Antiseizure meDication Exposure and Pregnancy and neonaTal outcomes research (ADEPT)

Title

Feasibility of estimating the risk of adverse pregnancy, neonatal and long-term child outcomes following either in utero maternal antiseizure medications (ASMs) exposure or peri-conceptional paternal ASM exposure.

Rationale and background

Evidence shows that certain ASMs such as valproate, pose teratogenic and neurodevelopmental risks during pregnancy. Conflicting findings also suggest potential neurodevelopmental impacts from paternal ASM exposure pre-conception. Thus, it is critical to assess the feasibility of causal studies on ASM exposure, especially given the complexity of father-child data linkage.

Research question and objectives

This study aims to understand whether data sources can be used to study the effects of maternal and paternal exposure to ASM, on pregnancy, neonatal and child outcomes. For this main objective, the following sub-objectives will be addressed:

a. To estimate the availability of relevant information/characteristics for pregnant women, using 15 different parameters that will inform the assessment of fitness for purpose.

b. To estimate availability of relevant information/characteristics for men and linkage with pregnancies, using 9 different parameters that will inform the assessment of fitness for purpose.

c. To estimate availability of relevant information/characteristics for neonates/children, using 17 parameters and comparing them between those that can and cannot be linked to mother and/or father where possible.

d. To assess fitness for purpose to different types of studies of pre-conceptional/prenatal exposure to antiepileptics and the development of adverse pregnancy and child outcomes.

Study design

This is a retrospective cohort study to assess the suitability of the available databases for ASM exposure and risk assessment studies. Exploratory research will be carried out to establish whether, and to what extent, data are available outside the routinely used electronic health records. This research will include data banks outside the healthcare systems or in tertiary referral centres to evaluate whether such data can be leveraged to enrich the information available on child outcomes.

Population

The source population comprises all persons of childbearing age who are registered with the data sources that participate in this study. From the source population, we will select study cohorts for each of the different sub-objectives.

Variables

The main exposures of interest are ASMs (N03A) and gabapentinoids (with ATC code N02BF) and all benzodiazepines with antiepileptic properties. Outcome parameters will be considered per sub-objective. Clinical outcomes of interest will include pregnancy outcomes (i.e., spontaneous pregnancy loss, stillbirth, preterm birth) neonatal/child outcomes (e.g., small gestational age, congenital anomalies, adverse neurodevelopment).

Data sources

This study will be conducted using electronic health record data from 9 data sources in 7 countries in Europe comprising a total active population of 65 million persons. This includes BIFAP (ES), SIDIAP (ES), VID (ES), CPRD (UK), Finnish registries (FI), EFEMERIS (FR), Norwegian registries (NO), PHARMO (NL), and Val Padana LHU (IT).

Data analysis

For objective *a-c* we will estimate the 41 feasibility parameters using descriptive analyses and visualizations and will describe whether data can and should be enriched. For objective *d*, we will

use the parameters from objectives a-c plus metadata on the data sources and assess the fitness-for-purpose of the data instance by using, implementing, and adapting the framework from Gatto and colleagues. The design elements, minimal criteria, and the scoring system for this specific study will be created in collaboration with the EMA.