First-episode psychosis pharmacotherapy: an antipsychotics comparative effectiveness study protocol

Background: Schizophrenia is a severe neuropsychiatric disorder which often leads to a significant functional and cognitive impairment. The term “First-episode psychosis” (FEP) refers to the first manifestation of psychotic symptoms in a person’s life and later such persons may be diagnosed with schizophrenia, bipolar disorder with psychotic features, schizoaffective disorder, and substance-induced psychosis [1]. Early treatment significantly improves symptom control, functional outcomes, and long-term disability [2]. However, optimal medication selection remains uncertain: current clinical practice guidelines cite heterogeneous trial designs and limited head-to-head comparisons as major barriers to evidence-based ranking of antipsychotics [3].This study seeks to address these gaps by leveraging large-scale, real-world data from multiple Observational Medical Outcomes Partnership Common Data Model (OMOP CDM)-converted datasets across the Observational Health Data Sciences and Informatics (OHDSI) network, using validated phenotype definitions, reproducible analytic pipelines, and empirical calibration to estimate the relative effectiveness of commonly used antipsychotics (APs) for relapse prevention in FEP.

Methods: We will conduct a large-scale, systematic observational study to compare the hazard ratios of rehospitalization with a psychotic relapse among patients who were administered one of 9 APs of interest as a first-line treatment for FEP. We will conduct 36 head-to-head pairwise comparisons as indicated in Table 1. For each of the target-comparator pairs, we will employ a new-user, active-comparator cohort design. Cohort definitions will be developed using the OHDSI ATLAS tool and implemented with the CohortDiagnostics package to assess phenotype performance across data sources. Propensity score modeling will be used to address confounding, including large-scale covariate adjustment via regularized regression. Both matching and stratification methods will be considered, with preference given to stratification unless matching yields better covariate balance. Hazard ratios will be estimated using Cox proportional hazards models within each data source. Results will be combined using random-effects meta-analysis, with leave-one-database-out sensitivity analyses to assess robustness. Negative control outcomes will be used to perform empirical calibration of effect estimates and p-values. To ensure reproducibility and consistency, all analyses will be performed using the OHDSI Health Analytics Data-to-Evidence Suite (HADES).

Table 1 Exposure-Comparator Matrix

Comparators	Haloperidol	Risperidone	Aripiprazole	Brexpiprazole	Olanzapine	Quetiapine ≥ 100 mg/day and above	Ziprazidone	Lurazidone	Paliperidone
Haloperidol									
Risperidone	X								
Aripiprazole	X	X							
Brexpiprazole	X	X	X						
Olanzapine	X	X	X	X					
Quetiapine ≥ 100 mg/day and above	X	X	X	X	X				
Ziprazidone	X	X	X	X	X	X			
Lurazidone	X	X	X	X	X	X	X		
Paliperidone	X	X	X	X	X	X	X	X	

Results: As a first milestone, we developed and validated 10 phenotype definitions for use in this study. The cohort design framework is presented in Figure 1, with detailed phenotype definitions and concept set structures available in the full-text study protocol [4] as well as in the respective OHDSI network study repository. Phenotype validation was conducted as part of the OHDSI 'Phenotype Phebruary' initiative. The final FEP phenotype comprises 986 diagnosis codes from 11 vocabularies, including all the psychotic disorders and non-chronic affective disorders with psychotic symptoms, and specifically excludes organic and drug-induced psychoses.

Results (cont.): The iterative development and validation process enabled removal of ambiguous diagnosis codes and establishment of reproducible cohort entry and censoring criteria.

Using the OHDSI Data Diagnostics tool and the database-level summary statistics produced by it, we identified potential data partners within the OHDSI Evidence Network. In order to control for detailed cohort entry criteria level requirements, we prepared the preliminary feasibility assessment script to be run by a potential data partner to assess data fitness for the study. Full network-wide study execution is planned for 2026.

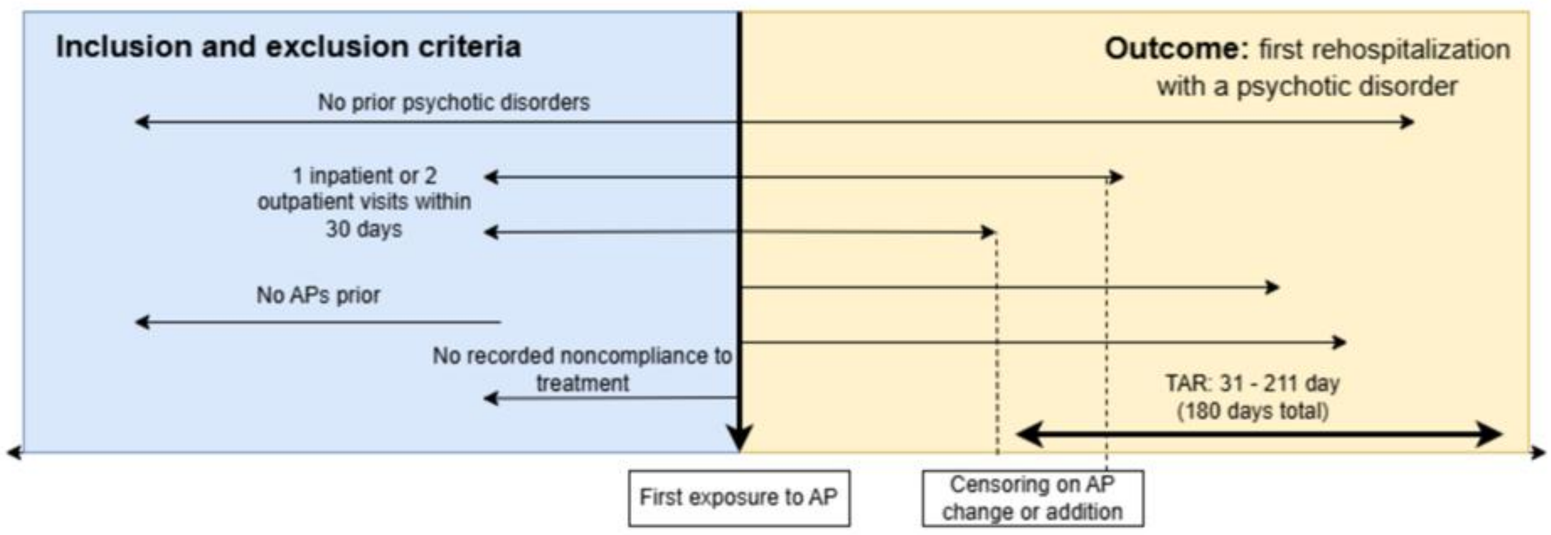

Figure 1 Cohort design framework

Discussion and conclusion: The study’s strengths are based on its large-scale, real-world, multi-national observational data, federated execution across the OHDSI network, and use of validated, transparent cohort definitions developed with open-source OHDSI tools. Being an observational study, our investigation may be affected by unmeasured or misspecified confounders, including confounding by indication and differences in care-seeking behavior. To mitigate this, we will be using a large list of negative controls, representing exposure-outcome pairs with no known effect. Our cohort definition requires data sources with comprehensive longitudinal patient histories, which may limit cohort inclusion. However, this stringent approach prioritizes specificity over sensitivity to capture true first-episode psychosis cases and minimize misclassification of recurrent psychotic episodes as FEP, thereby ensuring accurate representation of real-world treatment patterns and outcomes.

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References: 1 2 3 4