | Amniotic fluid concentration (ng/mL)[a] | Umbilical cord serum/plasma concentration (ng/mL)[a] | Breast milk concentration (ng/mL)[a] | Infant serum/plasma concentration (ng/mL)[a] | Quality score |
|---|---|---|---|---|---|---|---|---|---|---|
| Brivaracetam | Landmark et al. (2021) | 2 | 75–100 | LC-MS/MS | 0.93–1.44 | | 0.87–0.89 | 0.68–1.06 | ≤0.25 | 11 |
| Carbamazepine | Bank et al. (2017) | 9 | 800–1750 | LC-MS/MS | | | 1.7–4.9 | | | 12 |
| | Brent and Wisner (1998) | 1 | 600 | HPLC | 6.3–7.1 | | | ≤0.5 | ≤0.5 | 6 |
| | Froescher et al. (1984a) | 19 | 7.1–21.0[b] | HPLC | 6.1-7.7 | | 5.0–5.7 | | <1.5 | 13 |
| | Kacirova et al. (2015) | 9 | 300–750 | HPLC | 1.4–5.2 | | 0.8–4.0 | | | 13 |
| | Kacirova et al. (2022a) | 150 | 150–1200 | HPLC | 1.0–11.2 | | 0.5–6.7 | 0.5–6.8 | 0.13–4.7 (101) | 14 |
| | Kaneko et al. (1979) | 3 | NP | GC/IA | 3.2–62.0 | | | 0.8–3.8 | | 7 |
| | Kok et al. (1982) | 1 | 800 | IA | 4.0 | | | 1.0 | <1.0 | 5 |
| | Kuhnz et al. (1983) | 4 | 3.0–22.0[b] | HPLC | 1.1-10.0 | | | 0.85–3.0 | 2.2–6.1 | 14 |
| | Meyer et al. (1988) | 6 | 600–1000 | NP | 2.2–8.0 | 0.9–2.1 | 4.2–4.5 | 1.2–4.4 | 0.5–4.4 | 13 |
| | Omtzigt et al. (1993) | 93 | 9.7 ± 3.6[b] | HPLC | 6.11 ± 1.78 | 4.13 ± 1.3 | | | | 12 |
| | Pienimäki et al. (1995) | 16 | NP | HPLC | 1.8–8.6 | | 2.3–7.2 | | | 9 |
| | Pynnönen et al. (1977) | 18 | 0.9–15.1 | GC | 0.5–8.6 | 0.4–3.1 | 0.5–4.5 | 1.1–1.8 | ≤1.8 | 12 |
| | Sugawara et al. (1999) | 7 | 250–800 | HPLC | 3.2–15.0 | | 5.1 | 2.8–4.5 | | 11 |
| | Takeda et al. (1992) | 7 | 700–1200 | IA | 8.8 ± 3.3 | | 6.4 ± 2.0 | | | 10 |
| | Tanaka et al. (1991) | 11 | 845 ± 243 | NP | 8.6 ± 3.5 | | | 6.3 ± 2.7 | | 12 |
| | Veit et al. (2017) | 1 | NP | LC-MS/MS | 0.3 | | 0.05 | | | 8 |
| Clonazepam | Fisher et al. (1985) | 1 | NP | GC | 32.0 | | 19.0 | 11.0–13.0 | 4.4 | 7 |
| | Kriel and Cloyd (1982) | 1 | 5.5 | NP | 50.0–86.0 | | 33.0 | | ≤30 | 5 |
| Ethosuximide | Kaneko et al. (1979) | 4 | NP | GC/IA | 18.00–39.0 | | | 18.0–24.0 | | 7 |
| | Koup et al., 1978 | 1 | 1000 | GC | 40.0–75.0 | | 61.9 | | | 10 |
| | Meyer et al. (1988) | 1 | NP | NP | 28.0–39.1 | 31.0 | 29.0 | 36.0 | 24.7 | 13 |
| | Rane and Tunell (1981) | 1 | 500 | GC | 27.54–65.96 | | | 32.4–55.79 | 21.89–29.52 | 11 |
| | Tomson and Villén (1994) | 2 | 750–1000 | GC | 35.3–52.2 | | 35.3 | 33.9–52.3 | 16.9 | 12 |
| Gabapentin | Kristensen et al. (2006) | 1 | 1800 | HPLC | 6.6 | | | 5.7 | 0.4 | 10 |
| | Öhman et al. (2005) | 6 | 900–3200 | HPLC | 1.7–7.70 | | 0.38–2.74 (4) | 0.34–2.74 (3) | ≤0.9 | 16 |
| Lacosamide | Landmark et al. (2021) | 1 | 200 | LC-MS/MS | 7.1–10.9 | | | 7.9–9.4 | <1.1 | 11 |
| | Ylikotila et al. (2015) | 1 | 100 | GC | 3.8 ± 1.1 | | 3.9 ± 1.2 | 0.4 ± 0.2 | 0.2 ± 0.1 | 10 |
| Lamotrigine | Bank et al. (2017) | 38 | 125–1200 | LC-MS/MS | | | 1.1–16.3 | | | 12 |
| | de Haan et al. (2004) | 9 (12) | NP | HPLC/GC | 12.0–14.0 | | 89.8% of MP | 54% of MP | 1.7 (1) | 9 |
| | Fotopoulou et al. (2009) | 7 (7) | 300–1000 | HPLC | 2.9–11.9 | | 2.9–6.0 | 2.8–8.0 | 1.7–6.2 | 14 |
| | Kacirova et al. (2015) | 6 | 100–400 | HPLC | 3.9–12.3 | | 1.7–13.6 | | | 13 |
| | Kacirova et al. (2022b) | 148 | 25–600 | HPLC | 0.5–11.7 (158) | | 0.3–13.6 (40) | 0.3–10.3 (147) | 0.3–12.7 (132) | 14 |
| | | 17 | 100–500 | HPLC | 0.95–14.1 | | | 0.65–7.8 | | 17 |

(*continued on next page*)

**Table 1** (*continued*)

| | Reference | n | Daily dose (mg) | Quantification method | Maternal serum/plasma concentration (ng/mL)[a] | Amniotic fluid concentration (ng/mL)[a] | Umbilical cord serum/ plasma concentration (ng/mL)[a] | Breast milk concentration (ng/mL)[a] | Infant serum/ plasma concentration (ng/mL)[a] | Quality score |
|---|---|---|---|---|---|---|---|---|---|---|
| | Kohn et al. (2022) | | | | | | | | | |
| | Myllynen et al. (2003) | 2 | 300–400 | HPLC | 1.27–2.38 | | 1.97–2.42 | | | 11 |
| | Newport et al. (2008) | 26 | 50–800 | HPLC | 1.7–23.1 | | | 0.5–18.1 | ≤3.9 (12) | 13 |
| | Nordmo et al. (2009) | 1 | 525–850 | LC-MS/MS | 4.53–14.93 | | | 6.74–10.06 | 0.51–7.71 | 10 |
| | Ohman et al. (2000) | 9 | 100–800 | HPLC | 0.77–10.26 | | 1.02–4.36 | 0.51–6.41 | 0.51–3.59 (10) | 14 |
| | Paulzen et al. (2019) | 19 | 50–650 | HPLC | 0.3–8.4 | 0.5–8.3 (16) | 1.1–6.6 | 1.57–6.1 (9) | | 16 |
| | Rambeck et al. (1997) | 1 | 200–300 | HPLC | 3.59–9.61 | | | 1.26–6.4 | 2.68 | 10 |
| | Tomson et al. (1997) | 1 | 250–300 | HPLC | 0.84–5.67 | | 1.02 | 3.31–3.49 | 1.23–1.43 | 12 |
| | Veit et al. (2017) | 2 | 50–300 | LC-MS/MS | 0.2–1.4 | | 0.17–1.2 | | | 8 |
| Levetiracetam | Bank et al. (2017) | 10 | 750–5000 | LC-MS/MS | | | 4.0–76.0 | | | 12 |
| | Dinavitser et al. (2022) | 20 | 1500–3750 | HPLC | 17.4–37.4 | | | 8.6–42.3 | | 15 |
| | Johannessen et al. (2005) | 7 | 1500–3500 | LC | 11.39–48.30 | | 16.5–54.76 (4) | 4.76–26.02 | ≤13.1 | 15 |
| | Kacirova et al. (2021a) | 56 | 500–4000 (56) | LC | 1.3–36.6 (56) | | 2.3–36.6 (14) | 1.7–27.3 (58) | 0.5–6.3 (54) | 15 |
| | López-Fraile et al. (2009) | 5 | 2000-3000 | HPLC | 3.5–24.9 | | 5.7–29.6 | | | 13 |
| | Paulzen et al. (2014) | 3 | 1000–3000 | HPLC | 9.2–25.6 | 32.6–53.8 (2) | 9.5–25.6 | | | 9 |
| | Tomson et al. (2007) | 14 | 1000-3000 | LC-MS/MS | 1.87–20.41 | | 1.19–31.29 | | 0.68–3.4 (13) | 16 |
| | Ylikotila et al. (2015) | 1 | 1000 | GC–MS | 17.0 ± 5 0 | | 23.0 ± 7.0 | | | 10 |
| Lithium | Imaz et al. (2021) | 24 | NP | ISE | 0.19–0.95 | | 0.23–0.96 | | 0.01–0.14 | 16 |
| | MacKay et al. (1976) | 1 | 125–1250 | NP | 0.84–0.97 | 1.57 | 0.8 | | | 2 |
| | Newport et al. (2005) | 10 | 300–1800 | ISE | 0.2–1.03 (9) | | 0.2–1.02 | | | 12 |
| | Schou and Amdisen (1973) | 5 | NP | FP | 0.34–1.5 (4) | | | 0.16–0.6 | 0.1–0.3 (4) | 7 |
| | Tunnessen Jr. and Hertz (1972) | 1 | 600–1200 | NP | 1.5 | | | 0.6 | 0.6 | 5 |
| | Viguera et al. (2007a) | 10 | 600–1200 | ISE | 0.41–1.31 | | | 0.10–0.51 (9) | 0.05–0.30 | 13 |
| | Weinstein and Goldfield (1969) | 1 | 1000 | NP | 0.33–0.84 | | 0.35 | 0.12 | ≤0.37 | 7 |
| | Zamani et al. (2017) | 1 | NP | NP | 2.1–5.0 | | 4.8 | | | 7 |
| Oxcarbazepine | Bank et al. (2017) | 4 | 450–2400 | LC-MS/MS | | | 0.5–2.5 | | | 12 |
| | Bülau et al. (1988) | 1 | 300 | GC–MS | 0.25–0.55 | | | | 0.08 | 9 |
| | Lutz et al. (2007) | 1 | 600 | HPLC | 0.1–0.2 | | | 0.9–1.0 | ≤0.2 | 10 |
| | Myllynen et al. (2001) | 12 | 750–2100 | HPLC | ≤0.47 | | ≤0.65 | | | 12 |
| | Pienimäki et al. (1997) | 3 | 300–1800 | HPLC | 0.04–0.37 | | 0.04–0.37 | | | 10 |
| Perampanel | Landmark et al. (2021) | 1 | 8 | LC-MS/MS | 300.7–1055.9 | | | 52.4–108.4 | <171.3 | 11 |
| Phenobarbital | De Carolis et al. (1992) | 23 | 131.9 | IA | 7.0–36.0 | | 7.0–35.0 | | 6.0–20.0 | 10 |
| | Gomita et al. (1995) | 26 | NP | IA | 9.01 | | | 2.02 | 3.70 | 9 |
| | Ishizaki et al. (1981) | 5 | 50–200 | GC | 5.7–25.1 | | 5.4–35.8 | | | 11 |

(*continued on next page*)

**Table 1** (*continued*)

| | Reference | n | Daily dose (mg) | Quantification method | Maternal serum/plasma concentration (ng/mL)[a] | Amniotic fluid concentration (ng/mL)[a] | Umbilical cord serum/ plasma concentration (ng/mL)[a] | Breast milk concentration (ng/mL)[a] | Infant serum/ plasma concentration (ng/mL)[a] | Quality score |
|---|---|---|---|---|---|---|---|---|---|---|
| | Kacirova et al. (2015) | 4 | 56–74 (2) | HPLC | 2.2–15.1 | | 1.4–12.0 | | | 13 |
| | Kaneko et al. (1979) | 8 | NP | GC/IA | 2.5–42.0 | | | 0.5–33.0 | | 7 |
| | Kuhnz et al. (1988) | 13 | 325–875 | HPLC | 6.5–32.0 | | | | 2.0–13.0 | 9 |
| | Melchior et al. (1967) | 22 | 0.5–3.0[b] | GC | 0.5-25.35 | | 0.26–23.0 | | 4.6–21.2 (11) | 9 |
| | Pote et al. (2004) | 1 | 90 | NP | 28.21–36.2 | | | 4.34–5.47 | 12.06–54.71 | 5 |
| | Rayburn et al. (1989) | 31 | 60 | HPLC | 2.11–7.95 | | 2.27–8.04 | | | 10 |
| | Sugawara et al. (1999) | 4 | 30–150 | HPLC | 4.3–29.6 | | 3.4 | 4.5–7.6 | | 11 |
| | Takeda et al. (1992) | 13 | 30–150 | IA | 11.0 ± 5.2 | | 9.5 ± 4.7 | | | 10 |
| | Tanaka et al. (1991) | 19 | 85 ± 34 | NP | 10.9 ± 5.1 | | | 9.5 ± 4.5 | | 12 |
| Phenytoin | Bank et al. (2017) | 4 | 400–550 | LC-MS/MS | | | 6.3–17.5 | | | 12 |
| | Baughman Jr. and Randinitis (1970) | 1 | 400 | NP | 2.5 | | 1.2 | | ≤2.4 | 9 |
| | Ishizaki et al. (1981) | 3 | 2000 | GC | 4.3–6.6 | | 3.9–6.8 | | | 11 |
| | Kaneko et al. (1979) | 9 | NP | GC/IA | 2.1–5.7 | | | 0.5–14.0 | | 7 |
| | Kok et al. (1982) | 1 | 300 | IA | 5.0 | | | 1.0 | | 5 |
| | Meyer et al. (1988) | 3 | NP | NP | 2.6–5.1 | 0.7–2.4 (2) | 3.8–6.5 (2) | 1.7–2.7 (2) | 2.4–4.4 | 13 |
| | Mirkin (1971a) | 7 | 300–400 | Colometric | 1.0–6.3 | | 0.9–5.5 (6) | 1.3–2.3 (2) | ≤4.7 | 12 |
| | Mirkin (1971b) | 3 | 300 | Colometric | 3.5–6.3 | | 3.5–5.5 | | | 10 |
| | Rane et al. (1974) | 7 | 200–700 | GC | 0.7–19.0 | | | 0.260–2.38 (1) | 0.43–13.0 (7) | 12 |
| | Rodríguez-Palomares et al. (1995) | 27 | 100–600 | IA | 9.5 ± 6.1 | | 3.6 ± 3.2 | | | 12 |
| | Steen et al. (1982) | 6 | 200–400 | GC | 3.47–21.27 | | | 0.22–3.17 | 0.12–0.19 (2) | 13 |
| | Shimoyama et al. (1998) | 5 | 100–300 | HPLC | 1.6–3.4 | | 1.12–2.64 (2) | 0.68–1.30 | | 12 |
| | Takeda et al. (1992) | 7 | 200–300 | IA | 3.5 ± 1.3 | | | 3.2 ± 1.2 | | 10 |
| | Tanaka et al. (1991) | 9 | 233 ± 35 | NP | 3.4 ± 1.1 | | | 3.1 ± 1.0 | | 12 |
| Pregabalin | Lockwood et al. (2016) | 10 | 300 | HPLC/MS | 1.7–3.7 | | | 1.3–3.1 | | 17 |
| Primidone | Kacirova et al., 2016) | 5 | 250–750 | HPLC | 0.7–6.7 | | 2.4–9.0 | | | 15 |
| | Kaneko et al. (1979) | 12 | NP | GC/IA | 0.8–15.7 | | | 0.5–6.7 | | 7 |
| | Kuhnz et al. (1988) | 7 | NP | HPLC | | | | | 0.7–17.0 | 9 |
| | Martinez and Snyder (1973) | 10 | 250[c] | GC | 0.3–7.2 | | ≤8.3 | | | 11 |
| | Melchior et al. (1967) | 7 | 2-15[b] | GC | 0.99-19.24 | | 1.14–14.53 | | | 9 |
| | Meyer et al. (1988) | 9 | NP | NP | 4.5–15.0 | 5.5–23.0 (7) | 5.1–11.0 (8) | 5.2–13.7 | 2.2–6.1 (8) | 13 |
| Topiramate | Bank et al. (2017) | 2 | 600–800 | LC-MS/MS | | | 8.8–11.1 | | | 12 |
| | Fröscher and Jürges (2006) | 1 | 150–175 | HPLC | 4.9–5.3 | | | 3.1 | 0.8 | 7 |
| | Kacirova et al. (2021c) | 22 | 25–400 | GC | 1.0–9.7 (28) | | 0.8–6.2 (11) | 1.5–10.6 (26) | 0.3–6.5 (25) | 15 |
| | | 5 | 150–400 | IA | 0.88–6.78 | | 0.75–5.42 (4) | 0.54–4.95 (3) | ≤0.71 (3) | 15 |

(*continued on next page*)

**Table 1** (*continued*)

| | Reference | n | Daily dose (mg) | Quantification method | Maternal serum/plasma concentration (ng/mL)[a] | Amniotic fluid concentration (ng/mL)[a] | Umbilical cord serum/ plasma concentration (ng/mL)[a] | Breast milk concentration (ng/mL)[a] | Infant serum/ plasma concentration (ng/mL)[a] | Quality score |
|---|---|---|---|---|---|---|---|---|---|---|
| | Öhman et al. (2002) | | | | | | | | | |
| Valproate | Alexander (1979) | 1 | 1600 | NP | 68.95–84.36 | | | 3.0–7.2 | | 5 |
| | Bank et al. (2017) | 6 | 625–1500 | LC-MS/MS | | | 26.0–71.0 | | | 12 |
| | Dickinson et al. (1979) | 1 | 750 | GC | 15.6–34.3 | | 22.3 | 0.17–0.46 | | 10 |
| | Froescher et al. (1984b) | 18 | 300–2400 | GC | 3.6–74.2 | | 16.2–109.2 | | | 12 |
| | Ishizaki et al. (1981) | 4 | 600–1200 | GC | 14.8–56.0 | | 35.7–80.8 | | | 11 |
| | Kacirova et al. (2016) | 10 | 300–1250 | GC | 8.7–31.3 | | 17.5–55.6 | | | 15 |
| | Kacirova et al. (2021b) | 78 | 150–2250 | GC | 4.3–66.5 (90) | | 10.7–72.1 (41) | 0.5–5.9 (84) | 0.5–42.9 (78) | 14 |
| | Kaneko et al. (1983) | 6 | 600–1200 | GC | 5.0–49.9 | | 29.07 ± 16.59[d] | | | 10 |
| | Kondo et al. (1987) | 4 | 200–1200 | GC | 6.0–25.0 | | 8.0–44.0 | | | 10 |
| | Kulza et al. (2013) | 2 | 600–1000 | GC | 71.13–92.27 | | 81.79–89.95 | | | 9 |
| | Meyer et al. (1988) | 4 | NP | GC | 32.0–56.0 | 2.0–5.2 | 47.0–50.0 (3) | 1.0–3.8 | 13.0–41.0 (3) | 13 |
| | Nau et al. (1981) | 11 | 7.7–31.0[b] | GC–MS | 4.74-102.2 (9) | | 31.0–88.0 (6) | 0.12–5.4 (6) | | 13 |
| | Nau et al. (1984) | 17 | 18.4 ± 7.2[b] | GC–MS | 70.0 | | 128.0 | | | 8 |
| | Omtzigt et al. (1992) | 52 | 4.0–32.0[b] | GC–MS | 4.8-107.0 | 0.01–12.0 | | | | 13 |
| | Paulzen et al. (2014) | 2 | 600 | HPLC | 23.6–34.5 | ≤4.3 | 24.3–45.9 | | | 9 |
| | Takeda et al. (1992) | 8 | 400–2000 | IA | 30.1 ± 10.9 | | 48.0 ± 16.7 | | | 10 |
| | Tanaka et al. (1991) | 11 | 836 ± 425 | NP | 32.3 ± 12.2 | | | 47.8 ± 16.4 | | 12 |
| | Tsuru et al. (1988) | 3 | 800–1400 | GC/IA | 48.0–128.0 | | 50.0–75.0 (2) | 1.4–3.6 (2) | | 10 |
| | Von Unruh et al. (1984) | 16 | 300–2400 | GC–MS | 17.2–74.2 (11) | | 24.1–109.2 (5) | 0.4–3.9 (11) | ≤13.4 (5) | 14 |
| Vigabatrin | Tran et al. (1998) | 2 | 1000 | GC–MS | 3.24–17.9 | | 1.8–6.9 | 1.34–3.96 | | 15 |
| Zonisamide | Ando et al. (2014) | 2 | 100–300 | HPLC | 3.6–24.5 | | 6.0–14.4 | 3.4–18.0 | <0.5 | 11 |
| | Kawada et al. (2002) | 2 | 400 | HPLC | 17.5–25.2 | | 14.4 (1) | 8.8–10.9 | | 9 |
| | Öhman and Tomson (2011) | 2 | NP | HPLC | 125.9 | | | | 2.14 | 3 |
| | Shimoyama et al. (1999) | 1 | 300 | HPLC | 9.52–10.6 | | 6.72 | 8.250–10.5 | | 11 |

FP: flame photometry, GC: gas chromatography, HPLC: high performance liquid chromatography, IA: immunoassay, ISE: ion-selective electrode, LC: liquid chromatography, LC-MS/MS: liquid chromatography with tandem mass spectrometry, n: number of patients; when number of samples differed, we provided number of samples in parentheses in the concentrations columns, NP: not provided, MP: maternal serum/plasma concentration. Concentrations refer to mother compounds and not active metabolites (as e.g. in case of oxcarbazepine and phenobarbital). The quality score column represents the quality scores assigned to the study based on the ClinPK checklist (for details, see Supplementary table 3).

[a] Except for lithium, where concentrations were provided in mmol/L and clonazepam and perampanel, where concentrations were provided in ng/mL.

[b] Units in mg/kg/day.

[c] Single dose.

[d] Mean of umbilical artery and vein serum/plasma.

The highest penetration ratios were reported for oxcarbazepine (combined mean 3.75, range 0.5–7.0, n = 2), followed by levetiracetam (combined mean 1.09, range 0.46–1.79, $n = 90$) and gabapentin (combined mean 0.99, range 0.7–1.3, $n = 6$). On the other hand, the lowest ratios were observed for valproate (combined mean 0.04, range 0.01–0.22, $n = 121$), perampanel (mean 0.1, no range, n = 1) and phenytoin (combined mean 0.24, range 0.06–0.53, $n = 26$) (Fig. 3a).

For the subgroup analysis of penetration ratios in patients prescribed with or without concomitant inducers, the largest differences were reported for phenytoin, zonisamide and gabapentin (Fig. 3b), where penetration ratios in patients receiving concomitant inducers were 48.5, 55.6 and 66.7% respectively of ratios in patients without concomitant inducer use (Supplementary table 2). For the subgroup analysis of penetration ratios in patients prescribed different lithium and valproate formulations, no studies specified on used formulations, so that no analyses were performed.

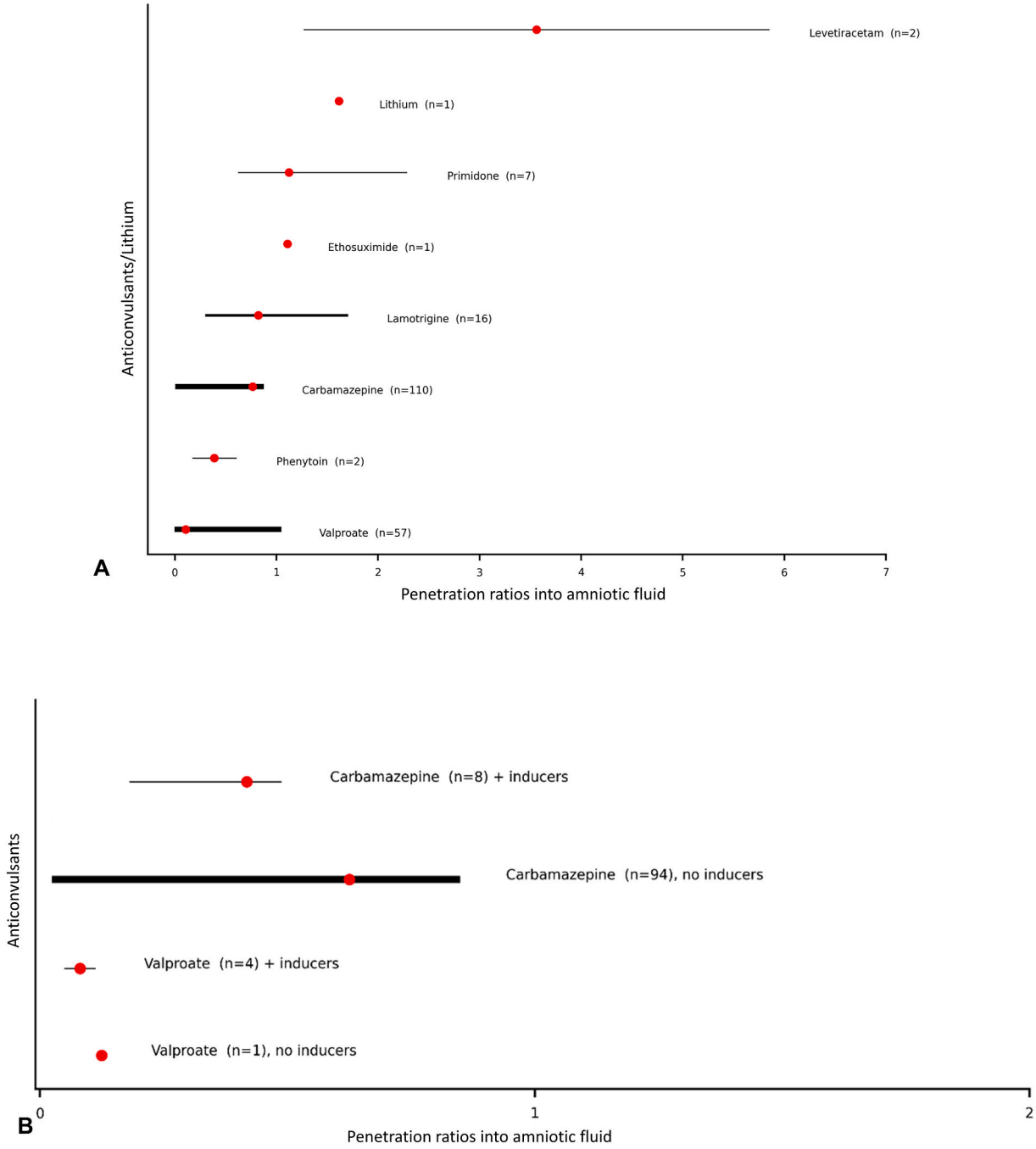



**Fig. 1.** a) Penetration ratios (combined means and ranges) of carbamazepine, ethosuximide, lamotrigine, levetiracetam, lithium, phenytoin, primidone and valproate into amniotic fluid. The width of lines is proportional to the number of patients providing data for the estimation of the penetration ratios (n: number of patients). b) Penetration ratios (combined means and ranges) of carbamazepine and valproate into amniotic fluid in patients receiving co-medications without vs. with inducers. The width of lines is proportional to the number of patients providing data for the estimation of the penetration ratios (n: number of patients).

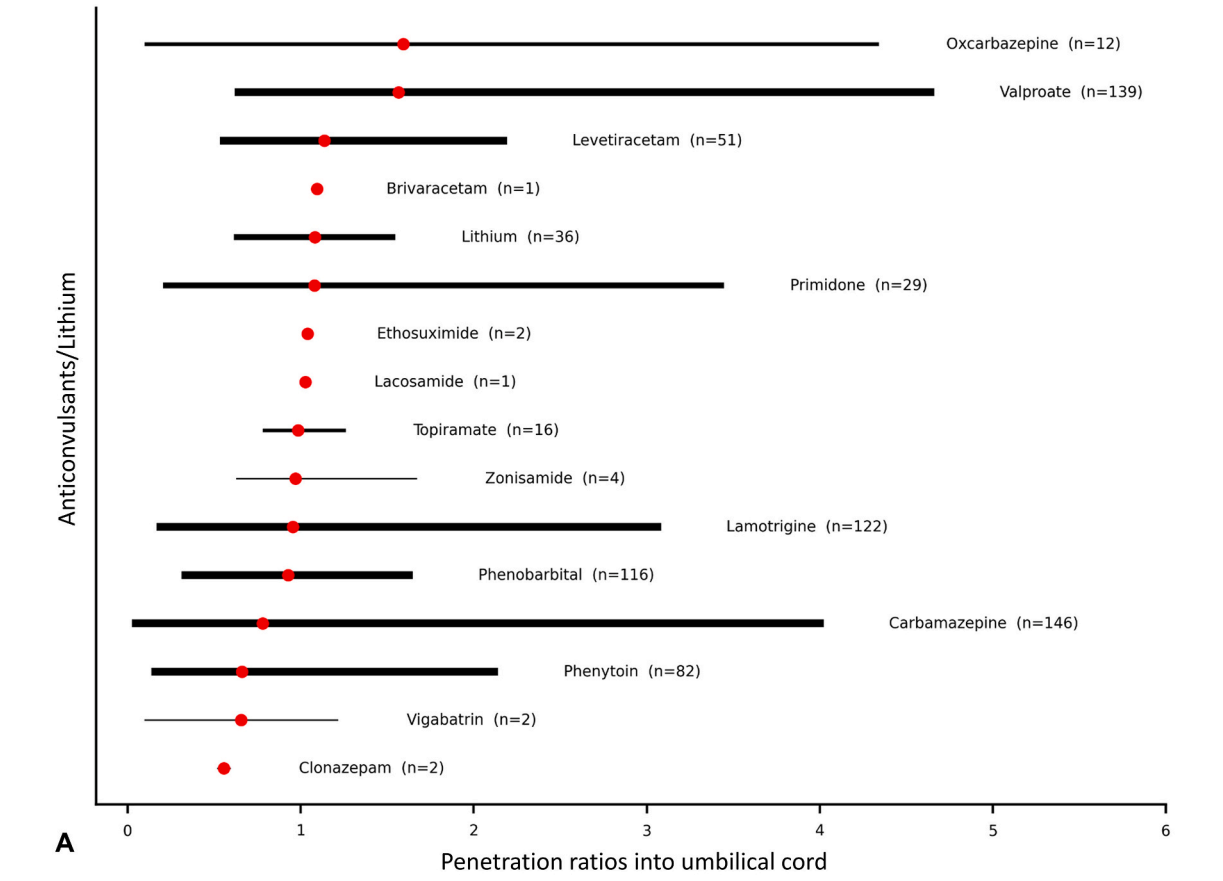
As data for concentrations in fore- vs. hindmilk were extremely limited (Landmark et al., 2021), we did not estimate any penetration ratios into fore- vs. hindmilk.

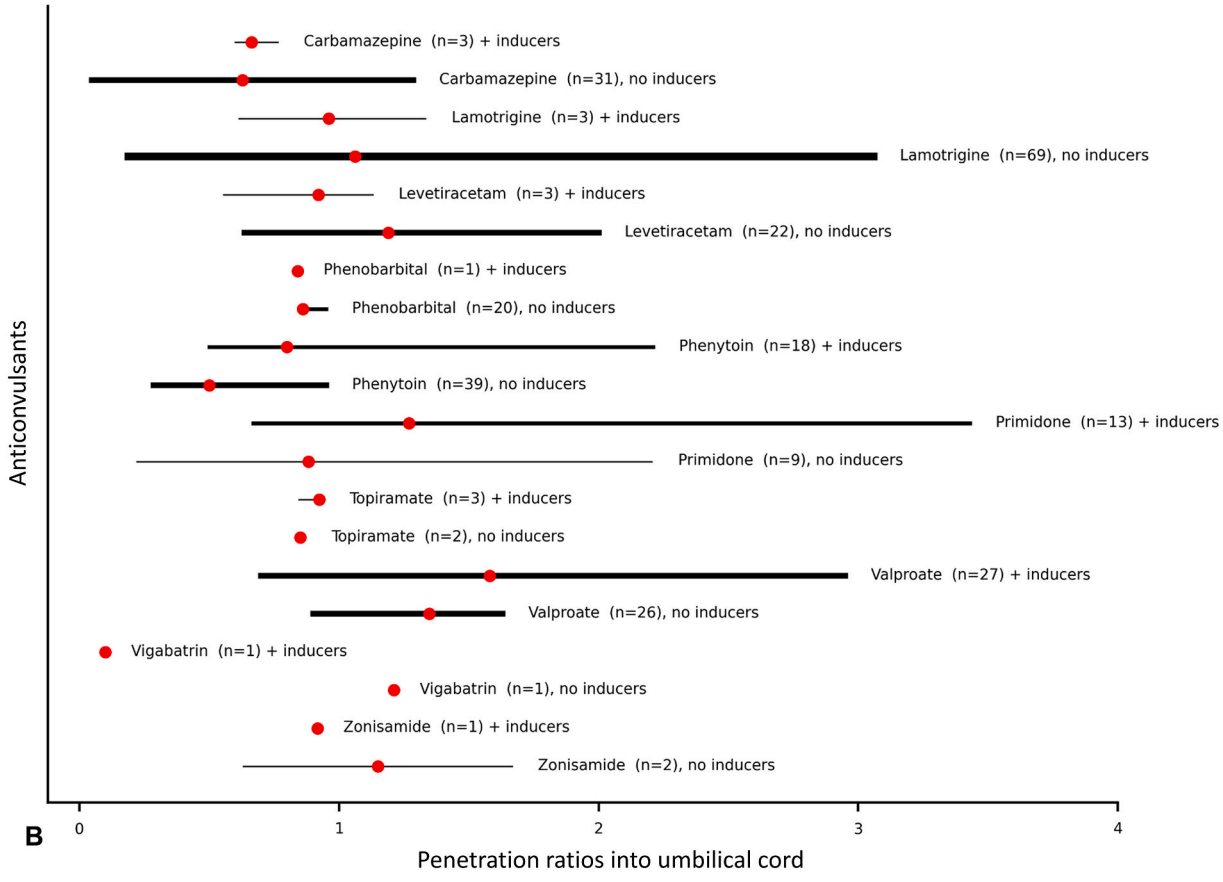
### 3.4. Quality assessment

The quality of the studies was acceptable with an average rating score of 10.9 (around 60% of the maximum score, Supplementary table 3). Some variation regarding quality was due to the lower quality in case reports, where details required within quality assessment were limited. Another common quality issue was the lack of trough concentrations, as maternal blood sampling was conducted at delivery.

## 4. Discussion

In this systematic review we determined patterns of transfer of anticonvulsants and lithium into fetal and newborn circulation via different pathways including amniotic fluid, umbilical cord blood and breast milk. Previous systematic works provided valuable insight into anticonvulsant exposure, but mainly through lactation (Hagg and Spigset, 2000; Malone et al., 2004; Pons et al., 1994; Shawahna and Zaid, 2022; Tomson et al., 2022; van der Meer et al., 2015; Yoshida




(caption on next page)

**Fig. 2.** a) Penetration ratios (combined means and ranges) of anticonvulsants and lithium into umbilical cord. The width of lines is proportional to the number of patients providing data for the estimation of the penetration ratios (max: maximum; n: number of patients). b) Penetration ratios (combined means and ranges) of carbamazepine, lamotrigine, levetiracetam, phenobarbital, phenytoin, primidone, topiramate, valproate, vigabatrin and zonisamide into amniotic fluid in patients receiving co-medications without vs. with inducers. The width of lines is proportional to the number of patients providing data for the estimation of the penetration ratios (n: number of patients).

et al., 1999). In this updated review we included TDM data from amniotic fluid and umbilical cord blood in order to provide a more comprehensive understanding of the passage of anticonvulsants and lithium into the fetal and newborn circulation.

### 4.1. Penetration into breast milk

As for psychotropic medications (Schoretsanitis et al., 2020; Schoretsanitis et al., 2021), evidence was more robustly available for breast milk compared to other matrices, with a very high penetration ratio into breast milk estimated for oxcarbazepine (Bülau et al., 1988; Lutz et al., 2007). However, available data for oxcarbazepine was particularly scarce and the estimated ratio was mainly driven by a strikingly high ratio reported in a case report (Lutz et al., 2007), where authors acknowledged that the lack of trough values may have accounted for their finding (Lutz et al., 2007). Moreover, a third case report described a range of 0.5–0.8 in two oxcarbazepine-treated lactating women (Pedersen, 1987); nevertheless, these two patients could not be included in our analysis as raw data in a meta-analyzable form were not available. Further, it may be reassuring that Bulau and associates concluded that accumulation of oxcarbazepine in newborns is unlikely (Bülau et al., 1988). Following oxcarbazepine, the second highest penetration ratio into milk was estimated for levetiracetam. In fact, measuring levetiracetam maternal concentrations in lactating women may prove valuable in light of evidence from a small cohort, where somnolence was reported in fully breastfed infants of three levetiracetam-treated women (Dinavitser et al., 2022). As somnolence resolved shortly after the infants changed to partial breastfeeding, we may hypothesize a concentration-dependent mechanism, although penetration ratio data in these three patients were not reported separately. An alternative strategy to minimize infant exposure to high concentrations of lipid-soluble drugs, which includes most anticonvulsants, previously included discarding lipid-rich hind-milk (Academy of Breastfeeding Medicine Protocol, 2008). However, given the valuable nutrient composition of hind-milk for the newborn, additional evidence is needed until this approach can be embraced.

### 4.2. Penetration into amniotic fluid

For amniotic fluid, evidence was very limited except from valproate and carbamazepine, which are both contraindicated during pregnancy. The highest penetration ratio was reported for levetiracetam, which was approximately 3 in two women (Paulzen et al., 2014). This ratio implies that fetal development may take place in threefold higher concentrations compared to maternal plasma. There are several mechanisms that could account for this ratio. For example, the low affinity of levetiracetam for the efflux pump P-glycoprotein (P-gp) could explain some trapping of levetiracetam in amniotic fluid (Behmard et al., 2022). Moreover, levetiracetam is not appreciably protein-bound (Patsalos, 2000); the low plasma protein binding may allow a larger part of the total plasma concentration to be excreted into amniotic fluid, as only the unbound drug concentration is able to cross cell membranes (Wang et al., 2008).

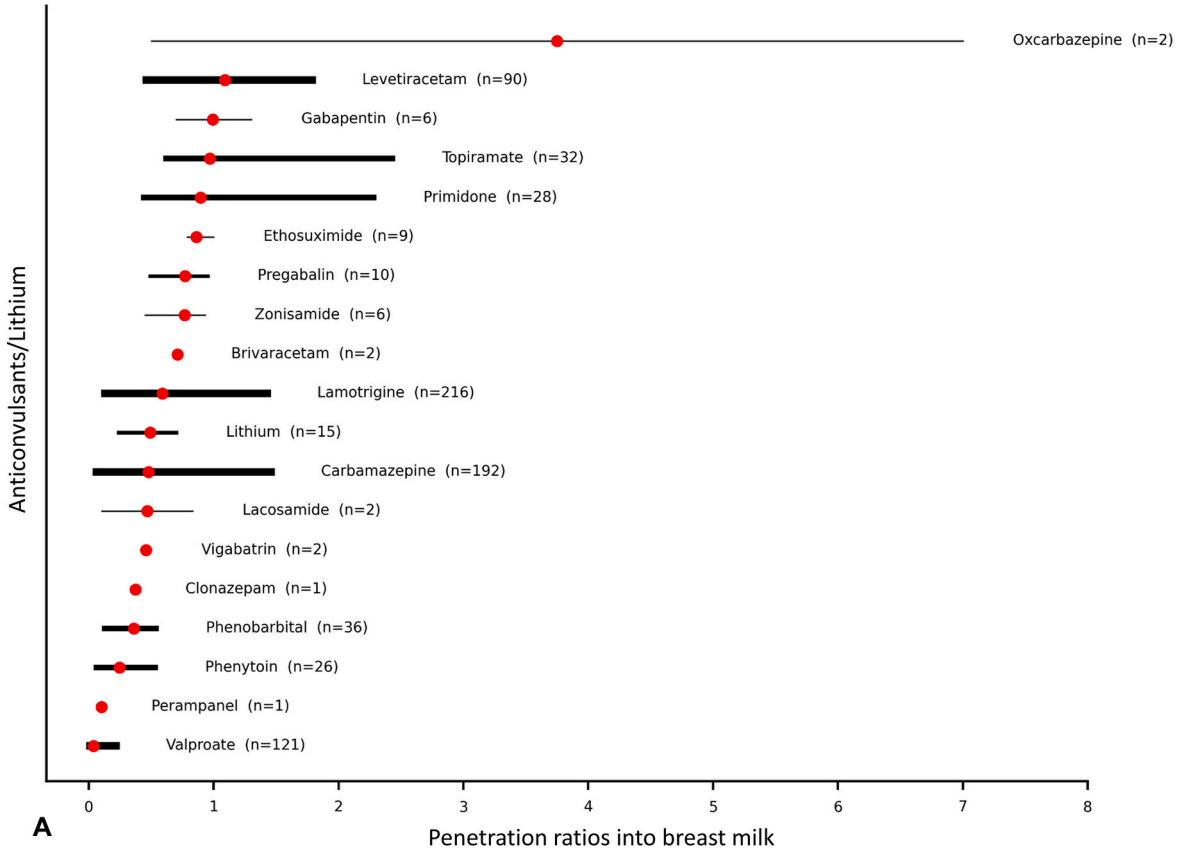
### 4.3. Penetration into umbilical cord

Interestingly, the ranking of penetration ratios into amniotic fluid did not always match the ranking of penetration ratios into umbilical cord implying different elimination processes in fetuses. Here, valproate deserves specific attention given the proton-linked saturable transport system mediating its transplacental passage (Tetro et al., 2018); the penetration ratio of valproate into amniotic fluid was the lowest compared to other anticonvulsants and lithium, but its penetration ratio into umbilical cord was among the highest. Thus, valproate is perfectly able to enter the fetal environment. The ratios refer to total and not free valproate; in fact, free concentrations of valproate may display an opposite pattern compared to total concentrations regarding penetration into umbilical cord with penetration ratios for free and total being $<1$ and $>1$ respectively (Froescher et al., 1984b). The lower maternal total valproate concentrations may be explained by the lower protein binding due to lowered serum albumin compared to umbilical blood (Froescher et al., 1984b). In other words, as for all highly protein-bound drugs, valproate may be more extensively protein-bound in the umbilical than the maternal blood (Ishizaki et al., 1981). It is currently unknown if protein binding is important to valproate's teratogenicity. On the other hand, an inverse correlation was reported between birth length and umbilical cord concentrations of total valproate in 53 infants (Kacirova et al., 2015). Of note, the mismatch in the penetration of anticonvulsants/lithium into umbilical cord and amniotic fluid may be partially affected by the early assessment of drug levels in the amniotic fluid in first/second trimester using amniocentesis in two studies (Omtzigt et al., 1992; Omtzigt et al., 1993).

Overall, the teratogenic profile of anticonvulsants does not seem to linearly relate to their ability to enter the fetal environment. Apart from valproate (which is contraindicated for use in women of childbearing age barring extraordinary clinical circumstances), increased risk for congenital malformations has been reported for ethosuximide, topiramate, phenobarbital, phenytoin and carbamazepine (Veroniki et al., 2017); all of these anticonvulsants present considerable differences between each other in terms of penetration into fetal circulation. For example, regarding penetration ratios into the umbilical cord valproate had a ratio of approximately 1.5, whereas phenytoin and carbamazepine had ratios of 0.7 and 0.8 respectively. Regarding penetration ratios into the amniotic fluid valproate was the least "invasive" anticonvulsant (ratio of 0.11), whereas primidone and ethosuximide had ratios of 1.12 and 1.11 respectively; the protein content in amniotic fluid binding to valproate might be a factor to take into account when interpreting these results (Tetro et al., 2018).

### 4.4. Limitations and clinical implications

Caution is advised when interpreting the findings of our review. Despite years of experience and clear recommendations (Hiemke et al., 2018), TDM for anticonvulsant treatment is not always part of clinical practice. Moreover, TDM in matrices as amniotic fluid, umbilical cord and mother milk has not been integrated into clinical practice. This may explain the lack of large-scale clinical data particularly for newer anticonvulsants. Thus, the challenge of addressing the intuitive notion of concentration-dependent toxicity risk remains unanswered limiting the utility of penetration ratios as safety surrogates. This concentration-dependent toxicity principle may be more useful for medications with lower teratogenic potential; for example, lithium may be safe when keeping maternal levels below 0.6 mmol/L (Fornaro et al., 2020; Newport et al., 2005). Alternatively, for medications such as valproate, prescription during pregnancy should be avoided regardless of maternal blood levels. More specific indices, such as relative infant dose for the degree of anticonvulsant exposure through lactation may provide more precise assessments of neonatal exposure. Also, the available body of



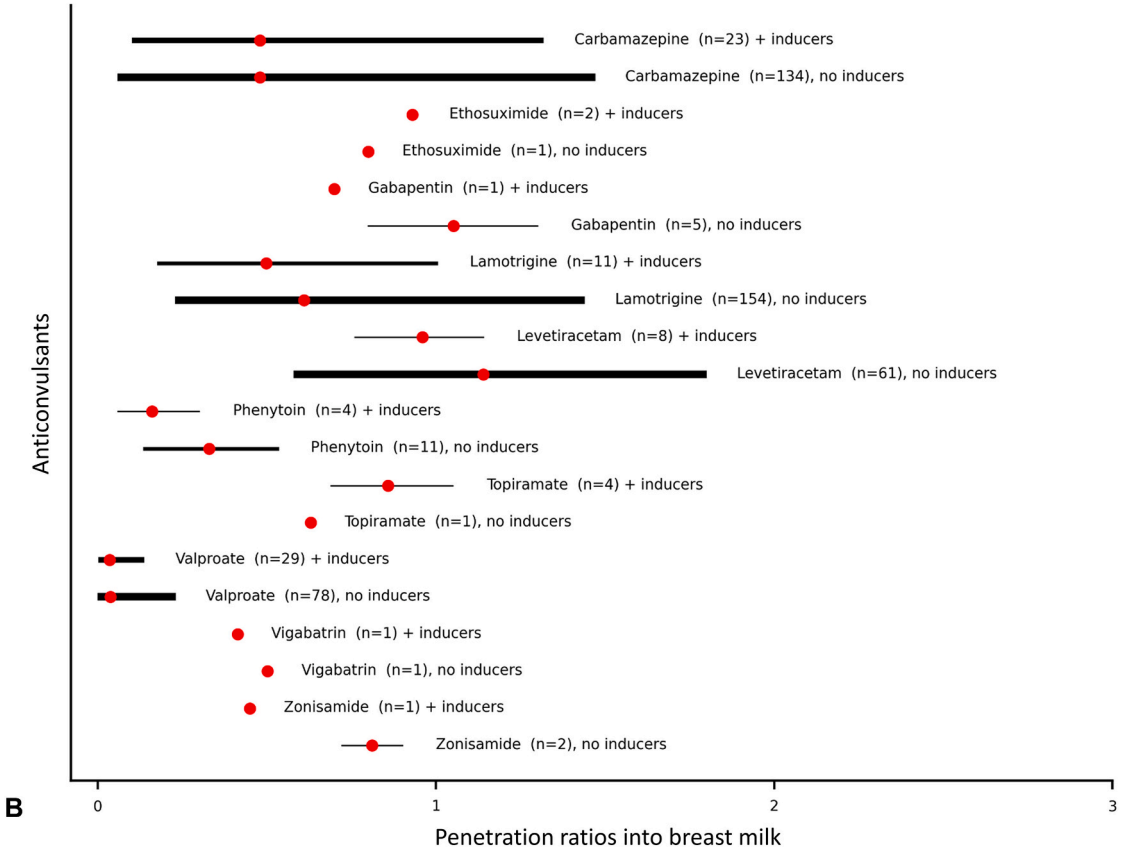




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**Fig. 3.** a) Penetration ratios (combined means and ranges) of anticonvulsants and lithium into breast milk. The width of lines is proportional to the number of patients providing data for the estimation of the penetration ratios (n: number of patients). b) Penetration ratios (combined means and ranges) of carbamazepine, ethosuximide, gabapentin, lamotrigine, levetiracetam, phenytoin, topiramate, valproate, vigabatrin and zonisamide into breast milk in patients receiving co-medications without vs. with inducers. The width of lines is proportional to the number of patients providing data for the estimation of the penetration ratios (n: number of patients).

literature has rarely examined potential moderators of anticonvulsant and lithium transplacental transfer including gestational age and body composition measures. For example, anticonvulsants may be bound to alpha-1 acid glycoprotein in plasma, where the concentration in newborns is only about half of that in adults, and even lower in premature infants (Anell-Olofsson et al., 2018). Nevertheless, gestational age was infrequently available in studies. However, the role of alpha-1 acid glycoprotein may be secondary, as anticonvulsants are mainly bound to glycoprotein (MacKichan and Zola, 1984; Madan et al., 2021). Further, transplacental transfer may also vary between trimesters, as the expression of placental drug-metabolizing enzymes may increase in the first trimester (Rubinchik-Stern and Eyal, 2012). Pregnancy-associated physiological effects of estradiol and progesterone on maternal phase I and II metabolism as well as changes in renal blood flow and glomerular filtration rate due to increased plasma expansion may also contribute to trimester effects on maternal metabolism and transplacental transfer (Deligiannidis et al., 2014). During lactation, it is also crucial to consider the half-life of the anticonvulsant in the infant, as the drug elimination is invariably slower (as phase I and II metabolic enzymes are not all functional at birth) (Lu and Rosenbaum, 2014) with the risk of adverse reactions being higher in premature and newborn infants than in older infants, even though the penetration ratio is constant. Milk-specific characteristics, such as its lipid content, may affect milk concentrations of anticonvulsants given that the majority of anticonvulsants are lipophilic substances (Marvanova, 2016); unfortunately, milk parameters were barely investigated in TDM studies of anticonvulsants and lithium in lactating women, as most studies did not specify fore-milk, mid-feed milk or hind-milk.

Additionally, pharmacogenetic variability in the maternal disposition of anticonvulsants related to drug transporters (Petrenaite et al., 2018; Rubinchik-Stern and Eyal, 2012; Tetro et al., 2018) could contribute to higher or lower transfer in amniotic fluid, umbilical cord blood and breast milk. We are not aware of any studies of pregnant or lactating patients treated with anticonvulsants or lithium including pharmacogenetic data. For many anticonvulsants we did not perform subgroup analyses on the role of concomitant inducer use, as data was not available, specifically for amniotic fluid. Additionally, the use of different quantification methods may have explained some part of the variability in the assessment of the levels of anticonvulsants; particularly, older quantification methods may have been less sensitive with co-medications potentially interfering with the analysis leading to falsely high levels (Kristensen et al., 1967).

The majority of the studies reflected single time point measures rather than more sophisticated pharmacokinetic analyses; in the future better precision outcomes could be expected using AUC estimates for blood and milk. Studies mainly used TDM assessments at steady state, however a fair number of studies did not provide sufficient information to determine if the levels of anticonvulsants were acquired at trough or steady state. Relatedly, a considerable number of studies included maternal blood sampling at delivery, with samples not being trough; specifically, concentrations in matrices other than maternal serum/serum invariably lag behind, which means that shortly after drug administration, the concentrations would be higher in maternal plasma ("falsely" lowered penetration ratios), whereas towards the end of the dosing interval concentrations will be decreasing leading to falsely higher ratios. Of note, specifically for lithium, some perinatal psychiatry programs instruct women to suspend lithium treatment just before delivery (Newport et al., 2005), so that lithium concentrations assessed close to delivery may lack precision. Lastly, use of different analytical methods may have accounted for some variation in pharmacokinetic findings.

Future studies investigating transfer of anticonvulsants and lithium into fetal and newborn circulation are required to improve the understanding of excretion mechanisms underlying variations in penetration ratios between medications. In light of the need for safe prescription of anticonvulsants in pregnancy and lactation we hope that the collection of larger-scale data will enhance the clinical utility of TDM in pregnancy and lactation. Specifically, pharmacovigilance data of international origin could make up for the lack of prospective clinical evidence due to ethical challenges. Clinicians may use maternal blood concentrations as surrogates of fetal/neonatal exposure to anticonvulsants and lithium by simply applying the penetration ratios estimated in our work.

## Authorship contributions

Participated in research design: CTS, KMD, SKS, OS, TF, MP, GS.
Performed data analysis: CTS, GS.
Wrote the manuscript: CTS.
Edited and corrected the manuscript: KMD, SKS, OS, TF, MP, GS.

## Declaration of Competing Interest

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## Data availability

Data will be made available on request.

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## Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.pnpbp.2023.110733.

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