



ORIGINAL REPORT

Did advice on the prescription of sodium valproate reduce prescriptions to women? An observational study in three European countries between 2007 and 2016

Rachel Charlton Research Fellow¹ | Christine Damase-Michel Associate Professor² |
 Caroline Hurault-Delarue Research Fellow²  | Rosa Gini³ |
 Maria Loane Reader in Public Health⁴ | Anna Pierini Researcher⁵ | Aurora Puccini⁶ |
 Amanda Neville Research Fellow and Registry Leader⁷ |
 Julia Snowball Database Manager/Research Fellow¹ |
 Joan K. Morris Professor of Medical Statistics⁸  | on behalf of the EUROmediSAFE consortium

¹Department of Pharmacy and Pharmacology, University of Bath, Bath, UK

²Pharmacologie Faculté de Médecine, Université Toulouse III, CHU Toulouse, INSERM UMR1027, France

³Agenzia regionale di sanità della Toscana, Italy

⁴Institute of Nursing and Health Research, Ulster University, Co Antrim, Northern Ireland

⁵Institute of Clinical Physiology - National Research Council (IFC-CNR)/Fondazione Toscana "Gabriele Monasterio", Pisa, Italy

⁶Drug Policy Service, Emilia Romagna Region Health Authority, Bologna, Italy

⁷IMER (Emilia Romagna Registry of Birth Defects), Centre for Clinical and Epidemiological Research, University of Ferrara and Azienda Ospedaliero-Universitaria di Ferrara, Ferrara, Italy

⁸Centre for Environmental and Preventive Medicine, Queen Mary University of London, London, UK

Correspondence

J. Morris, Centre for Environmental and Preventive Medicine, Queen Mary University of London, London, UK.
 Email: jmorris@sgul.ac.uk

Present Address

Joan K. Morris, Population Health Research Institute, St George's, University of London, London.

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Abstract

Objectives: In November 2014, the CMDh (a regulatory body representing EU Member States) advised doctors not to prescribe sodium valproate for epilepsy or bipolar disorder in pregnant women, in women who can become pregnant, or in girls unless other treatments are ineffective or not tolerated. This study aimed to determine if this warning led to changes in prescription patterns.

Design and setting: Cohort of 5.4 million women aged between 10 and 50 years identified in electronic health care data from United Kingdom, France, and Italy (2007–2016).

Main outcome measures: Anti-epileptic drug (AED) prescriptions.

Results: The prevalence of women receiving AED prescriptions in 2016 varied from 12.2 per 1000 to 29 per 1000 in the four regions. The incidence of prescribing any AED (excluding clonazepam, gabapentin, and pregabalin) fell each year on average by 7.5% (95% CI, 7.0%–8.0%; Emilia Romagna), 9.6% (8.3%–11.0%; France), 7.1% (6.7%–7.6%;

What is already known on this topic

- Sodium valproate exposure during the first trimester is associated with the occurrence of congenital anomalies and also neurodevelopmental delays.
- The European Medicines Agency sent warnings to health care professionals to limit sodium valproate prescriptions to women for whom other alternatives are not possible and to inform patients of the risks in November/December 2014.
- It is unknown if these warnings have any effect on prescribing patterns in Europe.

Tuscany), and 0.4% (0.2%-1.0%; United Kingdom). The relative odds of prescribing sodium valproate rather than any other AED decreased more after 2014 compared with before the end of 2014 in France (OR = 0.77; 95% CI, 0.60-0.98), Tuscany (0.81; 0.76-0.86), Emilia Romagna (0.83; 0.76-0.90), and the United Kingdom (0.92; 0.80-1.06; not statistically significant).

Conclusions: There is evidence that the CMDh warning did lead to changes in prescription patterns of sodium valproate in women of childbearing age. There were considerable differences in prescribing practice amongst regions of Europe.

KEYWORDS

antiepileptic medications, epidemiology, health care databases, sodium valproate

1 | INTRODUCTION

Antiepileptic drugs (AEDs) are a diverse class of medicines that are prescribed for an increasing number of indications including epilepsy, bipolar disorder, migraine prophylaxis, and neuropathic pain.¹⁻³ AEDs are commonly prescribed to women of childbearing age,⁴⁻⁹ and the prevalence of prescribing varies by geographic location.^{9,10} The chronic and serious nature of some of the indications for which they are prescribed means that it is not always possible for women to discontinue their treatment in advance of and during pregnancy.¹¹⁻¹³ For some time, there has been evidence that certain AEDs, when taken by women during their pregnancy, are associated with a two- to three-fold increase in risk of major congenital malformations in the offspring.¹⁴⁻¹⁷ The risk varies by AED, with sodium valproate often reported as having the highest risk¹⁴ and lamotrigine and levetiracetam the lowest risk,¹⁷ although for many of the other newer AEDs, the number of exposures during pregnancy available for study is low. In recent years, there has been a growing body of evidence of negative neurodevelopmental outcomes in children exposed to sodium valproate in utero.^{14,18-23}

In October 2013, the Medicines and Healthcare Regulatory Authority (MHRA) issued a referral into the use of sodium valproate in girls and women of childbearing potential. Following completion of the review by the Pharmacovigilance Risk Assessment Committee (PRAC) in the European Medicines Agency (EMA), the CMDh (a regulatory body representing EU Member States) strengthened warnings on the use of sodium valproate in women and girls because of the risk of malformations and developmental problems in babies exposed to sodium valproate in the womb. The warnings aim to ensure that patients are aware of the risks and that they take sodium valproate only when clearly necessary. The CMDh review resulted in a personal letter being sent to all health care professionals in all European countries in November/December 2014 informing them of the changes in the recommendations for valproate prescribing. This information was also posted on the EMA website on 21 November 2014 (<https://www.ema.europa.eu/en/medicines/human/referrals/valproate-related-substances#key-fac-ts-section>).

KEY POINTS

- The incidence of prescribing sodium valproate to women of childbearing age varied considerably between the UK, France and Italy from 2007 to 2016. Prescription rates for sodium valproate compared with other antiepileptic medications did fall in all three countries after warnings were sent to health care professionals in 2014.

This study, capturing data from three European countries, aimed to determine if there is any evidence that warnings about the harm of sodium valproate to the fetus have led to changes in prescription patterns of sodium valproate and other AEDs in women of childbearing potential.

2 | METHODS

Electronic health care databases from within four regions/countries contributed data to the study: the United Kingdom (UK-wide Clinical Practice Research Datalink [CPRD]), France (Echantillon Generaliste des Beneficiaires [EGB]: French Health Insurance System and Hospital Medical Information Systems [PMSI]), 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 can be found in Table 1 and has been reported elsewhere.²⁴ Ethical and data access approvals were obtained for each database from the relevant governance infrastructures, using a common protocol. The protocol was registered in the ENCePP PAS register (EUPAS21171).

2.1 | Study population

The study period ran from 1 January 2007 until 31 December 2016. The source population consisted of all females in each database, who were aged between 10 and 50 years at some point during the

TABLE 1 An overview of the databases contributing to the study

Country/region	Italy - Tuscany	Italy - Emilia Romagna	France	United Kingdom
Involves database record linkage	Yes	Yes	Yes	No
Population base	3 700 000	4 200 000	680 000 (1/97 of French population)	5 000 000 (~8% of the UK population)
Database for live and stillbirth pregnancy identification	Certificate of Delivery Assistance (CeDAP) Hospital Discharges Registry	Certificate of Delivery Assistance (CeDAP)	Echantillon Généraliste des bénéficiaires (EGB) ^c	Clinical Practice Research Datalink (CPRD)
Database for pregnancy loss identification	Discharges for Induced Terminations and Spontaneous Abortions. Hospital Discharges Registry	Not available	EGB, French Health Insurance System and PMSI	CPRD
Database for medicine use data	Tuscany Prescription Database (TPD)	Emilia-Romagna Prescription Database (ERPD)	French Health Insurance System Database	CPRD
Source for medicine use data	Pharmacy dispensing and Healthcare facilities dispensing (except inpatient exposure) ^b	Pharmacy dispensing and Healthcare facilities dispensing (except inpatient exposure) ^b	Pharmacy Dispensing	GP practice prescribing ^a
Start of first data collection	2003	2003	2005	1987
Capture outpatient prescribing	Yes	Yes	Yes	Yes
Capture inpatient prescribing	No	No	No	Some

^aIncluding nurse prescribers working within the GP practice

^bIncluding only products reimbursed by the Italian National Health Service and excluding those dispensed to outpatients in a hospital pharmacy

^cEGB includes data from French Health insurance system and Hospital Medical Information System databases (PMSI)

study period. Eligible females were required to have contributed a minimum of 365 days to the database.

2.2 | Exposure

The exposures of interest were AEDs with an anatomical therapeutic chemical (ATC) code starting N03A and also clobazam (ATC N05BA09), which is licensed for epilepsy in the countries under study. Sodium valproate included both prescriptions for valproic acid and for valpromide. All AED prescriptions that were issued in the United Kingdom or dispensed in France and Italy to any female during her time in the study cohort were identified. In all four regions, there was a large proportion of women with only a single-AED prescription during the entire time they were in the study (38% in France, 31% in Emilia Romagna, 28% in Tuscany, and 22% in the United Kingdom). Around 75% of these women were prescribed gabapentin, pregabalin, or clonazepam in France, the United Kingdom, and Emilia Romagna (54% in Tuscany). These three medications are often prescribed for neuropathic pain rather than epilepsy. Given the fact that AEDs are mostly associated with chronic treatment, irrespective of indication, it was decided that only females issued/dispensed more than one prescription for an AED during their time in the study cohort were defined as exposed. Sensitivity analysis including all women with only one prescription were performed.

A cohort of first-ever AED users was identified within the AED exposed cohort. "First-ever users" were defined as those who

received an AED prescription during the study period, who had been in the database for greater than 365 days prior to the date of their first AED prescription without any other AED prescribing during this time.

For each female receiving an AED attempts were made to determine the indication for the AED prescribing. In all databases, this involved the creation of a unique database specific algorithm to utilise all available information, which included some or all of the following: medical diagnoses, hospital discharge data, special reimbursement status or exemption codes, information on the type of prescriber, the specific name of the medicine, and co-prescribing of other medicines such as psychotropic drugs. In Italy, a modified version of the algorithm developed by Naldi et al was used,²⁵ because the original algorithm did not attempt to determine prescribing for migraines or pain. The level of detail available varied between databases with the main aim being to distinguish between prescribing for epilepsy and prescribing for psychiatric conditions (such as bipolar disorder or anxiety) or pain (neuropathic pain or migraine).

2.2.1 | Patient and public involvement

This research was done without patient involvement. Patients were not invited to comment on the study design and were not consulted to develop patient relevant outcomes or interpret the results. Patients were not invited to contribute to the writing or editing of this document for readability or accuracy.

3 | ANALYSIS

The analyses were carried out separately for each database at the host institution and shell tables of aggregated results were then provided to the lead institution to be compiled. The prevalence of AED prescribing in females of childbearing age was calculated per 1000 female population with 95% confidence intervals (CI_{95}) for 2016 using the Poisson distribution. The ten most common AEDs in 2016 were identified according to the prevalence in each region, with each region having the same weight (despite the differences in population sizes).

The annual change in incidence of AED prescribing in first-ever users was analysed using Poisson regression separately for each region. To determine if there was a change in the odds of prescribing sodium valproate rather than another AED from 2014 onwards, an interrupted time series logistic regression model was fitted using segmented regression assuming that the change will be a gradual change in the gradient of the trend starting in 2014. This means that two straight lines are fitted: one from 2007 to 2013 and one from 2014 to 2016. A sensitivity analysis was performed including women who had only one AED prescription during the study period. The incidence of AED prescribing was also stratified by age at first prescription in the categories: less than 20 years old, 20 to 29 years old, 30 to 39 years old, and 40+ years old. For France, the incidence of AED prescribing was also stratified by indication.

There were considerable missing data on the indication for AED prescribing. This variable was only analysed for France for whom there was sufficient information available, and the "other/unknown" outcome was identified on the table to enable the reader to be able to determine the possible extent of bias. As only core variables were analysed in this study, the variables were complete.

All analyses were performed using STATA 14.

4 | RESULTS

Data were available from the four regions on a total of 5.4 million women from 2007 to 2016. The number of females captured in the databases in each region differed in size from the United Kingdom with 2.4 million women, Emilia Romagna with 1.6 million, Tuscany with 1.3 million, and France with 190 000 women.

4.1 | Prevalence of women receiving AED prescriptions in 2016

Table 2 shows that the prevalence of women being prescribed AEDs in 2016 varied considerably both between and within countries with the prevalence being lowest in Emilia Romagna at 12.2 (95% CI, 12.0-12.4) per 1000, higher in Tuscany and France (17.7; 17.5-18.0 and 19.1; 18.3-19.8 per 1000, respectively), and highest in the United Kingdom at 29.0 (28.6-29.3) per 1000. The women in the Italian databases had a mean age 2 years older than those in France and the

United Kingdom, but those being prescribed AEDs had similar ages in all the databases.

Table 2 also shows the prevalence of the 10 most common medications in 2016. In contrast to the other regions, 10.4 women per 1000 in the United Kingdom were prescribed gabapentin, and 8.4 per 1000 were prescribed pregabalin—under three per 1000 women were prescribed either of these medications in the other regions apart from in France, where 6.3 per 1000 women were prescribed pregabalin. Excluding prescriptions for gabapentin and pregabalin, valproate was the most frequently prescribed AED medication in all regions except for in the United Kingdom, where lamotrigine was more frequently prescribed, with the prevalence of valproate prescriptions varying from 6.6 per 1000 in Tuscany down to 2.7 per 1000 in the United Kingdom.

4.2 | Incidence of AED prescribing from 2007 to 2016

Figure 1A shows the changes in prescribing of AEDs to women who were first-time users for the 10-year period from 2007. The trends appear very different in the four regions, with large increases observed in the United Kingdom contrasting with large decreases in France. However, only a very small number of specific AEDs were responsible for these trends. When prescriptions of clonazepam, gabapentin, and pregabalin were excluded, the trends were significantly decreasing in all regions by 9.6% (95% CI, 8.3%-11.0%) per year (France), 7.5% (7.0%-8.0%; Emilia Romagna), 7.1% (6.7%-7.6%; Tuscany), and 0.4% (0.2%-1.0%; United Kingdom) (Figure 1B). The incidence of prescribing clonazepam, gabapentin, and pregabalin in addition to the other eight most common AED medications according to year is given in Appendix 1 (Table A1 and Figure A1).

4.3 | Incidence of sodium valproate prescribing

Figure 2 shows that the incidence of prescribing sodium valproate has fallen in all regions (2A) and that this fall is greater than the fall in other AEDs in France and the United Kingdom (2B) for the whole study period and for Emilia Romagna and Tuscany for the period from 2014. Table 3 shows that the odds of prescribing sodium valproate compared with any other AED (excluding clonazepam, gabapentin, and pregabalin) decreased significantly from 2014 to 2016 and that this decrease was significantly greater from 2014 to 2016 than the annual changes from 2007 to 2016 in France and Italy—in the United Kingdom, there had been a greater decrease in 2014 to 2016, but it was not statistically significant. Extremely similar estimates were obtained in the sensitivity analysis, which included women with only a single-AED prescription in the study period, resulting in the same degrees of statistical significance for France and Italy and the decrease in the United Kingdom being greater but not statistically significant ($P = .09$).

TABLE 2 Numbers and prevalence of women aged 10 to 50 years with greater than one prescription for an AED during 2016 according to region and ten most common AEDs

	Tuscany	Emilia Romagna	France	United Kingdom
Number of women in database in 2016 [Mean age in y]	989 673 [33.0]	1 210 223 [33.2]	138 566 [31.4]	766 304 [31.2]
Number of women with >1 AED prescriptions in 2016 [Mean age in y]	17 559 [37.7]	14 733 [37.8]	2641 [38.3]	22 197 [37.7]
Prevalence per 1000 women (95% CI)				
Any AED	17.7 (17.5-18.0)	12.2 (12.0-12.4)	19.1 (18.3-19.8)	29.0 (28.6-29.3)
Gabapentin	1.9 (1.8-2.0)	1.1 (1.0-1.2)	1.8 (1.6-2.1)	10.4 (10.2-10.6)
Pregabalin	2.9 (2.8-3.0)	1.7 (1.6-1.7)	6.3 (5.9-6.7)	8.4 (8.2-8.6)
Valproate	6.6 (6.5-6.8)	3.1 (3.0-3.2)	4.4 (4.1-4.8)	2.7 (2.6-2.8)
Topiramate	2.2 (2.1-2.3)	1.6 (1.5-1.6)	1.7 (1.5-1.9)	2.5 (2.4-2.6)
Clonazepam	1.5 (1.4-1.6)	1.7 (1.7-1.8)	0.8 (0.7-1.0)	0.8 (0.7-0.8)
Carbamazepine	2.0 (1.9-2.1)	1.5 (1.5-1.6)	1.3 (1.1-1.5)	2.5 (2.4-2.6)
Lamotrigine	1.9 (1.8-2.0)	1.9 (1.8-1.9)	3.1 (2.9-3.4)	4.3 (4.1-4.4)
Levetiracetam	1.2 (1.2-1.3)	1.3 (1.3-1.4)	1.7 (1.5-1.9)	2.2 (2.1-2.3)
Clobazam	-	0.1 (0.1-0.1)	1.6 (1.4-1.8)	0.7 (0.6-0.7)
Oxcarbazepine	0.9 (0.8-0.9)	0.6 (0.5-0.6)	0.5 (0.3-0.6)	0.1 (0.1-0.1)

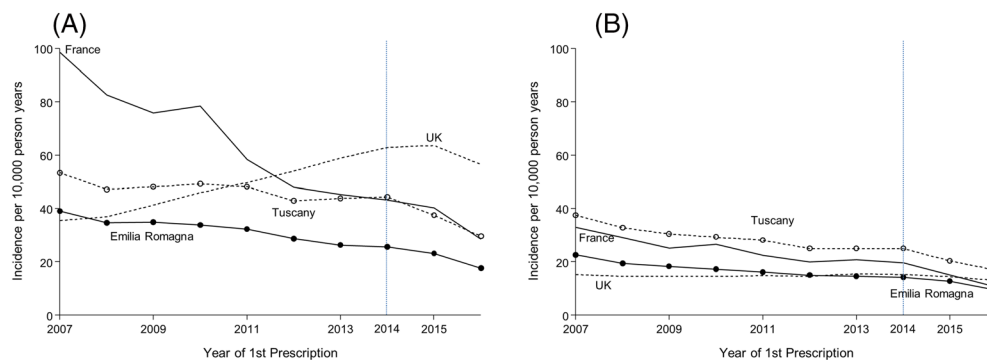
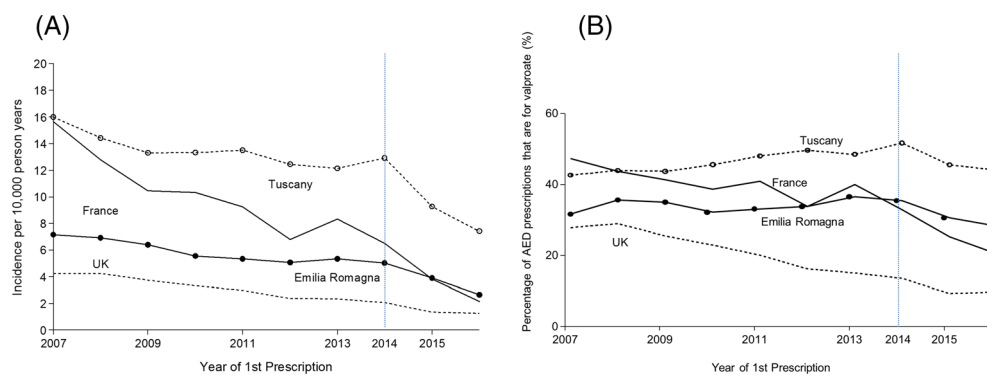
**FIGURE 1** Trends in the incidence of first prescriptions in the four regions from 2007 to 2016 (A) Incidence of any antiepileptic drug (AED) and (B) incidence of any AED excluding clonazepam, gabapentin, and pregabalin [Colour figure can be viewed at wileyonlinelibrary.com]**FIGURE 2** Incidence of prescribing sodium valproate according to year of first prescription and region (A) per 10 000 women and (B) expressed as a proportion of all antiepileptic drugs (AEDs) (excluding clonazepam, gabapentin, and pregabalin) [Colour figure can be viewed at wileyonlinelibrary.com]

TABLE 3 Odds ratio of prescribing sodium valproate compared with another AED (excluding clonazepam, gabapentin, and pregabalin) per year for each region: Comparing 2007 to end of 2014 with end of 2014 to 2016

	Odds Ratio of Prescribing Sodium Valproate Compared with Another AED Per Year		Ratio of OR 2014-2016 vs 2007-2013	P values for Comparison of Odds Ratios
	2007-2013	2014-2016		
Emilia Romagna	1.01 (1.00-1.03)	0.84 (0.78-0.91)	0.83 (0.76-0.90)	<.001
France	0.94 (0.90-0.98)	0.72 (0.56-0.91)	0.77 (0.60-0.98)	.033
Tuscany	1.05 (1.04-1.06)	0.85 (0.80-0.91)	0.81 (0.76-0.86)	<.001
United Kingdom	0.87 (0.85-0.89)	0.80 (0.69-0.92)	0.92 (0.80-1.06)	.262

4.4 | Incidence of prescribing sodium valproate according to age

Figure 3 shows that the incidence of prescribing sodium valproate is highest in the oldest age groups (>40 years and 30-39 years) and that it is in these age groups that the incidence is decreasing the greatest. A figure illustrating the incidence of prescribing the eleven most common AED medications according to age is given in Appendix 1 (Figure A2).

4.5 | Incidence of AED prescribing according to indication

In all regions/countries apart from France, there was a large proportion of females for which the indication could not be confidently assumed: 56% in Tuscany, 37% in Emilia Romagna, and 28% in the United Kingdom compared with 11% in France. Hence, only the incidence of AED prescribing according to indication is given for France, and the algorithm used is given in Appendix A. Table 4 shows that for all AEDs, 31% of prescriptions were for epilepsy and 40% for neuropathic pain, with some individual AED prescriptions being more likely to be for epilepsy (levetiracetam, oxcarbazepine, topiramate,

carbamazepine, lamotrigine, and clobazam), and valproate was more likely to be for bipolar disorders. The unknown indications were mainly for clonazepam prescriptions. Figure 4 shows that the incidence of valproate prescriptions is much greater for bipolar disorders than for epilepsy, apart from for women under 20 years of age. The incidence has decreased for both, with particularly large decreases for bipolar disorder following the warnings about sodium valproate in November/December 2014.

5 | DISCUSSION

5.1 | Study findings

This study analysed data from two regions in Italy, from France, and the United Kingdom on 5.4 million women aged 10 to 50 years between 1 January 2007 and 31 December 2016. In 2016, the United Kingdom had a much higher prevalence of AED prescribing than the other three regions (29 per 1000 compared with 19.1, 17.7, and 12.2, respectively, for France, Tuscany, and Emilia Romagna). However, two drugs (pregabalin and gabapentin) were taken by over 60% of AED exposed women in the United Kingdom, and when these

Incidence of sodium valproate according to age at first prescription, year of prescription by register

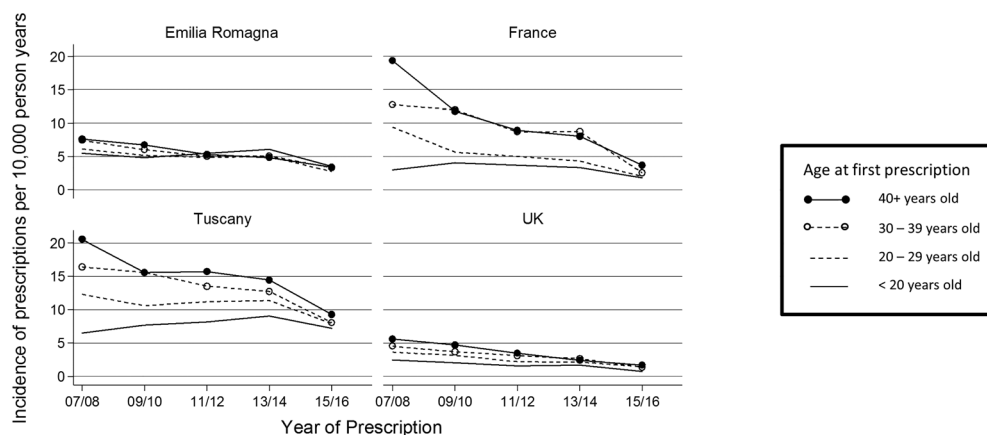
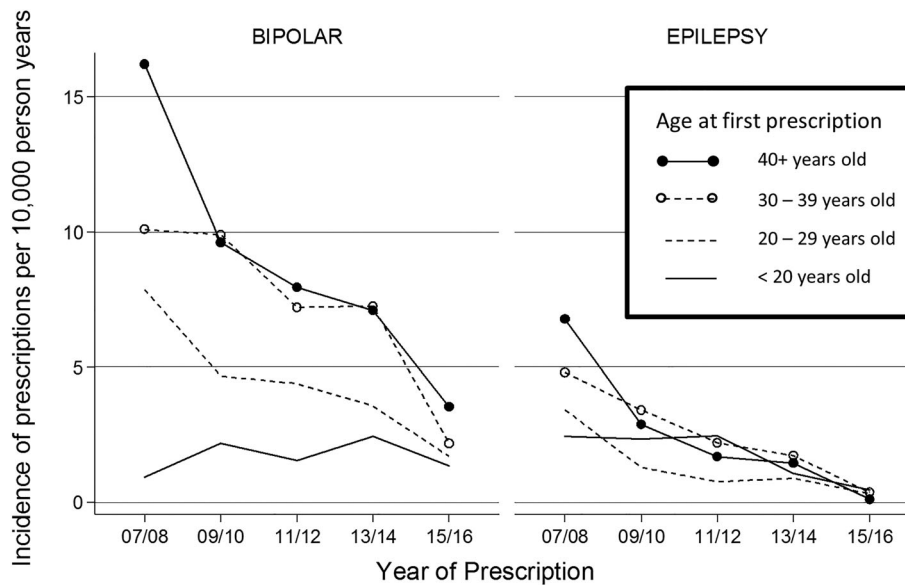


FIGURE 3 Incidence of sodium valproate prescriptions per 10 000 person years according to age at first prescription and year of prescription in the four regions

TABLE 4 Percentage of women with greater than one prescription for an AED for the first time from 2007 to 2016 according to indication in France (totals may be above 100% as some women are prescribed medications for multiple reasons)

	Number of women	Percentage of Women (%)					
		Epilepsy	Bipolar	Anxiety	Neuropathic pain	Migraine	Other/unknown
Any AED	7382	31	16	4	40	1	11
Gabapentin	418	23	2	2	73	0	0
Pregabalin	2584	15	2	4	79	0	0
Valproate	1059	29	81	0	0	0	0
Topiramate	388	80	3	1	0	16	0
Clonazepam	1874	20	6	0	37	0	43
Carbamazepine	214	76	20	1	3	0	0
Lamotrigine	243	67	34	0	0	0	0
Levetiracetam	189	100	0	0	0	0	0
Clobazam	579	67	6	25	0	0	3
Oxcarbazepine	41	100	7	0	0	0	0

**FIGURE 4** Incidence of prescriptions for valproate according to year at first prescription, indication, and age in France

two drugs were excluded, the prevalence in the United Kingdom was 12.8 per 1000, more consistent with the other regions. In 2016, valproate was the most frequently prescribed AED in Italy, the second most frequent in France after pregabalin, and the fourth in the United Kingdom after gabapentin, pregabalin, and lamotrigine, with between 2.7 and 6.6 per 1000 women receiving more than one prescription in 2016.

All regions did experience a reduction in the incidence of valproate prescribing during the whole study period. However, the results from fitting an interrupted time series model indicated that in all regions, there was a greater decline occurring post-2014 compared with pre-2014 for the prescription of valproate compared with the prescription of other AEDs. This decline was statistically significant in three of the regions.

5.2 | Strengths and weaknesses

Our study used electronic health care data, and therefore, exposure to AEDs was based on the issue/dispensing of a prescription. It was not possible to know whether the woman actually took the medicine and took it as and when instructed, although it is probably fair to assume that repeat prescribing of these products indicates actual use. Hence, in this study, a woman was only defined as being exposed to an AED if she had at least two AED prescriptions over the study period. However, this did result in excluding a large proportion of single-AED prescriptions, as has been observed in other studies.⁵

None of the databases captured all AED prescriptions, but the proportions missed were thought to be small. For example, none captured prescriptions issued during inpatient hospital stays. In the

United Kingdom, AED prescriptions issued by a specialist in secondary care were not captured, although the majority of AED prescribing, even if initiated by a specialist, would subsequently be undertaken by the GP. The number of cases where the woman continues to receive all AED prescribing via a specialist is thought to be relatively small for all indications. In France, AED prescriptions were not captured within the database if they were prescribed off label, which is an uncommon situation, and in Italy, a small number of AED products are not reimbursed by the Italian National Health Service. No information on the dose of AEDs prescribed was analysed.

A further weakness was that for three databases, it was not possible to determine the indication for prescribing, partly related to the increasing number of indications for which AEDs are now prescribed^{1,2,26} and an increase in the extent of off-label prescribing.²⁷ A study in the United Kingdom, using electronic health care data, found that 62% of prescriptions issued for pregabalin between 2004 and 2009 did not have a diagnosis code corresponding to one of the approved indications.²⁸ The pattern of medications prescribed, particularly the increases in gabapentin and pregabalin, indicates that much of the increase in prescriptions was due to non-epilepsy indications, particularly pain treatments. This increase in AED prescriptions for non-epilepsy indications has been observed in Canada,² Norway,²⁹ Italy,^{6,30} Denmark,⁵ and the United States.³¹

The results in this study are consistent with those in other earlier studies; the regional variations observed in the extent of AED prescribing and the AEDs most commonly prescribed have been reported elsewhere,^{9,10,32} including a high prevalence of valproate prescribing in Italy between 2005 and 2011.³⁰ The decline in the incidence of valproate prescribing in the United Kingdom is comparable with that reported by an Irish study between 2008 and 2013³³ and a study of prescriptions to 12 to 18 year olds in the United Kingdom.³⁴

The dramatic decline in the incidence of clonazepam prescribing observed in France is explained by changes in the rules on prescribing that came into effect between September 2011 and January 2012, following the observation of misuse and abuse of the product. Since September 2011, clonazepam can only be prescribed on a special prescription form that is usually specific to the prescribing of narcotics and controlled substances. Since January 2011, the initiation of clonazepam treatment has been restricted to neurologists and paediatricians. In November 2013, NICE published guidelines on neuropathic pain management, which may have influenced the prescription patterns for gabapentin and pregabalin.

The relatively high levels of prescriptions for gabapentin and pregabalin, usually for neuropathic pain and the recent increases particularly in the United Kingdom and to some extent, Tuscany have been reported earlier in Italy,^{3,30,6} the United Kingdom,⁹ and Norway.²⁹ Such increases have also occurred in non-European countries such as Canada² and Australia.⁷ These increases together with evidence that these AEDs have the strong potential for abuse^{35,36} mean that the utilisation of these products requires future monitoring. In addition, more information is needed on the safety in pregnancy of these new AEDs, particularly for pregabalin. Two recent studies have produced conflicting results on the teratogenicity of pregabalin in the first trimester; the first was a

multicentre study from the European Network of Teratology Information Services, which reported an odds ratio (OR) = 3.0 (95% CI, 1.2-7.9) for pregabalin use in pregnancy and major congenital malformations in the fetus.³⁷ The second study using the US Medicaid Analytic Extract (MAX) reported a relative risk (RR) = 1.16 (95% CI, 0.81-1.67) for pregabalin use in pregnancy and major congenital malformations in the fetus after propensity score adjustment.³⁸ A recent review included nine studies on the safety of gabapentin use during pregnancy and concluded that there was no evidence of an increased risk of major congenital anomalies, but the studies were all small.³⁹

5.3 | Implications

There is some evidence in the regions studied of a greater reduction in the prescribing of sodium valproate compared with other AEDs since 2014 compared with before 2014. However, it is still of concern that in 2016 after pregabalin and gabapentin, valproate was the most commonly prescribed AED in all regions except for the United Kingdom (where lamotrigine was more common) with the prevalences of valproate prescriptions varying from 6.6 per 1000 in Tuscany down to 2.7 per 1000 in the United Kingdom. Much of the decrease in the incidence of prescribing valproate is occurring in older women, who may have already completed their families. In February 2018, the EMA's PRAC recommended that sodium valproate must no longer be prescribed to women or girls of childbearing potential unless they are on the pregnancy prevention programme (PPP). The success of this could be monitored by studies similar to this one, but due to the differences observed across the regions studied here, in order to obtain a valid European measure of effect, more than four regions should be included.

This study has demonstrated that, in addition to epilepsy, AEDs are now being increasingly prescribed for other indications, which means that data to evaluate the safety of AEDs should cover the full range of indications in addition to disease-specific registries. It is important that all prescribing advice and warnings in addition to any interventions are made apparent to all potentially relevant prescribers, medical specialists, pharmacists, and AED users and are not restricted to having the emphasis put on a particular indication.

The rapid increases observed in the prescribing of gabapentin and pregabalin in women of childbearing age and the lack of evidence of their safety during pregnancy means that further investigations into the use and safety in pregnancy of these medications should be performed.

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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 or of reflecting the position of the European Medicines Agency or one of its committees or working parties.

AUTHORS CONTRIBUTIONS

R.C. and J.K.M. contributed to the planning, conduct, analysis, and reporting of the work and are responsible for the overall content. All other authors contributed to the conduct and analysis and provided input into the final paper. The corresponding author attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted.

DATA SHARING

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

TRANSPARENCY STATEMENT

Professor Joan Morris affirms that the manuscript is an honest, accurate, and transparent account of the study being reported, that no important aspects of the study have been omitted, and that any discrepancies from the study as originally planned (and, if relevant, registered) have been explained.

ORCID

Caroline Hurault-Delarue  <https://orcid.org/0000-0001-7651-9130>

Joan K. Morris  <https://orcid.org/0000-0002-7164-612X>

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SUPPORTING INFORMATION

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