**Objectives: To perform a mixed-treatment comparison of the safety of several antipsychotics in the treatment of schizophrenia**

# Introduction

Schizophrenia is a severe mental disorder, characterized by disintegration of thought processes and impaired emotional responsiveness. The disease most commonly manifests itself through auditory hallucinations, paranoid or bizarre delusions, and disorganized speech and thinking; it is also generally accompanied by significant social and/or occupational dysfunction. Schizophrenia is estimated to affect over 21 million people worldwide and five million in the European Union (EU), with an estimated 12-month prevalence of 1.2% amongst adults in the EU.

Symptoms typically first occur in young adulthood:
- Positive symptoms i.e. those that occur in people with schizophrenia but not in unaffected individuals, for example hallucinations and delusions
- Negative symptoms i.e. those that are lacking in people affected by the disease, but are commonly found in others, for example social withdrawal, lack of motivation and diminished emotional reactivity

Schizophrenia usually persists, continuously or episodically, over the course of the patient's life-time. Complete remission (i.e., a return to full premorbid functioning) is uncommon. Some individuals appear to have a relatively stable course, whereas others show a progressive worsening associated with severe disability.

The positive symptoms usually respond to treatment with antipsychotic medication, whereas the negative symptoms are less responsive to antipsychotic medication. Often the negative symptoms steadily become more prominent during the course of schizophrenia. The treatment strategy for schizophrenia is focused in the alleviation of the symptoms. Treatments include antipsychotic medications and various psychosocial treatments.

First antipsychotic medications are effective in treating positive symptoms such as hallucinations and delusions but can cause some serious side effects. Many patients experience significant weight gain, drowsiness, or dry mouth.

A newer type of medication has been developed and is known as atypical antipsychotics:
- The term is applied to drugs that are potentially more effective (particularly against depressive, negative, or cognitive symptoms) or better tolerated (especially causing fewer extrapyramidal side effects) than conventional antipsychotics
- Atypical antipsychotics are known to cause metabolic derangements including weight gain, dyslipidemia, and hyperglycemia.

Aripiprazole, olanzapine and risperidone are among the most commonly used atypical antipsychotics in schizophrenic patients.

## Project objectives

The aim of this project is to assess the safety of several antipsychotics in the treatment of schizophrenia using a mixed-treatment comparison, based on data from several clinical trials.

Although there are many drugs available for schizophrenia, this project is considering the following treatments:

- Olanzapine
- Quetiapine
- Risperidone
- Aripiprazole

## Outcomes considered

Two outcomes will be analysed:

- The mean change in weight from baseline to 6 months at week 26 +/- 4
- The proportion of patients who discontinued due to adverse event (AE)

## Material

This booklet contains the following:

- The publications of seven clinical studies comparing the treatments of interest and reporting the two outcomes listed above;
- The 2 publications from the ISPOR Task Force on conducting and interpreting network meta-analyses;
- An excerpt from the Cochrane Handbook for Systematic Reviews of Interventions, to address the issue of missing standard errors;
- Notes on mixed treatment comparisons from Bristol University, containing WinBUGS programs for multi-arm adjustment.

## Analyses, Deliverable and gradation

The expected deliverable is a short report (max 20 pages excluding appendices) in English, reporting at least the following:

- Definition of the study question
- Network of evidence and summary tables of the data
- Direct comparisons of each treatment versus olanzapine
    - With heterogeneity assessment, either qualitative or quantitative
    - With tables and graphical presentations
- Inconsistency assessment if applicable

- Mixed-treatment comparison results:
    - Mean difference in mean change, odds-ratios or other pairwise measures of treatment effects
    - Ranking of treatments, probabilities to be the best, SUCRA etc.

These results are expected for both outcomes.

Attention will be given to presentation, formatting and spelling.

**Deadline: April 3rd, 2022**

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