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ORIGINAL RESEARCH ARTICLE

Identifying Maternal Conditions Leading to Gabapentinoid Prescriptions in Pregnancy Using Electronic Health Records from Six European Countries: A Contribution from the IMI ConcePTION Project

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Abstract

Introduction and Objective Given the recent increase in the prescription and dispensation of gabapentinoids (gabapentin and pregabalin) and the importance of controlling for underlying maternal illnesses in drug safety studies, we aimed to develop algorithms for identifying maternal conditions leading to gabapentinoid prescribing among pregnant women using data from six electronic healthcare data sources across Europe.

Methods The study was conducted in Finland, France (Haute-Garonne), Italy (Emilia Romagna), Norway, Spain (Valencian region), and Wales (UK), covering three million pregnancies from 2006 to 2020. Algorithms were developed to detect epilepsy, neuropathic pain, and generalized anxiety disorder (GAD) (approved indications for gabapentinoids by the European Medicines Agency, with the exception of gabapentin for GAD) using data ± 1 year around the gabapentinoid prescription date. Data included prescriber specialty, primary and specialized health care diagnoses, and co-prescription/dispensation data. Additional analyses investigated potential unlicensed indications (such as fibromyalgia, restless legs syndrome, bipolar disorder) and potential for abuse (using codes for substance use disorders and alcohol withdrawal).

Results Gabapentinoids were prescribed/dispensed in 1770 pregnancies (7.7 per 1000) in Spain, 2912 pregnancies (6.6 per 1000) in Wales, 3163 pregnancies (3.6 per 1000) in Norway, 2406 pregnancies (3.0 per 1000) in Finland, 908 pregnancies (2.2 per 1000) in Italy, and 269 pregnancies (1.9 per 1000) in France. A maternal condition related to gabapentinoid prescriptions was identified by the algorithm in 2797 (88.4%) in Norway, 2180 (74.9%) in Wales, 1269 (71.7%) in Spain, 1534 (63.8%) in Finland, 163 (60.6%) in France, and 396 (43.6%) pregnancies in Italy. Anxiety (licensed or unlicensed) was the most commonly captured condition in Wales (70.5%), Spain (51.5%), Finland (42.0%), and Italy (26.2%), whereas neuropathic pain prevailed in Norway (76.9%) and France (49.8%). Epilepsy was the least frequent maternal condition leading to gabapentinoid prescriptions across all data sources (below 15% of all pregnancies). The relative preponderance of these conditions differed between pregabalin and gabapentin. Additionally, unlicensed indications were captured in 0% to 13% of pregnancies, depending on the data source. The analyses of potential for abuse showed that records of alcohol withdrawal and/or substance use disorders (within 1 year before and after the gabapentinoids prescription/dispensation date) were present in 3% of pregnancies in Italy and up to 23% in Wales.

Conclusions Our study provides valuable insights into gabapentinoid use during pregnancy, with anxiety being the most common condition among pregnant women with gabapentinoid prescriptions in Finland, Italy, Spain, and Wales, whereas neuropathic pain predominated in France and Norway. Moreover, we found that between 3 and 23% of these pregnancies were associated with substance abuse, underscoring the need for careful prescribing of commonly abused medicines. The proposed methods for detecting maternal conditions leading to prescribing will facilitate accurate assessment of medication use and safety during pregnancy, whilst addressing confounding by indication.

Extended author information available on the last page of the article

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Key Points

Gabapentinoids were most prescribed for anxiety in Finland, Italy, Spain, and Wales, and for neuropathic pain in France and Norway.

Our method enhances evaluation of medication use and safety during pregnancy.

1 Introduction

In studies evaluating the safety of prescribed medicines during pregnancy, it is important to distinguish between the effects of medications and those of maternal illness. Maternal conditions *per se* may be associated with distinct risks to the pregnancy and fetus/newborn, regardless of the medications administered. This is particularly meaningful for medications with several indications [3], where the risk of adverse pregnancy outcomes may vary according to the underlying maternal condition. The difficulty in separating the effect of the medications from the effect of the underlying disease and co-prescriptions represents a critical challenge in the interpretation of pregnancy medication safety studies, due to potential confounding by indication. Identifying the maternal conditions that motivate the prescriptions provides an opportunity to include pregnant women with the same condition but different or no treatment as comparison groups.

In data sources commonly used in pharmacoepidemiology such as electronic healthcare record (EHR) databases, determining the reason for medication use is challenging. These data sources do not typically capture the reason for treatment in a structured or standardized manner, and usually no electronic link exists between prescription and the condition for which it was issued. Therefore, determination of combinations of characteristics using data from primary care records, in- or out-patient diagnoses, prescriber specialty, and co-medications is required [4, 5].

Gabapentinoids (gabapentin and pregabalin) are GABA (gamma-aminobutyric acid) analogues. These compounds interact with multiple targets in neurons. They bind with high affinity to a protein in cortical membranes with an amino acid sequence identical to that of the α*2*-δ1 subunit of Ca*V*, the voltage-gated Ca^{2+} channel [6], thereby reducing nerve cell excitability in the brain. In Europe, both are licensed for epilepsy and neuropathic pain and pregabalin is also licensed for generalized anxiety disorder. Their use has markedly increased since 2000 [7]. This might be due to increased use for unlicensed indications, such as non-neuropathic pain or other mental health conditions or their abuse potential, particularly among patients with a history of substance misuse disorder [8–11]. A study showed a marked increase of use of gabapentin, especially in the US [12]. In the United Kingdom, the prescribing of pregabalin and gabapentin has increased markedly among pregnant women, from around 0.3 per 1000 in 2007 to 2.5–3.0 per 1000 in 2016, with about one-seventh of prescriptions likely intended for pain management [13]. A less pronounced increase was observed in France (the prevalence of pregabalin rose from 0.5 to 1.2 per 1000 over the same period) [13]. Despite the increasing use of gabapentinoids during pregnancy, little is known about the specific conditions for which pregnant women are prescribed these medications.

Recent studies reported associations between gabapentin and pregabalin use during pregnancy and adverse pregnancy outcomes, including overall major congenital anomalies, specific anomalies, fetal deaths, preterm birth, small-for-gestational age, and some specific neurodevelopmental outcomes [14–21], prompting regulatory agencies to advise against pregabalin use during pregnancy, unless the benefit clearly outweighs the risk to the fetus [22], whilst the British National Formulary indicates that manufacturers advise avoiding gabapentin "unless benefits outweighs risk—toxicity reported" [23]. Given the increased use of gabapentinoids during pregnancy and concerns about their risks in pregnancy, it is crucial to understand the reasons for prescription to support safer treatment choices.

The objective of this study was to develop algorithms for identifying maternal conditions leading to gabapentinoid prescriptions among pregnant women using data from six electronic healthcare data sources across Europe.

2 Material and Methods

2.1 Participating Data Sources

The study used healthcare data from six European countries: Finland, France, Italy, Norway, Spain, and Wales (UK). Detailed information on the data sources is given in eTable 1 (see electronic supplementary material [ESM]). Briefly, in Finland and Norway, data are from national EHR databases including patient, birth, prescription, and primary and secondary care registries, linked at the individual level by a unique national person identifier. In France, data are from the population-based EFEMERIS cohort of pregnant women living in Haute-Garonne containing data on pregnancy characteristics, outcomes, and child health. In Italy (Emilia Romagna) and Spain (Valencian region), data originated from regional administrative

health registries, including hospital and specialist care contacts (only for the Italian data source) and dispensed medicines in community and hospital pharmacies for outpatient use. In Wales (UK), data are from the SAIL databank, covering primary care, hospital (in-patient) contacts, and prescribed medicines as recorded in primary care.

Prescription and diagnosis data were complete for the entire observation period in Italy, Norway, Spain, and Wales. However, the length of the observation period varied between data sources. In Finland, prescription data were available from 3 months before pregnancy to 3 months after, whereas other Finnish registers covered the entire study period. In France, prescription data were available from 2.5 months before the pregnancy until the end of pregnancy, with maternal diagnoses (from inpatient data) recorded only during pregnancy (Table 1).

2.2 ConcePTION Distributed Network

All data sources (data access providers; DAPs) mapped their data into the ConcePTION common data model (CDM) [24], enabling standardized analytics and tools across the network. However, as the CDM is not fully syntactically harmonized, queries had to be adapted to local variables and coding systems. The analytic code was developed in R (The R Project, version 4.3.1) by a programmer and tested on the French data source (EFEMERIS). Programming accuracy was ensured through independent double coding in SAS. Each DAP executed the study code locally on their databases containing patient-level data, debugging and benchmarking the data before uploading aggregated results to the Medical University of Utrecht remote research environment (DRE), compliant with General Data Protection Regulation requirements. Each DAP obtained governance approval for the study. Final results were combined into tables and figures. Counts of 1 to 4 were masked; 0 was not.

2.3 Study Population

The study period ran from January 1, 2006 to December 31, 2020 (Table 1). Pregnancy episodes were identified using the ConcePTION pregnancy algorithm, which provided pregnancy outcomes and estimates of the pregnancy start date (corresponding to the last menstrual period [LMP] date) and pregnancy end date [25].

In the data sources, we identified the medications of interest using the Anatomical Therapeutic Chemical (ATC) codes N03 AX16 (pregabalin) and N03 AX12 (gabapentin).

A pregnancy was included if (i) the pregnancy start and end dates fell within the study period; (ii) the woman was aged between 15 and 49 years at the LMP date; (iii) at least one prescription/dispensation for pregabalin or gabapentin was recorded within 2.5 or 12 months before LMP date until the end of pregnancy. Additionally, for data sources with long-term follow-up (Norway and Wales), we required at least 12 months of available data both before and after the prescription/dispensation date of pregabalin or gabapentin.

Pregnancy types varied by data source. In Finland, pregnancies were limited to terminations of pregnancy, stillbirths, and live births. In France and Italy, pregnancies

Table 1 Study period and study population

Country *Coverage*	Study period	Data coverage	No. of pregnancies of women between 15 and 49 years of age at LMP date
Finland *National*	01/01/2006–31/12/2018	Prescription data: From 3 months before LMP date to 3 months after end of pregnancy date Other data: all years	812,554
France *Haute-Garonne region*	01/01/2006–31/12/2020	Prescription data: From 2.5 months before LMP date to end of pregnancy date Other data: during pregnancy	143,916
Italy *Emilia Romagna region*	01/01/2011–31/12/2020	All years	407,568
Norway *National*	01/01/2009–31/12/2019	All years	871,163
Spain *Valencian region*	01/01/2014–31/12/2020	All years	230,596
UK *Wales country* *All women from the 85% of primary care practices contributing data to the national databank (SAIL)*	01/01/2006–31/12/2020	All years	440,621

LMP last menstrual period

included ectopic pregnancies, spontaneous abortions, terminations of pregnancy, stillbirths, other non-live births (a non-live birth for which the type could not be determined), and live births. In Norway, pregnancies included spontaneous abortions, terminations of pregnancy, stillbirths, other non-live births, and live births. In Spain, only stillbirths and live births were present. In Wales, data on spontaneous abortions and terminations of pregnancy were redacted by Digital Health Wales, except for pregnancies complicated by congenital anomalies. For cases of early pregnancy termination, when the LMP date was not available, it was imputed using a random forest prediction model. However, data from France was derived from an existing cohort of pregnant women in which the start of pregnancy was already estimated. In this cohort, when the LMP date was missing, it was estimated by subtracting the mean gestational age of this type of event from the event date [25].

We excluded ongoing and lost-to-follow-up pregnancies in all data sources.

2.4 Description of the Algorithm to Detect the Maternal Conditions Leading to Prescriptions

Expanding on previous work on antiseizure medications [5, 13], we developed algorithms utilizing all available information in the data sources to detect maternal conditions that motivate gabapentinoid prescriptions.

2.4.1 Maternal Conditions

We identified the European Medicines Agency (EMA)-approved indications for gabapentin as epilepsy and neuropathic pain, and for pregabalin as epilepsy, neuropathic pain, and generalized anxiety disorder. In our main analyses, we considered these three conditions as potential maternal conditions leading to gabapentinoid prescribing, despite gabapentin not being approved for generalized anxiety disorder. Additionally, we conducted further analyses to explore unlicensed use (indications not approved by regulatory agencies), including restless legs syndrome, bipolar disorder, insomnia, fibromyalgia, pruritus, and multiple sclerosis.

2.4.2 Identification of Data Components

We used the following data components as markers of prescribing: prescription/dispensation data (indication for reimbursement of medication and prescriber specialty) maternal diagnostic data (primary care diagnoses, in- and outpatient diagnoses, and emergency contact diagnoses), and co-prescription/dispensation data. Table 2 shows the availability of these data components in the data sources.

2.4.3 Identification of Credible Markers as Proxies for Maternal Conditions

In each data component, we searched for codes enabling the identification of the conditions of interest in the individual-level data. The general definition of the conditions is described in Table 3 and specific data source derivation is presented in eTable2 (see ESM). Identification of the appropriate codes for the conditions was based on the literature and discussion with the clinical expert and representatives from the data sources. Coding system and coding practice varied by data source; hence we developed data source-specific markers.

2.4.4 Assignment of Maternal Condition(S) Leading to Gabapentinoid Prescription/Dispensation

Figure 1 shows the assignment algorithm. The algorithm first searched for maternal conditions using the data components 'indication for reimbursement of medication' and 'prescriber specialty' on the date of the gabapentinoid prescription/dispensation. If no markers were found, the search extended to 1 year before and 1 year after the gabapentinoid prescription/dispensation date, covering other components—'primary care diagnoses', 'inpatient diagnoses', 'outpatient diagnoses', 'emergency contact diagnoses', and 'co-medications'.

If at least one marker was detected in any of these components, the corresponding condition(s) were recorded for the gabapentinoid prescription/dispensation. If no markers were found, the maternal condition was classified as 'none', indicating that the algorithm did not identify epilepsy, neuropathic pain, or anxiety within the search window. The classification was not mutually exclusive, meaning a pregnant woman could have multiple conditions. We also reported the number of pregnancies where only one condition was detected.

2.4.5 Additional Analyses Exploring Multiple Assessment Windows and Coding Values

We conducted additional analyses to mainly investigate the pregnancies having no marker for any of the three conditions in the main analysis. First, we conducted an analysis including two additional categories for the reasons for gabapentinoid prescription/dispensation: potential other use (including restless legs syndrome, bipolar disorder, insomnia, fibromyalgia, pruritus, and multiple sclerosis) and potential for substance abuse, using codes for alcohol withdrawal and substance use disorders (detailed codes provided in Table 3). Second, given the lack of specific codes for neuropathic pain

Table 2 Type of data available in the participating data sources

Country *Coverage*	Health care setting	Source for medication data	Presence of data components						
			Indication for reimbursement of medication	Prescriber specialty	Primary care diagnoses data	Inpatient diagnoses data	Outpatient diagnoses data	Emergency contact diagnoses data	Co-medications
Finland *National*	Primary care, out- and in-patient specialist care	Dispensed medicines in community pharmacies	Yes (only epilepsy)	Yes	Yes	Yes	Yes	No	Dispensed
France *Haute-Garonne region*	Inpatient specialist care	Prescribed and dispensed medicines in community pharmacies	No	Yes	No	Yes	No	No	Dispensed
Italy *Emilia Romagna region*	Out- and in-patient specialist care	Dispensed medicines in community and hospital pharmacies (for outpatient use)	No	No	No	Yes	Yes	Yes	Dispensed
Norway *National*	Primary care, out- and in-patient specialist care	Dispensed medicines in community pharmacies	Yes (only epilepsy)	Yes	Yes	Yes	Yes	No	Dispensed
Spain *Valencian region*	Inpatient specialist care	Dispensed medicines in community and hospital pharmacies (for outpatient use)	No	No	No	Yes	No	No	Dispensed
UK *Wales country*	Primary care, including specialist-initiated prescriptions, secondary care admissions	Prescribed medicines as recorded in primary care, from GP and specialists	No	NR (all GPs and non-medical prescribers)	Yes	Yes	Yes	Yes	Prescribed

NR not relevant, *GP* general practitioner in primary care

in EHR data, we broadened the diagnostic codes to capture conditions with common neuropathic pain etiologies (codes provided in eTable 3, see ESM). Third, we tested the following different timeframes for identifying maternal conditions: (i) only 1 year before gabapentinoid prescription/dispensation date, (ii) ±2 years from gabapentinoid prescription/dispensation date, and (iii) any time during the study period.

2.5 Statistical Analyses

The unit of analysis was a pregnancy, that is, women could contribute with multiple pregnancies in the analysis. Prevalence of exposure was reported with 95% confidence interval (CI) using the Wilson score method. The proportions of pregnancies where gabapentin and pregabalin were prescribed/dispensed for different maternal conditions were tabulated. Pregabalin and gabapentin were analyzed together and separately.

2.6 Ethics

The study received all required approvals as part of the ConcePTION project, or was reported to the national data authority, according to local requirements of the participating countries (as detailed in the specific Statements and

Table 3 General definitions of maternal conditions

Condition	General definitions
Epilepsy	One of the following: • Specific reimbursement entitlements for people with epilepsy, OR; • Diagnostic codes: ICPC-2 code for epilepsy (N88, N07), OR; ICD-9 code for epilepsy (345.xx, 780.3x), OR; ICD-10 code for epilepsy (G40, G41), OR; ICD-10ES code for epilepsy (R56.9, R56.1, F44.5), OR; READ code for epilepsy (F25, 1O30, 667B), OR; • Co-prescribing/dispensing of antiseizure medication other than carbamazepine (see **eTable2** in the ESM for specific derivation per data source)
Neuropathic pain	One of the following: • Specific prescriber specialty of the gabapentinoid prescription (see **eTable2** in the ESM for specific derivation per data source), OR; • Diagnostic codes: ICPC-2 code for pain (A01, L86), OR; ICD-9 code for pain (see **eTable2** for specific derivation per data source), OR; ICD-10 code for pain (see **eTable2** for specific derivation per data source), OR; ICD-10ES code for pain (see **eTable2** for specific derivation per data source), OR; READ code for neuropathic pain (see **eTable2** for specific derivation per data source), OR; • Pain specific co-prescribing/dispensing (see **eTable2** for specific derivation per data source)
Generalized anxiety disorder	One of the following: • Specific prescriber specialty of the gabapentinoid prescription (see **eTable2** in the ESM for specific derivation per data source), OR; • Diagnostic codes: ICPC-2 code for anxiety (P01, P02, P74), OR; ICD-9 code for anxiety (300.0, 300.00, 300.02, 300.09, 309.21), OR; ICD-10 code for anxiety (F40, F41, F42, F43), OR; ICD-10ES code for anxiety (F40, F41, F42, F43), OR; • READ code for anxiety (E20., Eu40., Eu41., Eu34114), OR; • Anxiety specific co-prescribing/dispensing (see **eTable2** for specific derivation per data source)
Other	
Potential other use (known as unlicensed use in Europe)	• Diagnostic codes: • ICD-10 codes for fibromyalgia (M79.7), restless legs syndrome (G25.81), bipolar disorder (F31), insomnia (F51.0, G47.0), pruritus (L29), menopause (N95), multiple sclerosis (G35), motor neurone diseases (G12.2), OR; • ICD-9 codes for fibromyalgia (729.1), restless legs syndrome (333.94), bipolar disorder (296.0, 296.4, 296.5, 296.6, 296.7, 296.80, 296.89), insomnia (327.0, 307.4, 293.85), pruritus (698.0, 698.1, 698.8, 698.9), menopause (627), multiple sclerosis (340), motor neurone diseases (335.2)
Potential for abuse	• Diagnostic codes: ICD-10 codes for alcohol withdrawal (F10), substance use disorders (F11-F19, Z71.4–5), OR; ICD-9codes for alcohol withdrawal and substance use disorders (305, 304, 303, 291, V65.42)

ESM electronic supplementary material

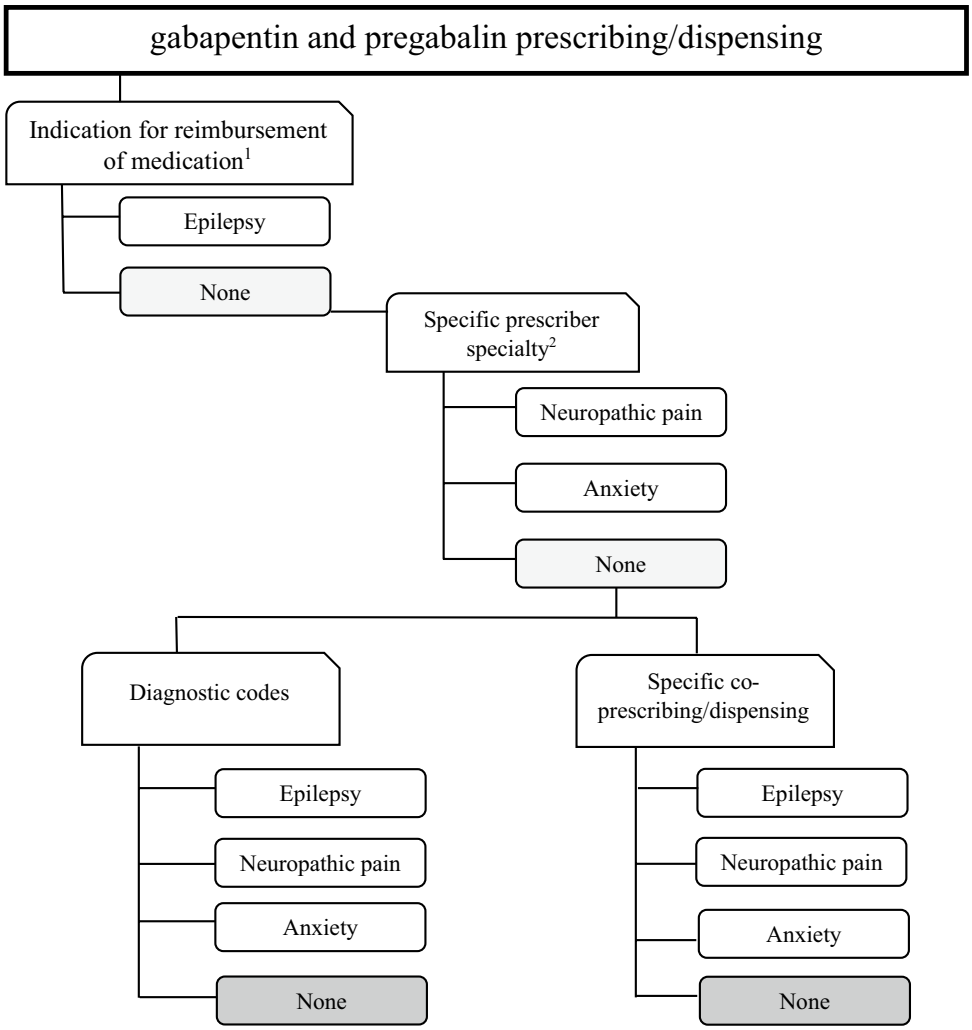

Fig. 1 Algorithm to assign potential maternal conditions leading to gabapentin and pregabalin prescriptions. [1]Available in Finland and Norway to identify epilepsy. [2]Available in Finland, France and Norway to identify neuropathic pain and anxiety

Declarations section). The study protocol was registered in the EUPAS Registry (EUPAS43385) and is available from the Zenodo repository [2]. All code lists and scripts are available from the Zenodo repository [1].

3 Results

Across all six databases, our study reports on data from 2,906,418 pregnancies. The size of the individual participating data sources varied from the smallest (in France; 143,916 pregnancies), to the largest (in Norway; 871,163 pregnancies) (Table 1).

From up to 1 year before pregnancy until end of pregnancy, 1770 (7.7 [95% CI 7.3–8.0] per 1000) in Spain, 2912 pregnancies (6.6 [95% CI 6.4–6.9] per 1000) in Wales, 3163 (3.6 [95% CI 3.5–3.8] per 1000) in Norway, 2406 (3.0 [95% CI 2.8–3.1] per 1000) in Finland, 908 (2.2 [95% CI 2.1–2.4] per 1000) in Italy, and 269 (1.9 [95% CI 1.7–2.1] per 1000) in France were prescribed/dispensed gabapentinoids (Fig. 2). In all data sources, except in Norway and Wales, pregabalin was prescribed/dispensed more than gabapentin (Fig. 3).

3.1 Main Analysis

In the main analysis, considering data from 1 year before to 1 year after each gabapentinoid prescription/dispensation date, at least one of the three maternal conditions of interest (epilepsy, anxiety, or neuropathic pain) was identified in 3244 (88.4%) in Norway, 2180 (74.9%) in Wales, 1269 (71.7%) in Spain, 1534 (63.8%) in Finland, 163 (60.6%) in France, and 396 pregnancies (43.6%) in Italy among those exposed to gabapentinoids (Table 4). When analyzing gabapentin and pregabalin separately, the frequency of recorded conditions varied: a higher frequency of detection of the three maternal conditions (epilepsy, anxiety, or neuropathic pain) was observed with gabapentin in Italy and Spanish data, whereas a higher frequency of capture was observed with pregabalin in Finland, Norway, and Wales (Table 4).

Anxiety was the most common captured condition in Wales (70.5%), Spain (51.5%), Finland (42.0%), and Italy (26.2%), whereas neuropathic pain prevailed in Norway (76.9%) and France (49.8%) (Table 4). Anxiety was detected less often with gabapentin than with pregabalin in Wales (65.7% vs 78.8%), Norway (45.3% vs 54.7%), Finland (34.2% vs 44.5%), and in France (18.6% vs 24.0%). However, it was the opposite in Spain (62.1% vs 49.5%) and Italy (27.6% vs 25.5%) (Table 4). Epilepsy was the least frequent maternal condition identified in relation to gabapentinoid prescriptions, ranging from 6.3% (France) to 15.0% (Finland).

Furthermore, anxiety was the sole identified maternal condition in 15.5% to 84.1% of pregnancies with gabapentin prescriptions and in 18.6% to 82.5% with pregabalin, with the lowest percentage observed in Norway and the highest in Wales. Finally, neuropathic pain was the only captured condition in 29.1% to 68.2% of pregnancies where gabapentin was prescribed and in 27.0% to 68.4% with pregabalin, with the lowest percentage in Spain or Wales and the highest in France.

Table 5 shows the contribution of various data components to the identification of maternal conditions leading to gabapentinoid prescribing across the data sources. Comedication data emerged as the most influential component, varying from 77.1% in Finland to 99.3% in Spain. When available, primary care data represented the second largest contributor to recording these conditions, ranging from 36.9% in Finland to 61.3% in Norway. Hospital data, encompassing in- and outpatient, and emergency care data, had a variable impact across data sources. Moreover, the prescriber specialty data, when available, played a discernible role, contributing from 8.3% in Finland to 14.1% in France.

3.2 Additional Analyses

In our first additional analysis, we found that including the categories 'other use' (unlicensed use: indications not approved by regulatory agencies) and 'abuse' as potential reasons for prescribing augmented the identification of any potential use. The increase was particularly marked in Wales (increasing from 74.9 to 78.8%) and Finland (increasing

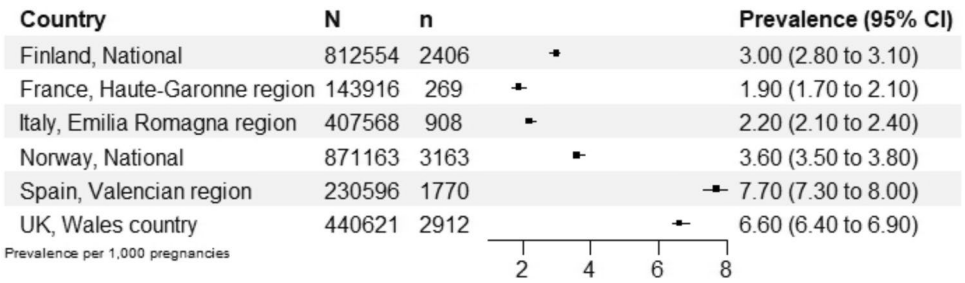

Fig. 2 Gabapentinoids prescribed/dispensed (from 1 year before pregnancy until end of pregnancy). In the participating data sources: number of pregnancies (*N*), number of exposed pregnancies (*n*), prevalence (95% CI) per 1000 pregnancies. In the Finnish and French data sources, gabentinoids prescription/dispensation was assessed from 3 months and 2.5 months before last menstrual period date until end of pregnancy, respectively. *CI* confidence interval

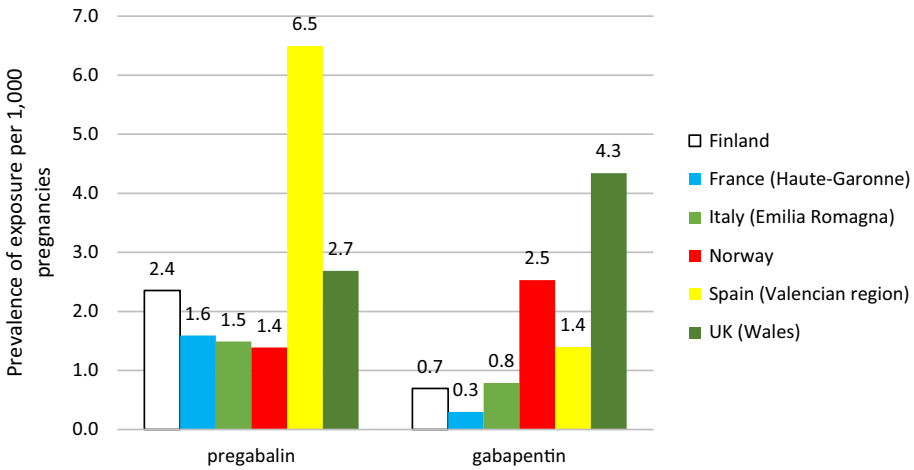

Fig. 3 Prevalence of pregabalin and gabapentin prescription/dispensation from 1 year before pregnancy until end of pregnancy (per 1000 pregnancies). In the Finnish and French data sources, gabapentinoids prescription/dispensation was assessed from 3 months and 2.5 months before last menstrual period date until end of pregnancy, respectively

from 63.8 to 68.1%) and more marginal in the other data sources (Table 6). 'Other use', including restless legs syndrome, bipolar disorder, insomnia, fibromyalgia, pruritus, and multiple sclerosis, ranged from 3.1% of pregnancies in Italy to 12.8% in Finland. Additionally, potential for abuse, as indicated by codes related to substance use disorders and alcohol withdrawal, was identified in up to 22.6% and 16.7% of pregnancies in Wales and Finland, respectively (Table 6).

In our second additional analysis, aimed at identifying neuropathic pain using diagnostic codes, we observed a significant increase in its capture across the data sources (see online resources eTable 4 to eTable 9 in the ESM). For instance, in Finland, the proportion of pregnancies with neuropathic pain increased from 31.5% in the main analysis to around 50%, and in Wales from 9.9% to around 30%, with less pronounced changes in the other data sources.

In our third additional analysis, the window of assessment for maternal conditions leading to gabapentinoid prescribing was extended to 2 years before or after prescription/dispensation date and to any time during the study period. This resulted in an increased detection of maternal conditions across all the data sources (see eFigure 1 in the ESM). The magnitude of the increase varied across sources, with more substantial changes observed in Finland, Wales, and Norway. When examining the impact on individual conditions, the capture of anxiety increased more markedly compared with epilepsy (which remained largely unchanged across sources) or neuropathic pain (where only marginal changes were observed).

4 Discussion

4.1 Principal Findings

Our study aimed to identify maternal conditions leading to gabapentinoid prescribing among pregnant women using EHR data across Europe. Although our study focuses on pregnant women, condition identification relied, also, on data from periods outside of pregnancy. Nevertheless, differences in healthcare utilization patterns between pregnant women and the general female population may still limit generalizability [5, 13]. Using markers within various data components, including prescriber specialty, primary

Table 4 Proportions of maternal conditions leading to gabapentinoid prescriptions from 1 year before to the end of pregnancy[a]

Maternal condition[b]	Participating data sources, n (%)					
	Finland *National*	France *Haute-Garonne*	Italy *Emilia Romagna*	Norway *National*	Spain *Valencian region*	UK *Wales*
Any gabapentinoids	*N* = 2406	*N* = 269	*N* = 908	*N* = 3163	*N* = 1770	*N* = 2912
Any conditions[c]	1534 (63.8)	163 (60.6)	396 (43.6)	2797(88.4)	1269 (71.7)	2180 (74.9)
Anxiety[d]	1011 (42.0)	62 (23.0)	238 (26.2)	1538 (48.6)	911 (51.5)	2054 (70.5)
Neuropathic pain[d]	759 (31.5)	134 (49.8)	165 (18.2)	2431 (76.9)	827 (46.7)	288 (9.9)
Epilepsy[d]	360 (15.0)	17 (6.3)	122 (13.4)	372 (11.8)	176 (9.9)	206 (7.1)
Gabapentin	*N* = 564	*N* = 43	*N* = 322	*N* = 2203	*N* = 322	*N* = 1913
Any conditions[c]	339 (60.1)	26 (60.5)	148 (46.0)	1930 (87.6)	259 (80.4)	1349 (70.5)
Anxiety (any use is unlicensed)[d]	193 (34.2)	8 (18.6)	89 (27.6)	997 (45.3)	200 (62.1)	1256 (65.7)
Neuropathic pain[d]	201 (35.6)	22 (51.2)	56 (17.4)	1711 (77.7)	151 (46.9)	197 (10.3)
Epilepsy[d]	81 (14.4)	5 (11.6)	49 (15.2)	237 (10.8)	65 (20.2)	110 (5.8)
Pregabalin	*N* = 1913	*N* = 229	*N* = 607	*N* = 1211	*N* = 1498	*N* = 1184
Any conditions[c]	1251 (65.4)	139 (60.7)	265 (43.7)	1102 (91.0)	1052 (70.2)	978 (82.6)
Anxiety[d]	852 (44.5)	55 (24.0)	155 (25.5)	662 (54.7)	742 (49.5)	933 (78.8)
Neuropathic pain[d]	594 (31.1)	114 (49.8)	118 (19.4)	940 (77.6)	705 (47.1)	115 (9.7)
Epilepsy[d]	297 (15.5)	13 (5.7)	81 (13.3)	169 (14.0)	120 (8.0)	105 (8.9)

LMP last menstrual period

[a]In the Finnish and French data sources, gabapentinoid prescription/dispensation was assessed from 3 months and 2.5 months before LMP date until end of pregnancy, respectively

[b]Assessed ±1 year from each gabapentinoid prescription/dispensing date

[c]Pregnancies where the woman did have at least one condition (epilepsy, anxiety, or neuropathic pain) related to gabapentinoid prescriptions

[d]Pregnancies in these categories are not mutually exclusive; the percentages may total more than 100%, as a woman may have >1 condition

Table 5 Contribution of individual data component in the detection of maternal conditions leading to gabapentinoid prescribed/dispensed from 1 year before pregnancy until end of pregnancy[a]

Data component[b]	Participating data sources, n (%)					
	Finland *National* $N = 2406$	France *Haute-Garonne* $N = 269$	Italy *Emilia Romagna* $N = 908$	Norway *National* $N = 3163$	Spain *Valencian region* $N = 1770$	UK *Wales* $N = 2912$
Any maternal conditions identified	1534 (100)	163 (100)	396 (100)	2791 (100)	1269 (100)	2180 (100)
Indication for reimbursement of medication[c]	60 (3.9)	NA	NA	30 (1.1)	NA	NR
Prescriber specialty[d]	127 (8.3)	23 (14.1)	NA	240 (8.6)	NA	NR
Primary care diagnoses data	566 (36.9)	NA	NA	1715 (61.3)	NA	830 (38.1)
Inpatient diagnoses data	232 (15.1)	13 (8.0)	64 (16.2)	241 (8.6)	95 (7.5)	573 (26.3)
Outpatient diagnoses data	579 (37.7)	NA	19 (4.8)	642 (23.0)	NA	NA
Emergency contact diagnoses data	NA	NA	47 (11.9)	NA	NA	NA[e]
Co-medication data	1183 (77.1)	159 (97.5)	355 (89.6)	2575 (92.1)	1260 (99.3)	2039 (93.5)

All prescriptions are issued by the GP or a non-medical prescriber

GP general practitioner, *LMP* last menstrual period, *NA* not available, *NR* not relevant

[a]In the Finnish and French data sources, gabapentinoid prescription/dispensation was assessed from 3 months and 2.5 months before LMP date until end of pregnancy, respectively

[b]The percentages may total more than 100%, as pregnancies may be in more than 1 category

[c]Finland and Norway: epilepsy

[d]Finland and Norway: neuropathic pain; France: neuropathic pain and anxiety

[e]Reported within the inpatient diagnoses data

and specialized health care diagnoses, and prescribed/dispensed co-medications, we identified maternal conditions for 43–90% of pregnancies. Detection improved when the assessment window was extended. Epilepsy was the least frequently captured maternal conditions across all data sources, falling below 15%. Conversely, anxiety was the most common maternal condition captured in Wales, Spain, Finland, and Italy, whereas neuropathic pain predominated in Norway and France. Further analyses suggested unlicensed use in 0–13% of pregnancies depending on the data sources. Analyses also suggested potential for abuse of gabapentinoids in 3–23% depending on the data sources. These findings emphasize the importance of comprehensive data to better understand prescribing practices and potential areas of concern.

4.2 Differences in Prevalence of Gabapentinoid Prescription/Dispensation Between European Countries

Almost three million pregnancies were identified in six data sources, including 11,428 pregnancies where gabapentinoids were prescribed/dispensed (3.9 [95% CI 3.9–4.0] per 1000). This prevalence varied by country, ranging from 1.9 per 1000 in France to 6.6 and 7.7 per 1000 in Wales and Spain, respectively. Our results align with previous studies in Europe [12–16] showing higher prevalence in the UK compared with other European countries in the most recent years [13]. The lower prevalence in Finland and France was expected as medication data were only available from a shorter period before pregnancy, compared with 1 year in the other countries. We also observed differences between specific medications; pregabalin was dispensed/prescribed more often than gabapentin in Finland, France, Italy, and Spain, whereas the opposite was observed in Norway and Wales. Similar patterns were reported in previous studies for the UK, France, and Italy [7, 13, 15, 26].

4.3 Differences in Maternal Conditions Leading to Gabapentinoid Prescribing Between European Countries

The literature on potential indications for use of gabapentinoids among pregnant women is limited and methods greatly varied, making comparisons challenging. Gabapentinoids are rarely used for epilepsy [11], which our study confirms. Previous findings have reported gabapentinoid use for epilepsy in around 6–7% of pregnancies in US data [17, 19] and from 1.5 to 6.6% in European data [7, 14, 15, 18, 27, 28]. Although epilepsy was the least frequently identified condition, exact figures varied from 6.3% and 7.1% of pregnancies in France and Wales to 14.0% and 15.0% in Italy and Finland, respectively.

Data on neuropathic pain and anxiety are scarce. A Nordic study reported neuropathic pain in 16% and 7.5% of

Table 6 Proportions of different potential reasons for prescribing amongst pregnant women where gabapentinoids were prescribed/dispensed from 1 year before pregnancy until end of pregnancy[a]

Potential reasons documented[b]	Participating data sources, n (%)					
	Finland *National* N = 2406	France *Haute-Garonne* N = 269	Italy *Emilia Romagna* N = 908	Norway *National* N = 3163	Spain *Valencian region* N = 1770	UK *Wales* N = 2912
Any gabapentinoids						
Any potential reasons[c]	1639 (68.1)	166 (61.7)	415 (45.7)	2831 (89.5)	1293 (73.1)	2295 (78.8)
Anxiety[d]	1011 (42.0)	62 (23.0)	238 (26.2)	1538 (48.6)	911 (51.5)	2054 (70.5)
Neuropathic pain[d]	759 (31.5)	134 (49.8)	165 (18.2)	2431 (76.9)	827 (46.7)	288 (9.9)
Epilepsy[d]	361 (15.0)	17 (6.3)	122 (13.4)	372 (11.8)	176 (9.9)	206 (7.1)
Other use[d]	309 (12.8)	0	30 (3.3)	143 (4.5)	37–42 (2.1–2.4)[e]	245 (11.9)
Potential for abuse[d]	403 (16.7)	14 (5.2)	27–32 (3.0–3.5)[e]	296 (9.4)	150 (8.5)	657 (22.6)

LMP last menstrual period

[a]In the Finnish and French data source, gabapentinoids prescription/dispensation was assessed from 3 months and 2.5 months before LMP date until end of pregnancy, respectively

[b]Assessed ±1 year from each gabapentinoid prescription/dispensing date

[c]Pregnancies where gabapentinoids were prescribed/dispensed, where the woman did have at least one potential reason documented (epilepsy, anxiety, neuropathic pain, other use, or potential misuse)

[d]Pregnancies in these categories are not mutually exclusive; the percentages may total more than 100% as pregnancies may be in more than 1 category

[e]Due to data privacy, exact proportion was not revealed

pregnancies where pregabalin was dispensed in Finland and Norway, respectively, and anxiety in 22% and 8.5% [14]. Our study found higher proportions for both conditions, likely due to the use of multiple data components, which improved the capture of conditions compared with methods relying only on hospital discharge codes.

By including potential diagnoses for unlicensed indications (including fibromyalgia, restless legs syndrome, bipolar disorder, or insomnia), we identified additional cases classified as 'other use'. This varied by country, from 2 to 3% in Spain and Italy to 12% in Finland and Wales. A previous study reported records of migraine in 8.1% and 9.8% of pregnancies where pregabalin was prescribed/dispensed in Norway and Finland, respectively, and records of bipolar disorder in 2.8% of Finnish pregnancies [14]. Another study on UK primary care data (1993–2017) found that when diagnostic codes up to 1 year before the prescription were used, indications were identified for only 60% of the individuals, half of which were considered unlicensed [8]. The high prevalence of 'other use' in Finland and Wales can be attributed to the inclusion of primary care data, where a wider range of conditions are treated. In Finland, gabapentinoids are recommended for fibromyalgia and restless legs syndrome, both common during pregnancy. While not formally indicated for insomnia, they are acknowledged to improve sleep disorders. These conditions (insomnia, fibromyalgia, and restless legs) likely explain the higher prevalence in these countries.

Our additional analyses revealed a concerning proportion of pregnancies with records of substance use disorders and/or alcohol withdrawal (within 1 year before and after the prescription/dispensation date of gabapentinoid), ranging from 3 to 5% in Italy and France to 17–23% in Finland and Wales. These results add to the growing concerns about gabapentinoid abuse worldwide [29–32].

4.4 Analysis of the Methodological Approach

In our main analyses, a notable proportion of pregnancies had no identified maternal conditions leading to gabapentinoid prescribing. This proportion varied greatly across data sources, from 11.6% in Norway to 56.4% in Italy. This can be attributed to several factors: (i) differences in available data components; some data sources, like France and Spain, provided data for only two or three components; (ii) differences in data coverage; France, for instance, only covered from 2.5 months before pregnancy to its end, whereas Norway, Italy, Spain, and Wales had full study period coverage; (iii) variations in how maternal conditions were defined across data sources. These factors likely impacted the algorithm's capacity to detect relevant maternal conditions that motivate prescribing, particularly in Italy, raising concerns about its accuracy when capture rates were low.

In addition, recorded anxiety was observed in many women prescribed gabapentin ranging from 18.6% in France to over 60% in the Spain and Wales. However, gabapentin is not licensed for anxiety in Europe, suggesting possible unlicensed prescribing.

A previous study that was used as a foundation of our methodology [5] reported a higher percentage of neuropathic pain indications for gabapentin and pregabalin. That study classified neuropathic pain by exclusion, if no epilepsy, bipolar, anxiety, or migraine markers were found; this meant no women were left without an identified indication, but at the risk of misclassification. In contrast, our approach did not make such assumptions, leading to a non-negligible proportion of pregnancies with no detected condition.

Similar findings were reported elsewhere. A Swedish study (2005–2009) found no record of approved indication for pregabalin in 60% of individuals [33], using only hospital and primary care data within 1 year of pregabalin prescription. A UK study (1993–2017) found no identified indication for 40% of the individuals, using primary care data up to 1 year before the gabapentinoid prescription [8]. These high percentages observed in both studies might reflect limited data availability, and/or follow-up. However, in Wales, where we integrated hospital discharge diagnoses and co-medications, maternal conditions were identified in 78% of pregnancies using a similar assessment window, suggesting that additional data components improve the capture of maternal conditions. Nevertheless, differences in the study populations may also explain variations. The UK study [8] included a more affluent population than our data from Wales, and pregnant women generally have more frequent contacts with primary care services than the general population due to prenatal monitoring. As in the Swedish study [33], these differences likely contribute to variations in identifying maternal conditions leading to gabapentinoid prescribing.

By integrating multiple data components such as prescriber specialty specialized health care diagnoses, and prescribed/dispensed co-medications, our algorithm improves upon previous methods relying solely on inpatient diagnoses [33]. Our findings suggest that co-medication data may contribute to the identification of maternal conditions leading to gabapentinoid prescribing. However, its use as a proxy remains subject to limitations, particularly regarding the specificity of the identified conditions. The inclusion of primary care data, when available, is particularly valuable for detecting maternal conditions typically managed in this setting. Whereas hospital data are commonly used to identify diseases and infer maternal conditions leading to prescribing, our results show that this component contributes less than co-medications and primary care data. Notably, outpatient data had a greater impact than inpatient data, possibly reflecting the nature of the conditions studied. Indeed, epilepsy, anxiety, and neuropathic pain are chronic conditions primarily managed in primary or specialized care, with few requiring overnight hospitalization. Healthcare system differences in primary care versus outpatient care use may also influence these patterns. Therefore, the contributions of each data component dependents on both the conditions studied and the healthcare settings from which the data originate.

Extending the assessment window improved the recoding of maternal conditions leading to gabapentinoid prescribing in most of the data sources, with variations by condition. Epilepsy detection remained stable, whereas anxiety detection increased. As a chronic condition, epilepsy is unlikely to be affected by the length of the assessment window, and extending it beyond 1 year did not identify additional cases. However, a longer assessment period may increase the detection of co-morbidities, such as anxiety, and misattribute resolved conditions as potential reasons for prescribing.

4.5 Strengths and Limitations

The main strength of the study is its comprehensive and multi-faceted approach to assessing maternal conditions that motivate gabapentinoid prescribing among pregnant women. By integrating multiple data components, such as prescriber specialty, primary and specialized healthcare diagnoses, prescribed/dispensed co-medications, and prospectively recorded data, our study enhanced our understanding of the reasons for gabapentinoids use during pregnancy. Notably, our study includes three million pregnancies identified in six European countries with 11,428 pregnancies with gabapentinoid prescription/dispensations. It covers entire national populations (Finland, Norway, and Wales) as well as regions (Valencian region—Spain, Emilia Romagna—Italy and Haute-Garonne—France). Additionally, the inclusion of data from various countries strengthens the generalizability of the findings throughout, at least, high-income countries.

The main limitation of the study is the absence of detailed clinical data to validate our approach using detailed medical records at the individual level. Whereas data quality is generally high in the Medical Birth Register, prescription databases and hospital discharge records are considered good. However, data quality of primary health care databases may be more challenging as validity of codes have been less studied [34, 35]. Moreover, dispensed medications for inpatient use were not recorded in any of the participating data sources. In addition, identification of early terminations and miscarriage are either impossible or incomplete, leading to an under-estimating of the prevalence of gabapentinoid prescribing/dispensing among pregnant women, especially if medication use is associated with early terminations [18]. Another limitation is that we were unable to distinguish between co-incidental co-morbidities and the true maternal condition driving the prescription, especially for common conditions and unlicensed indications, such as anxiety. Furthermore, coding practices varied both between and within data sources, introducing inconsistencies in the identification and classification of maternal conditions. Differences in data availability across data sources further limit direct

comparisons. Furthermore, the ability of the algorithm to detect maternal conditions depended on the data components available, as seen in Italy and France. Consequently, controlling for indication bias using our approach may be more effective in some data sources than others. Lastly, comparing our findings with other studies is challenging due to multiple factors: (i) differences in data availability; (ii) variation in disease coding; (iii) differences in study periods; (iv) differences in healthcare settings and population demographics; and (v) differences in gabapentinoid prescription patterns over the study period. Consequently, these factors must be considered when interpreting and extrapolating our results.

4.6 Implications

Our results provide a picture of the reasons why gabapentinoids are being prescribed to pregnant women. Understanding the prevalence of different maternal conditions, such as neuropathic pain and anxiety, can help regulatory agencies and health authorities to guide recommendations and decision making. Healthcare providers should carefully consider the potential risks and benefits of prescribing these medications during pregnancy, while also considering alternative treatment options. We found that a non-negligible proportion of women prescribed/dispensed gabapentinoids were at risk of substance or alcohol abuse and dependence, highlighting the need for careful consideration when prescribing gabapentinoids to avoid iatrogenic effects.

Our approach allows for detailed drug utilization analyses according to maternal conditions that could help to explain drivers behind the growing use of gabapentinoids during pregnancy, and further to examine their safety in different maternal contexts. In addition, in cases where diagnostic codes are less specific, integrating multiple data components becomes crucial to improving the detection of these conditions. Notably, incorporating primary care data significantly improved the detection process. This study explores the potential of EHR data as proxies for identifying maternal conditions leading to gabapentinoid prescribing. While our findings suggest that this approach may provide valuable insights, it remains exploratory and subject to limitations, particularly regarding its ability to correctly distinguish true maternal conditions leading to gabapentinoids prescription from unrelated co-medication use.

Lastly, further validation of our approach using detailed individual-level medical records would help strengthen confidence in its accuracy. One potential approach for validation could involve analyzing demographic characteristics and healthcare trajectories within a sample of pregnancies. Maternal conditions may cluster with specific demographic profiles or typical sequences of medical care (e.g., specialist consultations, hospital admissions, prescription patterns). Comparing these elements with clinical expert assessments would allow evaluation of the concordance between algorithm-based classifications and expert judgment.

5 Conclusion

Our study provides valuable insights into gabapentinoid use during pregnancy as we identified the maternal conditions leading to prescribing in a significant proportion of pregnancies. Notably, anxiety and neuropathic pain were the most frequently detected conditions, with anxiety being the most frequently captured in Finland, Italy, Spain, and Wales, whereas neuropathic pain predominated in France and Norway. Additionally, unlicensed indications ranged from 0% to 13%, depending on the data source. Moreover, 3% to 23% of pregnancies involved a risk of abuse, underscoring the need for careful prescribing.

Our study represents a step towards utilizing the extensive data available in EHRs to improve information on reasons for prescribing medications. By proposing methods to detect potential indications for use of medications, our findings illustrate how these data sources can improve evidence on reasons for prescribing. This is important for accurately assessing medication use and safety during pregnancy, by accounting for maternal conditions to address confounding by indication.

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Declarations

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Conflict of interest AG is an employee of Janssen Biologics B.V. and owns stock/stock options in Johnson & Johnson, of which Janssen is a subsidiary. XM has received financial support from Allergan-Abbvie, Amgen-Horizon, Aptyspharma, Biogen, BMS, Grünenthal, Lilly, Lundbeck, Teva, Merck-Serono, Novartis, Orion, Pfizer, Roche, Sanofi-Genzyme, and Sun Pharma and non-financial support from Dr Reddy's and SOS Oxygène not related to the submitted work. JM is an employee of Pfizer Inc. and owns stock/stock options of Pfizer Inc. All other co-authors have no competing interests to disclose.

Ethics approval *Finland:* Ethical approval is not required for register-based studies. The Institutional Review Board at the Finnish Institute for Health and Welfare approved the study and waived the requirement for obtaining informed consent for the secondary use of health administrative data from study participants (THL/543/6.02.00/2021). Data were handled and stored in accordance with the General Data Protection Regulation. *France:* The EFEMERIS cohort was approved by the French Data Protection Authority on 7 April 2005 (authorization number 05-1140). This study was performed on anonymized patient data. The women included in the EFEMERIS database were informed of their inclusion and of the potential use of their anonymized data for research purposes. They could oppose the use of their data at any time. The women included in the EFEMERIS database know that their collected and anonymized data can be used for medical research purposes and can thus be published. The study was approved by the EFEMERIS steering group. Data were handled and stored in accordance with the General Data Protection Regulation. *Italy:* The study was approved by the local ethical committee (approval number 593/2023/Oss/UniFe). Data were handled and stored in accordance with the General Data Protection Regulation and in agreement with the Authority for Healthcare and Welfare, Emilia Romagna Regional Health Service, Bologna, Italy. *Norway:* The study was approved by the Regional Committee for Research Ethics in South-East Norway (approval number 85224) and by the Data Protection Officer at the University of Oslo (approval number 519858). Data were handled and stored in accordance with the General Data Protection Regulation. *Spain (Valencian region):* The study (code: IMI-IMN-2019-01) was classified as an Observational Post-authorization Study "Other designs" (EPA-OD) by the Spanish Medicines Agency (AEMPS), available at: https://sede.aemps.gob.es and approved by the Arnau de Vilanova Hospital's Clinical Research Ethics Committee on 29 th January 2020, according to the Spanish regulations (approval number 1/2020). At a regional level following the national Personal Data Protection and guaranteeing digital rights (Law 3/2018), the study was approved by the Commission of the Regional Government (PROSIGA), which has the right to give RDRU Fisabio authorization to process the data (references: SD2556; SD2577; SD2578; SD2579; SD2580; SD2581; SD2582). *Wales:* This study uses anonymized data held in the Secure Anonymised Information Linkage (SAIL) Databank. The SAIL Databank independent Information Governance Review Panel (IGRP) approved the study as part of project 0823, on 16 th October 2020.

Consent to participate As the data were anonymized, informed consent was not required.

Consent for publication Not applicable.

Code availability All code lists and scripts are available from the Zenodo repository [1].

Author contributions The study was primarily conceived and designed by ABB and CDM. All authors reviewed and provided input on the study protocol. All authors reviewed the statistical analysis plan, assessed the feasibility of statistical analyses against the local data, and provided input for data source-specific tailoring. OP translated the statistical analysis plan, primarily written by ABB, into analysis script. All authors read and approved the final version. *Finland*: ML applied for the study approval and obtained the Finnish data in this study. VM and ML were responsible for the mapping of the Finnish data onto the ConcePTION CDM. VM was responsible for data curation, running scripts on the Finnish data and debugging. ML and MG contributed to data interpretation and benchmarking of the Finnish data in the study. ML reviewed the aggregated Finnish results and approved their upload to the DRE (safe server at UMC). *France*: CDM applied for the study approval and obtained the French data in this study. CDM and ABB were responsible for the mapping of the French data onto the ConcePTION CDM. ABB was responsible for data curation, running scripts on the French data and debugging. CDM, ABB, MB, JB contributed to data interpretation and benchmarking of the French data in the study. ABB reviewed the aggregated French results and approved their upload to the DRE (safe server at UMC). *Spain (Valencian region):* CCC obtained all required approvals—the Spanish Medicines Agency (AEMPS) classification and the Clinical Research Ethics Committee approval, and applied to the Regional Commission (PROSIGA) for the study data. LGV contributed to the reception and adequacy of the data format. LBB developed the mapping to the ConcePTION Common Data Model and executed the analysis scripts. During the script execution, LBB and CCC implemented the data quality assessment according to the study methodology and managed some issues during the process. LGV, CCC, and LBB contributed to data interpretation and the benchmarking of the Valencian region data and approved their upload to the DRE (safe server at UMC). CCC safeguarded custody of the local data into the institutional server. *Wales:* SJ applied for the study data and obtained all required approvals for the Wales data in this study. AC ran and cleaned the scripts. SJ curated and interpreted the data, benchmarked to published data, and approved uploading of aggregated data. *Italy:* EB and AN applied for the study data and obtained all required approvals for the Italian data in this study. AP was responsible for the mapping of the Italian data onto the ConcePTION CDM. MM was responsible for data curation, running scripts on the Italian data and debugging. AP and MM contributed to data interpretation and benchmarking of the Italian data in the study. MM reviewed the aggregated Italian results and approved their upload to the DRE (safe server at UMC). *Norway:* HN applied for the study data and obtained all required approvals for the Norwegian data in this study. HN was responsible for and HM and VRM contributed to data curation for the mapping of the Norwegian data onto the ConcePTION CDM. HN and VRM contributed to data interpretation and benchmarking of the Norwegian data in the study, and HN reviewed the aggregated Norwegian data and approved their upload to the DRE (safe server at UMC). Follow-up of data access providers and data analysis of aggregated data on the DRE was performed by ABB. The first draft of the manuscript was written by ABB and all authors commented on the previous versions of the manuscript. All authors contributed to the interpretation, discussed the results and approved the final version.

Availability of data and material All relevant data are within the paper and its supporting information files. Authors may not share the study

data due to regulations, which restrict access and distribution to those with ethical and legal permission to use the data. The study material is available to other researchers upon an application to relevant register holders. The study protocol was registered in the EUPAS Registry (EUPAS43385) and is available from the Zenodo repository [2]. All code lists and scripts are available from the Zenodo repository [1].

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