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NON-INTERVENTIONAL STUDY REPORT ABSTRACT

Title: A Population-based Cohort Study of Pregabalin to Characterize Pregnancy Outcomes.

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Rationale and background: Pregabalin (Lyrica®) was approved in July 2004 by the European Medicines Agency (EMA) for the treatment of peripheral neuropathic pain and as an adjunctive therapy for adult patients with partial onset seizures. Subsequently, the marketing authorizations were expanded to include generalized anxiety disorder (GAD), in March 2006 and central neuropathic pain, in September 2006. Per current European Union label, "Lyrica should not be used during pregnancy unless clearly necessary (if the benefit to the mother clearly outweighs the potential risk to the fetus)."[1] Overall in Europe, pregabalin is prescribed to approximately 0.5 per thousand pregnant women in Europe, based on data from the United Kingdom (UK), France, and two regions of Italy and a study from Denmark,[2,3] but in several countries the use has risen during the last decade and in the UK the prevalence of pregabalin prescribing during pregnancy was > 2 per thousand pregnancies in 2015-2016.[2]

In the general population (including men and women of all ages), pregabalin is mostly used for neuropathic pain (18-98%) and least used for epilepsy (4-6%).[4] Use of pregabalin in a non-pregnant population, as assessed in a study in Sweden, is primarily for neuropathic pain (36%) and only 1.3% for epilepsy, with 40% of pregabalin initiators having no identifiable approved indication based on routine records,[5] and no data on indication from other sources are available. A study from two distinct United States (US) datasets reported prevalence of epilepsy indication of 5.5% and 6.7% of pregabalin use in pregnant women.[6]

Evidence regarding pregabalin safety in pregnancy is limited. A recent study, using data from eight European Teratology Information Services, based on 164 pregabalin-exposed and 656 pregabalin-unexposed pregnancies, reported a 3-fold increased risk of any major non-chromosomal congenital malformation associated with first-trimester pregabalin exposure.[7] Major limitations of the analysis included lack of data on specific malformations, potential selection and detection bias due to self-referral, low precision, and confounding by indication. A subsequent study based on 477 pregabalin-exposed pregnancies among Medicaid beneficiaries in the US did not confirm the 3-fold increased risk but could not rule out a smaller effect. When all available evidence was combined, adjusted risk ratios (RRs) for any major malformation were 1.3 (95% confidence interval [CI] 0.8–2.2) for any first-trimester exposure to pregabalin and 1.0 (95% CI 0.7–1.5) for pregabalin monotherapy exposure in the first trimester compared with unexposed.[6] A recent Nordic study examining

the risk of major malformations for different antiepileptic drugs (AEDs) found no clear evidence of an increased risk of any malformation for pregabalin compared with lamotrigine (RR 1.2, 95% CI 0.9–1.7).[8] A recent French study examining AED exposure relative to 23 major malformations reported an odds ratio of 5.8 (95% CI 1.6–14.9) based on only 4 exposed cases.[9]

To extend the available evidence, safety of pregabalin use in pregnancy was examined using outcomes other than malformations including fetal growth indicators, and postnatal neurologic morbidity. This study evaluated use and safety of pregabalin in pregnancy using data on all pregnancies identifiable from population-based registries in Denmark, Finland, Norway, and Sweden. Safety was measured by occurrence of major congenital malformations, birth outcomes, and selected neurodevelopmental postnatal outcomes.

This non-interventional study is designated as a Post-Authorisation Safety Study (PASS) and was a commitment to the EMA.

Research question and objectives: The study objectives were to describe the use of pregabalin in pregnancy and to estimate the risk of major congenital malformations, birth outcomes other than congenital malformations, and neurodevelopmental outcomes with the use of pregabalin.

The specific primary objectives of the study were to:

- Describe use of pregabalin, lamotrigine, and duloxetine during pregnancy overall, by trimester, and by calendar year of delivery in pregnancies ending in live births or stillbirths, as characterized by:
  - Prevalence of use (proportion of pregnancies with 1 or more dispensing of a given drug),
  - Distribution of therapeutic indications among the exposed pregnancies (epilepsy, GAD, neuropathic pain),
  - Cumulative dose, based on dispensing count and amount dispensed in each pregnancy;
- Describe the prevalence of (proportion of live or stillborn children with) major congenital malformations after first-trimester in utero exposure to pregabalin (yes/no); after first-trimester exposure to lamotrigine, after first-trimester exposure to duloxetine, after first-trimester exposure to lamotrigine or duloxetine, in pregnancies ending in live birth or stillbirth; in live or stillborn children unexposed to antiepileptics in the first trimester; and in the total population of live or stillborn children;
- Estimate the association between first-trimester exposure to pregabalin and prevalence of major congenital malformations, as compared with no first-trimester exposure to pregabalin or other AEDs, with first-trimester exposure to lamotrigine, with first-trimester exposure to duloxetine, and first-trimester exposure to lamotrigine or duloxetine, in live or stillborn children;
- Describe the prevalence of birth outcomes other than major congenital

malformations according to exposure (yes/no) to pregabalin any time during gestation, according to exposure to lamotrigine any time during gestation, according to any in utero exposure to duloxetine, according to any in utero exposure to lamotrigine or duloxetine, and in live or stillborn children unexposed in utero to antiepileptics;

- Estimate the association between any in utero exposure to pregabalin and the birth outcomes other than major congenital malformations, as compared with no exposure to pregabalin or other AEDs; any in utero exposure to lamotrigine; any in utero exposure to duloxetine; any in utero exposure to lamotrigine or duloxetine, and no in utero exposure to antiepileptics;
- Estimate, in a sensitivity analysis to evaluate potential impact of selection bias, the association between first-trimester exposure to pregabalin and prevalence of major congenital malformations, as compared with no first-trimester exposure to pregabalin or other AEDs; first-trimester exposure to lamotrigine; first-trimester exposure to duloxetine; and first-trimester exposure to lamotrigine or duloxetine, in pregnancies ending in livebirth, stillbirth, or 2nd trimester induced abortion (in Denmark, Finland, and Norway).

The specific secondary objectives of the study were to:

- Describe, in liveborn infants, the incidence rates of pre-specified postnatal neurodevelopmental outcomes according to exposure (yes/no) to pregabalin any time during pregnancy, after any in utero exposure to lamotrigine, after any in utero exposure to duloxetine, and after any in utero exposure to lamotrigine or duloxetine;
- Estimate, in liveborn infants, the association between in utero exposure to pregabalin and the pre-specified postnatal neurodevelopmental outcomes, as compared with no in utero exposure to pregabalin or other AEDs; any in utero exposure to lamotrigine, any in utero exposure to duloxetine, and any in utero exposure to pregabalin or duloxetine.

Study design: This PASS is a population-based study using national administrative registries from four Nordic countries: Denmark, Finland, Norway, and Sweden.

Setting: In each country, all live births and stillbirths are recorded in the birth registries from gestational week 22 from July 2008 onwards. In addition, the Swedish birth register recorded live births and stillbirths born from gestational week 28 until July 2008). The start of the study period in each country was selected to ensure availability of pregabalin and the active comparators on the market and availability of data on outpatient dispensings for at least 12 months before the end of the earliest identified pregnancy. For example, a pregnancy ending at term with a live birth on 01 January 2005 in Denmark had prescription history from 01 January 2004, thus covering the 9 months of gestation and a 3-month period of preconception.

Subjects and study size, including dropouts: The study population consisted of all pregnancies identified in the respective administrative registries from 01 January 2005 to 31 December 2015 in Denmark, Finland, and Norway and all pregnancies identified from 01 July 2006 to 31 December 2016 in Sweden. Singleton and multiple pregnancies ending in live births or stillbirths were identified in each country's birth registry. For the medication use analysis, the unit of observation was pregnancy; for the other outcomes, in the main analysis, the unit of observation was birth. Pregnancies ending in an abortive outcome were considered to contain a single fetus.

The total number of live births, stillbirths, and births ending in a 2nd trimester induced abortion included in the analyses in the study period (2005-2015 for Denmark, Finland, and Norway and 2006-2016 for Sweden) were 670,704 in Denmark, 649,483 in Finland, 661,179 in Norway, and 1,152,002 in Sweden.

Variables and data sources:
Variables
Exposure to the medications under study is defined as follows:
Pregabalin exposure – At least one maternal dispensing of pregabalin during the first trimester for the analyses of major congenital malformations and during any trimester for all remaining outcomes.

Comparators/reference groups:
Unexposed to pregabalin or to other AEDs – This reference group consists of births with no maternal dispensing of any AED during the first trimester for the outcome of major congenital malformations and during any trimester for all remaining outcomes.

Lamotrigine exposure – At least one maternal dispensing of lamotrigine during the first trimester for the outcome of major congenital malformations and during any trimester for all remaining outcomes.

Duloxetine exposure – At least one maternal dispensing of duloxetine during the first trimester for the outcome of major congenital malformations and during any trimester for all remaining outcomes.

Lamotrigine or duloxetine exposure – At least one maternal dispensing of lamotrigine and/or duloxetine during the first trimester for the outcome of major congenital malformations and during any trimester for all remaining outcomes.

For analyses that use lamotrigine as the comparator, pregnancies exposed to both pregabalin and lamotrigine in the same relevant exposure window will be excluded. For analyses that use duloxetine as the comparator, pregnancies exposed to both pregabalin and duloxetine in the same relevant exposure window will be excluded.

Primary outcomes:
Birth outcomes

- Major congenital malformations
- Stillbirth
- Low birth weight
- Small for gestational age among singletons
- Preterm birth
- Low Apgar score at 5 minutes
- Microcephaly

Secondary outcomes:
Postnatal neurodevelopmental outcomes:

- Attention deficit hyperactivity disorder (ADHD) defined as hyperkinetic disorders, including ADHD (identified via inpatient or outpatient hospital diagnosis or a medication proxy).
- Autism spectrum disorders (ASD) defined as pervasive developmental disorders, including ASD (identified via inpatient or outpatient hospital diagnosis).
- Intellectual disabilities (IDs) (including mental retardation) (identified via inpatient or outpatient hospital diagnosis).

Follow-up for the postnatal neurodevelopmental outcomes, when available, will be a minimum of 1 year postnatally and for the maximum period available in the dataset for each birth. However, for a variety of reasons, either related to the individual or to the family (e.g. emigration, death), follow-up could be unfeasible in individual cases. It should be noted that not all livebirths will have available follow-up information into the school age, and as postnatal neurodevelopmental disorders are diagnosed after the first year of age, primarily at school age, the number of events in gabapentin-exposed (and other comparator groups) pregnancies in the study period may not be sufficient to yield stable estimates of association.

Covariates:
Characteristics of the study population that are to be described will include calendar year of delivery, maternal age at conception, parity (number of live births and stillbirths prior to the on-study pregnancy); indication for AED use, marital/cohabiting status; pregravid body mass index (BMI) as recorded at the first antenatal visit or via a hospital diagnosis of obesity; smoking during pregnancy as recorded at the first antenatal visit; single or multiple gestation; caesarean delivery; and child's sex.

The covariates be included in the propensity score model are:

- calendar year of delivery;
- maternal age in years at conception;
- marital/cohabiting status;
- smoking during pregnancy;
- obesity (BMI =>30 kg/m^2) or a hospital diagnosis of obesity;
- single or multiple gestation;

- hospital-recorded morbidity;
- indicators of maternal healthcare utilization in the 12 months pre-last menstrual period (LMP) (number of inpatient and specialized outpatient encounters);
- for congenital malformations outcome: maternal medication use, each as a dichotomous variable.

Data sources
Data from national population-based administrative registries in Denmark, Finland, Norway, and Sweden were used in this study. These national registries include patient, birth, prescription, and total population registries. Within each country, records from all registries are linkable at the individual level by a unique national person identifier. For births recorded in the birth registries, a maternal unique identifier is a variable on the record of the offspring, enabling exact linkage between a given offspring and maternal history of medication dispensing or diagnoses before or during pregnancy.

Statistical methods
Descriptive statistics of the use of pregabalin, lamotrigine and duloxetine in pregnancy, and the distributions of the maternal and offspring characteristics were calculated. Prevalence, crude and propensity-score adjusted prevalence ratios were estimated for the birth outcomes comparing pregnancies exposed to pregabalin during relevant exposure period (first trimester only for major congenital malformations, any trimester exposure for other birth outcomes) versus the four comparison groups. Similarly, incidence rate, crude and propensity-score adjusted hazard ratios were estimated for the neurodevelopmental outcomes. Country-specific crude and adjusted estimates of association were first calculated and presented; then these results were combined using meta-analysis and Mantel-Haenszel pooling method that allowed incorporation into combined estimates of associations while retaining information from strata with no exposed cases.

Results: The total number of users of pregabalin in a pregnancy ending in a live birth or stillbirth in the study period was 325/666,146 (0.048%) in Denmark, 965/643,088 (0.16%) in Finland, 307/657,451 (0.046%) in Norway, and 1275/1,152,002 (0.11%) in Sweden. In all countries, lamotrigine was used more frequently than pregabalin with an overall use in 0.32% of pregnancies in Denmark, 0.15% in Finland, 0.29% in Norway, and 0.26% in Sweden. Duloxetine was used more frequently than pregabalin in Denmark (0.12% vs. 0.048%) and Sweden (0.14% vs. 0.11%) but less frequently in Finland (0.11% vs. 0.16%) and Norway (0.02% vs. 0.046%). The distribution of those with a potential indication for pregabalin use, inferred by recorded disease diagnosis, differed between countries, with GAD being the most commonly recorded diagnosis of potential indication in Finland, Norway, and Sweden, and neuropathic pain as the main recorded diagnosis of potential indication in Denmark.

The maternal age distribution was similar in the four countries. Prevalence of smoking was 28-40% of the pregabalin-exposed births and 6-15% in AED-unexposed births. Most of the comorbidities and medication use was markedly more prevalent in the pregabalin-exposed than in the unexposed births. Births exposed to the active comparators had covariate profiles more similar to those of the pregabalin-exposed than to the unexposed births.

Major malformations
Regarding any congenital malformations, the adjusted prevalence ratios (aPRs) in the standard meta-analysis for first-trimester pregabalin-exposed vs.: unexposed, 1.13 (95% CI 0.97-1.33); lamotrigine, 1.36 (1.07-1.72); duloxetine, 1.37 (1.06-1.77); lamotrigine or duloxetine, 1.24 (1.00–1.54). Restricting to pregabalin, lamotrigine, and duloxetine monotherapy only marginally changed the results. For first-trimester pregabalin monotherapy vs.: unexposed, 1.14 (0.96-1.35); lamotrigine monotherapy, 1.29 (1.01-1.65); duloxetine monotherapy 1.39 (1.07-1.82); lamotrigine or duloxetine monotherapy 1.24 (1.00-1.54).

Birth outcomes
Results for the meta-analysis of stillbirth showed an aPR and (95% CI) 1.72 (1.02-2.91) for pregabalin-exposed compared to unexposed, and 1.87 (0.81-4.32) for comparison with lamotrigine, 1.46 (0.57-3.72) comparted to duloxetine, and 2.71 (1.25-5.90) compared with the combined lamotrigine and duloxetine group. In the post-hoc meta-analysis including countries with zero events, stillbirth was no longer associated with pregabalin exposure.

Results for the meta-analysis for low birth weight, preterm birth, SGA, low Apgar score at 5 minutes, and microcephaly for pregabalin-exposed compared to unexposed of 1.05 (0.91–1.21), 1.13 (0.99–1.29), 1.21 (1.01–1.44), 1.18 (0.95–1.48), and 1.09 (0.88–1.36) respectively, but with estimates closer to null effect for comparison to the active comparators. Although the prevalence of SGA was slightly elevated in the pregabalin-exposed compared to offspring unexposed to AEDs, it was not elevated in comparison with the active comparators. Pregabalin monotherapy compared to unexposed showed similar aPRs (95% CI) for low birth weight 1.06 (0.90–1.24), preterm birth 1.14 (0.99–1.32), SGA 1.19 (0.98–1.45), 1.05 (0.82–1.36) for low Apgar score at 5 minutes, and microcephaly 1.00 (0.78–1.27).

Postnatal neurodevelopmental outcomes
In the meta-analyses of the neurodevelopmental outcomes (ADHD, ASD, and ID), results for ADHD were an adjusted hazard ratio and (95% CI) for pregabalin-exposed vs.: unexposed, 1.32 (1.04–1.67); lamotrigine, 1.09 (0.79–1.52); duloxetine, 1.11 (0.76–1.61); duloxetine or lamotrigine, 1.20 (0.89–1.63). Crude estimates suggested markedly stronger associations indicating that confounder adjustment at least partly explained this association. For ASD and ID, the point estimates were close to unity.

Discussion: The results of this study do not provide strong evidence of human teratogenicity, or effects on birth outcomes and postnatal neurodevelopmental outcomes after pregabalin exposure. However, in line with previous studies, a small increased risk of adverse birth outcomes in the pregabalin-exposed group compared with unexposed or active comparator groups cannot be completely ruled out, and the associated estimates remain imprecise despite inclusion of data from four countries. Of note, prevalence of smoking during pregnancy, a known risk factor associated with adverse birth outcomes,[100] and included in the PS-adjusted models, was 28-40% of the pregabalin-exposed births and 6-15% in AED-unexposed births. Regarding the criteria for proof of teratogenicity mentioned by Shepard,[11] the present available information on pregabalin exposure lacks sufficient number of exposed cases and

even though detailed propensity score adjusted estimates have been provided, residual confounding cannot be excluded since this was an observational study. Also, no relative risks for any of the outcomes were observed with a maximum upper CI in the Mantel-Haenszel meta-analyses greater than 1.76 (excluding specific malformations and stillbirths with imprecise estimates due to low number of cases).

In conclusion, the present study is consistent with the earlier evidence from published population-based studies of an absence of substantially increased risks of congenital malformations, adverse birth outcomes, or postnatal neurodevelopment in pregabalin-exposed fetuses in identifiable pregnancies. Several estimates in this study were imprecise due to the low number of events and the results should be interpreted with caution.

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