Drug-Drug Interactions Between ADHD and Cardiometabolic Medications: a Pharmacovigilance Study

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Study Planned

Administrative details

EU PAS number

EUPAS1000000761

Study ID

1000000761

DARWIN EU® study

No

Study countries

- Australia
- Denmark
- Sweden
- United States

Study description

Attention-deficit/hyperactivity disorder (ADHD) is increasingly recognized as a lifelong condition, with rising diagnoses and medication use among adults. ADHD medications, while effective, can influence cardiovascular function, and many patients are co-prescribed cardiometabolic treatments. This project investigates the safety of concurrent use of ADHD and cardiometabolic medications, given elevated cardiometabolic risks and overlapping pharmacological effects. We first screened for drug–drug interaction (DDI) signals using disproportionality analyses in the U.S. Food and Drug Administration Adverse Event Reporting System (FAERS) and the European Medicines Agency's EudraVigilance database, and then estimated the prevalence of concurrent ADHD and cardiometabolic medication use with potential DDIs among ADHD medication users using population-based prescription databases from four countries.

Study status

Planned

Research institutions and networks

Institutions

Department of Medical Epidemiology and Biostatistics, Karolinska Institutet

Sweden

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Institution | Educational Institution | ENCePP partner

University of New South Wales (UNSW Sydney)

Australia

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Last updated: 01/02/2024

Institution | Educational Institution

Aarhus University

First published: 01/02/2024

Last updated: 01/02/2024

Institution

SUNY Upstate Medical University

Networks

TIMESPAN

Australia

Denmark

Germany

Hong Kong
Iceland
Ireland
Italy
Netherlands
Norway
Spain
Sweden
United Kingdom
United States

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Network

Contact details

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Primary lead investigator

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Study timelines

Date when funding contract was signed
Planned: 01/04/2024

Study start date
Planned: 01/10/2025

Date of final study report
Planned: 30/11/2026

Sources of funding

- EU institutional research programme

More details on funding

This project has received funding from the European Union's Horizon 2020 research and innovation programme under grant agreement No 965381. This research reflects only the authors' view, and the European Commission is not responsible for any use that may be made of the information it contains.

Study protocol

Common analysis protocol_DDI between ADHD and cardiometabolic medications.pdf (343.85 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:

Hypothesis generation (including signal detection)

Safety study (incl. comparative)

Data collection methods:

Secondary use of data

Study design:

Multi-country study.

Main study objective:

First, we screened for drug–drug interaction (DDI) signals from the FAERS and the EudraVigilance database.
Second, we examined the prevalence of concurrent ADHD and cardiometabolic medication use with potential DDI among ADHD medication users in four countries.

Study Design

Non-interventional study design
Case-control

Study drug and medical condition

Medicinal product name, other
ADHD medications including methylphenidate, amfetamine, dexamfetamine, lisdexamfetamine, atomoxetine and guanfacine.

Population studied

Short description of the study population
In the first step, we screened for drug–drug interaction (DDI) signals from the U.S. Food and Drug Administration Adverse Event Reporting System (FAERS) and the European Medicines Agency’s EudraVigilance database.
In the second step, we examined the prevalence of concurrent ADHD and cardiometabolic medication use with potential DDIs among ADHD medication users in Australia (residents in the state of New South Wales, MedIntel Data Platform), Denmark and Sweden (linkage of national health registers), as well

as the US (federated EHR from the TriNetX Research Network database).

Age groups

- **Paediatric Population (< 18 years)**
  - Neonate
    - Preterm newborn infants (0 – 27 days)
    - Term newborn infants (0 – 27 days)
  - Infants and toddlers (28 days – 23 months)
  - Children (2 to < 12 years)
  - Adolescents (12 to < 18 years)
- **Adult and elderly population (≥18 years)**
  - Adults (18 to < 65 years)
    - Adults (18 to < 46 years)
    - Adults (46 to < 65 years)
  - Elderly (≥ 65 years)
    - Adults (65 to < 75 years)
    - Adults (75 to < 85 years)
    - Adults (85 years and over)

Study design details

Data analysis plan

We analyzed individual case safety reports (ICSRs) from two pharmacovigilance databases: FAERS (2004-2024) and EudraVigilance (2002-2024). Both systems collect post-marketing reports submitted by healthcare professionals, patients, and marketing authorization holders. The reference set comprised reports that included at least one ADHD medication during the study period. ADHD medication was defined using WHO ATC codes and included methylphenidate (N06BA04), amphetamine (N06BA01), dexamfetamine (N06BA02), and

lisdexamfetamine (N06BA12), atomoxetine (N06BA09) and guanfacine (C02AC02). Cardiometabolic medications were defined as agents within ATC groups C (cardiovascular system), A10 (drugs used in diabetes), and B01 (antithrombotic agents). Serious outcomes were defined in FAERS as: death; life-threatening event; hospitalization (initial or prolonged); disability; congenital anomaly; required intervention to prevent permanent impairment or damage; and other medically important condition. In EudraVigilance, serious outcomes included: death; life-threatening event; hospitalization (initial or prolonged); disability; congenital anomaly; and other medically important condition. Potential DDI signals were screened using three disproportionality methods—reporting odds ratio (ROR), proportional reporting ratio (PRR), and the Bayesian confidence propagation neural network (BCPNN) - computed independently in each database.

We applied a common, preregistered protocol to assess the real-world prevalence of the identified DDI pairs in four countries (Australia, Denmark, Sweden, and the United States). For each calendar year, we calculate the prevalence of concurrent use of ADHD and cardiometabolic medication associated with DDIs identified in the first step among ADHD medication users.

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)

Linkage of Swedish national registers for psychiatric research

Danish Health Data Registries

Data source(s), other

Medicines Intelligence (MedIntel) Data Platform, a linked data resource of Medicare-eligible people who are ≥18 years and residing in New South Wales (NSW), Australia.

Merative MarketScan Research Databases

Data sources (types)

Administrative healthcare records (e.g., claims)

Use of a Common Data Model (CDM)

CDM mapping

No

Data quality specifications

Check conformance

Yes

Check completeness

Yes

Check stability

Yes

Check logical consistency

Yes

Data characterisation

Data characterisation conducted

Unknown