RESEARCH ARTICLE

Comparative Safety of Antiseizure Medication Monotherapy for Major Malformations

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Objective: This study was undertaken to examine the comparative safety of antiseizure medication (ASM) monotherapy in pregnancy with respect to risk of major congenital malformations (MCMs), overall and by MCM subtype.
Methods: We conducted a population-based cohort study using national health register data from Denmark, Finland, Iceland, Norway, and Sweden (1996–2020). We compared pregnancies with first trimester exposure to lamotrigine monotherapy to ASM-unexposed, carbamazepine, valproate, oxcarbazepine, levetiracetam, and topiramate to lamotrigine monotherapy, and stratified monotherapy groups by dose. The outcome was nongenetic MCM and specific subtypes. We estimated adjusted risk ratios (aRRs) and 95% confidence intervals (CIs) with log-binomial regression and propensity score weights.
Results: There was a higher crude risk of any MCM in pregnancies exposed to lamotrigine monotherapy (n = 8,339) compared to ASM-unexposed pregnancies (n = 4,866,362), but not after confounder adjustment (aRR = 0.97, 95% CI = 0.87–1.08). Compared to lamotrigine, there was an increased risk of malformations associated with valproate (n = 2,031, aRR = 2.05, 95% CI = 1.70–2.46) and topiramate (n = 509, aRR = 1.81, 95% CI = 1.26–2.60), which increased in a dose-dependent manner. We found no differences in malformation risk for carbamazepine (n = 2,674, aRR = 0.91, 95% CI = 0.72–1.15), oxcarbazepine (n = 1,313, aRR = 1.09, 95% CI = 0.83–1.44), or levetiracetam (n = 1,040, aRR = 0.78, 95% CI = 0.53–1.13). Valproate was associated with several malformation subtypes, including nervous system, cardiac, oral clefts, clubfoot, and hypospadias, whereas lamotrigine and carbamazepine were not.
Interpretation: Topiramate is associated with an increased risk of MCM similar to that associated with valproate, but lower doses may mitigate the risks for both drugs. Conversely, we found no increased risks for lamotrigine, carbamazepine, oxcarbazepine, or levetiracetam, which is reassuring.

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Introduction

Indications for antiseizure medications (ASMs) have expanded in recent decades. In addition to epilepsy, several ASMs are also used in the treatment of bipolar disorders, neuropathic pain, and migraine, and off-label for other indications.[1] Consequently, the use of ASMs in pregnancy has increased since at least the early 2000s.[2–4] In the Nordic countries, lamotrigine is the most commonly used ASM, and its use in pregnancy approximately doubled between 2006 and 2016.[5]

To optimize ASM use in pregnancy, the therapeutic effect of the drug must be weighed against its teratogenic potential. To date, there is strong evidence for an increased risk of major congenital malformations (MCMs) associated with valproate, phenytoin, and phenobarbital.[6–8] There is conflicting but suggestive evidence for increased risk with other ASMs, including carbamazepine and topiramate.[6,9–11] Lamotrigine has the most evidence for pregnancy safety;[12,13] however, recent data showed an increased risk of MCM with higher prepregnancy lamotrigine dose (>325mg/day).[9] Levetiracetam is also considered among the safest ASMs in terms of risk of MCM, but based on fewer exposures.[9,14] However, lamotrigine and levetiracetam are not effective treatments for all patients who need ASM, and serum concentrations decline in pregnancy, leading to a higher risk of breakthrough seizures.[15,16] Therefore, robust safety data on other ASMs is needed to improve the evidence base for ASM treatment in pregnancy.

Some of the best evidence for safety of ASM use in pregnancy is derived from dedicated exposure registries funded by the pharmaceutical companies.[7,9,17] Pregnancy exposure registries usually have detailed clinical information, which make it possible to study drug dose, seizure control, and other aspects such as the underlying indication for use. However, they rely on voluntary participation by patients, which could introduce selection bias, and they are usually underpowered to study the associations between specific ASMs and specific malformations. Data on outcomes in unexposed pregnancies are also limited in these registries. Other high-quality evidence comes from large case–control studies.[13,18] Case–control studies usually include validated outcomes, but because ASMs are rare exposures, precise estimates for specific malformations may be impossible to obtain. Very large cohort studies are therefore needed to study both less common exposures and rare outcomes.[10,19]

The linked Nordic registers provide comprehensive information on the use of prescribed drugs in pregnancy for the entire pregnant population and precise diagnoses in the offspring. Using this rich resource, we were able to construct a cohort of approximately 5 million births with the possibility to study both infrequently used drugs and rare outcomes.

Our objective was to study the comparative safety of ASMs in pregnancy with respect to the risk of MCM in offspring, overall and for specific malformation subtypes. We compared lamotrigine monotherapy to ASM-unexposed and compared other ASM monotherapies to lamotrigine monotherapy. Lamotrigine was used as an active comparator because it is used for both main indications, epilepsy and bipolar disorder, and has the most evidence for safety in pregnancy to date. We also stratified the monotherapy groups by dose and compared each stratum to low-dose lamotrigine.

Subjects and Methods

Study Design

We carried out a population-based cohort study based on national registers from the 5 Nordic countries: Denmark, Finland, Iceland, Norway, and Sweden. Similar health and social registers exist in each country, which are linkable by a personal identity number assigned to all residents. The Nordic countries all have publicly funded health care systems with reporting to the registers mandated by law.[20] The relevant authorities in all countries approved the project and granted a waiver of informed consent. Data on births, filled prescriptions, MCMs, and potential confounders were obtained from the medical birth registers linked with registers for prescribed drugs, congenital anomalies, specialist health care, and deaths.

Study Population

We included all pregnancies in the general population, including singleton and multiple births, live births and stillbirths, with a gestational age of at least 22 weeks occurring in the following years: Denmark 1997–2017, Finland 1996–2016, Iceland 2003–2017, Norway 2004–2020, and Sweden 2006–2019.

We did not include pregnancies with a missing or invalid gestational age (>44 weeks, or an implausibly high birthweight for gestational age, z score >4 at <35 weeks[21]), because the precise gestational timing of prescriptions fills for these pregnancies is unknown or uncertain. We excluded pregnancies without prescription data covering 90 days before the first day of the last menstrual period (LMP; confirmed primarily by ultrasound) to birth, mainly excluding births within the first year after the prescribed drug registers were established. We also excluded pregnancies with any potential exposure in the first trimester to known teratogenic drugs (prescription fills from 90 days before LMP to the end of the first trimester, 97 days after LMP), including warfarin, isotretinoin, systemic retinoids, misoprostol, thalidomide, and antineoplastic agents. We excluded pregnancies where one or more offspring were diagnosed with a teratogenic infection (rubella, cytomegalovirus, or toxoplasmosis), chromosomal anomaly, or genetic syndrome within 1 year of birth (Table S1).

Exposure Definition

We studied prenatal exposure to monotherapy of the most used ASMs for which lamotrigine (Anatomical Therapeutic Chemical [ATC] code N03AX09) was a relevant comparator drug: carbamazepine (N03AF01), valproate (N03AG01), oxcarbazepine (N03AF02), levetiracetam (N03AX14), and topiramate (N03AX11). Other ASMs were either rarely used or mainly used for neuropathic pain (gabapentin and pregabalin), not epilepsy or bipolar disorders, and thus lamotrigine monotherapy is unlikely to be considered a relevant alternative treatment.

ASM-unexposed pregnancies were defined as pregnancies in which the mother had not filled a prescription for any ASM (ATC code N03A) from 90 days before LMP to the end of the first trimester. ASM-exposed pregnancies were defined as those in which the mother had filled one or more prescriptions during the first trimester (primary definition). To define monotherapy, we excluded those with potential exposure to another ASM in the first trimester, requiring that the mother filled prescriptions for only one ASM substance from 90 days before LMP to end of first trimester. We applied a secondary (sensitive) exposure definition in which we additionally included pregnancies with filled prescriptions in the 30 days before LMP to capture first trimester users who filled their prescriptions before LMP. We applied another secondary (specific) exposure definition that required at least two prescriptions to be filled during pregnancy, with at least one in first trimester, to avoid including pregnancies of mothers who discontinued medication before conception or early in pregnancy.

We estimated the first trimester dose by dividing the amount of drug dispensed in the first prescription filled between 90 days before LMP and the end of the first trimester by the number of days to the subsequent prescription. We combined all prescriptions dispensed in the same week and used the total amount of drug dispensed and the earliest dispensing date if they had more than one fill in the same week as the earliest prescription. If the mother had only one prescription fill in that window, we used the date of the next fill in the second trimester, if it was a maximum of 120 days from the first date, or the median number of days to the subsequent prescription for individuals with at least two fills. Medians were specific to the drug, country, and number of defined daily doses (≤60 or >60) in the first prescription. It is relevant to assess prescriptions received immediately before pregnancy and early in the first trimester, because the doses are increased in pregnancy for several ASMs to maintain stable serum concentrations of the drug as pharmacokinetic changes occur in pregnancy.[15,16,22]

Outcome Definition

The primary outcome was MCM diagnosed within 1 year of birth and recorded in the medical birth, patient, malformation, or death register. The definition was aligned as closely as possible with the EUROCAT 1.4 classification (Table S1).[23] We considered any MCM (excluding genetic/chromosomal), and MCMs by organ system or type, such as nervous system, eye, ear–face–neck, cardiac, respiratory, orofacial clefts, gastrointestinal, abdominal wall, urinary, genital, limb, other, and multiple malformations. The specific malformations hypospadias and clubfoot (pes equinovarus) were also assessed. For Finland, we only considered validated diagnoses from the Finnish Register of Congenital Malformations. For Denmark, Iceland, Norway, and Sweden, we required at least two diagnosis codes from the same subgroup to be recorded on separate visit dates if the MCM was only diagnosed in outpatient specialist care to increase diagnostic validity.

Covariates

Covariates included in the analysis were country, year of delivery, maternal age at delivery, multiple pregnancy, parity, cohabitation, maternal country of birth (Nordic or non-Nordic), indications for ASM (epilepsy, bipolar disorder, migraine, chronic pain, other), other chronic conditions (diabetes, hypertension, depression, anxiety, personality disorder, psychotic disorder, substance use disorder), other medication used during first trimester (benzodiazepines and related drugs, opioids, antidepressants, antipsychotics, lithium, antidiabetics, antihypertensives, triptans, drugs for substance use disorders), use of any suspected teratogenic drugs in first trimester, and indicators of health care utilization in the 90 days before pregnancy (any hospitalization, any outpatient specialist visit). Definitions including all codes for diagnoses and drugs are provided in Table S2.

Data Analysis

The data were harmonized according to a common data model for the NorPreSS (Nordic Pregnancy Drug Safety Studies) collaboration.[24] Data from Finland, Iceland, Norway, and Sweden were individually pooled and analyzed as a single cohort. Data from Denmark were analyzed separately due to national restrictions on data exportation using the same analysis programs with minor adaptations as necessary. The unit of analysis was the pregnancy. For multiple pregnancies, if more than one infant had the outcome, the pregnancy was still only counted once. The results for the individually pooled data and Denmark were combined using fixed-effects meta-analysis.[25]

We compared the characteristics of pregnancies defined as ASM-unexposed and ASM monotherapy-exposed according to the primary exposure definition. Our main analyses focused on any MCM. We calculated the MCM prevalence per 1,000 pregnancies in the different study groups: ASM-unexposed and -exposed according to the primary and secondary exposure definitions. Pregnancies exposed to lamotrigine monotherapy were compared with ASM-unexposed. Other ASM monotherapy groups were compared with lamotrigine monotherapy.

We additionally stratified the monotherapy-exposed pregnancies (primary definition) according to estimated first-trimester dose and compared risk of MCM in pregnancies with low, medium, or high dose of each ASM to low-dose lamotrigine. We defined the dose cutoffs a priori, based on the distribution of doses in the population, examined in preliminary analyses. We aimed for cutoffs that represented real doses in clinical use, substantial proportions of patients with different indications across the dose groups, similar and sufficiently sized groups, and

comparability with published studies (eg, European and International Registry of Antiepileptic Drugs in Pregnancy [EURAP] used a 325mg cutoff for lamotrigine). We excluded pregnancies with extreme low and high values and stratified as follows: lamotrigine 25 ≤ 150, >150–325, >325–1,200mg; carbamazepine 150 ≤ 450, >450–700, >700–2,000mg; valproate 275 ≤ 650, >650–1,000, >1,000–2,700mg; oxcarbazepine 300 ≤ 750, >750–1,050, >1,050–2,400mg; levetiracetam 450–1,250, >1,250–7,000mg; topiramate 25–125, >125–600mg.

We calculated adjusted risk ratios (RRs) and 95% confidence intervals (CIs) with robust standard errors to account for clustering of pregnancies within mothers. Minimally adjusted RRs were estimated using log-binomial regression adjusted for maternal age, delivery year, and country. For fully adjusted RRs, we estimated propensity scores using logistic regression, including both confounders and risk factors for the outcome (such as multiple pregnancy) in the model to improve precision.[26] After trimming observations from the nonoverlapping regions of the exposed and unexposed propensity score distributions, the remaining pregnancies were stratified in up to 50 strata according to the distribution of the propensity score in the exposed pregnancies. Finally, stratum-specific weights were used in binomial regression models.[27]

We also described the distribution of the subtypes of MCM in ASM-unexposed and -exposed pregnancies. For secondary analyses estimating the RRs for MCM subtypes, we decided a priori to focus on the most commonly used ASMs (lamotrigine, carbamazepine, and valproate) and to increase power by comparing with the ASM-unexposed group. We also selected the MCM subtypes based on importance (nervous system, multiple malformations) or an expected prevalence of at least 1 per 1,000 pregnancies (cardiac, orofacial clefts, clubfoot, hypospadias).

Sensitivity Analyses

We explored the potential influence of not including terminations of pregnancy for fetal anomaly (TOPFAs). These pregnancies are recorded in Norway (Medical Birth Registry), Finland (Register of Congenital Anomalies and Register of Induced Abortions), and Denmark (maternal International Classification of Diseases, 10th Revision codes in the Danish National Patient Register since 2006)[28–30] but were not available for this study from Sweden or Iceland. We compared the percent of MCMs identified in births out of all MCMs identified from births and TOPFAs for the ASM-unexposed and monotherapy-exposed pregnancies in Finland, Norway, and Denmark (2007–2017).

Results

Among 4,917,523 pregnancies eligible for inclusion, we excluded 5,874 with exposure to strong teratogenic medications, an additional 3,759 with ASM polytherapy, and finally 12,898 with a chromosomal anomaly, genetic syndrome, or teratogenic infection. Women used an ASM monotherapy of interest in the first trimester of 15,906 (0.3%) pregnancies (8,339 lamotrigine, 2,674 carbamazepine, 2,031 valproate, 1,313 oxcarbazepine, 1,040 levetiracetam, and 509 topiramate) and no ASM in 4,866,362 pregnancies.

Epilepsy was the most common indication for each of the ASM monotherapies (47.0–98.9%; Tables 1, S3). Oxcarbazepine and levetiracetam were almost exclusively used for epilepsy. Lamotrigine was the ASM most commonly used for bipolar disorder, followed by valproate, topiramate, and carbamazepine. Topiramate was the ASM most used for migraine.

Except for levetiracetam and carbamazepine, pregnancies exposed to ASM monotherapy had a higher prevalence of any MCM than the ASM-unexposed pregnancies, with the highest prevalences among those exposed to valproate or topiramate (Table 2). When we used the specific exposure definition requiring at least two prescription fills in pregnancy, we included between 3 and 44% fewer exposed. The prevalence of MCM was higher for valproate and topiramate, but not other ASMs, using the specific exposure definition compared to the primary exposure definition. When we applied the more sensitive exposure definition, we identified an additional 8 to 37% who filled a prescription in the 30 days before LMP, and the prevalences of MCM were similar to the primary exposure definition.

Lamotrigine-exposed infants had an increased risk of MCM compared to ASM-unexposed after adjusting for maternal age, delivery year, and country, but not when adjusting for all confounders (RR = 0.97, 95% CI = 0.87–1.08) for the primary exposure definition (Fig 1). Compared to lamotrigine monotherapy, valproate and topiramate were both associated with an approximately 2-fold increased risk of MCM in both minimally adjusted and fully adjusted models. Carbamazepine and oxcarbazepine exposure were not associated with a higher risk of MCM (fully adjusted RRs = 0.91 [95% CI = 0.72–1. 15] and 1.09 [0.83–1.44], respectively), whereas levetiracetam exposure seemed to be associated with a lower risk of MCM than lamotrigine monotherapy (fully adjusted RR = 0.78, 95% CI = 0.53–1.13). Carbamazepine was the only drug for which there were substantially different RR estimates from Denmark versus from the pooled Nordic data (I^2 = 86% for the fully adjusted RRs, primary exposure definition). Carbamazepine was associated with an increased risk of MCM in Denmark (fully adjusted RR = 1.60, 95% CI = 0.99–2.57) but not in the pooled data from the remaining Nordic countries (RR = 0.77, 95% CI = 0.59–1.00; data not shown).

The risk of MCM also increased in a dose-dependent manner for valproate and topiramate (Fig 2). However, for low-dose topiramate, we did not find an increased risk of MCM, whereas valproate at all doses was

TABLE 1. Selected Characteristics of Antiseizure Medication-Unexposed and First Trimester Monotherapy-Exposed Pregnancies, n (%), from Denmark (1997–2017), Finland (1996–2016), Iceland (2003–2017), Norway (2004–2020), and Sweden (2006–2019)[a]

Characteristic	Unexposed, n = 4,866,362	LTG, n = 8,339	CBZ, n = 2,674	VPA, n = 2,031	OXC, n = 1,313	LEV, n = 1,040	TPM, n = 509
Maternal age at delivery, yr							
<25	715,332 (14.7)	1,237 (14.8)	280 (10.5)	435 (21.4)	256 (19.5)	163 (15.7)	89 (17.5)
25–29	1,541,693 (31.7)	2,654 (31.8)	787 (29.4)	616 (30.3)	426 (32.4)	347 (33.4)	143 (28.1)
30–34	1,645,992 (33.8)	2,748 (33.0)	941 (35.2)	644 (31.7)	425 (32.4)	353 (33.9)	177 (34.8)
35–39	794,996 (16.3)	1,401 (16.8)	533 (19.9)	270 (13.3)	165 (12.6)	150 (14.4)	81 (15.9)
≥40	168,349 (3.5)	299 (3.6)	133 (5.0)	66 (3.2)	41 (3.1)	27 (2.6)	19 (3.7)
Maternal education							
Compulsory	551,202 (15.4)	1,559 (20.9)	316 (21.8)	278 (29.3)	141 (30.4)	167 (18.9)	107 (26.8)
Secondary	1,517,103 (42.3)	3,307 (44.3)	664 (45.9)	427 (45.0)	193 (41.6)	358 (40.5)	183 (45.8)
Tertiary	1,522,114 (42.4)	2,595 (34.8)	468 (32.3)	243 (25.6)	130 (28.0)	359 (40.6)	110 (27.5)
Missing[b]	1,275,943	878	≈1,226	≈1,083	849	≈156	≈109
Indications for ASM use							
Epilepsy	15,385 (0.3)	4,690 (56.2)	2,371 (88.7)	1,632 (80.4)	1,265 (96.3)	1,029 (98.9)	239 (47.0)
Bipolar disorder	8,071 (0.2)	2,492 (29.9)	≈55 (2.1)	181 (8.9)	<5	≈8 (0.8)	≈35 (6.9)
Migraine or cluster headache	61,214 (1.3)	253 (3.0)	≈49 (1.8)	56 (2.8)	31 (2.4)	51 (4.9)	117 (23.0)
Chronic pain	124,587 (2.6)	433 (5.2)	109 (4.1)	69 (3.4)	44 (3.4)	44 (4.2)	40 (7.9)
Unknown	NA	1,220 (14.6)	218 (8.2)	222 (10.9)	44 (3.4)	11 (1.1)	137 (26.9)
Other chronic conditions							
Preexisting diabetes	37,736 (0.8)	107 (1.3)	30 (1.1)	≈35 (1.7)	21 (1.6)	≈17 (1.6)	≈8 (1.6)
Preexisting hypertension	41,506 (0.9)	94 (1.1)	44 (1.6)	≈19 (0.9)	24 (1.8)	≈12 (1.2)	15 (2.9)
Comedication[c]							
Opioids	113,524 (2.3)	548 (6.6)	106 (4.0)	72 (3.5)	36 (2.7)	41 (3.9)	71 (13.9)
Antidepressants	165,344 (3.4)	2,255 (27.0)	182 (6.8)	255 (12.6)	76 (5.8)	62 (6.0)	108 (21.2)
Antipsychotics	18,464 (0.4)	1,034 (12.4)	≈55 (2.1)	173 (8.5)	≈9 (0.7)	≈12 (1.2)	39 (7.7)
Triptans	60,758 (1.2)	238 (2.9)	51 (1.9)	37 (1.8)	27 (2.1)	≈21 (2.0)	123 (24.2)

[a]Data are presented for the 5 countries combined. Counts < 5 are not shown for data privacy. Cell values < 5 could not be exported from Denmark and were replaced by 3 to sum up the counts, denoted with the ≈ symbol.
[b]Data on education from Finland were not available in the pooled dataset.
[c]Comedication is defined as potential first trimester exposure, filled prescriptions from 90 days before pregnancy to end of first trimester.
Abbreviation: ASM = antiseizure medication; CBZ = carbamazepine; LEV = levetiracetam; LTG = lamotrigine; NA = not applicable; OXC = oxcarbazepine; TPM = topiramate; VPA = valproate.

associated with an increased risk of MCM. We observed no dose–response pattern for lamotrigine, carbamazepine, oxcarbazepine, or levetiracetam. There was a higher risk for MCM with medium-dose oxcarbazepine versus low-dose lamotrigine, but no differences for low- or high-dose oxcarbazepine.

A description of the types of malformations registered is shown in Table 3. Overall, there were 147,928

TABLE 2. Prevalence of Major Congenital Malformations per 1,000 Pregnancies in 5 Nordic Countries (1996–2020) in Antiseizure Medication-Unexposed and First Trimester Monotherapy-Exposed Pregnancies, by Exposure Definition

Treatment	Total, N	MCMs, n	MCMs per 1,000 (95% CI)
Unexposed	4,866,362	147,928	30.4 (30.2–30.6)
Lamotrigine			
Primary	8,339	314	37.7 (33.6–41.7)
Sensitive	9,512	358	37.6 (33.8–41.5)
Specific	6,984	260	37.2 (32.8–41.7)
Carbamazepine			
Primary	2,674	90	33.7 (26.8–40.5)
Sensitive	3,067	106	34.6 (28.1–41.0)
Specific	2,405	84	34.9 (27.6–42.3)
Valproate			
Primary	2,031	159	78.3 (66.6–90.0)
Sensitive	2,427	177	72.9 (62.6–83.3)
Specific	1,646	144	87.5 (73.8–101.1)
Oxcarbazepine			
Primary	1,313	58	44.2 (33.1–55.3)
Sensitive	1,449	69	47.6 (36.7–58.6)
Specific	1,260	55	43.7 (32.4–54.9)
Levetiracetam			
Primary	1,040	30	28.8 (18.7–39.0)
Sensitive	1,118	36	32.2 (21.9–42.5)
Specific	1,007	29	28.8 (18.5–39.1)
Topiramate			
Primary	509	32	62.9 (41.8–84.0)
Sensitive	697	42	60.3 (42.6–77.9)
Specific	284	27	95.1 (61.0–129.2)

Note: "Primary" refers to the primary exposure definition (≥1 prescription filled during first trimester), "sensitive" refers to the secondary exposure definition that is more sensitive (≥1 prescription filled during first trimester or the 30 days before pregnancy), and "specific" refers to the secondary exposure definition that is more specific (≥2 prescriptions filled during pregnancy with at least one in first trimester).
Abbreviation: MCM = major congenital malformation.

nongenetic MCMs among the ASM-unexposed pregnancies, the largest proportion of which were cardiac (41%), followed by limb (14%) and urinary (12%). We observed that approximately 20% of pregnancies with MCM after valproate or topiramate exposure had multiple malformations, whereas only 6% of cases had multiple malformations in children unexposed to ASMs.

Compared with ASM-unexposed subjects, lamotrigine monotherapy was associated with an increased risk of nervous system, cardiac, and multiple malformations in the minimally adjusted analysis but not in the fully adjusted analysis (Fig 3). Carbamazepine was associated with an increased risk for hypospadias in the minimally adjusted analysis, but the estimate was attenuated after further adjustment (RR = 1.64, 95% CI = 0.86–3.14). Valproate was strongly associated with all the subtypes of malformations examined, although the RRs were attenuated in the fully adjusted estimates (RRs = 1.86 for multiple malformations to 6.47 for hypospadias).

In our sensitivity analysis, approximately half of the TOPFAs had a chromosomal anomaly and were excluded. We identified 6% more MCMs when including TOPFAs in Norway and Finland among the ASM-unexposed group. This was similar for all the ASM monotherapy groups except for levetiracetam, for which TOPFAs contributed a significantly larger proportion of the identified MCMs. However, the absolute number of exposed TOPFAs was too small (<5) to be reported. Similarly, for Denmark, we identified 7% more MCMs in the ASM-unexposed and lamotrigine monotherapy groups when including TOPFAs (2007–2017), but no additional MCMs were identified in TOPFAs for the other ASM monotherapy groups of interest.

Discussion

We carried out a comparative safety study of 6 different ASM monotherapies in a population-based cohort of approximately 5 million births from the 5 Nordic countries. Lamotrigine was not associated with an increased risk of MCM compared to the risk in ASM-unexposed pregnancies. We found that valproate and topiramate increased the risk of MCM to a similar extent, approximately 2-fold, whereas carbamazepine, oxcarbazepine, and levetiracetam were not associated with an increased risk compared with lamotrigine monotherapy. The associations for valproate and topiramate increased in a dose-dependent manner and were stronger, especially for topiramate, when we required that the mother had filled

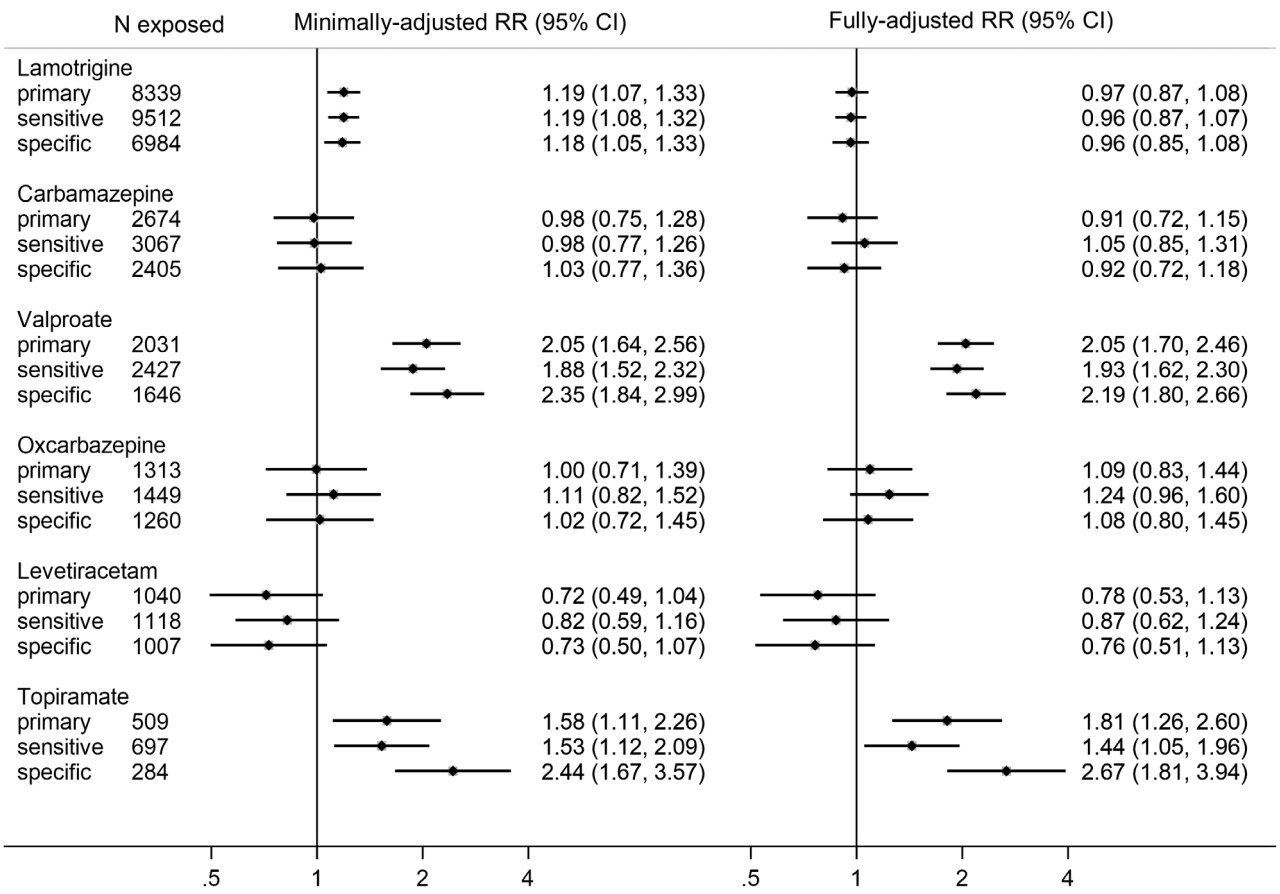

FIGURE 1: Association of first trimester antiseizure medication monotherapy with any major congenital malformation. Adjusted risk ratios (RRs) are shown for any major congenital malformation associated with first trimester lamotrigine monotherapy-exposed compared to antiseizure medication-unexposed pregnancies (n = 4,866,362) and other antiseizure medication monotherapy-exposed compared to lamotrigine monotherapy-exposed pregnancies. RRs presented in the figure are the overall pooled estimates combining Denmark, Finland, Iceland, Norway, and Sweden. Minimally adjusted RRs controlled for maternal age, delivery year, and country. Fully adjusted RRs additionally controlled for parity, multiple pregnancy, cohabitation, maternal country of birth, indications for antiseizure medication, diabetes, hypertension, psychiatric conditions, other medication used during first trimester, and indicators of health care utilization in the 90 days before pregnancy. "Primary" refers to the primary exposure definition (≥1 prescription filled during first trimester), "sensitive" refers to the secondary exposure definition that is more sensitive (≥1 prescription filled during first trimester or the 30 days before pregnancy), and "specific" refers to the secondary exposure definition that is more specific (≥2 prescriptions filled during pregnancy with at least one in first trimester). CI = confidence interval.

at least two prescriptions during the pregnancy. The data suggested that both valproate and topiramate may increase the risk for multiple malformations. We also found that valproate was associated with various subtypes of malformations, including nervous system, cardiac, oral clefts, clubfoot, and hypospadias, whereas lamotrigine and carbamazepine were not associated with any of these, compared with ASM-unexposed pregnancies.

Valproate has been a recognized teratogen for at least 2 decades. In 2018, the European Medicines Agency introduced stronger restrictions on the use of valproate to avoid exposure in pregnancy.[31] Topiramate is a potential alternative to valproate in the treatment of generalized epilepsy and other indications. In recent years, safety signals for topiramate have arisen, most consistently for oral clefts.[10] Our results confirm the teratogenic potential of topiramate and suggest that topiramate should not be viewed as a safer alternative with regard to MCM. Heightened concerns about topiramate safety in pregnancy are further supported by a recent study that identified approximately 3-fold higher risks of autism spectrum disorder and intellectual disability for children with prenatal exposure to topiramate.[32] We report lower RRs for MCM for valproate than prior studies,[6,7,33] which may be due to studying the risk in the general population, using lamotrigine as an active comparator, and use at lower doses for different indications. The lower risk estimates do not seem to be the result of bias from a differential rate of pregnancy termination for recognized malformations. We observed stronger RRs for valproate

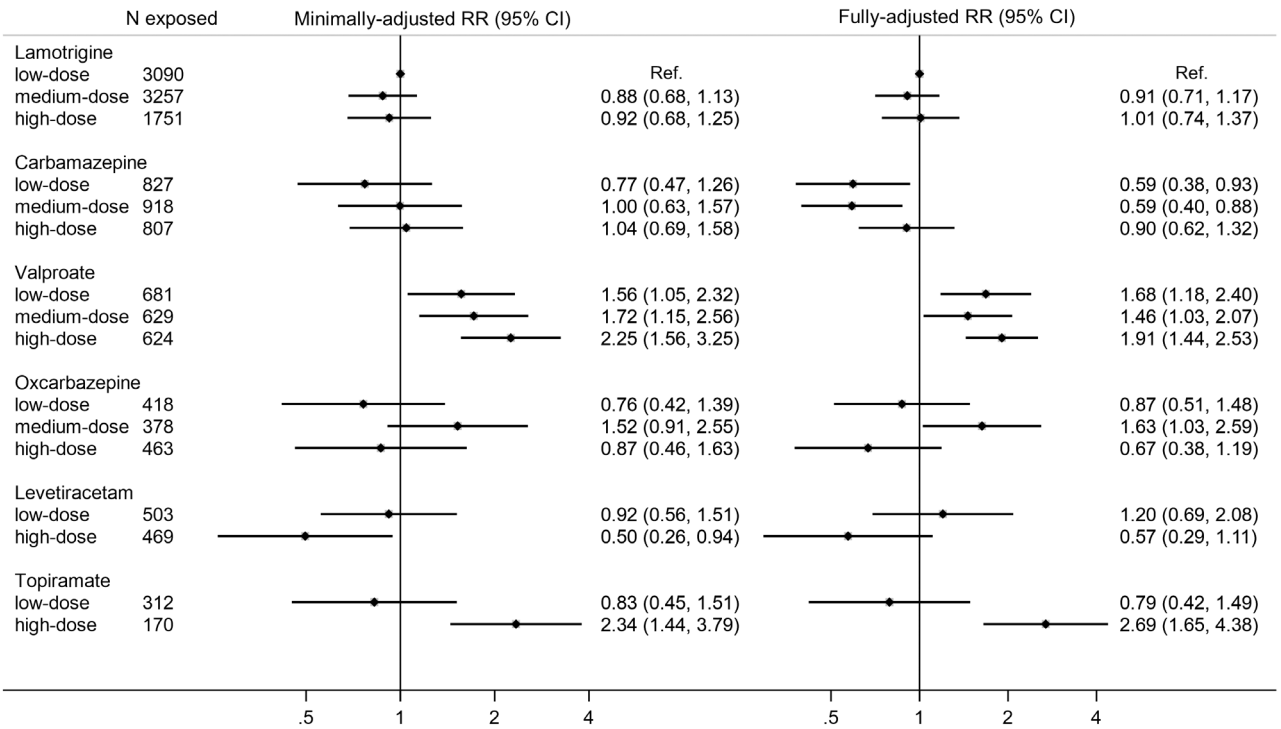

FIGURE 2: Association of first trimester antiseizure medication monotherapy at low-, medium-, or high-dose versus low-dose lamotrigine with any major congenital malformation. Adjusted risk ratios (RRs) are shown for any major congenital malformation associated with antiseizure medication use in the first trimester at low, medium, or high dose compared to pregnancies with use of lamotrigine at low dose. RRs presented in the figure are the overall pooled estimates combining Denmark, Finland, Iceland, Norway, and Sweden. Minimally adjusted RRs controlled for maternal age, delivery year, and country. Fully adjusted RRs additionally controlled for parity, multiple pregnancy, cohabitation, maternal country of birth, indications for antiseizure medication, diabetes, hypertension, psychiatric conditions, other medication used during first trimester, and indicators of health care utilization in the 90 days before pregnancy. Pregnancies with first trimester exposure to each antiseizure medication monotherapy according to the primary exposure definition (≥1 prescription filled during first trimester) were divided according to estimated first trimester dose. Dose categories were selected a priori. Due to the smaller numbers of exposed pregnancies, there were only two dose categories for levetiracetam and topiramate. CI = confidence interval; Ref. = reference group.

for MCM subtypes when compared to ASM-unexposed pregnancies.

In line with prior research, our results support the safety of lamotrigine and levetiracetam monotherapy during pregnancy.[6,13,14] We did not see evidence of an increased risk of MCM at higher lamotrigine doses, as was observed in EURAP, which was restricted to women with epilepsy and those who did not change their medication during the first trimester.[9] However, we have estimated the early pregnancy dose based on the amount of drug dispensed from the pharmacy, rather than using the prescribed dose at the estimated time of conception. It is also possible that more women discontinued lamotrigine treatment early in pregnancy compared with the EURAP registry, as our data also included women using ASM for indications other than epilepsy. Unlike the EURAP study, our analysis included those withdrawing treatment in the first trimester, but we still did not observe a higher risk of MCM for those with at least two prescriptions for lamotrigine. The analysis of TOPFAs suggested that our study was not at risk of important bias by excluding TOPFAs from the main analyses but could underestimate the risk of MCM for levetiracetam. We observed that the point estimate for levetiracetam suggested it was associated with a lower risk of MCM than lamotrigine, which could be at least partly explained by our underestimation of the risk of MCM in levetiracetam-exposed pregnancies when studying MCM among births only.

Our results do not suggest that carbamazepine or oxcarbazepine are teratogenic. There was no consistent pattern of increased risk across the different analyses for either drug. There was an increased risk for MCM associated with carbamazepine use in Denmark but not for the pooled Nordic data, and for medium but not high or low dose of oxcarbazepine. Although these two RRs are concerning, they do not fit with an overall pattern suggesting that either of these drugs is associated with an increased risk of MCM overall or subtypes compared with lamotrigine or ASM-unexposed subjects. These results differ from EURAP,[9] but are more in line with results from

TABLE 3. Description of Major Congenital Malformation Subtypes (Number and Percent of Total Malformations) in Antiseizure Medication-Unexposed and First Trimester Monotherapy-Exposed Pregnancies in Denmark (1997–2017), and Finland (1996–2016), Iceland (2003–2017), Norway (2004–2020), and Sweden (2006–2019)

Subtype	Unexposed	LTG	CBZ	VPA	OXC	LEV	TPM
Denmark	n = 35,242	n = 89	n = 21	n = 33	n = 11	n = 7	n = 8
Nervous system	1,814 (5)	<5	0	<5	0	0	0
Eye	1,340 (4)	<5	0	<5	0	0	0
Ear–face–neck	349 (1)	<5	0	0	0	0	0
Cardiac	11,118 (32)	34 (38)	6 (29)	15 (45)	<5	<5	<5
Respiratory	586 (2)	0	0	0	0	0	0
Orofacial clefts	2,045 (6)	<5	0	0	0	<5	<5
Digestive system	2,890 (8)	9 (10)	<5	<5	<5	<5	0
Abdominal wall	359 (1)	<5	0	0	0	0	0
Genital	3,672 (10)	<5	<5	8 (24)	0	<5	<5
Urinary	3,938 (11)	9 (10)	<5	<5	<5	<5	0
Limb	5,173 (15)	12 (13)	<5	8 (24)	<5	0	<5
Other	4,703 (13)	15 (17)	<5	<5	<5	0	0
Hypospadias	3,143 (9)	<5	<5	8 (24)	0	<5	<5
Clubfoot	1,978 (6)	6 (7)	<5	<5	0	0	<5
Multiple[a]	2,196 (6)	6 (7)	<5	5 (15)	<5	0	<5
Finland, Iceland, Norway, Sweden	n = 112,686	n = 225	n = 69	n = 126	n = 47	n = 23	n = 24
Nervous system	4,037 (4)	13 (6)	<5	11 (9)	<5	<5	<5
Eye	4,482 (4)	9 (4)	<5	9 (7)	<5	0 (0)	0 (0)
Ear–face–neck	1,210 (1)	2 (1)	0 (0)	<5	<5	0 (0)	0 (0)
Cardiac	49,717 (44)	99 (44)	25 (36)	61 (48)	25 (53)	12 (52)	13 (54)
Respiratory	1,139 (1)	<5	<5	0 (0)	<5	<5	0 (0)
Orofacial clefts	5,990 (5)	11 (5)	<5	10 (8)	<5	0 (0)	<5
Digestive system	6,538 (6)	12 (5)	<5	6 (5)	<5	<5	<5
Abdominal wall	1,249 (1)	<5	0 (0)	<5	<5	0 (0)	0 (0)
Genital	9,378 (8)	19 (8)	6 (9)	17 (13)	0 (0)	<5	<5
Urinary	13,128 (12)	20 (9)	16 (23)	14 (11)	6 (13)	3 (13)	<5
Limb	15,275 (14)	33 (15)	10 (14)	23 (18)	<5	<5	7 (29)
Other	10,285 (9)	25 (11)	<5	16 (13)	6 (13)	<5	<5
Hypospadias	8,056 (7)	17 (8)	6 (9)	15 (12)	0 (0)	<5	<5
Clubfoot	5,551 (5)	15 (7)	<5	7 (6)	<5	0 (0)	<5
Multiple[a]	6,962 (6)	17 (8)	<5	26 (21)	<5	<5	5 (21)

[a]Categories are not mutually exclusive and do not sum to the total, because those with multiple malformations are in at least two subgroups. Data are presented as n (%) where the percent is among all included major malformations. We did not present the 5 countries together because cell values < 5 could not be shared. Primary exposure definition was used.

Abbreviation: CBZ = carbamazepine; LEV = levetiracetam; LTG = lamotrigine; OXC = oxcarbazepine; TPM = topiramate; VPA = valproate.

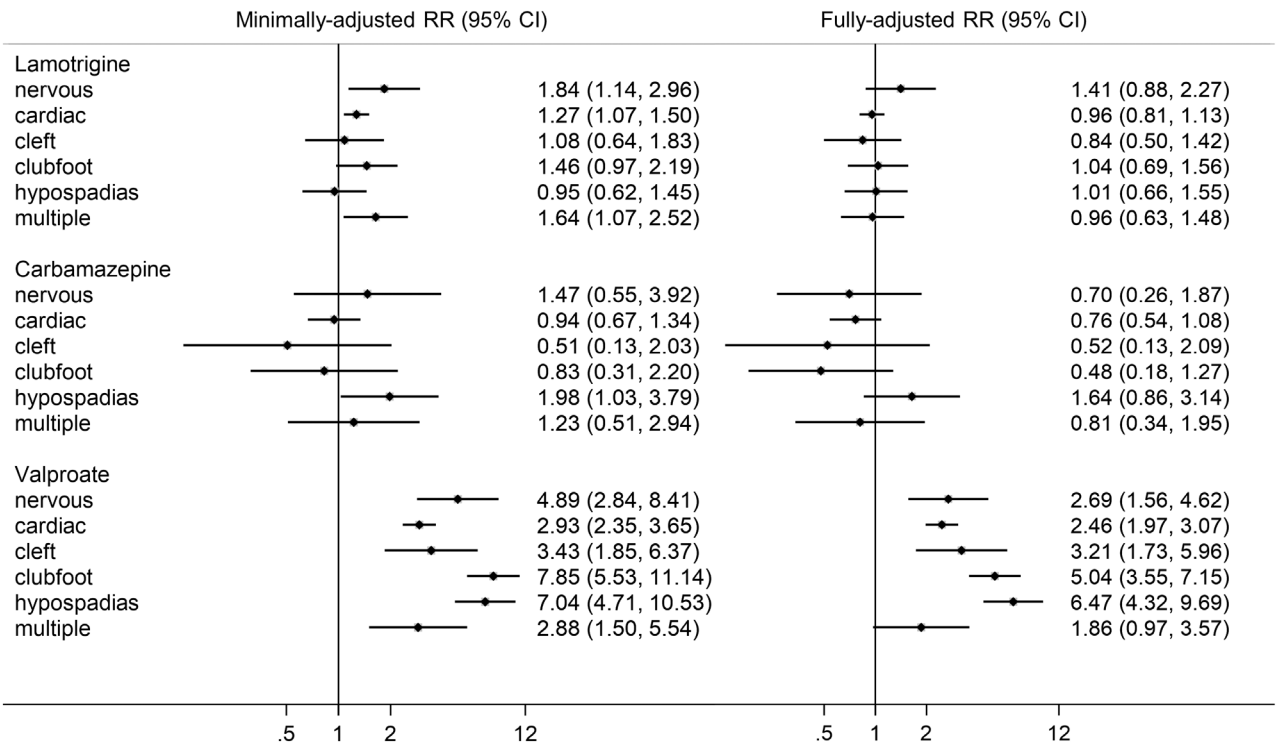

FIGURE 3: Association of first trimester use of lamotrigine, carbamazepine, or valproate monotherapy with subtypes of major congenital malformations. Adjusted risk ratios (RRs) are shown for selected subtypes of major congenital malformations (nervous system, cardiac system, orofacial clefts, clubfoot, hypospadias, multiple malformations affecting different organ systems) associated with first trimester use of lamotrigine, carbamazepine, or valproate monotherapy compared to antiseizure medication-unexposed pregnancies (n = 4,866,362). RRs presented in the figure are the overall pooled estimates combining Denmark, Finland, Iceland, Norway, and Sweden. Minimally adjusted RRs controlled for maternal age, delivery year, and country. Fully adjusted RRs additionally controlled for parity, multiple pregnancy, cohabitation, maternal country of birth, indications for antiseizure medication, diabetes, hypertension, psychiatric conditions, other medication used during first trimester, and indicators of health care utilization in the 90 days before pregnancy. The primary exposure definition (≥1 prescription filled during first trimester) was used. CI = confidence interval.

the North American AED Pregnancy Registry and UK and Ireland Epilepsy and Pregnancy Registers.[7,17]

We have studied the ASMs that are most commonly used among pregnant women. We decided a priori not to include drugs with <100 exposed pregnancies across the 5 countries. Therefore, we were not able to study the older ASMs phenytoin and phenobarbital, which are no longer frequently used in the Nordic countries, or some newer ASMs such as zonisamide and lacosamide. We chose not to include the more commonly used ASMs gabapentin and pregabalin, because our aim was to carry out a comparative safety study with lamotrigine monotherapy as the reference group. As these drugs are primarily used for neuropathic pain and rarely as monotherapy for epilepsy, comparison with lamotrigine monotherapy may have resulted in biased effect estimates due to the comparison of distinct patient populations.

In this large Nordic study of 4.9 million pregnancies, we found that valproate and topiramate were robustly associated with an increased risk of malformations. The risk estimates for valproate were even stronger for the specific malformations hypospadias and clubfoot. However, the other most commonly used ASMs did not seem to increase the risk compared with lamotrigine monotherapy. These results may provide reassurance for pregnant women who use ASMs other than valproate and topiramate. However, the risk of major congenital malformations is only one aspect of safety during pregnancy. Potential for adverse effects on neurodevelopment and effectiveness of the drug to prevent seizures or migraines, or to treat bipolar disorder, are important to weigh in treatment decisions.

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Author Contributions

All authors contributed to the conception and design of the study. J.M.C., C.E.C., M.K.L., M.N., Ø.K., R.M.S., S.P.U., H.Z., and K.F. contributed to the acquisition and analysis of data. J.M.C. contributed to drafting the text and preparing the figures.

Potential Conflicts of Interest

M.-H.B. reports grants to her institution from the European market authorization holders of valproate for a postauthorization safety study led by IQVIA, and consultancy fees from Novartis Norway, which owns patent rights to Tegretol (carbamazepine) and Trileptal (oxcarbazepine). T.T. reports the following relations to market authorization holders of different antiseizure medications: grants from Eisai, GSK, UCB, Bial, Sanofi, Angelini Pharma, GW Pharma, and Teva; advisory board honoraria from Angelini Pharma and GW Pharma; and speaker's honoraria from Eisai, Sanofi, Sun Pharma, and UCB, outside the submitted work.

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