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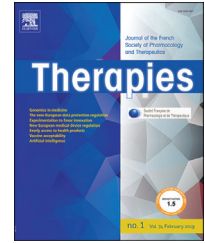


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DRUGS AND PREGNANCY

Systematic review of gabapentinoid use during pregnancy and its impact on pregnancy and childhood outcomes: A ConcePTION study

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 Gabapentin ;
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 Childhood outcomes ;
 Systematic review

Summary

Objective. – In the general population, there has been a noticeable rise in the dispensing of gabapentinoids in recent years. The aim of this study was to provide an overview of all available data on the use and safety of gabapentinoids during pregnancy.

Methods. – A systematic review was performed in PubMed and Reprotox using the search terms: “gabapentin”, “pregabalin”, “antiepileptic drugs” and terms associated with pregnancy. We included all studies in English that reported on the use and safety of gabapentin and pregabalin during pregnancy. We excluded abstracts, literature reviews, case reports and studies involving fewer than 5 exposures. Descriptive analyses and narrative syntheses were performed.

Results. – A total of 27 high-quality studies were described. The prevalence of gabapentinoid use during pregnancy remained very low, at less than 1%. Five studies reported significant findings with increased risks of overall congenital anomalies, specific anomalies (nervous system, eyes, oro-facial clefts, urinary and genital system), miscarriage, stillbirth and specific neurodevelopmental outcomes after exposure to pregabalin during pregnancy. Concerning exposure to gabapentin, increased risks of preterm birth, preeclampsia, small-for-gestational-age and NICU admission were reported in two studies.

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Conclusions. – Prenatal exposure to pregabalin is associated with an increased risk of congenital anomalies and long-term neurodevelopmental outcomes while gabapentin exposure was associated with an increased risk of preeclampsia, preterm birth and small-for-gestational age. Larger studies are needed to confirm these data and explore additional outcomes. The combined evidence from this systematic review and animal studies raises concerns about the safety of using gabapentinoids during pregnancy. Careful evaluation of the benefit–risk balance for both mother and fetus/infant is essential when these medications cannot be avoided during pregnancy.

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Abbreviations

ADHD	attention deficit hyperactivity disorder
ASD	autism spectrum disorder
ASM-exposure	antiseizure medication exposure
HR	hazard ratio
ICD-10	International Statistical Classification of Diseases and Related Health Problems 10th Revision
IMI	innovative medicines initiative
NCIU	Neonatal Intensive Care Unit
NOS	Newcastle–Ottawa-Scale
OR	odds ratio
PR	prevalence ratio
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-analysis
RR	risk ratio
SGA	small-for-gestational-age
SmPC	summary of product characteristics

Introduction

In Europe, pregabalin and gabapentin, initially approved for epilepsy, were subsequently approved to treat neuropathic pain and generalized anxiety disorder (pregabalin only). In addition, off-label use has been reported, such as in the treatment of non-neuropathic pain including migraine and fibromyalgia, restless leg syndrome, or bipolar disorders. Pregabalin and gabapentin cross the placenta barrier using active transport mechanisms [1,2], raising concerns about potential adverse effects on the fetus and infants when these medications are used during pregnancy.

In the general population, there has been an observed increase in the dispensing of gabapentinoids in recent years, possibly due in part to their various uses and abuse [3–6]. In pregnant women, a European study found that the prescribing of pregabalin and gabapentin during pregnancy has increased markedly in the United Kingdom 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 [7]. A less pronounced increase was observed in

France (prevalence of pregabalin rose from 0.5 to 1.2 per 1000 over the same period). In Italy, prevalence rates have remained stable in recent years [7].

In animal studies, prenatal exposure to gabapentin has been associated with fetal growth retardation and increased incidence of hydronephrosis, hydronephrosis and fetal loss [8,9]. Pregabalin exposure has been linked to a higher incidence of skeletal anomalies [10]. These findings, although derived from animals, highlight potential risks that warrant further investigation in humans.

Despite the increased use of gabapentinoids during pregnancy, there are limited publications and contradictory results regarding their effects on the fetus and/or child. Nevertheless, in March 2022, the summary of product characteristics (SmPC) for Lyrica® (pregabalin) was updated to state “use in the first trimester of pregnancy may cause major birth defects in the unborn child” [11]. Following this update, a critical appraisal of controlled studies was published, indicating the data from published studies did not support the SmPC statement of an increased risk of congenital anomalies following in utero exposure to pregabalin [12]. In parallel, a meta-analysis of eight cohort studies assessed the relationship between exposure to gabapentinoids and the risk of congenital anomalies, small-for-gestational-age (SGA), preterm birth, spontaneous abortion and termination of pregnancy [13]. The results were reassuring regarding congenital anomalies, but highlighted an increased risk of preterm birth, spontaneous abortion and termination of pregnancy following exposure to gabapentinoids during pregnancy. Thus, the UK regulator advises against the use of gabapentinoids during pregnancy [14].

The present review described the use of gabapentinoids and their safety during pregnancy. We extended the outcomes of interest by examining the long-term effects on the newborn. Consequently, we have compiled all the available data on the use and safety of gabapentinoids during pregnancy into a single document.

This study was conducted as part of the innovative medicines initiative (IMI) ConcePTION project, a large-scale collaboration between academic, regulatory and industry partners, to create an enhanced monitoring and communication system for the safe use of medications during pregnancy and lactation (<http://www.imi-conception.eu/>).

Table 1 Selection criteria for eligibility.	
Population	Pregnant women
Intervention	In utero exposure to gabapentin or pregabalin (monotherapy or combination therapy)
Controls/comparators	If present, <ul style="list-style-type: none"> – women not exposed to the medication of interest during pregnancy – women exposed to other antiepileptics during pregnancy – general population of pregnant women
Outcomes	Prevalence of gabapentoinoid use during pregnancy Pregnancy outcomes, such as live birth, miscarriage, stillbirth, congenital anomaly, preterm birth, small for gestational age... Childhood outcomes, such as cognitive outcomes, signal of atypical neurodevelopment (autism spectrum disorder, attention-deficit/hyperactivity disorder)
Type of study	Observational studies (cohort, case-control...) Pregnancy registry studies

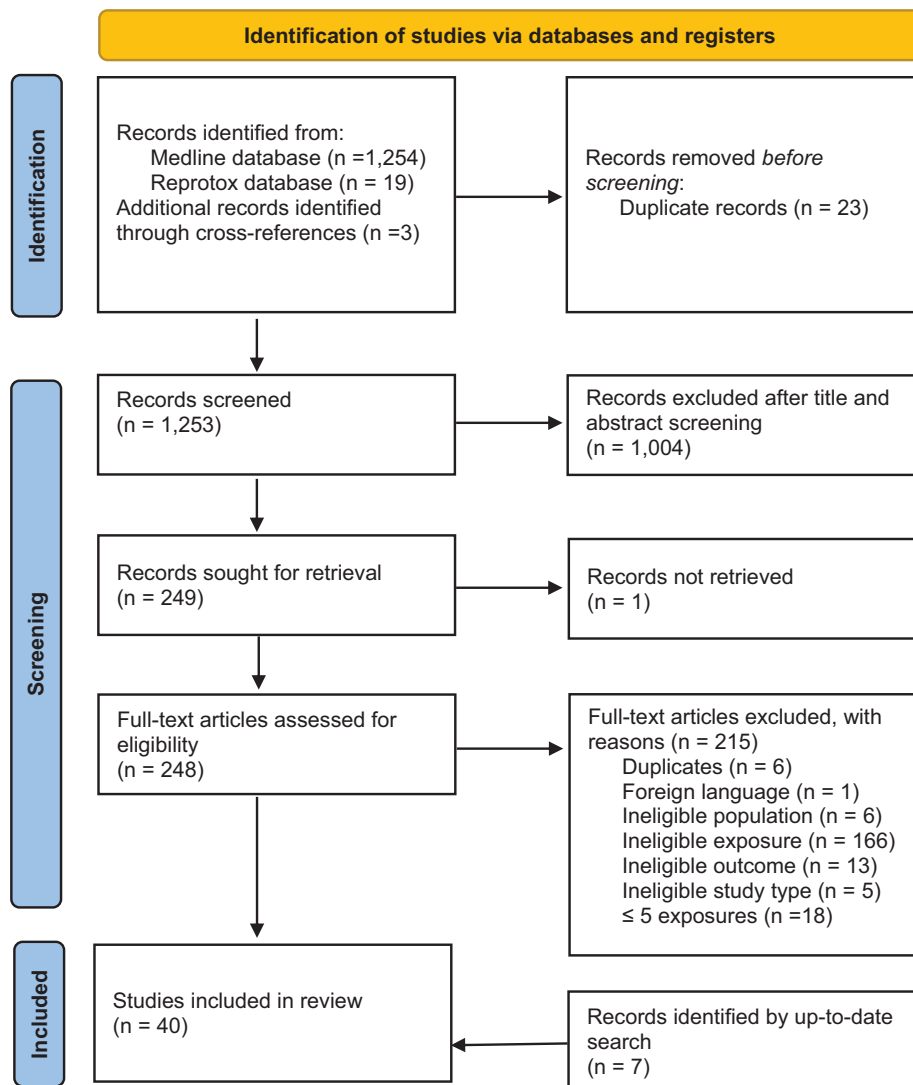


Figure 1. Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) 2020 flowchart.

Table 2 Overview of the 27 high-quality studies included in the review.

Author and year	Country, study period	Population-based	Study design, data source	Characteristics of study population, No.	Exposure ascertainment	Medications investigated	Outcomes investigated	Study quality
Almgren et al., 2009 [46]	Sweden, 1995–2005	Yes	Cohort, National registers	Singleton, $n = 900,739$ children	Structured interview made by a midwife (Swedish Medical Birth Registry)	ASM including gabapentin	Head circumference	8
Bech et al., 2018 [52]	Denmark, 2005–2008	Yes	Case-cohort, Danish national registers	Singletons born from mother exposed to antiepileptic drugs before or during pregnancy, $n = 1070$ children	Danish national prescription register	ASM including gabapentin	Learning disabilities in the first year of compulsory education	9
Bjørk et al., 2022 [48]	Denmark (1997–2017), Finland (1996–2016), Iceland (2004–2017), Norway (2005–2017), and Sweden (2006–2017)	Yes	Cohort, National registers	Live birth singletons without chromosomal disorders, $n = 4,494,926$ children	Nordic national prescription registers	ASM including gabapentin and pregabalin	Intellectual disability, autism spectrum disorder and any neurodevelopmental disorder	9
Blotière et al., 2018 [33]	France, 2007–2015	Yes	Cohort, National French healthcare databases	Pregnant women identified, $n = 9,647,843$ pregnancies	Prescription/dispensing database	ASM including gabapentin and pregabalin	Prevalence of ASM use during pregnancy	7
Blotière et al., 2019 [40]	France, 2011–2015	Yes	Cohort, National French healthcare databases	Pregnancies with at least 20 weeks of gestation, $n = 1,886,825$ pregnancies	Prescription/dispensing database	ASM including gabapentin and pregabalin	23 major congenital malformations	8
Blotière et al., 2020 [49]	France, 2011–2014 (follow-up until end 2016)	Yes	Cohort, National French healthcare databases	Live births prenatally exposed to ASM monotherapy, $n = 9034$ children	Prescription/dispensing database	ASM including gabapentin and pregabalin	Various neurodevelopmental outcomes	8

Table 2 (Continued)

Author and year	Country, study period	Population-based	Study design, data source	Characteristics of study population, No.	Exposure ascertainment	Medications investigated	Outcomes investigated	Study quality
Bobo et al., 2012 [53]	US, 2001–2007	Yes	Cohort	Live births, $n = 585, 615$ deliveries	Prescription/dispensing database	ASM including gabapentin and pregabalin	Use of ASM among pregnant women	7
Christensen et al., 2024 [47]	Denmark (1997–2017), Finland (1996–2016), Iceland (2004–2017), Norway (2005–2017), and Sweden (2006–2017)	Yes	Cohort, National registers	Live birth singletons without chromosomal disorders, $n = 4,494,918$ children	Nordic national prescription registers	ASM including gabapentin and pregabalin	Fetal growth indicators (birth weight and head circumference)	9
Coste et al., 2020 [50]	France, 2011–2014 (follow-up until end 2016)	Yes	Cohort, National French healthcare databases	Liveborn singleton, $n = 1,721,990$ children	Prescription/dispensing database	ASM including gabapentin and pregabalin	Early neurodevelopmental disorders	8
Desrochers et al., 2024 [32]	Canada, 1995–2019	Yes	Cohort, Manitoba Health Database	Pregnant women, $n = 289,227$ pregnancies	Prescription database	Gabapentin	Major congenital anomalies, cardiac and oro-facial anomalies, and neonatal intensive care unit admission	9
Dreier et al., 2023 [51]	Denmark (1997–2017), Finland (1996–2016), Iceland (2004–2017), Norway (2005–2017), and Sweden (2006–2017)	Yes	Cohort, National registers	Singleton without chromosomal disorders born from mother with epilepsy, $n = 38,661$ children	Nordic national prescription registers	ASM including gabapentin and pregabalin	Child psychiatric disorders	8

Table 2 (Continued)

Author and year	Country, study period	Population-based	Study design, data source	Characteristics of study population, No.	Exposure ascertainment	Medications investigated	Outcomes investigated	Study quality
Dudukina et al., 2023 [39]	Denmark, Finland, and Norway (2005–2015), Sweden (2006–2016) (follow-up until end 31 December 2017 in Sweden and Norway; 31 December 2016 in Denmark and Finland)	Yes	Cohort, National registers	Births (live births and stillbirths) from fetus without prenatal exposure to medications known as potentially teratogenic during the first pregnancy trimester and without chromosomal abnormality diagnosis, $n = 3,118,680$ pregnancies	Nordic national prescription registers	Pregabalin	Major congenital anomalies, 12 specific sub-group of major congenital anomalies, adverse birth outcomes (stillbirth, low birth weight, preterm birth, being small for gestational age, low Apgar score at 5 min, microcephaly), and postnatal neurodevelopmental outcomes (attention deficit/hyperactivity disorder, autism spectrum disorder, intellectual disability)	9
Forbes et al., 2024 [45]	United Kingdom, 1995–2018	Yes	Cohort, Clinical Practice Research Datalink (CPRD) Pregnancy Register	Single pregnancies with a known outcome identified in the CPRD Pregnancies Register using data from primary care, $n = 1,023,787$ pregnancies	Prescription from general practice	ASM including gabapentin and pregabalin	Miscarriage	9

Table 2 (Continued)

Author and year	Country, study period	Population-based	Study design, data source	Characteristics of study population, No.	Exposure ascertainment	Medications investigated	Outcomes investigated	Study quality
Hurault-Delarue et al., 2019 [7]	United Kingdom, France, and Italy, 2007–2016	Yes	Cohort, health care databases	All pregnancies with a known pregnancy outcome, $n = 66,681$ pregnancies in France, 294,151 in Tuscany (Italy), 355,767 in Emilia-Romagna (Italy), and 380,499 in the UK	Issue (UK) or dispensing (France and Italy) of a prescription	ASM including gabapentin and pregabalin	Patterns of antiepileptic medications	7
Källén et al., 2013 [36]	Sweden, 1996–2011	Yes	Cohort, Swedish Medical Birth Register	All infants born during the study period, $n = 1,575,847$ children	Standardized forms from the medical birth registry	ASM including gabapentin and pregabalin	Congenital anomalies	7
Kilic et al., 2014 [43]	Denmark, 1997–2008	Yes	Cohort, National registers	Singleton liveborn children, $n = 679,762$ children	Danish national prescription register	ASM including gabapentin and pregabalin	Adverse birth outcomes: birth weight, gestational age, head circumference, preterm birth, SGA	9
Margulis et al., 2019 [44]	Sweden, 1996–2013	Yes	Cohort, National registers	Liveborn children, $n = 6720$ children	Swedish national prescription register, Standardized forms from the medical birth registry	ASM including pregabalin	Pregnancy duration and birth weight, length, and head circumference	9
Mølgaard-Nielsen et al., 2011 [54]	Denmark, 1996–2008	Yes	Cohort, National registers	All live births during the study period, $n = 837,795$ live births	Danish national prescription register	ASM including gabapentin	Major congenital anomalies	8

Table 2 (Continued)

Author and year	Country, study period	Population-based	Study design, data source	Characteristics of study population, No.	Exposure ascertainment	Medications investigated	Outcomes investigated	Study quality
Morrow et al., 2006 [42]	UK, 1996–2005	No, enrolment	UK epilepsy and pregnancy register	Pregnant women with epilepsy, $n = 3607$ pregnancies with full outcome data	Retrospectively reported by healthcare professionals	ASM including gabapentin	Major congenital anomalies	7
Mostacci et al., 2018 [55]	Italy, 2009–2011	Yes	Cohort, administrative data bases	Women who had a delivery or underwent an abortion, $n = 145,243$ pregnancies	Prescription/dispensing database	ASM including gabapentin and pregabalin	Prevalence of ASM use during pregnancy, congenital anomalies, SGA, APGAR scores	9
Patorno et al., 2017 [38]	US, 2000–2010	Yes	Cohort, US Medicaid Analytic extract (MAX) and the Truven Health marketscan Commercial Claims and Encounters Database (marketscan)	MAX data: Pregnancies resulting in live births, $n = 1,323,432$ pregnancies Marketscan data: Pregnancies resulting in live births, n not reported	Prescription/dispensing database	Pregabalin	Major congenital anomalies	8
Patorno et al., 2020 [30]	US, 2000–2013	Yes	Cohort, administrative data bases	Pregnancies resulting in live births, $n = 1,753,865$ pregnancies	Prescription/dispensing database	Gabapentin	Major congenital anomalies, preeclampsia, preterm birth, SGA, NICU admission	9
Richards et al., 2018 [35]	New-Zealand, 2009–2014	Yes	Cohort, administrative data bases	Women who had a delivery or underwent an abortion, $n = 472,544$ pregnancies	Prescription/dispensing database	ASM including gabapentin	Rates of ASM use, pregnancy terminations, abortions	8

Table 2 (Continued)

Author and year	Country, study period	Population-based	Study design, data source	Characteristics of study population, No.	Exposure ascertainment	Medications investigated	Outcomes investigated	Study quality
Shouman et al., 2022 [31]	Canada, 1997–2018	Yes	Cohort, administrative data bases	Pregnant women, $n = 273,492$ pregnancies	Prescription/dispensing database	ASM including gabapentin	ASM use	7
Spoendlin et al., 2021 [34]	Switzerland, 2014–2018	Yes	Cohort, administrative data bases	Pregnant women who had a delivery (live birth or stillbirth), $n = 387,418$ pregnancies	Prescription/dispensing database	ASM including pregabalin	Valproate and other antiseizure drugs use	7
Veiby et al., 2014 [37]	Norway, 1999–2011	Yes	Cohort, National registers	Deliveries and termination of pregnancy for fetal anomaly at 12 or more weeks of gestation, $n = 779,362$ outcomes of pregnancy	Standardized forms from the medical birth registry	ASM including gabapentin and pregabalin	Major congenital anomalies, fetal growth restriction	7
Wide et al., 2004 [56]	Sweden, 1995–2001	Yes	Cohort, National registers	Live births, $n = 582,656$ children	Standardized forms from the medical birth registry	ASM including gabapentin	Congenital anomalies	7

ASM: antiseizure medications; CPRD: clinical practice research dataling; NCIU: neonatal intensive care unit; SGA: small-for-gestational-age.

Table 3 Prevalence of pregnancies exposed to pregabalin and gabapentin in 20 of the 27 high-quality studies included.

Reference number	Author and year	Exposure/period	Results
Pregabalin exposure			
[48]	Björk et al., 2022	Pregabalin monotherapy/from LMP date to end of pregnancy	1666 infants (0.04%)
[33]	Blotière et al., 2018	Pregabalin/from LMP date to end of pregnancy	2007–2014: 7250 (0.1%) 2007: 547 (0.06%) 2008: 652 (0.07%) 2009: 780 (0.08%) 2010: 901 (0.09%) 2011: 927 (0.10%) 2012: 1069 (0.11%) 2013: 1150 (0.12%) 2014: 1224 (0.13%)
[40]	Blotière et al., 2019	Pregabalin monotherapy/between 1 month before and 2 months after the beginning of pregnancy	2011–2015: 1671 (0.09%)
[53]	Bobo et al., 2012	Pregabalin/from the LMP date to the delivery date	73 pregnancies (0.01%)
[47]	Christensen et al., 2024	Pregabalin monotherapy/from 30 days before the first day of the last menstrual period to the date of birth	2214 children (0.05%)
[50]	Coste et al., 2020	Pregabalin monotherapy/the beginning of the month preceding onset of pregnancy and the end of pregnancy	1777 children (0.10%)
[39]	Dudukina et al., 2023	Pregabalin/from 90 days before LMP date to birth	Denmark: <i>n</i> = 325 pregnancies (0.05%) Finland: <i>n</i> = 965 pregnancies (0.15%) Norway: <i>n</i> = 307 pregnancies (0.05%) Sweden: <i>n</i> = 1275 pregnancies (0.11%)
[45]	Forbes et al., 2024	Pregabalin/first trimester of pregnancy	882 pregnancies (0.09%)
[7]	Hurault-Delarue et al., 2019	Pregabalin/during pregnancy	Emilia-Romagna: 61 pregnancies (0.02%) Tuscany: 149 pregnancies (0.05%) France: 53 pregnancies (0.08%) United Kingdom: 395 pregnancies (0.10%)
[36]	Källén et al., 2013	Pregabalin/during pregnancy	128 children (0.01%)
[43]	Kilic et al., 2014	Pregabalin/from 30 days before LMP date to birth	18 children (0.003%)
	Kilic et al., 2014	Pregabalin monotherapy/from 30 days before LMP date to birth	13 children (0.002%)
[55]	Mostacci et al., 2018	Pregabalin/first trimester of pregnancy	14 newborns (0.01%)

Table 3 (Continued)

Reference number	Author and year	Exposure/period	Results
[38]	Patorno et al., 2017	Pregabalin/first trimester of pregnancy	477 pregnancies (0.04%)
[34]	Patorno et al., 2017	Pregabalin monotherapy/first trimester of pregnancy	353 pregnancies (0.03%)
[34]	Spoendlin et al., 2021	Pregabalin/during pregnancy	2014: 2.7 per 10,000 pregnancies 2015: 5.6 per 10,000 pregnancies 2016: 3.2 per 10,000 pregnancies 2017: 2.3 per 10,000 pregnancies 2018: 5.6 per 10,000 pregnancies 2014–2018: 3.8 per 10,000 pregnancies (weighted prevalence, weighting factors included calendar year, canton, age, and sex)
[37]	Veiby et al., 2014	Pregabalin monotherapy/during pregnancy	30 children (0.004%)
Gabapentin exposure			
[48]	Björk et al., 2022	Gabapentin monotherapy/from LMP date to end of pregnancy	965 children (0.02%)
[33]	Blotière et al., 2018	Gabapentin/monotherapy/from LMP date to end of pregnancy	2007–2014: 2192 pregnancies (0.03%) 2007: 331 pregnancies (0.04%) 2008: 248 pregnancies (0.03%) 2009: 252 pregnancies (0.03%) 2010: 231 pregnancies (0.02%) 2011: 230 pregnancies (0.02%) 2012: 290 pregnancies (0.03%) 2013: 283 pregnancies (0.03%) 2014: 327 pregnancies (0.04%) 2011–2015: 365 pregnancies (0.02%)
[40]	Blotière et al., 2019	Gabapentin monotherapy/between 1 month before and 2 months after the beginning of pregnancy	2011–2015: 365 pregnancies (0.02%)
[53]	Bobo et al., 2012	Gabapentin/monotherapy/from the LMP date to the delivery date	988 pregnancies (0.17%)
[47]	Christensen et al., 2024	Gabapentin monotherapy/monotherapy/30 days before the first day of the last menstrual period to the date of birth	1336 children (0.03%)

Table 3 (Continued)

Reference number	Author and year	Exposure/period	Results
[50]	Coste et al., 2020	Gabapentin monotherapy/the beginning of the month preceding onset of pregnancy and the end of pregnancy	467 children (0.03%)
[32]	Desrochers et al., 2024	Gabapentin/during pregnancy	870 pregnancies (0.30%)
[45]	Forbes et al., 2024	Gabapentin/first trimester of pregnancy	1224 pregnancies (0.12%)
[7]	Hurault-Delarue et al., 2019	Gabapentin/during pregnancy	Emilia-Romagna: 36 pregnancies (0.01%) Tuscany: 102 pregnancies (0.03%) France: 16 pregnancies (0.02%) UK: 429 pregnancies (0.11%)
[36]	Källén et al., 2013	Gabapentin/during pregnancy	207 (0.01%) children (143 early exposures and 64 late exposures)
[43]	Kilic et al., 2014	Gabapentin/from 30 days before LMP date to birth	91 children (0.01%)
	Kilic et al., 2014	Gabapentin monotherapy/from 30 days before LMP date to birth	72 children (0.01%)
[54]	Mølgaard-Nielsen et al., 2011	Gabapentin/first trimester of pregnancy	59 children (0.01%)
[55]	Mostacci et al., 2018	Gabapentin/first trimester of pregnancy	10 newborns (0.01%)
[30]	Patorno et al., 2020	Gabapentin/first trimester of pregnancy	4642 pregnancies (0.26%)
	Patorno et al., 2020	Gabapentin/early in pregnancy (first 140 days of pregnancy and no gabapentin dispensing from the 141 and 245 days)	3745 pregnancies (0.21%)
	Patorno et al., 2020	Gabapentin/late in pregnancy (at least one dispensing in the 141 and 245 days of pregnancy and no dispensing in the first 140 days)	556 pregnancies (0.03%)
	Patorno et al., 2020	Gabapentin/early and late in pregnancy (at least one dispensing in the first 140 days and at least one in the 141 and 245 days of pregnancy)	1275 pregnancies (0.07%)
[35]	Richards et al., 2018	Gabapentin/during pregnancy	2009: 0.27 women per 1000 births 2014: 0.97 women per 1000 births
[31]	Shouman et al., 2022	Gabapentin/during pregnancy	785 pregnancies (0.29%)
[37]	Veiby et al., 2014	Gabapentin monotherapy/during pregnancy	39 children (0.005%)

Table 3 (Continued)

Reference number	Author and year	Exposure/period	Results
[56]	Wide et al., 2004	Gabapentin monotherapy/in early pregnancy	18 children (0.003%)

LMP: last menstrual period.

The study objective was to summarize published data on the use of gabapentinoids in pregnancy and its association with adverse pregnancy/childhood outcomes.

Methods

A narrative systematic review method was used to synthesize current research on all available literature regarding gabapentinoid exposure during pregnancy and childhood outcomes.

Protocol and registration

This study was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) group guidelines [15].

Eligibility criteria

Only observational studies (cohort, case-control, registry studies) were eligible, as no randomised clinical trials exist to assess safety of medication use among the pregnant population. Abstracts, literature reviews, case reports, case series, and spontaneous reports were excluded.

Eligible studies included those that evaluated the prevalence of gabapentin and/or pregabalin use during pregnancy, regardless of indication. Studies evaluating associations between the use of gabapentinoids during pregnancy and childhood outcomes were also eligible. Outcomes included major congenital malformations, birth and prenatal outcomes (such as miscarriage, stillbirth, preterm birth, small for gestational age); as well as long-term childhood outcomes (such as cognitive developmental delay, autism/dyspraxia, developmental delay and social impairment).

Information sources and search strategy

The studies were identified on January 24, 2022, by a search of the Medline (PubMed) and Reprotox databases. The last updated search, carried out on July 2, 2024, added 7 new studies. The search was limited to papers published in English from January 2000 onwards. The search strategy included terms associated with the medications of interest: gabapentin, pregabalin and antiepileptic drugs; as well as terms associated with pregnancy. The results were limited to humans. The search terms are available in the [Appendix \(Supplementary method\)](#).

Study selection

The list of studies generated after the database search was compiled in Rayyan, a platform for data management in systematic review projects, and duplicates were removed [16]. The screening and selection of relevant studies was performed in two stages. In the first round, the titles and abstracts of all citations retrieved from electronic databases were reviewed by one researcher (ABB). In the second round, the full-texts of the articles selected in the first round were independently evaluated on the basis of the predefined inclusion criteria (Table 1) by two researchers (ABB and JM). In case of disagreement, a consensus was reached on inclusion or exclusion by discussion and, if necessary, a third researcher (CDM) was consulted. Studies involving fewer than 5 exposures were excluded.

Data extraction and data elements

A data extraction form based on the Cochrane model for non-RCTs was used. Data collection was performed by two researchers (ABB and JM).

For each eligible study, the following information was extracted: (1) study characteristics, including country and study period; (2) design and methodology, including type of study, sample size, medication, comparator if present, pregnancy/childhood outcomes and (3) results, including prevalence and measures of association [such as odd ratio (OR), risk ratio (RR), hazard ratio (HR) and prevalence ratio (PR)].

Assessment of risk of study bias

We assessed the risk of bias in included studies using the Newcastle–Ottawa–Scale (NOS) for case-control or cohort studies. Two researchers (ABB, JM) applied the tool to each included study and recorded information and justifications for risk of bias judgements for each domain. The NOS ranged from a minimum of zero and a maximum of nine points. As there is no harmonized criterion for defining high quality, studies with an NOS score above six points were considered to be of high quality. Any discrepancies in the assessment of risk of bias or in the justification of assessments were resolved by discussion between the two researchers in order to reach a consensus, with a third author (CDM) acting as referee if necessary.

Synthesis of results

The results of the included studies were described narratively and combined in tables to describe (1) the

characteristics of the different studies, (2) the results reported for each study and (3) the quality of the data. Results were presented separately for pregabalin and gabapentin. We reported the results of studies considered to be of high quality (NOS score greater than six) in the main text.

Results

Search results

Our literature search identified 1253 records, which, after the screening process, yielded 248 potentially relevant articles for inclusion (Fig. 1). After full-text review, 40 studies met the eligibility criteria, including the 7 additional studies following the updated search.

Characteristics of the included studies

Thirty-one (31) studies were observational (all cohort studies) and 9 were studies based on pregnancy registries. The studies used 22 distinct data sources from 14 different countries [Australia, Canada, Denmark, Finland, France, Iceland, Israel, Italy, New-Zealand, Norway, Sweden, Switzerland, United Kingdom (UK), and United States (US)] (Table 2).

Methodological quality results

Overall, 27 studies (68%) had a NOS score greater than six and were thus considered to be of high-quality (Table 2). The 27 high-quality studies were described and discussed in the following sections, whereas results of the remaining 13 studies [17–29] ranked as studies of lower quality are reported in the Appendix Tables S1–S4. This ranking is explained by the lack of comparator or control group in the analysis [29], self-reported outcome or exposure assessment [18,21–23,25,27,29], non-exposed cohort drawn from a different source [19,23], selected group of users [18,19,21–23,25–29], and no description of ascertainment of the outcome or the exposure [20].

Prevalence of gabapentinoid use in pregnancy

Table 3 shows the 15 studies that estimated the prevalence of pregabalin use during pregnancy. Seven studies assessed exposure to monotherapy while the others did not mention the regimen of use. The prevalence of pregabalin use was less than 0.15%. The prevalence of gabapentin use during pregnancy was assessed in 18 studies: seven studies assessing exposure to monotherapy while the others did not mention the regimen of use. Prevalence has been estimated to range from 0.01% and to over 0.2–0.3% in the US [30] and Canada [31,32].

Only three studies reported the prevalence over time, and showed an increase in use in the recent years [33–35].

Overall and specific congenital anomalies

Of the five studies assessing the risk of congenital anomalies after pregabalin exposure [36–40], three reported significant results [38–40]. The first study found an increased

risk of overall congenital anomalies after first trimester pregabalin monotherapy exposure (crude RR = 1.31 [95% CI: 1.26–2.58], 15 exposed cases) [38]. However, the increase in risk was no longer significant after controlling for confounders, with a PS-adjusted RR = 0.87 (95% CI: 0.53–1.42) [38]. The second study reported significant associations when compared with exposure to lamotrigine and/or duloxetine (adjusted PR between 1.27 and 1.42 > 150 exposed cases) [39]. However, no increased risk was reported when compared with no exposure to antiepileptic [39]. In addition, after taking confounding factors into account, an increased risk of congenital anomalies of the nervous system, eyes, oro-facial clefts, and genital system was identified following pregabalin exposure [39]. The third study found an increased risk of coarctation of aorta following pregabalin monotherapy exposure [crude OR = 5.8 (95% CI: 1.6–14.9), 4 exposed cases] [40].

Of the six studies assessing the risk of congenital anomalies after gabapentin exposure [30,32,36,40–42], one study reported an increase of overall risk (crude RR = 1.49 [95% CI: 1.31–1.69], 230 exposed cases), as well as risk of major cardiac anomalies (crude RR = 1.77 [95% CI: 1.43–2.18], 87 exposed cases), however the increased risks were no longer observed after controlling for confounding factors (adjusted RR = 1.07 [95% CI: 0.94–1.21] for any major anomalies and adjusted RR = 1.12 [95% CI: 0.89–1.40] for major cardiac anomalies) [30] (Table 4).

Pregnancy outcomes

Pregnancy outcomes were examined in five studies and included miscarriage, stillbirth, preterm birth, and preeclampsia [30,39,43–45].

Comparing pregabalin to lamotrigine exposure, an increased risk of miscarriage was identified, specifically among women with epilepsy (adjusted HR = 2.18 [95% CI: 1.38–3.44], 13 exposed cases), but not among women with psychiatric or somatic conditions [45]. Additionally, an increased risk of stillbirth was reported when comparing pregabalin exposure to no ASM-exposure (antiseizure medication exposure), to lamotrigine, and to lamotrigine and/or duloxetine exposure, with adjusted PRs ranging from 1.25 to 2.71, although some 95% CIs for adjusted PR included 1 [39]. No increased risk of preterm birth was observed after exposure to pregabalin, after controlling for confounding factors. A study also reported an increased risk of preeclampsia (adjusted RR = 1.43 [95% CI: 1.03–2.00], 33 exposed cases) and preterm birth (adjusted RR = 1.28 [95% CI: 1.08–1.52], 107 exposed cases) following gabapentin exposure in late pregnancy [30]. No increased risk was observed in the remaining studies [43,44] (Table 5).

Short-term children outcomes

Seven studies examined low birth weight, small-for-gestational-age (SGA), microcephaly, low Apgar score and admission to neonatal intensive care unit (NICU) [30,32,39,43,44,46,47]. One study reported an increase risk of low birth weight (adjusted RR = 1.23 (95% CI: 1.03–1.47), 137 exposed cases) and SGA (adjusted RR = 1.16 [95% CI: 1.02–1.31], 318 exposed cases) when comparing pregabalin exposure to no ASM-exposure [47]. When the women were

Table 4 Overview of congenital anomalies risks described in the studies following exposure to gabapentinoids.

Reference number	Author and year	Outcomes investigated	Exposure No events/No participants (%)	Comparison No events/No participants (%)	Results Measure of association (95% CI)	
Pregabalin exposure Overall congenital anomalies	[39]	Major congenital anomalies detected up to 1 year after birth	First trimester exposure 162/2691 (6.02%)	ASM-unexposed 126,437/3,063,173 (4.13%)	Crude PR = 1.34 (1.15–1.57) PS-adjusted PR = 1.14 (0.98–1.34) MH-adjusted PR = 1.13 (0.98–1.32)	
				First trimester lamotrigine exposure 362/7216 (5.02%)	Crude PR = 1.10 (0.91–1.34) PS-adjusted PR = 1.31 (1.04–1.65) MH-adjusted PR = 1.27 (1.04–1.55)	
				First trimester duloxetine exposure NR/2972	Crude PR = 1.09 (0.87–1.36) PS-adjusted PR = 1.41 (1.09–1.81) MH-adjusted PR = 1.42 (1.12–1.79)	
				First trimester lamotrigine and duloxetine exposure 519/10,061 (5.16%)	Crude PR = 1.09 (0.90–1.31) PS-adjusted PR = 1.28 (1.03–1.57) MH-adjusted PR = 1.27 (1.05–1.53)	
	[36]	Källén et al., 2013	Relatively severe malformations	Monotherapy in early pregnancy 2/111 (1.80%)	Total population 49,499/1,575,847 (3.14%)	Not reported
	[38]	Paterno et al., 2017	Non-chromosomal structural major congenital anomalies detected up to 90 days after birth	First trimester exposure MAX data: 28/477 (5.87%) Marketscan data: not reported/174	Unexposed to any other anticonvulsant MAX data: 43,067/1,322,955 (3.26%) Marketscan data: not reported/427,304	MAX data: Crude RR = 1.80 (0.80–2.14) PS-adjusted RR = 1.16 (0.81–1.67) Marketscan data: PS-adjusted RR = 1.03 (0.56–1.90)

Table 4 (Continued)

Reference number	Author and year	Outcomes investigated	Exposure No events/No participants (%)	Comparison No events/No participants (%)	Results Measure of association (95% CI)
[37]	Paterno et al., 2017	Non-chromosomal structural major congenital anomalies detected up to 90 days after birth	First trimester monotherapy exposure MAX data: 15/353 (4.25%) Marketscan data: not reported/118	Unexposed to any other anticonvulsant MAX data: 43,067/1,322,955 (3.26%) Marketscan data: not reported/427,304	MAX data: Crude RR = 1.31 (1.26–2.58) PS-adjusted RR = 0.87 (0.53–1.42) Marketscan data: PS-adjusted RR = 1.26 (0.64–2.49)
	Veiby et al., 2014	Congenital anomaly detected up to 1 year after birth	Monotherapy any time during pregnancy 1/30 (3.33%)	No ASM in women with epilepsy 22,371/771,412 (2.90%)	Not reported
Specific congenital anomalies ^a [40]	Blotière et al., 2019	Spina bifida (detected up to 12 months after birth)	Monotherapy 1/1671 (0.06%)	Unexposed 616/1,875,733 (0.03%)	Crude OR = 1.8 (0.0–10.2)
	Blotière et al., 2019	Ventricular septal defect (detected up to 12 months after birth)	Monotherapy 5/1671 (0.30%)	Unexposed 4643/1,875,733 (0.25%)	Crude OR = 1.1 (0.5–2.8)
	Blotière et al., 2019	Atrial septal defect (detected up to 12 months after birth)	Monotherapy 6/1,671 (0.36%)	Unexposed 3268/1,875,733 (0.17%)	Crude OR = 1.9 (0.8–4.1)
	Blotière et al., 2019	Hypoplastic left heart syndrome (detected up to 12 months after birth)	Monotherapy 1/1671 (0.06%)	Unexposed 216/1,875,733 (0.01%)	Crude OR = 5.2 (0.1–29.4)
	Blotière et al., 2019	Coarctation of aorta (detected up to 12 months after birth)	Monotherapy 4/1671 (0.24%)	Unexposed 779/1,875,733 (0.04%)	Crude OR = 5.8 (1.6–14.9)
	Blotière et al., 2019	Cleft lip with or without cleft palate (detected up to 12 months after birth)	Monotherapy 1/1671 (0.06%)	Unexposed 1637/1,875,733 (0.09%)	Crude OR = 0.7 (0.0–3.8)

Table 4 (Continued)

Reference number	Author and year	Outcomes investigated	Exposure No events/No participants (%)	Comparison No events/No participants (%)	Results Measure of association (95% CI)
[39] ^b	Blotière et al., 2019	Cleft palate (detected up to 12 months after birth)	Monotherapy 2/1671 (0.12%)	Unexposed 1178/1,875,733 (0.06%)	Crude OR = 1.9 (0.2–6.9)
	Blotière et al., 2019	Anorectal atresia (detected up to 12 months after birth)	Monotherapy 1/1671 (0.06%)	Unexposed 544/1,875,733 (0.03%)	Crude OR = 2.1 (0.1–11.6)
	Blotière et al., 2019	Hypospadias (detected up to 24 months after birth)	Monotherapy 2/1671 (0.12%)	Unexposed 3371/1,875,733 (0.18%)	Crude OR = 0.7 (0.1–2.6)
	Blotière et al., 2019	Craniosynostosis (detected up to 12 months after birth)	Monotherapy 3/1671 (0.18%)	Unexposed 766/1,875,733 (0.04%)	Crude OR = 4.4 (0.9–13.0)
	Dudukina et al., 2023	Nervous system	First trimester exposure 6/2691 (0.22%)	ASM-unexposed 4134/3,063,173 (0.12%)	Crude PR = 2.50 (1.12–5.59) PS-adjusted PR = 2.02 (0.88–4.63) MH-adjusted PR = 1.15 (0.52–2.57)
	Dudukina et al., 2023	Nervous system	First trimester exposure 6/2586 (0.23%)	Lamotrigine 10/7,216 (0.14%)	Crude PR = 2.05 (0.67–6.30) PS-adjusted PR = 4.39 (1.36–14.13) MH-adjusted PR = 3.20 (0.86–12.0)
	Dudukina et al., 2023	Nervous system	First trimester exposure 6/2463 (0.24%)	Lamotrigine and duloxetine 18/10,061 (0.18%)	Crude PR = 1.98 (0.71–5.54) PS-adjusted PR = 3.85 (1.21–12.25) MH-adjusted PR = 1.70 (0.61–4.69)
	Dudukina et al., 2023	Eye	First trimester exposure NR/2691	ASM-unexposed NR/3,063,173	Crude PR = 1.92 (1.03–3.57) PS-adjusted PR = 2.09 (1.12–3.90) MH-adjusted PR = 1.88 (1.01–3.49)

Table 4 (Continued)

Reference number	Author and year	Outcomes investigated	Exposure No events/No participants (%)	Comparison No events/No participants (%)	Results Measure of association (95% CI)
	Dudukina et al., 2023	Congenital heart defects	First trimester exposure NR/2691	ASM-unexposed NR/3,063,173	Crude PR = 1.36 (1.06–1.74) PS-adjusted PR = 1.08 (0.84–1.39) MH-adjusted PR = 1.07 (0.84–1.37)
	Dudukina et al., 2023	Oro-facial clefts	First trimester exposure 5/2691 (0.19%)	ASM-unexposed 5541/3,063,173 (0.18%)	Crude PR = 2.90 (1.21–6.98) PS-adjusted PR = 2.90 (1.19–7.04) MH-adjusted PR = 0.87 (0.36–2.10)
	Dudukina et al., 2023	Oro-facial clefts	First trimester exposure 5/2586 (0.19%)	Lamotrigine 14/7,216 (0.19%)	Crude PR = 3.02 (0.88–10.34) PS-adjusted PR = 4.21 (1.23–14.42) MH-adjusted PR = 0.87 (0.37–2.04)
	Dudukina et al., 2023	Oro-facial clefts	First trimester exposure 5/2557 (0.20%)	Duloxetine 5/2972 (0.17%)	Crude PR = 1.39 (0.27–7.20) PS-adjusted PR = 3.30 (0.54–20.27) MH-adjusted PR = 2.18 (0.51–9.36)
	Dudukina et al., 2023	Oro-facial clefts	First trimester exposure NR/2463	Lamotrigine and duloxetine NR/10,061	Crude PR = 3.34 (1.06–10.54) PS-adjusted PR = 4.97 (1.56–15.86) MH-adjusted PR = 1.03 (0.43–2.44)
	Dudukina et al., 2023	Digestive system	First trimester exposure 7/2691 (0.26%)	ASM-unexposed 6921/3,063,173 (0.23%)	Crude PR = 1.30 (0.62–2.73) PS-adjusted PR = 1.02 (0.48–2.15) MH-adjusted PR = 0.90 (0.43–1.90)
	Dudukina et al., 2023	Digestive system	First trimester exposure 7/2586 (0.27%)	Lamotrigine 22/7,216 (0.30%)	Crude PR = 1.05 (0.44–2.51) PS-adjusted PR = 1.54 (0.60–4.00) MH-adjusted PR = 1.47 (0.60–3.60)

Table 4 (Continued)

Reference number	Author and year	Outcomes investigated	Exposure No events/No participants (%)	Comparison No events/No participants (%)	Results Measure of association (95% CI)
	Dudukina et al., 2023	Digestive system	First trimester exposure 7/2463 (0.28%)	Lamotrigine and duloxetine 29/10,061 (0.29%)	Crude PR = 1.19 (0.51–2.76) PS-adjusted PR = 1.34 (0.56–3.22) MH-adjusted PR = 1.22 (0.53–2.78)
	Dudukina et al., 2023	Urinary	First trimester exposure 15/2691 (0.56%)	ASM-unexposed 11,394/3,063,173 (0.37%)	Crude PR = 1.49 (0.90–2.48) PS-adjusted PR = 1.41 (0.85–2.35) MH-adjusted PR = 1.27 (0.77–2.11)
	Dudukina et al., 2023	Urinary	First trimester exposure NR/2586	Lamotrigine NR/7216	Crude PR = 1.29 (0.67–2.51) PS-adjusted PR = 3.02 (1.34–6.80) MH-adjusted PR = 2.53 (1.09–5.86)
	Dudukina et al., 2023	Urinary	First trimester exposure 12/2463 (0.49%)	Lamotrigine and duloxetine 45/10,061 (0.45%)	Crude PR = 1.14 (0.60–2.20) PS-adjusted PR = 1.66 (0.80–3.45) MH-adjusted PR = 1.37 (0.67–2.80)
	Dudukina et al., 2023	Genital	First trimester exposure NR/2586	Lamotrigine NR/7216	Crude PR = 2.00 (0.99–4.03) PS-adjusted PR = 2.13 (1.05–4.31) MH-adjusted PR = 1.94 (0.97–3.89)
	Dudukina et al., 2023	Genital	First trimester exposure NR/2557	Duloxetine NR/2972	Crude PR = 0.96 (0.49–1.90) PS-adjusted PR = 2.64 (1.13–6.16) MH-adjusted PR = 2.69 (1.09–6.65)
	Dudukina et al., 2023	Genital	First trimester exposure NR/2463	Lamotrigine and duloxetine NR/10,061	Crude PR = 1.45 (0.79–2.68) PS-adjusted PR = 2.26 (1.16–4.38) MH-adjusted PR = 2.03 (1.06–3.87)

Table 4 (Continued)

Reference number	Author and year	Outcomes investigated	Exposure No events/No participants (%)	Comparison No events/No participants (%)	Results Measure of association (95% CI)
	Dudukina et al., 2023	Limb	First trimester exposure 29/2691 (1.08%)	ASM-unexposed 30,308/3,063,173 (0.99%)	Crude PR = 1.02 (0.71–1.47) PS-adjusted PR = 0.93 (0.64–1.34) MH-adjusted PR = 0.93 (0.65–1.33)
	Dudukina et al., 2023	Limb	First trimester exposure 28/2586 (1.08%)	Lamotrigine 84/7216 (1.16%)	Crude PR = 0.86 (0.54–1.35) PS-adjusted PR = 1.61 (0.86–3.01) MH-adjusted PR = 1.12 (0.71–1.77)
	Dudukina et al., 2023	Limb	First trimester exposure 27/2463 (1.10%)	Lamotrigine and duloxetine 111/10,061 (1.10%)	Crude PR = 0.90 (0.58–1.39) PS-adjusted PR = 1.11 (0.67–1.84) MH-adjusted PR = 1.05 (0.68–1.62)
	Dudukina et al., 2023	Other	First trimester exposure 24/2691 (0.89%)	ASM-unexposed 14,534/3,063,173 (0.47%)	Crude PR = 1.82 (1.22–2.71) PS-adjusted PR = 1.42 (0.95–2.13) MH-adjusted PR = 1.32 (0.89–1.97)
	Dudukina et al., 2023	Other	First trimester exposure NR/2586	Lamotrigine NR/7216	Crude PR = 1.37 (0.80–2.35) PS-adjusted PR = 2.33 (1.21–4.47) MH-adjusted PR = 2.10 (1.16–3.81)
Gabapentin exposure Overall congenital anomalies [32]	Desrochers et al., 2024	Major congenital anomalies detected up to 1 year	First trimester exposure 41/870 (4.70%)	Unexposed 10,390/288,357 (3.60%)	Crude OR = 1.30 (0.94–1.81) Adjusted OR = 1.00 (0.72–1.38)
[36]	Källén et al., 2013	Relatively severe malformations	Monotherapy in early pregnancy 2/119 (1.68%)	Total population 49,499/1,575,847 (3.14%)	Not reported
[54]	Mølgaard-Nielsen et al., 2011	Major congenital anomalies detected up to 1 year	1/59 (1.70%)	Unexposed to any newer-generation antiepileptic drugs during pregnancy 19,911/83,6263 (2.40%)	Crude POR = 0.71 (0.10–5.10) Adjusted POR = 0.53 (0.07–3.85)

Table 4 (Continued)

Reference number	Author and year	Outcomes investigated	Exposure No events/No participants (%)	Comparison No events/No participants (%)	Results Measure of association (95% CI)
[42]	Morrow et al., 2006	Major congenital anomalies detected up to 6 weeks after birth	Monotherapy 1/31 (3.23%)	Carbamazepine monotherapy 20/900 (2.22%)	Crude OR = 1.33 (0.17–10.20) Adjusted OR = 0.76 (0.22–14.49)
[30]	Patorno et al., 2020	Major congenital anomalies detected up to 3 months after birth	First trimester exposure 230/4642 (4.95%)	Unexposed 58,086/1,744,447 (3.33%)	Crude RR = 1.49 (1.31–1.69) Adjusted RR = 1.07 (0.94–1.21)
Specific congenital anomalies ^a					
[40]	Blotière et al., 2019	Spina bifida (detected up to 12 months after birth)	Monotherapy 1/365 (0.27%)	Unexposed 616/1,875,733 (0.03%)	Crude OR = 8.4 (0.2–47.1)
	Blotière et al., 2019	Ventricular septal defect (detected up to 12 months after birth)	Monotherapy 1/365 (0.27%)	Unexposed 4643/1,875,733 (0.25%)	Crude OR = 1.1 (0.0–6.3)
	Blotière et al., 2019	Hypospadias (detected up to 24 months after birth)	Monotherapy 1/365 (0.27%)	Unexposed 3371/1,875,733 (0.18%)	Crude OR = 1.6 (0.0–8.9)
[32]	Desrochers et al., 2024	Cardiac anomalies detected up to 1 year	First trimester exposure 14/870 (1.61%)	Unexposed 2255/288,357 (0.78%)	Crude OR = 2.01 (1.12–3.62) Adjusted OR = 1.29 (0.72–2.31)
[32]	Desrochers et al., 2024	Oro-facial anomalies	First trimester exposure ≤ 5/870	Unexposed 648/288,357 (0.22%)	Crude OR = 1.97 (0.69–5.60) Adjusted OR = 1.37 (0.50–3.77)
[30]	Patorno et al., 2020	Major cardiac anomalies	First trimester exposure 87/4642 (1.87%)	Unexposed 18,514/1,744,447 (1.06%)	Crude RR = 1.77 (1.43–2.18) Adjusted RR = 1.12 (0.89–1.40)

ASM: antiseizure medications; CI: confidence interval; MH: Mantel–Haenszel; NR: not reportable to keep masking of a low number of individuals (< 5) in other cells; OR: odds ratio; POR: proportion odds ratio; PR: prevalence ratio; PS: propensity score; RR: relative risk.

^a Only finding with at least one exposed case are reported.

^b Only significant findings or findings with at least 5 exposed cases are reported, in bold significant results.

Table 5 Overview of pregnancy and short-term children outcomes risks described in the studies following exposure to gabapentinoids.

Reference number	Author and year	Outcomes investigated	Exposure No events/No participants (%)	Comparison No events/No participants (%)	Results Measure of association (95% CI)
Pregnancy outcomes Pregabalin exposure [39] ^a	Dudukina et al., 2023	Stillbirth	NR/2851	ASM-unexposed NR/3,061,487	Crude PR = 2.14 (1.27–3.60) PS-adjusted PR = 1.72 (1.02–2.91) MH-adjusted PR = 1.25 (0.74–2.11)
	Dudukina et al., 2023	Stillbirth	NR/2740	Lamotrigine NR/7742	Crude PR = 2.24 (1.10–4.57) PS-adjusted PR = 1.87 (0.81–4.32) MH-adjusted PR = 1.30 (0.69–2.47)
	Dudukina et al., 2023	Stillbirth	NR/2609	Lamotrigine and duloxetine NR/10,631	Crude PR = 2.09 (1.05–4.17) PS-adjusted PR = 2.71 (1.25–5.90) MH-adjusted PR = 1.93 (0.98–3.78)
	Dudukina et al., 2023	Preterm birth	225/2812 (8.00%)	ASM-unexposed 151,114/3,009,386 (5.02%)	Crude PR = 1.78 (1.57–2.03) PS-adjusted PR = 1.13 (1.00–1.29) MH-adjusted PR = 1.12 (0.99–1.27)
	Dudukina et al., 2023	Preterm birth	217/2704 (8.03%)	Lamotrigine 578/7580 (7.63%)	Crude PR = 1.28 (1.10–1.51) PS-adjusted PR = 0.98 (0.83–1.15) MH-adjusted PR = 0.99 (0.85–1.15)
	Dudukina et al., 2023	Preterm birth	207/2674 (7.74%)	Duloxetine 248/2967 (8.36%)	Crude PR = 1.03 (0.85–1.24) PS-adjusted PR = 1.04 (0.86–1.27) MH-adjusted PR = 1.04 (0.87–1.24)
	Dudukina et al., 2023	Preterm birth	201/2577 (7.80%)	Lamotrigine and/or duloxetine 810/10,418 (7.78%)	Crude PR = 1.21 (1.04–1.42) PS-adjusted PR = 1.05 (0.89–1.23) MH-adjusted PR = 1.06 (0.92–1.23)

Table 5 (Continued)

Reference number	Author and year	Outcomes investigated	Exposure No events/No participants (%)	Comparison No events/No participants (%)	Results Measure of association (95% CI)
[45]	Forbes et al., 2024	Miscarriage	165/882 (18.71%)	Lamotrigine 253/1916 (13.20%)	Fully-adjusted HR = 1.13 (0.89–1.44)
[45]	Forbes et al., 2024	Miscarriage	Among women with epilepsy 13/37 (35.14%)	Among women with epilepsy Lamotrigine 208/1656 (12.56%)	Fully-adjusted HR = 2.18 (1.38–3.44)
[45]	Forbes et al., 2024	Miscarriage	Among women with bipolar or other psychiatric conditions 153/831 (18.41%)	Among women with bipolar or other psychiatric conditions Lamotrigine 142/983 (14.45%)	Fully-adjusted HR = 1.12 (0.86–1.46)
[45]	Forbes et al., 2024	Miscarriage	Among women with other somatic conditions 88/434 (20.28%)	Among women with other somatic conditions 56/371 (15.09%)	Fully-adjusted HR = 0.98 (0.66–1.46)
[43]	Kilic et al., 2014	Preterm birth	Monotherapy 4/18 (22.22%)	No ASM 33,974/676,834 (5.02%)	Not reported
[44]	Margulis et al., 2019	Preterm birth	76/562 (13.52%)	Lamotrigine 180/2254 (7.99%)	Adjusted OR = 1.5 (1.0–2.4) Among mother with epilepsy: crude OR = 4.2 (1.6–11.4) Among first trimester user: crude OR = 1.9 (1.2–3.0)
Gabapentin exposure					
[45]	Forbes et al., 2024	Miscarriage	201/1224 (16.42%)	Lamotrigine 253/1916 (13.20%)	Fully-adjusted HR = 1.00 (0.80–1.26)
[45]	Forbes et al., 2024	Miscarriage	Among women with epilepsy 11/75 (14.67%)	Among women with epilepsy Lamotrigine 208/1656 (12.56%)	Fully-adjusted HR = 1.13 (0.65–1.97)
[45]	Forbes et al., 2024	Miscarriage	Among women with bipolar or other psychiatric conditions 183/1105 (16.56%)	Among women with bipolar or other psychiatric conditions Lamotrigine 142/983 (14.45%)	Fully-adjusted HR = 1.02 (0.79–1.31)

Table 5 (Continued)

Reference number	Author and year	Outcomes investigated	Exposure No events/No participants (%)	Comparison No events/No participants (%)	Results Measure of association (95% CI)
[45]	Forbes et al., 2024	Miscarriage	Among women with other somatic conditions 91/565 (16.11%)	Among women with other somatic conditions 56/371 (15.09%)	Fully-adjusted HR = 0.80 (0.54–1.17)
[43]	Kilic et al., 2014	Preterm birth	Monotherapy 11/91 (12.09%)	No ASM 33,974/676,834 (5.02%)	Crude RR = 2.41 (1.39–4.17)
[30]	Patorno et al., 2020	Preterm birth	Exposure early in pregnancy 571/3745 (15.25%)	Unexposed 182,445/1,744,447 (10.46%)	Crude RR = 1.46 (1.35–1.57) Adjusted RR = 1.00 (0.93–1.08)
	Patorno et al., 2020	Preterm birth	Exposure late in pregnancy 107/556 (19.24%)	Unexposed 182,445/1,744,447 (10.46%)	Crude RR = 1.84 (1.55–2.18) Adjusted RR = 1.28 (1.08–1.52)
	Patorno et al., 2020	Preterm birth	Exposure early and late in pregnancy 258/1275 (20.24%)	Unexposed 182,445/1,744,447 (10.46%)	Crude RR = 1.93 (1.73–2.16) Adjusted RR = 1.22 (1.09–1.36)
	Patorno et al., 2020	Preeclampsia	Exposure early in pregnancy 182/3745 (4.86%)	Unexposed 72,197/1,744,447 (4.14%)	Crude RR = 1.17 (1.01–1.35) Adjusted RR = 0.87 (0.75–1.00)
	Patorno et al., 2020	Preeclampsia	Exposure late in pregnancy 33/556 (5.94%)	Unexposed 72,197/1,744,447 (4.14%)	Crude RR = 1.43 (1.03–2.00) Adjusted RR = 1.43 (1.03–2.00)
	Patorno et al., 2020	Preeclampsia	Exposure early and late in pregnancy 80/1275 (6.27%)	Unexposed 72,197/1,744,447 (4.14%)	Crude RR = 1.52 (1.23–1.87) Adjusted RR = 0.92 (0.74–1.13)
Short-term children outcomes Pregabalin exposure [47]	Christensen et al., 2024	Low birth weight	Monotherapy 136/2214 (6.14%)	ASM-unexposed 141,442/4,467,848 (3.17%)	Adjusted OR = 1.23 (1.03–1.47) Among children with mother with epilepsy: Adjusted OR = 0.92 (0.44–1.92) Among children with mother without epilepsy: Adjusted OR = 1.25 (1.04–1.51)

Table 5 (Continued)

Reference number	Author and year	Outcomes investigated	Exposure No events/No participants (%)	Comparison No events/No participants (%)	Results Measure of association (95% CI)
[47]	Christensen et al., 2024	Small for gestational age	Monotherapy 318/2214 (14.36%)	ASM-unexposed 446,267/4,467,848 (9.99%)	Adjusted OR = 1.16 (1.02–1.31) Among children with mother with epilepsy: Adjusted OR= 1.01 (0.58–1.77) Among children with mother without epilepsy: Adjusted OR = 1.17 (1.03–1.32)
[47]	Christensen et al., 2024	Microcephaly	Monotherapy 83/2214 (3.75%)	ASM-unexposed 134,023/4,467,848 (3.00%)	Adjusted OR = 1.01 (0.80–1.27) Among children with mother with epilepsy: NA Among children with mother without epilepsy: Adjusted OR = 1.02 (0.80–1.28)
[39] ^a	Dudukina et al., 2023	Small for gestational age	NR/2776	ASM-unexposed NR/2,959,022	Crude PR = 1.55 (1.25–1.91) PS-adjusted PR = 1.12 (0.91–1.39) MH-adjusted PR = 1.10 (0.90–1.36)
	Dudukina et al., 2023	Small for gestational age	NR/2669	Lamotrigine NR/7461	Crude PR = 1.56 (1.17–2.09) PS-adjusted PR = 1.06 (0.79–1.42) MH-adjusted PR = 1.09 (0.84–1.43)
	Dudukina et al., 2023	Small for gestational age	NR/2543	Lamotrigine and/or duloxetine NR/10,280	Crude PR = 1.41 (1.08–1.83) PS-adjusted PR = 0.99 (0.75–1.31) MH-adjusted PR = 0.93 (0.73–1.19)
	Dudukina et al., 2023	Low birth weight	178/2811 (6.33%)	ASM-unexposed 121,039/3,009,100 (4.02%)	Crude PR = 1.60 (1.38–1.85) PS-adjusted PR = 1.04 (0.90–1.21) MH-adjusted PR = 1.04 (0.90–1.20)
	Dudukina et al., 2023	Low birth weight	172/2703 (6.36%)	Lamotrigine 394/7578 (5.20%)	Crude PR = 1.28 (1.06–1.55) PS-adjusted PR = 0.91 (0.75–1.10) MH-adjusted PR = 0.94 (0.79–1.11)

Table 5 (Continued)

Reference number	Author and year	Outcomes investigated	Exposure No events/No participants (%)	Comparison No events/No participants (%)	Results Measure of association (95% CI)
	Dudukina et al., 2023	Low birth weight	166/2673 (6.21%)	Duloxetine 187/2966 (6.30%)	Crude PR = 0.97 (0.78–1.20) PS-adjusted PR = 0.80 (0.64–1.00) MH-adjusted PR = 0.78 (0.64–0.95)
	Dudukina et al., 2023	Low birth weight	162/2576 (6.29%)	Lamotrigine and/or duloxetine 574/10,415 (5.51%)	Crude PR = 1.17 (0.97–1.40) PS-adjusted PR = 0.87 (0.72–1.05) MH-adjusted PR = 0.87 (0.74–1.03)
	Dudukina et al., 2023	Low Apgar score	81/2812 (2.88%)	ASM-unexposed 39,807/3,009,480 (1.32%)	Crude PR = 2.05 (1.65–2.55) PS-adjusted PR = 1.17 (0.94–1.46) MH-adjusted PR = 1.16 (0.94–1.44)
	Dudukina et al., 2023	Low Apgar score	76/2704 (2.81%)	Lamotrigine 165/7580 (2.18%)	Crude PR = 1.05 (0.79–1.39) PS-adjusted PR = 0.93 (0.69–1.26) MH-adjusted PR = 0.86 (0.66–1.12)
	Dudukina et al., 2023	Low Apgar score	70/2577 (2.72%)	Lamotrigine and/or duloxetine 233/10,418 (2.24%)	Crude PR = 1.01 (0.77–1.33) PS-adjusted PR = 0.86 (0.64–1.15) MH-adjusted PR = 0.83 (0.64–1.08)
	Dudukina et al., 2023	Microcephaly	69/2762 (2.50%)	ASM-unexposed 56,404/2,940,009 (1.92%)	Crude PR = 1.34 (1.06–1.69) PS-adjusted PR = 1.10 (0.86–1.40) MH-adjusted PR = 1.10 (0.87–1.38)
	Dudukina et al., 2023	Microcephaly	64/2654 (2.41%)	Lamotrigine 156/7419 (2.10%)	Crude PR = 1.06 (0.77–1.44) PS-adjusted PR = 1.01 (0.72–1.43) MH-adjusted PR = 1.05 (0.77–1.44)
	Dudukina et al., 2023	Microcephaly	66/2625 (2.51%)	Duloxetine 52/2936 (1.77%)	Crude PR = 1.27 (0.87–1.85) PS-adjusted PR = 1.05 (0.70–1.58) MH-adjusted PR = 1.06 (0.74–1.51)

Table 5 (Continued)

Reference number	Author and year	Outcomes investigated	Exposure No events/No participants (%)	Comparison No events/No participants (%)	Results Measure of association (95% CI)
	Dudukina et al., 2023	Microcephaly	62/2528 (2.45%)	Lamotrigine and/or duloxetine 207/10,227 (2.02%)	Crude PR = 1.13 (0.84–1.52) PS-adjusted PR = 1.07 (0.77–1.48) MH-adjusted PR = 1.07 (0.80–1.44) Not reported
[43]	Kilic et al., 2014	Low birth weight	Monotherapy 3/18 (16.67%)	No ASM 23,503/673,844 (3.49%)	Not reported
	Kilic et al., 2014	Small for gestational age	Monotherapy 5/18 (27.78%)	No ASM 65,118/673,844 (9.66%)	Not reported
[44]	Margulis et al., 2019	Birth weight z-score	Mean: -0.2 ± 1.1 $n = 561$	Lamotrigine Mean: 0.0 ± 1.1 , $n = 2248$	Mean difference: -0.1 (-0.3 to 0.0)
	Margulis et al., 2019	Birth length z-score	Mean: -0.3 ± 1.0 $n = 553$	Lamotrigine Mean: 0.0 ± 1.0 , $n = 2218$	Mean difference: -0.1 (-0.2 to 0.0)
	Margulis et al., 2019	Birth head circumference z-score	Mean: 0.1 ± 1.1 $n = 549$	Lamotrigine Mean: 0.2 ± 1.1 , $n = 2193$	Mean difference: -0.0 (-0.1 to 0.1)
	Margulis et al., 2019	Microcephaly	15/549 (2.73%)	Lamotrigine 48/2193 (2.19%)	Adjusted OR = 1.2 (0.5–2.9)
	Margulis et al., 2019	Small for gestational age	22/547 (4.02%)	Lamotrigine 52/2184 (2.38%)	Adjusted OR = 1.3 (0.6–3.0)
Gabapentin exposure [46]	Almgren et al., 2009	Birth weight-adjusted mean head circumference (mean SDS from population control material)	Monotherapy $n = 56$ children	Population control $n = 900,739$ children	SDS, Mean \pm SEM; P -value: -0.02 ± 0.13 ; 0.39

Table 5 (Continued)

Reference number	Author and year	Outcomes investigated	Exposure No events/No participants (%)	Comparison No events/No participants (%)	Results Measure of association (95% CI)
[47]	Christensen et al., 2024	Low birth weight	Monotherapy 76/1336 (5.69%)	No ASM 141,442/4,467,848 (3.17%)	Adjusted OR = 1.25 (0.98–1.59) Among children with mother with epilepsy: Adjusted OR = 1.04 (0.50–2.14) Among children with mother without epilepsy: Adjusted OR = 1.28 (1.00–1.66)
[47]	Christensen et al., 2024	Small for gestational age	Monotherapy 168/1336 (12.57%)	No ASM 446,267/4,467,848 (9.99%)	Adjusted OR = 1.13 (0.96–1.34) Among children with mother with epilepsy: Adjusted OR = 0.91 (0.52–1.57) Among children with mother without epilepsy: Adjusted OR = 1.16 (0.97–1.38)
[47]	Christensen et al., 2024	Microcephaly	Monotherapy 32/1336 (2.40%)	No ASM 134,023/4,467,848 (3.00%)	Adjusted OR = 0.67 (0.46–0.97) Among children with mother with epilepsy: NA Among children with mother without epilepsy: Adjusted OR = 0.69 (0.47–1.02)
[32]	Desrochers et al., 2024	NICU admission	78/870 (8.97%)	Unexposed 17,689/288,357 (6.13%)	Crude OR = 3.40 (2.85–4.05) Adjusted OR = 2.18 (1.81–2.62)
[43]	Kilic et al., 2014	Low birth weight	Monotherapy 5/91 (5.49%)	No ASM 23,503/673,844 (3.49%)	Crude RR = 1.58 (0.67–3.70)

Table 5 (Continued)

Reference number	Author and year	Outcomes investigated	Exposure No events/No participants (%)	Comparison No events/No participants (%)	Results Measure of association (95% CI)
[30]	Kilic et al., 2014	Small for gestational age	Monotherapy 11/91 (12.09%)	No ASM 65,118/673,844 (9.66%)	Crude RR = 1.25 (0.72–2.18)
	Patorno et al., 2020	Small for gestational age	Exposure early in pregnancy 205/3745 (5.47%)	Unexposed 55,803/1,744,447 (3.20%)	Crude RR = 1.71 (1.50–1.96) Adjusted RR = 1.17 (1.02–1.33)
	Patorno et al., 2020	Small for gestational age	Exposure late in pregnancy 35/556 (6.29%)	Unexposed 55,803/1,744,447 (3.20%)	Crude RR = 1.97 (1.43–2.71) Adjusted RR = 1.39 (1.01–1.91)
	Patorno et al., 2020	Small for gestational age	Exposure early and late in pregnancy 92/1275 (7.22%)	Unexposed 55,803/1,744,447 (3.20%)	Crude RR = 2.26 (1.85–2.75) Adjusted RR = 1.32 (1.08–1.60)
	Patorno et al., 2020	NICU admission	Exposure early in pregnancy 411/3745 (10.97%)	Unexposed 101,202/1,744,447 (5.80%)	Crude RR = 1.89 (1.73–2.07) Adjusted RR = 1.01 (0.93–1.11)
	Patorno et al., 2020	NICU admission	Exposure late in pregnancy 68/556 (12.23%)	Unexposed 101,202/1,744,447 (5.80%)	Crude RR = 2.11 (1.69–2.63) Adjusted RR = 1.21 (0.97–1.51)
	Patorno et al., 2020	NICU admission	Exposure early and late in pregnancy 224/1275 (17.57%)	Unexposed 101,202/1,744,447 (5.80%)	Crude RR = 3.03 (2.69–3.41) Adjusted RR = 1.35 (1.20–1.52)

ASM: antiseizure medications; CI: confidence interval; MH: Mantel–Haenszel; NICU: neonatal intensive care unit; NR: not reportable to keep masking of a low number of individuals (< 5) in other cells; OR: odds ratio; PR: prevalence ratio; PS: propensity score; RR: relative risk; SGA: small-for-gestational-age.

^a Only significant findings or findings with at least 5 exposed cases are reported, in bold significant results.

stratified by conditions, the increased were only observed among children with mother without epilepsy [47]. When comparing gabapentin exposure to no exposure during pregnancy, one study reported an increased risk of SGA (adjusted RR = 1.39 [95% CI: 1.01–1.91], 35 exposed cases late in pregnancy) and an increased risk of NICU admission (adjusted RR = 1.35 [95% CI: 1.20–1.52], 224 exposed cases early and late in pregnancy) [30]. The increase risk of NICU admission was also observed in a second study (adjusted OR = 2.18 [95% CI: 1.81–2.62], 78 exposed cases) [32]. No increased risk was observed in the remaining studies [39,43,44,46] (Table 5).

Long-term outcomes in children

Six studies examined overall neurodevelopmental disorders outcomes, as well as specific outcomes (such as autism spectrum disorder or mental retardation), learning disabilities and speech therapist visits [39,48–52]. One study reported an increased risk of hyperkinetic disorders following exposure to pregabalin when compared with no ASM-exposure (adjusted HR = 1.29 [95% CI: 1.03–1.63], 72 exposed cases), but the association was not present when compared with lamotrigine and/or duloxetine exposure [39]. Another one reported an increased risk of mental retardation (adjusted HR = 3.1 [95% CI: 1.2–8.3], 4 exposed cases) and utilization of orthoptics services (adjusted HR = 1.4 [95% CI: 1.1–1.6], 98 exposed cases) after monotherapy exposure to pregabalin when compared with no ASM-exposure in the absence of maternal mental illness [50]. No increased risk was observed after prenatal exposure to gabapentin [48–52] (Table 6).

Discussion

Main findings

The objective of this systematic review was to comprehensively analyze the existing literature on gabapentinoid use during pregnancy and its association with adverse pregnancy/childhood outcomes, as well as to identify research gaps in this area. The prevalence of gabapentinoid use during pregnancy remained very low, at less than 1%. Three studies reported an increased risk of overall congenital anomalies, certain specific anomalies (nervous system, eyes, oro-facial clefts, and genital system), miscarriage, stillbirth and specific neurodevelopmental outcomes after exposure to pregabalin during pregnancy [39,40,50]. Concerning exposure to gabapentin, increased risks of preterm birth, preeclampsia, small-for-gestational-age and NICU admission were reported in two studies [30,32].

Interpretation

All studies reported a very low prevalence of gabapentinoid use during pregnancy, below 1% in the general population of pregnant women. However, the prevalence of use varied by country, with lower rates observed in Europe (below 0.05%) compared to the US or Canada. The prevalence of use of pregabalin were higher in France and UK (but still below 1%) compared to other European countries. Although limited data on gabapentinoid use over time were available, it seemed that an increase in use was observed in recent years.

Animal safety studies following prenatal exposure to gabapentinoids have shown some adverse effects on embryo development and viability. In mice, gabapentin exposure at doses ranging from 1 to 5 times the human equivalent was associated with fetal growth retardation [8], and increased incidence of hydroureter and hydronephrosis, conditions previously linked to developmental delay. Rabbits exposed during gestation to gabapentin at 0.3 to 8 times the human dose exhibited a higher rate of fetal loss [9]. Furthermore, an increased incidence of skeletal malformations was observed after prenatal exposure to pregabalin in mice [10]. While these findings from animals may not directly extrapolate to humans, they raise potential concerns that necessitate further investigation.

Regarding the risks associated with pregabalin, one recent large multicentric study with rigorous methodology reported an increase in risk of major congenital anomalies after first trimester exposure to pregabalin [39]. Sensitivity analyses showed similar results for monotherapy exposure [39]. The strengths of the study include a large sample size (including around 3 million pregnancies with more than 100 exposed cases), the use of national health registers in 4 countries (allowing accurate identification of the exposure and the outcomes), the use of several comparison groups (including active comparators) to strengthen the results, and the control for a large set of covariates. For specific congenital anomalies, no clear conclusions could be drawn from the limited number of studies investigating this aspect [39,40]. Significant signals were identified after exposure to pregabalin for anomalies from the nervous system, eyes, oro-facial clefts, urinary and genital system [39]. Although the results were not consistent across all the comparison groups, making it difficult to interpret the results, it is important to explore these signals further. In addition, an increased risk of coarctation of aorta was found after exposure to pregabalin monotherapy, however there were only 4 exposed cases and the study did not control for covariates [40]. Regarding pregnancy outcomes, one study pointed towards an increased risk of stillbirth after exposure to pregabalin [39]; however, this analysis was based on very few cases. Additionally, a recent study reported an increased risk of miscarriage among women with epilepsy [45], but this was not observed among women with psychiatric or somatic conditions, which are the primary conditions treated by gabapentinoids. Increased risk of low birth weight and SGA were reported in one study only, and especially among the children with mother without epilepsy [47].

The data on gabapentin exposure showed reassuring results regarding the risk of congenital anomalies, but the limited number of exposed cases in some studies limits the generalizability of these findings. The largest study including around 200 exposed cases (in mono or polytherapy), reported no significant association after adjustment for the covariates [30]. However, the authors presented in a subsequent post-hoc analyses a potential increase in the risk of conotruncal defects that should be investigated further [30]. The same study also reported an increased risk of preterm birth, preeclampsia, small-for-gestational-age and NICU admission after exposure to gabapentin [30]. The strengths of the study include a large sample size (including around 1.7 million pregnancies with around 4500 exposed women during the first trimester of pregnancy), the use of

Table 6 Overview of long-term children outcomes risks described in the studies following exposure to gabapentinoids.

Reference number	Author and year	Outcomes investigated	Exposure No events/No participants (%)	Comparison No events/No participants (%)	Results Measure of association	Other results
Pregabalin exposure						
Overall neurodevelopmental disorders						
[48]	Bjørk et al., 2022	Any neurodevelopmental disorder (ICD-10 codes: F70-F73, F79, F84.0, F84.1, F84.3, F84.4, F84.5, F84.8, F84.9)	Monotherapy 33/2064 (1.60%)	Women discontinuing pregabalin before pregnancy 51/3195 (1.60%)	Adjusted HR = 0.86 (0.54–1.38)	
[49]	Blotière et al., 2020	Neurodevelopmental disorders (ICD-10 codes: F70–F98)	Monotherapy 28/not reported (5.0 per 1000 PY)	Lamotrigine monotherapy 51/not reported (4.9 per 1000 PY)	Adjusted HR = 0.6 (0.4–1.0)	
[50]	Coste et al., 2020	Neurodevelopmental disorders (ICD-10 codes: F70–F98)	Monotherapy 28/not reported (5.0 per 1000 PY)	Unexposed 15,270/not reported (2.5 per 1000 PY)	Adjusted HR = 1.5 (1.0–2.1)	Among children born to a mother with no known mental illness
[51]	Dreier et al., 2023	Combined Psychiatric End Point (ICD-10 codes: F)	Monotherapy 8/120 (6.67%)	No ASM among women with epilepsy 1892/22,203 (8.52%)	Basic adjusted HR = 1.61 (0.80–3.26) Full adjusted HR = 1.06 (0.52–2.16)	Adjusted HR = 1.3 (0.6–2.7)
Specific neurodevelopmental disorders						
[48]	Bjørk et al., 2022	Intellectual disability (ICD-10 codes: F70-F73)	Monotherapy 5/1666 (0.60 [95% CI: 0.25–1.45] per 1000 PY)	General population 16,384/4,463,879 (0.42 [95% CI: 0.42–0.43] per 1,000 PY)	Adjusted HR = 1.31 (0.54–3.14)	
	Bjørk et al., 2022	Autism spectrum disorder (ICD-10 codes: F84.0, F84.1, F84.5)	Monotherapy 16/1666 (1.93 [95% CI: 1.18–3.15] per 1000 PY)	General population 38,437/4,463,879 (1.00 [95% CI: 0.99–1.01] per 1000 PY)	Adjusted HR = 1.55 (0.95–2.54)	

Table 6 (Continued)

Reference number	Author and year	Outcomes investigated	Exposure No events/No participants (%)	Comparison No events/No participants (%)	Results Measure of association	Other results
[49]	Blotière et al., 2020	Pervasive developmental disorders (ICD-10 codes: F84)	Monotherapy 7/not reported (1.2 per 1000 PY)	Lamotrigine monotherapy 11/not reported (1.1 per 1000 PY)	Adjusted HR = 1.1 (0.4–3.0)	
	Blotière et al., 2020	Mental retardation (ICD-10 codes: F70–F79)	Monotherapy 7/not reported (1.2 per 1,000 PY)	Lamotrigine monotherapy 15/not reported (1.4 per 1000 PY)	Adjusted HR = 0.6 (0.2–1.8)	
	Blotière et al., 2020	Visits to a speech therapist	Monotherapy 61/not reported (11.0 per 1000 PY)	Lamotrigine monotherapy 157/not reported (15.2 per 1000 PY)	Adjusted HR = 0.7 (0.4–1.2)	
[50]	Coste et al., 2020	Pervasive developmental disorders (ICD-10 codes: F84)	Monotherapy 7/not reported (1.2 per 1000 PY)	Unexposed 4280/not reported (0.7 per 1000 PY)	Adjusted HR = 1.4 (0.7–2.9)	Among children born to a mother with no known mental illness Adjusted HR = 0.7 (0.1–4.8)
	Coste et al., 2020	Mental retardation (ICD-10 codes: F70–F79)	Monotherapy 7/not reported (1.2 per 1000 PY)	Unexposed 3398/not reported (0.6 per 1000 PY)	Adjusted HR = 1.7 (0.8–3.6)	Among children born to a mother with no known mental illness Adjusted HR = 3.1 (1.2–8.3)
	Coste et al., 2020	Disorders of psychological development (ICD-10 codes: F80–F89)	Monotherapy 16/not reported (2.9 per 1000 PY)	Unexposed 10,010/not reported (1.6 per 1000 PY)	Adjusted HR = 1.3 (0.8–2.2)	Among children born to a mother with no known mental illness Adjusted HR = 1.1 (0.4–3.0)
	Coste et al., 2020	Behavioural and emotional disorders with onset usually occurring in childhood and adolescence (ICD-10 codes: F90–F98)	Monotherapy 9/not reported (1.6 per 1000 PY)	Unexposed 4398/not reported (0.7 per 1000 PY)	Adjusted HR = 1.4 (0.8–2.8)	Among children born to a mother with no known mental illness Adjusted HR = 1.4 (0.3–5.5)

Table 6 (Continued)

Reference number	Author and year	Outcomes investigated	Exposure No events/No participants (%)	Comparison No events/No participants (%)	Results Measure of association	Other results
[50]	Coste et al., 2020	Health care utilization of speech therapy	Monotherapy 61/not reported (11.0 per 1000 PY)	Unexposed 72,012/not reported (1.6 per 1000 PY)	Adjusted HR = 0.9 (0.7–1.2)	Among children born to a mother with no known mental illness Adjusted HR = 1.0 (0.7–1.5)
	Coste et al., 2020	Health care utilization of orthoptics	Monotherapy 225/not reported (43.3 per 1000 PY)	Unexposed 203,489/not reported (1.6 per 1000 PY)	Adjusted HR = 1.2 (1.1–1.4)	Among children born to a mother with no known mental illness Adjusted HR = 1.4 (1.1–1.6)
	Coste et al., 2020	Health care utilization of psychiatry	Monotherapy 23/not reported (4.1 per 1000 PY)	Unexposed 22,365/not reported (1.6 per 1000 PY)	Adjusted HR = 0.9 (0.6–1.3)	Among children born to a mother with no known mental illness Adjusted HR = 1.0 (0.5–2.1)
[39] ^a	Dudukina et al., 2023	Hyperkinetic disorders including ADHD	72/14,315 PY (5.0 per 1000 PY)	ASM-unexposed 38,693/17,874,961 PY (2.2 per 1000 PY)	Crude HR = 3.62 (2.87–4.55) PS-adjusted HR = 1.29 (1.03–1.63) MH-adjusted HR = 1.22 (0.97–1.54)	
	Dudukina et al., 2023	Hyperkinetic disorders including ADHD	67/13,634 PY (4.9 per 1000 PY)	Lamotrigine 139/39,148 PY (3.6 per 1000 PY)	Crude HR = 1.52 (1.12–2.06) PS-adjusted HR = 1.04 (0.75–1.42) MH-adjusted HR = 1.06 (0.80–1.42)	
	Dudukina et al., 2023	Hyperkinetic disorders including ADHD	69/13,058 PY (5.3 per 1000 PY)	Lamotrigine and/or duloxetine 227/55,645 PY (4.1 per 1000 PY)	Crude HR = 1.54 (1.17–2.04) PS-adjusted HR = 1.20 (0.89–1.61) MH-adjusted HR = 1.12 (0.86–1.47)	

Table 6 (Continued)

Reference number	Author and year	Outcomes investigated	Exposure No events/No participants (%)	Comparison No events/No participants (%)	Results Measure of association	Other results	
Gabapentin exposure Overall neurodevelopmental disorders [48]	Dudukina et al., 2023	Pervasive development disorders including ASD	NR/NR	ASM-unexposed 21,180/17,891,330 PY (1.2 per 1000 PY)	Crude HR = 1.99 (1.38–2.89) PS-adjusted HR = 0.98 (0.67–1.42) MH-adjusted HR = 0.95 (0.66–1.38)		
	Dudukina et al., 2023	Intellectual disability	NR/NR	ASM-unexposed 45,943/17,796,832 PY (2.6 per 1000 PY)	Crude HR = 1.58 (1.23–2.02) PS-adjusted HR = 1.00 (0.78–1.29) MH-adjusted HR = 0.98 (0.77–1.26)		
	Bjørk et al., 2022	Any neurodevelopmental disorder (ICD-10 codes: F70-F73, F79, F84.0, F84.1, F84.3, F84.4, F84.5, F84.8, F84.9)	Monotherapy 19/1658 (1.15%)	Women discontinuing gabapentin before pregnancy 57/3402 (1.68%)	Adjusted HR = 0.54 (0.30–0.98)		
	[49]	Blotière et al., 2020	Neurodevelopmental disorders (ICD-10 codes: F70–F98)	Monotherapy 4/not reported (3.1 per 1000 PY)	Lamotrigine monotherapy 51/not reported (4.9 per 1000 PY)	Adjusted HR = 0.4 (0.1–1.3)	
	[50]	Coste et al., 2020	Neurodevelopmental disorders (ICD-10 codes: F70–F98)	Monotherapy 4/not reported (3.1 per 1000 PY)	Unexposed 15,270/not reported (2.5 per 1000 PY)	Adjusted HR = 0.8 (0.3–2.1)	Among children born to a mother with no known mental illness Adjusted HR = 1.4 (0.4–5.7)

Table 6 (Continued)

Reference number	Author and year	Outcomes investigated	Exposure No events/No participants (%)	Comparison No events/No participants (%)	Results Measure of association	Other results	
[51]	Dreier et al., 2023	Combined Psychiatric End Point (ICD-10 codes: F)	Monotherapy 16/138 (11.59%)	No ASM among women with epilepsy 1892/22,203 (8.52%)	Basic adjusted HR = 1.48 (0.90–2.42) Full adjusted HR = 1.30 (0.78–2.18)		
Specific neurodevelopmental disorders	[52]	Bech et al., 2018	Learning disabilities in the first year of compulsory education	Monotherapy < 4/29 (< 13.8%)	No ASM 16/434 (3.69%)	Adjusted OR = 1.22 (0.14–10.52)	
		Bech et al., 2018	Learning disabilities in the first year of compulsory education	Monotherapy < 4/29 (< 13.8%)	Another ASM 37/527 (7.02%)	Adjusted OR = 0.31 (0.04–2.58)	
	[48]	Bjørk et al., 2022	Autism spectrum disorder (ICD-10 codes: F84.0, F84.1, F84.5)	Monotherapy 8/965 (1.73 [95% CI: 0.87–3.46] per 1000 PY)	General population 38,437/4,463,879 (1.00 [95% CI: 0.99–1.01] per 1000 PY)	Adjusted HR = 1.25 (0.63–2.51)	
	[49]	Blotière et al., 2020	Pervasive developmental disorders (ICD-10 codes: F84)	Monotherapy 3/not reported (2.3 per 1000 PY)	Lamotrigine monotherapy 11/not reported (1.1 per 1000 PY)	Adjusted HR = 1.8 (0.4–7.0)	
	Blotière et al., 2020	Visits to a speech therapist	Monotherapy 11/not reported (8.5 per 1000 PY)	Lamotrigine monotherapy 157/not reported (15.2 per 1000 PY)	Adjusted HR = 0.7 (0.5–1.0)		

Table 6 (Continued)

Reference number	Author and year	Outcomes investigated	Exposure No events/No participants (%)	Comparison No events/No participants (%)	Results Measure of association	Other results
[50]	Coste et al., 2020	Pervasive developmental disorders (ICD-10 codes: F84)	Monotherapy 3/not reported (2.3 per 1000 PY)	Unexposed 4280/not reported (0.7 per 1000 PY)	Adjusted HR = 2.3 (0.8–7.3)	Among children born to a mother with no known mental illness Adjusted HR = 2.7 (0.4–19.2)
	Coste et al., 2020	Disorders of psychological development (ICD-10 codes: F80–F89)	Monotherapy 4/not reported (3.1 per 1000 PY)	Unexposed 10,010/not reported (1.6 per 1000 PY)	Adjusted HR = 1.3 (0.5–3.3)	Among children born to a mother with no known mental illness Adjusted HR = 2.2 (0.5–8.6)
	Coste et al., 2020	Health care utilization of speech therapy	Monotherapy 11/not reported (8.5 per 1000 PY)	Unexposed 72,012/not reported (11.9 per 1000 PY)	Adjusted HR = 0.6 (0.4–1.2)	Among children born to a mother with no known mental illness Adjusted HR = 0.9 (0.4–2.1)
	Coste et al., 2020	Health care utilization of orthoptics	Monotherapy 42/not reported (35.1 per 1000 PY)	Unexposed 203,489/not reported (35.6 per 1000 PY)	Adjusted HR = 0.9 (0.7–1.2)	Among children born to a mother with no known mental illness Adjusted HR = 1.1 (0.7–1.7)
	Coste et al., 2020	Health care utilization of psychiatry	Monotherapy 6/not reported (4.6 per 1000 PY)	Unexposed 22,365/not reported (3.7 per 1000 PY)	Adjusted HR = 0.9 (0.4–2.0)	Among children born to a mother with no known mental illness Adjusted HR = 1.7 (0.5–5.3)

ASM: antiseizure medications; CI: confidence interval; HR: hazard ratio; ICD-10: International Statistical Classification of Diseases and Related Health Problems 10th Revision; MH: Mantel–Haenszel; NR: not reportable to keep masking of a low number of individuals (<5) in other cells; OR: odds ratio; PS: propensity score; PY: person-year.

^a Only significant findings or findings with at least 5 exposed cases are reported, in bold significant result.

a population-based cohort of Medicaid-enrolled women, the control for a large set of covariates (more than 70), and the conduct of several sensitivity and post-hoc analyses to assess the robustness of the results [30].

Regarding long-term childhood neurodevelopmental outcomes, data on overall neurodevelopmental outcomes reported reassuring findings [48–51]. Nevertheless, in two studies the mean follow-up was around 3.5 years, which limits the capacity to assess the occurrence of neurodevelopmental outcomes [49,50]. The reported associations between specific disorders such as mental retardation and hyperkinetic disorders including attention deficit hyperactivity disorder (ADHD), as well as utilization of orthoptics services and pregabalin exposure need further investigations [39,50]. In addition, the long-term outcomes investigated mainly focused on severe neurodevelopmental outcomes identified with International Statistical Classification of Diseases and Related Health Problems 10th Revision (ICD-10 codes), and more research is needed to explore potential effects on specific and less severe neurodevelopmental outcomes.

Data on the indication for gabapentinoid use were reported in 10 out of the 27 high-quality studies [30,31,38–40,44,45,47,48,50]. Pregabalin and gabapentin were mostly used for non-epilepsy indications, such as pain or psychiatric disorder, with epilepsy accounting for less than 10% of the exposed pregnancies. Only two recent studies have reported associations based on maternal diseases (one study distinguished between epilepsy, psychiatric and somatic conditions [45] while the other distinguished between epilepsy and no epilepsy) [47], limiting the ability to assess the impact of different conditions on outcomes. Nevertheless, the results indicated that maternal conditions influenced the outcomes, highlighting the importance of identifying underlying maternal diseases and stratifying analyses accordingly. The impact of different treatment indications should be explored further, as recent studies have provided valuable information on potential effects.

Data on the patterns of use during pregnancy were very rarely presented. Chronic or occasional use, as well as dosage, were barely not reported. Less than one third of the pregnancies were exposed during the first trimester of pregnancy and through the rest of the pregnancy [30,44,50,53].

Strengths and limitations

This systematic review comprehensively analysed the existing literature on gabapentinoid use during pregnancy and its association with adverse pregnancy/childhood outcomes. It provides valuable information regarding the assessment of gabapentinoid risks during pregnancy and highlights gaps that need to be filled by further studies. This study provided guidance for future research aimed at assessing the safety of gabapentinoids during pregnancy. The recent IMI project ConcePTION, which the authors are part of, is addressing some of the research gaps by combining data from several large data sources across Europe. Future studies will aim to overcome limitations by including larger sample sizes, standardized outcome definitions, identification of treatment indications, and adjustment for confounding factors.

In this systematic review, we have not tried to realize a quantitative meta-analysis as the studies outcome mea-

surements and comparison groups were too heterogeneous. Some studies included in the review had relatively small sample sizes, leading to imprecise estimation of medication effect (with measures of associations with wide confidence intervals). Additionally, there was limit considerations for covariates control in some studies. The heterogeneity in defining comparison groups and ascertaining outcomes also posed challenges in interpreting the results. Concerning the comparison groups, some studies used a group of women not exposed to any ASM during pregnancy, other used active comparators for example with women exposed during pregnancy to lamotrigine. The use of active comparators is important to control for indication bias. As gabapentinoids has several indications, it might be relevant to use several active comparators for which the indications overlap with those of gabapentin and pregabalin, such as in the study by Dudukina et al. [39]. Concerning the ascertainment of the outcomes, some studies were based on medical files, other on women reports and others on validated diagnosis codes. However, even validated diagnosis codes do not allow for the identification of all cases, such as less severe cases. We could also note that there was a lack of data on the evolution of gabapentinoid use over time, on indication for treatment, on the patterns of use during pregnancy and on cases of misuse.

Conclusion

Studies found an overall increased risk of congenital anomalies and long-term neurodevelopmental outcomes associated with prenatal exposure to pregabalin. Larger studies are needed to confirm the potential increased risks of specific congenital anomalies and stillbirth. Similarly, exposure to gabapentin was associated with an increased risk of preeclampsia, preterm birth and small-for-gestational age. More extensive studies are needed to evaluate the risk of congenital anomalies and fetal death associated with gabapentin. Collectively, the findings from this systematic review, combined with animal data, raise concerns about the safety of using gabapentinoids during pregnancy.

The benefit–risk balance for both mother and fetus/infant should be carefully evaluated if the use of these medications cannot be avoided during pregnancy.

Author contributions

ABB, JM, CDM conceived the review. All authors contributed to the study design. ABB developed the search strategy. ABB and JM extracted data. All authors contributed to data analysis. ABB drafted the manuscript. All authors revised and approved the manuscript.

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Disclosure of interest

ABB, JB and CDM declare that they have no competing interest.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at <https://doi.org/10.1016/j.therap.2024.10.049>.

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