Paternal exposure to valproate and the risk of neurodevelopmental disorders in children

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Study Ongoing

Administrative details

EU PAS number

EUPAS1000000417

Study ID

1000000417

DARWIN EU® study

No

Study countries

Norway

Taiwan

Study description

The use of valproate by male patients during the three months before conception has recently drawn attention due to concerns about a potential

increase in the risk of neurodevelopmental disorders (NDDs) in their offspring. Following a review of pertinent data, the European Medicines Agency's (EMA) safety committee, the Pharmacovigilance Risk Assessment Committee (PRAC), has advised caution in prescribing these medicines. However, this recommendation is based on limited, unpublished data and the findings have not yet been replicated.

Therefore, this study aims to investigate the association between paternal exposure to valproate and the risk of NDDs in two distinct populations, Norway and Taiwan, to provide more comprehensive evidence.

Study status

Ongoing

Research institutions and networks

Institutions

National Taiwan University

Pharmacoepidemiology and Drug Safety Research Group (PharmaSafe), University of Oslo

Norway

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Institution | Educational Institution | ENCePP partner

Contact details

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Primary lead investigator

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Study timelines

Date when funding contract was signed

Actual: 01/08/2024

Study start date

Actual: 01/12/2024

Data analysis start date

Planned: 20/12/2024

Date of final study report

Planned: 31/05/2025

Sources of funding

More details on funding

This study was supported by the International Alliance for PharmacoGenetic Epidemiology Excellence (iAPOGEE) project funded by the Norwegian Research Council (grant No 322176) and the National Science and Technology Council (NSTC 113-2314-B-002-167-MY3) of Taiwan. The funders had no role in the study design; the collection, analysis, and interpretation of data; the writing of the report; or the decision to submit the article for publication.

Study protocol

Paternal exposure to valproate and the risk of neurodevelopmental disorders in children.pdf (628.7 KB)

Regulatory

Was the study required by a regulatory body?

No

Is the study required by a Risk Management Plan (RMP)?

Not applicable

Methodological aspects

Study type

Study type list

Study topic:

Human medicinal product

Study type:

Non-interventional study

Scope of the study:

Safety study (incl. comparative)

Data collection methods:

Secondary use of data

Study design:

A multinational cohort study will be conducted using the Norwegian national health registries, which cover all residents in Norway, and Taiwan's population health insurance data, which cover more than 99% of the population in Taiwan.

Main study objective:

This study aims to investigate the association between paternal exposure to valproate and the risk of NDDs.
The study will identify all pregnancies resulting in live-born singletons with birth years from 2010 to 2015, as recorded in the Norwegian Medical Birth Register and from 2010 to 2015 in Taiwan's National Birth Certificate Application.
This approach ensures a minimum of six years of follow-up by the end of the study period, which extends to 2021 for both cohorts.

We will use both active-comparator and non-active comparator designs (compared to non-exposure).
For the non-active-comparator design, we will restrict the cohort to individuals with indications for antiepileptic drugs (AEDs), including epilepsy, psychiatric

disorders (bipolar disorder, depression, schizophrenia, anxiety, and other psychiatric conditions), as well as somatic conditions (migraine, neuropathic pain, and chronic pain).

Study Design

Non-interventional study design

Cohort

Study drug and medical condition

Medicinal product name, other

Valproic acid

Anatomical Therapeutic Chemical (ATC) code

(N03AG01) valproic acid

valproic acid

Population studied

Short description of the study population

All pregnancies resulting in live-born singletons will be linked with paternal data in Norway and Taiwan.

The paternal linkage to pregnancies is possible in 91.0% and 95.6% in the Norwegian cohort and in the Taiwanese cohort, respectively.

Study design details

Setting

This cross national cohort study was conducted using population based data from Norway and Taiwan.

The Norwegian cohort included data from the Medical Birth Registry of Norway, the Norwegian Prescription Database, the Norwegian Patient Registry, and the Norwegian control and payment of health reimbursements.

The Taiwanese cohort used information from the National Birth Certificate Application database, the National Health Insurance database, and the Maternal and Child Health Database.

Comparators

We will evaluate the risk of NDDs in offspring of fathers exposed to valproate, compared to the risk in the offspring of fathers exposed to a comparator or to no exposure during the sperm development period (SDev), which is defined as the 3 months (90 days) prior to conception.

Exposure refers to the period when there is an overlap in the days' supply of the dispensed medication during SDev.

We will compare the following two groups (active-comparator and non-active comparator designs) under both monotherapy and combination therapy conditions (resulting in a total of four analysis):

Monotherapy:

1. Valproate vs lamotrigine or levetiracetam (grouped as composite exposure)
2. Valproate vs no exposure, restricted to those with indications for AEDs

Combination therapy:

3. Valproate vs lamotrigine or levetiracetam (grouped as composite exposure)
4. Valproate vs no exposure, restricted to those with indications for AEDs

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Outcomes

Primary outcome: Overall NDDs, including autism spectrum disorder (ASD), attention deficit hyperactivity disorder (ADHD), specific learning disorders, developmental speech/language disorder, developmental coordination disorder, intellectual disability, behavioral disorder, grouped as one composite variable.

Secondary outcome: Individuals NDDs.

Data analysis plan

Descriptive statistics will be compared between groups using standardized differences; covariates with standardized differences less than 15% will be considered balanced.

The propensity score (PS), representing the probability of receiving valproate, will be derived using a multivariable logistic regression model that included all paternal and maternal covariates.

When selecting the appropriate PS method, we considered the prevalence of paternal valproate use in the study population, the method’s precision, and its ability to reduce bias.

Based on the initial exploration of sample size and the prevalence of paternal valproate use, we chose PS fine stratification weighting (FSW), with stratification based on the PS in the exposed group.

A pooled logistic regression model will be used to estimate the hazard ratio (HR), which approximates the odds ratio from the pooled logistic regression, along with 95% confidence intervals (CI). We chose pooled logistic regression, because it produces more reliable and robust estimates and to minimize the inherent bias associated with Cox proportional hazards regression. Moreover, we then avoid pitfalls of proportional hazards assumptions in Cox regression when they may not hold true.

Standardized incidence risk curves will also be plotted by fitting weighted pooled logistic regression models and calculating weighted risk differences. Robust standard errors will be applied to account for both weighting and data clustering, given the potential for multiple offspring per father.

Data management

ENCePP Seal

The use of the ENCePP Seal has been discontinued since February 2025. The ENCePP Seal fields are retained in the display mode for transparency but are no longer maintained.

Data sources

Data source(s), other

The Norwegian cohort will include data from the Medical Birth Registry of Norway, the Norwegian Prescription Database, the Norwegian Patient Registry, and the Norwegian control and payment of health reimbursements. The Taiwanese cohort will use information from the National Birth Certificate Application database, the National Health Insurance database, and the Maternal and Child Health Database.

Data sources (types)

Non-interventional study

Use of a Common Data Model (CDM)

CDM mapping

Yes

Data quality specifications

Check conformance

Unknown

Check completeness

Unknown

Check stability

Unknown

Check logical consistency

Unknown

Data characterisation

Data characterisation conducted

Unknown