

# Drug transporter protein -mediated drug interactions during pregnancy and offspring outcome; with special emphasis on second-generation antipsychotics and SSRIs (PgP and BCRP interactions and pregnancy)

**First published:** 26/04/2016

**Last updated:** 31/01/2020

Study

Finalised

## Administrative details

### EU PAS number

EUPAS13051

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### Study ID

33382

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### DARWIN EU® study

No

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### Study countries

☐ Finland

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## Study description

**Background.** Drug transporter proteins play an important role in the bioavailability and toxicity of drugs. P-glycoprotein (P-gp) and breast cancer resistance protein (BCRP) are the two important efflux transporter proteins in the human placenta. It is not known if drug transporter protein-mediated drug interactions account for the possible teratogenicity of drugs or if such interactions can also predispose to neonatal drug toxicity.

**Objectives.** To investigate if concomitant use of two or more drug transporter substrates or a substrate and an inhibitor during first trimester is associated with an increased risk of offspring major congenital malformations. Specifically, we will assess the risk of overall malformations in offspring of women using SGAs, and the risk of cardiac malformations in offspring of women using SSRIs or bupropion, and the risk of severe or prolonged neonatal adaptation problems.

**Methods.** This is a population-based cohort study based on the Drugs and Pregnancy project database in Finland. Data are derived from national health registers: the Medical Birth Register, the Register on Induced Abortions, the Malformation Register and the Prescription Register and Special Refund Entitlement Register. Data in these registers have been collected during Jan 1st 1996 - Dec 31st 2011 and include all births (live and still births), pregnancy terminations due to major congenital malformation, and information on drug purchases during pregnancy and 3 months before pregnancy. To this database we will further link data on individual drugs and their relation (substrate, inhibitor) to P-gp and BCRP from the University of Washington Metabolism and Transport Drug Interaction Database (DIDB). Offspring of women with concomitant use of two or more drug transporter substrates, or a combination of a substrate and an inhibitor, are compared to offspring of women using only one drug transporter specific substrate, and to unexposed.

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## Study status

Finalised

## Research institutions and networks

## Institutions

### Finnish Institute for Health and Welfare (THL)

☐ Finland

**First published:** 01/02/2024

**Last updated:** 01/02/2024

**Institution**

Educational Institution

Laboratory/Research/Testing facility

### Teratology Information Service, Helsinki (TIS Helsinki), HUSLAB

☐ Finland

**First published:** 09/04/2010

**Last updated:** 16/08/2011

**Institution**

Educational Institution

Hospital/Clinic/Other health care facility

ENCePP partner

### Department of Clinical Pharmacology Helsinki University and Helsinki University Hospital

## Contact details

**Study institution contact**

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Study contact

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**Primary lead investigator**

Heli Malm

Primary lead investigator

## Study timelines

**Date when funding contract was signed**

Actual: 02/01/2015

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**Study start date**

Planned: 31/08/2016

Actual: 19/11/2018

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**Data analysis start date**

Planned: 30/11/2016

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**Date of interim report, if expected**

Planned: 31/05/2017

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**Date of final study report**

Planned: 30/05/2018

Actual: 10/12/2019

## Sources of funding

- Other

## More details on funding

Finnish Medical Agency, National Institute of Health and Welfare, Social Insurance Institution

## Study protocol

[Research protocol\\_APR\\_25\\_2016.pdf](#)(401.08 KB)

## Regulatory

**Was the study required by a regulatory body?**

No

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

Not applicable

## Methodological aspects

### Study type

### Study type list

**Study topic:**

Human medicinal product

Disease /health condition

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**Study type:**

Non-interventional study

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**Scope of the study:**

Assessment of risk minimisation measure implementation or effectiveness

**Data collection methods:**

Secondary use of data

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**Main study objective:**

To investigate if concomitant use of two or more drug transporter substrates or a substrate and an inhibitor during first trimester is associated with an increased risk of offspring major congenital malformations. Specifically, we will assess the risk of overall malformations in offspring of women using SGAs, and the risk of cardiac malformations in offspring of women using SSRIs or bupropion.

## Study Design

**Non-interventional study design**

Cohort

## Study drug and medical condition

**Study drug International non-proprietary name (INN) or common name**

BUPROPION

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**Anatomical Therapeutic Chemical (ATC) code**

(N05A) ANTIPSYCHOTICS

ANTIPSYCHOTICS

(N06AB) Selective serotonin reuptake inhibitors

Selective serotonin reuptake inhibitors

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**Medical condition to be studied**

Congenital anomaly

## Population studied

**Short description of the study population**

Women exposed one month before pregnancy or during the first trimester to P-gp/BCRP polytherapy; P-gp/BCRP monotherapy; non-P-gp/BCRP polytherapy, and unexposed.

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**Age groups**

Preterm newborn infants (0 – 27 days)

Term newborn infants (0 – 27 days)

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**Special population of interest**

Pregnant women

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**Estimated number of subjects**

1000000

## Study design details

## Outcomes

Major congenital malformations and major cardiac malformations, according to EUROCAT coding ([www.eurocat-network.eu](http://www.eurocat-network.eu) ). Neonatal outcomes: Apgar score <7, need for respirator treatment, need for treatment in neonatal (intensive) care unit, need for care outside home at the age of one week

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## Data analysis plan

All data are anonymized and coded prior to statistical analysis. The prevalence of specific outcomes is compared between the different exposure groups of pregnant women and their offspring. Crude and adjusted odds ratios (cOR and aOR) and 95% confidence intervals (CI) were calculated. Statistical significance was set at a P value of less than 0.05. Univariate analyses are used to study demographic differences between the study cohorts. Univariate and logistic regression are used to calculate crude and adjusted odds ratios (cOR and aOR), and 95% confidence intervals (CI) and to assess the association between exposures during pregnancy and major congenital malformations and other perinatal outcomes. Covariates will be tested using a P -value of < 0.1 to detect associations with exposure and outcome. If associated with both exposure and outcome, the covariate will be included as a true confounder in the analysis.

## Documents

### Study results

[Asiakirja1.pdf](#)(5.24 KB)

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## Data management

## ENCePP Seal



**This study has been awarded the ENCePP seal**



### **Conflicts of interest of investigators**

[H\\_MALM\\_Annex5\\_DoIForm.pdf](#)(920.86 KB)

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### **Composition of steering group and observers**

[ENCEPP\\_Clarification of steering group.pdf](#)(17.49 KB)

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### **Signed code of conduct**

[DECL\\_COMPLIANCE\\_with ENCePP CoC.pdf](#)(83.84 KB)

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### **Signed code of conduct checklist**

[Checklist\\_ENCePP\\_CoC\\_for ENCePP Studies.pdf](#)(374.03 KB)

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### **Signed checklist for study protocols**

[ENCEPP\\_checklist\\_study\\_protocols.pdf](#)(536.83 KB)

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## **Data sources**

### **Data source(s), other**

Drugs and Pregnancy Finland

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### **Data sources (types)**

[Administrative healthcare records \(e.g., claims\)](#)

[Drug dispensing/prescription data](#)

## **Use of a Common Data Model (CDM)**

**CDM mapping**

No

Data quality specifications

**Check conformance**

Unknown

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**Check completeness**

Unknown

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**Check stability**

Unknown

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**Check logical consistency**

Unknown

Data characterisation

**Data characterisation conducted**

No