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ORIGINAL REPORT

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Prevalence trends and individual patterns of antiepileptic drug use in pregnancy 2006-2016: A study in the five Nordic countries, United States, and Australia

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Abstract

Purpose: To describe recent international trends in antiepileptic drug (AED) use during pregnancy and individual patterns of use including discontinuation and switching.

Methods: We studied pregnancies from 2006 to 2016 within linked population-based registers for births and dispensed prescription drugs from Denmark, Finland, Iceland, Norway, Sweden, and New South Wales, Australia and claims data for public and private insurance enrollees in the United States. We examined the prevalence of AED use: the proportion of pregnancies with ≥1 prescription filled from 3 months before pregnancy until birth, and individual patterns of use by trimester.

Results: Prevalence of AED use in almost five million pregnancies was 15.3 per 1000 (n = 75 249) and varied from 6.4 in Sweden to 34.5 per 1000 in the publicly-insured US population. AED use increased in all countries in 2006-2012 ranging from an increase of 22% in Australia to 104% in Sweden, and continued to rise or stabilized in

the countries in which more recent data were available. Lamotrigine, clonazepam, and valproate were the most commonly used AEDs in the Nordic countries, United States, and Australia, respectively. Among AED users, 31% only filled a prescription in the 3 months before pregnancy. Most filled a prescription in the first trimester (59%) but few filled prescriptions in every trimester (22%).

Conclusions: Use of AEDs in pregnancy rose from 2006 to 2016. Trends and patterns of use of valproate and lamotrigine reflected the safety data available during this period. Many women discontinued AEDs during pregnancy while some switched to another AED.

KEYWORDS

antiepileptics, drug utilization, pharmacoepidemiology, population registers, pregnancy, valproate

1 | INTRODUCTION

Antiepileptic drugs (AEDs) are used for epilepsy, bipolar disorder, neuropathic pain, and migraine. Continuous treatment with AEDs, including throughout pregnancy, is often required to prevent seizures in women with epilepsy and relapse or recurrence in women with bipolar disorder.[1,2] However, some drugs including valproate, phenytoin, and topiramate have been found to be teratogenic.[3] Therefore, women may request or be advised by their healthcare providers to switch to another AED in preparation for a planned pregnancy or upon discovery of pregnancy. Some women may discontinue medication altogether, risking uncontrolled illness and associated risks.[1,2] To quantify the extent of fetal exposure and potential for uncontrolled maternal illness, it is important to understand if and how AED use in pregnant women has changed over time.

Several AED utilization studies among pregnant women have been published in recent years, with most including data up to 2007.[4-7] These studies showed that use of AEDs increased internationally in the preceding two decades, driven by the uptake of newer second-generation AEDs (eg, lamotrigine, topiramate, pregabalin) and expanding approved indications and off-label use for psychiatric and pain conditions for both first- and second-generation AEDs. One UK study found that prescribing of valproate and lamotrigine in the 6 months before pregnancy continued to increase from 2007 to 2012.[8] Another study that described the prevalence of AED use overall between 2004 and 2010 in seven European regions found a decline in AED prescribing within pregnancy.[9]

Reports based on more recent data are needed to understand changes in AED use with a focus on patterns of use in and around pregnancy for AEDs overall and specific drugs. In particular, attention should be paid to patterns of use of valproate in pregnancy, following the US Food and Drug Administration's 2011 and 2013 Safety Announcements[10,11] and the European Medicine Agency's (EMA) 2014 recommendation[12] for more restrictions on the use of valproate in women and girls. This is due to the now recognized neurodevelopmental impacts on offspring, in addition to the well-known risk of congenital malformations.[13]

KEY POINTS

- Some antiepileptic drugs (AEDs) including valproate are recognized teratogens but many women require treatment in pregnancy
- Among 4.9 million pregnancies from 2006-2016 in linked population-based registers (Nordic countries and Australia) and claims databases (United States), prevalence of any AED use and specific drugs varied widely
- Any AED use ranged from 6.4 (Sweden) to 12.6 (Australia), and up to 34.5/1000 pregnancies (United States), and increased in all countries during the study period, while few had continuous use in pregnancy
- Valproate use in pregnancy declined from 2006 to 2016 in the Nordic countries and United States, but not in Australia where it was the most commonly used AED
- This study provides important information about recent trends and treatment patterns of AEDs during pregnancy on three continents

The purpose of this study is to describe AED use during pregnancy in recent data from the five Nordic countries (Denmark, Finland, Iceland, Norway, and Sweden), New South Wales (NSW), the most populous state in Australia, and the United States. In addition, we sought to describe the individual patterns of use in pregnancy including the extent of discontinuation, AED polytherapy, and switching between AEDs.

2 | MATERIALS AND METHODS

This study is based on data from the nationwide prescription and medical birth registers in Denmark, Finland, Iceland, Norway, and

Sweden, and data from NSW, Australia and two US insurance claims databases (**Table S1**). The start of the study period was 2006 with the aim to present the use and patterns up to as recent as possible.

2.1 | Data sources

Personal identity numbers in the Nordic countries allowed for deterministic linkage of data from the medical birth registers to prescribed drug registers, which capture all prescribed drugs dispensed in pharmacies. These registers in the Nordic countries cover the entire population in each country (general population). The Australian data were probabilistically linked,[14] and the study population was restricted to pregnancies among concessional beneficiaries (eligible due to low income, chronic illness, or disability) who have complete pharmaceutical dispensing data (20.3% of births in NSW, 2006-2012). The US data were linked based on a unique enrollment identifier and cover a large population of privately- and publicly-insured individuals from all regions of the United States. The Truven Health MarketScan Commercial Claims and Encounters Database contains healthcare claims for privately-insured individuals enrolled in various employer-sponsored health plans.[15] The Medicaid Analytic eXtract Database (MAX) includes claims from publicly-insured individuals from 46 states and the District of Columbia (mandatory coverage for low income families and individuals with disability).[16]

2.2 | Study population

The study included all pregnancies with a gestational age of at least 22 weeks resulting in a live birth or stillbirth. Each pregnancy had a minimum coverage in the prescription data from 90 days before the first day of the last menstrual period (LMP) to birth. For the US MAX database and for secondary analyses for all countries regarding timing of use in the 6 months before and after pregnancy, we included pregnancies that had prescription data covering 180 days before LMP to 180 days after birth.

2.3 | AED use

We defined use of AEDs in pregnancy as individuals filling at least one prescription for a drug in the Anatomical Therapeutic Chemical (ATC) group N03A (antiepileptics) from 90 days before LMP until the end of pregnancy.[17] In the US databases, drugs were identified by the generic drug names. We classified use of any AED, lamotrigine, valproate, pregabalin, carbamazepine, levetiracetam, topiramate, oxcarbazepine, clonazepam, gabapentin, and the remaining AEDs grouped together as other AEDs, according to drugs dispensed in the following periods: 3 months before pregnancy (PRE, LMP-90 to LMP-1 day), first trimester (T1, LMP to LMP + 97 days), second trimester (T2, LMP + 98 to LMP + 202 days), and third trimester (T3, LMP + 203 days to birth). We chose lamotrigine, valproate, and carbamazepine for more in-depth analysis because they are used as both anticonvulsants and mood stabilizers. We defined selected patterns of use of interest based on prescription fills (yes/no) in the periods described above (PRE, T1, T2, T3) (Box 1).

Box 1 Exposure definitions of interest

- Any pregnancy use = 1 or more prescription fills from LMP-90 to birth (PRE, T1, T2, T3)
- Polytherapy = prescription fills for 2 or more distinct AEDs in a single pregnancy trimester
- Switching = discontinuation of one AED, initiation of another
- Discontinuation = prescription fill in PRE or T1, but not after
- Early discontinuation = prescription fill in PRE only; no refill within pregnancy
- First trimester exposure = prescription fill in T1, irrespective of other periods
- Initiation = prescription fill in T2 or T3, but not before
- Continuous use = prescription fill in each trimester, T1, T2, and T3

We defined polytherapy as prescription fills for two or more distinct AEDs in the same pregnancy trimester (T1, T2, or T3) and monotherapy as prescription fills for only a single AED in each exposed pregnancy trimester. We defined switching as discontinuation of one AED and initiation of another AED. This was operationalized as no prescription fills for the second AED before the last trimester in which the first AED was filled, and with fills for the second AED in at least one trimester after the last trimester of the first AED.

We conducted sub-analyses on reimbursement indications in the prescription data from Finland and Norway to characterize patterns of discontinuation for AED users with epilepsy, bipolar disorder, or other conditions.

2.4 | Maternal and pregnancy characteristics

We examined the following characteristics for all pregnancies where available: country and year of birth, maternal age at delivery, parity, smoking status; marital/cohabitation status, multiple pregnancy, pregnancy outcome (live birth, stillbirth; in the case of multiple pregnancies where one or more infants died, the pregnancy was grouped with stillbirths), and gestational age at birth in completed weeks. For women with AED use, we described co-medication with other psychotropic drugs (≥1 prescription fill from LMP-90 to birth; yes/no).

2.5 | Data analysis

We examined the proportion of users of any AED and specific AEDs anytime in pregnancy (prevalence per 1000 pregnancies) by year of birth, maternal age, and pregnancy outcome (preterm birth and stillbirth) for any AED. We tested for trends in the proportion of users

across years, maternal age categories, and pregnancy outcomes. Among women with any AED use in pregnancy, we calculated the proportion (%) with selected patterns of use: early discontinuation, first trimester use, initiation after first trimester, and continuous pregnancy use (Box 1). We calculated the absolute change in AED use per 1000 pregnancies from the first to last year of data available for each data source (and to 2012 for all countries), the relative change (%) in AED use, and annual increase (%). We described the most commonly used specific drugs in each country, the use of specific drugs in polytherapy regimens, proportion of users of specific drugs who discontinued use before the first and second trimesters, and the number of users switching AED treatment to/from specified drugs. Finally, we compared the prevalence of any AED use during an extended time window of 6 months before and after pregnancy. Analyses were performed separately and pooled across countries by summing counts from aggregated data.

3 | RESULTS

The pooled prevalence of any AED use in 4 924 536 pregnancies was 15.3 per 1000 (n = 75 249) and varied widely, ranging from 6.4 (Sweden) to 10.7 (Iceland) in the Nordic countries, to 12.6 in NSW, Australia, and up to 34.5/1000 in the US MAX database (Table 1). Among users, AED polytherapy in pregnancy was lowest in Iceland (9%) and highest in Australia (15%). AED use was higher in the youngest (≤24 years) and oldest women (≥40 years), with some variation by country (**Table S2**). Characteristics of the overall study population of pregnancies for all countries/databases are summarized in **Table S3.** Pregnant women in the US MAX database and NSW, Australia were more likely to be younger than in the Nordic countries and US MarketScan. Characteristics of AED users in each country or database are presented in **Tables S4-S11.** Women who used AEDs in pregnancy were more likely to be smokers, less likely to cohabitate with a partner, and there was a high prevalence of co-medication with other psychotropic drugs, in particular antidepressants.

AED use increased from 2006 to 2012 in all countries, and continued to rise or stabilized in countries with more recent data (Figure 1). This ultimately represented a relative increase in use of 22% (3.3% annually) in Australia to 104% (8.2% annually) in Sweden. Lamotrigine was consistently the most commonly used AED in the Nordic countries where use increased by 1.5/1000 pregnancies (relative increase 78%) from 2006 to 2012 and continued to increase thereafter. Use of lamotrigine also increased in NSW, Australia and US MAX, but not in US MarketScan (2012-2015). Clonazepam was the most commonly used AED in the United States, with higher use than in the Nordic countries or NSW, Australia. Its use increased in US MAX by 2.5/1000 (31%) by 2013 and was mostly stable around 7/1000 in US MarketScan. Valproate was the most commonly used AED in NSW, Australia, with higher use than in the Nordic countries and United States. Valproate use decreased by 0.2/1000 (−21%) in the Nordic countries by 2012, 0.9/1000 (−18%) in US MAX by 2013 and by 0.2/1000 (−26%) in US MarketScan but no decrease was observed in NSW, Australia, by 2012. Topiramate use increased by 0.1/1000 (19%) in the Nordic countries and more substantially in Australia (1.1/1000, 376%) by 2012. However, use was higher in the United States and increased by 3.3/1000 (76%) in US MAX by 2013 and by 0.9/1000 (20%) from 2012 to 2015 in US MarketScan. Pregabalin use increased by 1.2/1000 (474%) in the Nordic countries by 2012 and in US MAX (1.7/1000), whereas use decreased by 0.2/1000 (−21%) in US MarketScan.

Among women with AED use, 31% had early discontinuation (Figure 2). This varied somewhat by country (19%-38% for any AED) (Figure S1). Most of the AED users filled a prescription in the first trimester and few initiated after the first trimester. A minority of the AED users had prescription fills in every trimester; continuous use through pregnancy was highest for lamotrigine and lowest for

TABLE 1 Composition of the overall study population and prevalence of use of antiepileptic drugs in pregnancy

	Overall Study Population		Any AED Use in Pregnancy		AED Monotherapy			AED Polytherapy		
	N	%	N[a]	per 1000	N[b]	per 1000	%	N[b]	per 1000	%
Total	4 924 536	100	75 249	15.3	45 565	9.3	88	6265	1.3	12
Denmark	660 560	13.4	4547	6.9	3335	5.0	90	358	0.5	10
Finland	634 528	12.9	6022	9.5	4116	6.5	87	601	0.9	13
Iceland	32 267	0.7	346	10.7	197	6.1	91	19	0.6	9
Norway	590 168	12.0	4141	7.0	2830	4.8	89	361	0.6	11
Sweden	1 028 732	20.9	6630	6.4	4580	4.5	89	580	0.6	11
NSW Australia	114 360	2.3	1442	12.6	914	8.0	85	157	1.4	15
US MarketScan	855 763	17.4	17 388	20.3	9614	11.2	90	1086	1.3	10
US MAX	1 008 158	20.5	34 733	34.5	19 979	19.8	87	3103	3.1	13

Abbreviations: AED, antiepileptic drug; MAX, Medicaid Analytic Extract database; NSW, New South Wales; US, United States.

[a]At least one prescription filled from 3 months before pregnancy to birth.

[b]Monotherapy and polytherapy do not sum to any AED use because they exclude pregnancies with prescription fills only in the 3 months before pregnancy.

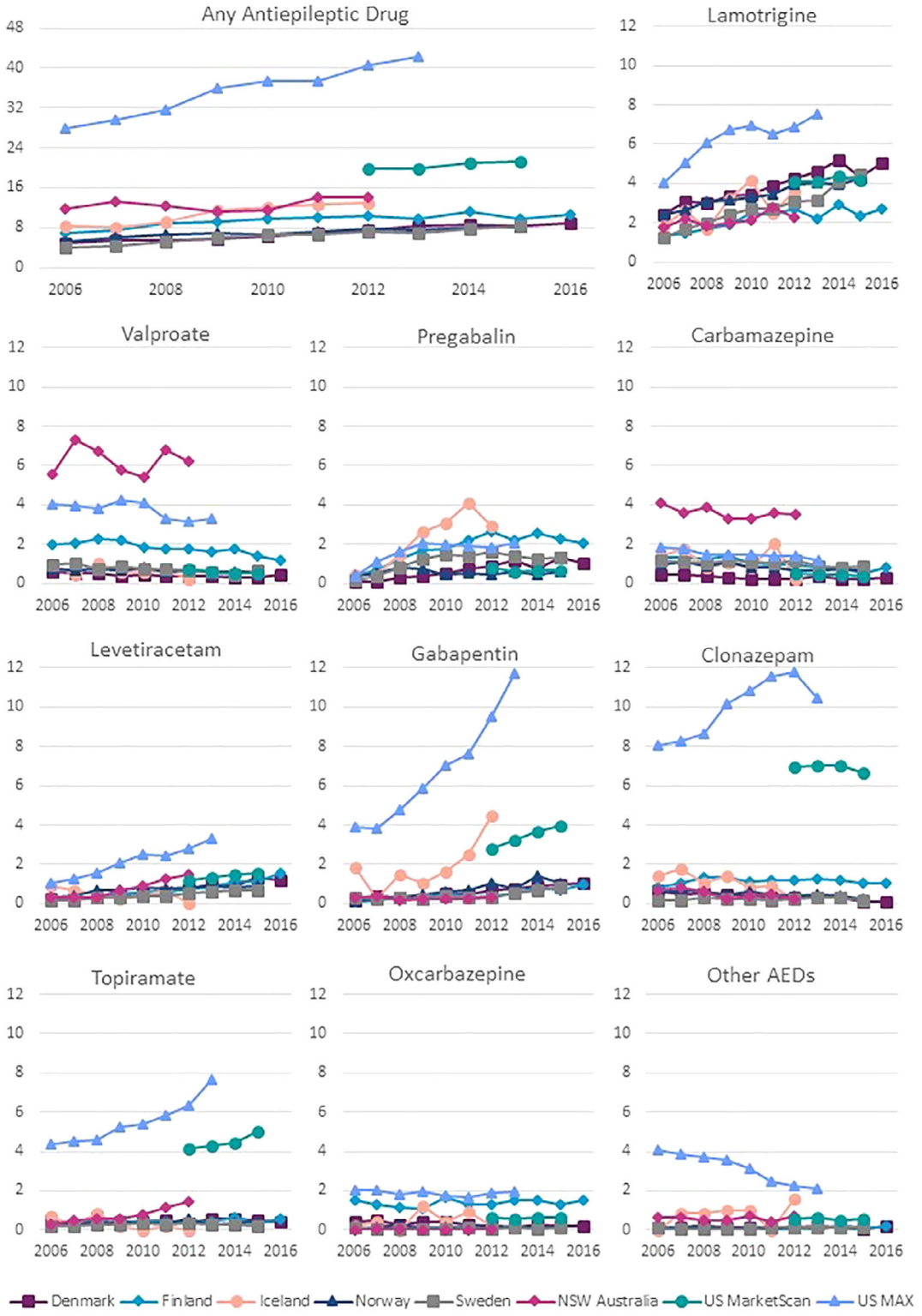

FIGURE 1 Prevalence of antiepileptic drug use per 1000 pregnancies, by year of birth. Pregnancy exposure defined as ≥1 prescription filled from 3 months before pregnancy to birth. One or more years had <5 exposed pregnancies for valproate (Iceland), carbamazepine (Iceland), levetiracetam (Iceland), pregabalin (Denmark, Iceland), gabapentin (NSW Australia, Iceland), clonazepam (NSW Australia, Iceland), topiramate (Iceland), oxcarbazepine (NSW Australia, Iceland, Sweden), and other AEDs (Finland, Iceland, Norway). Pregabalin was not reimbursed during the period of 2006–2012 in Australia and is therefore not included for NSW Australia. AED, antiepileptic drug

valproate, most common in Denmark (49%), least common in Iceland (13%) followed by the United States. In United States, only 5%-8% of valproate users filled prescriptions in every trimester, while it was 11% in Australia and 14%-39% in the Nordic countries.

Prevalence of AED use was highest before pregnancy, declined throughout pregnancy reaching 27%-70% of pre-pregnancy use in the third trimester, then rebounded after pregnancy to levels between first and second trimester use by 3 months, and not yet reaching pre-pregnancy levels by 6 months (Figure 3). Among the Nordic countries, the use of AEDs decreased during pregnancy most substantially in Iceland, becoming more in line with use in the other Nordic countries, with a similar trend observed for the US

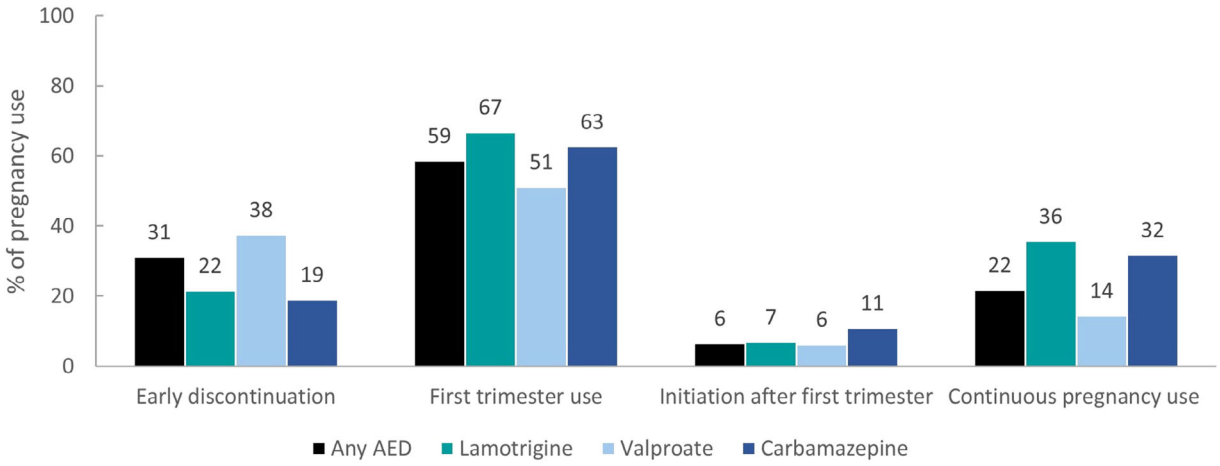

FIGURE 2 Selected patterns of antiepileptic drug use in pregnancy. These selected patterns are not mutually exclusive (continuous pregnancy use is a subset of the first trimester exposed) and they do not cover all 15 mutually exclusive categories of AED use by period (yes/no in PRE, T1, T2, T3). 4% of AED exposed (PRE + T2, PRE + T2 + T3, PRE + T3) did not fit any of the selected patterns

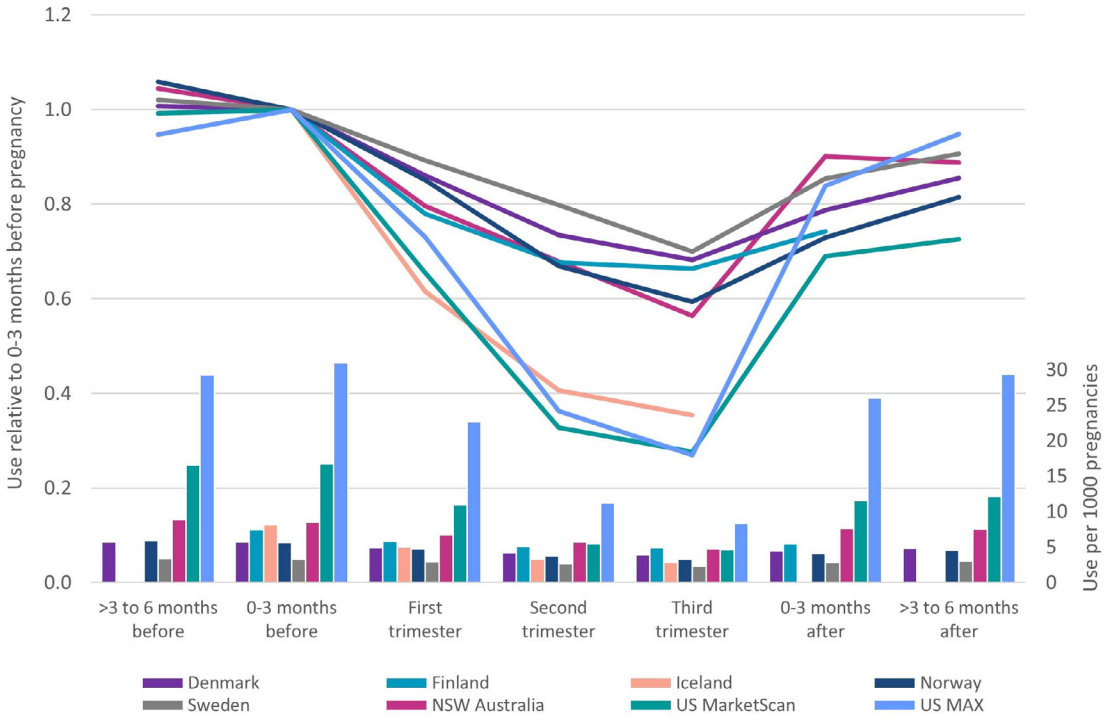

FIGURE 3 Timing of antiepileptic drug use surrounding pregnancy. The bars show the prevalence of use in each period and the lines show the number of users in each period, relative to the number of users in 0-3 months before pregnancy in a subset of the study population with prescription data covering 6 months before pregnancy to 6 months after birth, where available (Ns: Denmark 629 986, Finland 634 528, Iceland 32 267 [same as primary study population], Norway 561 014, Sweden 983 176, NSW Australia 111 488, US MarketScan 851 077, US MAX 1008158 [same as primary study population])

databases, which had the highest absolute prevalence of AED use in every time period.

Use of lamotrigine and carbamazepine showed less variation during pregnancy than valproate for which the number of users declined substantially during pregnancy, but there was an increase in T3 for some countries (**Figure S2**). There was also a more consistent decrease in use before pregnancy for valproate than lamotrigine or carbamazepine. Valproate and carbamazepine use after pregnancy reached levels closer to pre-pregnancy than lamotrigine.

In the Nordic countries, lamotrigine was used in 3/1000 pregnancies, followed by pregabalin, valproate, and carbamazepine, each with around 1 exposed per 1000 pregnancies and the group of other AEDs was infrequently used, mostly as part of AED polytherapy regimens (Table 2). In NSW, Australia and the United States, there was higher use of other AEDs. In NSW, Australia, valproate was used in more than 6/1000 pregnancies and was higher than carbamazepine (3.6/1000) and lamotrigine (2.1/1000), but was the most commonly discontinued AED. In the United States, clonazepam and topiramate use was much higher than in the Nordic countries and Australia and less commonly part of polytherapy. Pregabalin and gabapentin were infrequently used in polytherapy and commonly discontinued. More details on country-specific use of individual AEDs is presented in **Tables S12-S19**. Finland had high levels of switching, whereas switching was infrequent in Iceland and NSW, Australia. In general, more than twice as many switched from valproate or topiramate to another drug than to these drugs. The only drugs more commonly switched to, than switched from, were levetiracetam and lamotrigine. As a proportion of its overall pregnancy use, levetiracetam was the most commonly initiated or switched to AED in pregnancy. Overall, 46% of pregnancies with AED polytherapy included lamotrigine, 29% included levetiracetam, and 19% included valproate (**Table S20**).

Based on indications for reimbursement in Norway and Finland, 48% of women with any AED use had epilepsy and of those, 16% (Norway) and 4% (Finland) discontinued use. In contrast, 63% of women with bipolar disorder and 70% with other conditions discontinued AEDs (data not shown). In both Norway and Finland, women with epilepsy were least likely to discontinue oxcarbazepine, levetiracetam, and lamotrigine and most likely to discontinue topiramate, pregabalin, and gabapentin. The proportion using AEDs for other indications increased over the study period.

4 | DISCUSSION

Using high-quality data from seven countries and including almost five million pregnancies, we described prevalence trends and individual patterns of use in over 75 000 AED users in recent years. We observed that in each country, AED use in pregnancy has increased since 2006. Lamotrigine was the most commonly used AED in the Nordic countries and its use increased in all countries. Pregabalin use increased dramatically during this time to become the second most

TABLE 2 Description of use of individual antiepileptic drugs in each population

	Pooled Nordic (2006–2016) N = 2 946 255			NSW Australia (2006-2012) N = 114 360			US MarketScan (2012-2015) N = 855 763			US MAX (2006-2013) N = 1 008 158		
Drug or group	Use per 1000	% Dis-continue	% Poly-therapy	Use per 1000	% Dis-continue	% Poly-therapy	Use per 1000	% Dis-continue	% Poly-therapy	Use per 1000	% Dis-continue	% Poly-therapy
Lamotrigine	3.0	31.2	14.7	2.1	17.7	36.4	4.2	47.9	19.3	6.0	60.5	26.2
Pregabalin[a]	1.1	80.3	12.7	-	-	-	0.7	82.9	22.3	1.5	78.9	24.0
Valproate	0.9	38.3	24.6	6.3	61.1	17.7	0.6	79.7	30.8	3.8	84.1	25.5
Carbamazepine	0.8	21.4	16.7	3.6	30.8	19.6	0.5	47.0	26.5	1.5	55.0	33.3
Levetiracetam	0.6	9.9	45.3	0.7	12.0	59.7	1.4	17.3	30.0	2.0	26.0	39.6
Gabapentin	0.5	81.5	11.0	0.3	31	44.0	3.3	77.6	15.3	6.1	74.2	19.4
Clonazepam	0.5	49.2	29.2	0.5	39.3	39.1	6.9	80.1	13.0	9.9	69.4	18.8
Oxcarbazepine	0.4	9.6	23.0	<5	<5	<5	0.6	60.5	31.5	1.9	73.6	27.0
Topiramate	0.4	59.9	37.8	0.8	48.3	50.9	4.4	88.3	14.9	5.2	81.1	25.8
Other AEDs	0.1	18.9	52.4	0.6	44.8	38.5	0.6	45.8	41.1	3.3	61.9	31.5

[a]Pregabalin was not reimbursed in Australia during this time.

commonly used AED in pregnancy in the Nordic countries and use may have peaked during the study period. Topiramate use also increased in all countries and was substantially higher in the United States than in the Nordic countries or Australia. Clonazepam was the most commonly used drug in the United States, far exceeding use in the Nordic countries or Australia and partially accounts for the higher overall AED use in the United States. Clonazepam is a benzodiazepine and its use mirrors the wider trend of high and increasing use of benzodiazepines in the United States.[18] Valproate use decreased in most countries since 2006 but remained steady in Australia as the most commonly used AED in pregnant women. Valproate use in Finland was about twice as high as in the other Nordic countries, but use has fallen sharply in the most recent years. The trends for 2006-2016 suggest there may be ongoing declines in use of valproate, carbamazepine, and other AEDs and ongoing increases in use of gabapentin and levetiracetam in pregnancy.

We observed that around one-third of women with AED use only filled a prescription before but not during pregnancy. While the majority of the AED users filled a prescription in the first trimester, a minority continued to use AEDs in each pregnancy trimester. This picture has been described for other psychotropic drugs used for chronic conditions.[19,20] Discontinuation of AEDs was common, in particular for the drugs pregabalin and gabapentin, which are more frequently used to treat pain.[21] Initiation of use during pregnancy was more common for valproate than lamotrigine or carbamazepine. This may suggest that valproate use was avoided in the first trimester, but not necessarily later in pregnancy, when it could still exert negative effects on fetal brain development.[22,23] Valproate is among the most effective drugs for seizure control[24] and the only effective medication for certain patients with epilepsy or bipolar disorder. Untreated epilepsy and bipolar disorder are associated with perinatal risks, so AED discontinuation may not be the safest option for many patients.[1,25] Switching and discontinuation patterns suggested an effort to decrease the number of drugs being used in pregnancy and switch to safer alternatives when possible (namely, from valproate and topiramate, and to lamotrigine and levetiracetam).[3,24] Observed patterns of use suggest the need for more pre-pregnancy counseling to encourage adjustments to treatment before pregnancy.

4.1 | Strengths and limitations

A strength of this study is that it covered the entire population in the Nordic countries. Unlike the Nordic data, it is not clear if AED use in Australia is higher than in the Nordic countries in general, or only in this population, restricted to concessional beneficiaries who may qualify due to disability. However, a publication from Australia reporting data from 2000 to 2011 showed that valproate use in the general population was higher than carbamazepine or lamotrigine.[26] Similarly, for the United States, MAX includes all women on Medicaid, the public insurance that covers almost 50% of the deliveries, and the data from private insurance in MarketScan represents the other half of the population. AED use is likely to be higher among women enrolled in MAX than in the general population because disability is one of the reasons for eligibility, but we can reasonably infer US national trends and patterns of AED use from these data. The inclusion of recent data for a privately-insured US population shows that AED use is higher in the United States in general and that trends of increasing use may have slowed in the most recent years. Our study was restricted to live births and stillbirths (US MAX database only live births), and if AED use is associated with miscarriage or abortion, actual use in pregnancy could be higher than what we observed in the included study population.

The use of AEDs in pregnancy is inferred based on prescriptions filled at the pharmacy, and we do not know if the medication was consumed or precisely when, though, records of filled prescriptions are one step closer to actual use than prescribing records.[27] Additionally, filled prescriptions are not subject to recall bias. However, our definitions of polytherapy and switching could be sensitive to the assumption that prescription filling patterns represent use of the medication at that time.

We did not have information on the exact indication for AED use. A US study of pregnancy use of AEDs in 2001 to 2007 reported that 21% had epilepsy, 48% psychiatric disorder, 22% pain disorder, and 20% had no diagnosis suggesting indication during or in the 6 months prior to pregnancy.[6] When we explored indication for reimbursement in Norway and Finland, about half used AEDs for indications other than epilepsy, with the proportion increasing over the study period. Overall, we observed similar individual patterns of use as reported in a recent Danish study, which focused on AEDs defined as mood stabilizers with exclusion of women with epilepsy.[28] In a study that evaluated use of AEDs in pregnant women with epilepsy in 38 countries, there was more AED polytherapy (up to 30%)[4]; roughly double what we observed in the general population. Our findings suggest that AED use for non-epilepsy indications further expanded from 2006 to 2016 and predominated the observed patterns of use.

4.2 | Conclusions and implications

Reasons for the most striking differences in AED use between countries may include differences in reimbursement policies, prevalence of use for indications other than epilepsy and off-label use, guideline recommendations, contraindications, and local factors including medical culture. Higher use of gabapentin in the United States may reflect an effort to use alternative pain medications in the context of the recent opioid use epidemic and more off-label use.

The persistent use of valproate in pregnancy during this period and the relatively high use in Finland and Australia are noteworthy. International health authorities (eg, Health Canada, FDA, EMA) have issued safety warnings regarding neurodevelopmental problems associated with valproate in pregnancy since at least 2011. In Australia, lamotrigine and clonazepam are subsidized for epilepsy only; in contrast, carbamazepine and valproate have no restrictions on their use. Therefore, reimbursement policies may incentivize treatment with valproate or carbamazepine, rather than lamotrigine, which is only reimbursed for epilepsy but may be a safer alternative for use in pregnant

women with bipolar disorder.[29] Furthermore, it appears that international safety alerts may contribute to decreasing valproate use in pregnancy; we observed a sharper decrease in Finland since the EMA published an assessment in October 2014, sent out leaflets to prescribing physicians, issued product warnings, and introduced risk minimization measures.[12] New regulations may contribute to future declines in use. In March 2018, EMA banned the use of valproate for migraine in girls or women of reproductive age, and strongly discouraged use in this population for bipolar disorder or epilepsy unless there is no other effective treatment.[30] These policy changes both strengthen restrictions and increase requirements to inform women and girls of the risks. However, it is unlikely that all exposure in pregnancy can be completely avoided.

The increased use of AEDs in pregnancy in recent years suggests the need for further comparative safety studies to inform the balance of risks and benefits for use of different AEDs as well as those of modification, or discontinuation of treatment in pregnancy. Future studies could explore whether women who discontinue AEDs switch to alternative treatments. While there is convincing evidence that valproate is associated with harm, it is important to continue to study the long-term neurodevelopmental outcomes in children exposed to AEDs in pregnancy to guide clinical and policy decision-making in the future.

ETHICS STATEMENT

Ethical approval was not required for studies based on registry data only in Denmark. This study was approved by the National Institute for Health and Welfare and Social Insurance Institution of Finland (Kela); the National Bioethics Committee and the Data Protection Authority in Iceland; the Norwegian Data Inspectorate and the Regional Ethics Committee for Medical Research of South/East Norway; the New South Wales Population and Health Services Research Ethics Committee and the Australian Institute of Health and Welfare Ethics Committee; the regional ethical review board at Karolinska Institutet in Sweden; the institutional review boards of Harvard T.H. Chan School of Public Health (for use of MarketScan) and Brigham and Women's Hospital (for use of MAX).

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CONFLICT OF INTEREST

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AUTHOR CONTRIBUTIONS

All authors contributed to the planning, conduct, and reporting of the work described in the article. Jacqueline M. Cohen, Kari Furu, and Øystein Karlstad drafted the initial protocol which was reviewed, critically revised, and approved by all co-authors. Jacqueline M. Cohen, Carolyn E. Cesta, Maarit K. Leinonen, Andrea Schaffer, and Yongfu Yu did the statistical analysis. Jacqueline M. Cohen, Carolyn E. Cesta, Kari Furu, Helga Zoega, and Øystein Karlstad wrote the first draft of the manuscript. All authors contributed to critical revision of the manuscript and approved the final version for submission.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.

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