Role of α1-adrenergic antagonist activity and 5-HT1A antagonism in the occurrence of ischaemic stroke and TIA within one year after a first prescription of antipsychotics in France: a cohort study in the EGB between 2009 and 2019

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Study Ongoing

Administrative details

EU PAS number

EUPAS40828

Study ID

40829

DARWIN EU® study

No

Study countries

☐ France

Study description

Antipsychotics are widely prescribed in the French general population. They constitute a heterogeneous pharmacological class, are non-selective, and each antipsychotic binds differently to α1-adrenergic or serotonin 5-HT1A receptors. Cardiovascular adverse effects are a major cause of mortality in patients exposed to antipsychotics, including ischaemic strokes within the first few weeks of prescription. These could be explained by early cardiovascular pharmacodynamic effects (orthostatic hypotension, QT prolongation). However, another class of drugs presents an increased risk of early strokes, particularly ischaemic strokes: alpha-blockers. These drugs act by strongly blocking α1-adrenergic and serotonin 5-HT1A receptors. Moreover, activation of these receptors in the cerebral arteries can lead to vasoconstriction. Blocking these receptors could therefore lead to vasodilatation, resulting in cerebral hypoperfusion which could favour the occurrence of ischaemic stroke. To date and to to our knowledge, only two studies have investigated the risk of early ischemic stroke associated with antipsychotic drugs in relation to these two receptors, but they are inconsistent and have several limitations. We hypothesise that antipsychotic drugs with 5-HT1A antagonism and strong α1-adrenergic antagonism are associated with a greater risk of hospitalisation for cerebral ischaemic events. The primary objective of our study is to evaluate whether prescribing antipsychotic drugs with strong α1-blocking affinity and 5-HT1A antagonist activity is associated with an increased risk of hospitalisation for ischaemic stroke or TIA within one year of initiation, compared with prescribing antipsychotic drugs with low α1-adrenergic affinity and no 5-HT1A antagonism (reference group). The secondary objective of our study is to assess the possible risk factors for ischaemic stroke or TIA hospitalisations associated with incident prescribing of these two groups of antipsychotics.

Study status

Ongoing

Research institutions and networks

Institutions

Toulouse University Hospital

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Institution

Pharmacologie En Population cohorteS et biobanqueS - Centre d’Investigation Clinique 1436

Contact details

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Primary lead investigator

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Primary lead investigator

Study timelines

Date when funding contract was signed
Actual: 13/01/2021

Study start date
Actual: 08/02/2021

Data analysis start date
Planned: 03/05/2021

Date of final study report
Planned: 30/07/2021

Sources of funding

- Other

More details on funding

Congrès Français de Psychiatrie

Study protocol

Antipsychotics and ischaemic cerebral events - Role of a1-adrenergic antagonist activity and 5-HT1A antagonism - Cohort study in the French EGB.pdf (564.39 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 type:

Non-interventional study

Scope of the study:

Assessment of risk minimisation measure implementation or effectiveness

Main study objective:

Evaluate whether prescribing antipsychotic drugs with high α1-blocker affinity and 5-HT1A antagonist activity is associated with an increased risk of hospitalisation for ischaemic stroke or transient ischaemic attack (TIA) within one year of initiation, compared with prescribing antipsychotic drugs with low α1-adrenergic affinity and absence of 5-HT1A antagonism (reference group).

Study Design

Non-interventional study design

Cohort

Other

Non-interventional study design, other

Pharmacodynamic study

Study drug and medical condition

Anatomical Therapeutic Chemical (ATC) code

(N05A) ANTIPSYCHOTICS

ANTIPSYCHOTICS

Population studied

Age groups

- Adults (18 to < 46 years)
- Adults (46 to < 65 years)
- Adults (65 to < 75 years)
- Adults (75 to < 85 years)
- Adults (85 years and over)

Estimated number of subjects

33120

Study design details

Outcomes

Difference in survival without hospitalisation for ischaemic stroke (ICD code I63) or transient ischaemic attack (G45) during the follow-up period in the cohort, between the two exposure groups. Occurrence of a hospitalization with a principal diagnosis of ischemic stroke (ICD code I63) during the follow-up period in the cohort. Occurrence of a hospitalization with a principal diagnosis of TIA (G45) during the follow-up period in the cohort. Death during the follow-up period in the cohort.

Data analysis plan

Main analysis : Statistical analyses will be performed without blinding procedures. The main analysis will be performed as treated. The crude incidence rate of occurrence of the primary endpoint will be estimated in each exposure group. The 12-month risk of hospitalisation for ischemic cerebrovascular events will be estimated by Kaplan-Meier analysis for both exposure groups. We will use a Cox proportional hazards regression model to estimate Hazard Ratios (HRs) and their 95% confidence intervals for the risk of occurrence of the primary endpoint of the "strong α1-blocker-5-HT1A antagonist" antipsychotic group, compared with the "weak α1-blocker-non-5-HT1A antagonist" antipsychotic group. Sensitivity and additional analyses : cf. protocol.

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 sources (types)

Administrative healthcare records (e.g., claims)

Use of a Common Data Model (CDM)

CDM mapping

No

Data quality specifications

Check conformance

Unknown

Check completeness

Unknown

Check stability

Unknown

Check logical consistency

Unknown

Data characterisation

Data characterisation conducted

No