DARWIN EU® - Clozapine and the incidence of agranulocytosis over time

First published: 11/04/2025

Last updated: 11/08/2026

Study Finalised

Administrative details

EU PAS number

EUPAS1000000549

Study ID

1000000549

DARWIN EU® study

Yes

Study countries

- Croatia
- Denmark
- Finland
- Germany
- Spain

Study description

Clozapine is an effective treatment for treatment-resistant schizophrenia and Parkinson’s disease psychosis, but it carries a risk of severe hematological complications, including neutropenia and agranulocytosis.
Emerging evidence suggests that the risk is highest in the initial months of treatment, yet stringent hematological monitoring requirements remain in place throughout long-term use.
These requirements may hinder clinical practice, leading to underuse, early treatment discontinuation, or reluctance to initiate therapy.
This study aims to provide epidemiological evidence on the incidence and timing of clozapine-associated neutropenia and agranulocytosis across Europe.

Study status

Finalised

Research institutions and networks

Institutions

Department of Medical Informatics - Health Data Science, Erasmus Medical Center (ErasmusMC)

Netherlands

First published: 03/11/2022

Last updated: 02/05/2024

Institution | Educational Institution | ENCePP partner

Networks

Data Analysis and Real World Interrogation Network (DARWIN EU®)

- Belgium
- Croatia
- Denmark
- Estonia
- Finland
- France
- Germany
- Greece
- Hungary
- Italy
- Netherlands
- Norway
- Portugal
- Spain
- Sweden
- United Kingdom

First published: 01/02/2024

Last updated: 30/04/2025

Network

Contact details

Study institution contact

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Study contact

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Primary lead investigator

Dina Vojinovic

Primary lead investigator

Study timelines

Date when funding contract was signed

Planned: 17/02/2025

Actual: 17/02/2025

Study start date

Planned: 31/03/2025

Actual: 31/03/2025

Date of final study report

Planned: 30/05/2025

Actual: 28/05/2025

Sources of funding

- EMA

Study protocol

DARWIN EU_Protocol_P4-C1-001_Clozapine_agranulocytosis_V2.pdf (760.15 KB)

Regulatory

Was the study required by a regulatory body?

Yes

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

Not applicable

Methodological aspects

Study type

Study type list

Study topic:

Disease /health condition

Human medicinal product

Study type:

Non-interventional study

Scope of the study:

Disease epidemiology

Safety study (incl. comparative)

Data collection methods:

Secondary use of data

Study design:

A cohort study will be conducted using routinely collected health data from 5 data sources. The study will comprise three consecutive parts:

• Population-level cohort study (Objective 1, Population-level descriptive epidemiology of agranulocytosis and neutropenia in new users of clozapine).

• Cohort

Main study objective:

1. To estimate the incidence rates of agranulocytosis and neutropenia in consecutive weekly and monthly intervals following the initiation of clozapine treatment, overall and stratified by age and sex.

2. To characterise the timing of agranulocytosis and neutropenia events during clozapine treatment using Kaplan-Meier curves, overall and stratified by age and sex.

3. To characterise individuals initiating clozapine treatment in terms of demographics and pre-specified conditions related to the indication for clozapine use.

4. To determine the treatment duration for clozapine use.

Study Design

Non-interventional study design

Cohort

Study drug and medical condition

Medicinal product name, other

Clozapine

Anatomical Therapeutic Chemical (ATC) code

(N05AH02) clozapine

clozapine

Medical condition to be studied

Agranulocytosis

Population studied

Short description of the study population

The study population will include all new users of clozapine registered in the respective data sources between 1st of January 2010 and 31st of December 2024 (or latest date available).

“New use” refers to a first prescription of clozapine within the study period with no clozapine prescription in the medical history.

Eligibility Criteria:

At least 1 year of data visibility before starting clozapine treatment.

Additional eligibility criteria:

To ensure sufficient follow-up, only individuals who initiated clozapine treatment at least one year before the end of the available data in the respective data source will be included.

Age groups

- **In utero**
- **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

Outcomes

A combined outcome of neutropenia and agranulocytosis (broad definition) following the initiation of clozapine treatment. Cohort diagnostics showed that coding limitations and inconsistent SNOMED mappings prevented reliable distinction between neutropenia and agranulocytosis. To reduce misclassification and ensure consistency, the outcome was defined as a composite of both conditions. To ensure that only incident cases were captured, individuals with a prior history of agranulocytosis or neutropenia were excluded.

Data analysis plan

Population-level descriptive epidemiology: Incidence rates of newly diagnosed agranulocytosis and neutropenia were estimated following clozapine treatment

initiation (objective 1). These rates are expressed as the number of individuals with the newly diagnosed outcome of interest following clozapine initiation per 1,000 person-years of individuals fulfilling inclusion criteria. Incidence rates were calculated for consecutive weekly (0-7 days, 8-14 days, 15-21 days etc.) and monthly intervals (0-30 days, 31-60 days, 61-90 days etc.) since the initiation of clozapine treatment (index date), with a maximum follow-up period of 24 months for reporting both weekly and monthly estimates. The statistical analysis was performed based on OMOP-CDM mapped data using the IncidencePrevalence" R package. The results are reported overall and stratified by age and sex.

Patient-level characterisation: The timing of agranulocytosis and neutropenia events during clozapine treatment was characterised using Kaplan-Meier curves (objective 2). This analysis was conducted using the "CohortSurvival" R package based on OMOP-CDM mapped data. The results were stratified by age and sex.

Patient-level utilisation of clozapine: Characterisation including age and sex was assessed at the date of new
(incident) prescription of clozapine (index date) (objective 3). The frequency of pre-specified conditions related to clozapine initiation was assessed at any time prior to 1 day before index date, 365 days prior to 1 day before index date and at the index date (objective 3). Duration of treatment was calculated and summarised providing the minimum, quartiles and maximum, where available (objective 4). Statistical analyses were conducted using the "CohortCharacteristics" and "DrugUtilisation" R packages based on OMOP-CDM mapped data.

Sensitivity analysis: [truncated]

Summary results

Discussion

This multi-database cohort study provides evidence on incidence and timing of

agranulocytosis and neutropenia following clozapine treatment initiation across different European countries. The findings reaffirm that these adverse events are rare and typically occur early in treatment, consistent with prior evidence. This underscores the importance of close monitoring during the initial treatment period, aligning with existing clinical guidance.

However, several methodological limitations should be considered when interpreting these findings. Specifically, it was not feasible to reliably differentiate between agranulocytosis and neutropenia, nor to assess the severity of individual events. Furthermore, challenges in accurately capturing treatment duration of clozapine may have affected estimates of both event timing and frequency, although overall incidence rates remained low.

Despite these limitations, the consistently low incidence of events observed beyond the early months following clozapine initiation raises important questions about the necessity of prolonged intensive haematological monitoring. This highlights a potential opportunity to revisit and refine existing monitoring guidelines to balance safety with improved treatment accessibility and patient adherence.

Documents

Study report

DARWIN EU Report_P4-C1-001_Clozapine-risk agranulocytosis_V4.0_Clean.pdf (2.19 MB)

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)

Danish Health Data Registries

Croatia National Public Health Information System (Nacionalni javnozdravstveni informacijski sustav)

IQVIA Disease Analyzer Germany

The Information System for Research in Primary Care (SIDIAP)

Data source(s), other

FinOMOP-HILMO

Use of a Common Data Model (CDM)

CDM mapping

Yes

CDM Mappings

CDM name

OMOP

CDM website

https://www.ohdsi.org/Data-standardization/

CDM version

https://ohdsi.github.io/CommonDataModel/index.html

Data quality specifications

Check conformance

Unknown

Check completeness

Unknown

Check stability

Unknown

Check logical consistency

Unknown

Data characterisation

Data characterisation conducted

Unknown