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

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BACKGROUND

Clozapine is an effective antipsychotic for treatment-resistant schizophrenia and is also indicated for Parkinson's disease psychosis. However, its use is limited by the risk of severe haematological complications, including neutropenia and agranulocytosis, which require intensive and prolonged haematological monitoring.[1,2,3] While emerging evidence suggests the risk is highest in the initial months of treatment, the necessity of long-term monitoring remains debated and may hinder optimal clinical use.

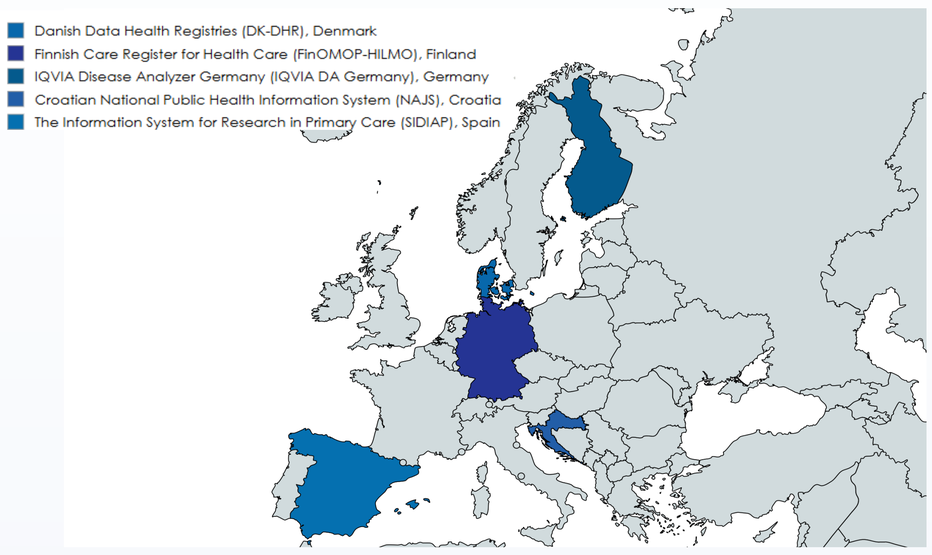
OBJECTIVES

This study aimed to generate epidemiological evidence on the temporal patterns of these haematological adverse events in individuals initiating clozapine across multiple European populations and to characterise the individuals initiating clozapine treatment.

MATERIALS AND METHODS

Study design: A retrospective cohort study.

Data sources:



All data sources previously mapped their data to the OMOP Common Data Model (CDM).

Study population: All new users of clozapine registered in the respective data sources during the study period with at least one year of prior data visibility and no history of clozapine use. 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 were included.

Study period: 2010 − 2024.

Drug of interest: Clozapine.

Conditions of interest: A combined outcome of neutropenia and agranulocytosis following the initiation of clozapine treatment.

Data analysis: Incidence rates of agranulocytosis and neutropenia were estimated as the number of individuals with the newly diagnosed outcome of interest following clozapine initiation per 1,000 person-years (PYs). Incidence rates were calculated for consecutive weekly and monthly intervals since initiation, with a maximum follow-up period of 24 months. The analyses were done using the *IncidencePrevalence* R package. Characteristics of clozapine initiators and drug utilisation were conducted using the *CohortCharacteristics* and *DrugUtilisation* packages.

RESULTS

A total of 40,956 new clozapine users were identified (DK-DHR: 4,253; FinOMOP-THL: 14,944; IQVIA DA Germany: 4,029; NAJS: 13,382; SIDIAP: 4,348). Overall, incidence rates of agranulocytosis and neutropenia among new users of clozapine were low across all data sources (**Figure 1**, **Figure 2**). In FinOMOP-THL, incidence rates ranged from 24.5 per 1,000 PYs during the first week following treatment initiation, peaked at 58.7 per 1,000 PYs in week nine after clozapine initiation, and then decreased, with most subsequent weeks showing zero or very few events. Monthly rates were highest in the first three months (17.7–31.4 per 1,000 PYs), followed by low or no events. In SIDIAP, weekly and monthly rates remained low and stable, with most intervals showing zero or few events, and a peak of 18.7 per 1,000 PYs in month two. In DK-DHR, IQVIA DA Germany, and NAJS, most intervals reported zero events, while others had small event counts (< 5 events). Most events occurred early, with median time to diagnosis ranging from 53 days (FinOMOP-THL) to 278 days (IQVIA DA Germany).

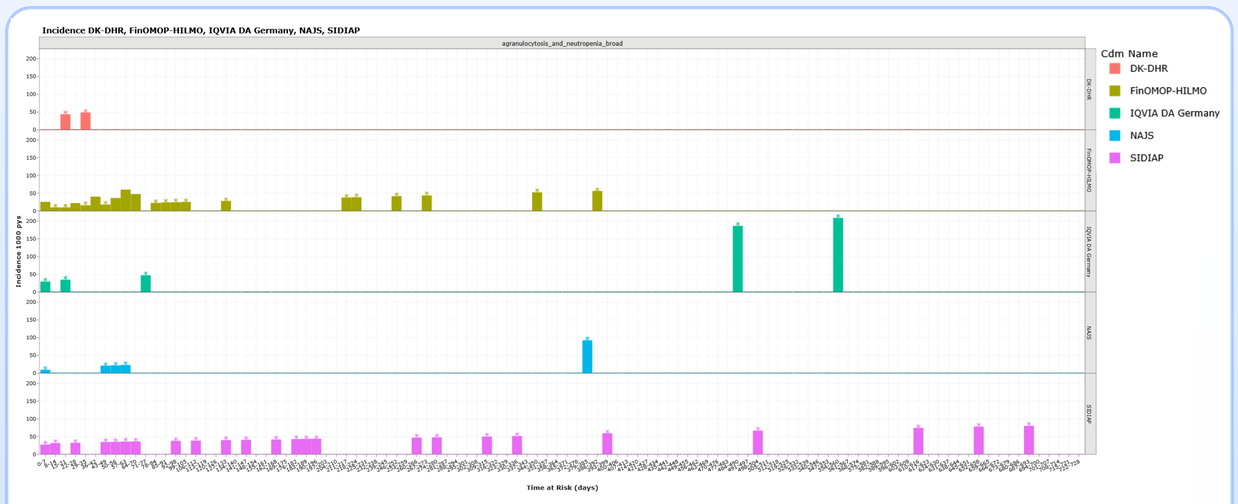


Figure 1. Incidence rates of agranulocytosis and neutropenia following initiation of clozapine treatment by consecutive weekly intervals in each data source, from 2010 to 2024.

**Intervals with <5 events were censored due to data privacy requirements; censored intervals were imputed using 2.5 events (midpoint of 1–4) and are marked with an asterisk.*

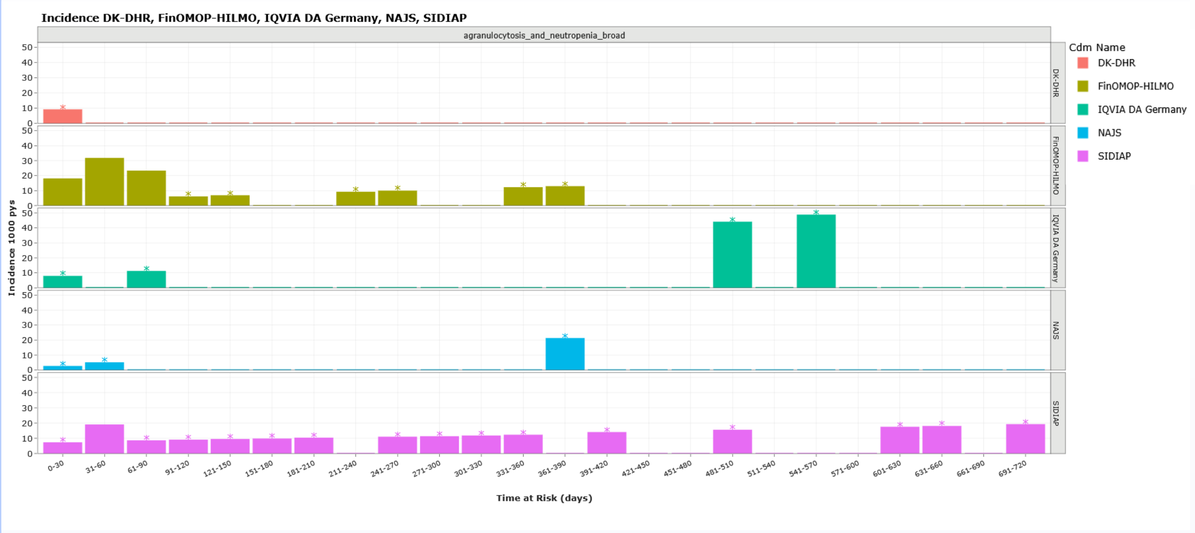


Figure 2. Incidence rates of agranulocytosis and neutropenia following initiation of clozapine treatment by consecutive monthly intervals in each data source, from 2010 to 2024.

**Intervals with <5 events were censored due to data privacy requirements; censored intervals were imputed using 2.5 events (midpoint of 1–4) and are marked with an asterisk.*

The median age at clozapine initiation ranged from 39 years (DK-DHR) to 63 years (IQVIA DA Germany). Most users were male, except in NAJS, where the sex distribution was balanced. Treatment-resistant schizophrenia was the predominant diagnosis in the year prior to clozapine start (5.1% in IQVIA DA Germany to 43.0% in DK-DHR), while other indications, such as suicidal or aggressive behaviours and psychotic disorders in Parkinson's disease, were rare. Most individuals had other or unspecified recorded indications.

CONCLUSIONS

This multi-data source cohort study provides evidence on the 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. Despite these limitations, the consistently low incidence of events observed beyond the early months following clozapine initiation raises questions about the necessity of prolonged intensive haematological monitoring and suggests an opportunity to refine current guidelines to balance safety, access, and adherence.

REFERENCES

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DISCLOSURE

This study was funded by the European Medicines Agency (EMA) and performed via DARWIN EU® (EUPAS1000000549). EMA was involved in conceiving the research, objectives, and reviewing the study protocol and the study report including the results. Data partners do not have an investigator role. They execute analytical code at their respective data sources, review, and approve their results. This communication represents the DARWIN EU® Coordination Centre only and cannot be interpreted as reflecting those of the EMA or the European Medicines Regulatory Network.

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