Antiseizure meDication Exposure and Pregnancy and neonaTal outcomes research: ADEPT

The utilisation of antiseizure medications in pregnant women, and women and men of childbearing age: a multi-database study from 6 European countries

Study Report Abstract, 24 July 2026

Disclaimer & acknowledgement

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This study has been registered in the HMA-EMA Catalogue of Real-World Data under the EU PAS number: EUPAS1000000212.

Title	The utilisation of antiseizure medications in pregnant women, and women and men of childbearing age (ADEPT): a multi-database study from 6 European countries
Date of last version of report	24 July 2026
EU PAS number	EUPAS1000000212
Active substance	Methylphenobarbital, phenobarbital, primidone, barbexaclone, metharbital, ethotoin, phenytoin, amino(diphenylhydantoin) valeric acid, mephenytoin, fosphenytoin, paramethadione, trimethadione, ethadione, phensuximide, mesuximide, ethosuximide, clonazepam, carbamazepine, oxcarbazepine, rufinamide, valproic acid, valpromide, aminobutyric acid, vigabatrin, progabide, sultiame, phenacemide, lamotrigine, felbamate, topiramate, pheneturide, levetiracetam, zonisamide, stiripentol, lacosamide, carisbamate, retigabine, perampanel, brivaracetam, cenobamate, fenfluramine, ganaxolone, beclamide, gabapentin, pregabalin, mirogabalin, eslicarbazepine, diazepam, lorazepam, clobazam, midazolam.
Medicinal product	(See above)
Product reference	n/a
Procedure number	n/a
Marketing authorisation holder(s)	n/a
Research question and objectives	This is a drug utilisation study for antiseizure medications (ASMs) in pregnant women, and women and men of childbearing age, using data from 8 electronic healthcare databases in 6 European countries. The specific objectives were: Sub-objective 1.1 To estimate the annual incidence and prevalence rate of ASM use in women (12-55 years old) and men (≥12 years old) of childbearing age; Sub-objective 1.2 To describe treatment duration, discontinuation, and treatment switches of ASMs to other ASMs or alternative medications and polytherapy in women and men of childbearing age; Sub-objective 1.3 To estimate pre-pregnancy ASM use, and initiation and continuous use of ASMs during pregnancy period; Sub-objective 1.4 To estimate pre-pregnancy, early and late discontinuation of ASMs, treatment switches to other ASMs or alternative medications and polytherapy among pregnant women; Sub-objective 1.5 To estimate dose changes of ASMs in women prior to and during pregnancy.
Countries of study	Finland, France, Italy, Norway, Spain, the United Kingdom
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Reviewers	ADEPT core team, the participating DEAPs, ADEPT advisors, EMA.

ABSTRACT

Background: Currently there is substantial evidence on teratogenicity of several antiseizure medications (ASMs) and a potential increased risk of neurodevelopmental disorders in young children exposed *in utero* to ASMs. Little evidence has emerged expanding this risk when there was paternal exposure before conception, and questions remain regarding the feasibility of studying this association in large electronic healthcare databases. In that context, European Medicines Agency (EMA) asked for an updated evaluation on trends in use of various ASMs and related drugs in pregnant women, and in women and men of childbearing age.

Objectives: The main objective of this study was to describe the utilisation of ASMs and related drugs (i.e., antiepileptics (ATC codes N03A), gabapentinoids (N02BF), and benzodiazepines with antiepileptic properties (selected N05B/C)) in pregnant women, and women (12-55 years of age), and men of childbearing age (12 years and older). The specific objectives were: 1.1) To estimate the annual incidence rate and prevalence of ASM use in women and men of childbearing age; 1.2) To describe treatment duration, discontinuation, and treatment switches to other ASMs or alternative medications and polytherapy in women and men of childbearing age; 1.3) To estimate pre-pregnancy ASM use, and initiation and continuous use of ASMs during pregnancy period; 1.4) To estimate pre-pregnancy, early and late discontinuation of ASMs, treatment switches to other ASMs or alternative medications and polytherapy among pregnant women; 1.5) To estimate dose changes of ASMs in women prior to and during pregnancy.

Study Design: Retrospective population-based cohort study.

Study Population: The source population comprised over 69.6 million individuals in the included data sources from 6 European countries (EFEMERIS from France, Finnish health registries, Val Padana LHU from Italy, Norwegian health registries, BIFAP, SIDIAP, and VID from Spain, and CPRD Gold from the United Kingdom [UK]). Persons without information on age and sex, and those without at least one day of observation in the study period (1/1/2000-31/12/2024 or latest availability) were excluded.

Exposure and outcomes: The main exposures of interest were all ASMs [N03A], as well as gabapentinoids [N02BF] and benzodiazepines with antiepileptic properties [selected N05B/C]. A literature review was conducted to classify the 58 included ASMs into the 4 sub-groups of older antiepileptics (22 substances, including valproate, carbamazepine, phenytoin, and phenobarbital), newer antiepileptics (20 substances, including levetiracetam, lamotrigine, and topiramate), gabapentinoids (3 agents, including gabapentin, pregabalin), and benzodiazepines with antiepileptic properties (5 agents, including clonazepam, and diazepam). Treatment episodes were constructed using the estimated treatment duration of ASM prescription/dispensings by local algorithms and AdhereR function. The drug utilisation outcome measures were the incidence and prevalence of ASM use among women and men of childbearing age, treatment duration of ASM, discontinuation of ASMs, initiation of ASM and continuous use during pregnancy, switching to another ASM or an alternative medication, dose changes of ASMs before and during pregnancy, and polytherapy of ASMs.

Data Management: The study was conducted in a distributed manner using the EU PE&PV, ConcePTION, and VAC4EU tools, procedures, and programming pipeline. All partners extracted, transformed, and loaded (ETL-ed) their data instances into the ConcePTION

Common Data Model tables. To verify the correctness of the ETL process and validity of findings, the INSIGHT level 1 to 2 quality checks were deployed.

Data Analysis: According to the sub-objectives stated above, statistical estimates were produced, such as descriptives (counts, percentages), distributions (mean, percentiles), rates (incidence, prevalence), or other relevant measures. Various visualisations (e.g., flow diagrams, line and bar charts) depicted the findings. Analysis was conducted using a common R script.

Results: Across 6 European countries, this multi-database post-authorisation safety study demonstrated clear shifts in ASM utilisation over the past two and half decades.

ASM use in women and men of childbearing age. Incidence and prevalence of older antiepileptics such as valproate, carbamazepine, and phenytoin declined steadily (e.g., from 10, or above 12 users per 1000 females and males in the UK in 2000 to 3, and 8 in 2024, respectively), particularly following the 2014 and 2018 EU risk minimisation measures (RMMs). Newer ASMs including lamotrigine, levetiracetam, and topiramate became the predominant choices among women and men of childbearing age (prevalence rose from 6, or 5 users per 1000 females and males in Spain [BIFAP] in 2006, respectively, to 16 and 13 in 2024). This shift was mirrored by sharp increase of gabapentinoids and benzodiazepines prescribing, particularly in Spain (e.g., from 15, or 21 gabapentinoid users per 1000 females and males in VID in 2010, to 32, and 38 in 2024, respectively), although a decline was evident in the UK after 2019.

Discontinuation and switching rates in women and men of childbearing age. Valproate discontinuation was generally declining over the study period, with lowest rates in the UK (ranging below 20 per 100 valproate users per year), and highest in Catalonia (ranging around 40), Norway and Italy (both ranging around 30). Over time, switching from valproate to alternative ASMs among the general population occurred less often in recent years. However, the discontinuation and switching rates of topiramate in the general population seemed to be either gradually increasing or steady (e.g., ranging between 10-40 switches per 100 topiramate users per year across centres).

AMS use in pregnancy. Pre-pregnancy treatment was not very common with older (always below 5 uses per 1000 pregnancies across data sources) or newer antiepileptics (always below 10). Besides, the use of older substances decreased and the use of newer substances increased throughout the study period. Initiation during pregnancy was rare for older and newer antiepileptics (always ≤1 per 1000 pregnancies across centres), but more frequent for gabapentinoids and benzodiazepines (up to 4, and 30 in Spanish databases, respectively). Patterns of persistence also varied: Continuous use during pregnancy was mainly observed for newer antiepileptics and had a rising trend (from ≤1 per 1000 pregnancies per year in decade 2000s, to around 2-3 in 2024 across the 8 centres). Continuous use of gabapentinoids in pregnancy also rose towards the end of study period (always below 1), benzodiazepines had a strong rising trend only in Spanish databases (with rates up to 8 per 1000 pregnancies in BIFAP in 2021).

Discontinuation rates in pregnancy. Pre-pregnancy discontinuation of valproate seemed to be high, with a range between 10-50% across centres and study period, highlighting more careful choices of ASMs before start of pregnancy and in line with 2018 EU RMMs for valproate. However, the valproate discontinuation rates remained high in the 1st trimester (between 10-60%) across most databases and study years. The discontinuation rates of topiramate were high

in both pre-pregnancy (ranging between 30-60%) and 1st trimester (ranging between 20-50%) across databases and study period. Still, these results should be interpreted carefully due to the small absolute counts of discontinuations (numerators) and AMS users (denominators) during pregnancy.

Dose changes of ASMs in pregnancy. Teratogenic ASMs, such as valproate and topiramate were mostly used in low daily doses (i.e., <0.5 DDD per day) in pregnant women, both before and during pregnancy. However, a substantial proportion (between 50-70%) of mid daily users (i.e., 0.5-1.49 DDD per day), and a smaller proportion (10-30%) of high daily users (i.e., >1.5 DDD per day) of valproate and topiramate were observed during the 2nd and 3rd trimesters of pregnancy in Finland, Norway, and Italy, although the absolute counts were small.

Conclusion: This study provides an updated and comprehensive overview of ASM use in Europe, showing a progressive transition away from older agents towards newer antiepileptics. While these trends reflect successful uptake of regulatory measures and evolving prescribing practices, continued valproate exposure in pregnancy and rising use of topiramate, gabapentinoids and benzodiazepines highlight the need for continued monitoring of ASM use and implementation of EU RMMs.