# THE CONTRIBUTIONS OF RANDOMISED CONTROLLED TRIALS AND REAL-WORLD STUDIES TO THE TREATMENT OF SCHIZOPHRENIA

**Ph.D thesis**

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# 1. Introduction

## 1.1 Background

Real-world data (RWD) have increasingly played an important role in how pharmacotherapies are conducted in real life. Evidence for the effectiveness of a new medication recently approved by the authorities is rather limited. Randomised controlled trials (RCTs) can only address the efficacy and safety of a new drug candidate to become a medication for human use.

Schizophrenia is a severe mental disorder which cannot be cured and last for life-long in most of the cases. Persons concerned are not able to distinguish what is real and what is imagined. The disorder has a wide range of symptoms which are classified into three main domains: positive, negative and cognitive. Symptoms can be controlled to some extent with various therapeutic interventions.

## 1.2 The treatment of schizophrenia

The principal goal in the treatment of schizophrenia is to ease the symptoms and to reduce the chance of relapses. The “gold standard” is the use of antipsychotic medications (APs). There are two main classes of APs: First-generation Antipsychotics (FGAs) and Second-generation Antipsychotics (SGAs). The factors which can basically increase the likelihood of treatment

success are: (1) Patients have to visit their physicians on a regular basis; (2) and they need to take their antipsychotic medications as prescribed with no major gaps, i.e., they need to evidence good adherence. If one is treated with a long-acting injectable (LAI) AP medication, it has to be administered regularly, according to the approved product specification. In contrast, there are at least three major factors that work against the successful treatment with APs: (1) patients only have partial or even complete lack of insight; (2) a wide range of side effects that can be caused by AP medications; and finally, there are cases when AP treatments fail to work, which leads to treatment resistant schizophrenia.

### 1.3 Randomised Controlled Trials, „traditional" observational studies and database analyses

Before the approval of a medication, regulatory authorities assess whether the benefit of a new treatment significantly exceeds the harm it can potentially cause. The assessment is conducted on the basis of RCTs' results, including Phase 1, 2 and 3 trials; and the total number of subjects involved in these trials is rather limited. Subjects selected to RCTs are typically aged between 18 and 55, have no or just a few comorbidities, are not violent, have better adherence and better ability to communicate, compared to the population of subjects suffering

from schizophrenia. The study and follow-up period are rather limited in these trials. Furthermore, the overwhelming majority of RCTs measures efficacy instead of effectiveness. For example, psychometric rating scale scores, which are usually feature as primary endpoints of RCTs, do not necessarily reflect everyday life functioning.

After the approval, mainly non-randomised trials, also called as observational studies, with large sample sizes and long follow-up periods are conducted in order to gain information on further adverse events which have not been detected yet; and/or to assess the effectiveness of a new medication compared to an active comparator already available in the market.

In many countries electronic medical records, health insurance databases or other medical data are collected and are available to use for scientific purposes. For about the past 2-3 decades numerous studies have been conducted on the basis of RWD. Many of them were aimed to measure the effectiveness of a given medication or medications, comparing them to multiple treatments as controls.

We use the terminology of Real-world Studies (RWSs) to include both “traditional” observational studies and the ones which are based on database analyses.

It is not only the RCTs that have limitations, but also the RWSs. For example, typically it is not possible to assess endpoints such as psychometric rating scale scores, which could help eliminate differences between study arms, or to conduct detailed laboratory evaluations. Furthermore, it would be rather difficult to control treatment adherence to medications. Finally, in "traditional" observational studies there is a possibility, for instance, to assess the physical health of subjects; however, in those studies which rely on database analysis such data are usually not collected.

The studies that underlined my thesis were: (1) an effectiveness study based on the health insurance database of Hungary, analysing the records of medications which were used for the treatment of schizophrenia; and (2) a meta-analysis based on the results of previously published real-world studies, with a comparison of the results of our meta-analysis with the findings from the meta-analyses of randomised controlled trials.

## 2. Objectives

### 2.1 First study

Based on leading guidelines the recommended strategy for treatment of schizophrenia is to use one of the APs in monotherapy. However, in everyday clinical practice the use of two APs in parallel, called polypharmacy, is quite common. Our first study based on real-world data aimed to evaluate this practice and investigate whether polypharmacy had any advantages over monotherapy.

### 2.2 Second study

RCTs play a crucial role in clinical drug development; however, the generalisability of their findings has been questioned. To investigate this question, sufficient empirical evidence for drug effects from RWSs has been gathered for 2-3 decades. The principal interest of the second study was to assess whether the results of RWSs and RCTs are congruent or incongruent with each other.

## 3. Methods

### 3.1 First study

In our first study the principal outcome measure was all-cause treatment discontinuation. The secondary outcome measures were psychiatric hospitalisation and mortality, respectively. And finally, the main independent variable was the study arm, namely comparing monotherapy arm to polypharmacy arm.

The study period ranged from 01 January 2007 to 31 December 2009. Patients had to purchase one of the antipsychotic medications covering more than 60 days with treatment, without discontinuation. Their diagnosis had to be schizophrenia or schizoaffective disorder in the majority of prescriptions (≥67%). Monotherapy arm (MA) was defined as switching from a more than 60 days of initial AP monotherapy to a new AP medication. The polypharmacy arm (PA) was defined as adding a second AP medication to the existing one, which was taken for more than 60 days as an initial monotherapy. To exclude transient polypharmacies and to achieve an equal baseline condition for both arms only those patients were included in the analysis who continued to receive, the assigned AP monotherapy for >60 days in MA; in the polypharmacy arm, a combined treatment with two AP

medications in parallel for >60 days was specified. The observational (follow-up) period was one year beyond the above defined 60-day transition period. If subjects progress to 365 days on treatment or had no more data/records, they were considered as censored. The list of APs we investigated were two oral FGAs: haloperidol and zuclopenthixol; four LAI FGAs: haloperidol, flupentixol, fluphenazine, and zuclopenthixol; seven oral SGAs: amisulpride, aripiprazole, clozapine, olanzapine, quetiapine, risperidone, and ziprasidone; and one LAI SGA: risperidone.

For statistical analysis, we applied survival analysis with the Kaplan-Meier model in order to determine the median time to all-cause treatment discontinuation. Furthermore, Cox proportional hazards model was applied for time to all-cause treatment discontinuation and psychiatric hospitalisation, respectively, in order to calculate the hazard ratios. Logistics regression modelling was applied for mortality. To adjust for any potential demographic or clinical differences between study arms, we conducted matched-pair analyses with propensity score matching. For propensity score calculation logistic regression model was used. The list of independent variables we included in propensity score calculation were: gender, age and

the number of days of hospitalisations, on psychiatric or on other wards, respectively, during 1-year prior to the study.

### 3.2 Second study

We used a two-stage approach to investigate whether the results of RWSs and RCTs are congruent or incongruent with each other. First, we conducted a meta-analysis summarising the results of RWSs available in the literature. Second, we compared the RWS results with the results of previously published meta-analyses using data obtained from RCTs in order to investigate the congruency between them.

The set of APs we included in the analysis were one oral FGA: haloperidol; six oral SGAs: amisulpride, aripiprazole, clozapine, olanzapine, quetiapine, and risperidone; and one LAI SGA: risperidone. The meta-analysis was designed to compare the above listed APs in pairs.

The major selection criteria of RWSs for the meta-analysis were: study type, which had to be „traditional" observational studies or database analysis based on electronic medical records, health insurance databases; the indication for schizophrenia or schizoaffective disorder; a direct comparison by using at least 2 of the 8 selected APs; adoption of all-cause

treatment discontinuation as an endpoint; the inclusion of the hazard ratio or relative risk as a measure of effectiveness.

The selection criteria for prior meta-analyses based on data obtained from RCTs were: The meta-analyses had to be based on the results of RCTs; the indication for schizophrenia or schizoaffective disorder was needed; a direct comparison of at least 2 of the 8 selected APs was required; the endpoint had to be all-cause treatment discontinuation, or, in case this was not available, the drop-out from the RCTs was investigated; the measurements had to include relative risk.

We assessed the results of our meta-analysis based on RWSs according to two separate criteria: (1) Is the pooled meta-analytic estimate statistically conclusive (i.e., is there a statistically significant difference between the two AP medications investigated)?; (2) Are the individual study outcomes pointing always in the same direction with respect to their effect size estimate?

Based on the above approaches, the outcomes of comparisons were classified into three distinct categories: (1) RWSs were statistically conclusive and consistent; (2) RWSs were statistically conclusive but inconsistent; and (3) RWSs were neither statistically conclusive nor consistent.

During the overall comparison and evaluation of RWS results and of published meta-analytic RCT findings we formed 4 categories: (1) Data from the two types of studies were statistically conclusive and congruent; (2) RWSs were statistically inconclusive but congruent with RCT meta-analyses; (3) RWSs were statistically conclusive but incongruent with RCT meta-analyses; and (3) the RWSs were inconclusive and incongruent with RCT meta-analyses.

## 4. Results

### 4.1 First study

#### 4.1.1 Primary endpoint: Time to all-cause treatment discontinuation

Oral and long-acting injectable SGAs had a clear advantage for monotherapy compared to polypharmacy. The only exception was clozapine, which is expected to be mainly used in treatment resistant schizophrenia. Regarding oral FGAs, we found no statistically significant difference between the two strategies. As for the long-acting injectable FGAs, there was a significant advantage for polypharmacy; however, the median times of treatment discontinuation were rather limited for both strategies. Finally, the pooled result indicated a statistically significant advantage for monotherapy.

#### 4.1.2 Secondary endpoints: Psychiatric hospitalisation and mortality

As for psychiatric hospitalisation, there was a statistically significant advantage for clozapine, quetiapine and risperidone favouring polypharmacy. On the other hand, for amisulpride, haloperidol, olanzapine, ziprasidone, fluphenazine LAI and risperidone LAI, there was a numerical advantage for

polypharmacy. The pooled result indicated a statistically significant advantage for polypharmacy.

Based on the pooled result for mortality, there was a statistically significant advantage for polypharmacy.

4.2 Second study

Our meta-analysis was based on the results of 11 real-world studies. There were 2 types of RWSs we investigated: 8 of them were database analyses, and 3 of them were "traditional" observational studies. The RWSs differed in the length of follow-up periods, ranging from 1 to 3 years. We included 25 pairwise AP comparisons in the meta-analysis.

In our meta-analysis based on RWSs, out of the 25 AP comparisons there were 17 pairs with 3 or more input data. Only 5 out of the 17 comparisons yielded inconsistent results; the analogous number was 8 when all the 25 comparisons were considered. A total of 13 AP comparisons were conclusive, having statistically significant results. Twelve had consistent and significant pooled estimates: in 4 cases, olanzapine was superior over its comparators; furthermore, superiority was detected in 5 cases for risperidone LAI; and there were 3 cases where the haloperidol was less efficacious. There was only one comparison where the pooled estimate was inconsistent but

statistically significant (favouring olanzapine over haloperidol). Finally, there were only 4 AP comparisons with inconsistent and non-significant estimates.

For the comparison of results of RWSs and RCTs, we were not able to identify RCT findings for all of the 17 AP comparisons just for 12. Out of the 9 AP comparisons yielding significant differences between the AP pairs, there were 7 comparisons which showed congruency with the results of RCTs; while out of the 3 AP comparisons yielding no significant difference based on RWSs, we identified 2 comparisons showing congruency with the findings of RCTs.

## 5. Conclusions

### 5.1 First study

Monotherapy is superior over polypharmacy for long-term sustained treatment of schizophrenia; while polypharmacy shows an advantage in psychiatric hospitalisations and mortality, respectively. Polypharmacy may be more effective during acute exacerbations of psychotic symptoms.

Single composite endpoints, such as all-cause treatment discontinuation, may not be able to distinguish specific differences in major clinically relevant events, such as hospitalisation and death. Our results highlight the significance of examining multiple secondary endpoints in long-term studies of schizophrenia. Furthermore, hospitalisation and death are important hard endpoints for testing clinical effectiveness. Finally, time elapsing to all-cause treatment discontinuation offers a practical metric for physicians, combining efficacy and tolerability.

### 5.2 Second study

In the majority of comparisons, real-world studies yielded consistent results with each other, and were congruent with the findings of randomised controlled trials.

The findings of real-world studies can provide support for clinical practice, especially if, for example: (1) two APs of clinical interest have never been compared to each other in a randomised controlled trial; or (2) if the clinical/scientific question raised would be difficult to address in randomised controlled trials.

Furthermore, real-world study results can support the formulation of relevant hypotheses which could be tested in randomised controlled trials. Finally, the results of real-world studies can give critical information to regulators on design needs for future research.

## 5.3 General summary and conclusions

RCTs as “gold standard” are the foundations of drug development, and help physicians and the “health care system” as a whole, for choosing the best treatment for the patients. While RCTs can have limited diversity of data for treatment comparisons (such as comparator bias, regulatory bias, and restricted target population), in the majority of RWSs these issues are taken into consideration. Furthermore, the results coming from RWSs can potentially validate the findings of RCTs. For the purpose of validation efforts, we defined two

metrics in our second study: consistency and congruency, operationalised as a benchmark index.

Moreover, implementing our approach, we were able to investigate relatively rare events (e.g., death), and examine special patterns of treatments (e.g., polypharmacy), in real-world data, using a large, full-population insurance database.

Our results also highlight the importance of capturing multiple relevant endpoints in RCTs in the future.

## 6. Bibliography of the candidate's publications

### 6.1 Bibliography of the candidate's publications related to the thesis

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