

ORIGINAL REPORT

Prescription of antiepileptic medicines including valproate in pregnant women: A study in three European countries

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Abstract

Purpose: To study patterns of antiepileptic drugs (AED) prescribing, particularly valproate, during pregnancy over a 10-year period in the UK, Italy, and France.

Methods: Data on pregnancies conceived after 1 January 2007 with outcomes before 31 December 2016 were extracted from four European electronic health care databases (380 499 in the United Kingdom (UK), 66 681 in France, and 649 918 in Italy [355 767 in Emilia Romagna and 294 151 in Tuscany]). Prevalence of AEDs with an ATC code starting N03A and clobazam (N05BA09) were stratified by country and calendar year.

Results: AED prescribing during pregnancy varied from 3.0 (2.8–3.1) per 1000 pregnancies in Emilia Romagna to 7.8 (7.5–8.0) in the UK, 5.9 (5.6–6.1) in Tuscany, and 6.3 (5.7–6.9) in France. Lamotrigine was commonly prescribed in all regions with a third of women exposed to an AED during pregnancy taking lamotrigine in the UK and France. Valproate was prescribed to 28.6% of AED exposed pregnant women in Tuscany, 21.6% in France, 16.7% in Emilia Romagna, and 11.9% in the UK. Over the study period, the prevalence of AED prescribing increased in the UK mainly due to increases in pregabalin and gabapentin, declined in France mainly related to decreases in clonazepam, and remained constant in Italy. Valproate prescriptions declined to a prevalence <1 per 1000 pregnancies in 2015 to 2016 in the UK, France, and Emilia Romagna.

Conclusions: Variations in AED prescribing during pregnancy indicate the potential for further reductions, particularly of valproate. Increases in pregabalin/gabapentin prescribing, for which risks are not well known, are a cause for concern.

KEYWORDS

antiepileptic drugs, Europe, linkage, pregnancy, valproate

1 | INTRODUCTION

Drugs classified as “Antiepileptics” in the Anatomical Therapeutic Chemical (ATC) classification may be indicated in several disorders depending on the country: epilepsy, bipolar disorder, anxiety, neuropathic pain, and migraine prophylaxis. A recent European study, involving the United Kingdom (UK), France, and Italy, showed that 1.2% to 2.9% of women of childbearing age received a prescription for a drug from the antiepileptic drugs (AED) ATC class in 2016.¹

It is now well demonstrated that exposure to some AEDs during pregnancy increases the risk of major congenital malformations in the offspring, such as neural tube defects and cleft palate, from two-fold to three-fold.²⁻⁵ The risk varies by AED⁶: valproate is known to have the highest risk² whereas lamotrigine may represent the safest AED during pregnancy.⁵ Furthermore, since the early 2000s, several studies have suggested a risk of neurodevelopmental problems in children exposed in utero to valproate⁷ including delayed walking and talking or difficulty with language.^{3,8,9} In-utero valproate exposure can also affect intelligence quotient (IQ)¹⁰ and can increase the risk of autistic spectrum disorder^{11,12} and possibly the risk of attention deficit hyperactivity disorder (ADHD),¹³ although these data are more limited.

In October 2014, following the warnings from the European Medicines and Healthcare products Regulatory Agency (MHRA) about the risks associated with the use of valproate in girls capable of becoming pregnant and women of childbearing potential, the European Medicines Agency (EMA) Pharmacovigilance Risk Assessment Committee (PRAC) issued recommendations for valproate prescribing.¹⁴ The recommendations included that valproate and related substances (valproic acid, valproate, and valpromide) should not be used in girls, women of childbearing potential, and pregnant women unless alternative treatments are ineffective or not tolerated; valproate and related substances should be contraindicated in prophylaxis of migraine attacks in pregnancy and women of childbearing potential who are not using effective methods of contraception.

These guidelines were relayed by the EMA and by Health Authorities in European countries such as in the UK where a guide was published for health care professionals in January 2015¹⁵ and in France where several letters have been sent to health care professionals since December 2014,^{16,17} and in Italy by the Italian National Medicines Agency (AIFA). Simultaneously, recommendations and blackbox warnings for valproate prescribing during pregnancy were disseminated by the Food and Drug Administration (FDA) in the United States.¹⁸⁻²⁰

The present descriptive drug utilisation study, capturing data from three European countries (UK, Italy, and France) aims to study patterns of AED prescribing, particularly valproate, during pregnancy over a 10-year period. The objective consisted in providing prevalence of AED prescribing during pregnancy by country, by specific AEDs and by indications and also to describe evolution over time.

Key points

- Exposure to some AEDs during pregnancy increases the risk of major congenital malformations in the offspring, such as neural tube defects and cleft palate. The risk varies by AED with valproate having the highest risk.
- Antiepileptic drugs (AED) should be prescribed with caution during pregnancy.
- The study using electronic health care database analyses AEDs prescribed to over 1 million pregnant women from the UK, France, and Italy; 2007 to 2016.
- AED prescribing during pregnancy was 3.0(2.8-3.1) per 1000 in Emilia Romagna, 5.9(5.6-6.1) in Tuscany, 6.3(5.7-6.9) in France, and 7.8(7.5-8.0) in the UK.
- Valproate was prescribed to 28.6% of AED exposed pregnant women in Tuscany, 21.6% in France, 16.7% in Emilia Romagna, and 11.9% in the UK.
- Variations in AED prescribing including that of valproate during pregnancy indicate the potential for reductions in some regions.

2 | METHODS

2.1 | Study design

The study is a descriptive drug utilisation study, from 1 January, 2007 to 31 December, 2016.

2.2 | Data source

Anonymous data from linked electronic health care databases from four regions/countries contributed to the study: the UK (Clinical Practice Research Datalink (CPRD), capturing a sample of approximately 8% of the UK population), France (Echantillon Generaliste des Beneficiaires [EGB]: French Health Insurance System and Hospital Medical Information Systems [PMSI], concerning a representative 1/97 sample of the French Population), Emilia Romagna in Italy (Certificate of Delivery Assistance [CeDAP] and Emilia-Romagna Prescription Database [ERPD]) and Tuscany in Italy (CeDAP, Hospital Discharges Registry and Tuscany Prescription Database [TPD]). An overview of the databases has been reported in previous articles.^{1,21} Ethical and data access approvals were obtained for each database from the relevant governance infrastructures.

2.3 | Pregnancy

All pregnancies with a known pregnancy outcome were included. The start and end dates of each pregnancy in women aged between

10 and 50 years were identified within each of the databases during the study period using database specific algorithms. In the UK CPRD, the algorithm incorporated all pregnancy-related codes in the mother's electronic medical record. In the Italian databases, the start of pregnancy was determined based on gestational age data, and in the French database, the start of pregnancy was determined from information on gestational age or an algorithm incorporating other available pregnancy related data. In the UK, French, and Tuscany databases, pregnancies that ended in a live birth, stillbirth, spontaneous abortion, and induced termination (including those induced for nonmedical reasons) were identifiable. In Emilia Romagna, pregnancy data were limited to those pregnancies ending in a live or stillbirth.

Multiple pregnancies were also included. Pregnancies were eligible for inclusion if the woman had been present in the study cohort for the 6 months before pregnancy and throughout the pregnancy.

2.4 | Exposure to antiepileptic drugs (AEDs)

AEDs with an ATC classification code starting with N03A and also clobazam (N05BA09) were used. These drugs can be licenced, depending on the countries, for epilepsy but also for bipolar disorder, anxiety, migraine prophylaxis, and neuropathic pain.

AED exposure was based on the issue (UK) or the dispensing (France and Italy) of a prescription. Prescription duration and dose were not taken into account. Women were considered to be exposed to AEDs if they had received at least one prescription during the pregnancy. Considering the period of exposure during pregnancy, women were considered to be exposed during trimester 1 if they had received at least one prescription during the first 3 months of pregnancy, in trimester 2 if they had received a prescription during months 4 to 6, and in trimester 3 if they had received a prescription from month 6 to the end of pregnancy.

Valproate, including prescriptions for valproic acid and valpromide, was of particular interest.

2.5 | Indications of AED prescriptions

Indications for prescriptions were not available, or only partially available, in the four databases used for this study. Consequently, each country/region developed a specific algorithm to determine indications for AED prescriptions, using medical information available such as medical diagnoses, hospital discharge data, special reimbursement status or exemption codes, information on the type of prescriber, the specific name of the medicine, and coprescribing of other medicines. However, in Emilia Romagna and in Tuscany, 31% and 49% of the indications could not be identified; consequently, only French and UK indication data were analysed.

3 | STATISTICAL METHODS

Prevalence of AED prescribing was computed overall and, for specific AEDs, stratified by country/region and calendar year at pregnancy start. The number of pregnancies in 2016 was low as generally only pregnancies conceived before April had outcomes before the end of the year. Prevalence were calculated per 1000 pregnancies (expressed with the symbol ‰), with 95% confidence intervals (CI95) calculated using the binomial distribution.

Data were analysed using STATA 15 in the UK and SAS (SAS Institute, North Carolina, USA) in France and Italy.

4 | RESULTS

During the study period, more than one million pregnancies were captured in the databases: 66 681 pregnancies in France, 294 151 in Tuscany (Italy), 355 767 in Emilia Romagna (Italy), and 380 499 in the UK.

4.1 | Prevalence of AED prescribing during pregnancy

The prevalence of AED prescribing during pregnancy varied between countries/regions from 3.0 (2.8-3.1) per 1000 pregnancies in Emilia Romagna to 7.8 (7.5-8.0) in the UK, with 5.9 (5.6-6.1) in Tuscany, and 6.3 (5.7-6.9) in France.

As presented in Table 1, lamotrigine was one of the four most commonly prescribed AEDs in all regions and the highest-prescribed AED in France and the UK. In France, 29.1% of women exposed to an AED during pregnancy and 33.2% in the UK were exposed to lamotrigine.

In Tuscany, valproate was the most frequently prescribed AED during pregnancy with 28.6% of pregnant women exposed to an AED being prescribed it, compared with 11.9% in the UK, 16.7% of women in Emilia Romagna, and 21.6% in France.

Clonazepam, carbamazepine, and levetiracetam were also commonly prescribed in Italy, France, and the UK during pregnancy. For more than 10% of pregnant women exposed to an AED, clonazepam was prescribed in Italy (14.9% in Emilia Romagna and 13.7 in Tuscany) and France (18.2%). The same applied to levetiracetam in France (10.7%), Emilia Romagna (10.6%), and the UK (12.9). Carbamazepine was prescribed for more than 15% of pregnant women exposed to an AED in Emilia Romagna (22.2%), UK (16.4%), and Tuscany (15.1%).

In France and the UK, pregabalin prescribing concerned, respectively, 12.6% and 13.4% of pregnant women exposed to an AED.

The prevalence of AED prescribing during pregnancy increased with age in all countries, particularly in women over 40 years of age in France and the UK. For example, in the UK, 15.2 per 1000 pregnant women aged 45 years and older received an AED during their pregnancy. Gabapentin and pregabalin were largely responsible for this increase.

TABLE 1 Proportion of each specific AED prescription per 100 AED exposed women during pregnancy in each region

		Emilia Romagna		Tuscany		France		United Kingdom	
		N	%	N	%	N	%	N	%
	Any AED	1057 ^a	100.0%	1722 ^b	100.0%	422 ^c	100.0%	2956 ^d	100.0%
Lamotrigine	N03AX09	197	18.6%	221	12.8%	123	29.1%	980	33.2%
Any valproate		177	16.7%	492	28.6%	91	21.6%	353	11.9%
Valproic acid	N03AG01	172	16.3%	490	28.5%	74	17.5%	353	11.9%
Valpromide	N03AG02	5	0.5%	2	0.1%	18	4.3%	0	--
Carbamazepine	N03AF01	235	22.2%	260	15.1%	31	7.3%	485	16.4%
Pregabalin	N03AX16	61	5.8%	149	8.7%	53	12.6%	395	13.4%
Levetiracetam	N03AX14	112	10.6%	115	6.7%	45	10.7%	382	12.9%
Gabapentin	N03AX12	36	3.4%	102	5.9%	16	3.8%	429	14.5%
Clonazepam	N03AE01	158	14.9%	236	13.7%	77	18.2%	72	2.4%
Topiramate	N03AX11	72	6.8%	113	6.6%	20	4.7%	183	6.2%
Phenobarbital	N03AA02	80	7.6%	174	10.1%	6	1.4%	6	0.2%
Oxcarbazepine	N03AF02	44	4.2%	82	4.8%	10	2.4%	15	0.5%
Clobazam	N05BA09	5	0.5%	0	--	44	10.4%	91	3.1%

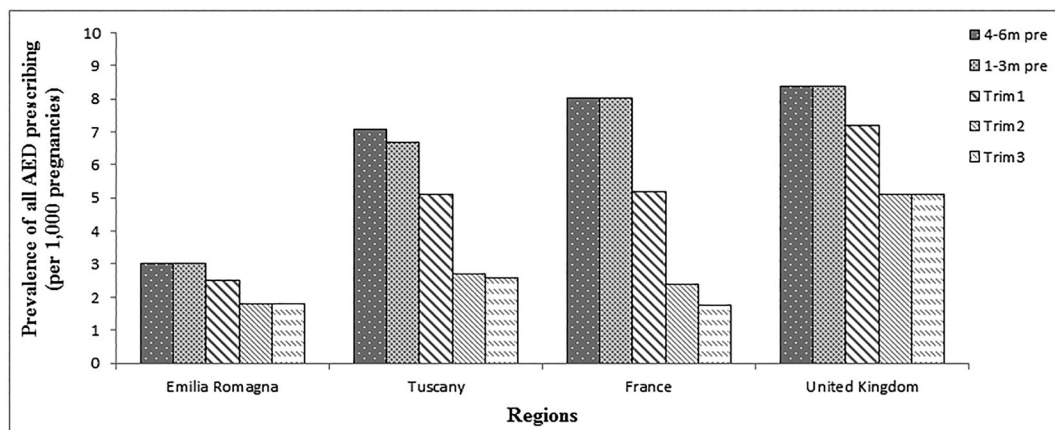
On a total of

^a355 767 pregnancies (3.0%).

^b294 151 pregnancies (5.9%).

^c66 681 pregnancies (6.3%).

^d380 499 pregnancies (7.8%).

**FIGURE 1** Prevalence of AED prescribing during each of the pregnancy trimesters and the 6 months before the start of pregnancy by region

4.2 | Prevalence of AED prescribing by trimesters of pregnancy (expressed per 1000 pregnancies as ‰)

In all regions, there was evidence of a decline in the prevalence of women exposed to an AED during pregnancy when compared with the 6-month period before the start of pregnancy and also a decline during early pregnancy (trimester 1 and trimester 2) (Figure 1). The prevalence of prescribing before pregnancy was highest in the UK (8.4‰) and France (8.0‰) and lowest in Emilia Romagna (3.0‰). The prevalence of prescribing in Tuscany was close to France during pregnancy, but higher than that observed in Emilia Romagna. The UK had the highest prevalence of AED prescribing in all three trimesters.

4.3 | Prevalence of AED prescribing in relation to pregnancy by calendar year (expressed per 1000 pregnancies as ‰)

In the UK, the prevalence of AED prescribing increased more than two-fold over the study period, with a greater increase occurring from 2012 mainly due to increases in pregabalin and gabapentin prescribing (Figures 2 and 3). After exclusion of pregabalin/gabapentin, the prevalence of AED prescribing in the UK was relatively stable during the study period. In 2015, more than 2‰ of pregnant women received pregabalin or gabapentin prescriptions (2.3‰ and 2.7‰, respectively), compared with less than 1‰ in 2011 (0.8‰). This trend seems to be

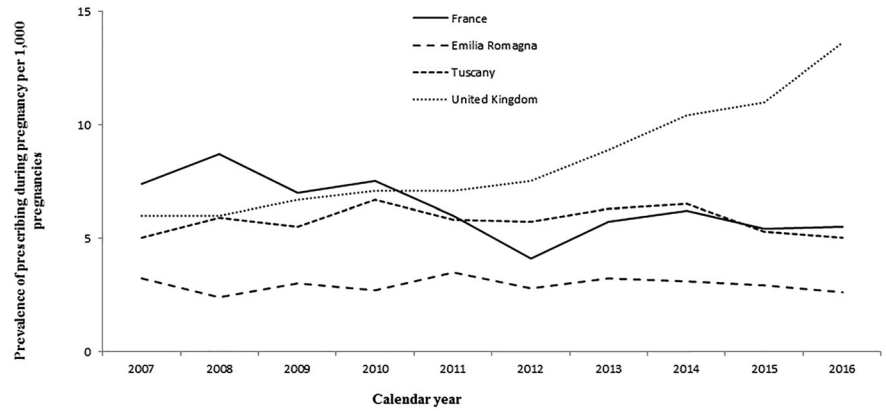


FIGURE 2 Prevalence of AED prescribing during pregnancy by year from 2007 to 2016

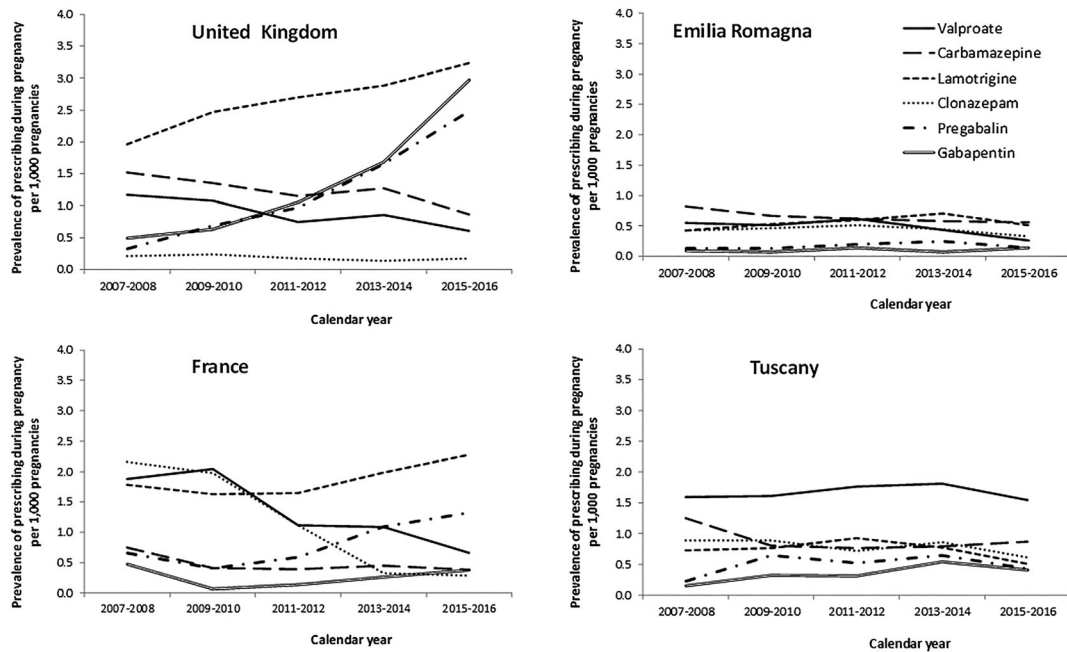


FIGURE 3 Prevalence of AED prescribing during pregnancy by country and by year from 2007 to 2016

confirmed in 2016. To a lesser extent, an increase in lamotrigine prescribing was identifiable, with the prevalence increasing from 1.8‰ in 2007 to 3.4‰ in 2015. In contrast, a decline in valproate prescribing was observed, from 1.4‰ in 2007 to 0.6‰ in 2015.

In France, there was a general decline in the prescribing of any AED during the study period with a prevalence of 7.4‰ in 2007 and 5.4‰ in 2015. The greatest reduction occurred between 2008 and 2012 and was likely to be related to the large reductions in clonazepam prescribing. After exclusion of clonazepam, the prevalence of AED prescribing was relatively stable during the study period. For valproate, the prevalence of prescribing during pregnancy declined between 2009 and 2011 after which it has remained constant with a prevalence of 0.7‰ in 2015 and 2016. By contrast, prevalence of lamotrigine prescribing increased during the same period from 1.5‰ in 2007 to 2.6‰ in 2015.

In Italy, in both Emilia Romagna and Tuscany, Figure 2 shows AED prescribing was stable between 2007 and 2015. However, a small decline from 0.6‰ in 2007 to 0.3‰ in 2015 in valproate prescribing

was identified in Emilia Romagna, while in Tuscany AED prescribing decreased from 2.0‰ in 2007 to 1.4‰ in 2015.

4.4 | Indications

In the French and UK databases, 4.2‰ and 4.8‰ of pregnant women, respectively, received an AED for the treatment of epilepsy (278 out of a total of 66 681 pregnancies in France and 1826 out of 380 499 in the UK) (Table 2). They represent 65.9% and 61.8%, respectively, of the women exposed to AEDs during pregnancy, while 16.4% received AEDs for bipolar disorder in France compared with 5.4% in the UK and 11.6% for pain in France compared with 15.4% in the UK (including 8.6% for neuropathic pain). Other indications were less frequent, with for example only 2.8% and 2.4% of women who received an AED due to an anxiety disorder. About 9% and 12.8% of indications were not identifiable in France and the UK, respectively.

Amongst women exposed to valproate during pregnancy in France, only prescriptions for bipolar disorder and epilepsy could be identified

TABLE 2 Indications of AED prescriptions during pregnancy in France and United Kingdom

	France		United Kingdom	
	N	%	N	%
Any AED	422	100.0%	2956	100.0%
Epilepsy	278	65.9%	1826	61.8%
Bipolar disorder	69	16.4%	161	5.4%
Anxiety	12	2.8%	72	2.4%
Pain	49	11.6%	457	15.4%
Migraine	3	0.7%	66	2.2%
Gen psych			57	1.9%
Unknown	38	9.0%	377	12.8%

with 73.6% of them treated for epilepsy and 26.4% for bipolar disorder. In the UK, 77.1% of women exposed to valproate during pregnancy were treated for epilepsy, 15.9% for bipolar disorder, 4.8% with unknown indications, and the remaining 2.2% for migraines and other psychiatric disorders.

5 | DISCUSSION

5.1 | Exposure to AEDs during pregnancy: differences between European countries

More than one million pregnancies were identified in the three European countries including over 6000 pregnant women who received an AED (around 6 per 1000). The prevalence of AED prescribing during pregnancy varies between regions and ranges from 3 per 1000 in Emilia Romagna to almost 8 per 1000 in the UK. In the UK, the prevalence was slightly higher and in Emilia Romagna slightly lower than that reported by a previous EUROmedICAT study, which used the same databases (excluding France) but covered an earlier time period from 2004 to 2010.²² The UK prevalence was also higher than that reported in another UK-based study between 1994 and 2009.²³ In France, the prevalence of AED and valproate prescribing were in line with figures reported by recent studies using the national health insurance database linked to hospitalisation data.²⁴

5.2 | Fewer AED prescriptions in Europe than in the United States during pregnancy

The prevalence of AED prescribing during pregnancy in all four regions was around 3 times less than that reported in a US-based study²⁵ where an increase in the prevalence of AED use was observed between 2001 and 2007, partly explained by an increase in the prescribing of lamotrigine and gabapentin. The US study used data from the Medication Exposure in Pregnancy Risk Evaluation Program (MEPREP), a collaborative program between the US Food and Drug Administration (FDA) and researchers from different institutions concerning around 12 million individuals enrolled within nine states, covering geographically and demographically diverse populations.

5.3 | Heterogeneous evolution between European countries

There was an increase over time in the prevalence of AED use during pregnancy in the UK due to a sharp increase in prescribing of gabapentin and pregabalin. This situation was also observed, to a lesser extent, for pregabalin in France, showing a new trend of AED prescribing. Concerning gabapentin, data in human pregnancy are insufficient to conclude whether or not there is a potential risk to the fetus.²⁶ Concerning pregabalin, studies in rats have shown adverse effects on embryo-fetal development, and a signal for increased risk of major birth defects was reported²⁷ but not confirmed thereafter.²⁸ Moreover, pregabalin and gabapentin present a potential for abuse and dependence²⁹ as mentioned in advice for prescribers disseminated in the UK, from late 2014.³⁰ Therefore, further investigations into their use and safety in pregnancy should be performed.

In Italy, the prevalence of AED use during pregnancy remained stable, while in France, the decline in AED prescriptions over time was mainly due to the decline in clonazepam prescriptions linked to changes in the rules on prescribing in 2011 to 2012 to prevent abuse and misuse.³¹ These trends were also observed in the recent study concerning women of childbearing potential using the same databases.¹

5.4 | Prescription of AED mainly for the treatment of epilepsy during pregnancy

Indications were not available in the electronic health care databases, and algorithms to identify indications could only be developed successfully for France and the UK. In France, four per 1000 French pregnant women were treated by AEDs for epilepsy. This is consistent with a previous study, carried out in another European country, which showed that around 3 in 1000 pregnant women suffer from epilepsy.³² The figures were similar for pregnant women in the UK.

Over 60% of French and UK pregnant women exposed to AEDs were treated for the indication "epilepsy," compared with 31% of the general population of women of childbearing potential.¹ This can be explained by the fact that, in Europe, it is recommended that the use of these medications during pregnancy must be limited to the cases where no other treatment is effective, a situation which occurs especially for women with epilepsy.

In contrast, in the United States, psychiatric disorders were the most prevalent diagnoses in pregnant women exposed to AED, followed by epilepsy and pain.²⁵

5.5 | Drug choice differs according to countries

In all regions, valproate prescriptions were issued to at least 10% of women exposed to an AED during pregnancy and almost 30% in Tuscany, where valproate was the most frequently prescribed AED throughout the entire study period. From 2007 to 2016, all regions, with the exception of Tuscany, observed a slight decreasing prevalence of valproate prescribing during pregnancy as reported in previous general

population studies in Ireland and the UK.^{33,34} However, since 2013 for Italy and 2014 for France and the UK, several warnings around valproate have been published each year by National Medicines Agencies (on the AIFA [Italian Medicines Agency] website in Italy, on the ANSM [French Medicines Agency] website in France, and on the MHRA [Medicines and Healthcare products Regulatory Agency] website for the UK), and risks associated with valproate exposure during pregnancy have been described in the scientific literature since the 1980s.

A significant number of newborns are still exposed in utero to valproate despite the recommendations. It may be that the “minimal essential level” of valproate exposure in pregnant women has been reached (less than 1 per 1000 pregnant women in 2015 to 2016 in the UK, France, and Emilia Romagna) and that all exposures are to women where no other treatment is effective. However, it remains important to inform health professionals to try to further reduce exposure to valproate to women of childbearing age.

Lamotrigine is the most frequently prescribed AED in France and the UK, with respectively, one-quarter and one-third of AED exposed women exposed to this AED which is in the top 4 of the most prescribed AEDs during pregnancy in all regions. Moreover, this drug appears to be increasingly used over time as observed previously in Denmark, Norway and Wales,²² and Australia.³⁵ This situation is rather reassuring because several reviews have concluded that lamotrigine may be associated with a lower risk of teratogenicity.^{36,37} In 2009, an increased risk of cleft palate and lip was reported after an exposure during the first trimester of pregnancy.³⁸ However, this risk was not confirmed by other studies.³⁹

During the first years of the study period, carbamazepine was the most frequently prescribed AED in Emilia Romagna, with more than 20% of pregnant women exposed to AEDs receiving carbamazepine. Carbamazepine use in pregnancy is associated with an increased risk of malformations (RR = 2.2),⁴⁰ including neural tube defects, cardiovascular and urinary tract defects, and cleft palate.^{41,42}

5.6 | Fewer AED prescriptions in pregnant women than in the general population of women

The two-fold lower use of AEDs during the 6 months preceding the start of pregnancy may indicate that these pregnancies are planned. However, some women who have an AED prescription in early pregnancy (the most risky period for congenital anomalies) have no more prescriptions during the second and the third trimesters, suggesting that the AED treatment can be stopped or replaced. This emphasises the need of systematic counselling of epileptic women of childbearing age.

5.7 | Study with some weaknesses but representative of European population

Health care administrative databases allow comparison studies between countries to be conducted. However, some weaknesses are linked to the use of these databases,¹ in particular the absence of data

on compliance with treatment and on prescriptions during hospital stays. Prescription duration and dose were not available, and AED exposure was based solely on the issue or the dispensing of at least one prescription during individually specified 3-month periods relating to the pregnancies. In France, AED medications are dispensed each month by the pharmacist, irrespective of the duration of the prescription. The patient returns to the pharmacy each month to get that month's AED medication, and therefore exposure during the three months will be reported. In Emilia Romagna (Italy), pharmacists can dispense a 2-month supply of any medication and in the UK medications can also be dispensed for different durations, but are extremely unlikely to be for more than 3 months at a time. Therefore, exposure during any specified 3-month period is also likely to be captured in these databases.

The underlying disease for which the prescription was issued was often not available in the databases, raising the need to develop and validate algorithms to determine indications for prescribing. For drugs with several indications, like AEDs, where the benefit/risk balance for adverse pregnancy outcomes could be different according to the maternal disease, lack of indication can represent a limitation for the interpretation of pregnancy medication safety studies. Moreover, prevalence of AED prescribing in Emilia Romagna must be considered with caution because pregnancy data were limited to those pregnancies ending in livebirth or stillbirth. In other countries, spontaneous abortions, induced terminations, and unknown losses represent between 20% and 30% of pregnancies included in the study. Likewise, prevalence rates in 2016 must be treated with caution since they concern only a few pregnancies (only those pregnancies which start in 2016 and finish in 2016). Although they represent a rich source of information, administrative health care databases, such as those used here, were not designed to perform research studies. Algorithms had to be used to calculate start and end dates of the pregnancy; consequently, estimations of exposure periods may not be always accurate.

The UK and French databases used in this study are broadly representative samples of the general population of these countries (around 8% of the UK population and around 1% of the French population). However, in Italy, dispensed prescriptions of two different regions only were captured, and women included may not be representative of the general Italian population.

Nevertheless, the major strength of this study is that it concerned more than one million pregnancies from four European regions allowing patterns of AED prescription during pregnancy to be compared in countries with different guidance on prescribing, recommendations^{15,17} and lifestyles.

6 | FUTURE RECOMMENDATIONS

During the 10-year period, physicians were increasingly drawing on new drugs like pregabalin or gabapentin. However, risks associated with the use of these drugs during pregnancy are not well-known due to the lack of relevant studies. Further evaluation on their effects during pregnancy is needed. Until then, health care practitioners should limit their prescriptions of pregabalin and gabapentin during pregnancy.

Observed differences in the prevalence of AED exposure, particularly valproate, during pregnancy indicate that information on the risks associated with these exposures should continue to be further disseminated to reduce the exposure levels. Safety information should also highlight that valproate is contraindicated for prophylaxis of migraine headaches in pregnant women and in women of childbearing potential who are not using effective contraception. Valproate should not be used to treat women with epilepsy or bipolar disorder who are pregnant or who plan to become pregnant unless other medications have failed to provide adequate symptom control and a pregnancy prevention plan is in place.

7 | CONCLUSION

Although the prevalence of AED prescribing during pregnancy varied between European countries, during the 10-year period, prescriptions for valproate during pregnancy decreased. However, at least 10% of pregnant women receiving an AED prescription in the study were prescribed valproate, hence there is further potential for reduction. At the same time, AED prescriptions for pregabalin and gabapentin, for which risks for the embryo or the fetus are not well-known, increased. Information on risks associated with exposure to valproate during pregnancy should continue to be widely circulated to health care providers, and studies on potential alternative medications should be promptly conducted.

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CONFLICTS OF INTEREST

This document expresses the opinion of the authors of the paper and may not be understood or quoted as being made on behalf of or reflecting the position of the European Medicines Agency or one of its committees or working parties.

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AUTHOR CONTRIBUTION

Rachel Charlton and Julia Snowball performed the analysis in the UK, Caroline Hurault-Delarue in France, Rosa Gini in Tuscany (Italy), and Aurora Puccini in Emilia Romagna (Italy). Rachel Charlton and Joan K. Morris coordinated the project, wrote the protocol, collected, and interpreted the results; they wrote the study report. Caroline Hurault-Delarue and Joan K. Morris wrote the manuscript with

support from Christine Damase-Michel. All authors discussed the protocol and the results and commented on the final manuscript.

AVAILABILITY OF DATA AND MATERIAL

The authors are willing to consider reasonable requests for access to the aggregate data used in the analysis in this paper.

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